Fred Hutch Cancer Center

Esophageal and Gastric Cancer

2024 Comprehensive Oncology Review

Veena Shankaran MD, MS
Professor, Medical Oncology
Co-Director, Hutchinson Institute for Cancer Outcomes Research
University of Washington School of Medicine
Fred Hutchinson Cancer Center

Land Acknowledgement

Fred Hutchinson Cancer Center acknowledges the Coast Salish peoples of this land, the land which touches the shared waters of all tribes and bands within the Duwamish, Puyallup, Suquamish, Tulalip and Muckleshoot nations.

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Emerging Questions / Topics in Upper GI Cancers

1. Esophageal adenocarcinoma – CROSS regimen OR perioperative chemotherapy (ESOPEC)

2. Immune checkpoint inhibitors in perioperative treatment for gastric cancer

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4. Targeting claudin 18.2 – what's coming up

Epidemiology and Risk Factors

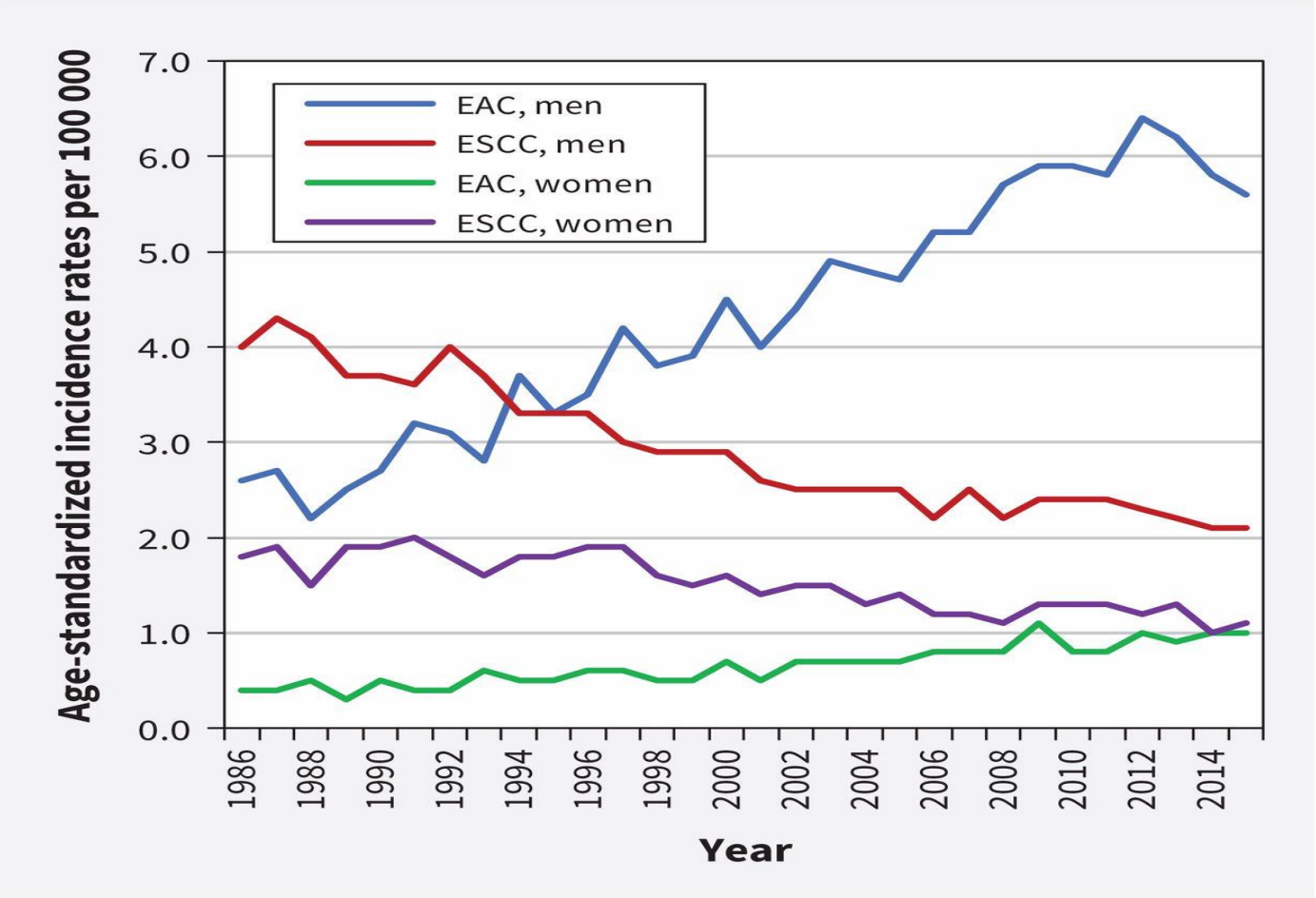
Incidence and Mortality - 2024

	Estimated new cases			Estimated deaths		
	Male	Female	**TOTAL**	Male	Female	**TOTAL**
Esophageal	17,690	4,680	**22,370**	12,880	3,250	**16,130**
Gastric	16,160	10,730	**26,890**	6,490	4,390	**10,880**

Esophageal Cancer: 6th most common cause of cancer death worldwide
Gastric Cancer: 3rd most common cause of cancer death worldwide

American Cancer Society, Facts & Figures, 2024

Esophageal Cancer Epidemiology



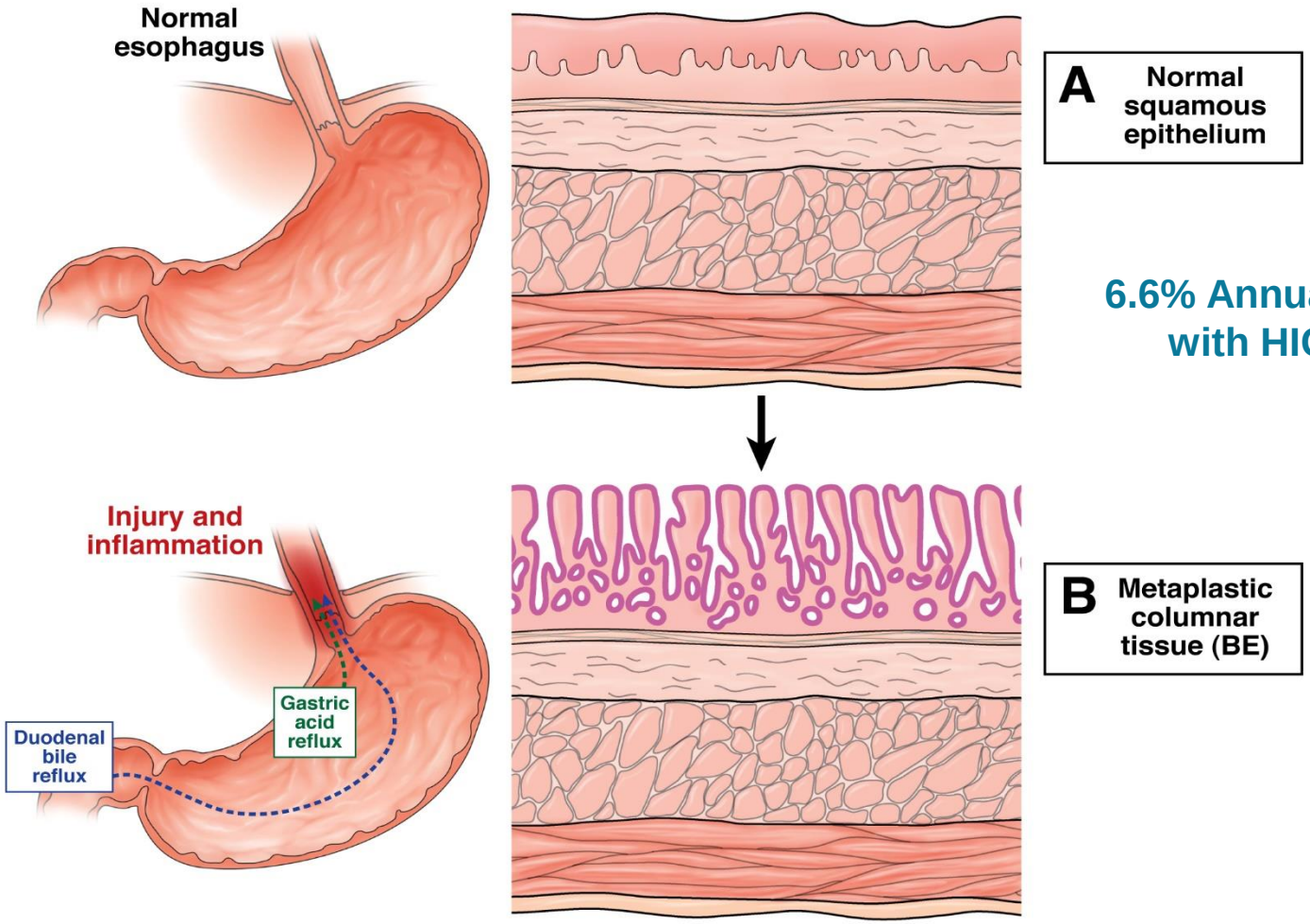
Groulx, S. et al. CMAJ. 192(27), July 2020.

Esophageal Cancer: Risk Factors

Squamous Cell Carcinoma	Adenocarcinoma
•***Tobacco (5-10 x risk)***	•Tobacco (2 x risk)
•***EtOH (3-7 x risk)***	•EtOH (1.2 x risk)
•Betel nut	•***GERD (7.7 x risk)***
•Hot liquids – burns	•***Obesity (3 x risk)***
•Nitroso compounds	

Crew, KD and Neuget AI. *World J Gastroenterology*. 2006 Jan; 12(3): 354-62
Lagergren, J et al. *NEJM*. 1999; 340(11): 825.
Lagergren, J et al. *Ann Intern Med*. 1999: 883-890

Barrett's Esophagus



6.6% Annual risk for adenocarcinoma with HIGH GRADE DYSPLASIA

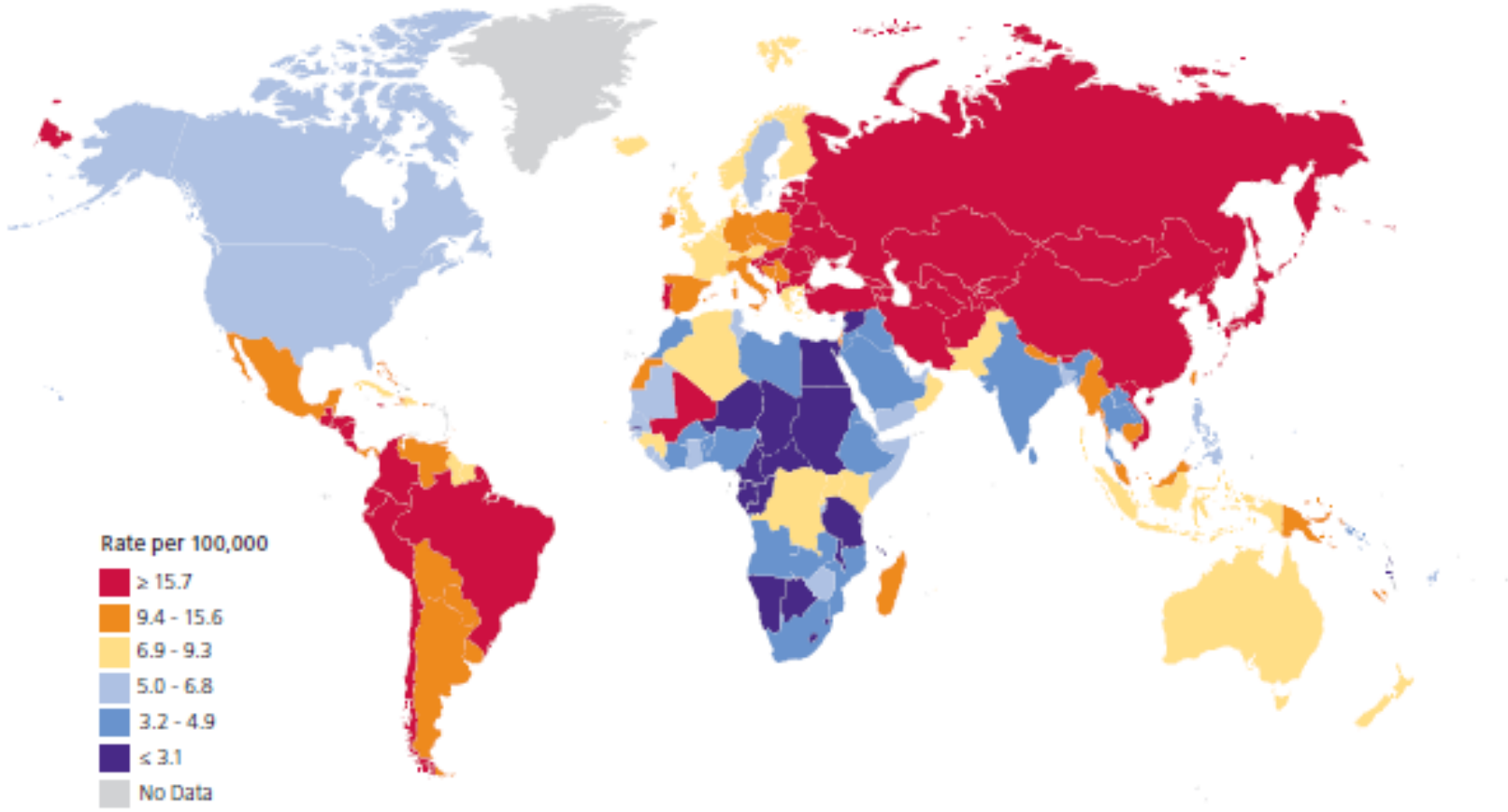
Morales CP et al. *Lancet*. 360: 9345, 2002
American Gastroenterological Association

Gastric Cancer: Risk Factors

Gastric Cancer
•Nitrite-containing, salt preserved foods •Smoking (distal gastric cancers) (OR 2.1 vs. nonsmoker) •GERD (cardia tumors) (OR 2.0) •Obesity (2-3x higher risk in obese vs. normal BMI) •**H. pylori** (intestinal subtype; body/distal) (1.2-16.7 fold increased risk, particularly CagA strain) •**Familial** (Hereditary diffuse gastric cancer (CDH1 mut; E. cadherin loss); HNPCC (Lynch); Peutz-Jehgers (STK11); Li-Fraumeni (p53); FAP (APC)

Gastric Cancer Trends

International variation in age-standardized gastric cancer incidence globally



American Cancer Society, Global Facts & Figures 2nd ed, 2008

Gastric Cancer in Asian vs. Western Populations

- In Asia:
- Younger age at diagnosis
- More localized disease at presentation (53% in Japan vs. 27% in US) – screening programs
- More common in distal stomach
- More aggressive surgical resection
- More lines of systemic therapy

- ***Better Survival***

Diagnosis and Staging

Esophageal Cancer Staging: AJCC 8th ed

AJCC 8th Edition - Esophageal Cancer Staging	
T stage	Tis = high grade dysplasia T1a = Tumor invades lamina propria or muscularis mucosae T1b = Tumor invades submucosa) T2 = Tumor invades muscularis propria T3 = Tumor invades adventitia T4a = Resectable tumor invading pleura, pericardium, or diaphragm T4b = Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.)
N stage	N0 = No lymph node metastases N1 = Metastases in 1-2 regional lymph nodes N2 = Metastases in 3-6 regional lymph nodes N3 = Metastases in 7 or more regional lymph nodes
M stage	M0 = no distant metastases M1 = distant metastases

Stage groupings

-Location for squamous (not adeno)

-Grade is included in stage grouping for both

Gastric Cancer Staging: AJCC 8th ed

AJCC 8th Edition - Esophageal Cancer Staging	
T stage	Tis = high grade dysplasia T1a = Tumor invades lamina propria or muscularis mucosae T1b = Tumor invades submucosa T2 = Tumor invades muscularis propria T3 = Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures T4a = Tumor invades serosa (visceral peritoneum) T4b = Tumor invades adjacent structures/organs
N stage	N0 = No lymph node metastases N1 = Metastases in 1-2 regional lymph nodes N2 = Metastases in 3-6 regional lymph nodes N3 = Metastases in 7 or more regional lymph nodes
M stage	M0 = no distant metastases M1 = distant metastases*

M1 disease: positive peritoneal cytology (without gross peritoneal disease) is considered M1 disease

Esophageal and Gastric Cancer Staging Workup

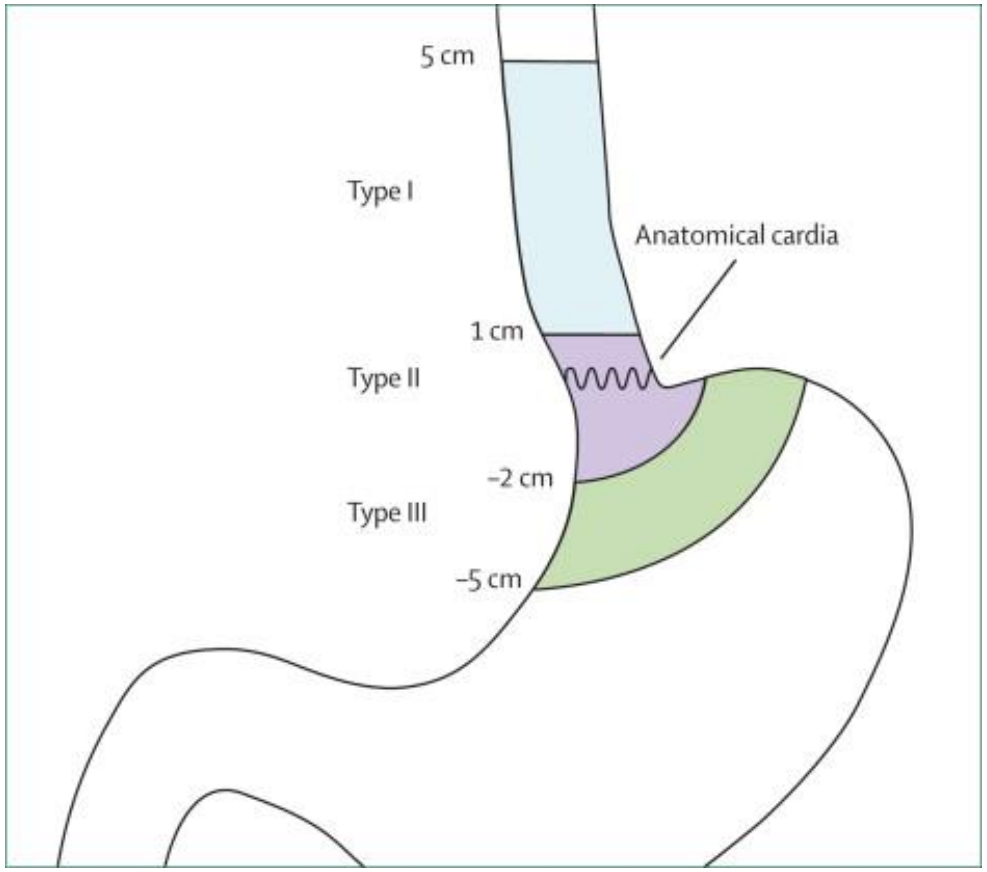
- **T-stage**: EUS*, Bronchoscopy (if above carina)

- **N-stage**: EUS (round, hypoechoic, smooth
- bordered), PET

- **M-stage**: CT, PET, diagnostic laparoscopy (gastric)

** Dysphagia is usually indicative of T3 lesion regardless of EUS*
EUS may not be helpful in linitis plastica / diffuse-type gastric cancer

GE Junction– Siewert Classification



Type 1	Located between 1-5cm proximal to anatomic cardia
Type 2	Located between 1cm proximal and 2cm distal to anatomic cardia
Type 3	Located between 2 and 5cm distal to anatomic cardia

Gronnier C, et al. *Journal of Visceral Surgery*. 149:1, Feb 2012

Esophageal Cancer Staging Nomenclature

- Clinical staging (u or c prefix)
- Pathologic staging (after chemoradiation): yp prefix
- Example: uT3N1 (stage IIIB) distal esophageal adeno → chemoRT → surgery → ypT1N0

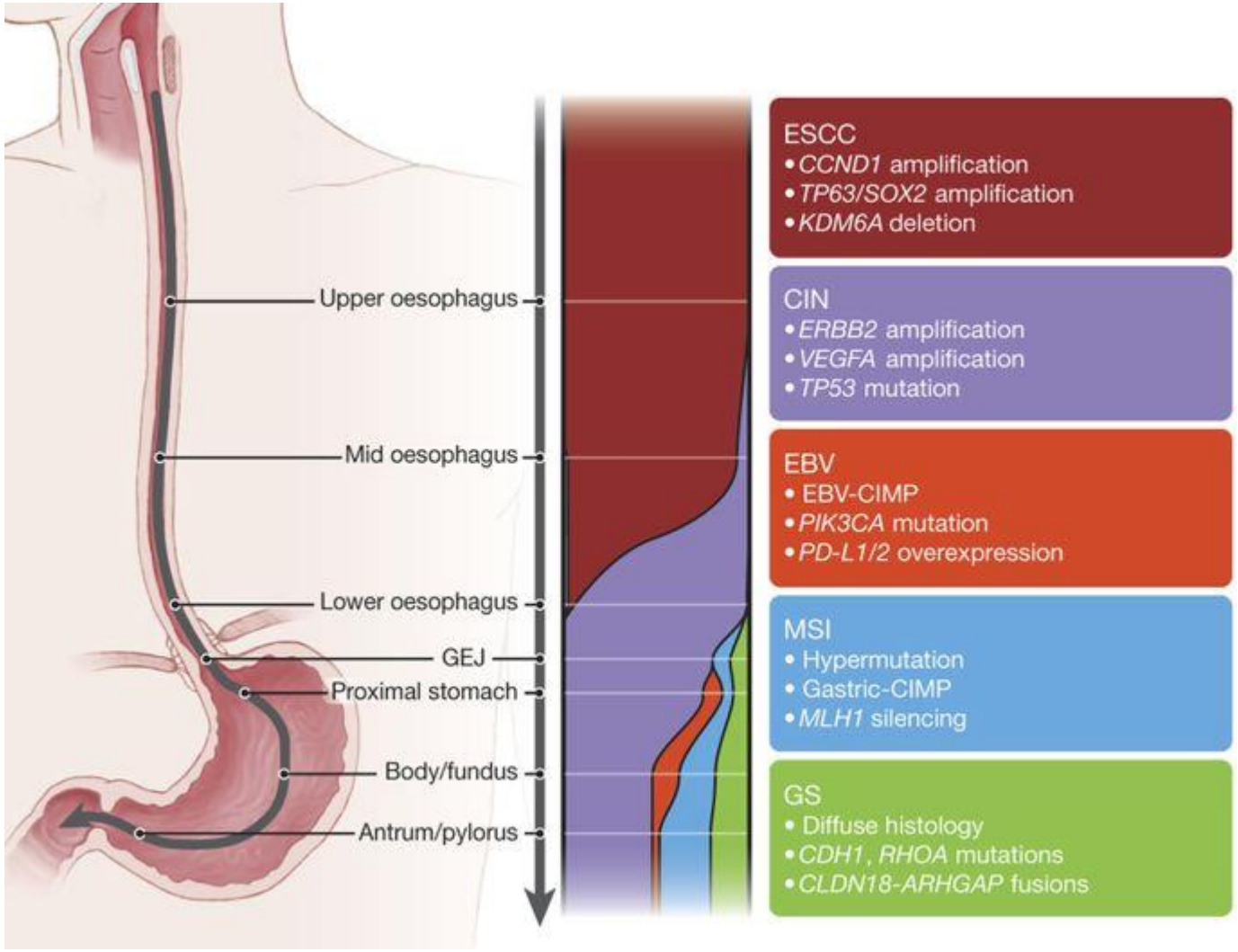
Tumor Regression Grading

Modified Ryan Scheme	
Description	**Tumor Regression Score**
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near complete response)	1
Residual cancer with evident tumor regression, but more then single or rare groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumor regression (poor or no response)	3

Ryan, R. et al. *Histopathology*. 2005; 47(2): 141-146

Pathology

Upper GI Cancer Molecular Subtypes



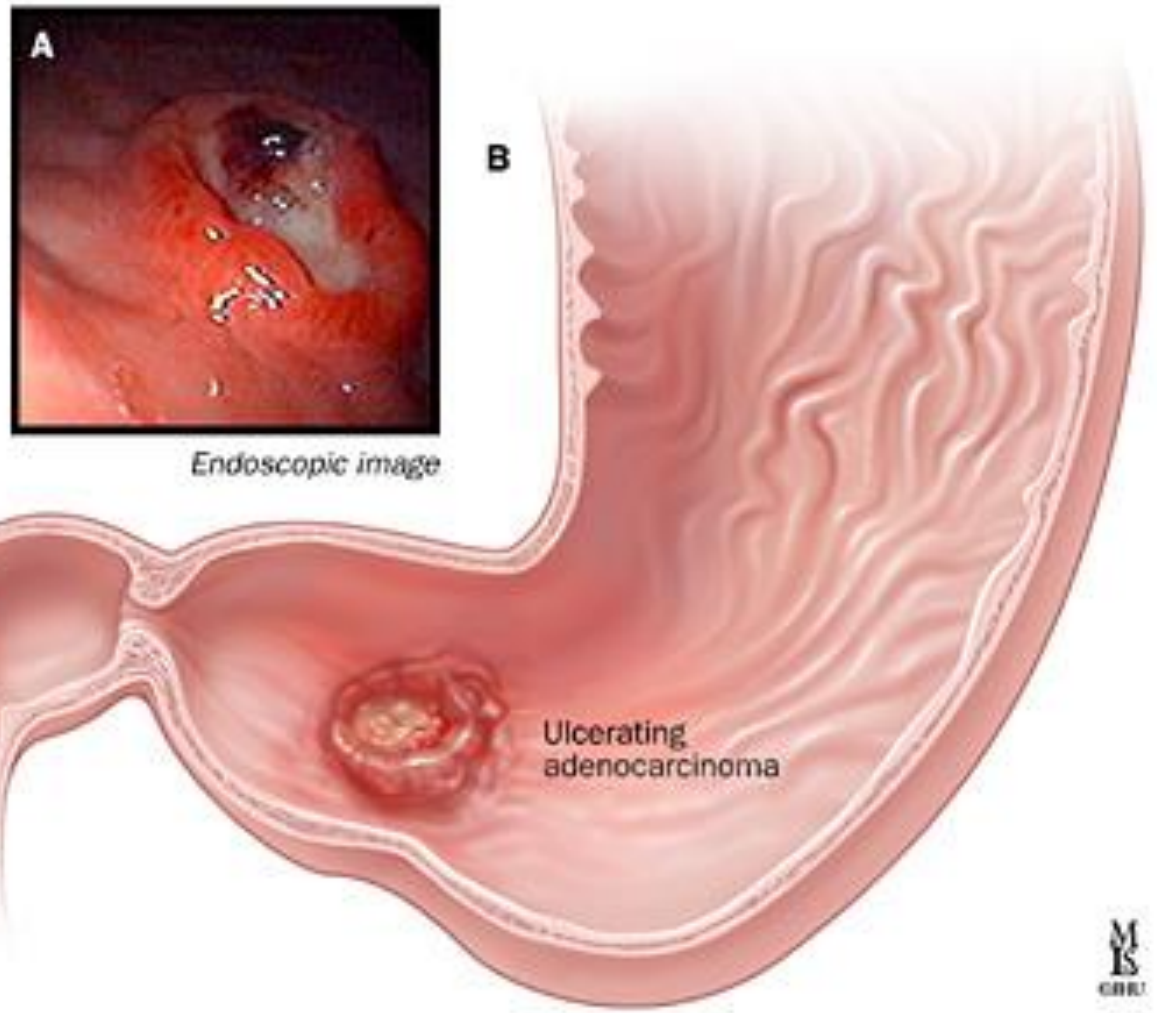
The Cancer Genome Atlas Research Network.
Nature, 2017. 541: 69–175

Lauren Classification - Adenocarcinoma

Intestinal	Diffuse
• **Inflammation** present *(H. pylori, atrophic gastritis, glandular dysplasia)* • '**Cascade**' of events: inflammation → intestinal metaplasia → dysplasia → invasive carcinoma • **Mucosal mass** • Develop over years, **better prognosis**	• **No inflammation** • Loss of E-cadherin **-- no clear precancerous lesion** • No clear mucosal mass - **Invades gastric wall** (e.g. linitis plastica) • Highly metastatic, invasive, **poor prognosis**

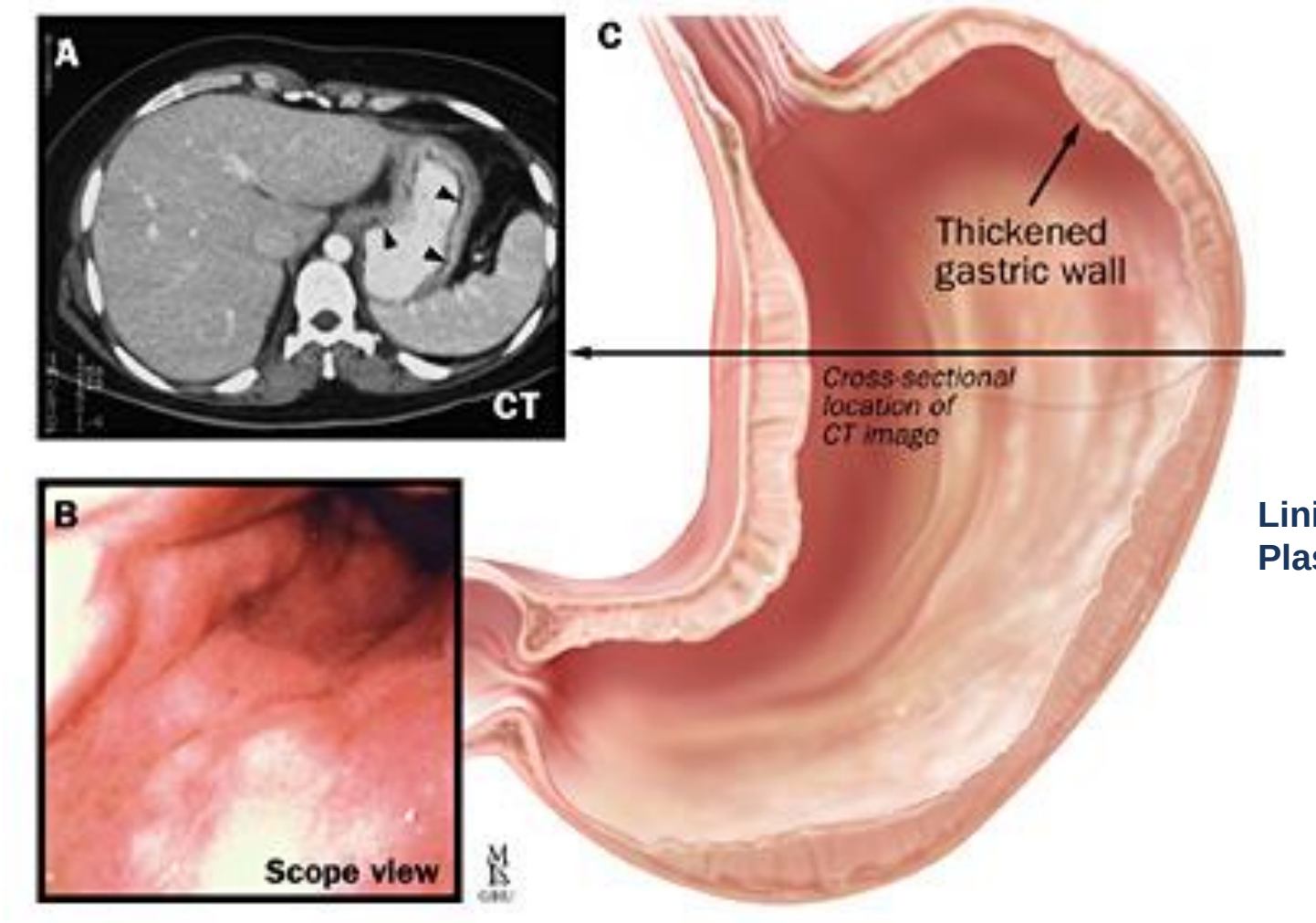
Lauren, P. *Acta Pathol Microbiol Scand*. 1965; 64(31).
Shah, M. et al. *Clin Cancer Research*. 2011; 17: 2693-2701

Intestinal Type Adenocarcinoma



Huntsman, et al. New England Journal of Medicine. 344;1904, 2001

Diffuse Type Adenocarcinoma



Linitis Plastica

Huntsman, et al. New England Journal of Medicine. 344;1904, 2001

Hereditary Diffuse Gastric Cancer

- Germline mutations in CDH1 gene (leading to loss of E-cadherin)
- Autosomal dominant with > 70% penetrance
- Diffuse, signet ring type adenocarcinoma
- Increased incidence lobular breast cancer
- Prophylactic gastrectomy should be considered

Huntsman, et al. New England Journal of Medicine. 344;1904, 2001

Her2 + Esophageal and Gastric Cancers

- **15-20%** of all gastric/esophageal adenocarcinoma (distal esophageal, GE junction, intestinal-type)
- Her2 3+ OR FISH + (*HER2*/CEP17 ratio ≥2.0) considered eligible

Gastric / Eso	**Breast**
• Heterogeneous expression • Interpretation criteria differs between biopsy and resection • Apical membrane often does not stain - + result requires only lateral / basolateral staining	• Uniform expression • Same interpretation criteria regardless of specimen • Complete circumferential staining required for positive result.

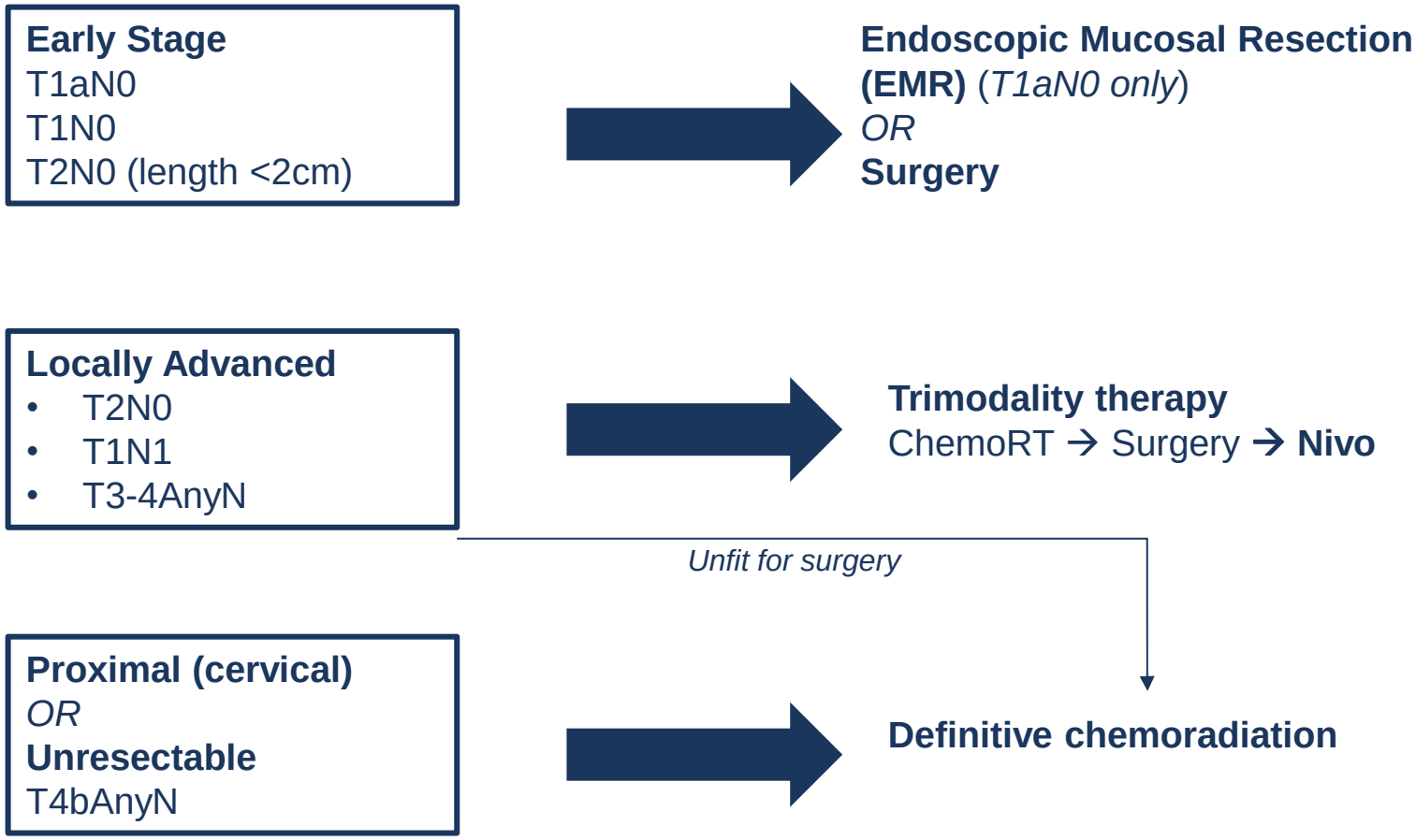
College of American Pathologists 2013; Questions Relating to Immunohistochemistry for Her2 on Gastric and Gastroesophageal Junction Adenocarcinoma

PDL1 Assessment in Upper GI Cancer

- PD-L1 is expressed in approximately 40% of esophagogastric cancers.
- **CPS Score** -- Unlike melanoma or lung cancer, membranous PD-L1 expression is rare ; occurs predominantly on infiltrating immune cells.
- Pembro / Keynote studies = PD-L1 **IHC 22C3** PharmaDx
- Nivo / BMS gastric studies = PD-L1 **IHC 28-8** PharmaDx

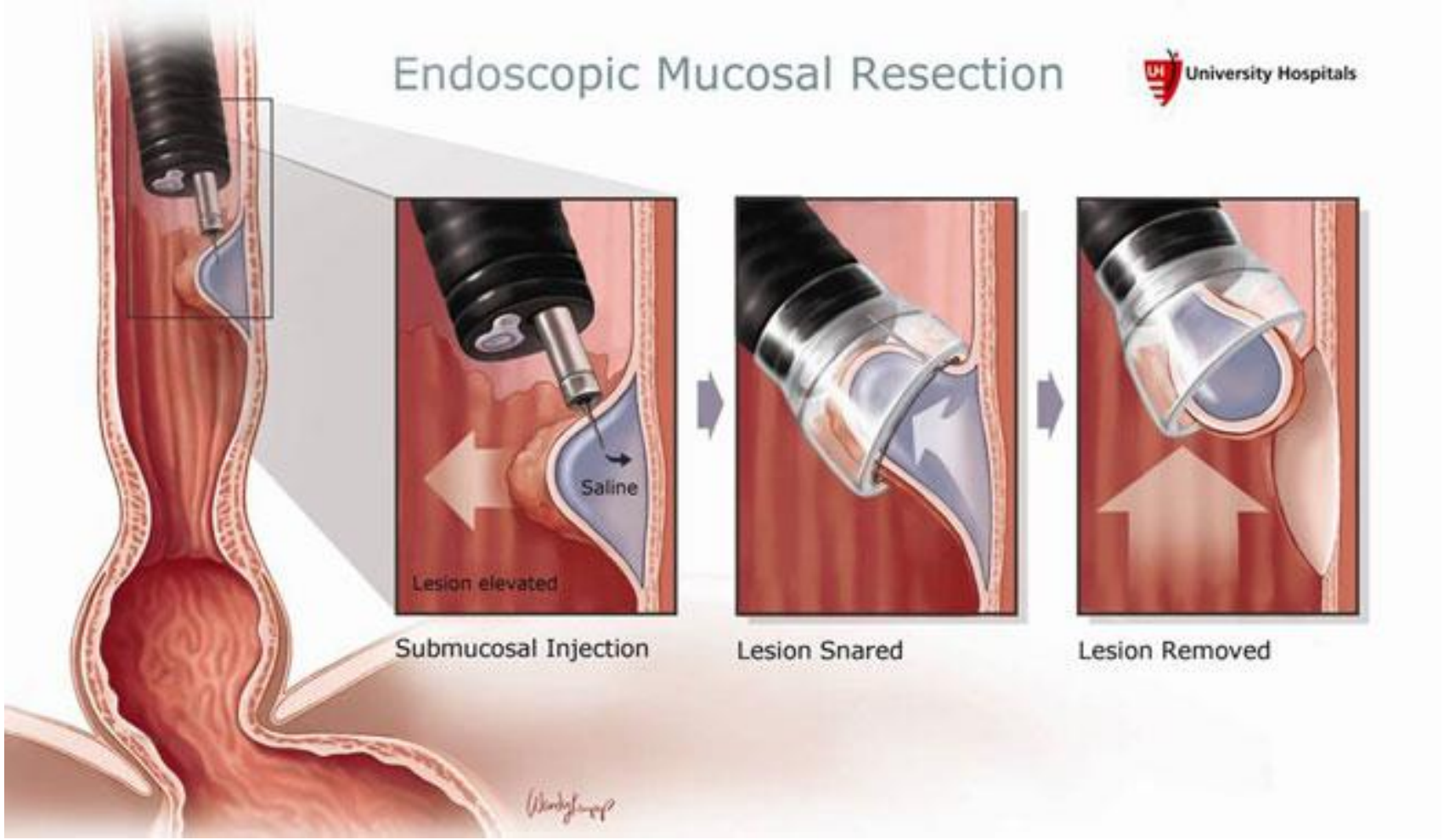
Stage I-III Esophageal Cancer

Esophageal Cancer Treatment Algorithm



Perioperative FLOT (ESOPAC) – esophageal adenocarcinoma

Endoscopic Mucosal Resection – T1a lesions



Surgery (Esophagectomy)

Transhiatal approach	Transthoracic (Ivor Lewis)
• Blind dissection of tumor • **Thoracotomy not required** • Anastomotic leak more common, but easier to manage • Abdominal and cervical incisions • Shorter ICU / hospital stay	• Direct visualization of tumor • **Thoracotomy required** • Anastomotic leak less common, but mediastinal leaks difficult to manage – higher morbidity • Abdominal and thoracic incisions

Surgery should be done at a high-volume center

Barreto and Posner. *World J Gastroenterol*. Aug 2010
Chang AC, et al. Ann Thoracic Surgery. 85(2), 2008.

Rationale for Chemoradiation in Esophageal Cancer

- Staging tests aren’t perfect
- Esophagus nearby heart, great vessels, and lungs
- Neoadjuvant chemoradiation helps:
  - Downstage the tumor
  - Sterilizes the surgical field
  - Treat micrometastatic dx
  - Much more challenging to give adjuvant chemoRT

Dutch CROSS Trial

ORIGINAL ARTICLE

Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

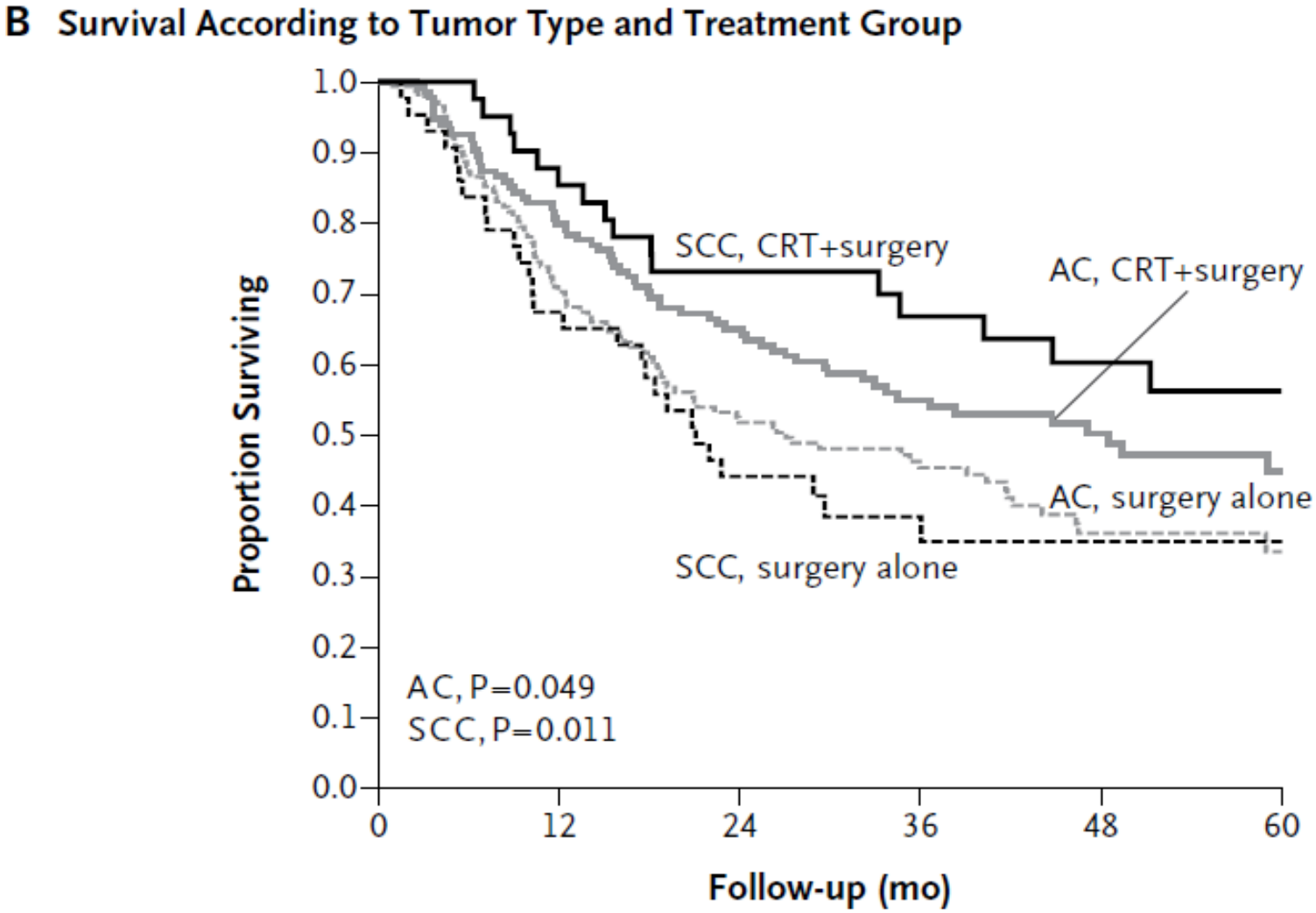
P. van Hagen, M.C.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg, M.I. van Berge Henegouwen, B.P.L. Wijnhoven, D.J. Richel, G.A.P. Nieuwenhuijzen, G.A.P. Hospers, J.J. Bonenkamp, M.A. Cuesta, R.J.B. Blaisse, O.R.C. Busch, F.J.W. ten Kate, G.-J. Creemers, C.J.A. Punt, J.T.M. Plukker, H.M.W. Verheul, E.J. Spillenaar Bilgen, H. van Dekken, M.J.C. van der Sangen, T. Rozema, K. Biermann, J.C. Beukema, A.H.M. Piet, C.M. van Rij, J.G. Reinders, H.W. Tilanus, and A. van der Gaast, for the CROSS Group*

Dutch CROSS Trial

Rationale	• Does **preoperative chemoradiation** add to benefit of surgery?
N = 368	• 188 surgery vs 180 chemoRT + surgery
Inclusion	• **Adenocarcinoma or SCC** • Esophagus and GE Junction (Siewert 3 excluded); T1N1, T2-3N0-1
Treatment Arms	• **Surgery alone** (Transthoracic for mid-thoracic tumors, Transhiatal for distal tumors) • **Preoperative chemoRT→ surgery** ○ Total Radiation Dose = 41.4 Gy ○ Weekly Carboplatin AUC 2 + Paclitaxel 50mg/m2

Van Hagen P et al. *NEJM*. 366;22, 2012

Histologic Subtype and Survival



Dutch CROSS Trial – Key Results

	Surgery alone	CRT + surgery
N	188	175
R0 resection rate	67%	92.3%
Path complete response	N/A	32%
Med survival	**26 months**	**49 months**
1-year survival	70%	82%
3-year survival	48%	59%
Anastomotic leakage	25%	22%
In-hospital mortality	3.8%	3.4%

Trimodality + Trastuzumab ? RTOG 1010

Step 1: Registration

⬇

Mandatory Central Her2 Testing

⬇

Step 2: Randomization (stratification by celiac lymphadenopathy > or ≤ 2cm (n=571)

Arm 1

1. Radiation (50.4 Gy), paclitaxel, carboplatin, and **trastuzumab**
2. Surgery
3. Maintenance trastuzumab, q3 wks x 13

Arm 2

1. Radiation (50.4 Gy), paclitaxel, carboplatin
2. Surgery

Addition of trastuzumab does not improve DFS – HR 0.99, 95% CI 0.71, 1.35)

Safran H. et al. *Lancet Oncology.* 23(2): 259-69. Feb 2022.

Radiation Esophagitis

- **Topical anesthetics** (e.g. viscous lidocaine)
- **Analgesics and antiinflammatories** (narcotics, dex elixir, carafate)
- **Dietary modification** (bland, soft, pureed, less acidic, room temp, converting to liquid medication when possible
- **Supplementary nutrition**
  - **Avoid PEG/G tubes in surgical candidates**; NG / Dobhoff preoperatively in the short term

Adjuvant Therapy -- Checkmate 577

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 1, 2021 VOL. 384 NO. 13

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

R.J. Kelly, J.A. Ajani, J. Kuzdzal, T. Zander, E. Van Cutsem, G. Piessen, G. Mendez, J. Feliciano, S. Motoyama, A. Lièvre, H. Uronis, E. Elimova, C. Grootscholten, K. Geboes, S. Zafar, S. Snow, A.H. Ko, K. Feeney, M. Schenker, P. Kocon, J. Zhang, L. Zhu, M. Lei, P. Singh, K. Kondo, J.M. Cleary, and M. Moehler, for the CheckMate 577 Investigators*

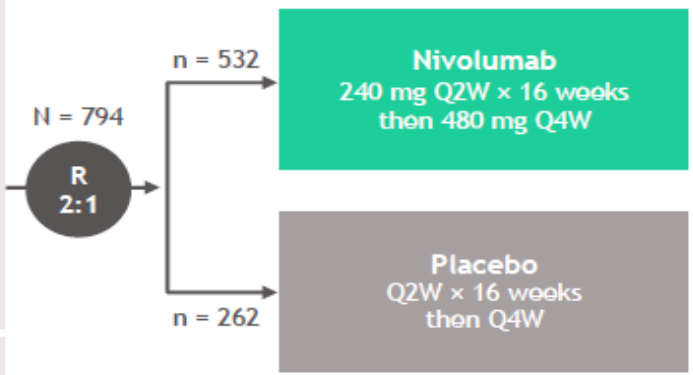
Checkmate 577 Study Design

CheckMate 577 study design

- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria
- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

Stratification factors
- Histology (squamous vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])



Total treatment duration of up to 1 year[d]

Primary endpoint:
- DFS[e]

Secondary endpoints:
- OS[f]
- OS rate at 1, 2, and 3 years

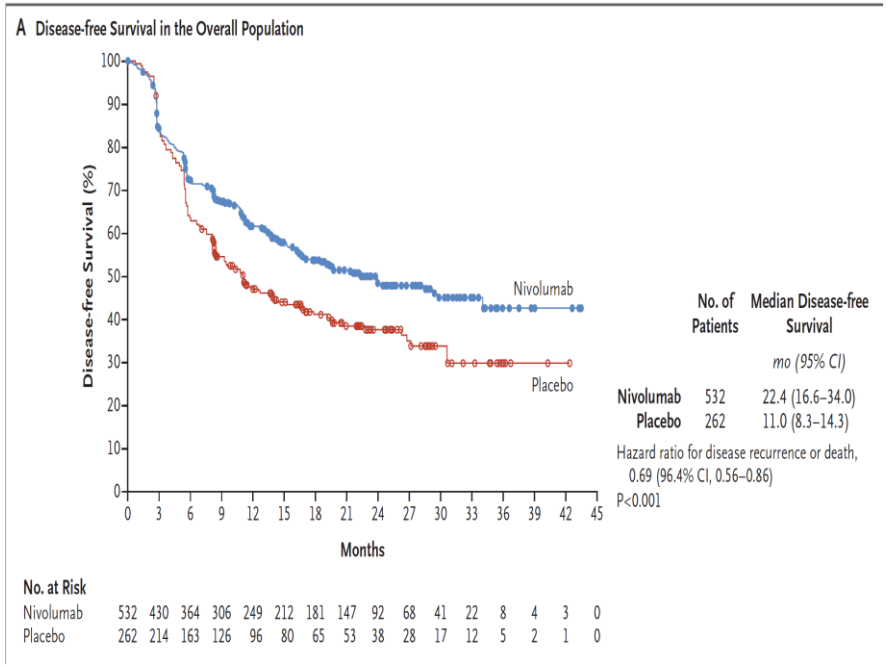
- Median follow-up was 24.4 months (range, 6.2-44.9)[g]
- Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)

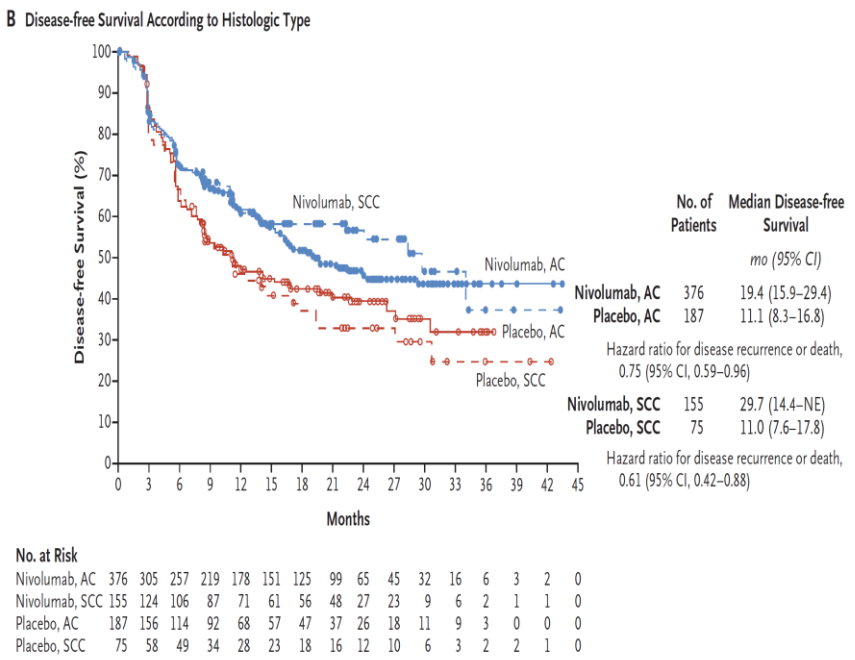
[a]ClinicalTrials.gov number, NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a pre-specified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]Time from randomization date to clinical data cutoff (May 12, 2020).

Kelly, RJ et al. NEJM. 384(13): 2021.

Disease-Free Survival

Median DFS 22.4 months (Nivo) vs. 11.0 months (Placebo)



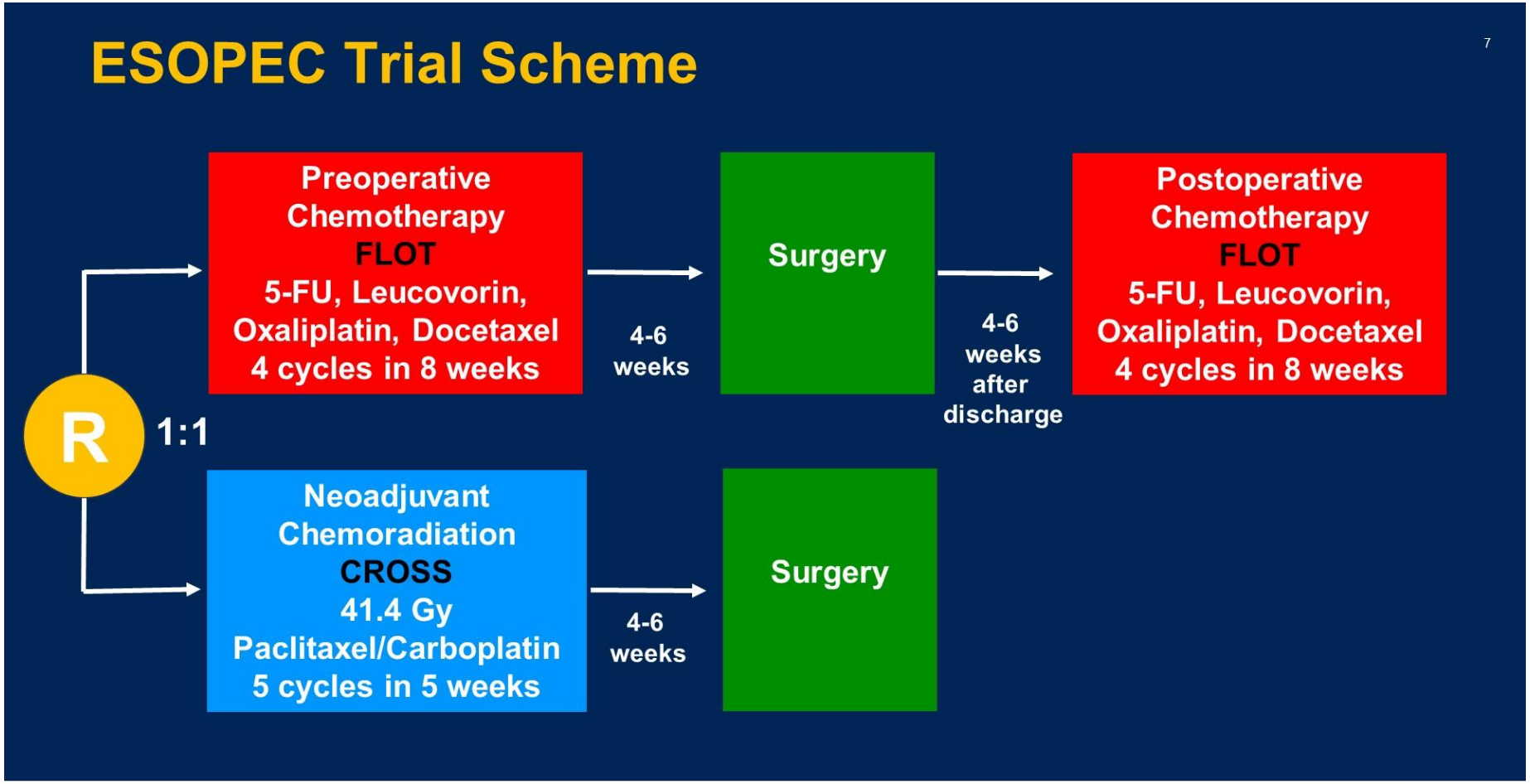


Benefit seen across all pre-specified subgroups; PD-L1 expression did not matter

Nivolumab was FDA approved in May 2021 for adjuvant esophageal cancer with residual disease after trimodality therapy (i.e. not for patients with pathological CR)

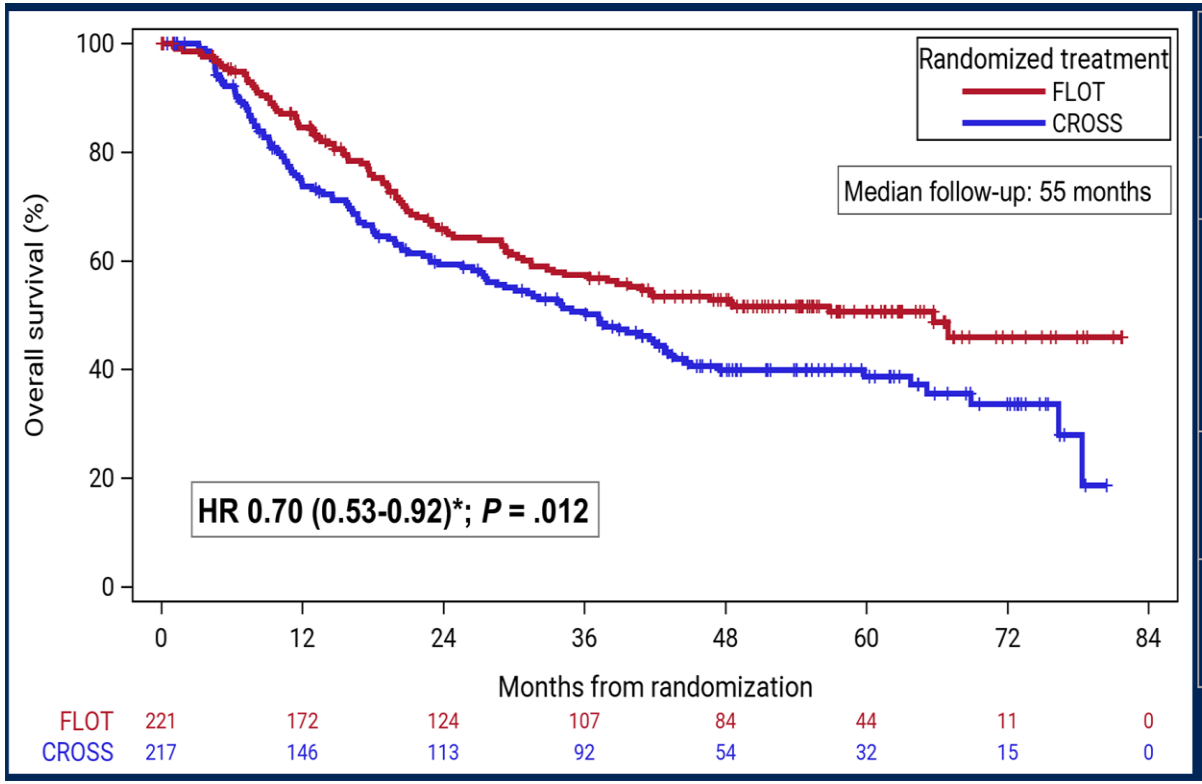
Kelly, RJ et al. NEJM. 384(13): 2021.

ESOPEC – Periop FLOT vs. CROSS in Esophageal Adeno



Hoeppner, J. et al. 2024 ASCO Annual Meeting

ESOPEC – Key Results



	FLOT	CROSS
Events	97	121
Median OS time (months)	66 95% CI 36 – NE	37 95% CI 28 – 43
3-year OS rate	57.4%	50.7%
5-year OS rate	50.6%	38.7%

	FLOT	CROSS
Completed neoadjuvant Tx	87.3%	**67.7%**
Completed adjuvant Tx	52.5%	
R0 resection	94.2%	95.0%
Path CR	16.8%	**10%**

ESOPEC – Summary

- Lower RT dose (41.4 Gy) than we typically use here in the US ; low rates of completion of neoadjuvant Tx and low pCR rates compared with CROSS Trial (32%)
- Control arm does not include adjuvant nivolumab
- Systemic therapy given in CROSS might be too little in adenocarcinoma
- For fit healthy patients with esophageal adenocarcinoma would prefer perioperative FLOT

Definitive Chemoradiation: RTOG 8501

Survival Estimates by Histologic Type after Combined Modality Therapy		
Year	Adenoca (% alive)	Squamous Cell (% alive)
0	100%	100%
1	52%	59%
2	22%	38%
3	17%	30%
4	13%	26%
5	13%	21%

Herskovic, A. NEJM. 1992 Jun 11;326(24):1593-8

Take – Home Points – Stage I-III Esophageal Cancer

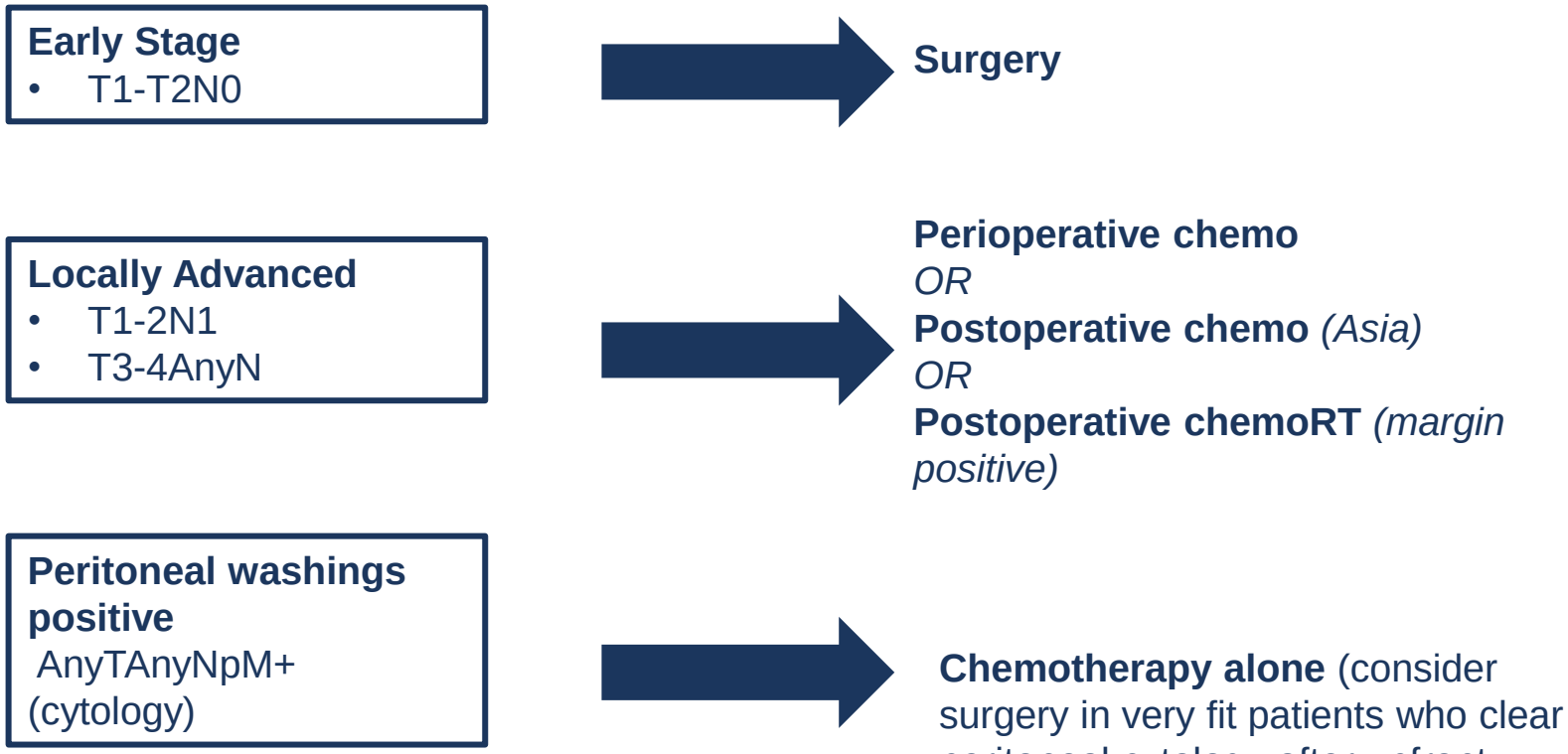
1. Endoscopic resection for T1a lesions

2. For T2+ or N1+ tumors, Trimodality therapy → Adjuvant nivolumab is still a standard approach for squamous cell carcinoma and adenocarcinoma

3. Esophageal adenocarcinoma – recent data supports a non-radiation approach with perioperative FLOT

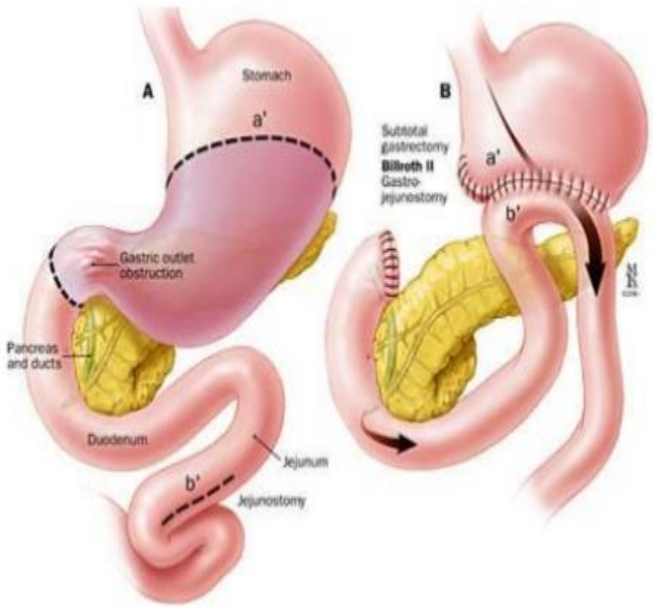
Stage I-III Gastric Cancer

Gastric Cancer Treatment Algorithm

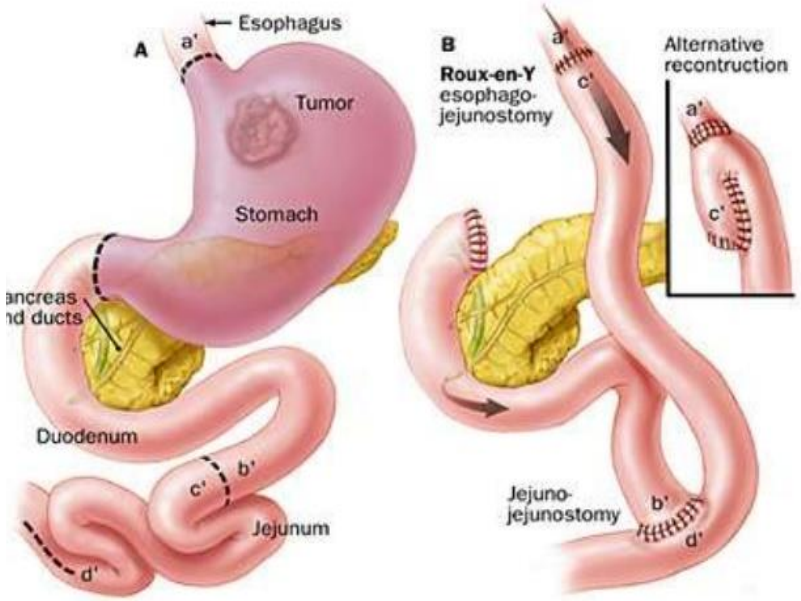


Gastric Resection

Distal Gastrectomy



Total Gastrectomy



Gastric Cancer Lymph Node Dissection

Lymph Node Dissection	Description
D1	lesser and greater curvature, paracardial
D2	Left gastric, hepatic, celiac, splenic (could require pancreatectomy or splenectomy to access these nodes)
D3	D2 + portahepatic, hepatoduodenal
D4	retropancreatic, root of mesentery, transverse mesocolon, paraaortic

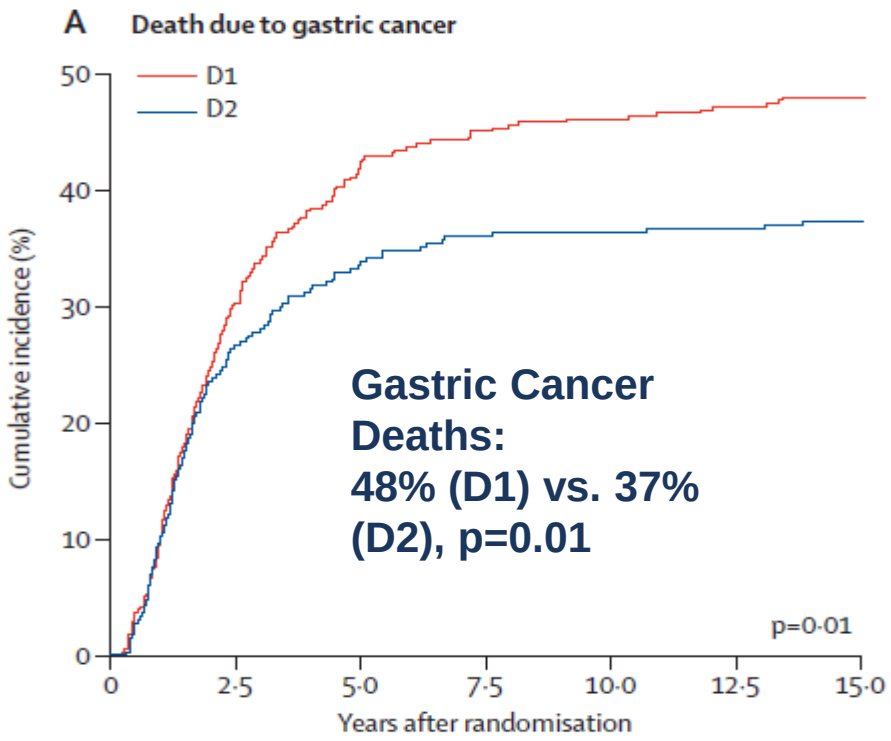
The Dutch Gastric Cancer Group: D1 vs. D2

711 patients undergoing curative resection of gastric cancer

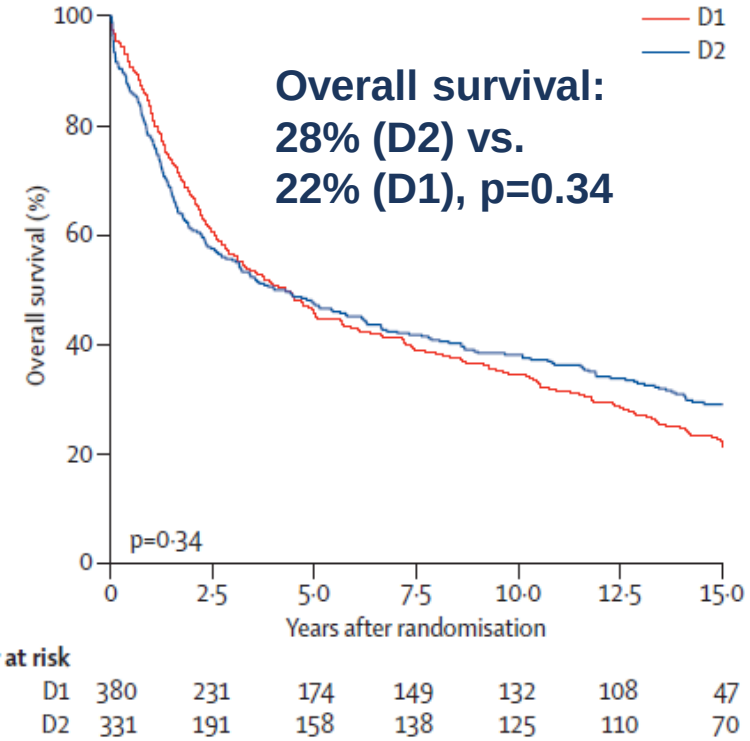
	Peri operative morbidity	Peri operative mortality	5-yr survival
D1	25%	4%	45%
D2	43%	10%	47%

Bonenkamp JJ et al, NEJM 1999; 340:908-914

15 Year Follow Up



Gastric Cancer Deaths: 48% (D1) vs. 37% (D2), p=0.01



Overall survival: 28% (D2) vs. 22% (D1), p=0.34

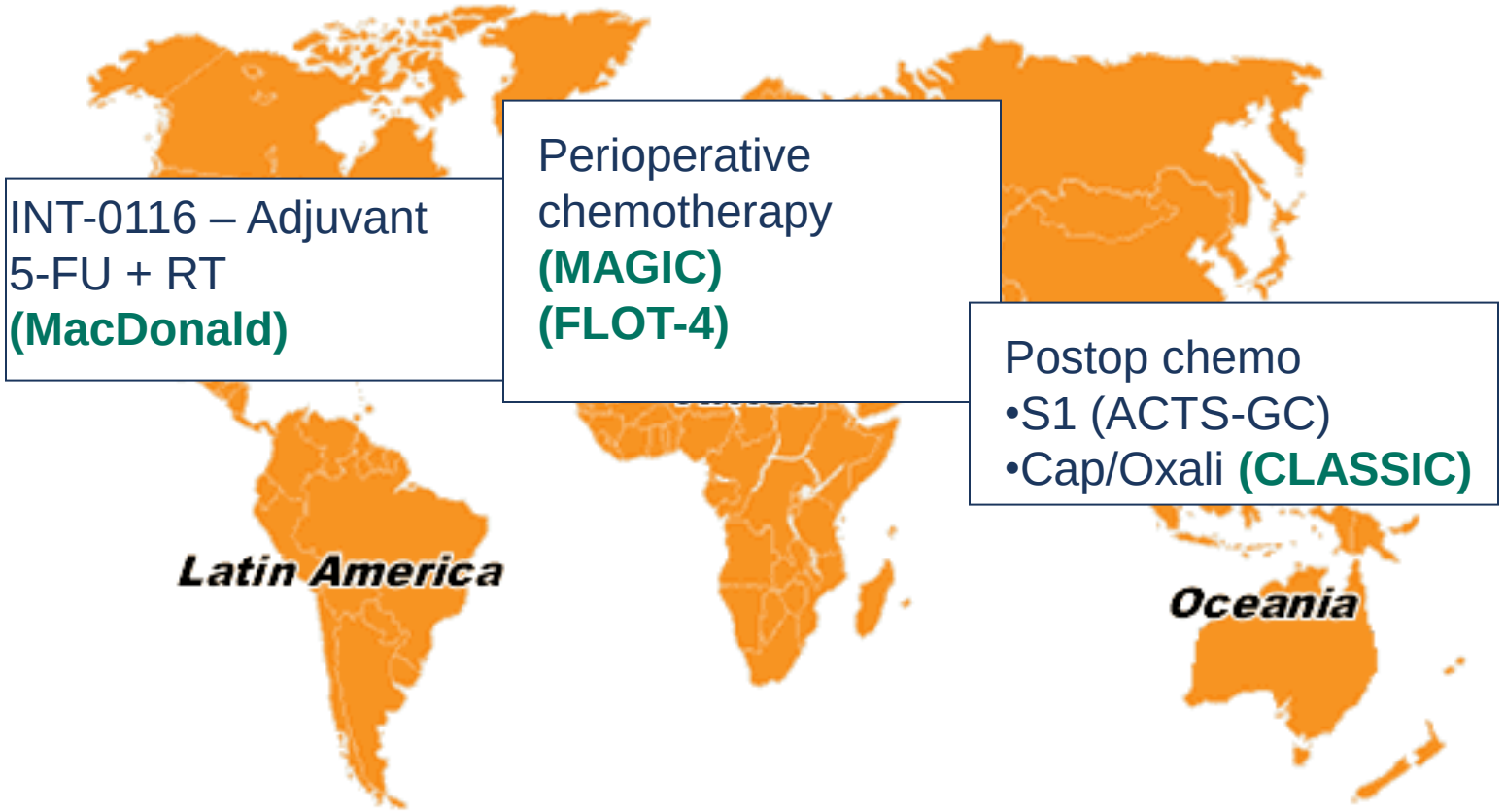
- **High rates of over/under dissection; 45% node negative**
- **D2 dissection is preferred over D1**

Songun, I et al. Lancet Oncology. 2010; 11:439-49.

Post-Gastrectomy Considerations

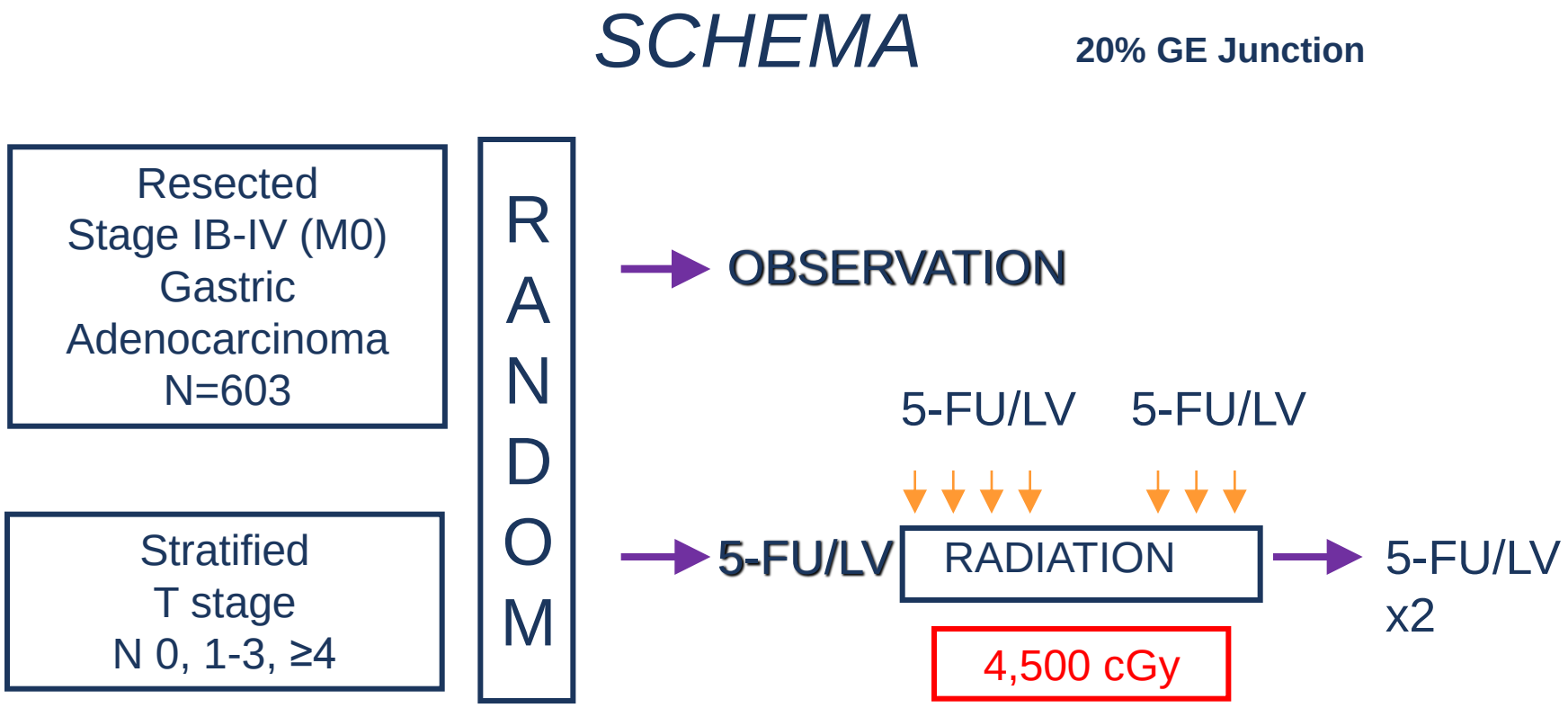
- Inability to store and break down food – frequent SMALL meals
- Vitamin B12 deficiency – lack of instrinsic factor production (cardia)
- Iron deficiency – decreased gastric acid
- Dumping syndrome – rapid emptying into small bowel – lightheadedness, nausea, diarrhea

Adjuvant and Neoadjuvant Treatment



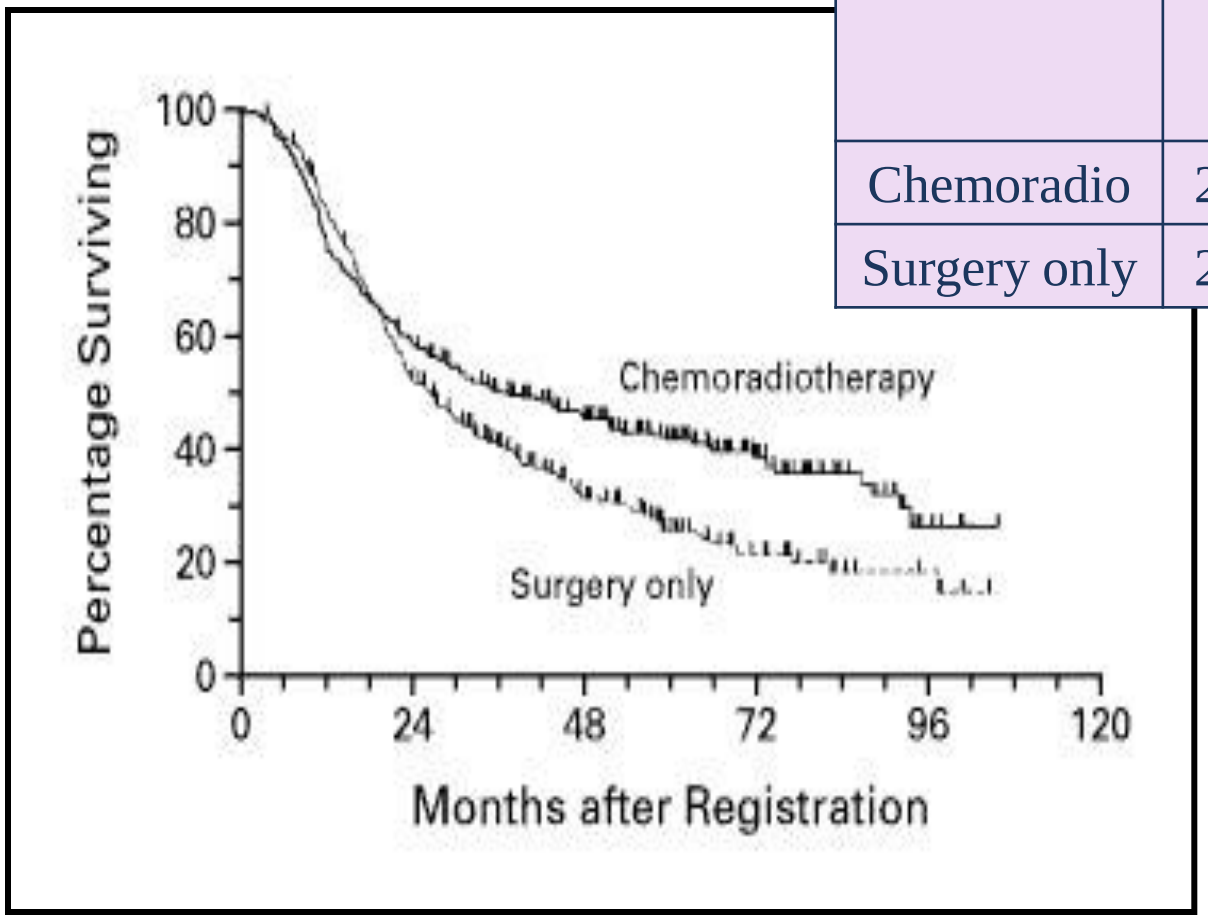
Sasako, M. et al. *J Clin Oncol*. 2011; 29(33): 4387
Cunningham, D et al. *NEJM*. 2006; 355(1): 11
MacDonald, JS et al. *NEJM*. 2001; 345(10): 725

Adjuvant ChemoRT: INT 0116/SWOG 9008



Macdonald *NEJM* 2003; 345: 725-730

Adjuvant ChemoRT: INT 0116/SWOG 9008



	N	Events	Median (mos)
Chemoradio	282	192	35
Surgery only	277	214	27

P = .006

Macdonald *NEJM* 2003; 345: 725-730

Adjuvant ChemoRT: INT 0116/SWOG 9008

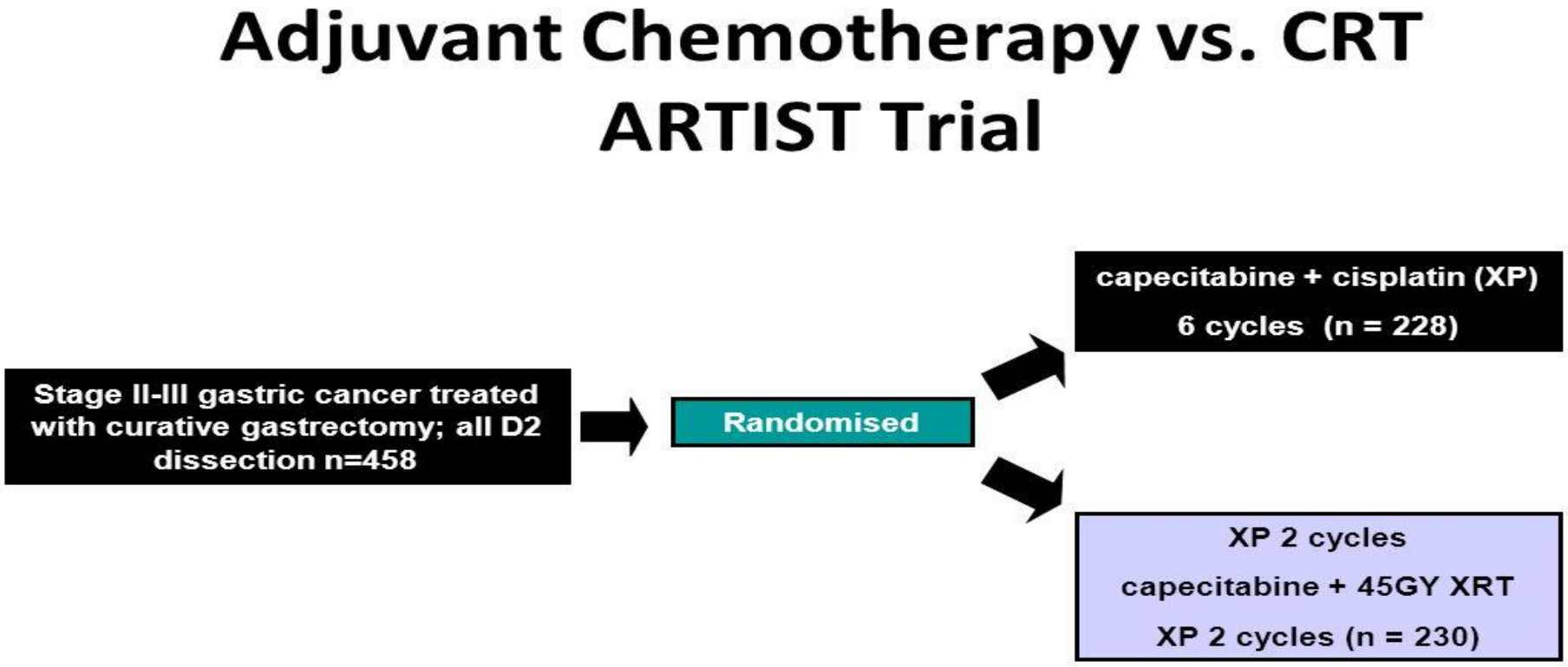
Level of lymph node dissection	%
< D1	**54%**
D1	36%
D2	10%

Criticisms of INT 0116/SWOG 9008:

- Survival benefit with chemoRT because of inadequate surgery
- Better chemotherapy regimens after this trial (so we may not need RT)

Macdonald *NEJM* 2003; 345: 725-730

ARTIST and ARTIST II Trials: Adjuvant Chemo vs. RT



Park, S. et al. J Clin Oncol. 2015; 33(28)

ARTIST and ARTIST II Trials: Adjuvant Chemo vs. RT

ARTIST II Trial

- 900 Patients with D2 resected gastric adenocarcinoma
- pStage II to III, LN+
- Stratified by (1) stage,
  (2) type of surgery (STG vs. TG),
  (3) Lauren classification

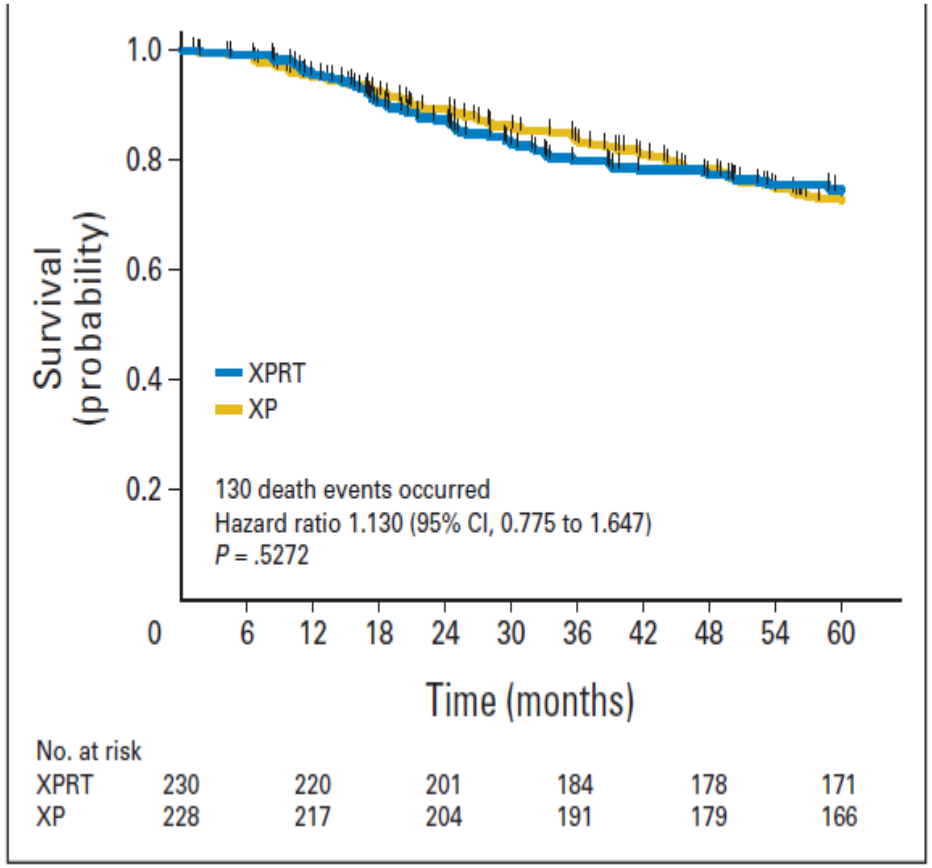
RANDOMIZATION

- Adjuvant chemoRadioTherapy with S-1 (S-1 for 1 year)
- Adjuvant chemoRadioTherapy with SOX (S-1/oxaliplatin for 6 months)
- Adjuvant chemoRadioTherapy (SOX ×2→S-1/RT→SOX ×4)

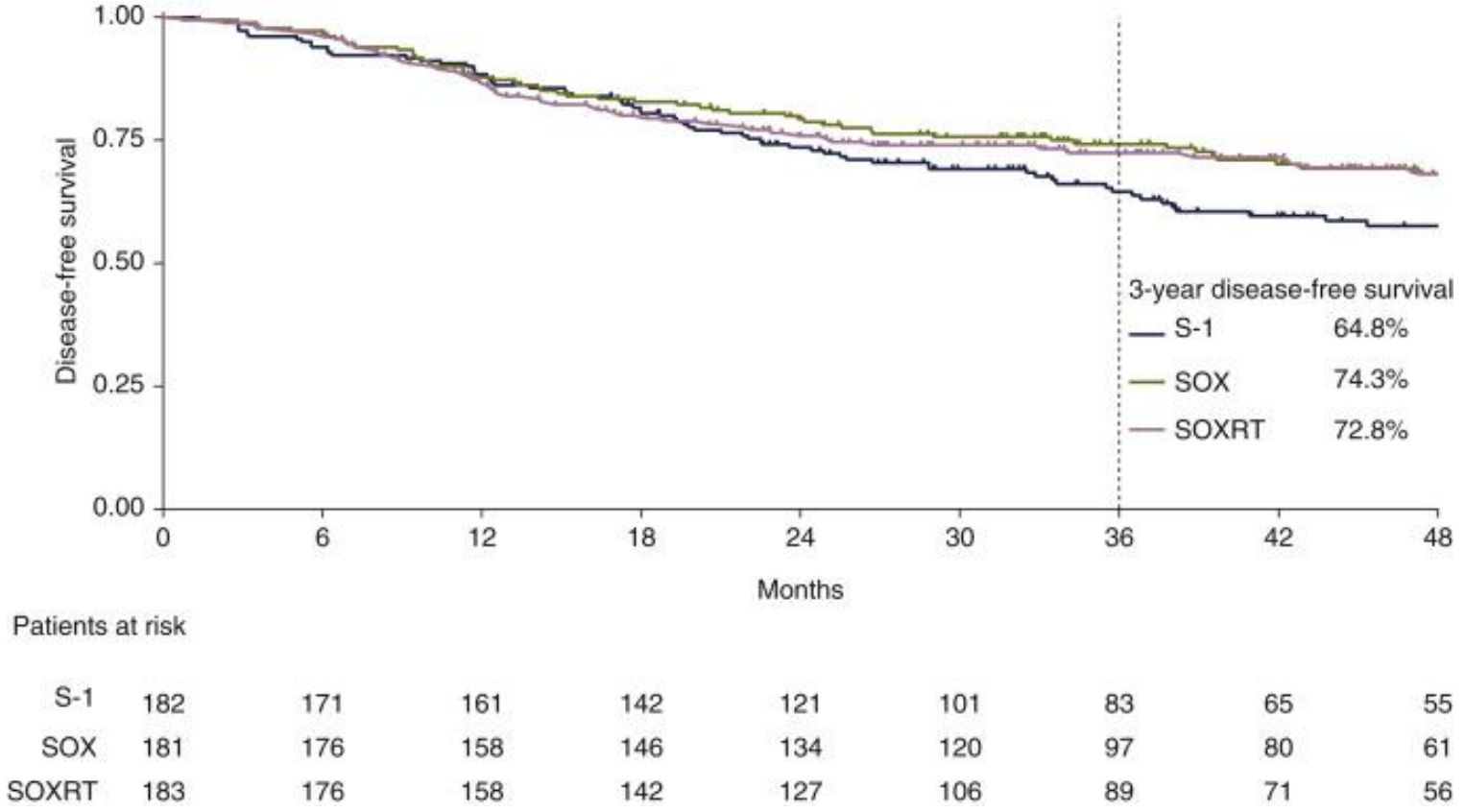
S-1: 40–60 mg bid 4/2 weeks q6 weeks
SOX: S-1 40 mg/m^2 bid 2/1 weeks q3 weeks+oxaliplatin 130 mg/m^2 D1
SOXRT: S-1 40 mg bid daily concurrently with RT 45 Gy for 5 weeks

Park S. et al. Prec Future Med. 2019;3(1):24-29

ARTIST and ARTIST II Trials: Adjuvant Chemo vs. RT



Median OS – ARTIST I



DFS – ARTIST II

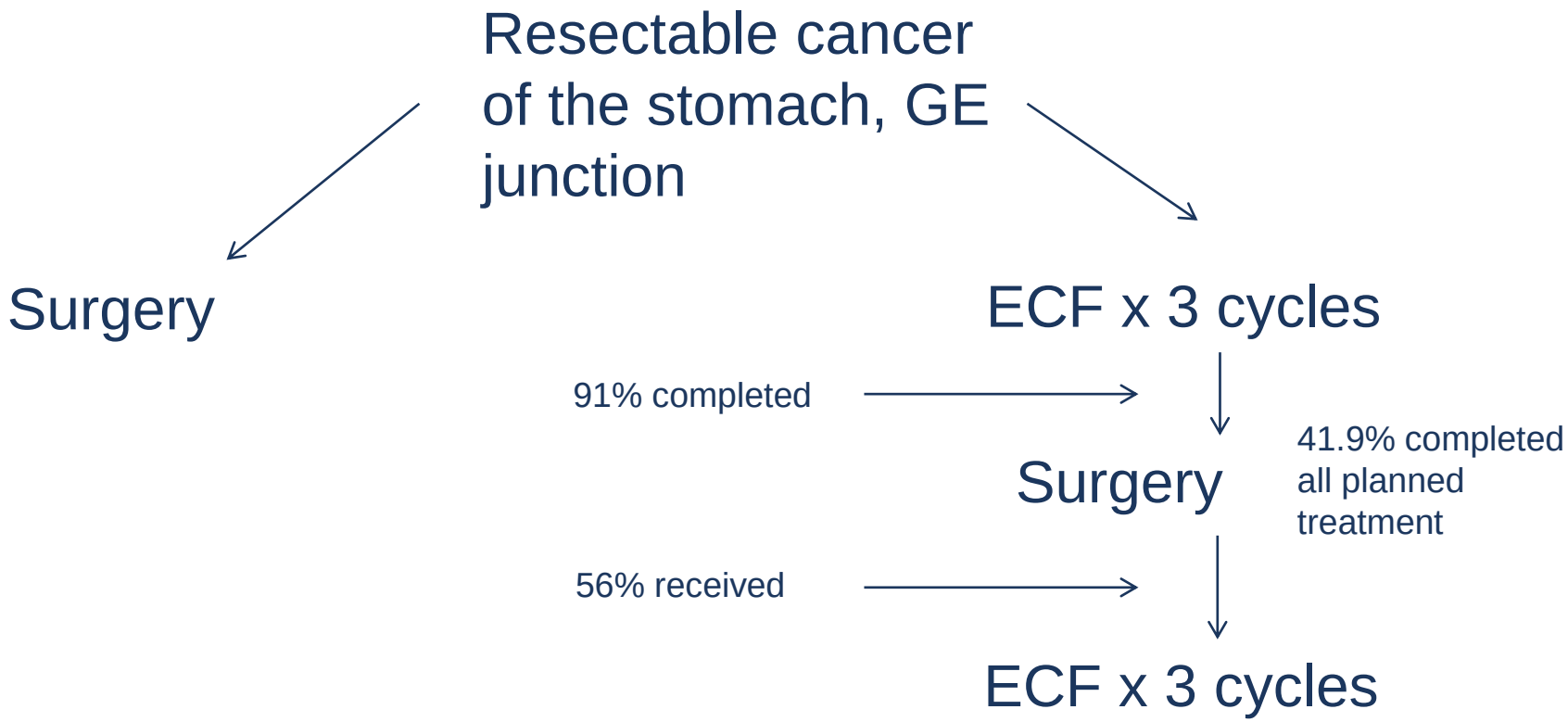
Park, S. et al. J Clin Oncol. 2015; 33(28)
Park, S. et al. Annals of Onc. Volume 32, Issue 3P368-374March 2021

Is there a role for Postoperative Radiation?

NO, except …

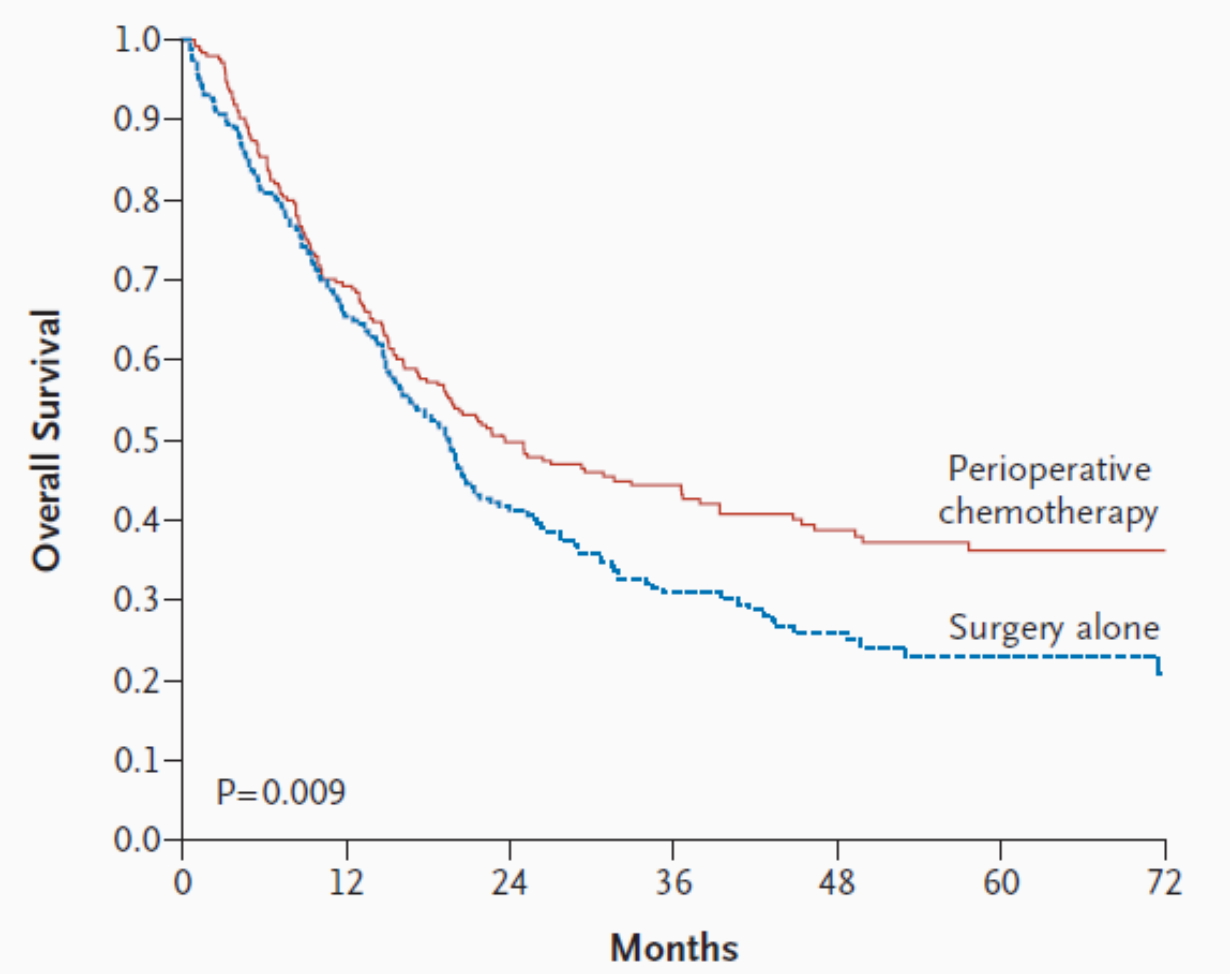
- Inadequate resections / lymph node dissection
- Positive margin (R1 resection)
- Studies evaluating radiation in neoadjuvant setting for gastric cancer (e.g. TOPGEAR)

Perioperative Chemotherapy: MAGIC Trial



Cunningham D, et al. *NEJM* July 2006

Perioperative Chemotherapy: MAGIC Trial

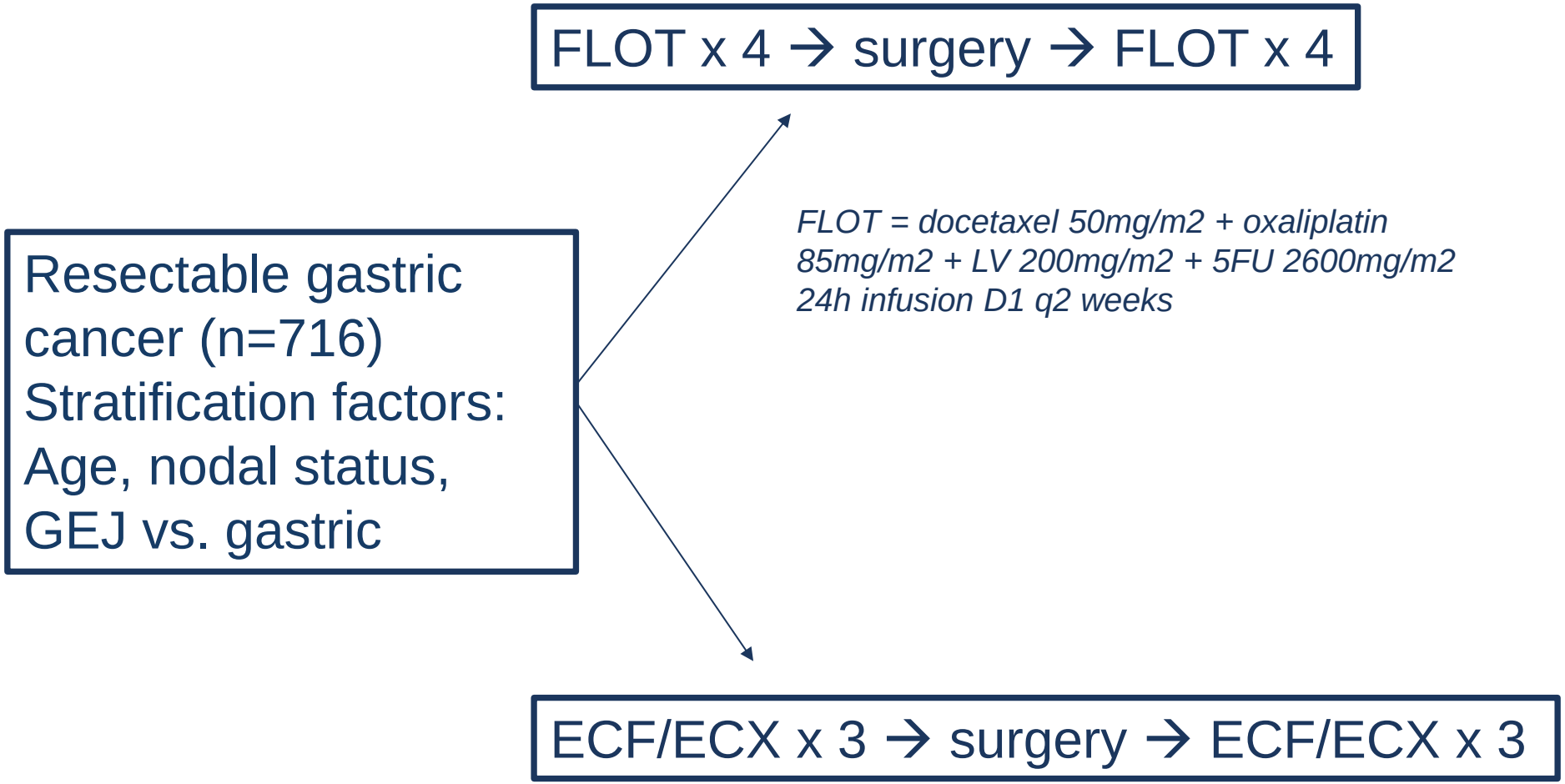


5-year survival
- 36.3% (Chemo)
- 23.0% (Surgery)

Median Survival
- 24 months (Chemo)
- 20 months (Surgery)

Cunningham D, et al. *NEJM* July 2006

Perioperative Chemotherapy: FLOT-4



Al-Batran S, et al. Lancet. 393(10184): 1948-1957. May 2019

Perioperative Chemotherapy: FLOT-4

Key Results:

- 50% FLOT vs. 37% ECF/X completed post-operative chemotherapy
- Median OS 50 months vs. 35 months (HR 0.77, p=0.012)
- 3yr OS 57% FLOT vs. 48% ECF/X
- Postop complications and 30/90 day mortality were similar

Al-Batran S, et al. Lancet. 393(10184): 1948-1957. May 2019

Adding to FLOT-4?

PETRARCA study (phase II/III) (FLOT +/- Trastuzumab)

- 81 patients randomized
- No benefit with addition of trastuzumab to FLOT – path CR, R0 resection rate, DFS, OS
- Study ended early and did not proceed to phase III

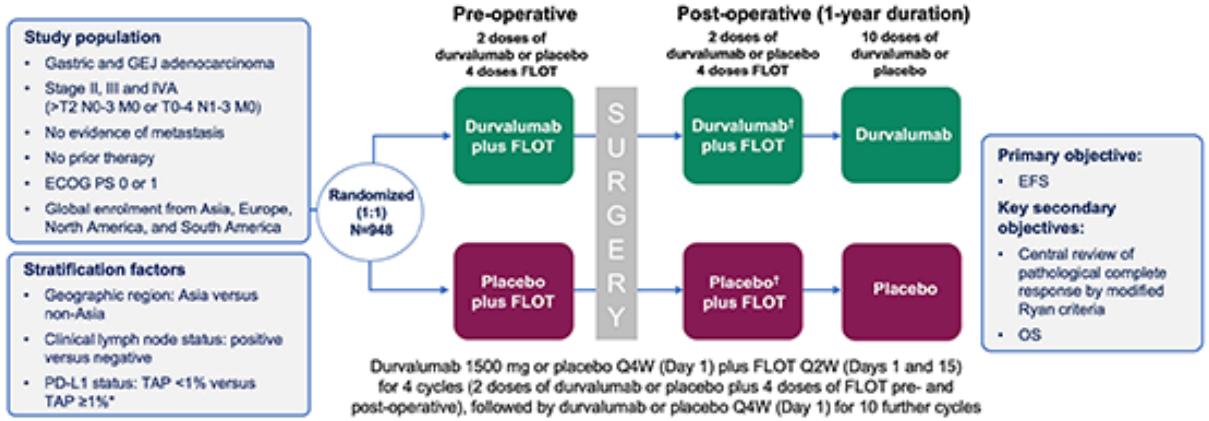
Ramses/FLOT-7 (phase II/III) (FLOT-4 +/- Ramucirumab)

- 180 patients randomized (excluding Siewert type I)
- Endpoints: Path response, R0 resection rate, safety
- Findings: Increased AEs, Improved R0 resection rate (97% vs. 83%, p=0.0049), similar path response

Hofheinz, RD et al. J Clin Onc. 40(32): June 2022
Al Batran, SE et al. J Clin Onc. 15_suppl.4501 (2020)

Incorporating IO into Perioperative Treatment

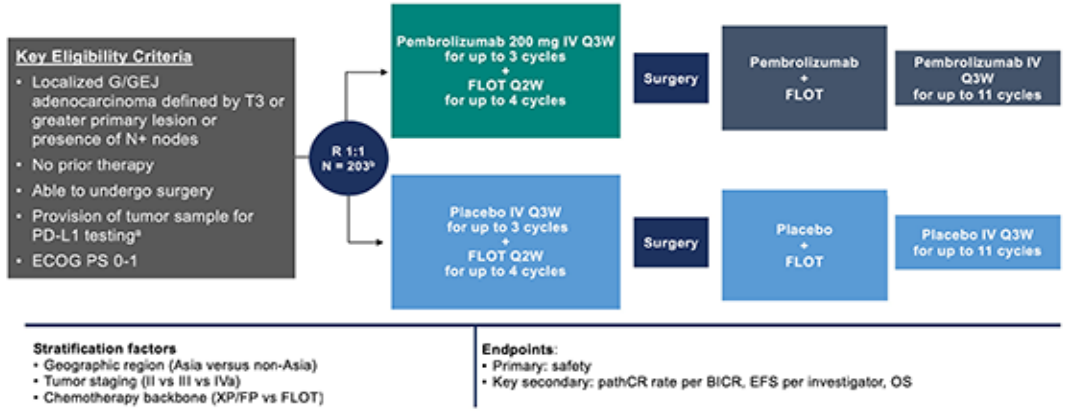
Matterhorn study – Perioperative FLOT +/- Durvalumab resected Gastric + GEJ cancer



Improved path CR rate (19% vs. 7%)

DFS / OS data still pending

Keynote 585 – Perioperative FLOT +/- Pembrolizumab resected Gastric + GEJ cancer



Improved path CR rate (12.9% vs. 2%)

DFS: 44.4 mo vs. 25.3 mo, HR 0.81, p=0.0198, NS*

mOS: 60.7 mo vs. 58 mo, HR 0.90, p=0.174

* Above threshold of significance p=0.0178

1. Shitara K, et al; *Lancet Oncol*. 2024 Feb;25(2):212-224.
2. Janjigian YY, et al. LBA73 *Ann Oncol*. 2023;34(suppl 2):S1315-S1316.

Take – Home Points – Stage I-III Gastric Cancer

1. D2 gastrectomy should be performed when possible

2. Post-gastrectomy B12 and iron supplementation

3. Perioperative chemotherapy with FLOT-4 regimen

4. Vanishing role of radiation therapy in gastric cancer treated with D2 lymph node dissection

5. Perioperative chemotherapy is a preferred strategy in GE jxn adenocarcinoma

6. Role for IO in perioperative therapy is still unclear

Advanced / Metastatic Esophageal and Gastric Cancers

Initial Diagnostic Evaluation

Clinical Assessment

- ECOG PS
- Comorbidities
- Nutritional status
  - Stent
  - G or J tube

Labs and Imaging

- CT C/A/P w/ IV contrast (peritoneal dz)
- CEA
- CA 19-9

Molecular testing

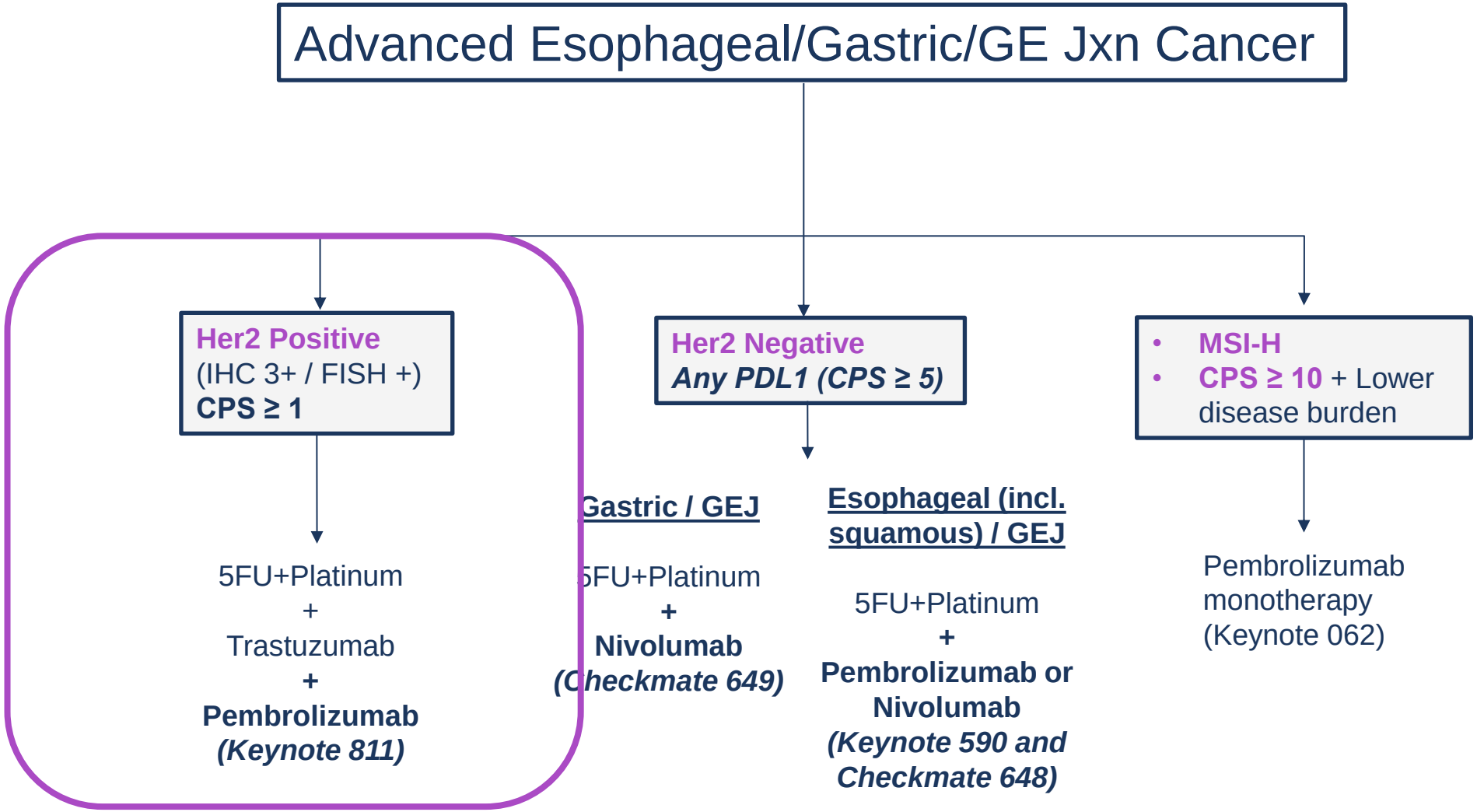
- Her2 IHC and FISH (3+ or FISH+)
- PDL1 (CPS score)
- MSI
- EBV (Gastric)
- *NGS for most – tumor mutational burden*

First-Line Chemotherapy Backbones

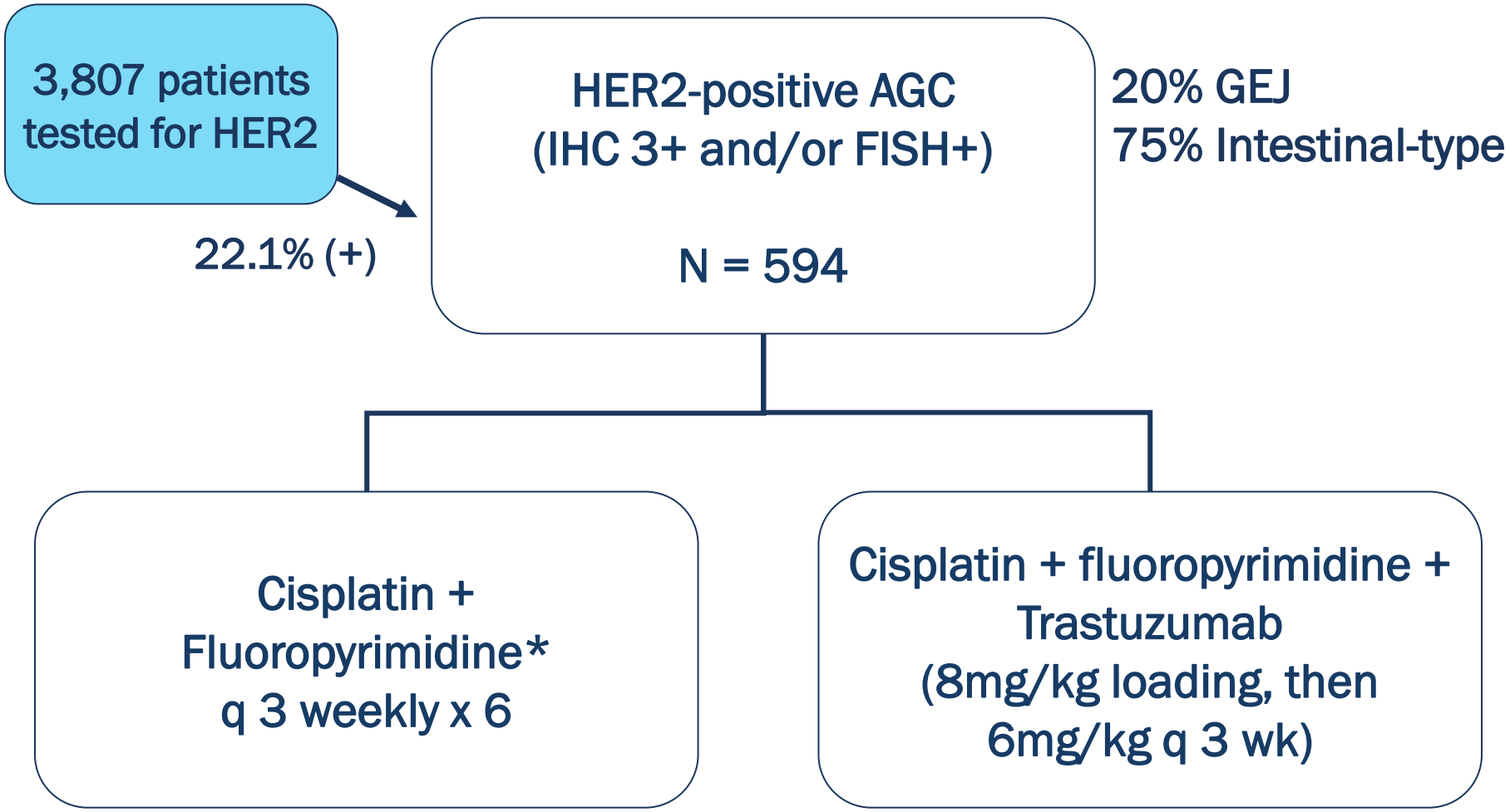
2-drug regimens are preferred to the older 3-drug regimens (e.g. ECF, EOX, EOF, DCF, modified DCF)

- FOLFOX (US)
- 5-FU + cisplatin
- FOLFIRI
- Can use capecitabine (but ensure patient can swallow)

Initial Treatment - 2024

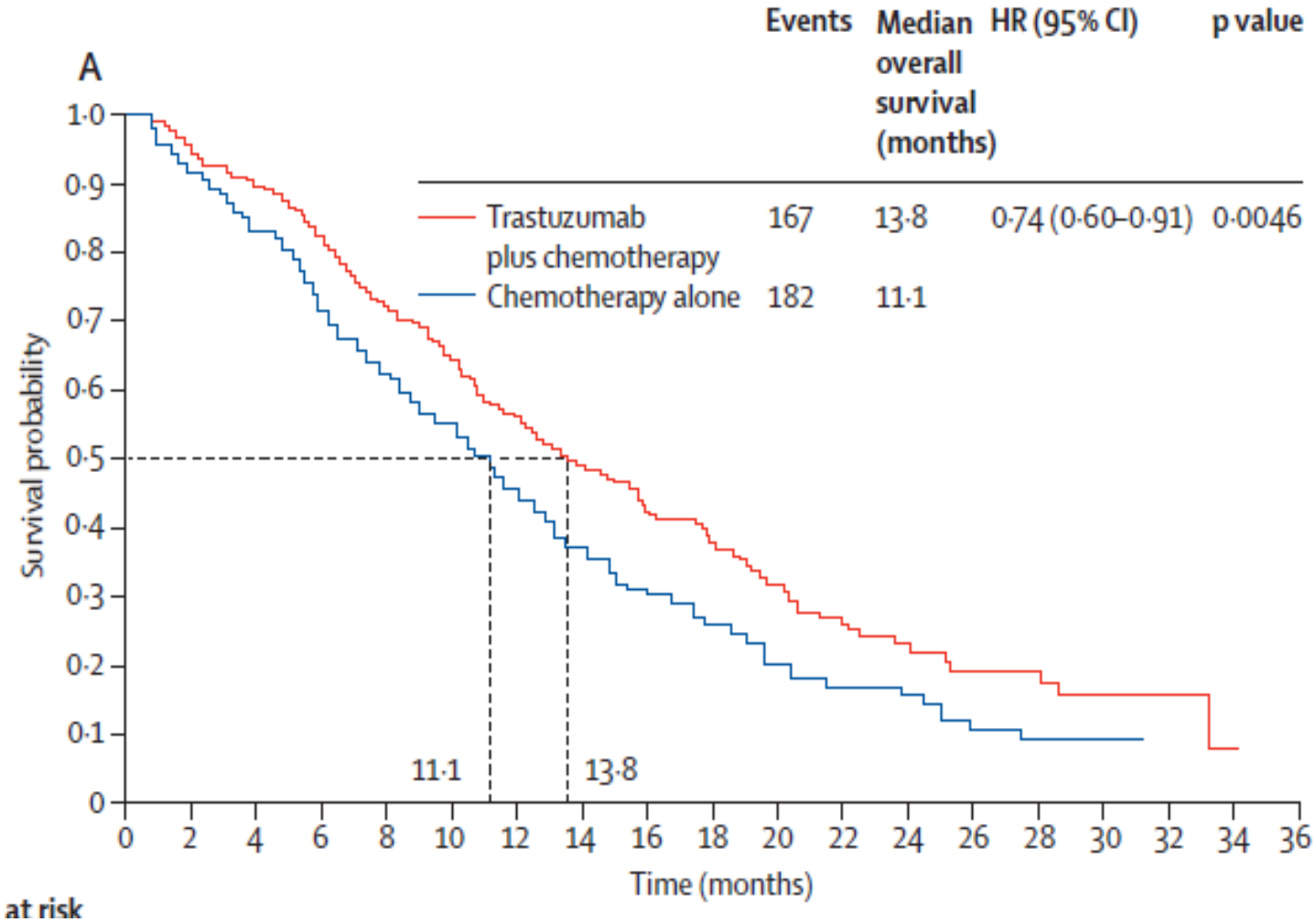


Targeting Her2 – TOGA Trial



Bang, YJ et al. *Lancet* 2010; 376: 698-97

TOGA Trial - Results



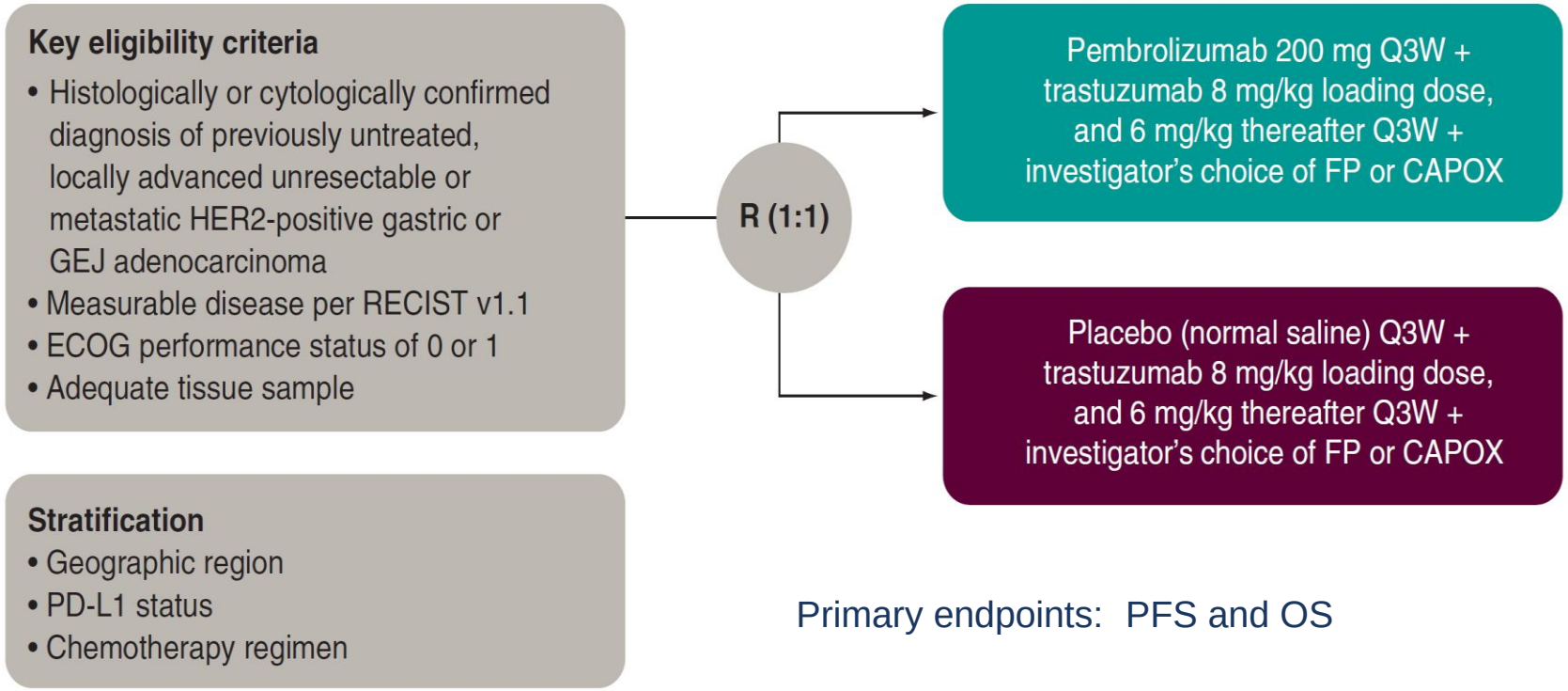
Bang, YJ et al. *Lancet* 2010; 376: 698-97

Her2 Agents in Gastric Cancer

- **TRIO-013/LOGiC 1st line**: CapOx +/- **Lapatinib**
- **JACOB Trial 1st line**: FU+Cis+Trastuzumab +/-
- **Pertuzumab**
- **TyTAN study 2nd line**: Paclitaxel +/- **Lapatinib**
- **GATSBY trial 2nd line**: Taxane vs. **TDM-1**

Hecht, R et al. J Clin Oncol. 2016, 34(5): 443-451.
Satoh, T et al. J Clin Oncol. 2014, 32(19): 2039-49
Thuss-Patience, PC et al. Lancet Oncol. 2017, 18(5): 640-53
Tabernero, J et al. ESMO 2017.

Merck 811 – Chemo + Trastuzumab + Pembro



Primary endpoints: PFS and OS

Chung, H. et al. Future Oncology. 2021, 17(5): 491-501.

Merck 811 – Chemo + Trastuzumab + Pembro

	Chemo + Trast + Pembro (n=133)	Chemo + Trast + Placebo (n=131)
ORR* (95% CI)	**74% (66, 82)**	**52% (43, 61)**
Complete response rate	11%	3.1%
Partial response rate	63%	49%
p-value	<0.0001	
PFS (CPS ≥ 1)	**10.0 (10.9)**	**8.1 (7.3)**
HR 0.73; 95% CI, 0.61-0.87		
OS (CPS ≥ 1)	**20 (20.1)**	**16.8 (15.7)**
HR 0.80; 95% CI, 0.67-0.94; p=0.0040		

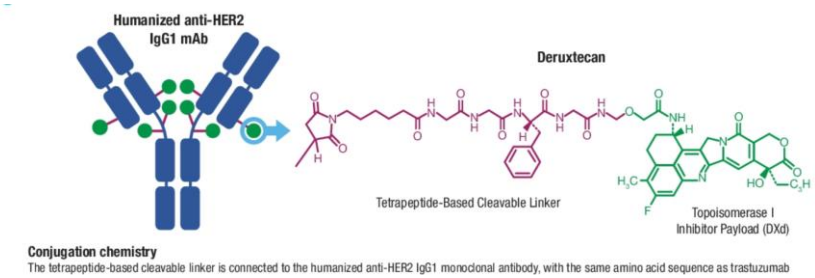
FDA *accelerated* approval for **Pembro** with chemo and trastuzumab in advanced Her-2+ gastric/GEJ cancer in May, 2021

Updated results June 2023: Benefit confined to patients with **CPS ≥ 1** (80% of subjects in trial)

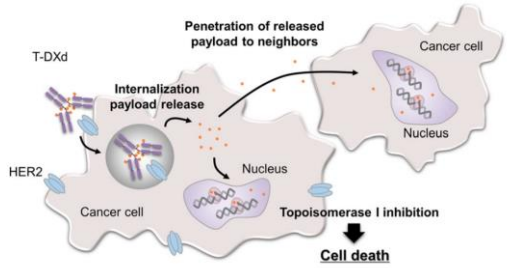
Chung, H. et al. Future Oncology. 2021, 17(5): 491-501.
Lonardi, S. et al. ESMO Sept 2024

2nd line and beyond: Trastuzumab Deruxtecan – Destiny Gastric01

- **Destiny Gastric 01** study: Randomized phase II study in Japan and Korea
- Patient population: Her2 positive gastric and GE jxn cancer patients who received at least **2 prior lines of therapy** (including prior trastuzumab)
- 188 patients randomized (2:1) to trastuzumab deruxtecan versus physician's choice (irinotecan or paclitaxel)
- Primary endpoint = objective response



T-DxD is a novel antibody drug conjugate (ADC) with a topoisomerase I payload



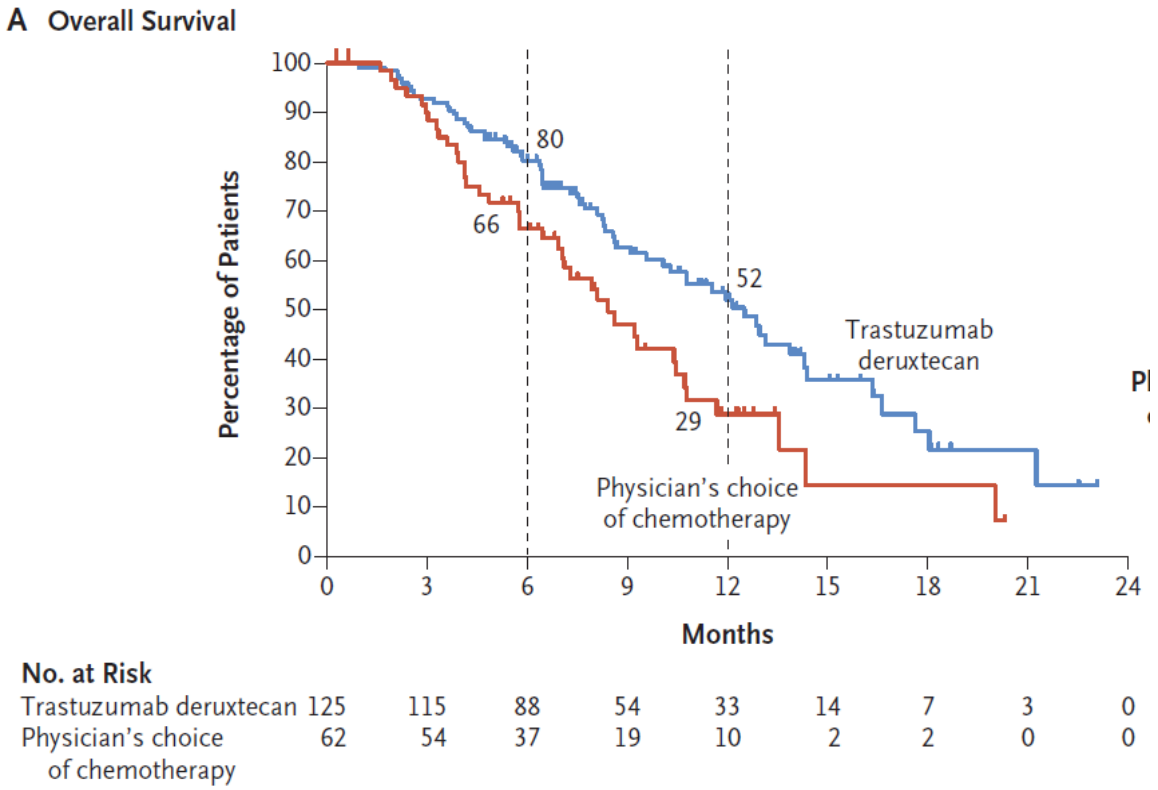
*Potential to overcome resistance via "by-stander effect"

Shitara K. et al. NEJM 2020; 382:2419-30.
Shitaa K. et al. Abstract 4513, ASCO 2020.
Shitara K et al. Gastric Cancer 2021; 24:780–789

Trastuzumab Deruxtecan

OR: 51% vs. 14%

PFS: 5.6 vs. 3.5 months (HR 0.47, 95% CI 0.31, 0.71)



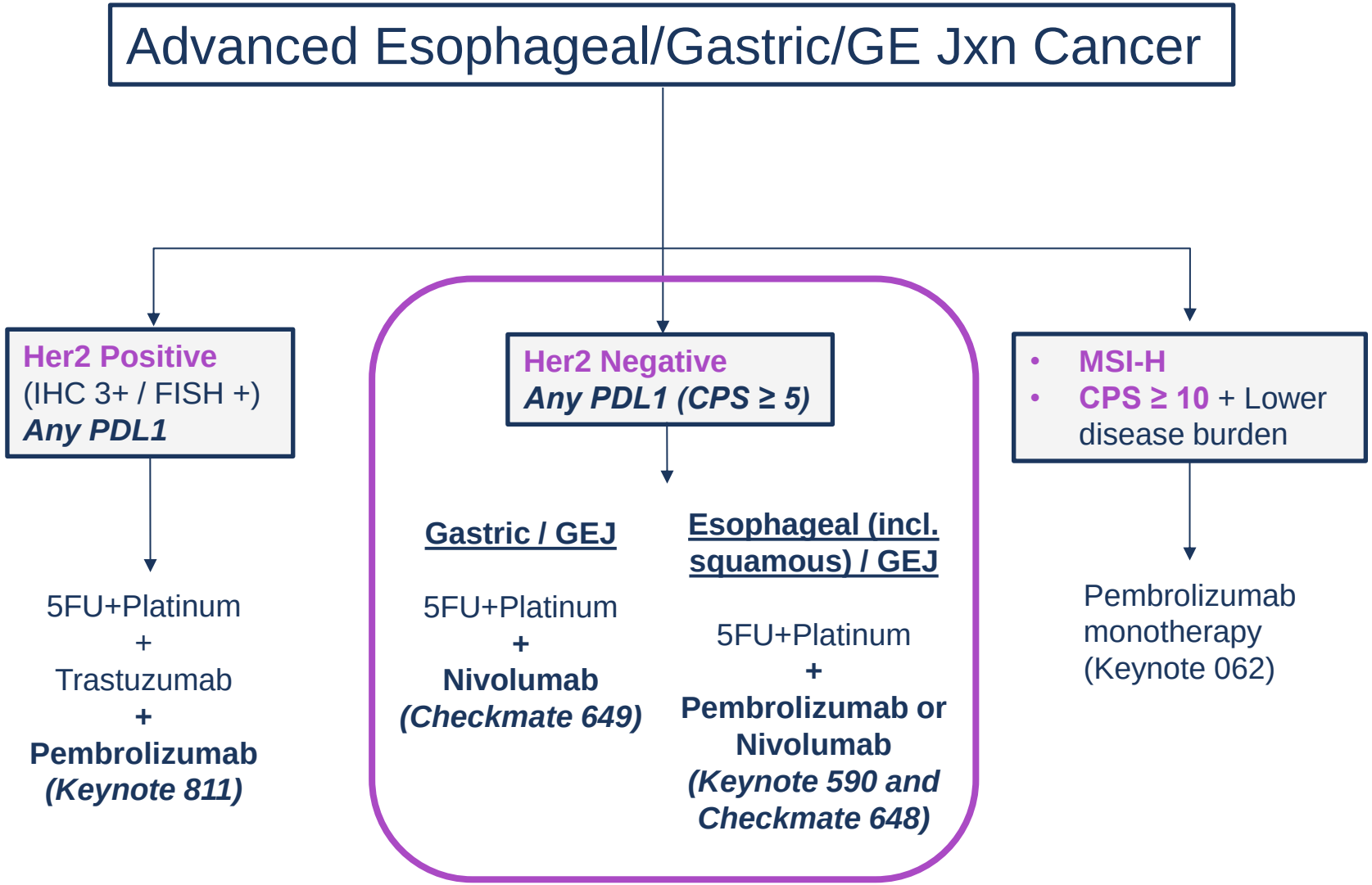
Median OS: 12.5 vs. 8.4 months
HR 0.59, 95% CI 0.39-0.88)

Safety: neutropenia (51% vs. 24%) and ILD or pneumonitis (10%)

FDA Approval January 2021

Shitara, K. et al. NEJM 2020; 382:2419-30.

Initial Treatment - 2024



CPS-Based treatment algorithm for checkpoint inhibitors in Her2 negative disease

	Gastric / GEJ adenocarcinoma	Esophageal squamous cell
CPS ≥ 10	Chemotherapy (FOLFOX) + **Nivolumab or Pembrolizumab**	Chemo + Pembrolizumab or Nivolumab Or Nivo/Ipi (selected patients) CPS higher benefit most Meta-analyses suggest benefit in no/low CPS
CPS 5-9	Chemotherapy (FOLFOX) + **Nivolumab**	
CPS < 5	Chemotherapy alone (emerging role for zolbetuximab anti-claudin 18.2 – pending FDA review/approval)	

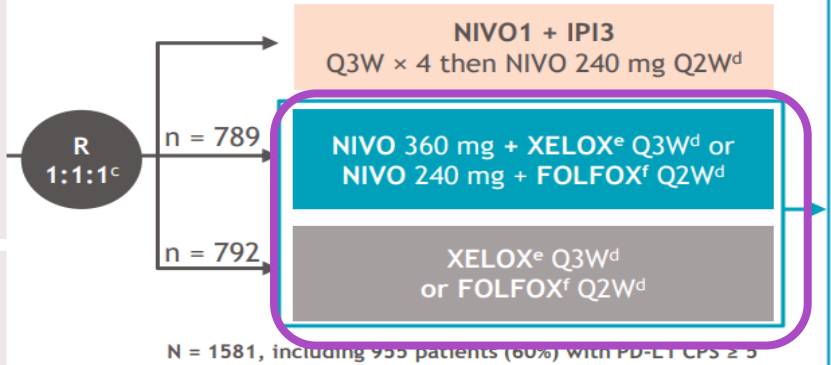
First-line Nivolumab ESO/Gastric Adeno (Checkmate 649 Study)

CheckMate 649 study design

- CheckMate 649 is a randomized, open-label, phase 3 study[a]

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/ esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0-1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



Dual primary endpoints:
- OS and PFS[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:
- OS (PD-L1 CPS ≥ 1 or all randomized)
- OS (PD-L1 CPS ≥ 10)
- PFS[g] (PD-L1 CPS ≥ 10, 1, or all randomized)
- ORR[g]

- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]

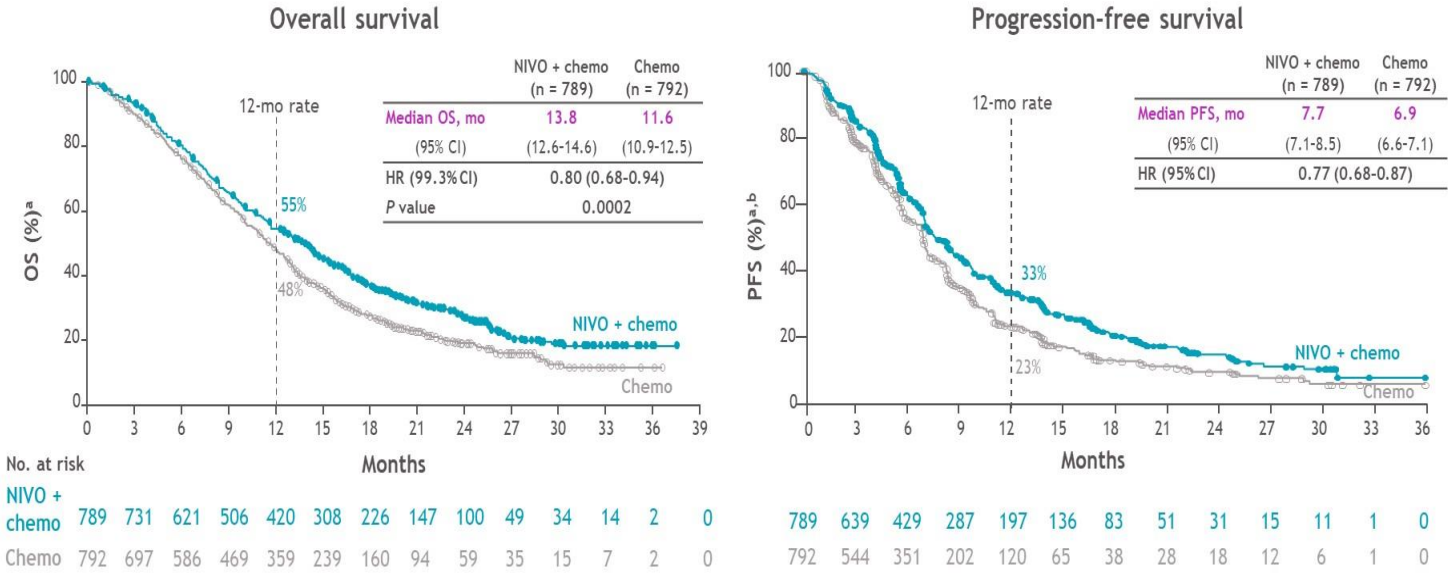
[a]ClinicalTrials.gov number, NCT02872116; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]After NIVO + chemo arm was added and before new patient enrollment in the NIVO1+IPI3 group was closed; [d]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1-14); [f]Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1-2); [g]BICR assessed; [h]Time from concurrent randomization of the last patient to NIVO + chemo vs chemo to data cutoff.

Janjigian, Y. et al. The Lancet. 398(10294): 27-40, Jul 2021

First-line Nivolumab ESO/Gastric Adeno (Checkmate 649 Study)

CheckMate 649

Overall survival and progression-free survival in all randomized patients



	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS, mo	13.8	11.6
(95% CI)	(12.6-14.6)	(10.9-12.5)
HR (99.3% CI)	0.80 (0.68-0.94)	
P value	0.0002	

	NIVO + chemo (n = 789)	Chemo (n = 792)
Median PFS, mo	7.7	6.9
(95% CI)	(7.1-8.5)	(6.6-7.1)
HR (95% CI)	0.77 (0.68-0.87)	

- Superior OS benefit and clinically meaningful PFS improvement in all randomized patients with NIVO + chemo vs chemo
- Median OS with NIVO + chemo vs chemo in patients with PD-L1 CPS ≥ 5 was 14.4 vs 11.1 months and median PFS was 7.7 vs 6.0 months[1]

[a]Minimum follow-up, 12.1 months; [b]Per BICR assessment.

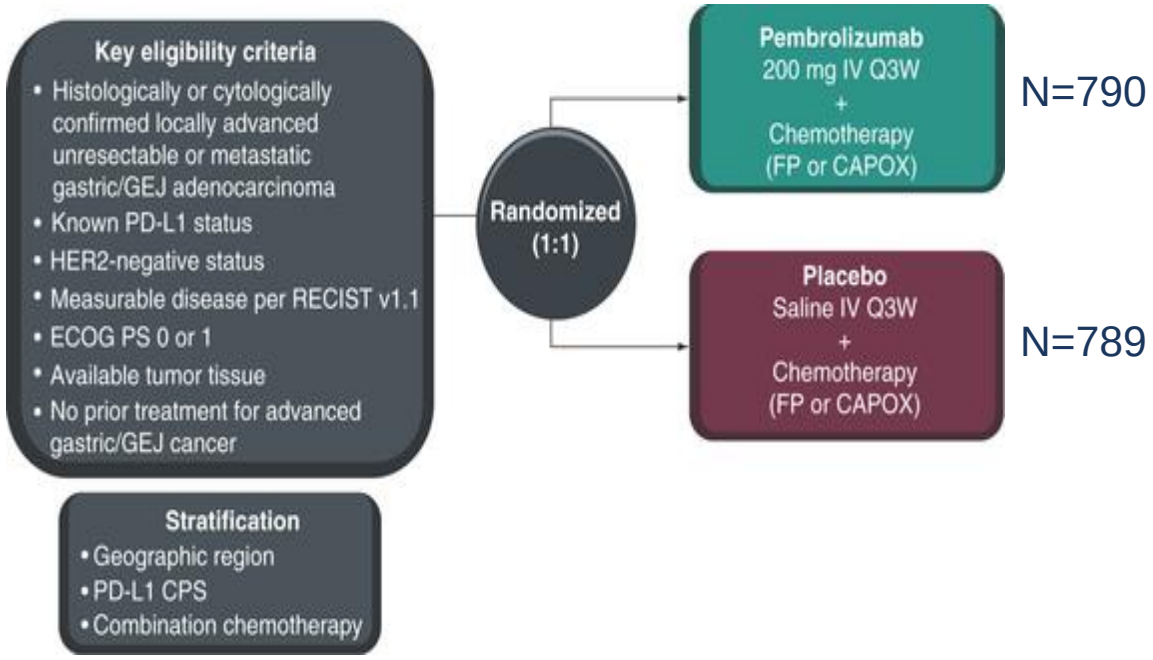
1. Moehler M, et al. Oral presentation at the ESMO Virtual Annual Meeting; September 19-21, 2020. Presentation LBA6.

5

- **Magnitude of benefit is greater in pts with PD-L1 CPS ≥5**
- FDA approval of nivolumab in May, 2021 in advanced Her-2 negative gastric/GEJ *regardless of CPS*
- European Medicines Agency limited approval to CPS ≥5
- **NCCN recommends limiting first-line nivolumab to CPS ≥5**

Moehler M, et al. Abstract 4002. ASCO 2021 Annual Meeting
Janjigian Y et al. Lancet 2021; 398: 27–40

First-line Pembro in Gastric/GEJ Adeno (Keynote-859)



Primary endpoint OS (ITT, CPS ≥ 1, and CPS ≥ 10)

	Chemo	Chemo + Pembro	HR
ITT	11.5	12.9	HR 0·78 [95% CI 0·70–0·87]; p<0·0001
CPS ≥ 1	11.4	13.0	HR 0·74 [0·65–0·84]; p<0·0001)
CPS ≥ 10	**11.8**	**15.7**	**HR 0·65 [0·53–0·79]; p<0·0001**

FDA approval of pembrolizumab in March, 2021 in advanced Her-2 negative gastric/GEJ *regardless of CPS*

Benefit driven largely by **CPS ≥ 10**

Rha, S. et al. The Lancet Oncology. Volume 24, Issue 11P1181-1195 November 2023

First-Line Pembrolizumab in ESO Adeno + Squamous (Keynote 590 Study)

Patient population: Advanced esophageal cancer and GEJ (Siewert I)
CPS assessed by 223C assay

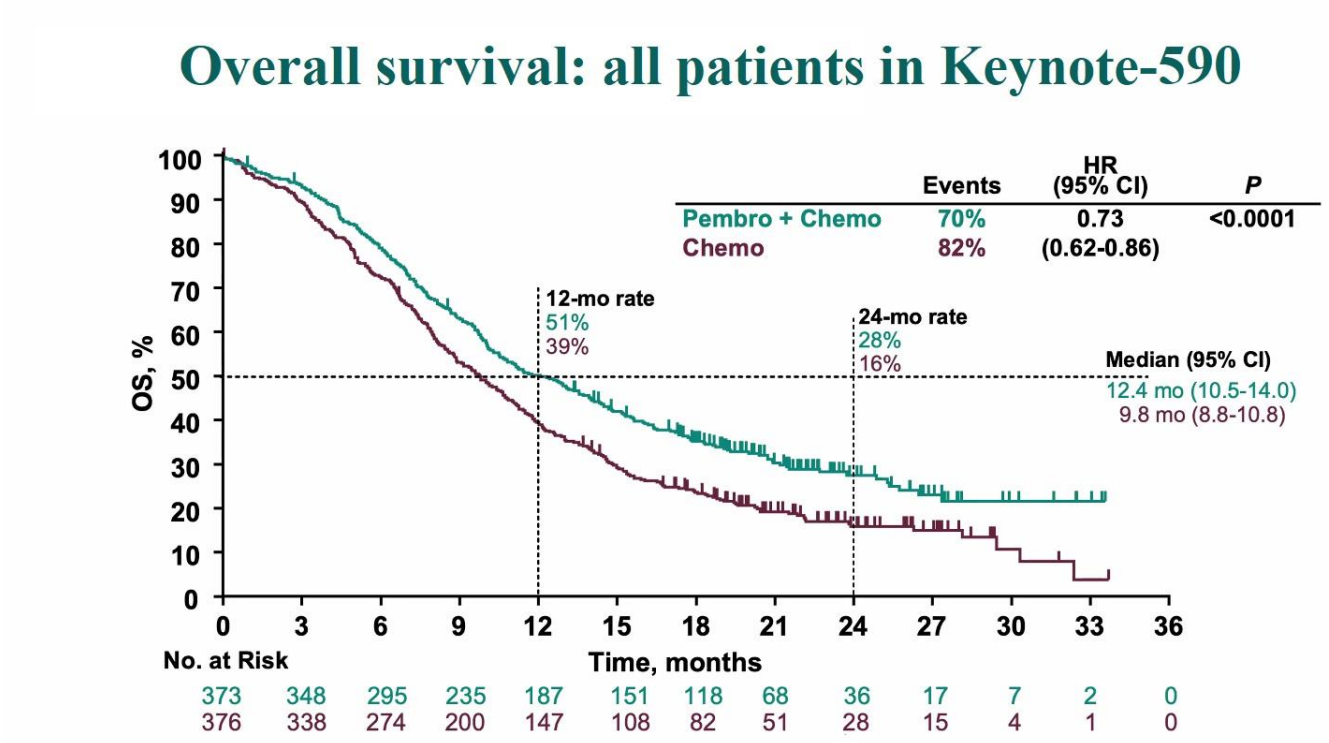
Randomization: N = 749 to 5-FU + cisplatin + / - Pembrolizumab

Primary endpoints: OS / PFS in Squamous cell CPS ≥ 10, Squamous cell, CPS ≥ 10, and all patients

Kato K et al. Abstract LB8_PR. ESMO 2020.
Sun J-M et al. Lancet 2021

First-Line Pembrolizumab in ESO Adeno + Squamous (Keynote 590 Study)

N = 749 (83 % Male ; 73% Squamous cell)



OS: 12.4 vs 9.8 mo (HR: 0.73, p<0.0001)

PFS: 6.4 vs. 5.8 mo (HR 0.65, p<0.001)

ORR: 45% vs. 29.3% (p<0.0001)

Kato K et al. Abstract LB8_PR. ESMO 2020.
Sun J-M et al. Lancet 2021

Keynote 590: Results by Histology and CPS

Median Overall Survival (months)			
	C	C + Pem	
All patients	12.4	9.8	HR 0.73
Squamous cell CPS ≥ 10	13.9	8.8	HR 0.57
Squamous cell	12.6	9.8	HR 0.72
Any histology, CPS ≥ 10	13.5	9.4	HR 0.62
Adenocarcinoma	*11.6*	*9.9*	*HR 0.74*

Fluoropyrimidine + platinum + pembrolizumab FDA approved for use in esophageal cancer, regardless of CPS, *March, 2021*

Benefit seen largely in SCC patients and CPS ≥ 10

Kato K et al. Abstract LB8_PR. ESMO 2020.
Sun J-M et al. Lancet 2021

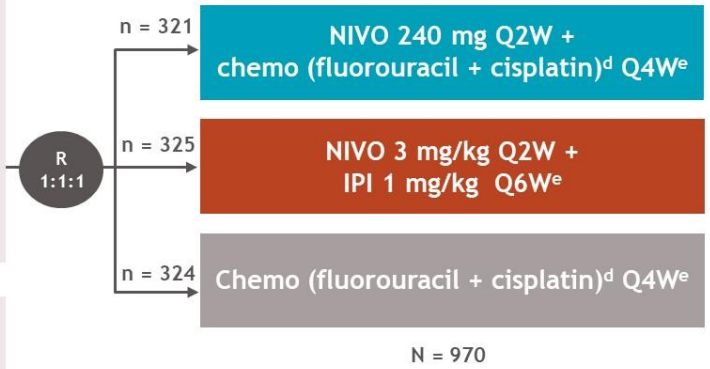
First-line Nivolumab in Esophageal Squamous Cell (Checkmate 648)

CheckMate 648 study design

- CheckMate 648 is a global, randomized, open-label phase 3 study[a]

Key eligibility criteria
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤ 1 vs ≥ 2)



Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

Can we use a non-chemotherapy option for patients with squamous cell carcinoma ?

- At data cutoff (January 18, 2021), the minimum follow-up was 12.9 months[g]

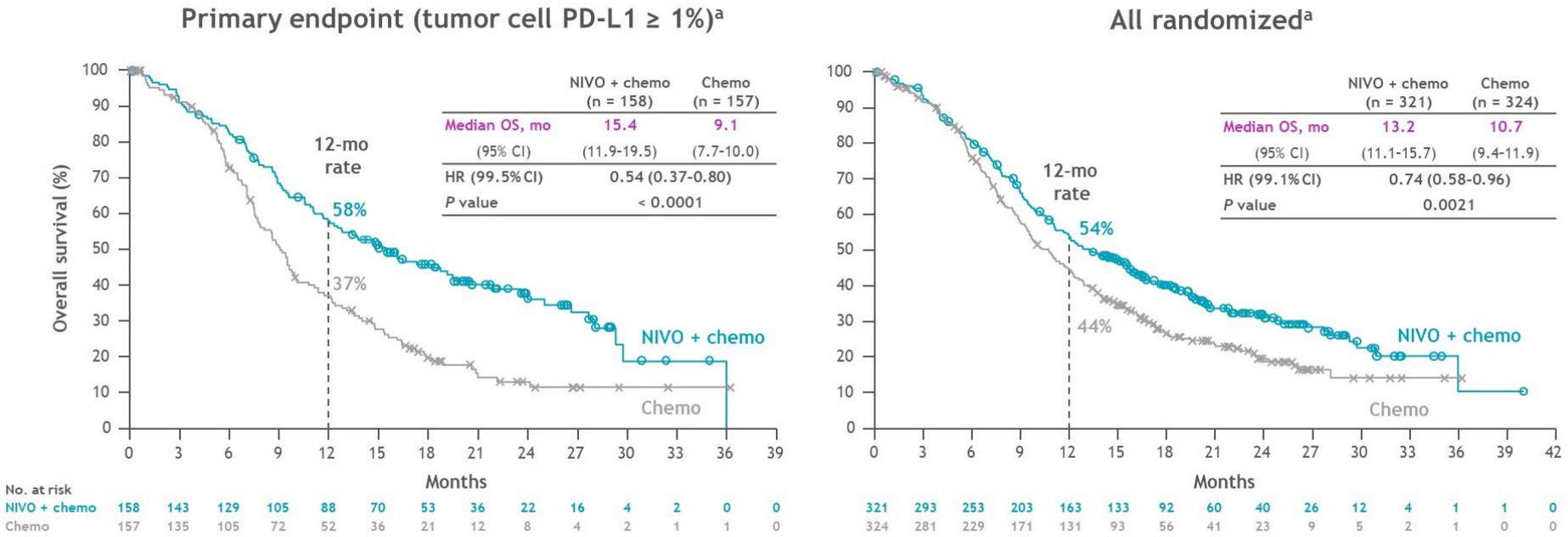
[a]ClinicalTrials.gov. NCT03143153; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]East Asia includes patients from Japan, Korea, and Taiwan; [d]Fluorouracil 800 mg/m^2 IV daily (days 1-5) and cisplatin 80 mg/m^2 IV (day 1); [e]Until documented disease progression (unless consented to treatment beyond progression for NIVO + IPI or NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given alone or in combination with IPI for a maximum of 2 years; [f]Per blinded independent central review (BICR); [g]Time from last patient randomized to clinical data cutoff.

Chau I, et al. Abstract LBA4001. ASCO 2021 Annual Meeting;
Doki Y et al. N Engl J Med 2022.

First-line Nivolumab in Esophageal Squamous Cell (Checkmate 648)

CheckMate 648

Overall survival: NIVO + chemo vs chemo



- Superior OS with NIVO + chemo vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 46% reduction in the risk of death and a 6.3-month improvement in median OS
  - All randomized: 26% reduction in the risk of death and a 2.5-month improvement in median OS

[a]Minimum follow-up 12.9 months.

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First-line Nivolumab in Esophageal Squamous Cell (Checkmate 648)

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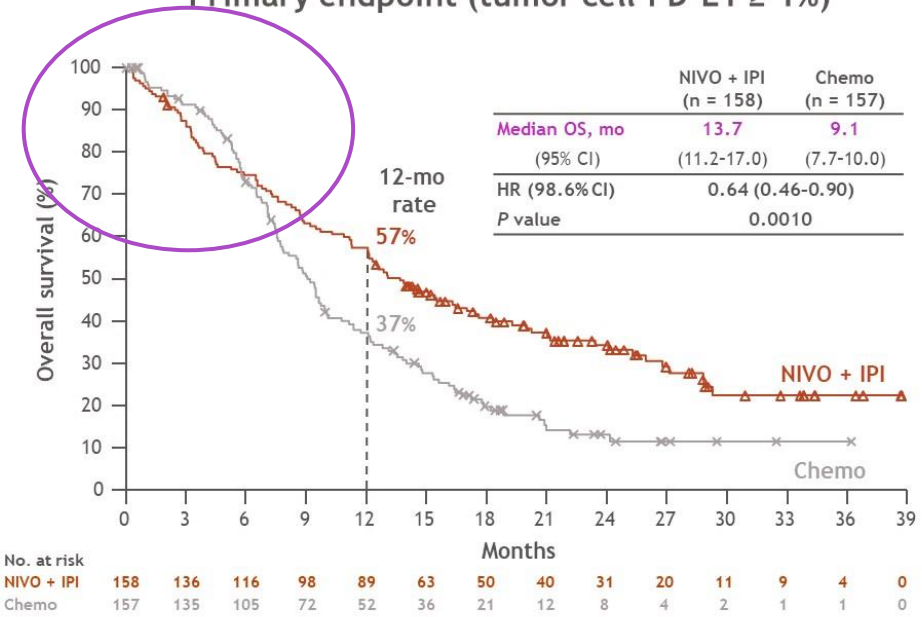
Overall survival: NIVO + IPI vs chemo

Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]

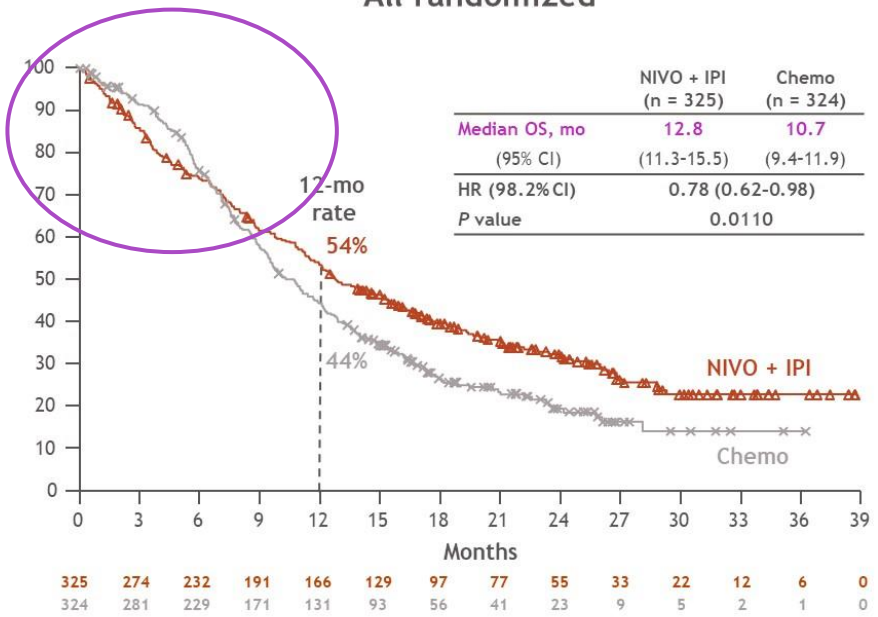


	NIVO + IPI (n = 158)	Chemo (n = 157)
Median OS, mo	13.7	9.1
(95% CI)	(11.2-17.0)	(7.7-10.0)
HR (98.6% CI)	0.64 (0.46-0.90)	
P value	0.0010	

No. at risk

NIVO + IPI	158	136	116	98	89	63	50	40	31	20	11	9	4	0
Chemo	157	135	105	72	52	36	21	12	8	4	2	1	1	0

All randomized[a]



	NIVO + IPI (n = 325)	Chemo (n = 324)
Median OS, mo	12.8	10.7
(95% CI)	(11.3-15.5)	(9.4-11.9)
HR (98.2% CI)	0.78 (0.62-0.98)	
P value	0.0110	

NIVO + IPI	325	274	232	191	166	129	97	77	55	33	22	12	6	0
Chemo	324	281	229	171	131	93	56	41	23	9	5	2	1	0

- Superior OS with NIVO + IPI vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 36% reduction in the risk of death and a 4.6-month improvement in median OS
  - All randomized: 22% reduction in the risk of death and a 2.1-month improvement in median OS

[a]Minimum follow-up 12.9 months.

FDA approved chemo + nivo AND nivo + ipi for advanced esophageal SCC in May 2022, regardless of PDL1 expression

Chau I, et al. Abstract LBA4001. ASCO 2021 Annual Meeting;
Doki Y et al. N Engl J Med 2022.

First-line Nivolumab in Esophageal Squamous Cell (Checkmate 648)

Treatment-related adverse events

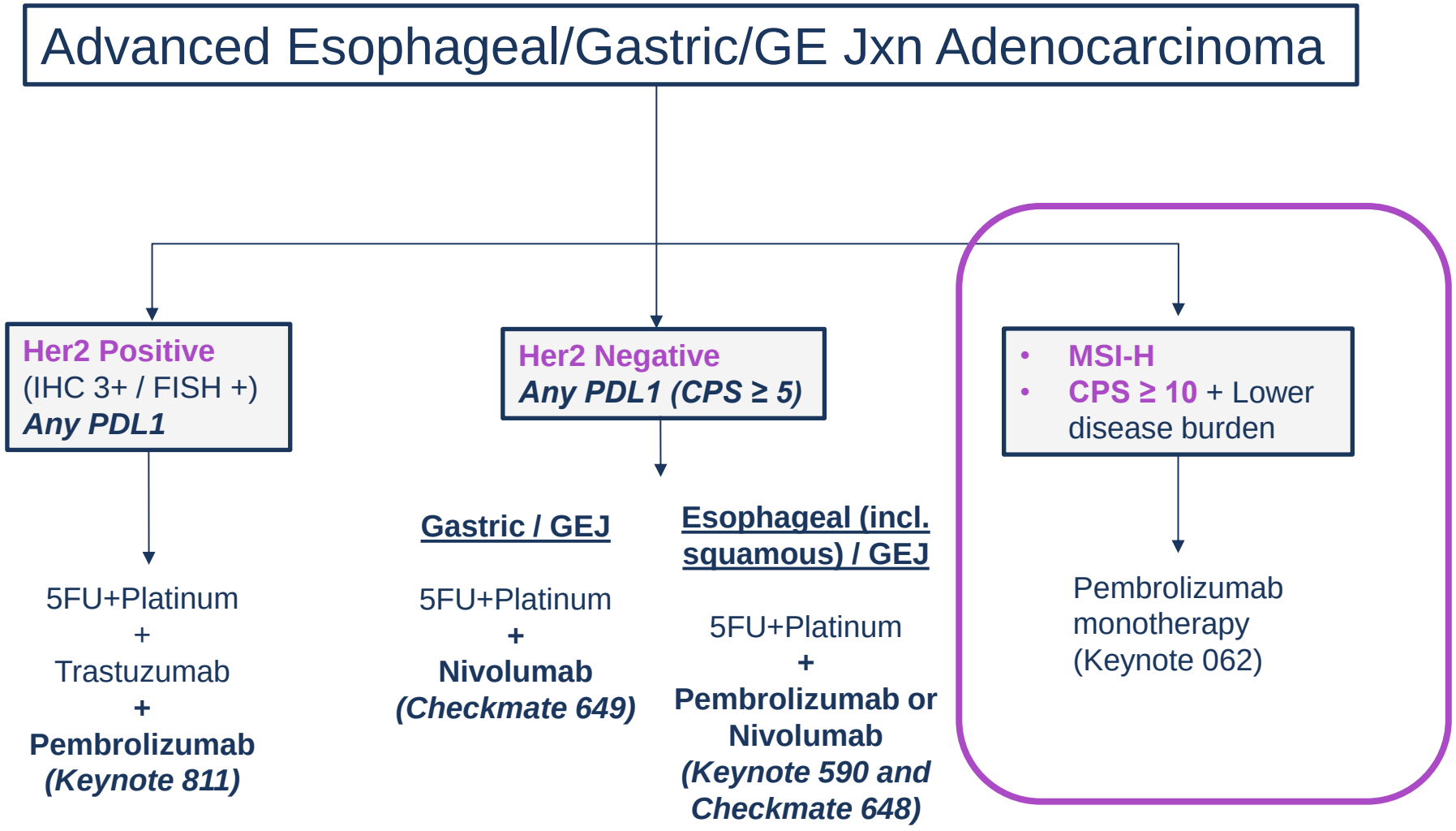
All treated,[a] n (%)	NIVO + chemo (n = 310)		NIVO + IPI (n = 322)		Chemo (n = 304)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAEs[b]	297 (96)	147 (47)	256 (80)	102 (32)	275 (90)	108 (36)
Serious TRAEs[b]	74 (24)	57 (18)	103 (32)	73 (23)	49 (16)	38 (13)
TRAEs leading to discontinuation[b,c]	106 (34)	29 (9)	57 (18)	41 (13)	59 (19)	14 (5)
Treatment-related deaths[d]	5 (2)[e]		5 (2)[f]		4 (1)[g]	

- Most common any-grade TRAEs (≥ 10%) included:
  - NIVO + chemo and chemo arms: nausea, decreased appetite, and stomatitis
  - NIVO+ IPI arm: rash, pruritus, and hypothyroidism
- The incidence of TRAEs in patients with tumor cell PD-L1 ≥ 1% was consistent with all treated patients across all arms

[a]Patients who received ≥ 1 dose of study drug; [b]Assessed in all treated patients during treatment and for up to 30 days after the last dose of study treatment; [c]TRAEs leading to discontinuation of any drug in the regimen; [d]Treatment-related deaths were reported regardless of timeframe; [e]Included 1 event each of pneumonia, pneumatosis intestinalis, acute kidney injury, pneumonitis, and pneumonitis/respiratory tract infection; [f]Included 2 events of pneumonitis and 1 event each of interstitial lung disease, acute respiratory distress syndrome, and pulmonary embolism; [g]Included 1 event each of septic shock, sepsis, acute kidney injury, and pneumonia.

Chau I, et al. Abstract LBA4001. ASCO 2021 Annual Meeting;
Doki Y et al. N Engl J Med 2022.

Initial Treatment - 2024



Takeaways – First-Line Checkpoint Inhibitors

Initial therapy in ADENOCARCINOMA – Nivolumab + Chemo (FOLFOX) if CPS ≥ 5 (Pembro + chemo is an option for CPS ≥ 10)

Pembro monotherapy for patients with MSI-H or CPS ≥ who do not need immediate response / low disease burden

Initial therapy for SQUAMOUS CELL CARCINOMA – Pembrolizumab or Nivolumab + Chemo (FOLFOX)

Nivo + Ipi alone for fit patients with no contraindication who do not need immediate response / low disease burden

Remaining/Evolving Questions:

- What if patients progress quickly on 1L therapy after very little immune checkpoint inhibitor exposure?
- What about patients who recur in the midst of adjuvant therapy?
- What other biomarkers to better predict response/resistance to checkpoint inhibitors?

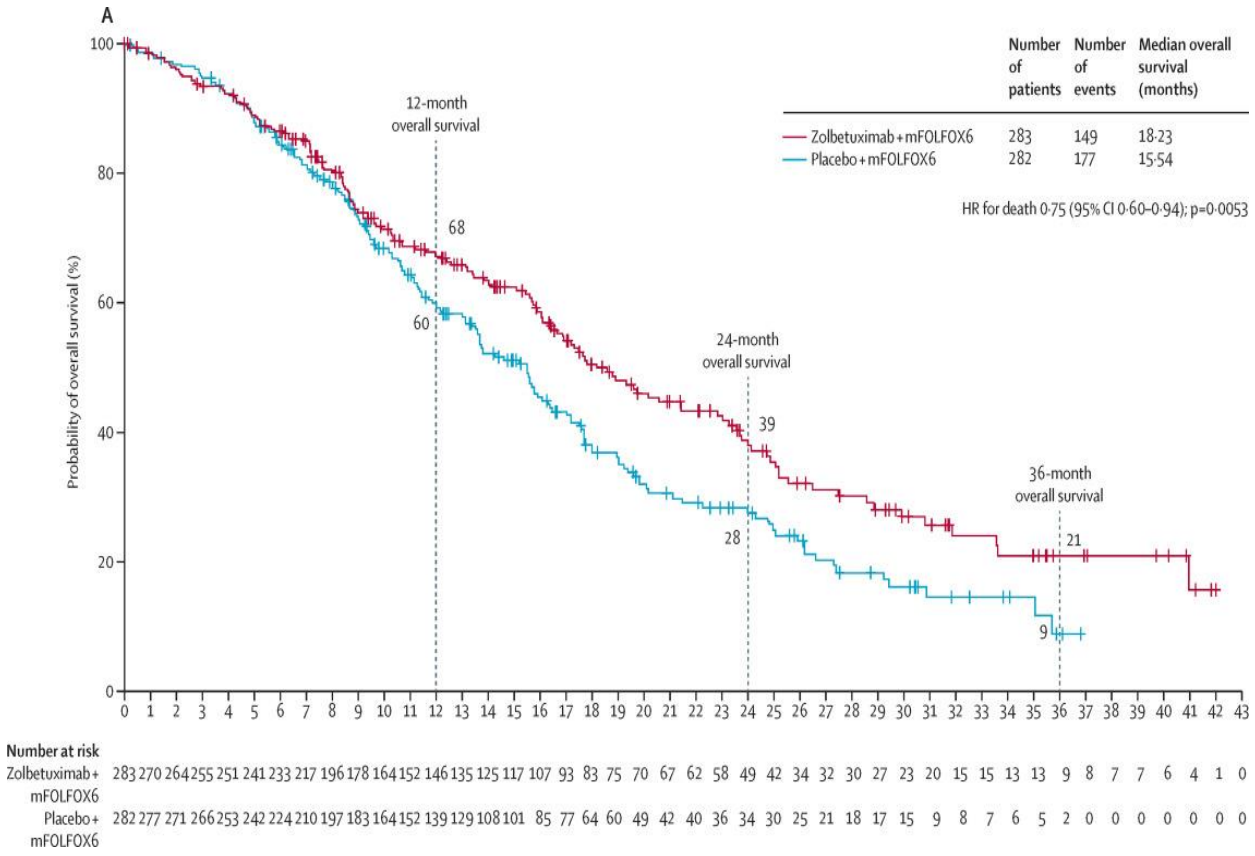
Targeting Claudin 18.2 in Gastric Adenocarcinoma

- Claudin 18.2 expressed in tight junctions exclusively in the gastric mucosa; expression retained in gastric / GEJ cancers
- Zolbetuximab is a monoclonal antibody targeting claudin 18.2
- **First-line GLOW study**: CAPOX + / - Zolbetuximab
- **First-line SPOTLIGHT study**: mFOLFOX6 + / - Zolbetuximab

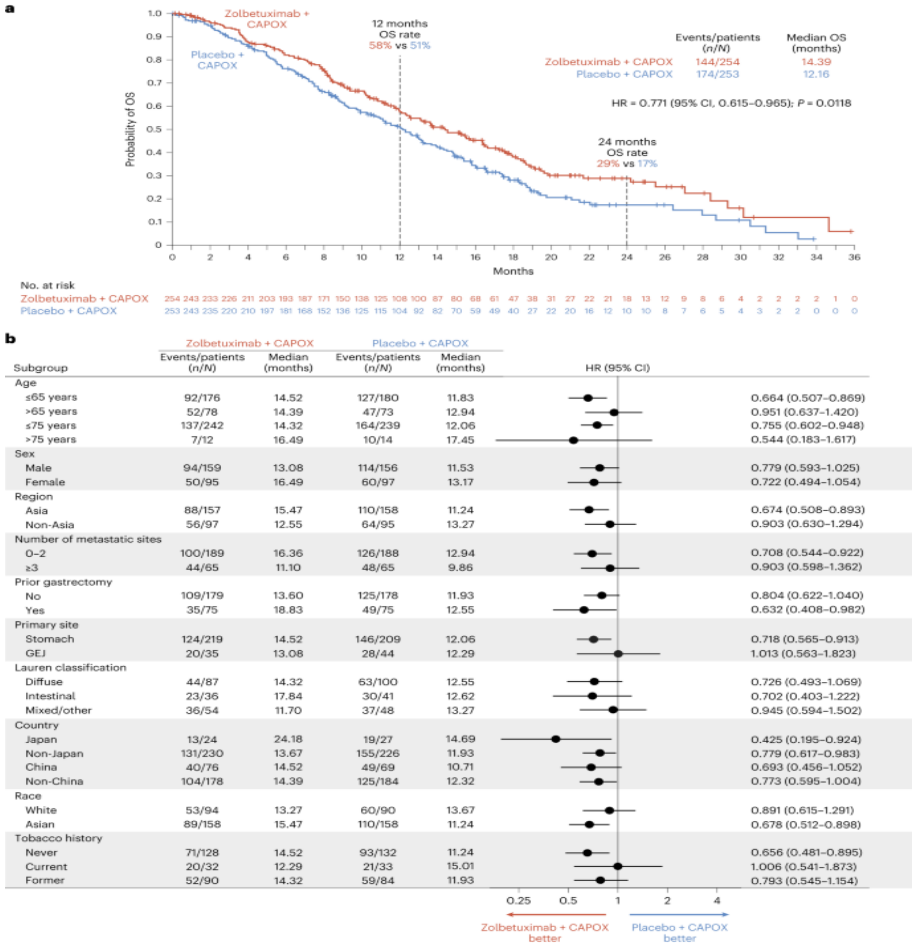
Shitara, K. et al. *Lancet*; 401: 1655–68 , Apr 2023
Shah, M. et al. *Nature Medicine;* volume 29, pages 2133–2141, July 2023

Targeting Claudin 18.2 in Gastric Adenocarcinoma

SPOTLIGHT



GLOW



Shitara, K. et al. *Lancet*; 401: 1655–68 , Apr 2023
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Second Line Therapy in ESO/Gastric Cancers

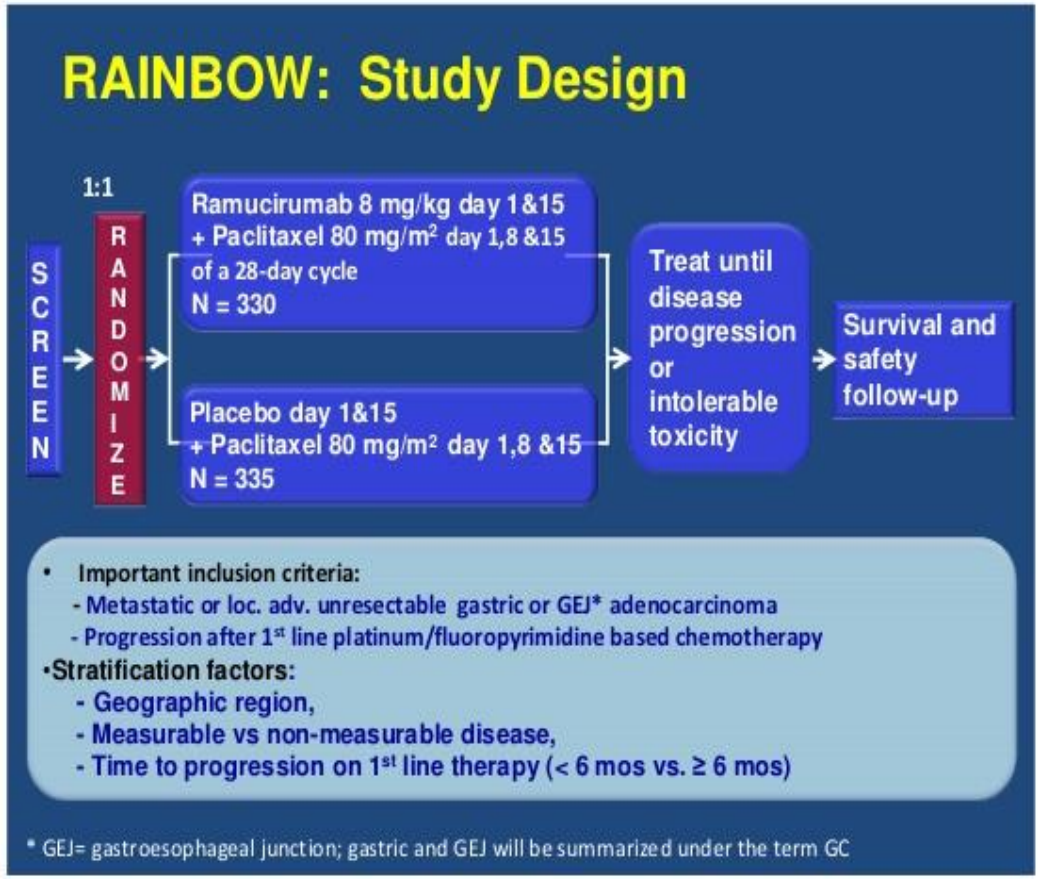
For patients who retain good PS

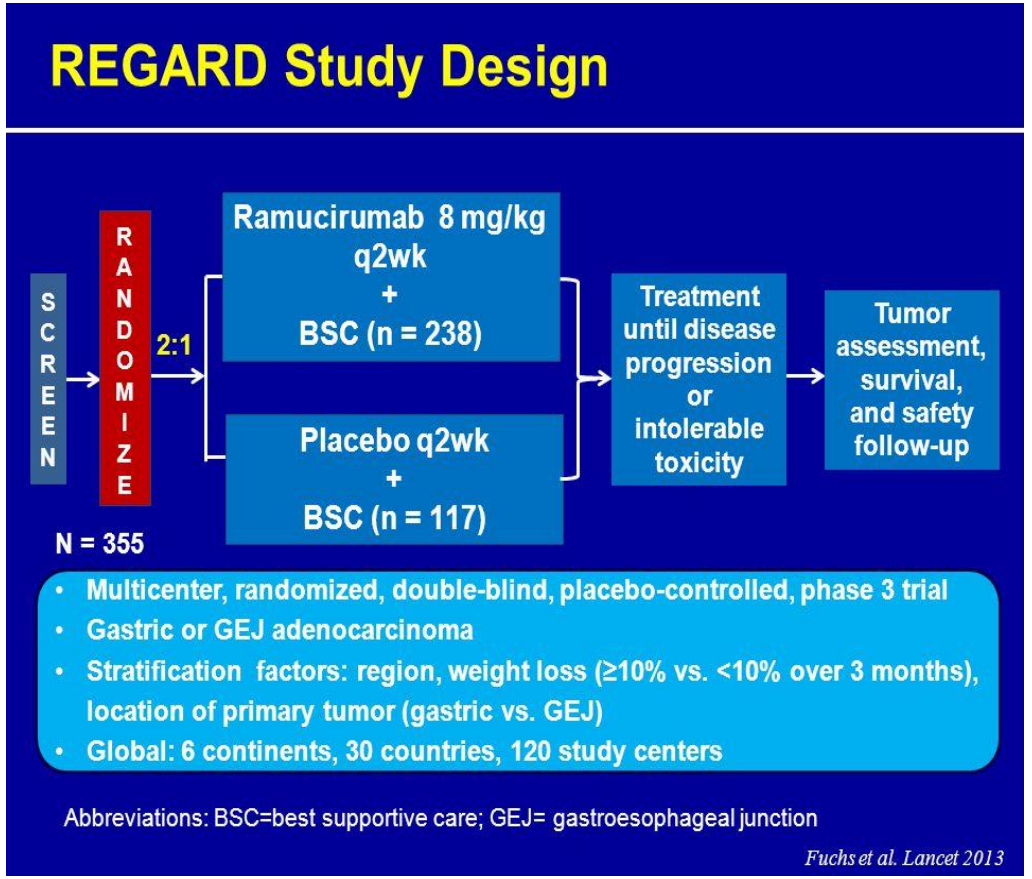
- Paclitaxel (+ Ramucirumab, if adeno)
- Ramucirumab monotherapy (adeno)
- Irinotecan
- Trifluridine/Tipiracil (Lonsurf, TAS-102) (Gastric/GEJ)
- *Pembrolizumab / Nivolumab*

How to choose ?

- Neuropathy
- Bleeding from primary tumor
- Pace and extent of disease progression
- First-line checkpoint inhibitor receipt?

Ramucirumab: REGARD and RAINBOW





Fuchs, C et al. *Lancet*. Oct 3, 2013
Wilke, H et al. Lancet Oncology. 2014, 15(11): 1224-35.

Ramucirumab: REGARD and RAINBOW

RAINBOW

	Ram + Paclitaxel	Placebo + Paclitaxel
RR	28%	16%
DCR	80%	64%
PFS	4.4 mo	2.86 mo
OS	**9.63 mo**	**7.36 mo**

REGARD

	Ram	Placebo
PFS	2.1 mo	1.3 mo
OS	**5.2 mo**	**3.8 mo**

Fuchs, C et al. *Lancet*. Oct 3, 2013
Wilke, H et al. Lancet Oncology. 2014, 15(11): 1224-35.

Ramucirumab: Adverse Events

	Ramucirumab plus paclitaxel (n=327)				Placebo plus paclitaxel (n=329)			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Bleeding or haemorrhage	123 (38%)	12 (4%)	1 (<1%)	1 (<1%)	51 (16%)	4 (1%)	2 (<1%)	2 (<1%)
Proteinuria	51 (16%)	4 (1%)	0	0	20 (6%)	0	0	0
Liver injury or failure	39 (12%)	12 (4%)	3 (<1%)	0	28 (9%)	11 (3%)	2 (<1%)	0
Hypertension	34 (10%)	48 (15%)	0	0	10 (3%)	9 (3%)	0	0
Gastrointestinal haemorrhage†	21 (6%)	10 (3%)	1 (<1%)	1 (<1%)	15 (5%)	3 (<1%)	1 (<1%)	1 (<1%)
Infusion-related reaction	17 (5%)	2 (<1%)	0	0	12 (4%)	0	0	0
Renal failure	16 (5%)	4 (1%)	2 (<1%)	0	11 (3%)	0	1 (<1%)	2 (<1%)
Congestive heart failure	6 (2%)	2 (<1%)	0	0	2 (<1%)	1 (<1%)	0	1 (<1%)
Venous thromboembolic events	5 (2%)	7 (2%)	0	1 (<1%)	7 (2%)	8 (2%)	1 (<1%)	2 (<1%)
Arterial thromboembolic events	3 (<1%)	1 (<1%)	2 (<1%)	0	2 (<1%)	2 (<1%)	0	1 (<1%)
Gastrointestinal perforation	0	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0	0	0

Fuchs, C et al. *Lancet*. Oct 3, 2013
Wilke, H et al. Lancet Oncology. 2014, 15(11): 1224-35.

3rd Line: Trifluridine/Tipiracil

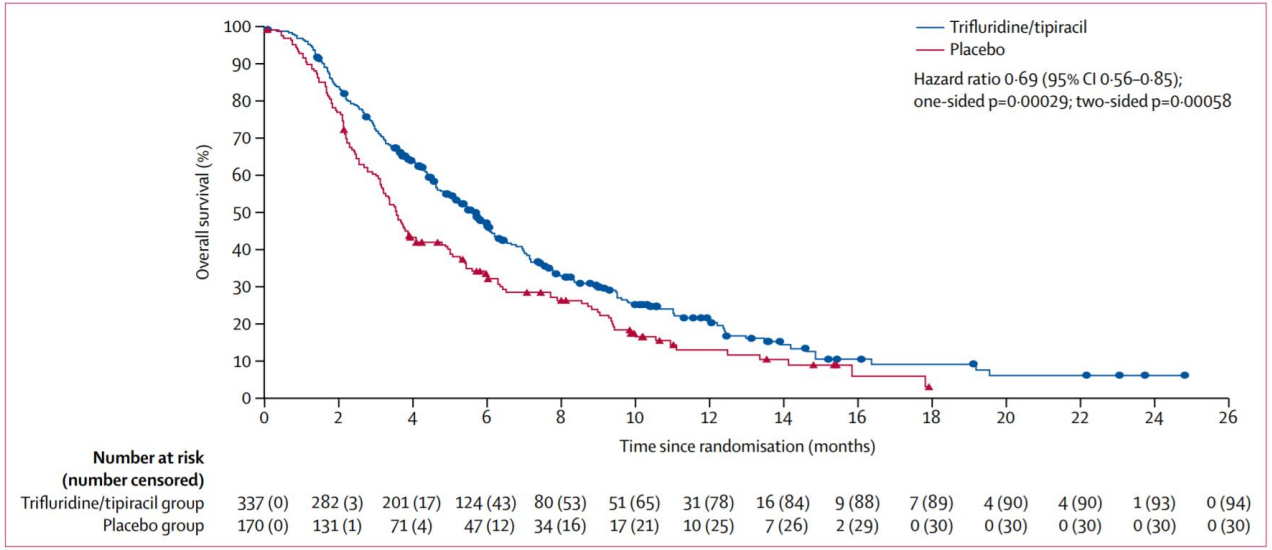


Figure 2: Overall survival in the intention-to-treat population

- Ph 3 RCT trifluridine/tipircil vs placebo for gastric/GEJ, ≥2 lines therapy
- **Median OS 5.7 vs 3.6 mo**
- Median PFS 2.0 vs 1.8 mo
- ORR 4% vs 2%
- **FDA approved in 3rd line setting for gastric/GEJ**

Shitara, K. et al. Lancet Oncol 2018; 19: 1437–48

Take – Home Points – Metastatic Gastric / Esophageal Cancer

1. 5-FU + Platinum (2 drugs, not 3 drugs) is the chemotherapy backbone

2. **Her2 positive**: Chemo + Trastuzumab (+ Pembro if CPS ≥ 1); Fam-trastuzumab-deruxtecan in second line or later

3. **Her2 negative gastric/eso adenocarcinoma**: Chemo + Nivo in CPS ≥ 5 or Chemo + Pembro in CPS ≥ 10]

4. **Squamous cell esophageal cancer**: Chemo + Pembro or Nivo; Nivo + Ipi

5. 2nd line and beyond: Consider previous toxicities

Fred Hutch Cancer Center

Thank you