



Hollings Cancer Center
An NCI-Designated Cancer Center

Update on Esophageal Cancers 2025

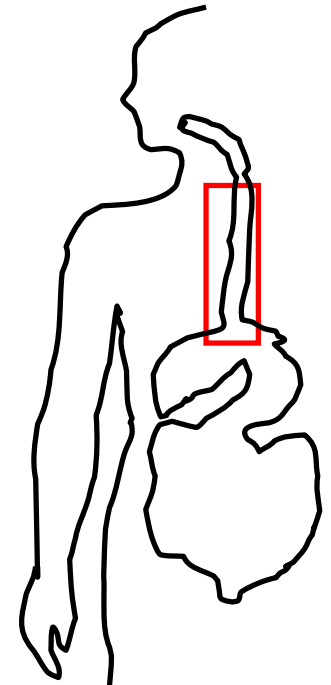
A. Craig Lockhart, MD, MHS | Hematology/Oncology

Esophageal Cancer 2023: Statistics

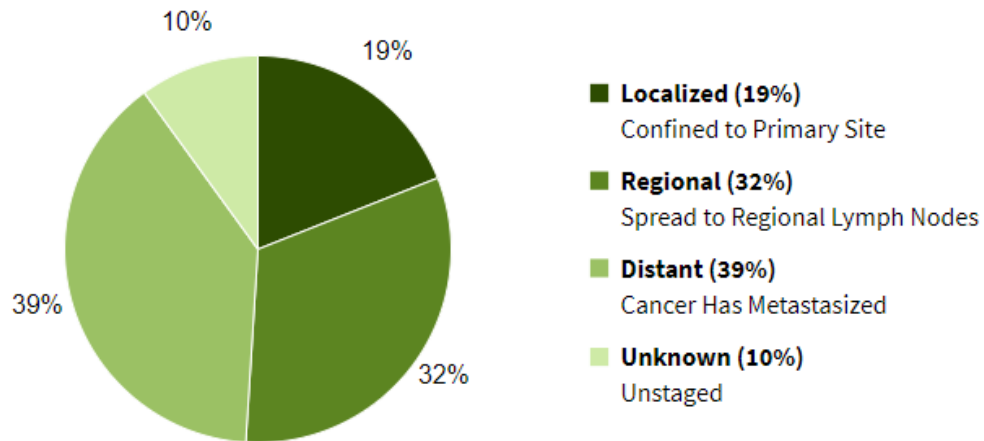
Estimated New Cases in 2023	21,560
% of All New Cancer Cases	1.1%

Estimated Deaths in 2023	16,120
% of All Cancer Deaths	2.6%

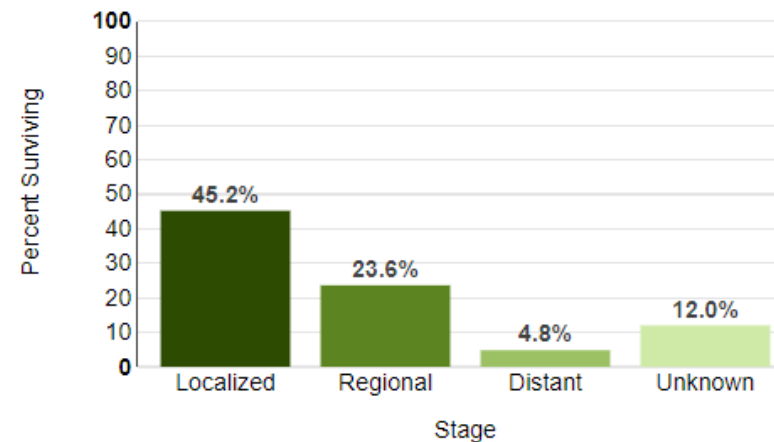
5-Year Relative Survival
21.7%
2013–2019



Percent of Cases by Stage



5-Year Relative Survival

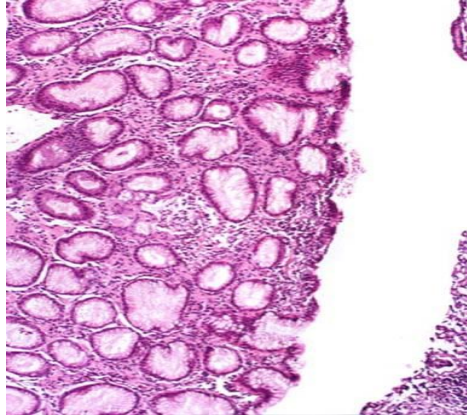


seer.cancer.gov

Esophageal Cancer: Risk Factors

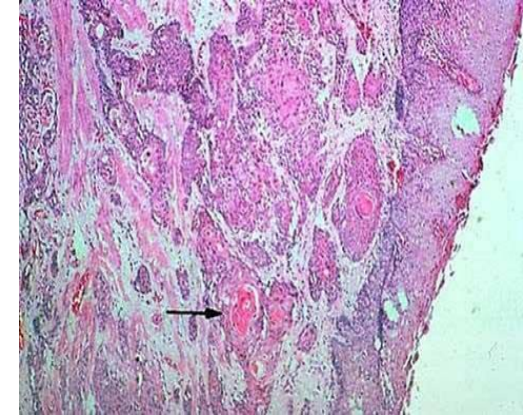
Adenocarcinoma

- Male sex
- Obesity
- GERD
- Barrett's metaplasia
- Smoking
- EtOH



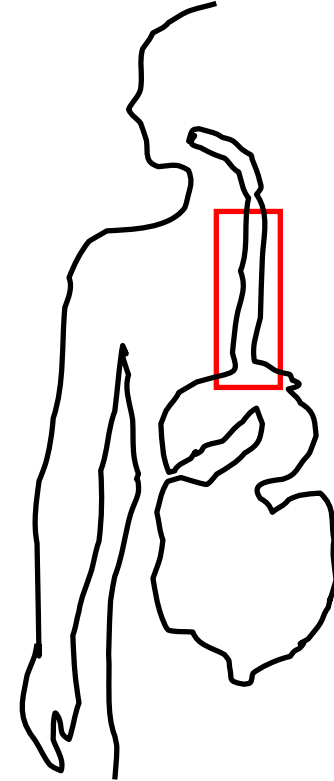
Squamous

- Gender (M:F ~ 3:1)
- Tobacco abuse
- Alcohol abuse
- Race (AA 50% more likely vs. Caucasians)
- Achalasia
- Lye ingestion
- Esophageal webs (Plummer-Vinson syndrome)



EC: Diagnostic/Staging Procedures

- CXR
- Barium swallow
- ✓ EGD
- Bronchoscopy
 - upper and middle third lesions
- ✓ CT chest and upper abdomen
- ✓ Endoscopic ultrasound (EUS) - staging accuracy ~ 85%
- ✓ PET



EC: Approach to the Patient

- **Esophageal Cancer:**

- Stage IA or IB: →

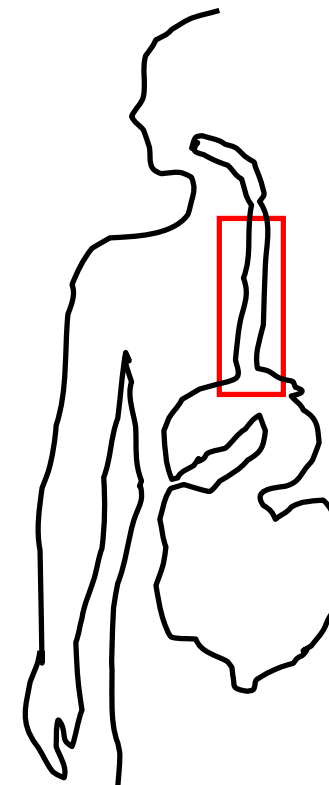
- surgery
- definitive chemo + RT

- Stage IIA to IIIC (T4a): →

- perioperative FLOT
- chemo + RT → surgery → immunotherapy
- definitive chemo + RT

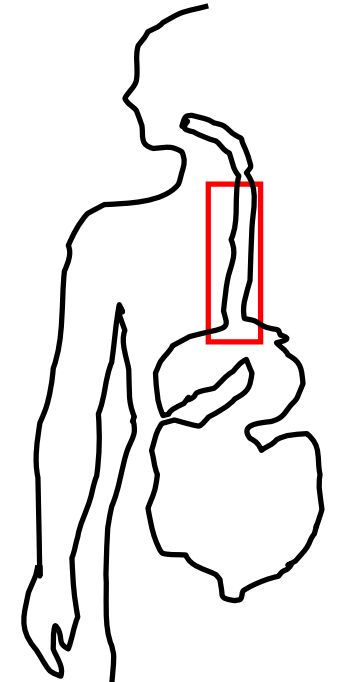
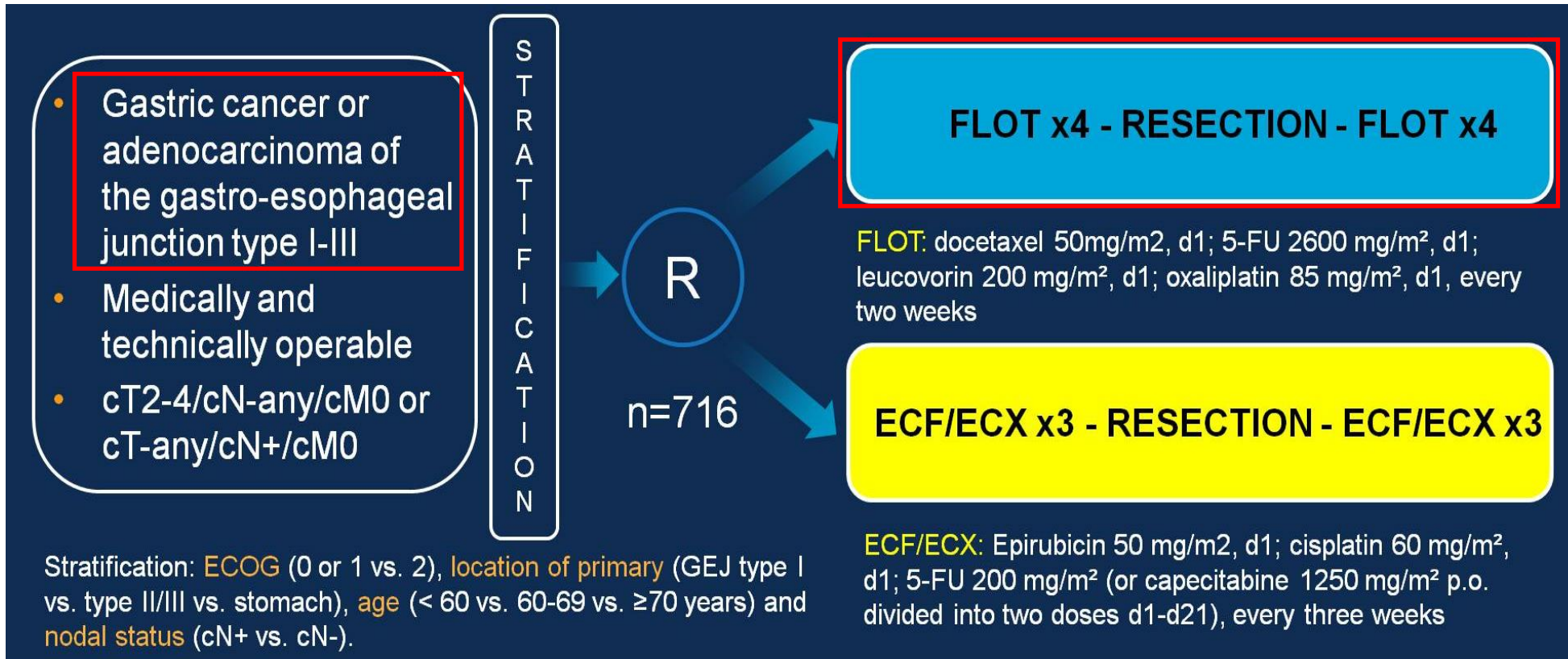
- Stage IV:

- if dysphagia → local therapy → chemo (e.g. stent, RT only, feeding tube)
- if no dysphagia → systemic chemotherapy



EC: Periop Chemo - FLOT4 Study

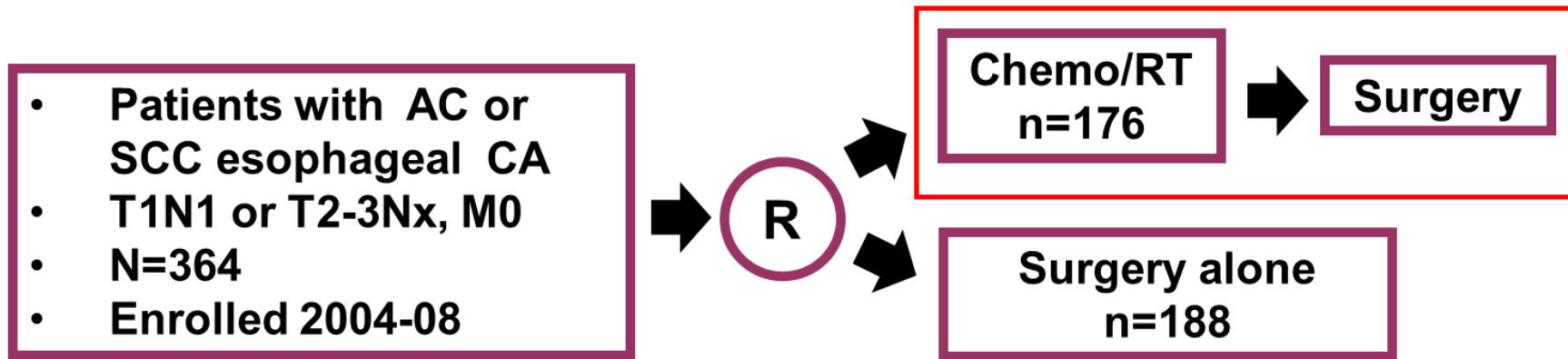
Study Schema:



Al-Batran, Lancet. 2019 May 11;393(10184):1948-1957

EC: Pre-op CRT – CROSS Study

Study Schema:



- Paclitaxel: 50mg/m²
- Carboplatin AUC=2 } Days 1,8,15,22,29
- RT: 41.4 Gy in 23 fractions
- Surgery within 6 weeks of ChemoRT completion

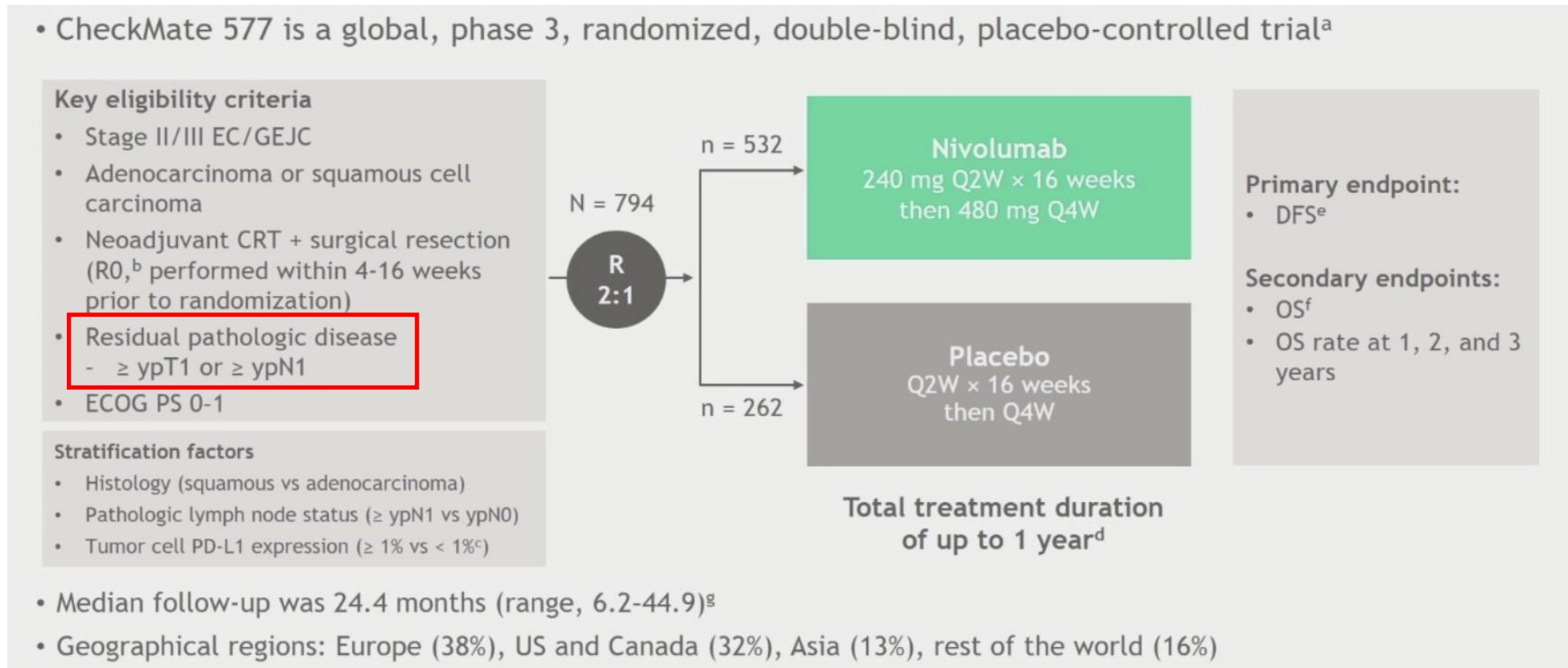
Stratification: Tumor type
WHO PS
N-stage
Study site

Endpoints:
1° : OS* & QoL
2° : pCR*, PFS,
toxicity* & costs

van Hagen, N Engl J Med. 2012 May 31;366(22):2074-84

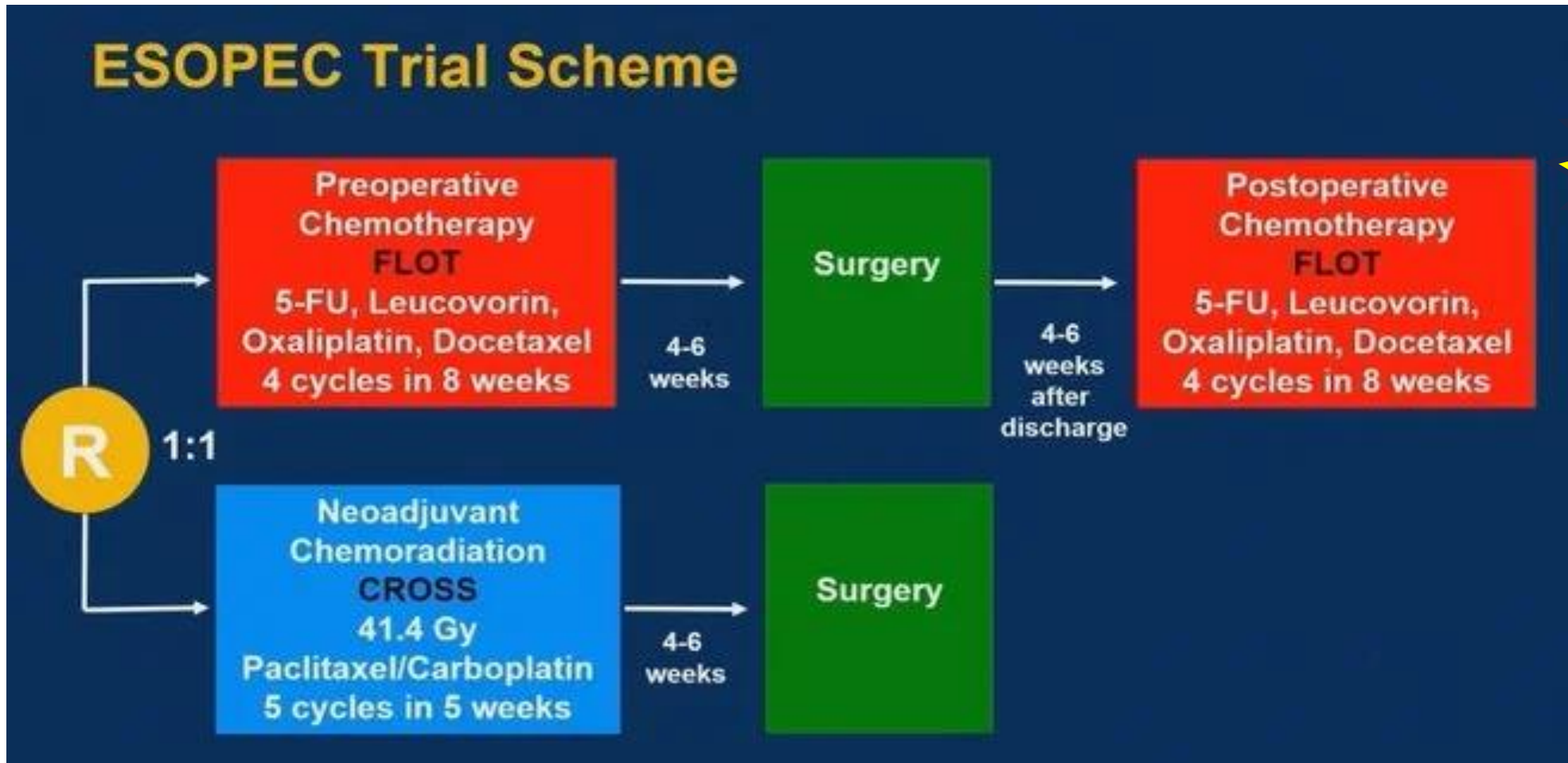
EC: Adjuvant Immunotherapy - CheckMate-577

Adjuvant Nivolumab following trimodality therapy:



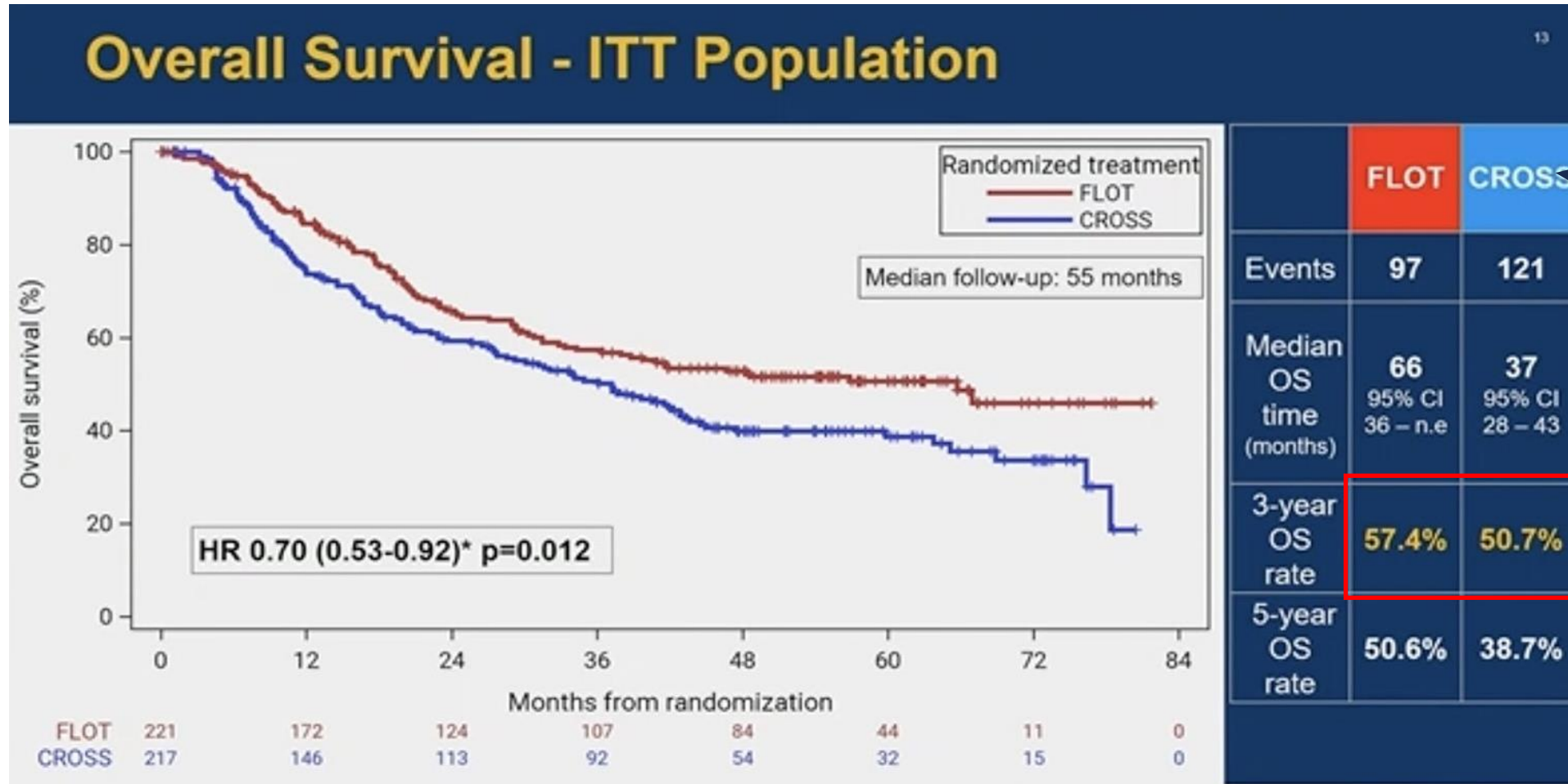
Kelly et al. Ann. of Oncol. (2020) 31 (suppl_4): S1142-S1215

EC: Periop Chemo vs. ChemoRT – ESOPEC Study



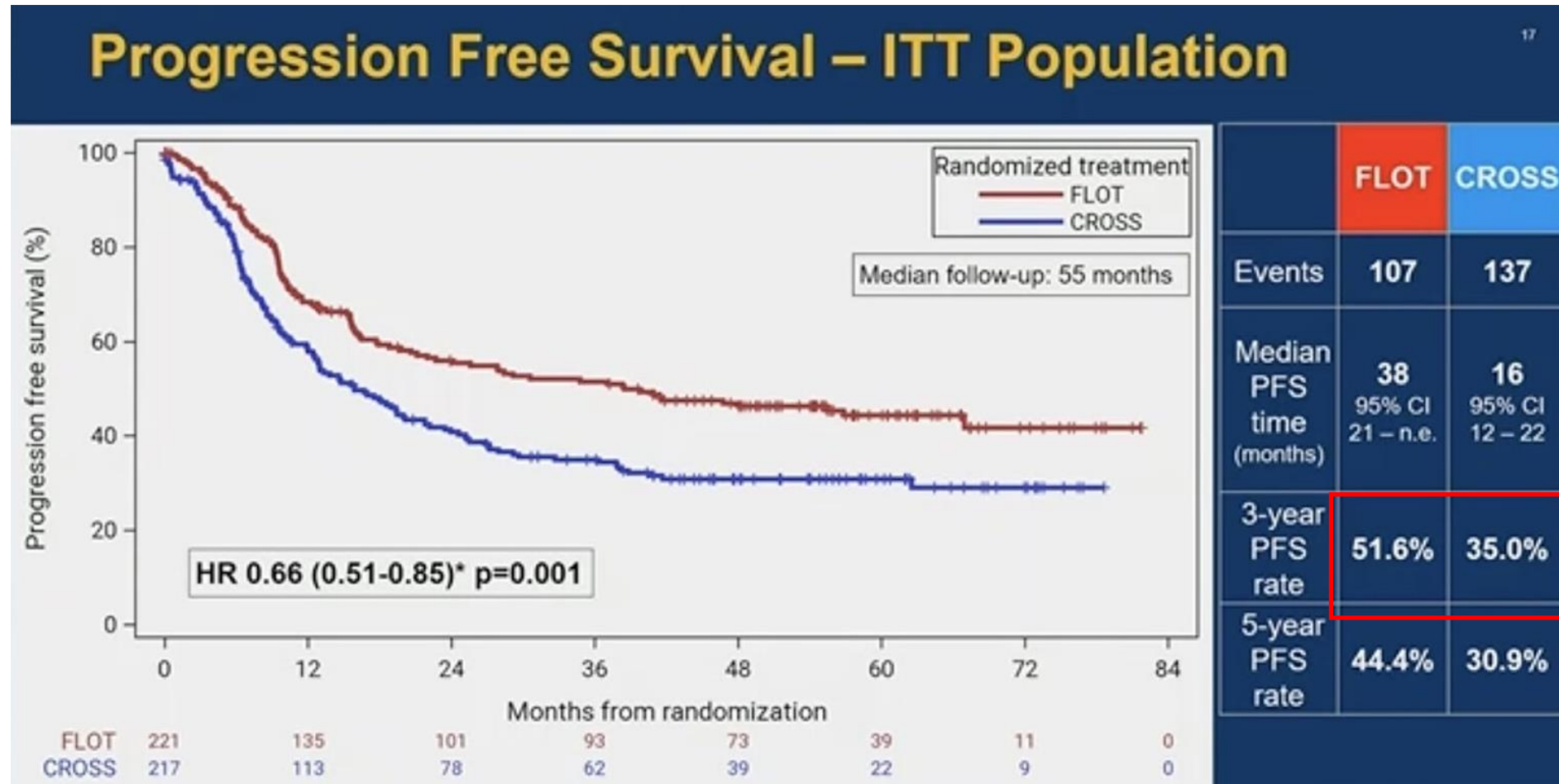
Hoepfner et al. J. Clin. of Oncol. Vol. 42 (Suppl_17): LBA1

EC: Periop Chemo vs. ChemoRT – ESOPEC Study



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EC: Periop Chemo vs. ChemoRT – ESOPEC Study

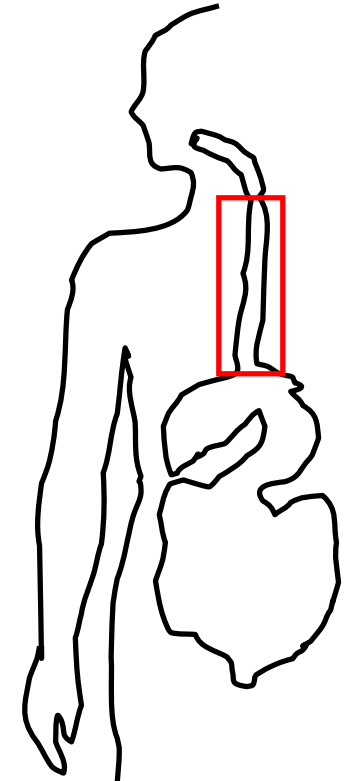


Hoepfner et al. J. Clin. of Oncol. Vol. 42 (Suppl_17): LBA1

EC: Curative Therapy

My approach:

- T2 (diffuse histology) or greater
- Any N+
- Definite surgery?
 - FLOT → surgery → FLOT
- Borderline surgery? → CRT → immunotherapy
- Question... role of immunotherapy in the perioperative setting?

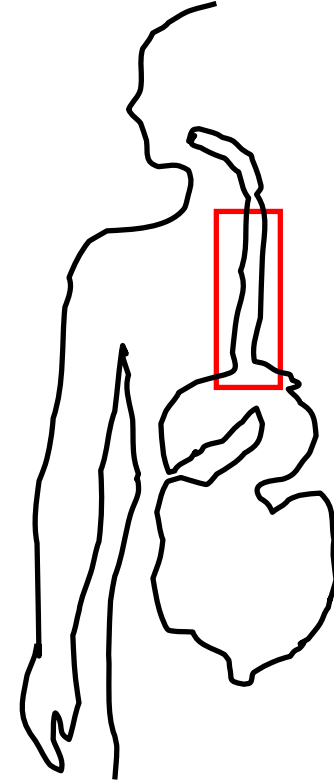


EC: Approach to the Patient

- **Esophageal Cancer:**

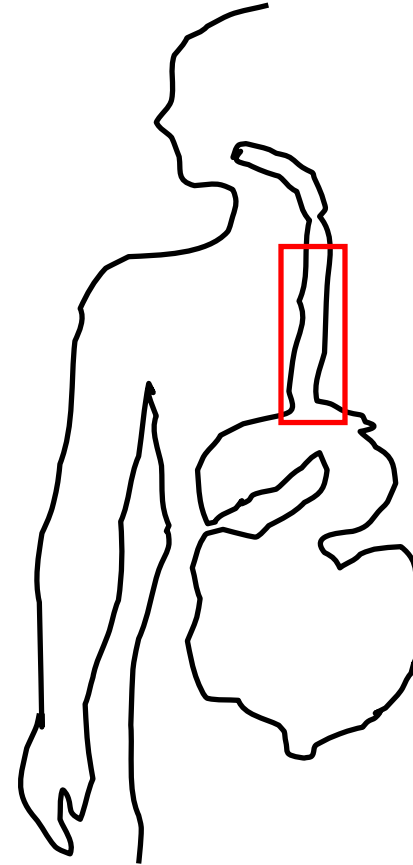
- Stage IA or IB: →
 - surgery
 - definitive chemo + RT
- Stage IIA to IIIC (T4a): →
 - perioperative FLOT
 - chemo + RT → surgery → immunotherapy
 - definitive chemo + RT

- Stage IV:
 - if dysphagia → local therapy → chemo (e.g. stent, RT only, feeding tube)
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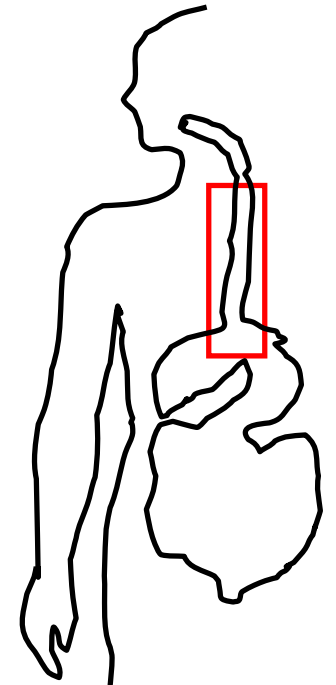
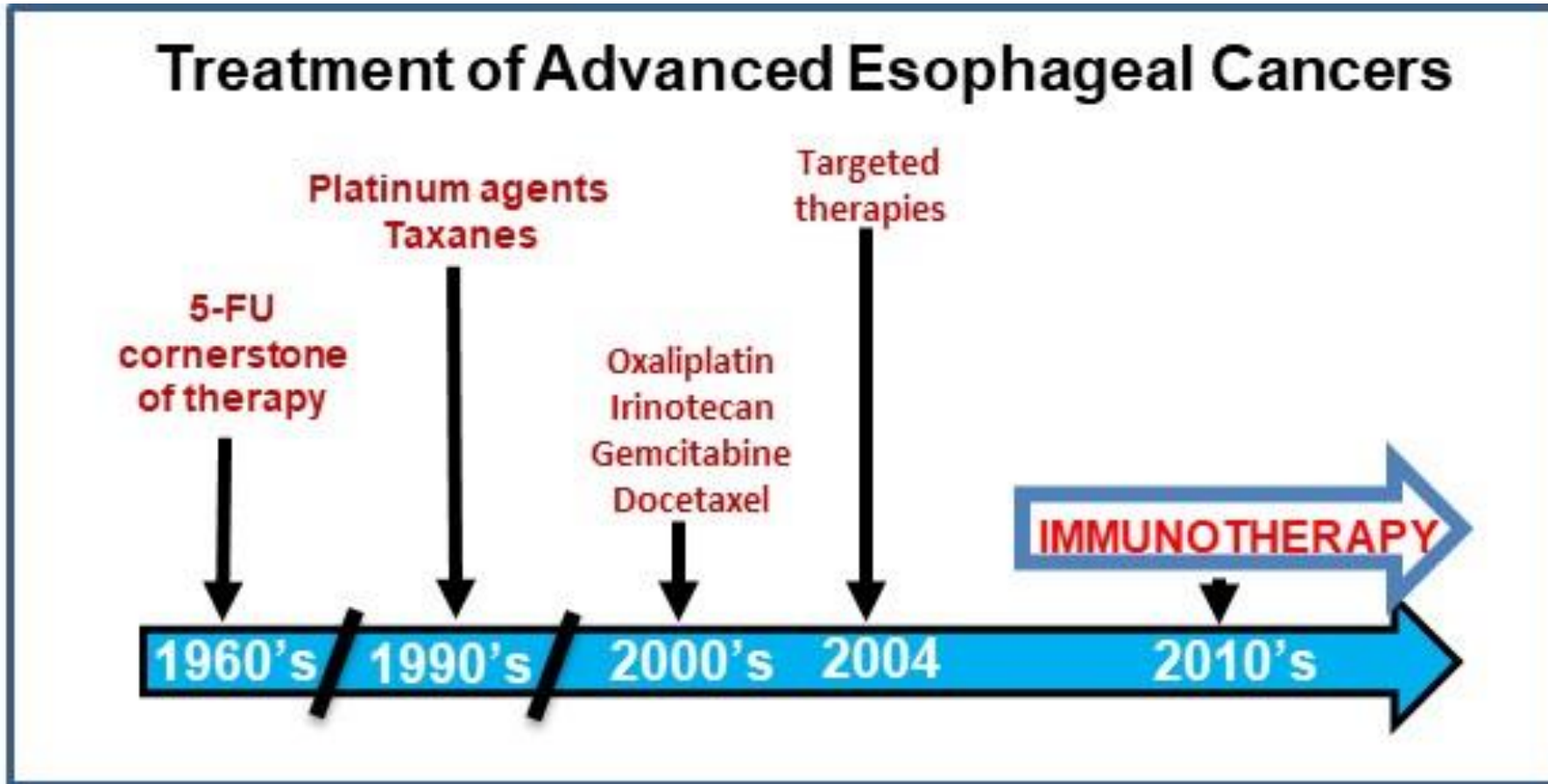


Esophageal Cancers

Metastatic Disease



EC: Perspectives on Systemic Treatment



EC: Systemic Therapy Menu

CHEMOTHERAPY

- 5-FU, capecitabine
- Platinums – oxaliplatin, carboplatin, cisplatin
- Taxanes – paclitaxel, docetaxel
- Irinotecan
- Trifluridine/tipiracil

TARGETED THERAPY

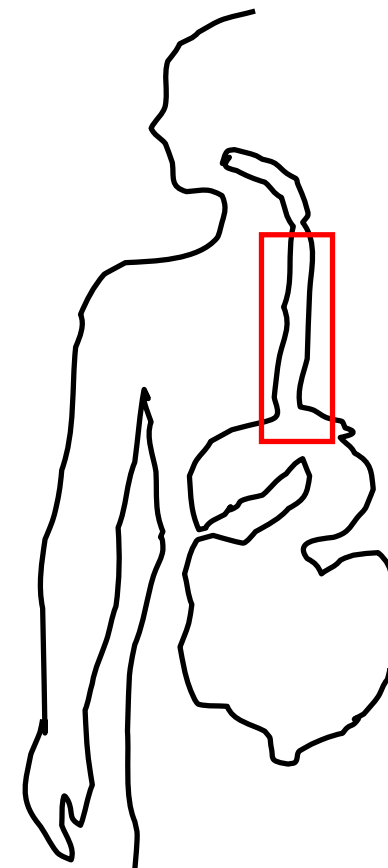
- Trastuzumab
- Trastuzumab deruxtecan
- Ramucirumab - VEGF
- Zolbetuximab – CLDN18.2

HER-2

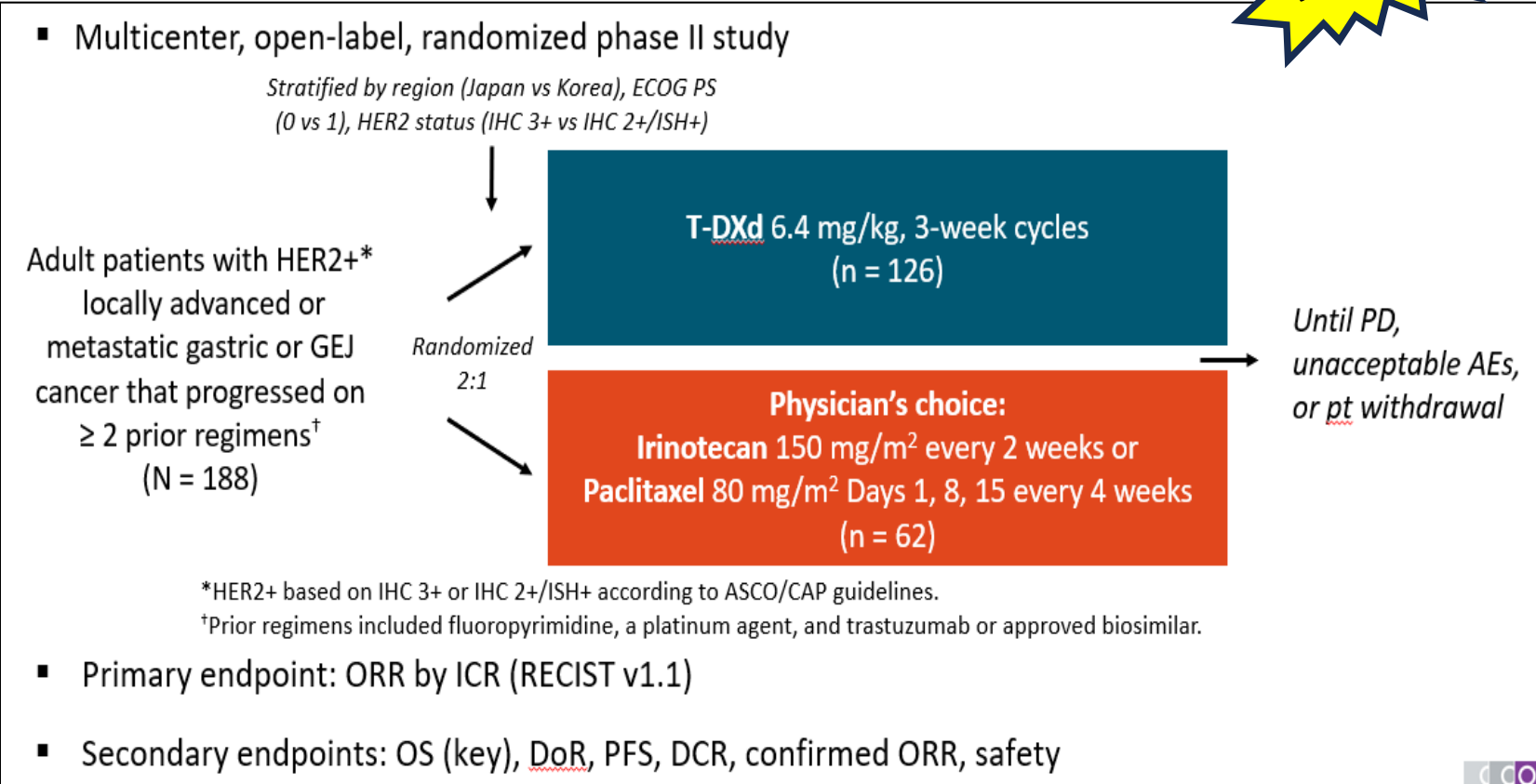
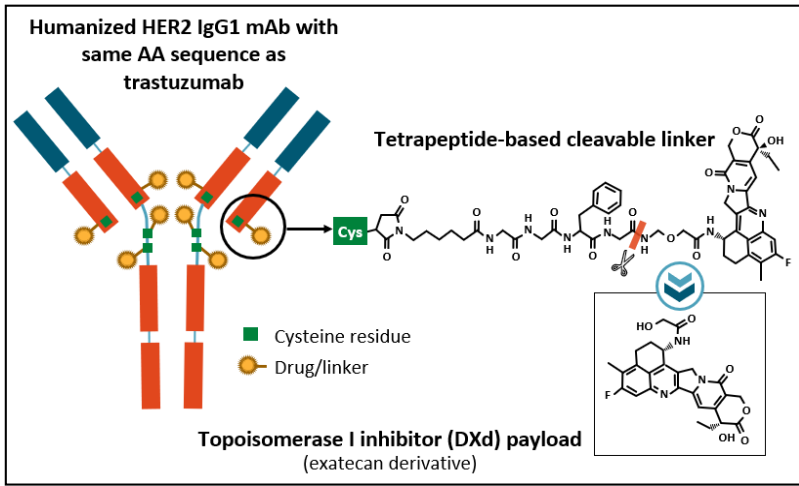
IMMUNOTHERAPY

- Nivolumab
- Pembrolizumab
- Tislelizumab

NEW!

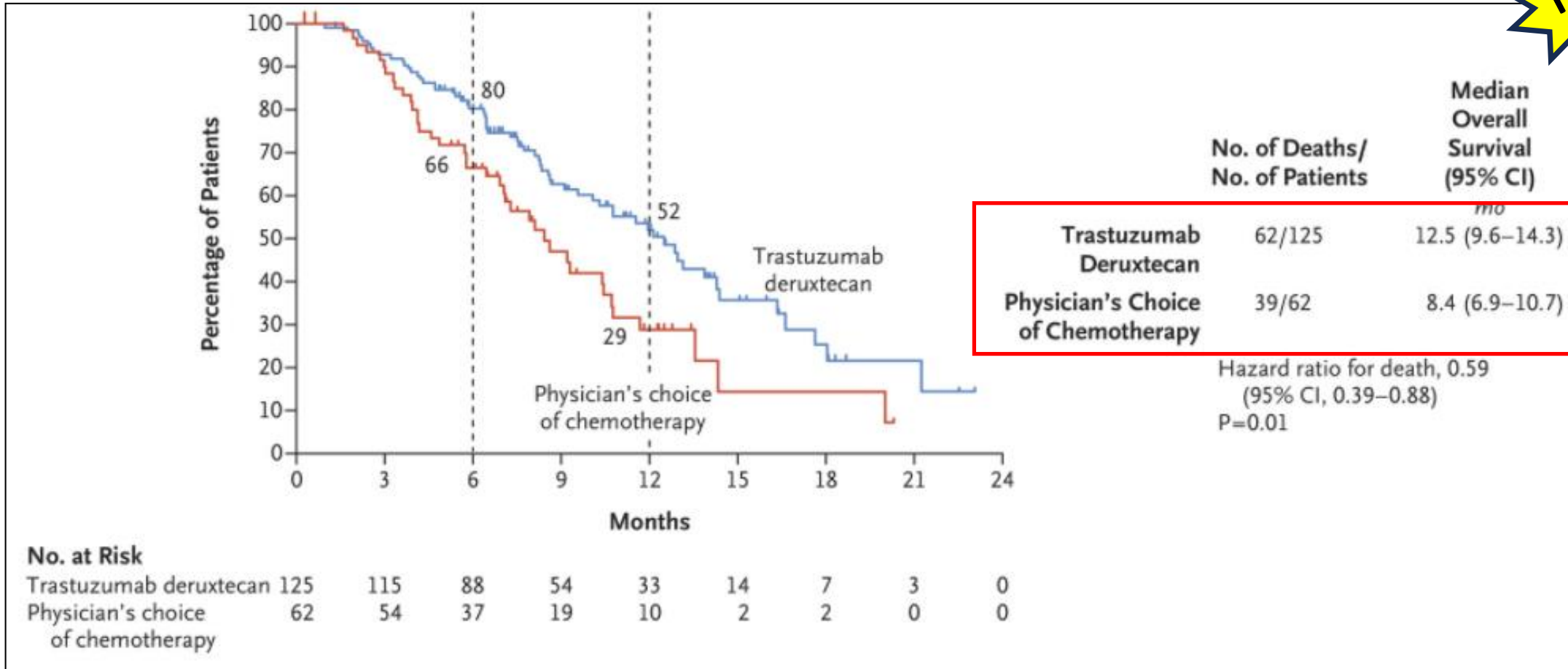


HER2 Receptor: DESTINY-Gastric01



Shitara, N Engl J Med 2020; 382:2419-2430

HER2 Receptor: DESTINY-Gastric01



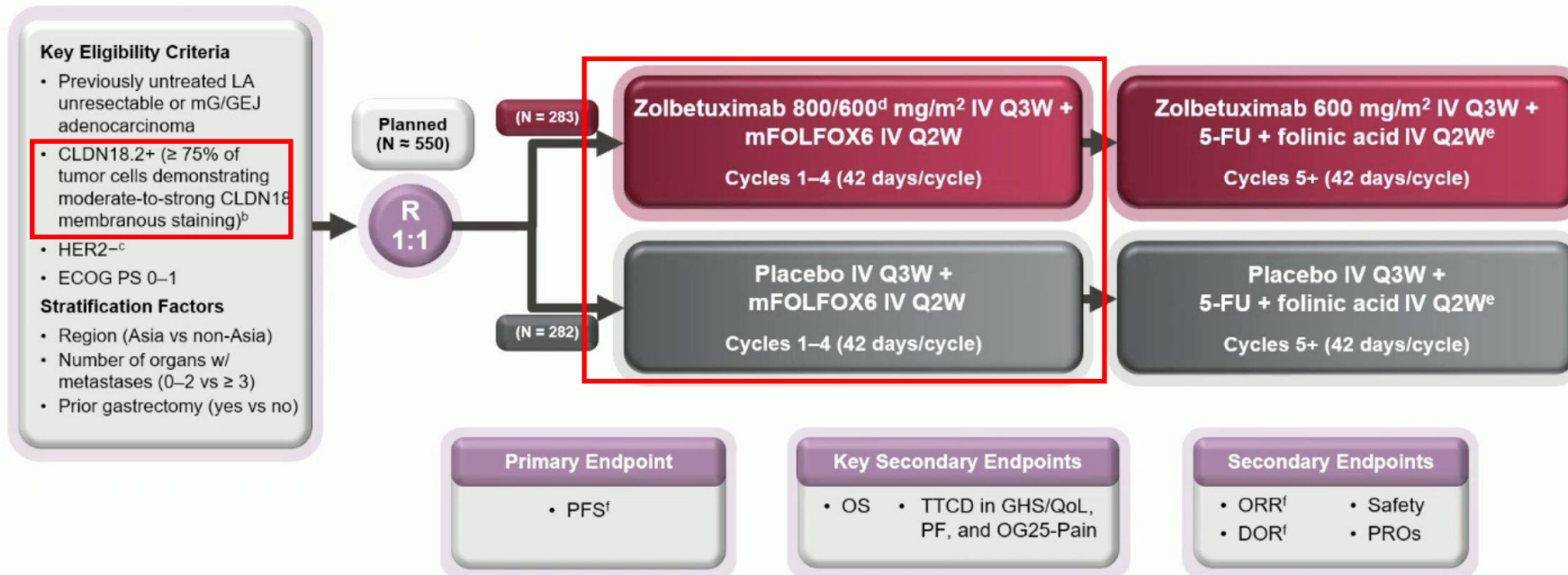
Shitara, N Engl J Med 2020; 382:2419-2430

CLDN18.2: SPOTLIGHT Study



Study Design: SPOTLIGHT

Global^a, Randomized, Double-blinded, Placebo-controlled, Phase 3 Trial



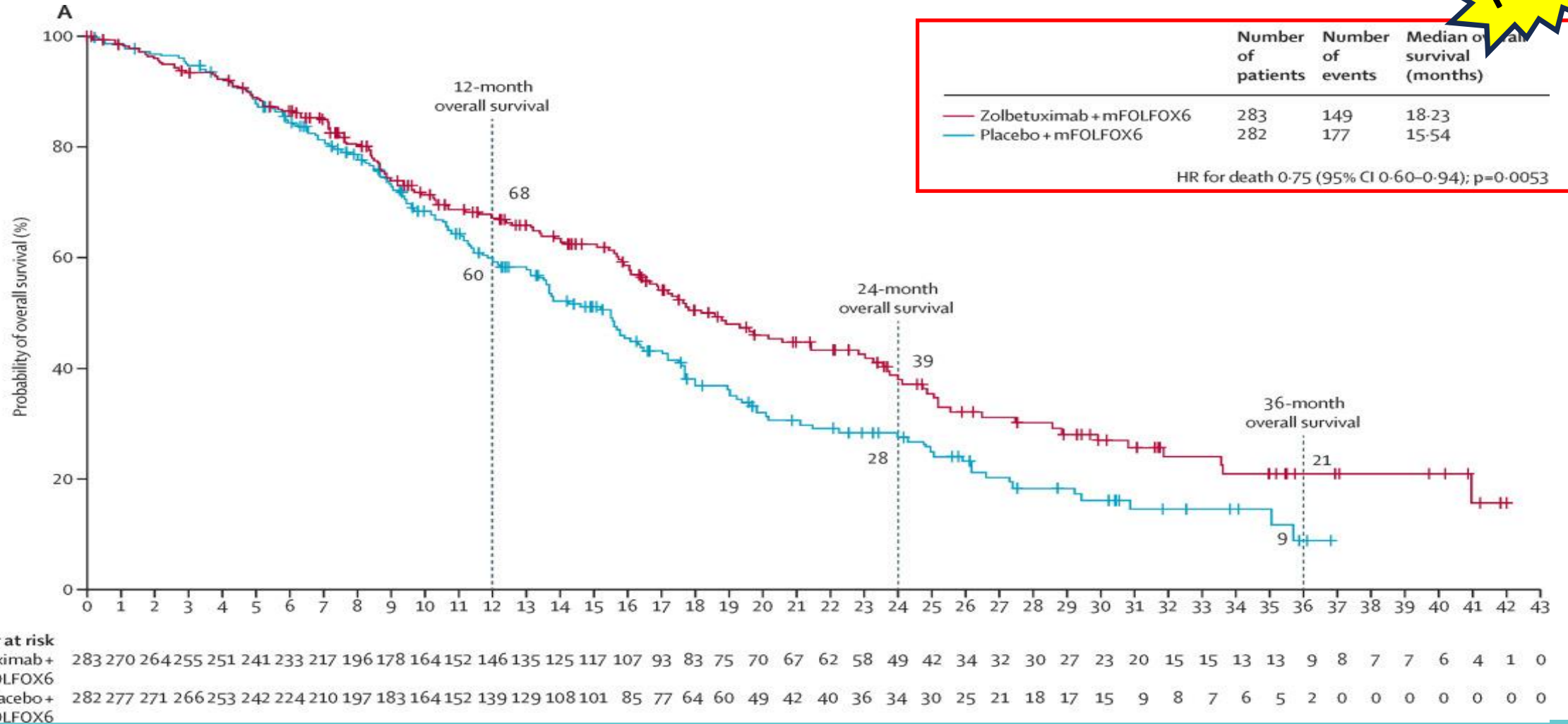
*Study was conducted at 215 sites in 20 countries across Australia, Asia, Europe, N. America, and S. America; ^bBy central IHC using the VENTANA CLDN18 (43-14A) RxDx Assay (for Investigational Use Only; Roche); ^cBy central or local HER2 testing; ^d800 mg/m² at cycle 1 day 1 followed by 600 mg/m² on cycle 1 day 22 and days 1 and 22 of subsequent cycles; ^eAt discretion of investigator; ^fPer RECIST version 1.1 by independent review committee. Shitara K et al. *Lancet*. 2023;401(10389):1655-1668.



Dr. Jaffer A. Ajani

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CLDN18.2: SPOTLIGHT Study



Immunotherapy: RATIONALE-305 Study



Study Design

Randomized, double-blind, global phase 3 study

Key eligibility criteria:

- Histologically confirmed GC/GEJC
- Exclude patients with HER2-positive tumors
- No previous therapy for unresectable, locally advanced or metastatic GC/GEJC

R
1:1

Initial up to 6 treatment cycles^a

TIS 200 mg IV Q3W
+ chemo (XELOX or FP^d)

Maintenance treatment until unacceptable toxicity or disease progression

Placebo IV Q3W
+ chemo (XELOX or FP^d)

Primary endpoints

OS in PD-L1+ (PD-L1 score $\geq 5\%$ ^b) and ITT analysis set

Secondary endpoints^c

PFS, ORR, DoR, DCR, CBR, TTR, HRQoL, safety

Stratification

- Region of enrolment
- Peritoneal metastasis
- PD-L1 score (PD-L1 $\geq 5\%$ vs $< 5\%$ ^b)
- Investigator's choice of chemo

Statistical considerations:

- If OS in the PD-L1+ analysis set is statistically significant, OS in the ITT analysis set is tested hierarchically
- An interim analysis was performed based on 291 actual observed events for the PD-L1+ analysis set, and the updated one-sided *P* value boundary was 0.0092

EC: Systemic Therapy Menu

CHEMOTHERAPY

- 5-FU, capecitabine
- Platinums – oxaliplatin, carboplatin, cisplatin
- Taxanes – paclitaxel, docetaxel
- Irinotecan
- Trifluridine/tipiracil

TARGETED THERAPY

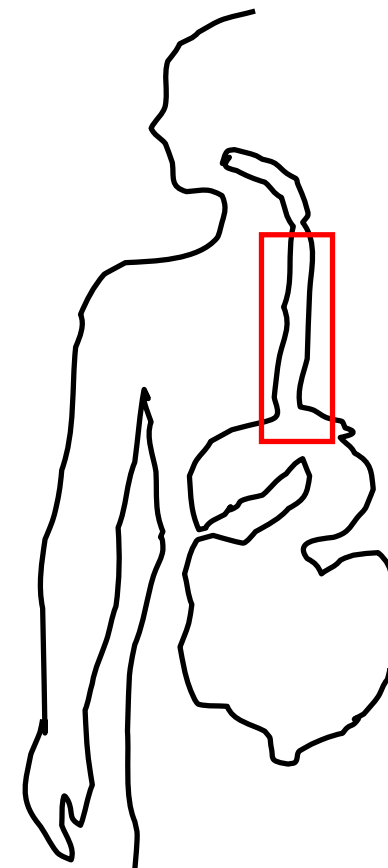
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- Ramucirumab - VEGF
- ✓ Zolbetuximab – CLDN18.2

HER-2

IMMUNOTHERAPY

- Nivolumab
- Pembrolizumab
- ✓ Tislelizumab

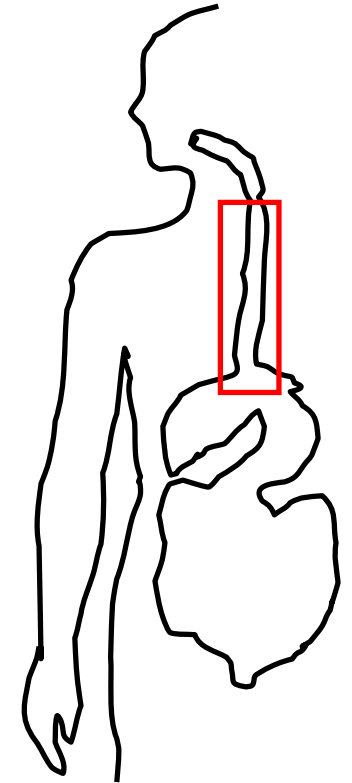
NEW!



EC: Metastatic Disease

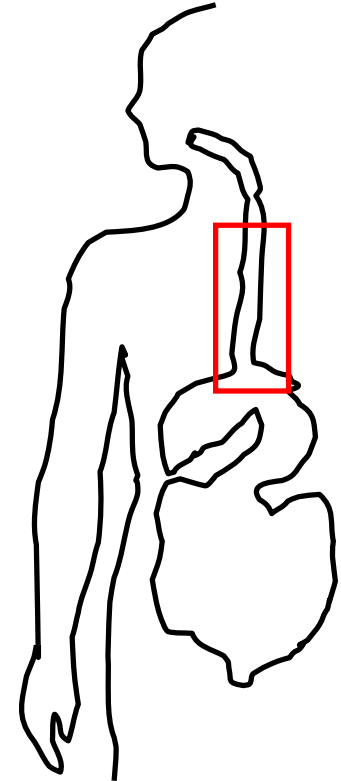
My approach:

- **Esophagus**
 - MSI
 - HER-2
 - PD-L1
 - CLDN18.2
- **1st-line – 5-FU/Platinum ± trastuzumab**
- **2nd-line – paclitaxel + ramucirumab**
 - trastuzumab-deruxtecan (HER-2+)
 - irinotecan
 - ramucirumab
- **3rd-line – whatever is left**
 - trifluridine, tipiracil



Conclusions

- **Curative esophageal cancer therapies are well established, however clinical outcomes need improvement**
- **Targeted therapies (i.e. HER-2 & VEGF, CLDN18.2) are a validated treatment approach in the advanced disease setting**
- **Immunotherapies are approved in the adjuvant and advanced settings but benefits are modest**
- **Optimizing treatment lines is an ongoing process in the advanced setting**
- **Novel treatment approaches remain a priority**



Questions



Hollings Cancer Center

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