Gastric Cancer: Best Options in Non-metastatic Disease

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Medically Fit Localized Cancer

- A 54 y/o smoker man
- Dyspepsia and epigastric discomfort
- No other symptoms
- No comorbidity
- Normal CBC and comprehensive chemistry profile
- Upper GI endoscopy: *Antral erythema with small (1 cm in diameter) mass lesion of lesser curvature*
- Pathology of endoscopic biopsy: *moderately differentiated adenocarcinoma, intestinal type*

Medically Fit Localized Cancer

- What is the next step?

Medically Fit Localized Cancer

- Chest/abdomen/pelvis CT with oral and IV contrast: *Normal*
- H. Pylori test: *Positive*

Medically Fit Localized Cancer

- H. pylori test:

1. If positive, discuss recommendations with family members as appropriate

- Tumor EBV test:

1. If the morphology of the tumor contains prominent lymphoid stroma
2. A potential biomarker for personalized treatment strategies for gastric cancer, but not currently recommended for clinical care

Medically Fit Localized Cancer

- When we need PET-CT?

Medically Fit Localized Cancer

- T staging:

1. CT scan: overall accuracy of 43% to 82%
2. FDG-PET: lower accuracy rate because of low FDG uptake in diffuse and mucinous tumor types

- N staging:

1. CT scan: sensitivity of 78% and specificity 62%
2. FDG-PET: lower sensitivity compared to CT (56% vs. 78%), but better specificity (92% vs. 62%)

Medically Fit Localized Cancer

- Overall staging:

1. CT scan: overall accuracy of 53%
2. FDG-PET: overall accuracy of 47%
3. Combined FDG-PET/CT: overall accuracy of 68% (does not take the place of staging laparoscopy given its inability to detect peritoneal disease)

Medically Fit Localized Cancer

- What is the next step?

Medically Fit Localized Cancer

- Endoscopic ultrasound (EUS): *A dark expansion of layers 1–3 with no abnormal or enlarged lymph nodes and no ascites*

Medically Fit Localized Cancer

- What is the next step?

Medically Fit Localized Cancer

- Microsatellite instability (MSI) or Mismatch Repair (MMR) test: *Proficient MMR*

Medically Fit Localized Cancer

- What is the next step?

NCCN Guidelines Version 5.2024
Gastric Cancer

NCCN Guidelines Index
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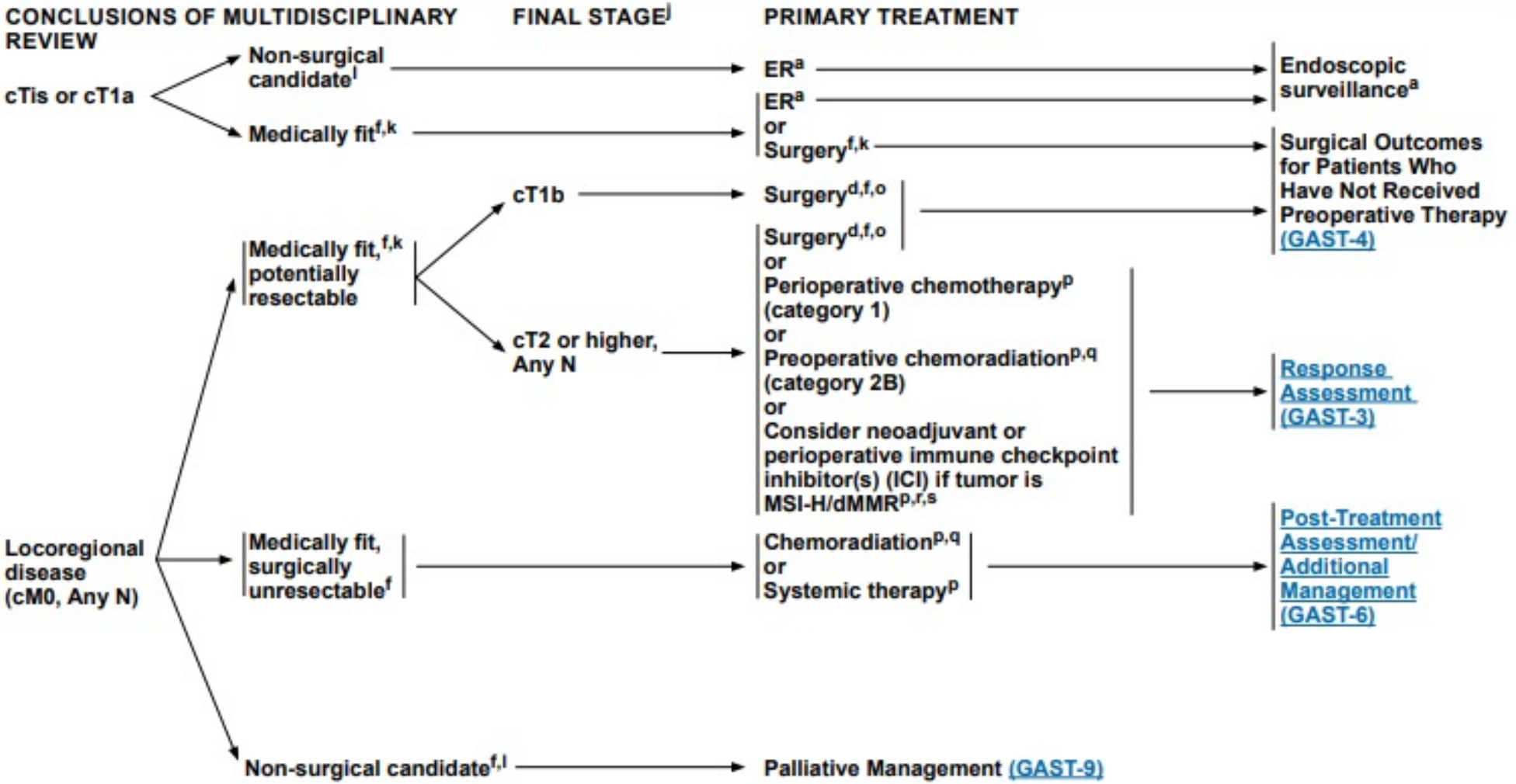
Discussion



Medically Fit Localized Cancer

- Endoscopic resection (ER):

1. Essential for the accurate staging of early-stage cancers (T1a or T1b)
2. Early-stage cancers can best be diagnosed by ER
3. May also be therapeutic for early-stage disease/lesions

- Endoscopic resection (ER):

1. Endoscopic Mucosal Resection (EMR)
2. Endoscopic Submucosal Dissection (ESD)

Medically Fit Localized Cancer

- Pathology of ER:

1. *Adenocarcinoma, intestinal type*
2. *Moderately differentiated*
3. *Free mucosal and deep margins*
4. *Tumor extends to sub-mucosa with maximum sub-mucosal invasion of 0.3 mm*
5. *No lymphovascular invasion*

Medically Fit Localized Cancer

- What is the next step?

Medically Fit Localized Cancer

- Principles of follow-up/surveillance:

1. H&P every 3–6 months for 1–2 years, every 6–12 months for 3–5 years
2. CBC and chemistry profile as clinically indicated
3. EGD every 6 months for 1 year, then annually for up to 5 years

Loco-regionally Recurrent Cancer

- In the last follow up in the 4th year:

1. H&P: *Some weight loss and melena*
2. CBC: *Microcytic anemia*
3. Upper GI endoscopy: *Large (5 cm in diameter) ulcerative tumoral lesion of lesser curvature*
4. Pathology of endoscopic biopsy: *moderately differentiated adenocarcinoma, intestinal type*

Loco-regionally Recurrent Cancer

- What is the next step?

Loco-regionally Recurrent Cancer

- FDG-PET/CT:

1. *Large FDG avid tumoral lesion of lesser curvature (SUV=8) with no extension to adjacent organs*
2. *Multiple FDG avid perigastric LNP (SUV=9)*
3. *No other metabolic active lesion in the reminder of imaged portion of body*

Loco-regionally Recurrent Cancer

- What is the next step?

Loco-regionally Recurrent Cancer

- Laparoscopy:

1. *Multiple perigastric and para-aortic LNP with invasion to aorta and retroperitoneum*
2. *No visible peritoneal implants*
3. *No ascites*

- Pathology of laparoscopic biopsy of LNP and peritoneal washing:

1. *Moderately differentiated adenocarcinoma, intestinal type*
2. *Negative peritoneal cytology*

Loco-regionally Recurrent Cancer

- What is the next step?

Loco-regionally Recurrent Cancer

- HER2 test: *Positive (3+)*
- PD-L1 test: *Positive (CPS 2%)*
- MSI or MMR test: *Proficient MMR*
- Claudin 18 isoform 2 (CLDN18.2) test: *Negative*
- NGS (may be considered)

Loco-regionally Recurrent Cancer

- What is the next step?

✓Systemic therapy?

✓Chemoradiation therapy?

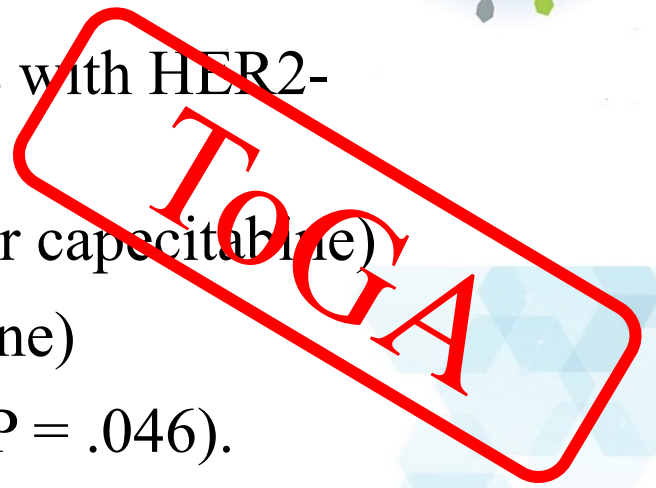
✓Sequential systemic therapy plus chemoradiation therapy?

Loco-regionally Recurrent Cancer

- CAPOX plus Pembrolizumab and Trastuzumab 3 weekly

1. Pembrolizumab 200 mg IV on Day 1
2. Trastuzumab 6 mg/kg IV on Day 1 (8 mg/kg IV loading dose in cycle 1)
3. Oxaliplatin 130 mg/m2 IV on Day 1
4. Capecitabine 850–1000 mg/m2 PO BID on Days 1–14

Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or GE junction cancer (ToGA): a phase 3, open-label, randomised controlled trial



- The 1st phase III RCT for evaluation of Trastuzumab in patients with HER2-positive advanced gastric or EGJ adenocarcinoma

1. *Trastuzumab* plus chemotherapy (cisplatin plus fluorouracil or capecitabine)
2. Chemotherapy alone (cisplatin plus fluorouracil or capecitabine)

- Improvement in median OS (13.8 vs. 11 months, respectively; P = .046).
- Post-hoc subgroup analysis:

1. OS in IHC 2+ and FISH positive or IHC 3+ (16 vs. 11.8 months; HR, 0.65)
2. OS in IHC 0 or 1+ and FISH positive (10 vs. 8.7 months; HR, 1.07)

Phase II study to evaluate the efficacy of Trastuzumab in combination with Capecitabine and Oxaliplatin in first-line treatment of HER2-positive advanced gastric cancer: HERXO trial

- A single arm phase II study (2019)

1. *Trastuzumab* plus chemotherapy (*CAPOX*)

- At a median follow-up of 13.7 months

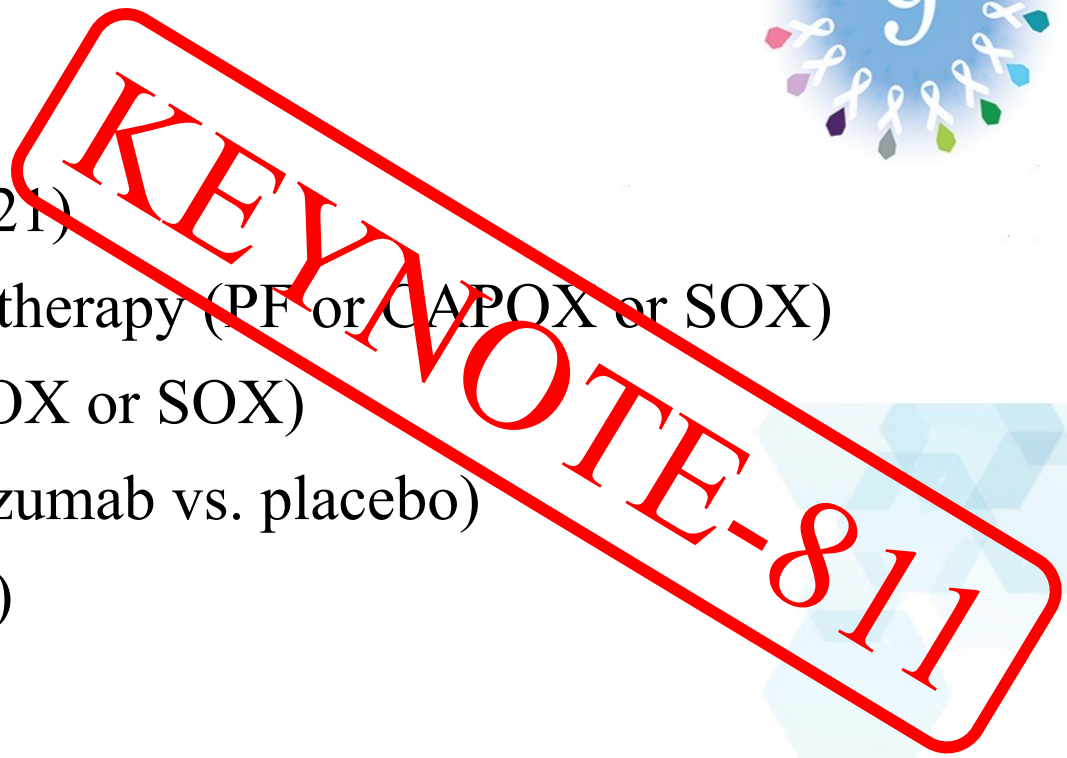
1. PFS of 7.1 months
2. OS of 13.8 months
3. CR of 8.9%
4. PR of 37.8%
5. SD of 31.1%

Efficacy and safety of trastuzumab in combination with oxaliplatin and fluorouracil-based chemotherapy for patients with HER2-positive metastatic gastric and GE junction adenocarcinoma patients: A retrospective study

- A single arm retrospective study (2015)

1. *Trastuzumab* plus chemotherapy (*mFOLFOX* or *CAPOX*)
2. PFS of 9 months
3. OS of 17.3 months
4. ORR of 41%

The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer



- The 1st interim analysis of a phase III RCT (2021)

1. *Pembrolizumab* and *Trastuzumab* plus chemotherapy (PF or CAPOX or SOX)
2. *Trastuzumab* plus chemotherapy (PF or CAPOX or SOX)

- At a median follow-up of 12 months (Pembrolizumab vs. placebo)

1. PFS of 10 months vs. 8.1 months (P = 0.0002)
2. CR of 11.3% vs. 3.1%
3. PR of 63.2% vs. 48.9%
4. SD of 21.8% vs. 37.4%
5. PD of 3.8% vs. 5.3%

Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial.

KEYNOTE-811

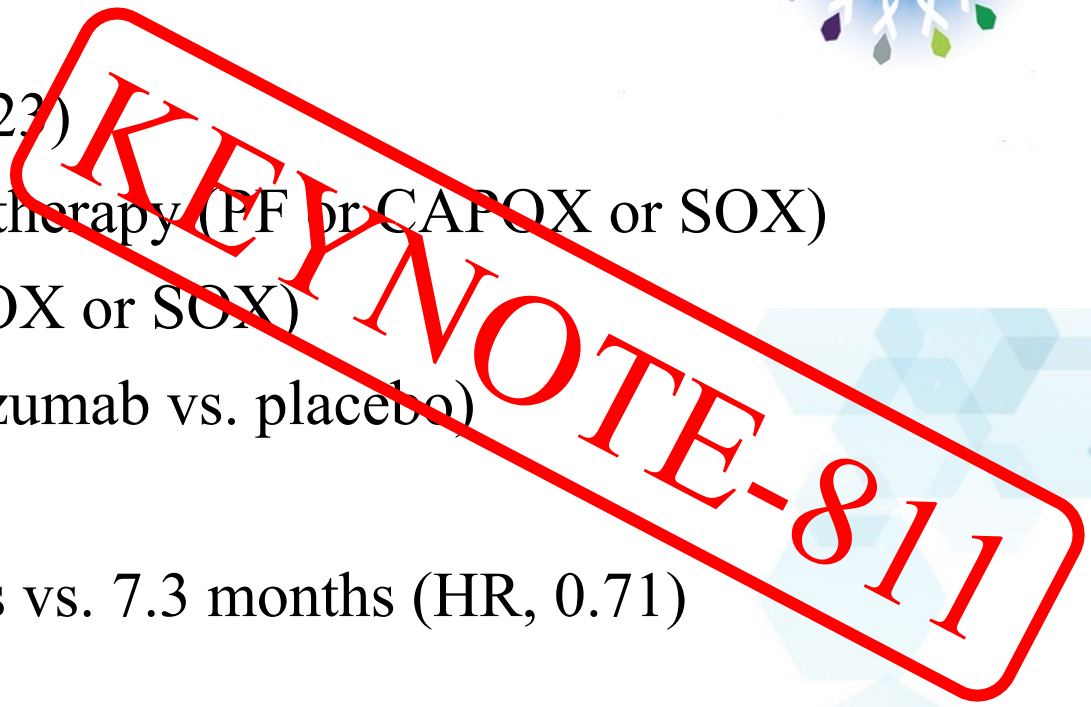
- The 2nd interim analysis of a phase III RCT (2023)

1. *Pembrolizumab* and *Trastuzumab* plus chemotherapy (PF or CAPOX or SOX)
2. *Trastuzumab* plus chemotherapy (PF or CAPOX or SOX)

- At a median follow-up of 28 months (Pembrolizumab vs. placebo)

1. PFS of 10 months vs. 8.1 months (HR, 0.72)
2. PD-L1 CPS ≥1 subgroup: PFS of 10.8 months vs. 7.2 months (HR, 0.70)
3. OS of 20 months vs. 16.9 months (HR, 0.87)
4. PD-L1 CPS ≥1 subgroup: OS of 20.5 months vs. 15.6 months (HR, 0.79)

Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-oesophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial.

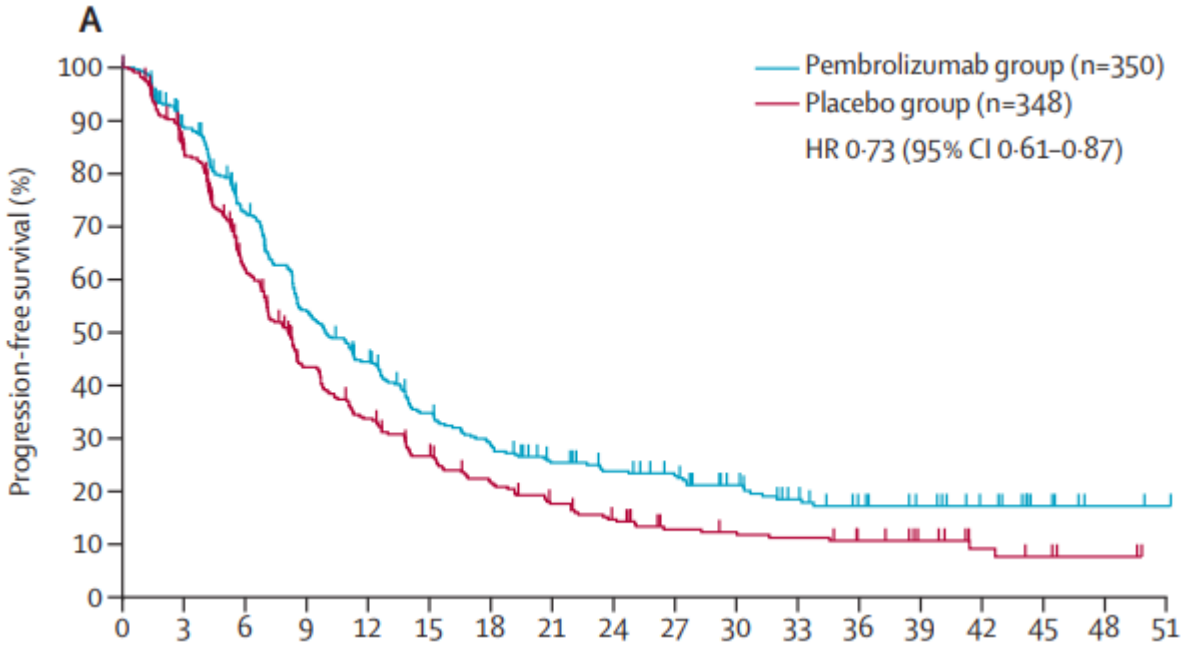


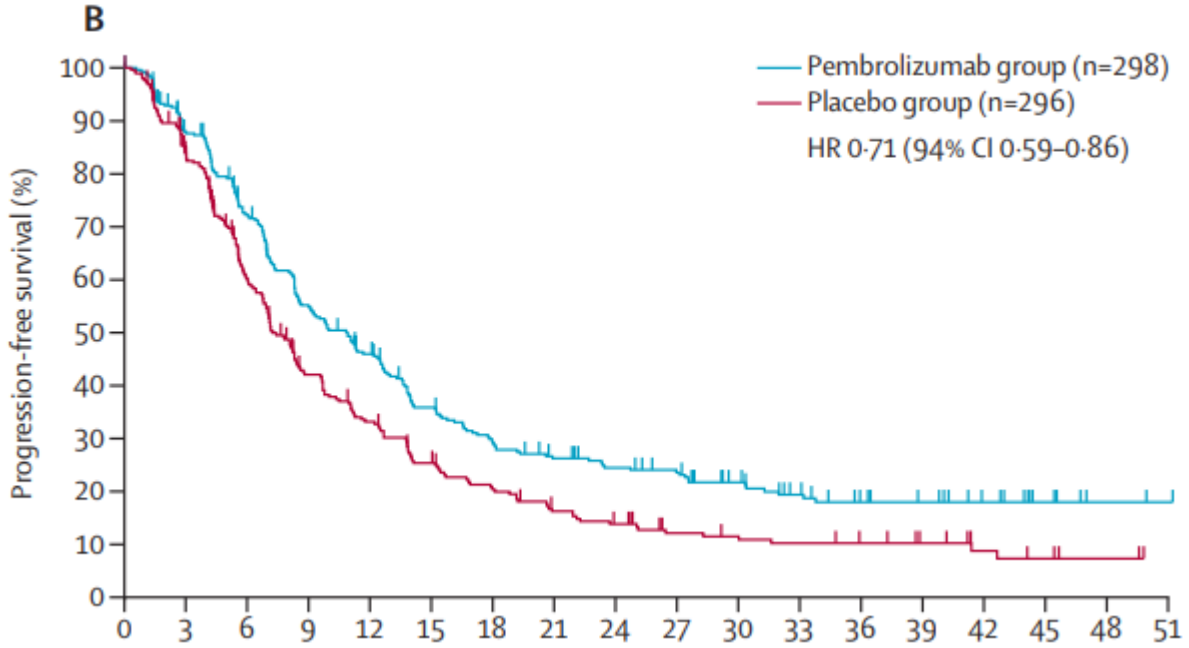
- The 3rd interim analyses of a phase III RCT (2023)

1. *Pembrolizumab* and *Trastuzumab* plus chemotherapy (PF or CAPOX or SOX)
2. *Trastuzumab* plus chemotherapy (PF or CAPOX or SOX)

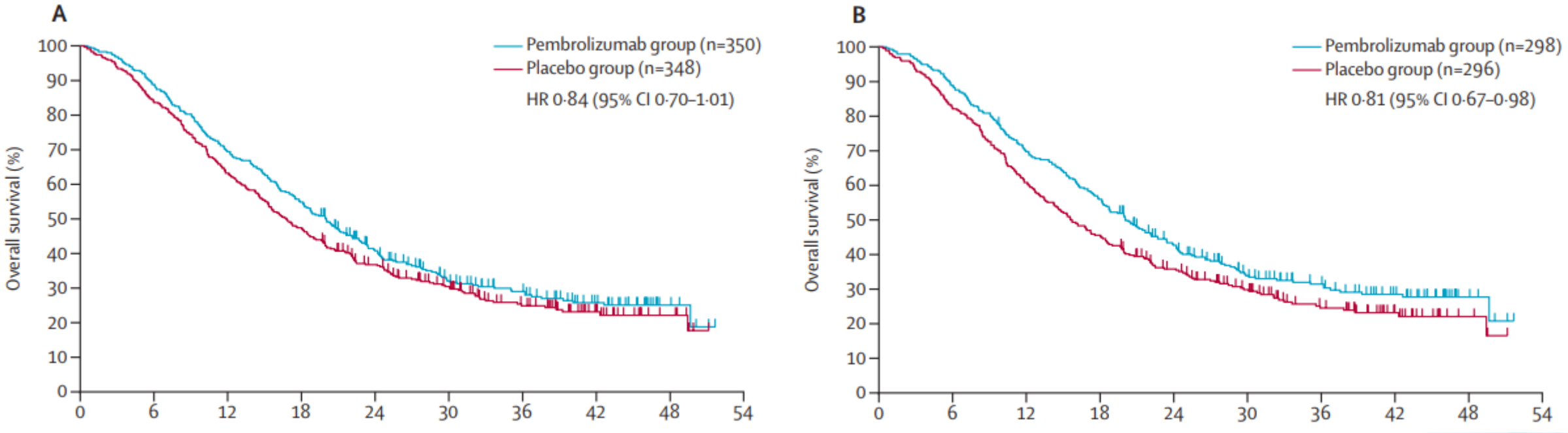
- At a median follow-up of 38 months (Pembrolizumab vs. placebo)

1. PFS of 10 months vs. 8.1 months (HR, 0.73)
2. PD-L1 CPS ≥1 subgroup: PFS of 10.9 months vs. 7.3 months (HR, 0.71)
3. OS of 20 months vs. 16.8 months (HR, 0.84)
4. PD-L1 CPS ≥1 subgroup: OS of 20 months vs. 15.7 months (HR, 0.81)





Kaplan-Meier estimates of PFS in all patients (A) and in the subgroup of patients with tumors with a PD-L1 CPS of 1 or more (B).



Kaplan-Meier estimates of OS in all patients (A) and in the subgroup of patients with tumors with a PD-L1 CPS of 1 or more (B).

Loco-regionally Recurrent Cancer

- What about concurrent CRT?

Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomized controlled trial

- A multicenter phase III RCT

1. *Preoperative* CRT with weekly paclitaxel and carboplatin
2. Surgery alone

- Resectable (T2–3, N0–1, M0) esophageal or EGJ cancer
- At a median follow up of 84.1 months (CRT plus Sx vs. Sx)

1. Median OS: 48·6 months vs. 24·0 months (P = 0.003)
2. Median OS for SCC: 81·6 months vs. 21·1 months (P = 0.008)
3. Median OS for adenocarcinomas: 43·2 months vs. 27·1 months (P = 0.038)

Phase III Trial of Trimodality Therapy With Cisplatin, Fluorouracil, Radiotherapy, and Surgery Compared With Surgery Alone for Esophageal Cancer: CALGB-9781

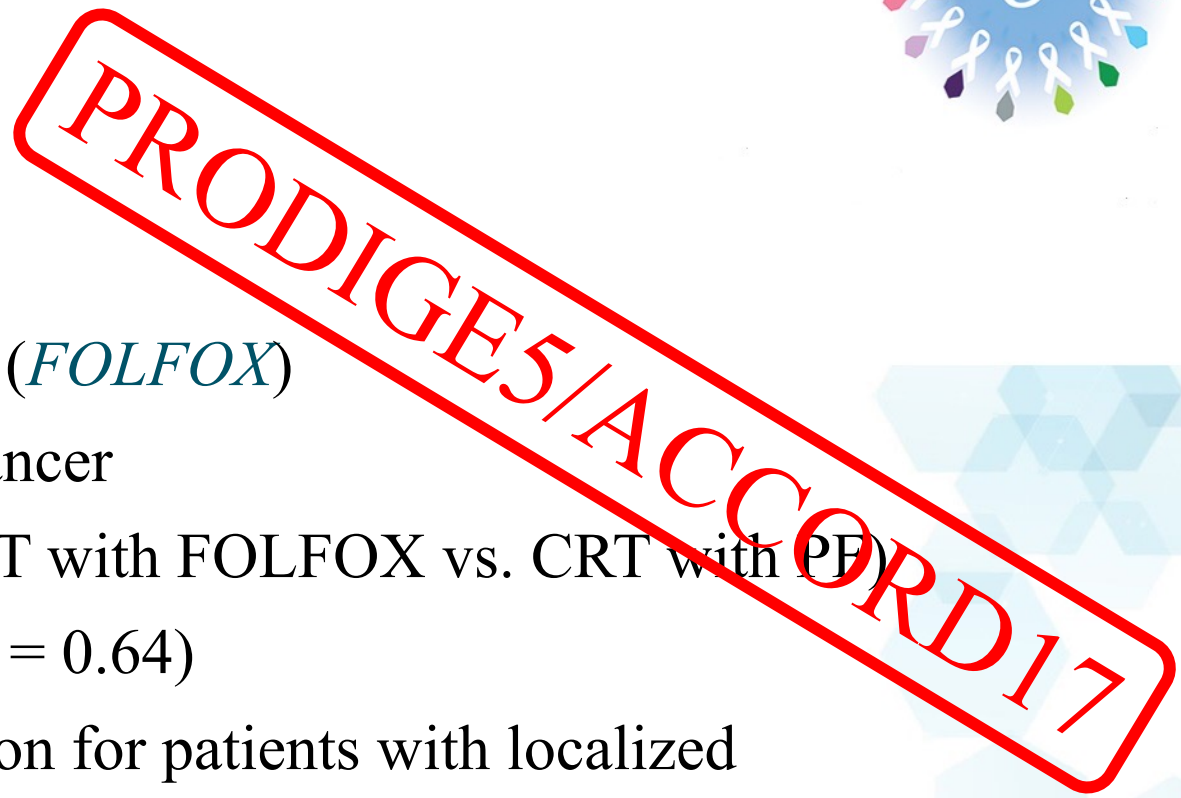
- A phase III RCT

1. *Preoperative* CRT with cisplatin and 5FU
2. Surgery alone

- Resectable (stage I-III) esophageal cancer
- At a median follow up of 72 months (CRT plus Sx vs. Sx)

1. Median OS: 54 months vs. 21 months (P = 0.02)
2. 5 year OS: 39% vs. 16%
3. Median PFS: 41 months vs. 12 months
4. 5 year PFS: 28% vs. 15%

Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial



- A phase II/III RCT

1. *Definitive* CRT with 5FU and cisplatin
2. *Definitive* CRT with 5FU and oxaliplatin (*FOLFOX*)

- Medically unfit/unresectable esophageal cancer
- At a median follow up of 25.3 months (CRT with FOLFOX vs. CRT with PF)
- Median PFS: 9.7 months vs. 9.4 months (P = 0.64)
- FOLFOX might be a more convenient option for patients with localized esophageal cancer unsuitable for surgery

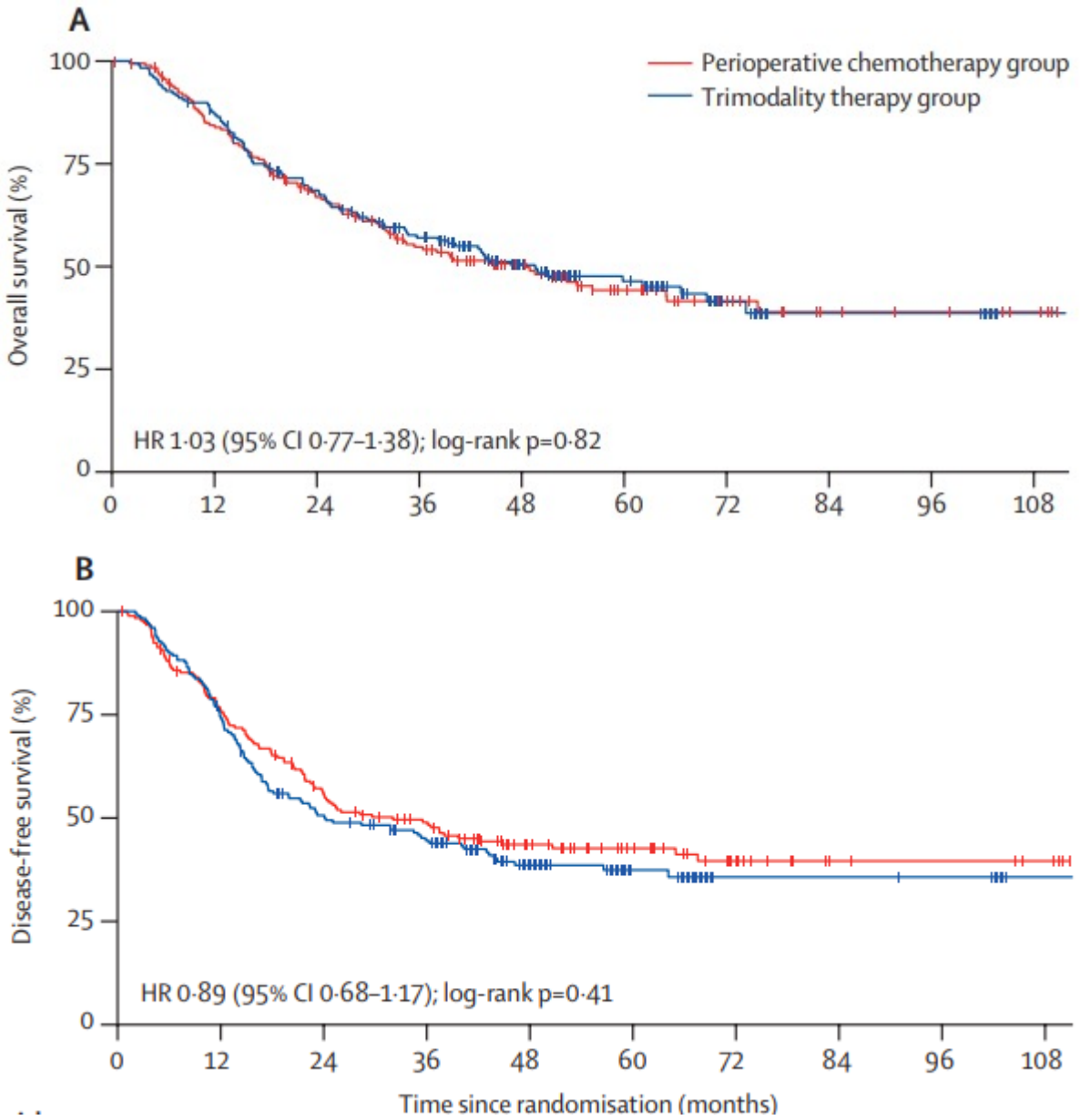
Trimodality therapy versus perioperative chemotherapy in the management of locally advanced adenocarcinoma of the oesophagus and oesophagogastric junction (Neo-AEGIS): an open-label, randomised, phase 3 trial

- A multicenter phase III RCT (2023)

1. *Preoperative* CRT (*CROSS* regimen)
2. *Perioperative* ECF/ECX/EOF/EOX (modified *MAGIC*) or FLOT (2019-2020)

- Resectable (T2-3, anyN, M0) EGJ or oesophageal adenocarcinoma
- At a median follow up of 38.8 months (preoperative CRT vs. perioperative CT):

1. pCR (p=0·012), pRR (p<0·0001), and R0 rates (p=0·0003) favored trimodality
2. Median OS: 49.2 months vs. 48 months
3. 3 years OS: 57% vs. 55% (P = 0.82)
4. Median DFS: 24 months vs. 32.4 months (P = 0.41)


A
Perioperative chemotherapy group
Trimodality therapy group
Overall survival (%)
100
75
50
25
0
HR 1·03 (95% CI 0·77–1·38); log-rank p=0·82
0
12
24
36
48
60
72
84
96
108
B
Disease-free survival (%)
100
75
50
25
0
HR 0·89 (95% CI 0·68–1·17); log-rank p=0·41
0
12
24
36
48
60
72
84
96
108
Time since randomisation (months)

Prospective randomized multicenter phase III trial comparing perioperative chemotherapy (FLOT protocol) to neoadjuvant chemoradiation (CROSS protocol) in patients with adenocarcinoma of the esophagus (ESOPEC trial)

- A multicenter phase III RCT (2024)

1. *Preoperative* CRT (*CROSS* regimen)
2. *Perioperative* FLOT

- Resectable (T1–4a, N0–1, M0) esophageal adenocarcinoma
- At a median follow up of 55 months (CROSS plus Sx vs. FLOT plus Sx)

1. pCR: 13.5% vs. 19.3%
2. Median OS: 37 months vs. 66 months
3. 3 years OS: 50.7% vs. 57.4% (P = 0.012)

Loco-regionally Recurrent Cancer

- What about sequential systemic therapy plus CRT?

Phase II Trial of Preoperative Chemoradiation in Patients With Localized Gastric Adenocarcinoma (RTOG-9904): Quality of Combined Modality Therapy and Pathologic Response

- A single arm multicenter phase II trial

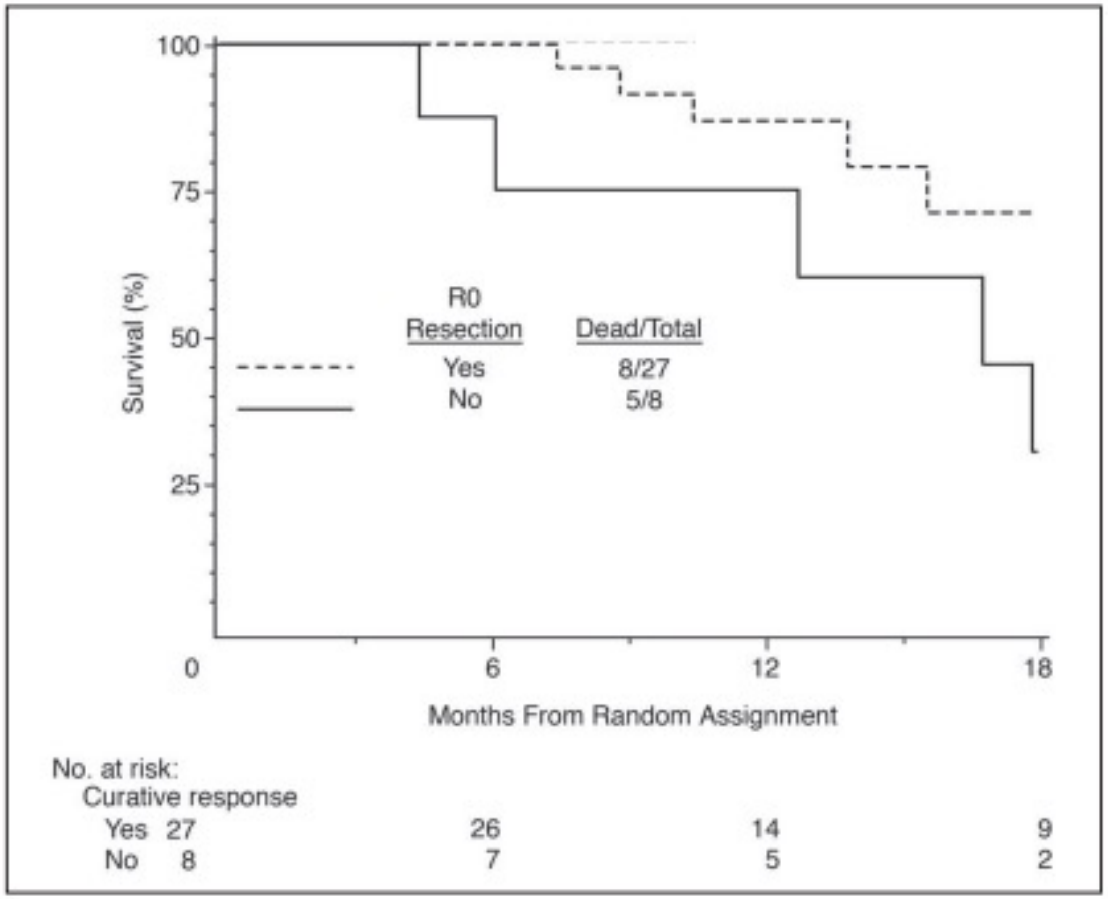
1. Induction chemotherapy (PF) and concurrent CRT (*CROSS* regimen)

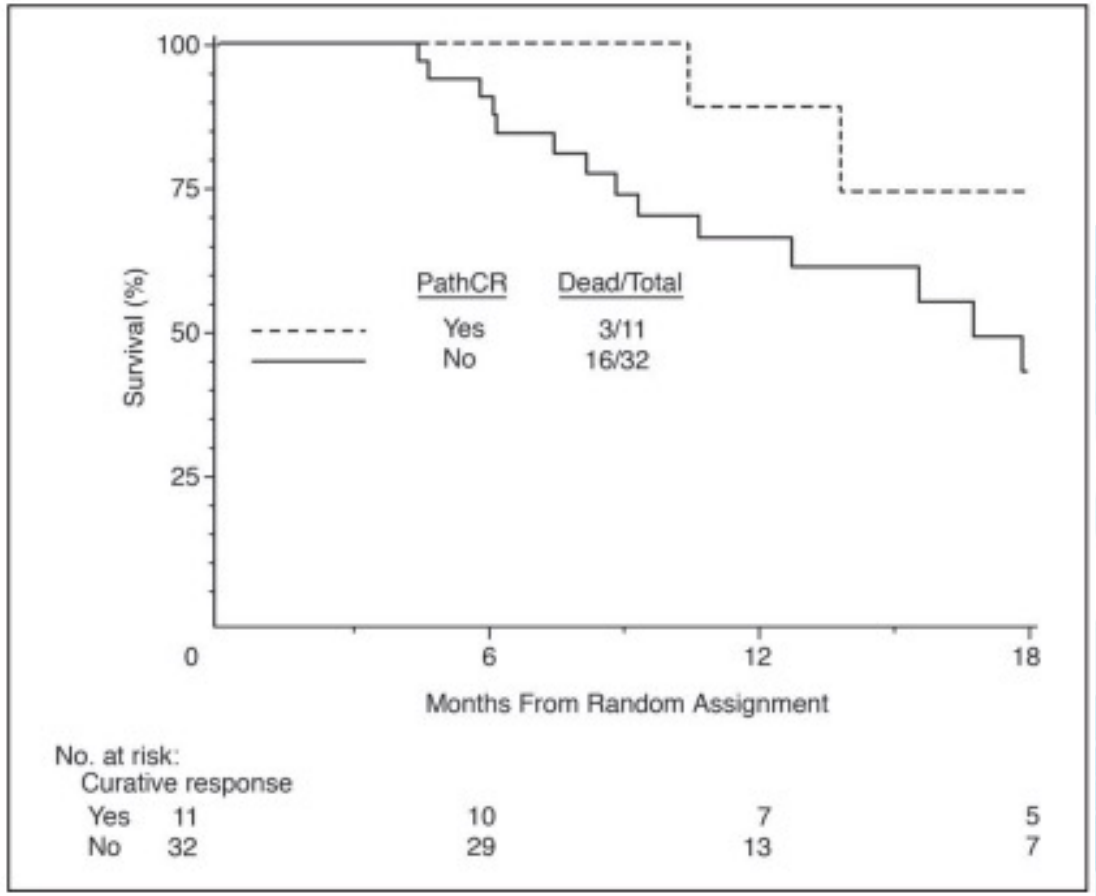
- Localized (stage I-III) gastric cancer
- At a 1 year follow up:

1. pCR rate: 26%
2. R0 resection rate: 77%
3. 1 year survival in patients with pCR: 82%
4. 1 year survival in patients with less than pCR: 69%

RTOG-9904

Overall survival by R0 resection and pathologic complete response





Phase II trial of preoperative irinotecan-cisplatin followed by concurrent irinotecan-cisplatin and radiotherapy for resectable locally advanced gastric and esophagogastric junction adenocarcinoma

- A single arm phase II trial (2009)

1. Induction chemotherapy and concurrent CRT

- Resectable Stage II-IV gastric or EGJ cancer

1. pCR rate: 9%
2. R0 resection rate: 65%
3. 2 year survival: 35%
4. Median OS: 14.5 months

Phase II trial of induction irinotecan-cisplatin followed by concurrent irinotecan-cisplatin and radiotherapy for unresectable, locally advanced gastric and oesophageal-gastric junction adenocarcinoma

- A single arm phase II trial (2011)

1. Induction chemotherapy and concurrent CRT

- Unresectable gastric or EGJ cancer (invasion to the head of the pancreas, hepatic hilium, SMA, aorta, transverse mesocolon, retro-peritoneum, or diaphragm)
- At a median follow up of 25 months:

1. pCR rate: 0%
2. R0 resection rate: 29%
3. 2 year survival: 27%
4. Median OS: 10.5 months

Phase III Comparison of Preoperative Chemotherapy Compared With Chemoradiotherapy in Patients With Locally Advanced Adenocarcinoma of the Esophagogastric Junction

- A phase III RCT (2009)

1. Induction CT (15 weeks) followed by Sx
2. Induction CT (12 weeks) followed by CRT (3 weeks) followed by Sx

- Locally advanced (T3-4NXM0) EGJ adenocarcinoma
- At a median follow up of 46 months (without CRT vs. with CRT):

1. pCR rate: 2% vs. 15.6% (P = 0.03)
2. 3 year survival: 27.7% vs. 47.4% (P = 0.07)
3. Median OS: 21 months vs. 33 months
4. No statistical significance because of premature closure due to low accrual

TOPGEAR: a randomized, phase III trial of perioperative ECF chemotherapy with or without preoperative chemoradiation for resectable gastric cancer: interim results from an international, intergroup trial of the AGITG, TROG, EORTC and CCTG

- A multicenter phase III RCT (2017)

1. *Perioperative* ECF/ECX (modified *MAGIC*) 3 cycles both pre- and postoperatively
2. 2 cycles of preoperative ECF/ECX (modified *MAGIC*) followed by preoperative CRT and then 3 cycles of postoperative CT

- Resectable (anyT, anyN, M0) EGJ or gastric adenocarcinoma
- No significant difference in treatment toxicity or surgical morbidity (without CRT vs. with CRT) :

1. Grade 3 or higher surgical complications: 22% in both groups
2. Grade 3 or higher gastrointestinal toxicity: 32% vs. 30%
3. Grade 3 or higher hematologic toxicity: 50% vs. 52%

Preoperative Chemoradiotherapy for Resectable Gastric Cancer

TOPGEAR

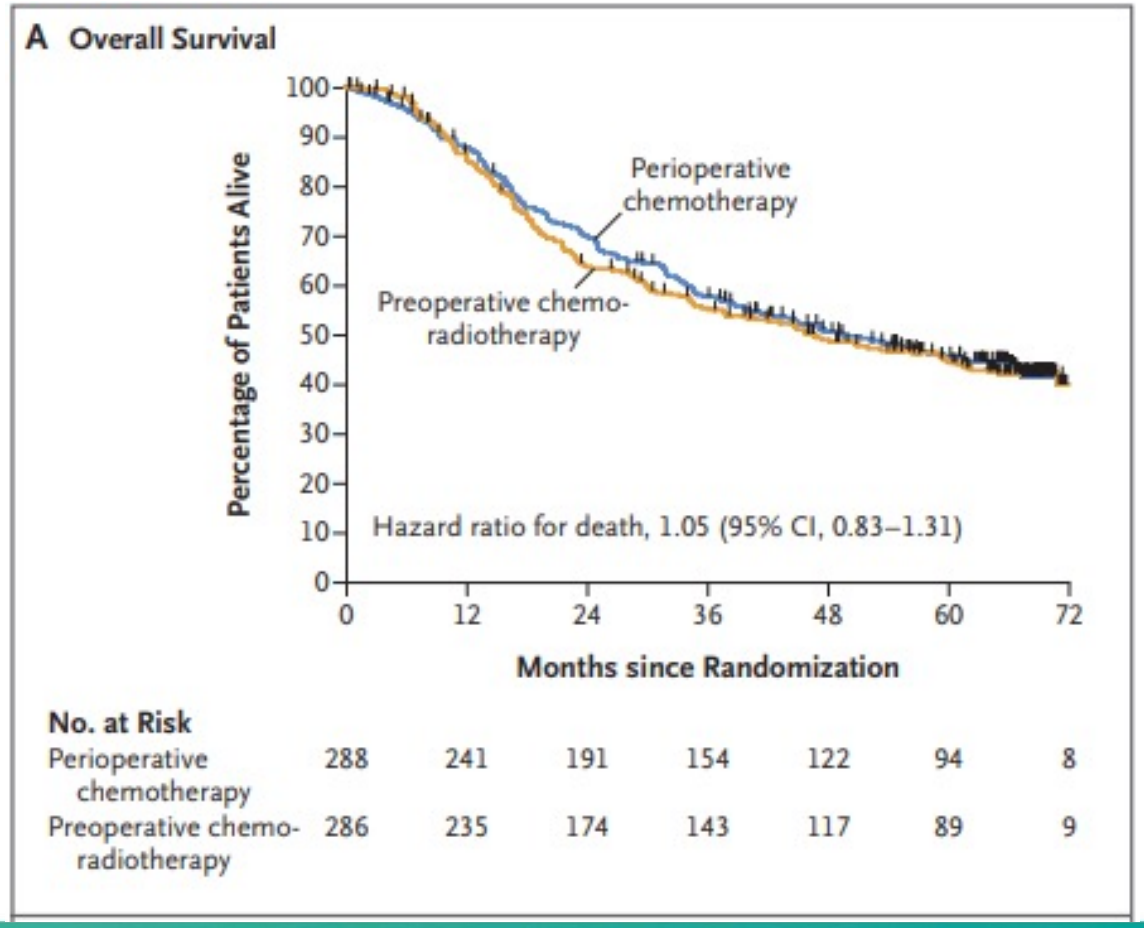
- A multicenter phase III RCT (2024)

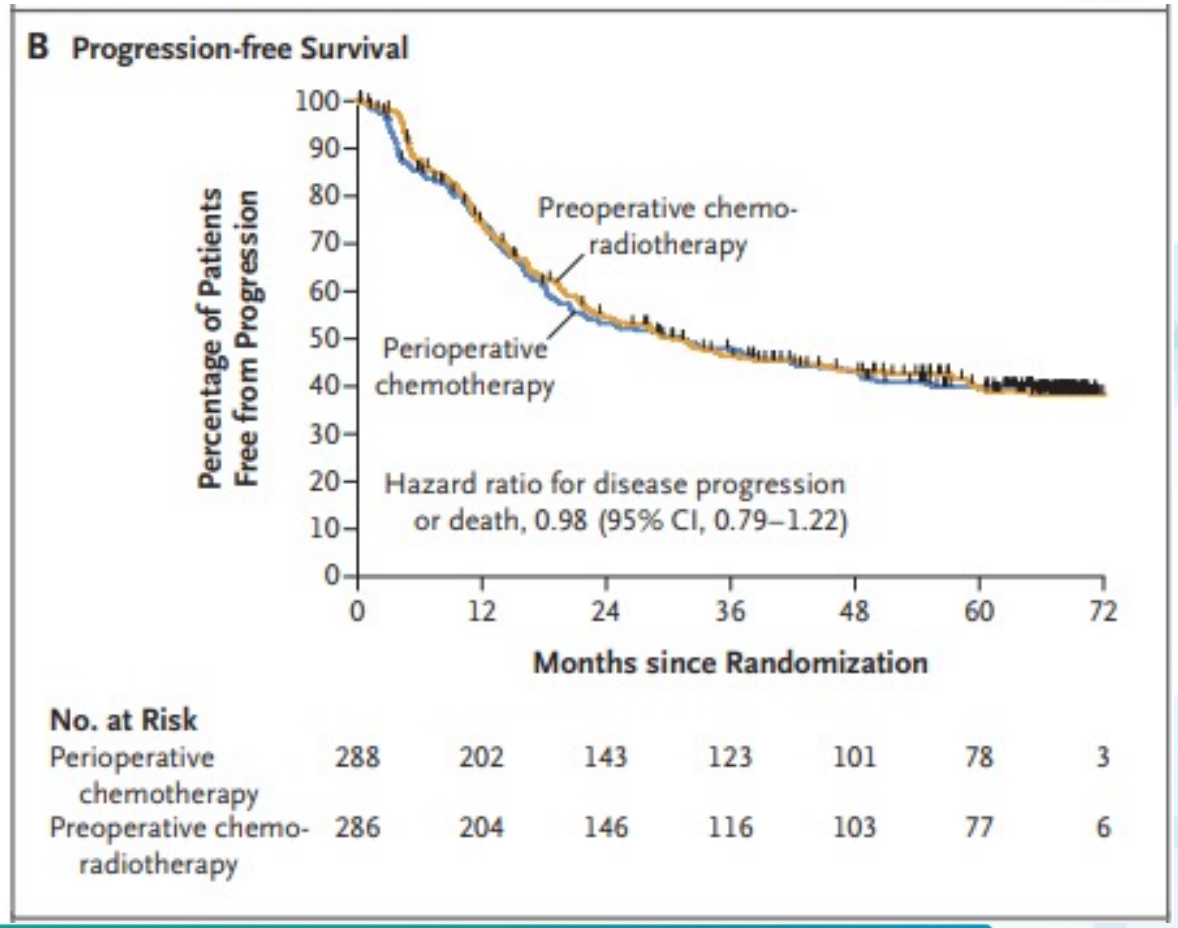
1. *Perioperative* ECF/ECX (modified *MAGIC*) 3 cycles both pre- and postoperatively
2. 2 cycles of preoperative ECF/ECX (modified *MAGIC*) followed by preoperative CRT and then 3 cycles of postoperative CT

- At a median follow up of 67 months (without CRT vs. with CRT) no improvement in OS or PFS:

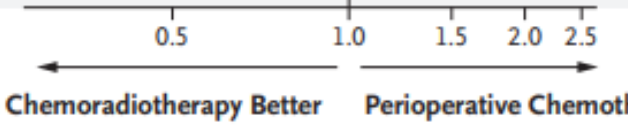
1. pCR rate: 8% vs. 17%
2. R0 resection rate: 88% vs. 92%
3. Median OS: 49 months vs. 46 months
4. Median PFS: 32 months vs. 31 months

Kaplan–Meier estimates of overall survival (Panel A) and progression-free survival (Panel B) according to treatment group





Subgroup	Preoperative Chemoradiotherapy	Perioperative Chemotherapy	Hazard Ratio for Death (95% CI)
	no. of deaths/total no. of patients (%)		
Overall	153/286 (53)	151/288 (52)	1.05 (0.83–1.31)
Age			
<50 yr	26/45 (58)	27/46 (59)	0.94 (0.55–1.62)
50–70 yr	96/180 (53)	97/181 (54)	1.03 (0.78–1.37)
>70 yr	31/61 (51)	27/61 (44)	1.17 (0.70–1.96)
Sex			
Female	44/78 (56)	41/78 (53)	1.12 (0.73–1.72)
Male	109/208 (52)	110/210 (52)	1.02 (0.78–1.33)
Primary tumor site			
Gastroesophageal junction	55/98 (56)	65/101 (64)	0.78 (0.55–1.12)
Upper or middle third of the stomach or multiple sites	60/116 (52)	57/117 (49)	1.02 (0.71–1.47)
Lower third of the stomach	38/72 (53)	29/70 (41)	1.70 (1.05–2.77)
Clinical tumor stage			
T1 or T2	12/33 (36)	14/31 (45)	0.63 (0.29–1.37)
Tx, T3, or T4	141/253 (56)	137/257 (53)	1.12 (0.88–1.41)
Clinical nodal stage			
Node-negative	56/110 (51)	50/111 (45)	1.19 (0.81–1.74)
Node-positive or unknown	97/176 (55)	101/177 (57)	0.97 (0.73–1.28)
Chemotherapy regimen			
ECF or ECX	106/192 (55)	105/194 (54)	1.01 (0.77–1.32)
FLOT	47/94 (50)	46/94 (49)	1.14 (0.76–1.71)



Treatment effect on OS. The size of the square is proportional to the amount of statistical information in that category. Interaction tests between treatment and subgroup were not significant (P>0.05), except for the tumor site in this forest plot.

Loco-regionally Recurrent Cancer

- What about concurrent targeted therapy and RT or CRT?

Trastuzumab with trimodality treatment for oesophageal adenocarcinoma with HER2 overexpression (NRG Oncology/RTOG 1010): a multicentre, randomised, phase 3 trial

- A multicenter phase III RCT (2022)

1. Preoperative CRT with weekly paclitaxel and carboplatin
2. Preoperative CRT with weekly paclitaxel and carboplatin plus *trastuzumab*

- Resectable (T1–3, N0–2, M0) esophageal or EGJ cancer
- At a median follow up of 34 months (without trastuzumab vs. with trastuzumab) no improvement in OS or PFS:

1. pCR rate: 29% vs. 27% (P = 0.71)
2. Median DFS: 14.2 months vs. 19.6 months (P = 0.97)
3. Median OS: 38.9 months vs. 38.5 months (P = 0.85)
4. Grade 3 treatment-related adverse events: 54% vs. 43%

Loco-regionally Recurrent Cancer

- What is the next step?

Loco-regionally Recurrent Cancer

- FDG-PET/CT: *complete clinical response*
- Upper GI endoscopy: *No residue*

Loco-regionally Recurrent Cancer

- What is the next step?

Loco-regionally Recurrent Cancer

- Pathology of total gastrectomy and D2 dissection:

1. *No residue in stomach*
2. *Negative 31 dissected LNs*

Loco-regionally Recurrent Cancer

- What is the next step?

Loco-regionally Recurrent Cancer

- Maintenance Pembrolizumab and Trastuzumab 3 weekly

1. Pembrolizumab 200 mg IV on Day 1
2. Trastuzumab 6 mg/kg IV on Day 1 (8 mg/kg IV loading dose in cycle 1)

Take-home Messages

- Role of *EUS* in early-stage disease
- Diagnostic and therapeutic role of *ER* in early-stage cancers
- Role of *PET-CT* in locally advanced/metastatic disease
- *MSI/MMR* test in all newly diagnosed patients
- *Multidisciplinary decision-making* especially for follow-up/surveillance

Take-home Messages

- Role of preoperative or sequential *CRT*:

1. Better response rates?
2. No improvement in OS or PFS
3. No difference in treatment toxicity or surgical morbidity

- Role of *concurrent targeted therapy* and RT or CRT:

1. Feasible and safe
2. No improvement in OS or PFS