Esophageal and Gastric Cancer

Comprehensive Oncology Board Review

2021

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Objectives

- Epidemiology and Risk Factors
- Diagnosis, and Staging
- Pathology
- Stage I-III Esophageal Cancer
- Stage I-III Gastric Cancer
- Advanced Esophageal and Gastric Cancer

New FDA Approvals 2021

Trastuzumab deruxtecan

- Jan 2021: Metastatic gastric / GE jxn after trastuzumab

Nivolumab

- April 2021: **First-line** metastatic gastric/eso adenocarcinoma
- May 2021: **Adjuvant** therapy (esophageal / GE jxn)

Pembrolizumab

- May 2021: **First-line** esophageal/GE jxn cancers
- May 2021 (Accelerated approval): **First-line Her2+** metastatic gastric / GE jxn

Epidemiology and Risk Factors

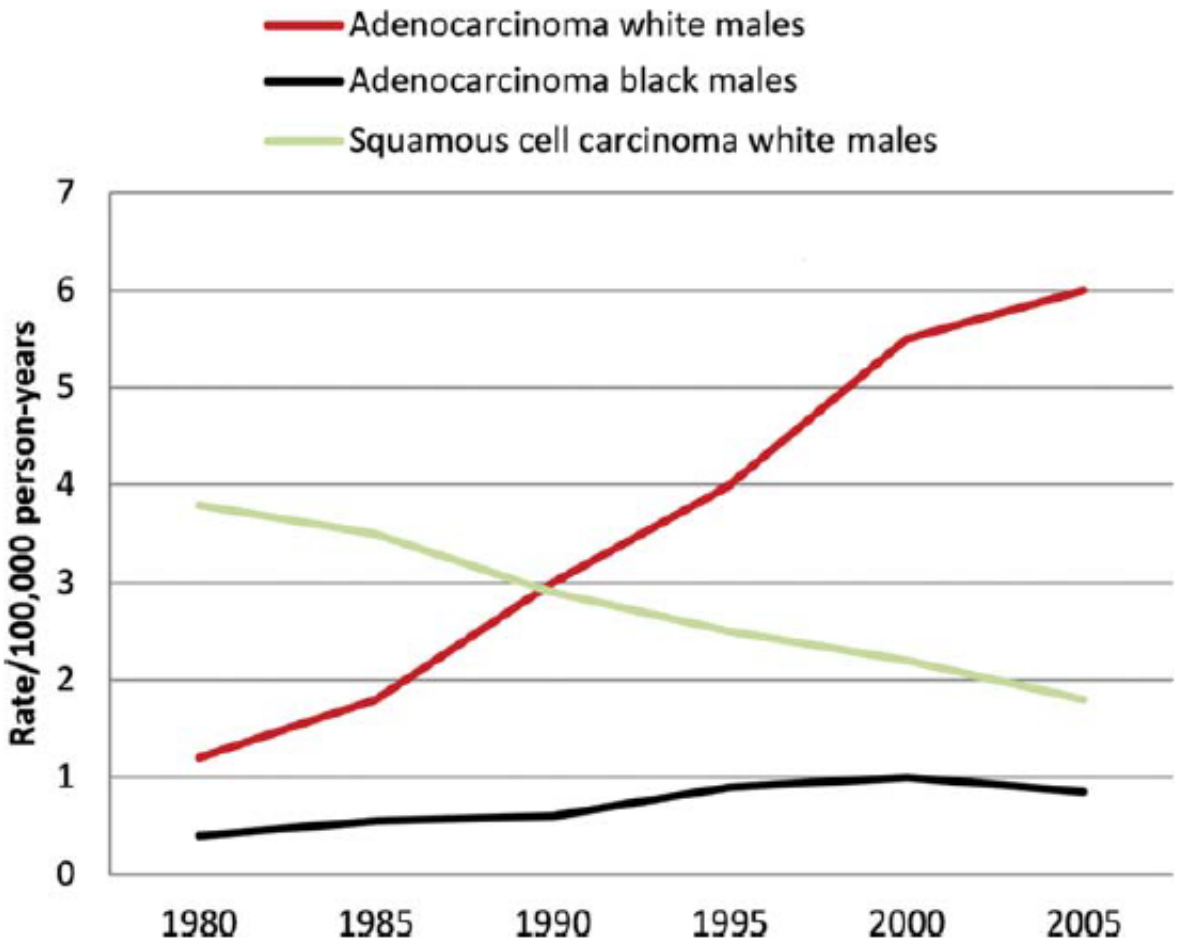
Incidence and Mortality - 2021

	Estimated new cases			Estimated deaths		
	Male	Female	**TOTAL**	Male	Female	**TOTAL**
Esophageal	15,310	3,950	**19,260**	12,410	3,120	**15,530**
Gastric	16,160	10,400	**26,560**	6,740	4,440	**11,180**

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, 2021

Esophageal Cancer Epidemiology



FRED HUTCH

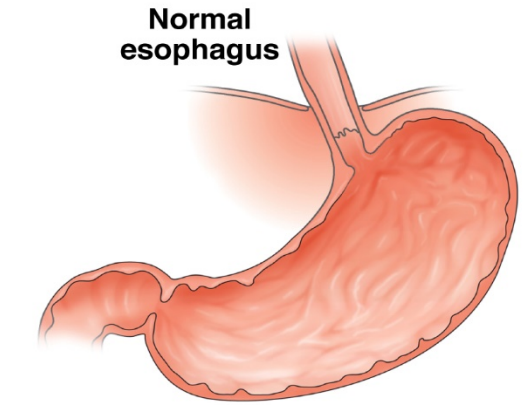
Lagergren J and Lagergren P. *Cancer*. 2013; 64: 232-248.

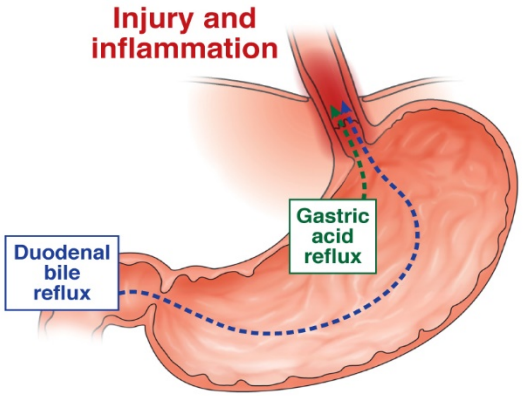
Esophageal Cancer: Risk Factors

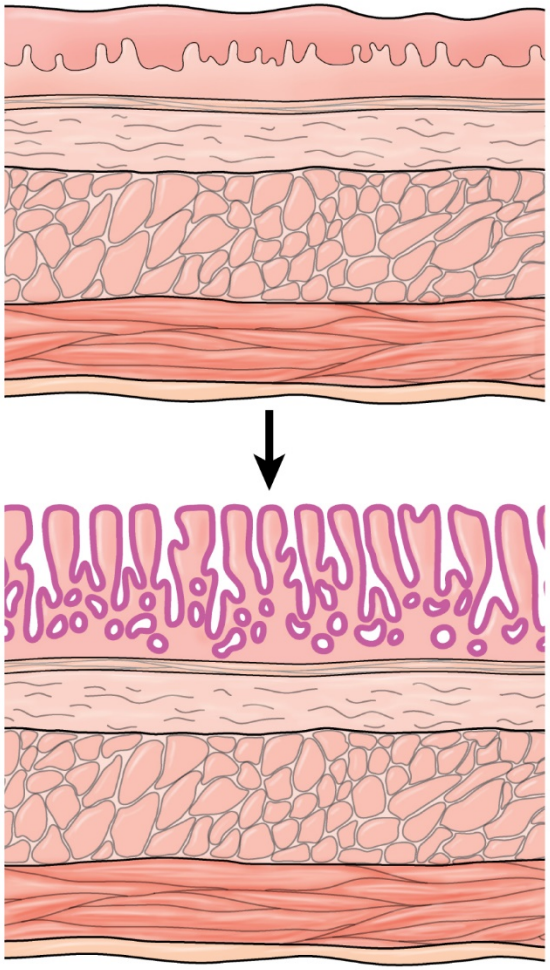
Squamous Cell Carcinoma	Adenocarcinoma
•***Tobacco (5-10 x risk)***	•Tobacco (2 x risk)
•***EtOH (3-7 x risk)***	•EtOH (1.2 x risk)
•Betel nut	•***GERD (7.7 x risk)***
•Hot liquids – burns	•***Obesity (3 x risk)***
•Nitroso compounds	

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







A Normal squamous epithelium

B Metaplastic columnar tissue (BE)

6.6% Annual risk for adenocarcinoma with HIGH GRADE DYSPLASIA

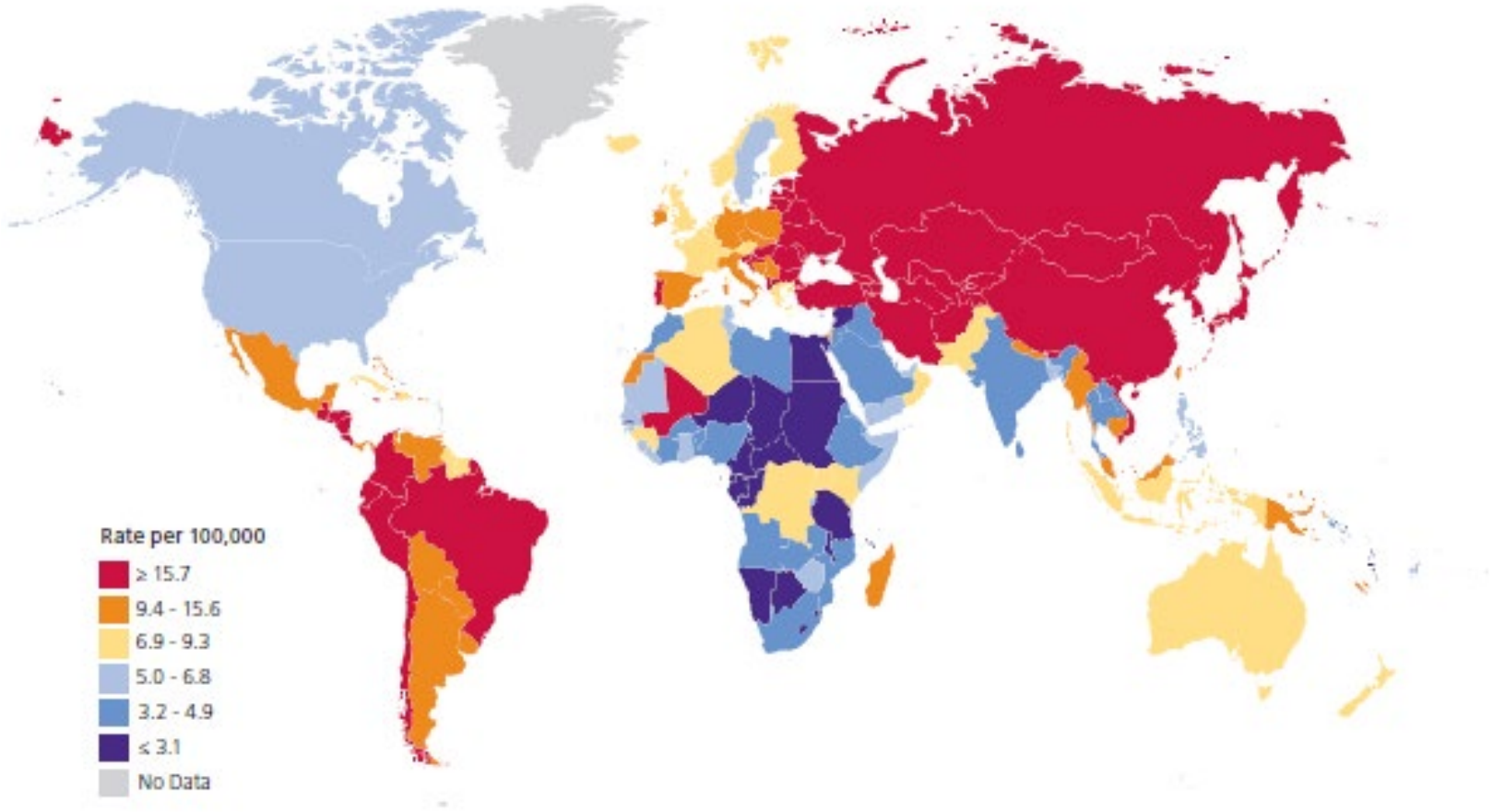
Morales CP et al. *Lancet*. 360: 9345, 2002
American Gastroenterological Association

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



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

Gastric Cancer: Asian vs. Western

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 in Asia***

Diagnosis and Staging

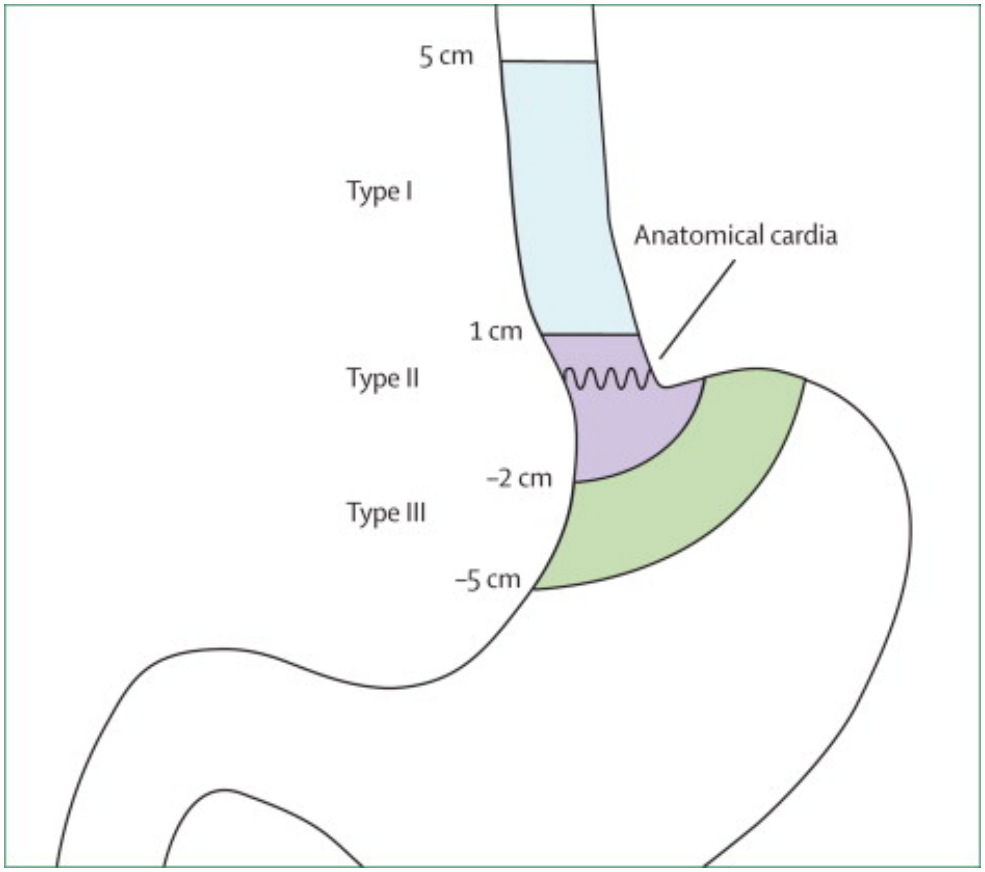
Esophageal Cancer Staging Workup

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

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

M-stage: CT, PET, staging laparoscopy (GE jxn or cardia)

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 Principles

- Different stage groupings for SCC vs. Adeno
- TNM, Grade, and Location (Squamous only)
- Nomenclature:
  - Clinical staging (u or c prefix)
  - Pathologic staging after chemoRT (yp prefix)
- Example: uT3N1 (stage IIIB) distal esophageal adeno → chemoRT → surgery → ypT1N0

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

Squamous Cell Ca: AJCC 8th ed

Stage Groupings: Squamous Cell Carcinoma

Stage	T	N	M	G	Location
Stage 0	Tis	N0	M0#	N/A	Any
Stage IA	T1a	N0	M0	1 or X	Any
Stage IB	T1a	N0	M0	2 or 3	Any
	T1b	N0	M0	Any	Any
	T2	N0	M0	1	Any
Stage IIA	T2	N0	M0	2, 3, or X	Any
	T3	N0	M0	Any	Lower
	T3	N0	M0	1	Upper, middle
Stage IIB	T3	N0	M0	2 or 3	Upper, middle
	T3	N0	M0	X	Any
	T3	N0	M0	Any	location X
	T1	N1	M0	Any	Any
Stage IIIA	T1	N2	M0	Any	Any
	T2	N1	M0	Any	Any
Stage IIIB	T2	N2	M0	Any	Any
	T3	N1-2	M0	Any	Any
	T4a	N0-1	M0	Any	Any
Stage IVA	T4a	N2	M0	Any	Any
	T4b	N0-2	M0	Any	Any
	Any	N3	M0	Any	Any
Stage IVB	Any T	Any N	M1	Any	Any

Adenocarcinoma: AJCC 8th ed

Stage Grouping: Adenocarcinoma

Stage	T	N	M	G
Stage 0	Tis (HGD#)	N0	M0	N/A
Stage IA	T1	N0	M0	1 or X
Stage IB	T1a	N0	M0	2
	T1b	N0	M0	1, 2, or X
Stage IC	T1	N0	M0	3
	T2	N0	M0	1 or2
Stage IIA	T2	N0	M0	3 or X
Stage IIB	T1	N1	M0	Any
	T3	N0	M0	Any
Stage IIIA	T1	N2	M0	Any
	T2	N1	M0	Any
Stage IIIB	T2	N2	M0	Any
	T3	N1-2	M0	Any
	T4a	N0-1	M0	Any
Stage IVA	T4a	N2	M0	Any
	T4b	N0-2	M0	Any
	Any	N3	M0	Any
Stage IVB	Any T	Any N	M1	Any

Gastric Cancer Staging

Endoscopy/Endoscopic ultrasound

- Lesser curve / proximal cancers
- Diffuse-type / linitis plastica
  - ? EUS – may not be helpful
  - Multiple biopsies

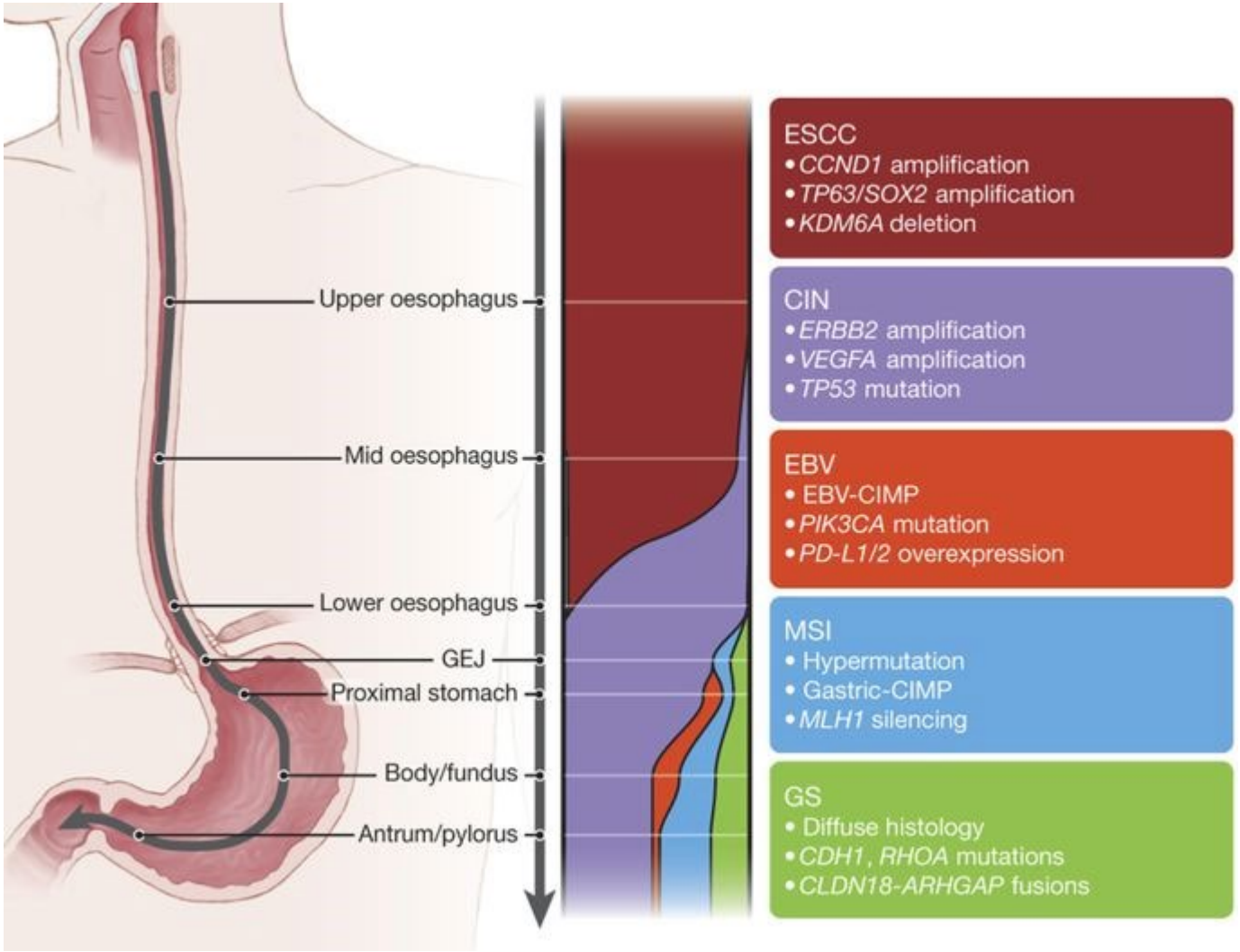
Diagnostic laparoscopy

- Evaluation of the peritoneum
- + cytology = pM1

College of American Pathologists June 2017

Pathology

Upper GI Cancer Molecular Subtypes



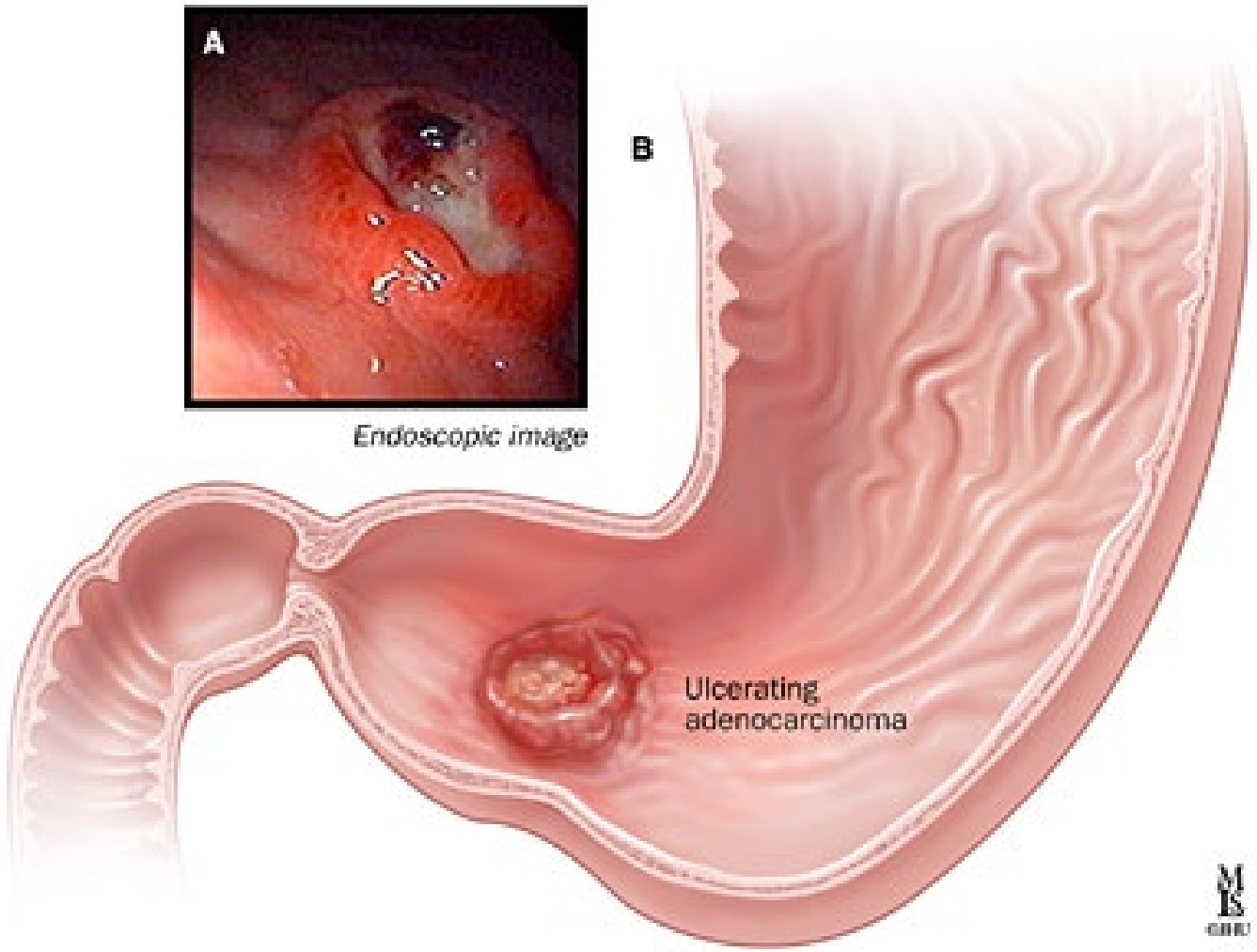
The Cancer Genome Atlas Research Network. *Nature*, 2017. 541: 69–175

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



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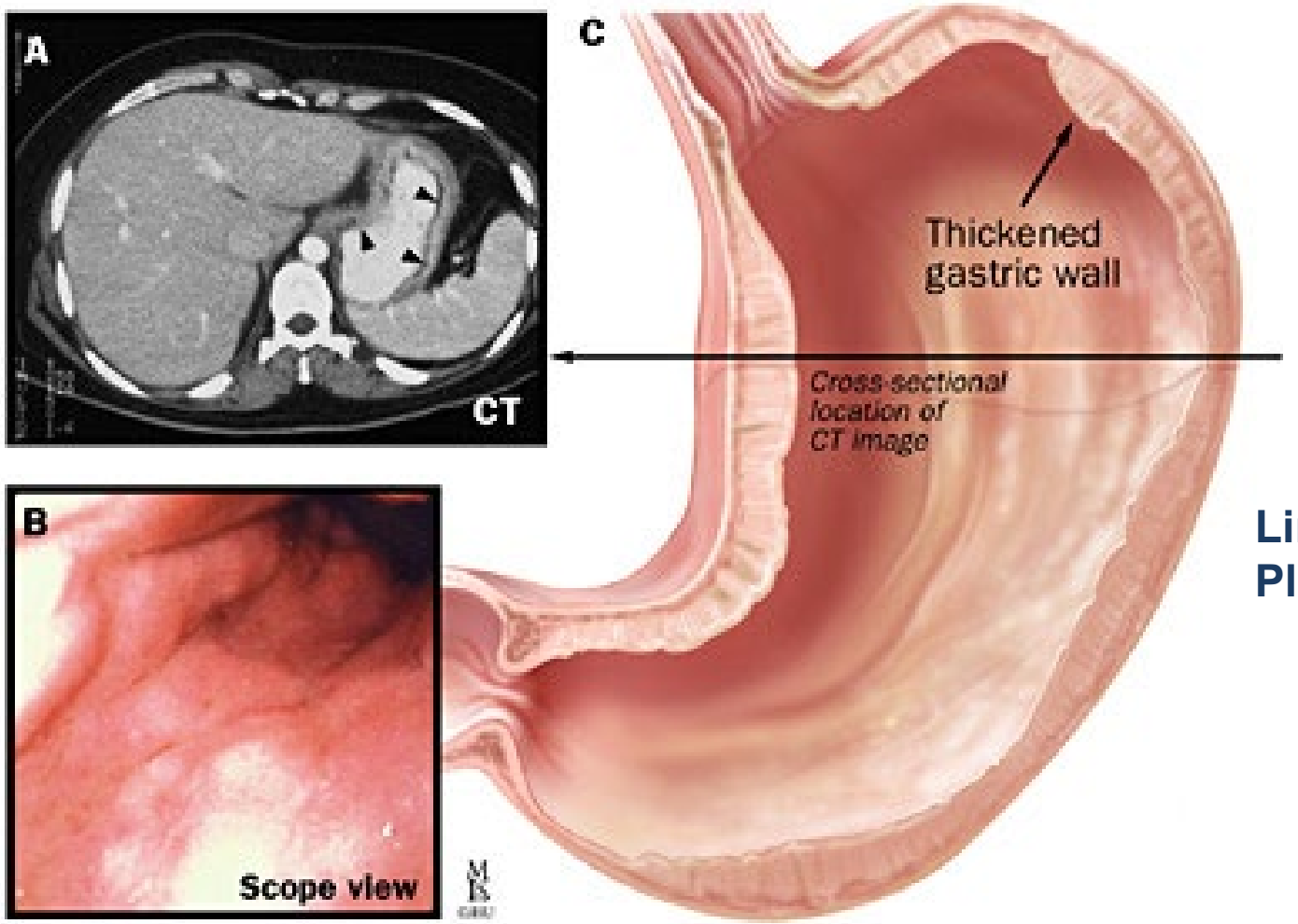
Diffuse Type Adenocarcinoma



Linitis Plastica

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.
- Unlike melanoma or lung cancer, membranous PD-L1 expression is rare in esophageal and gastric cancers and occurs predominantly on infiltrating immune cells.

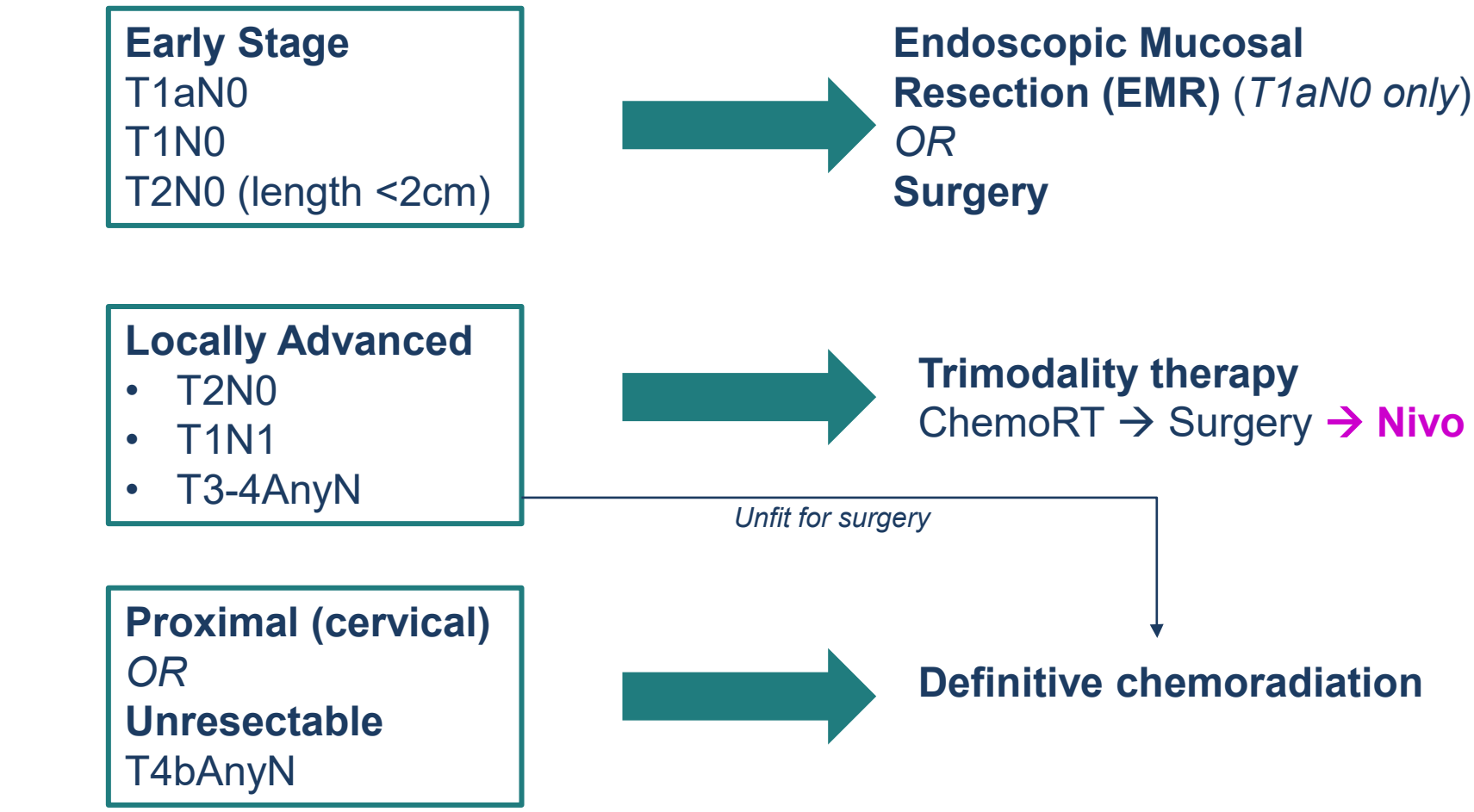
$$\text{CPS} = \frac{\#\ \text{PD-L1 positive Tumor Cells + Immune Cells}}{\#\ \text{Viable Tumor Cells}} \times 100$$

Pembro / Keynote studies = PD-L1 **IHC 22C3** PharmaDx

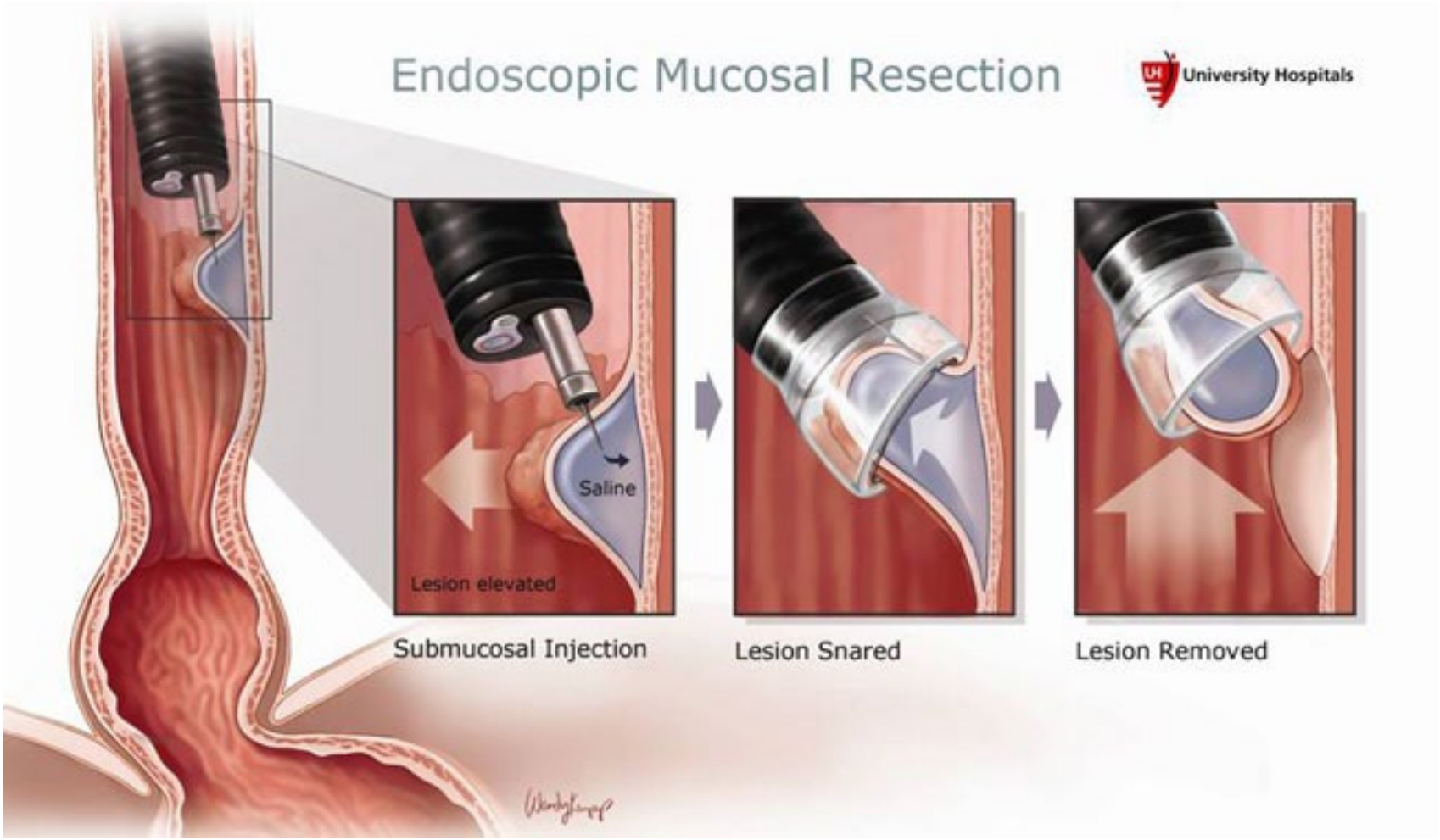
Nivo / BMS gastric studies = PD-L1 **IHC 28-8** PharmaDx

Stage I-III Esophageal Cancer

Esophageal Cancer Treatment Algorithm



Endoscopic Mucosal Resection – T1a lesions



Surgery (Esophagectomy)

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

Surgery should be done at a high volume center

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

Dutch CROSS Trial

ORIGINAL ARTICLE

Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

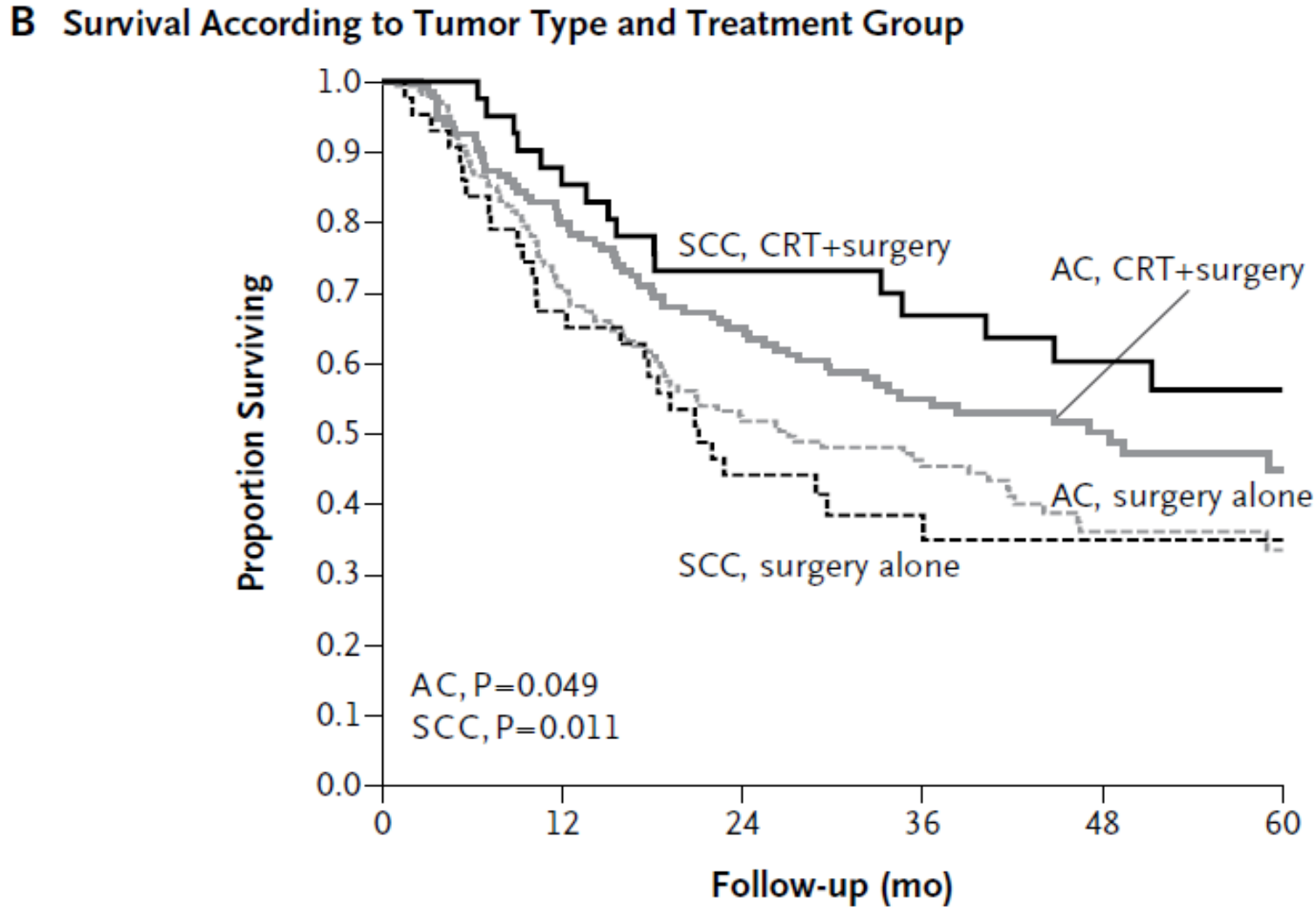
P. van Hagen, M.C.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg, M.I. van Berge Henegouwen, B.P.L. Wijnhoven, D.J. Richel, G.A.P. Nieuwenhuijzen, G.A.P. Hospers, J.J. Bonenkamp, M.A. Cuesta, R.J.B. Blaisse, O.R.C. Busch, F.J.W. ten Kate, G.-J. Creemers, C.J.A. Punt, J.T.M. Plukker, H.M.W. Verheul, 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

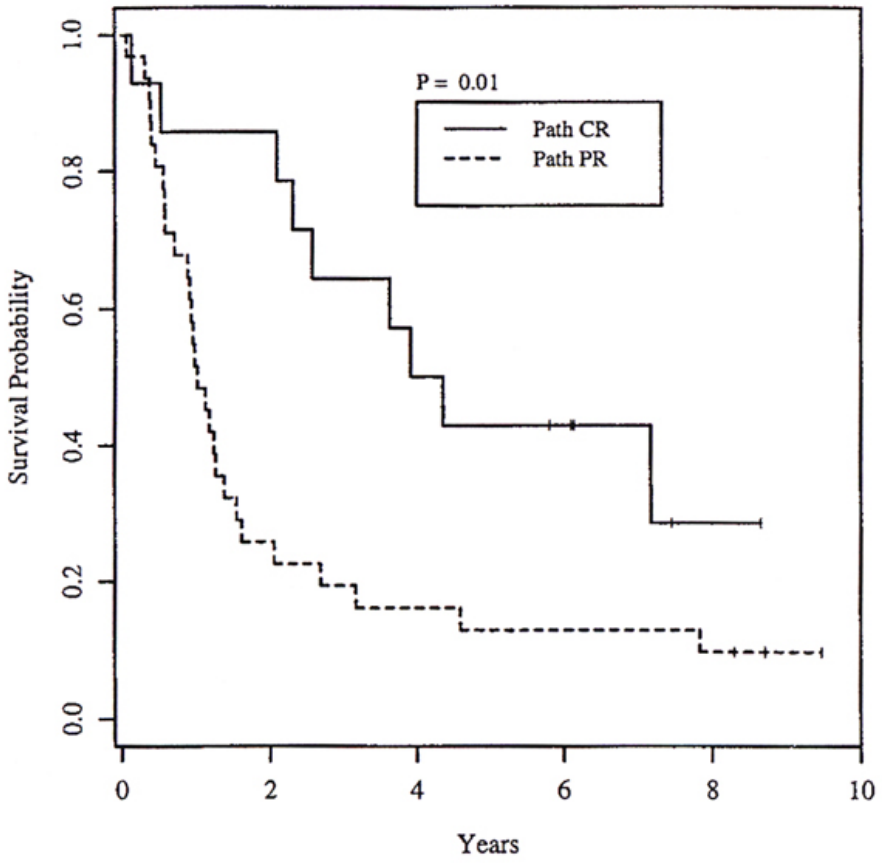
	Surgery alone	CRT + surgery
N	188	175
R0 resection rate	67%	92.3%
Path complete response	N/A	32%
Med survival	**26 months**	**49 months**
1-year survival	70%	82%
3-year survival	48%	59%
Anastomotic leakage	25%	22%
In-hospital mortality	3.8%	3.4%

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

Pathologic Response after Trimodality Therapy



Path CR vs. Residual Disease

Median Survival (49.7 vs. 12 months)

3-yr survival (64% vs. 19%)

Urba S. *J Clin Oncol*. 19(2), 2001

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

ASCO 2020: Addition of trastuzumab does not improve DFS – HR 0.97, 95% CI 0.69, 1.36)

Safran H. et al. *Journal of Clinical Oncology* 38, no. 15_suppl (May 20, 2020) 4500-4500.

What to do after Trimodality therapy?

Nutrition / Dietary Counseling – Learning how and what to eat!

Routine Surveillance

NCCN Guidelines

- Years 1-2: q3-4 month clinical assessment and labs
- Years 3-5: q6 month clinical assessment and labs
- Years 1-5: Annual CT imaging

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

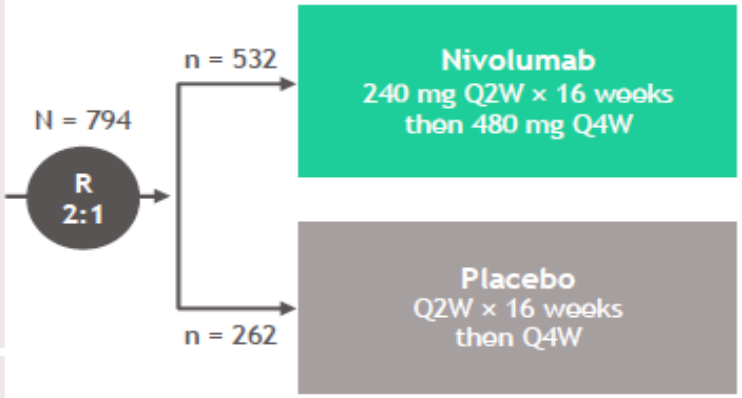
- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

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])



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).

Patient Characteristics

Baseline characteristics

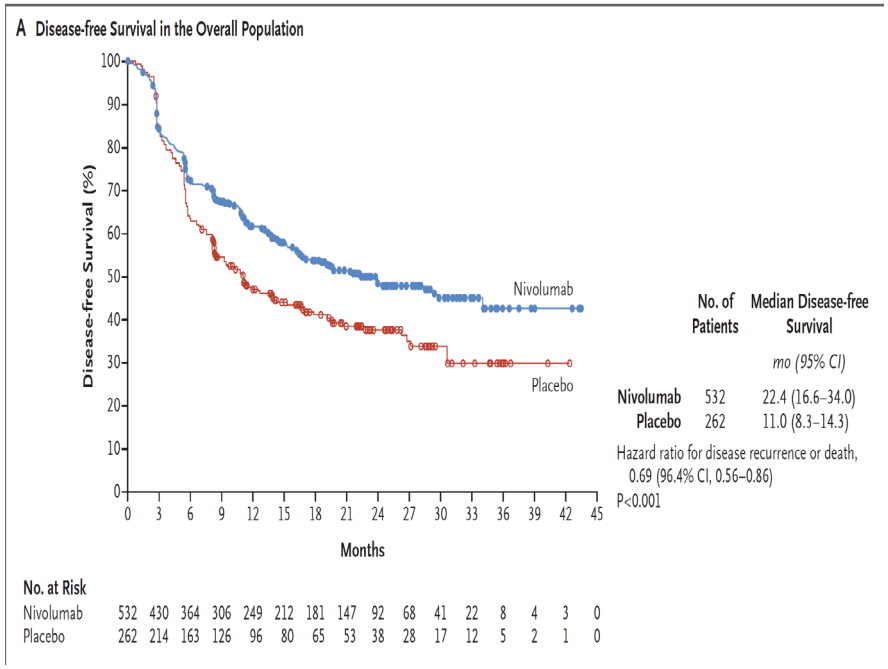
	Nivolumab (n = 532)	Placebo (n = 262)
Median age (range), years	62.0 (26-82)	61.0 (26-86)
Male, %	84	85
Race,[a] %		
White	81	82
Asian	16	13
ECOG PS, %		
0	58	60
1	42	40
Disease stage at initial diagnosis, %		
II	34	38
III	66	62
Tumor location, %		
EC	60	59
GEJC	40	41
Histology, %		
Squamous cell carcinoma	29	29
Adenocarcinoma	71	71
Pathologic lymph node status ≥ ypN1, %	57	58
Tumor cell PD-L1 expression,[b] %		
≥ 1%	17	15
< 1%	70	75
Indeterminate/nonevaluable	13	10

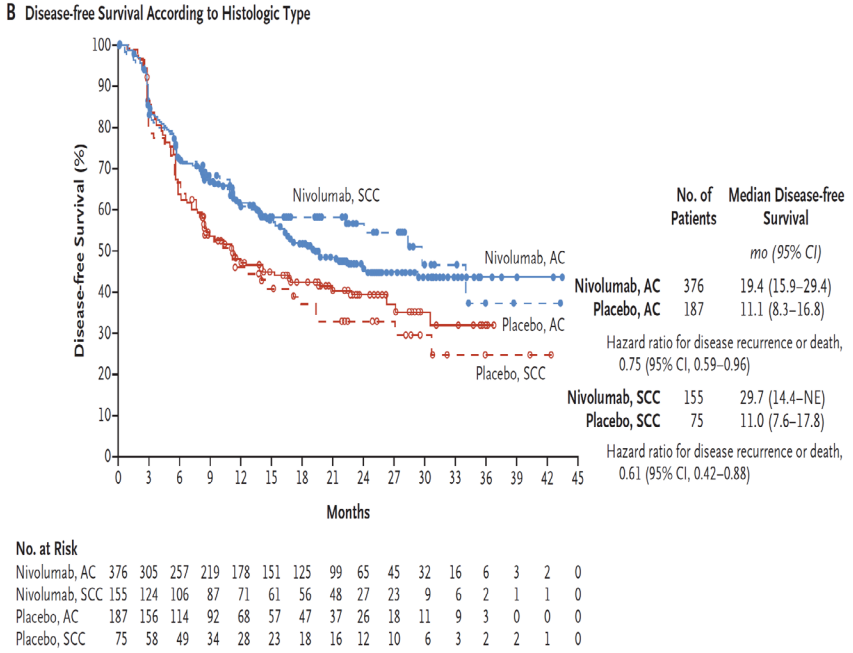
[a]Other races not shown; [b]Tumor cell PD-L1 expression determined from surgical specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako).

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; TPS did not matter

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

BMS 577 Takeaways

New Standard of care? YES (FDA Approval May 2021)

Timing post surgery? Allowed 16 weeks …

Use in pathCR? NO

PDL1 status? doesn't seem to matter

What about early recurrences?

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

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 tube feedings preferred in the short term preoperatively

Take-home points: Esophageal Cancer

- Endoscopic resection for T1a lesions
- For T2+ or N1+ tumors, **trimodality therapy** is still the standard of care
- Trastuzumab does not improve DFS when added to trimodality therapy in Her2 + patients
- **Nivolumab post chemoRT** – new standard of care in patients with residual pathologic disease

Stage I-III Gastric Cancer

Gastric Cancer Treatment Algorithm

Early Stage
- T1-T2N0

→ **Surgery**

Locally Advanced
- T1-2N1
- T3-4AnyN

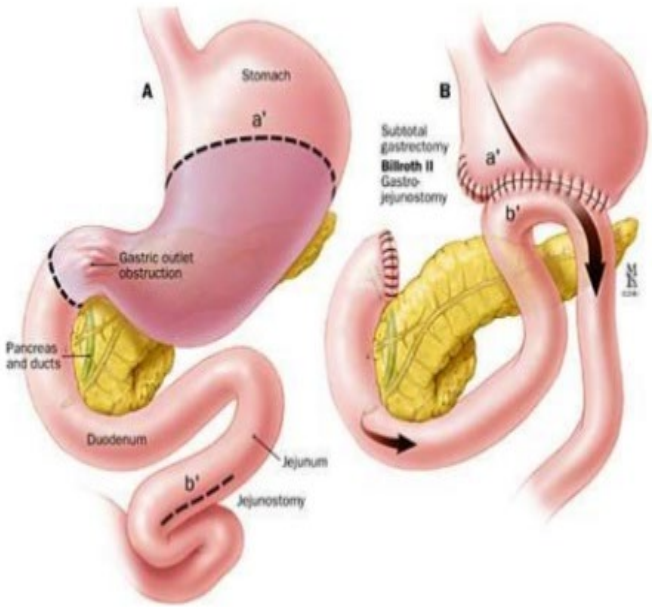
→ **Perioperative chemo**
OR
Postoperative chemo *(Asia)*
OR
Postoperative chemoRT
(margin positive)

Peritoneal washings positive
AnyTAnyNpM+
(cytology)

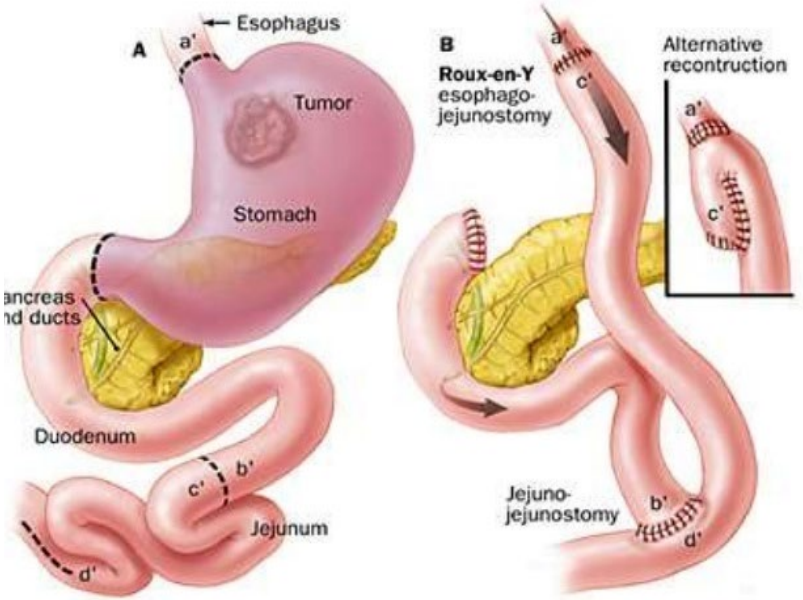
→ **Chemotherapy alone**
(consider surgery in very fit patients who clear peritoneal cytology after upfront chemo)

Gastric Resection

Distal Gastrectomy



Total Gastrectomy



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

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

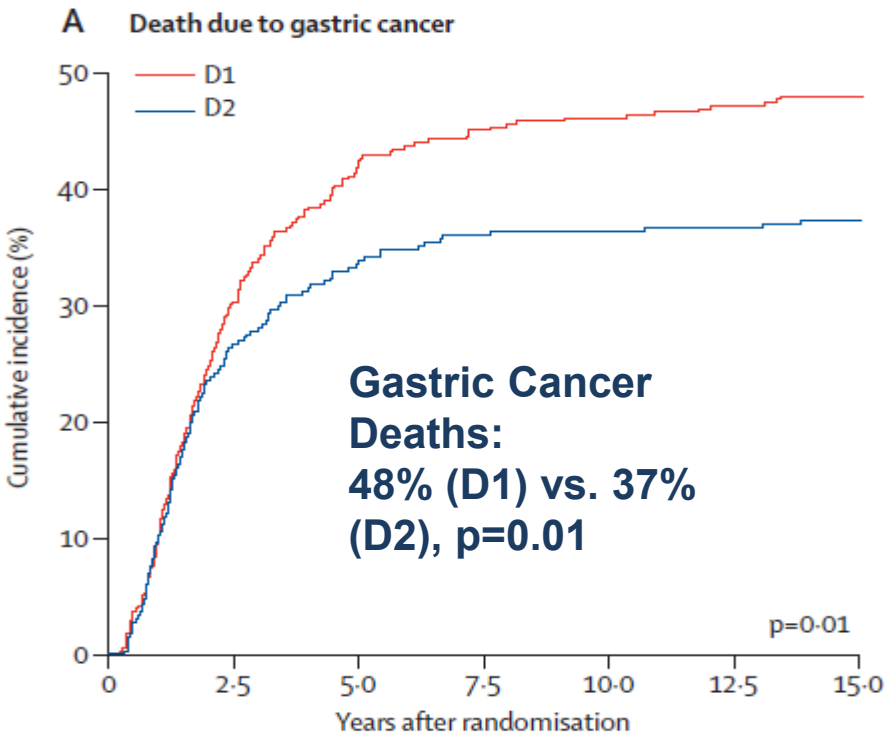
The Dutch Gastric Cancer Group: D1 vs. D2

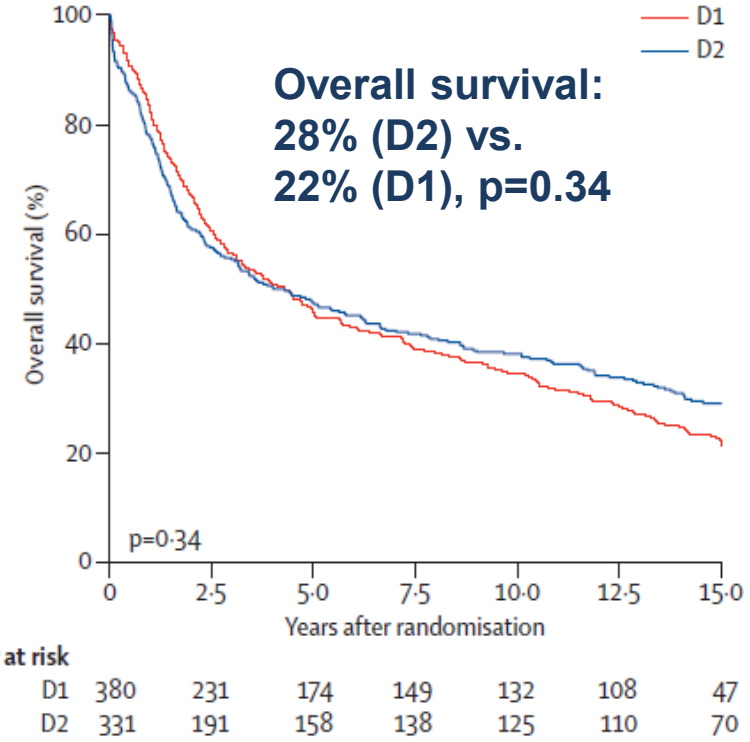
711 patients undergoing curative resection of gastric cancer

	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





Number at risk

D1	380	231	174	149	132	108	47
D2	331	191	158	138	125	110	70

- High rates of over/under dissection
- 45% node negative

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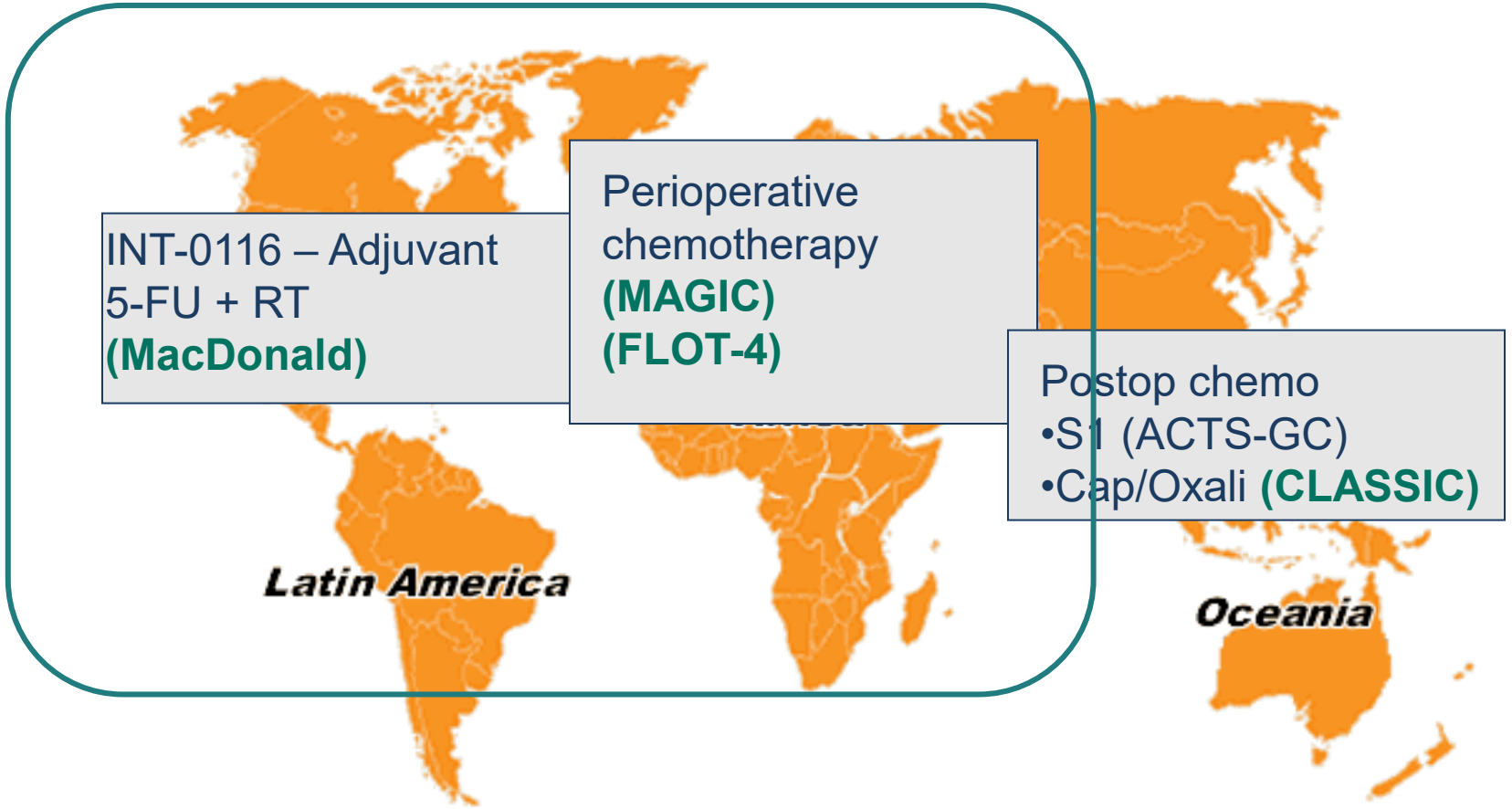
Songun, I et al. Lancet Oncology. 2010; 11:439-49.

D1 vs. D2 Lymph Node Dissection

D2 lymph node dissection is preferred over D1 dissection, only when the surgery can be performed without increasing morbidity

Adjuvant and Neoadjuvant Treatment

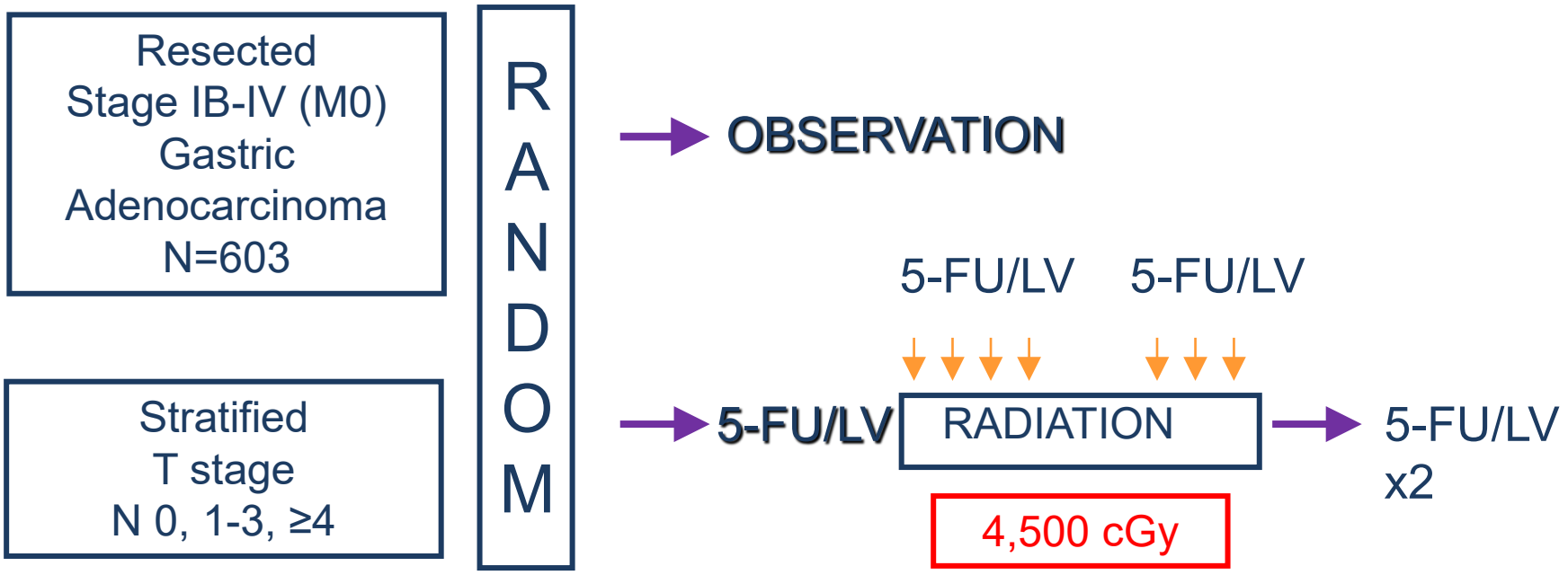


Sasako, M. et al. *J Clin Oncol*. 2011; 29(33): 4387
Cunningham, D et al. *NEJM*. 2006; 355(1): 11
MacDonald, JS et al. *NEJM*. 2001; 345(10): 725

Adjuvant ChemoRT: INT 0116/SWOG 9008

SCHEMA

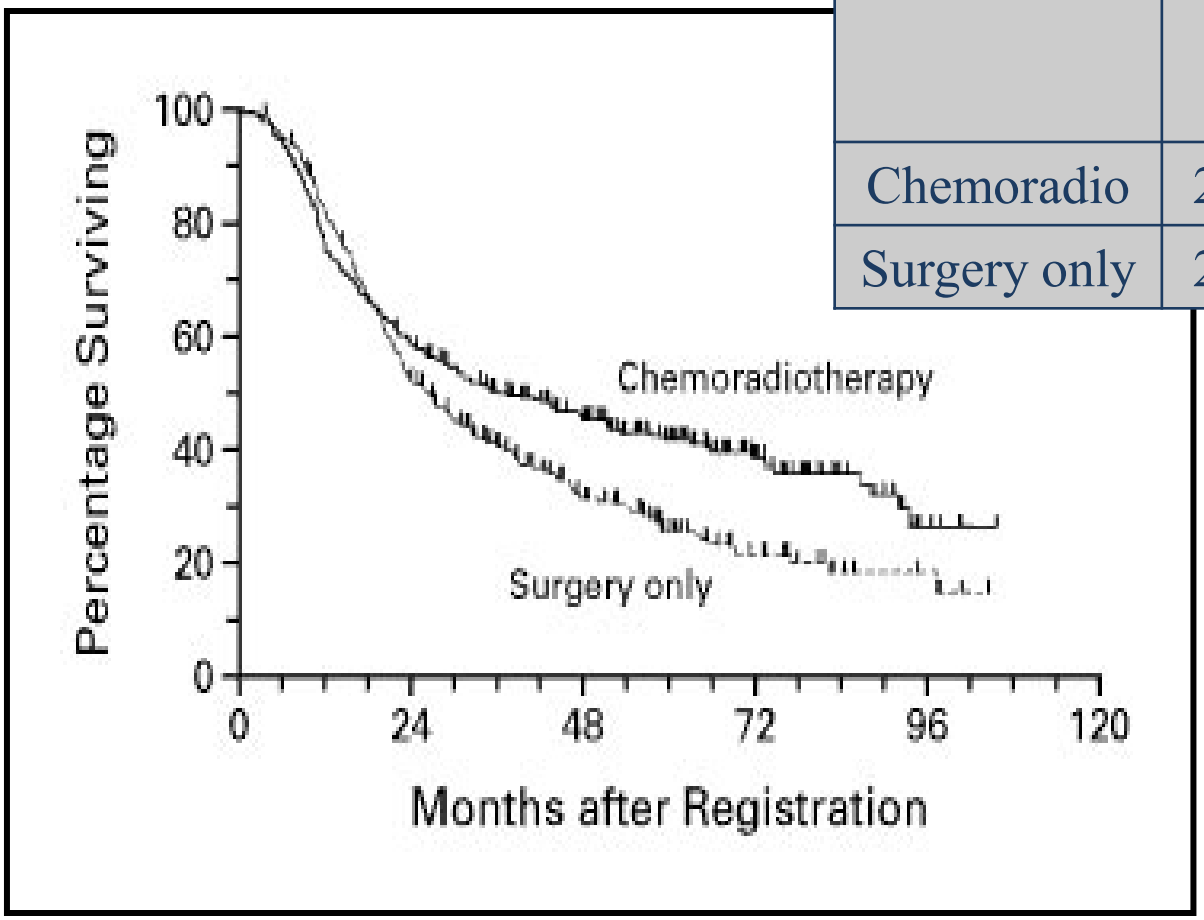
20% GE Junction



Macdonald *NEJM* 2003; 345: 725-730

FRED HUTCH

Adjuvant ChemoRT: INT 0116/SWOG 9008



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

P = .006

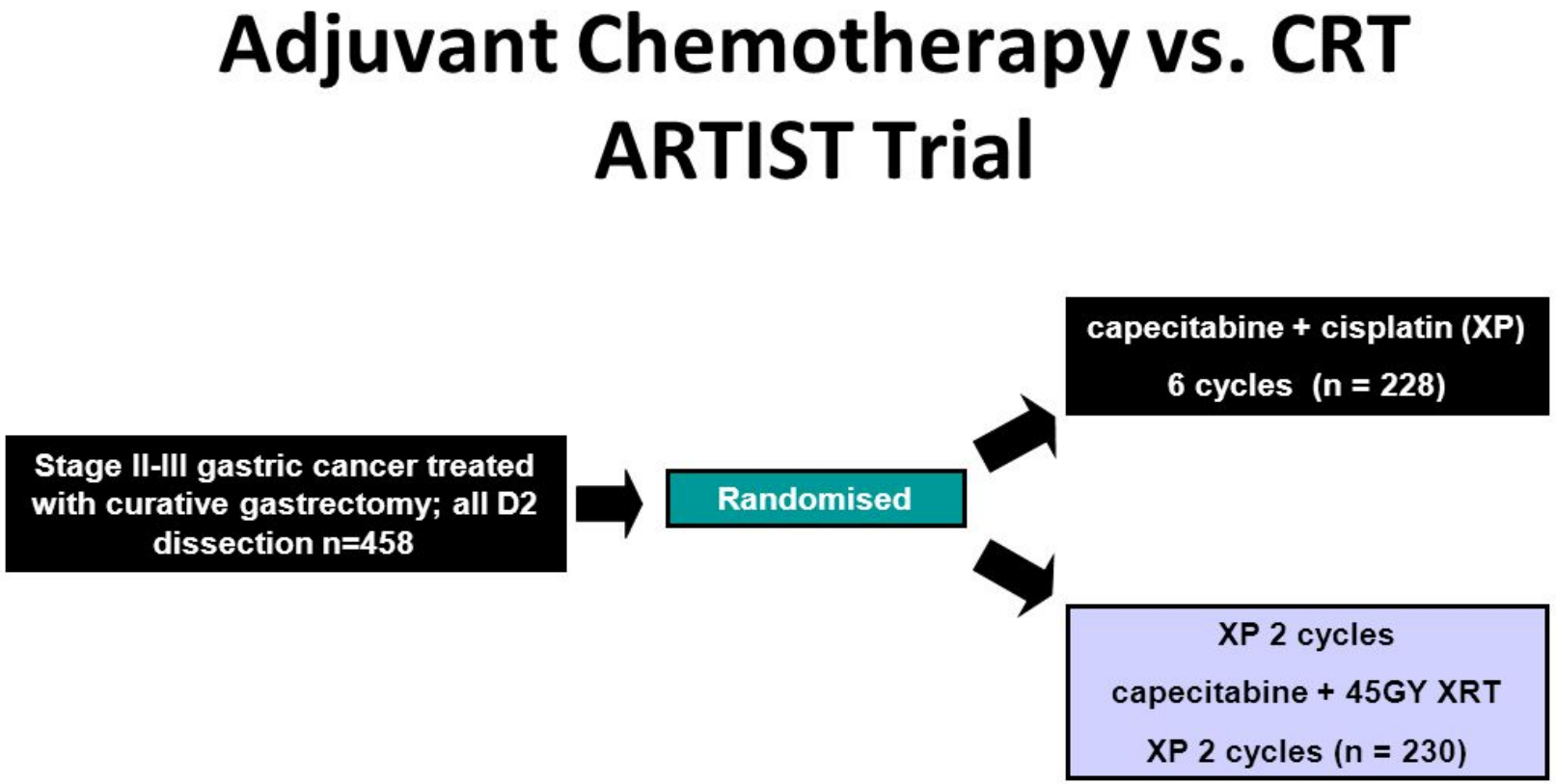
Macdonald *NEJM* 2003; 345: 725-730

Adjuvant ChemoRT: INT 0116/SWOG 9008

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

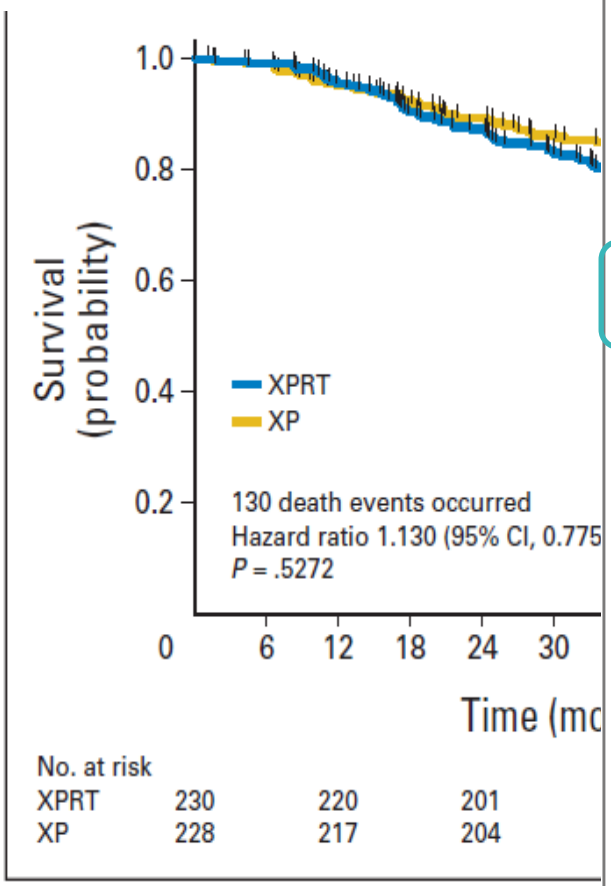
Macdonald *NEJM* 2003; 345: 725-730

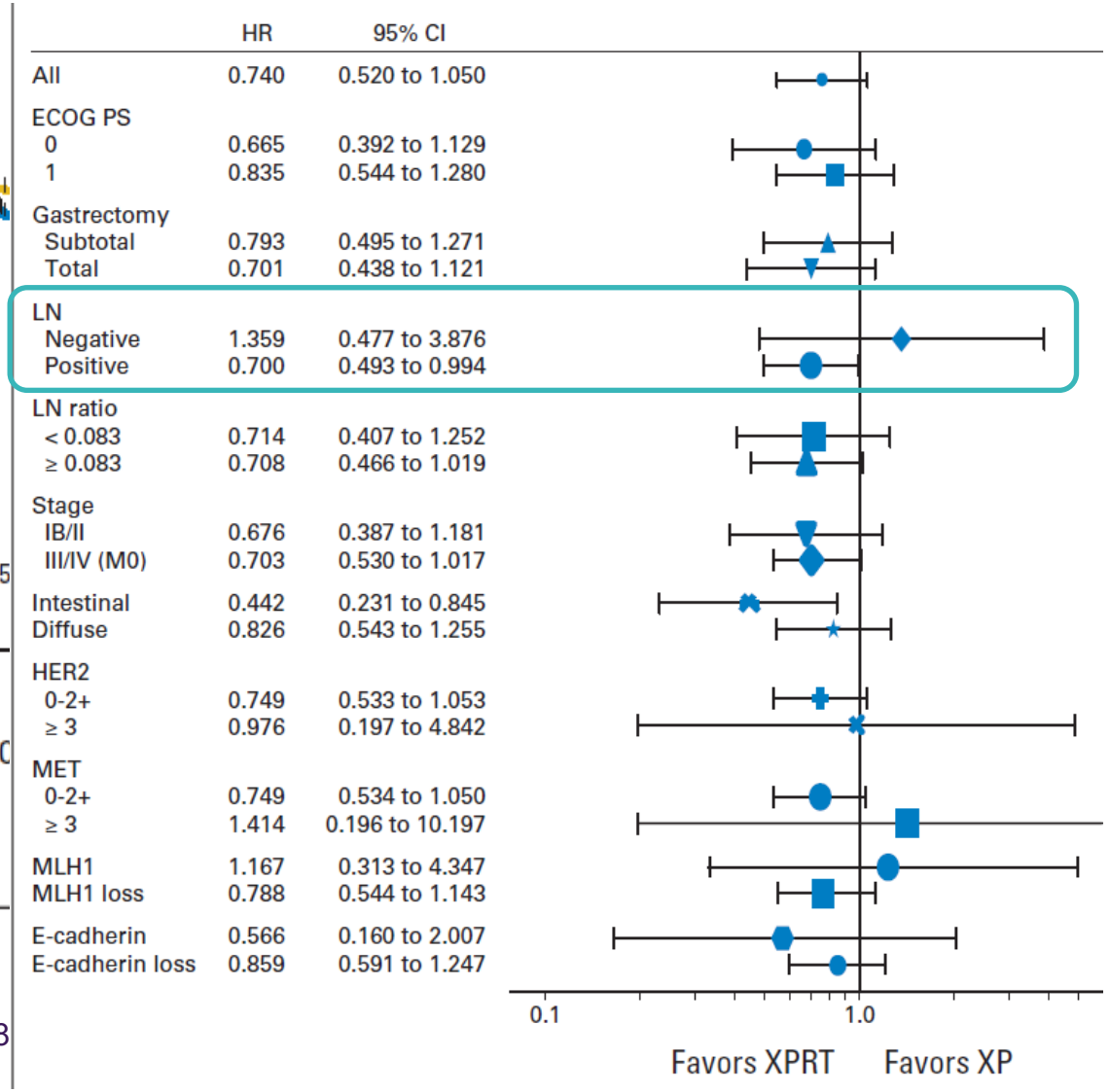
ARTIST Trial: Adjuvant Chemo vs. RT



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

ARTIST: Adjuvant Chemo vs. chemoRT





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

FRED HUTCH

ARTIST-II: Adjuvant chemo vs. chemoRT (Node+)

Randomize 900 patients
with D2 resected NODE
POSITIVE Gastric Cancrer

Key Results

- SOX and SOXRT >> S1 alone
- **No difference in DFS between SOX and SOXRT** (HR 0.91, p=0.67)

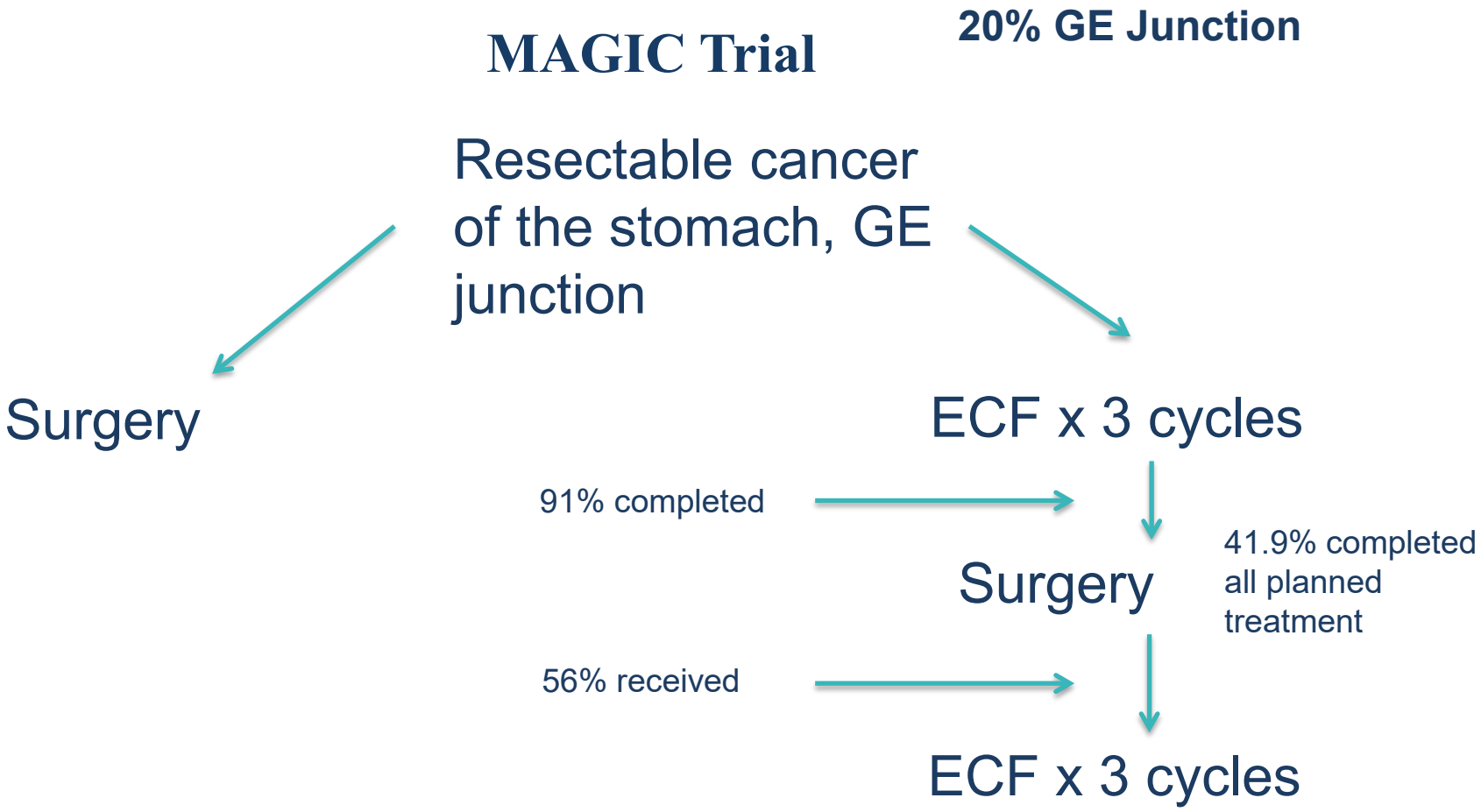
Park, SH et al. 2019 May ASCO / J Clin Oncol

Is there a role for Postoperative Radiation?

NO, except …

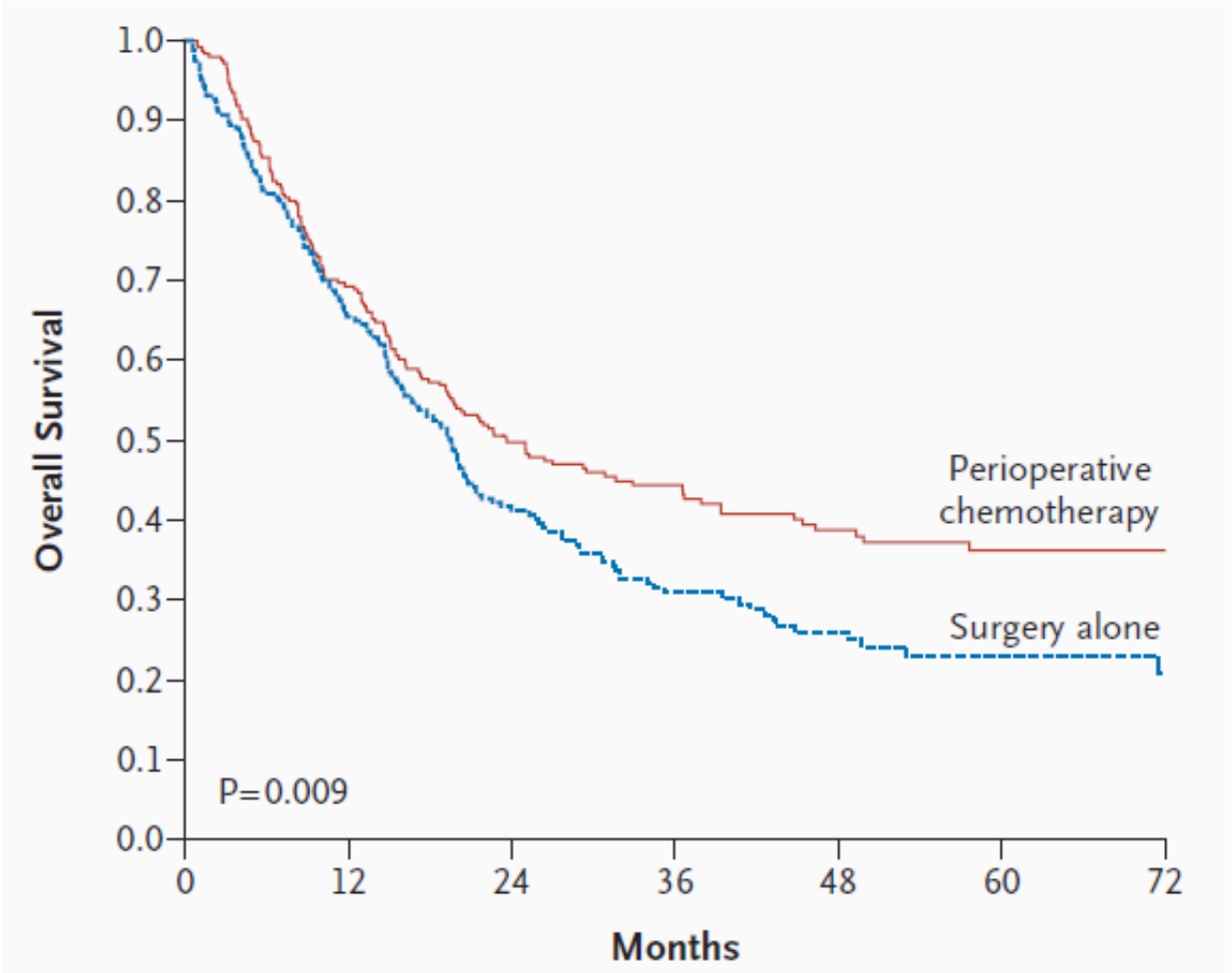
- Inadequate resections / lymph node dissection
- Positive margin (R1 resection)

Perioperative Chemotherapy: MAGIC Trial



Cunningham D, et al. *NEJM* July 2006

Perioperative Chemotherapy: MAGIC Trial

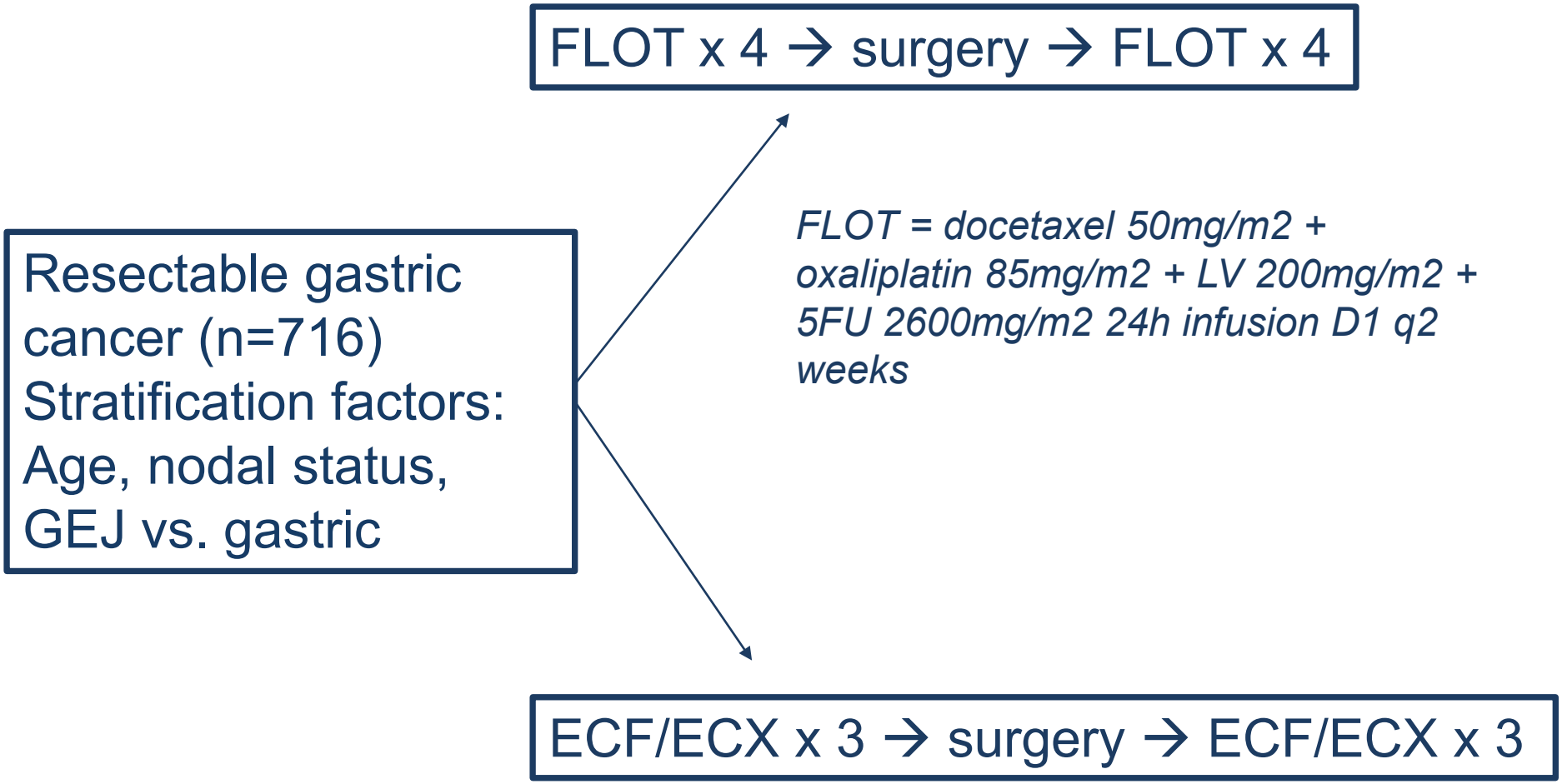


5-year survival
- 36.3% (Chemo)
- 23.0% (Surgery)

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

Cunningham D, et al. *NEJM* July 2006

Perioperative Chemotherapy: FLOT-4



Al-Batran S, et al. ASCO 2017 Annual Meeting.

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. ASCO 2017 Annual Meeting.

FLOT-4 – ASCO 2020 Updates

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

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

- 180 patients randomized
- 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. ASCO 2020
Al Batran, SE et al. ASCO 2020

GE Junction Adeno: FLOT vs. CROSS?

Neo-AEGIS 2013-2018: CROSS vs (modified) MAGIC regimen

Esophageal and GEJ adenocarcinoma:

AEG

cT2-3

CROSS Regimen

Higher rates R0 resection, path CR

OS was similar between arms (3 year OS 56% vs. 57%)

Arm A

Arm B 1

Arm B 10% superior to A (n= 628)

Neo CRT (CROSS)
wCP-RT(41.4Gy)+Surgery

Arm B

Primary endpoint: Overall survival

Secondary end points: Disease free survival;
Time to treatment failure: TRG: R0: Toxicity: Postoperative complications; HR-QL

Take Home Points: Localized and Locally Advanced Gastric Cancer

Post-gastrectomy B12 and iron supplementation

D2 gastrectomy should be performed when possible

Perioperative chemotherapy – general approach for Western patient

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

Metastatic Esophageal and Gastric Cancer

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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

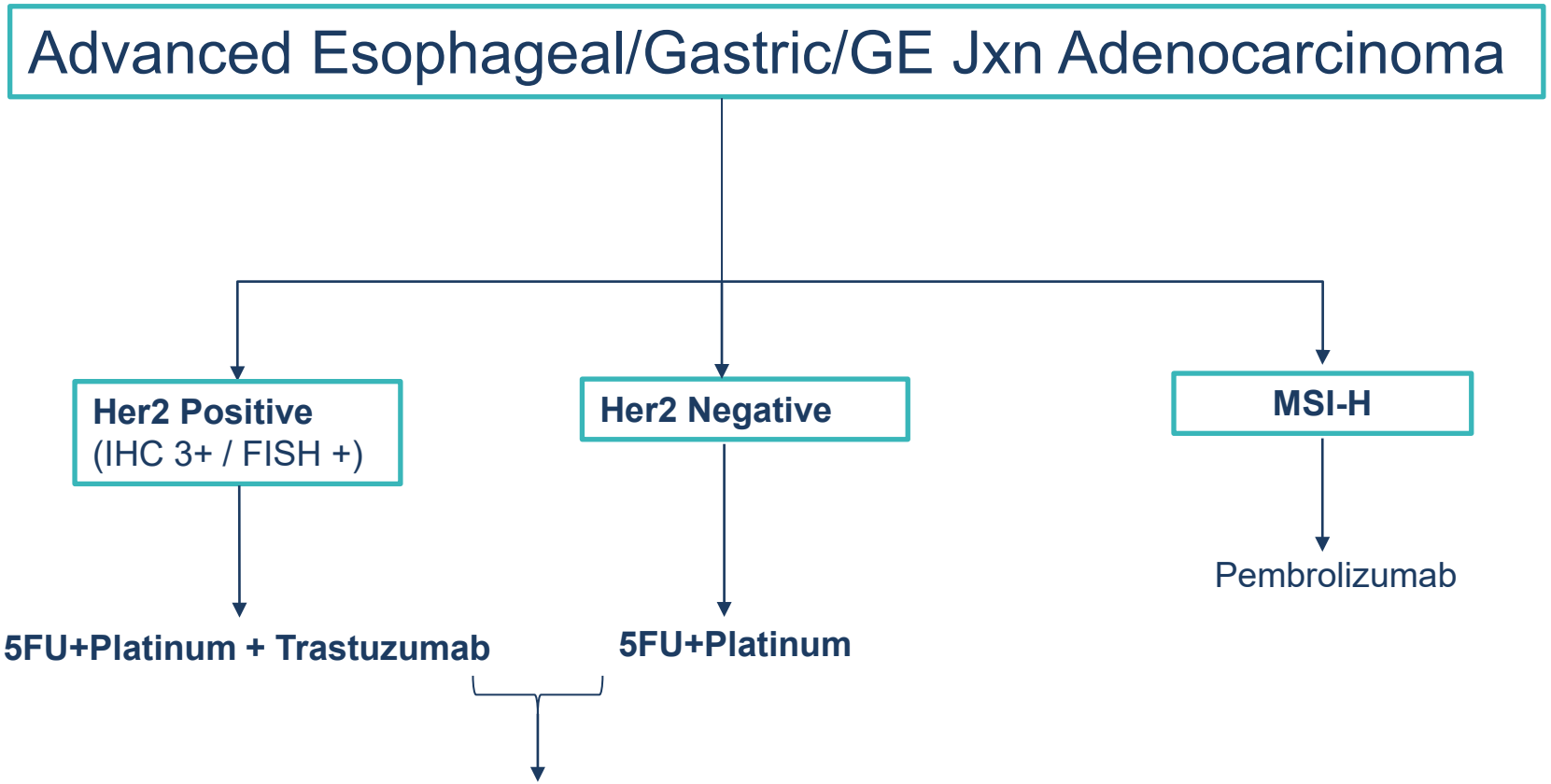
Author	Regimen	RR	Median OS (months)
Van Cutsem, 2006	DCF	37%	9.2
C			
Al			
Sh			
Bo			
Narahara, 2011	Irinotecan/S-1	41.5%	12.8

2 DRUG REGIMENS PREFERRED

- **FOLFOX**
- 5-FU+Cisplatin
- FOLFIRI

Less Toxic, Similar Outcomes

Initial Treatment - 2018



Initial Treatment - 2021

Advanced Esophageal/Gastric/GE Jxn Adenocarcinoma

Her2 Positive
(IHC 3+ / FISH +)
Any PDL1

5FU+Platinum
+
Trastuzumab
+
Pembrolizumab
(Keynote 811)

Her2 Negative
Any PDL1

Gastric / GEJ

5FU+Platinum
+
Nivolumab
(Checkmate 649)

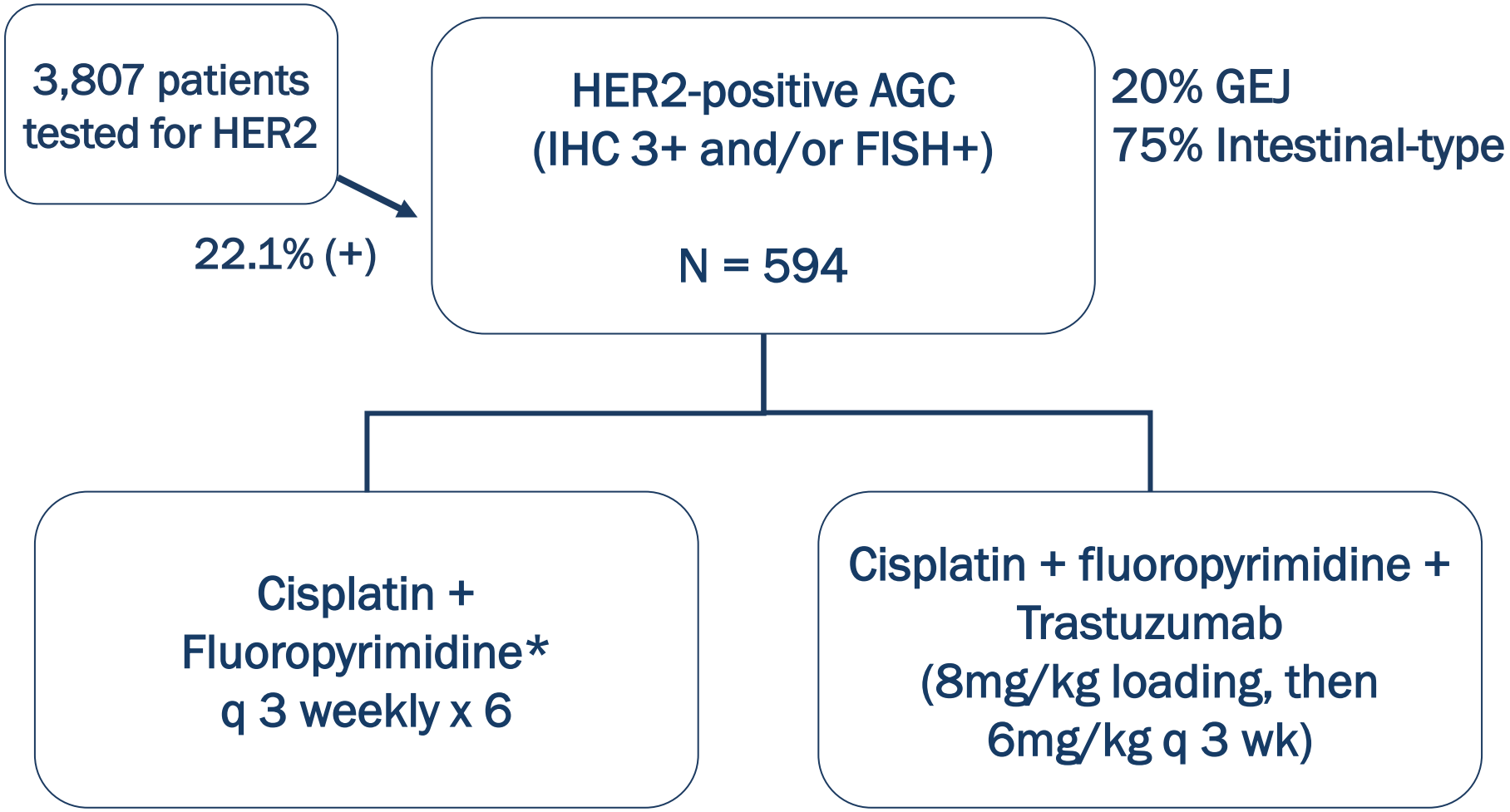
Esophageal (incl. squamous) / GEJ

5FU+Platinum
+
Pembrolizumab or Nivolumab
(Keynote 590 and Checkmate 648)

- **MSI-H**
- **CPS ≥ 10** + Lower disease burden

Pembrolizumab
(Keynote 062)

Targeting Her2 – TOGA Trial



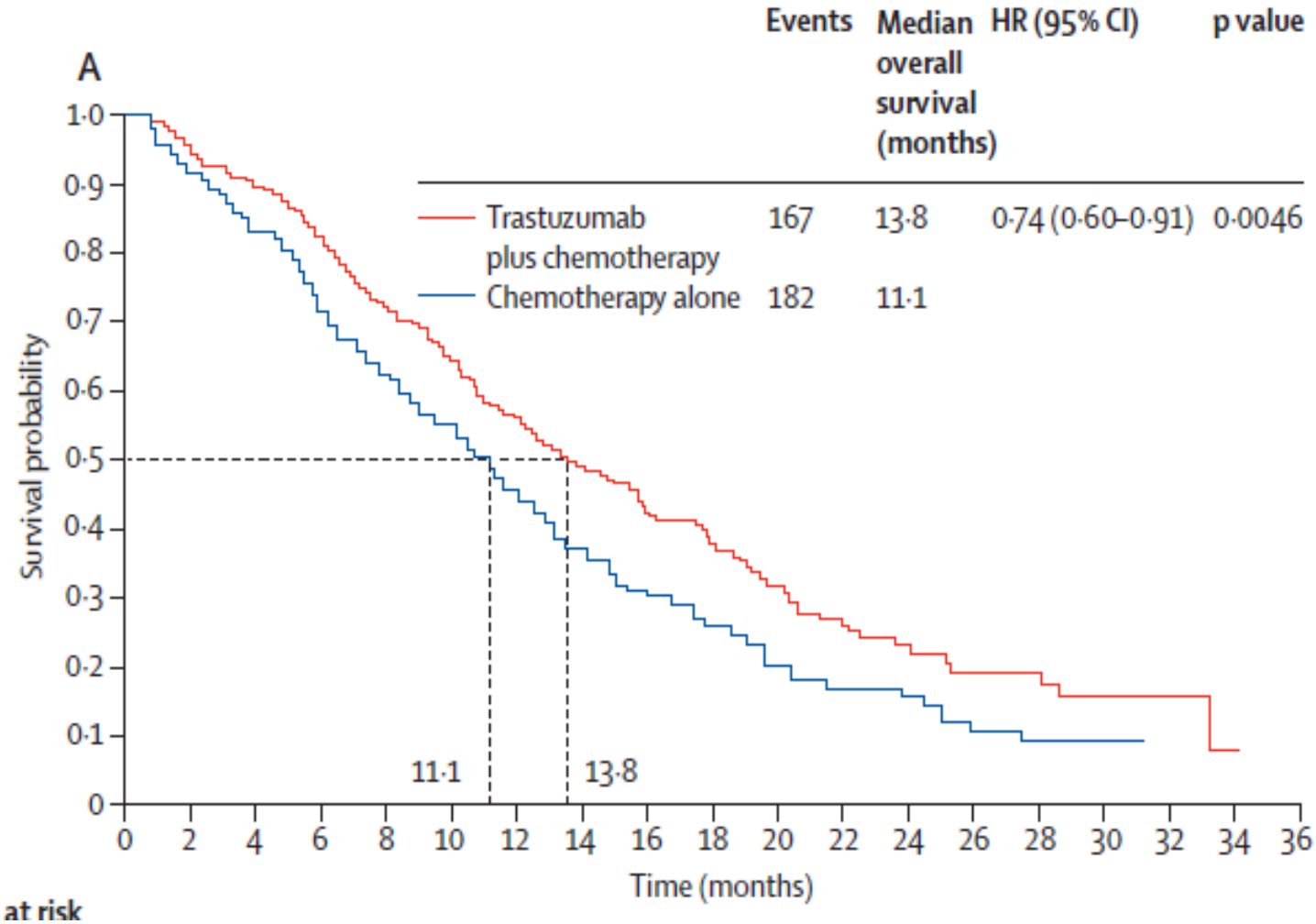
Bang, YJ et al. *Lancet* 2010; 376: 698-97

TOGA Trial - Results

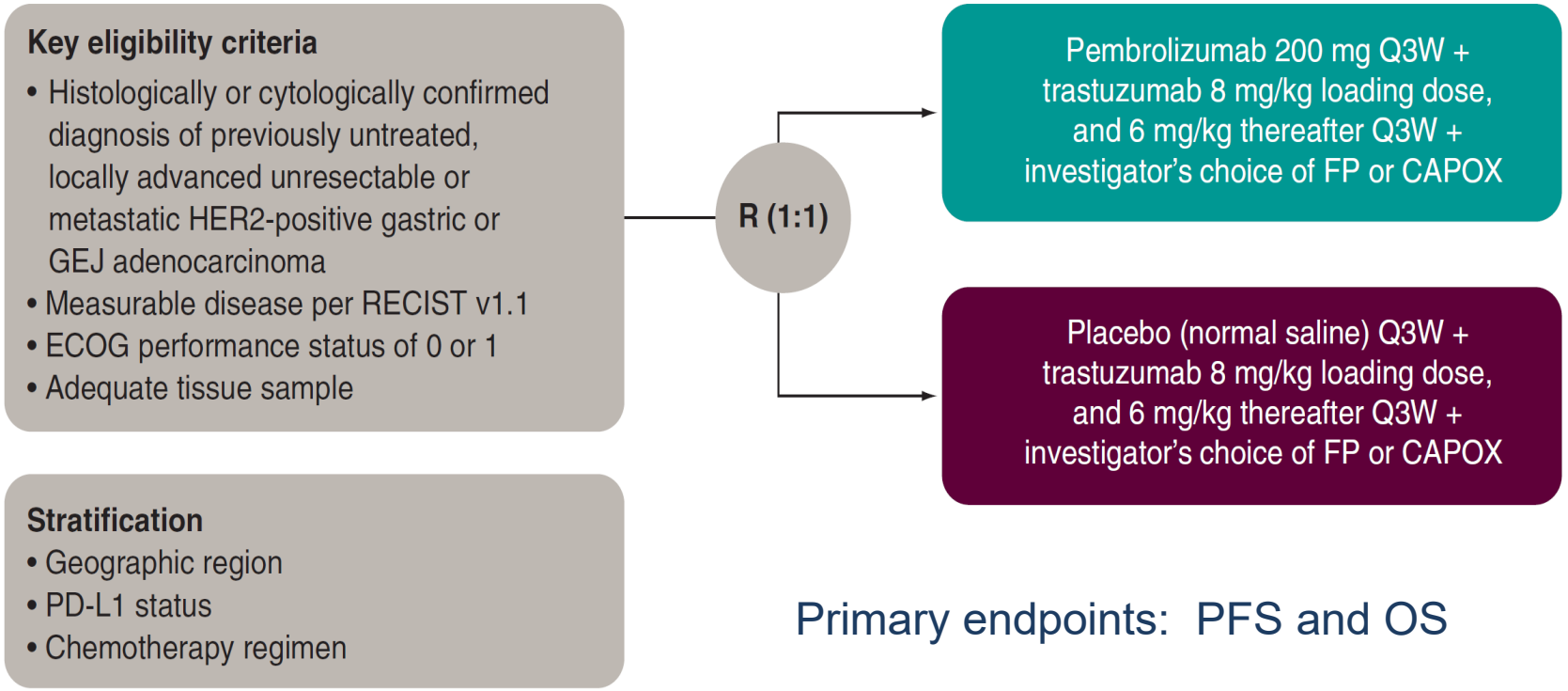
	Chemo alone	Chemo + trastuzumab	P value
ORR	34.5%	47.3%	P=0.0017
Median PFS	5.5 months	6.7 months	P=0.0002, HR 0.71
Median survival	11.1 months	**13.8 months**	P=0.0048, HR 0.74

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

TOGA Trial - Results



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 + Trastuzumab + Pembro (n=133)	Chemo + Trastuzumab + 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	
DOR	n=99	n=68
Median in months (range)	10.6 (1.1+, 16.5+)	9.5 (1.4+, 15.4+)
% with duration ≥ 6 months	65%	53%
*Response: Best objective response as confirmed complete response or partial response		

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

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.

Trastuzumab "Beyond Progression"

WJOG Study: 2nd line paclitaxel +/- trastuzumab *(in Her2+ pts who progressed on 5-FU/platinum + trastuzumab)*

- No PFS benefit with trastuzumab
- In cases where pre-treatment biopsies could be performed, only 1/3 retained Her2 positivity (IHC 2/3+)

Sukawa, Y. et al. ASCO 2018

Trastuzumab Deruxtecan – Destiny Gastric01

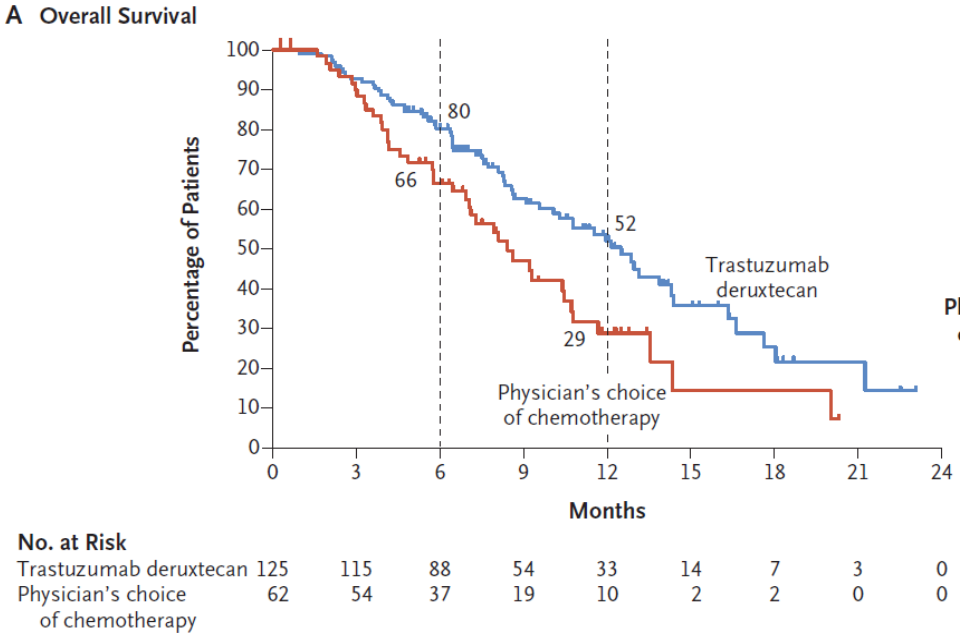
- Destiny Gastric 01 study: Randomized phase II study in Japan and Korea
- Patient population: Her2 positive gastric and GE jxn cancer patients who received at least 2 prior lines of therapy (including prior trastuzumab)
- 188 patients randomized (2:1) to trastuzumab deruxtecan versus physician's choice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

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

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%)

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

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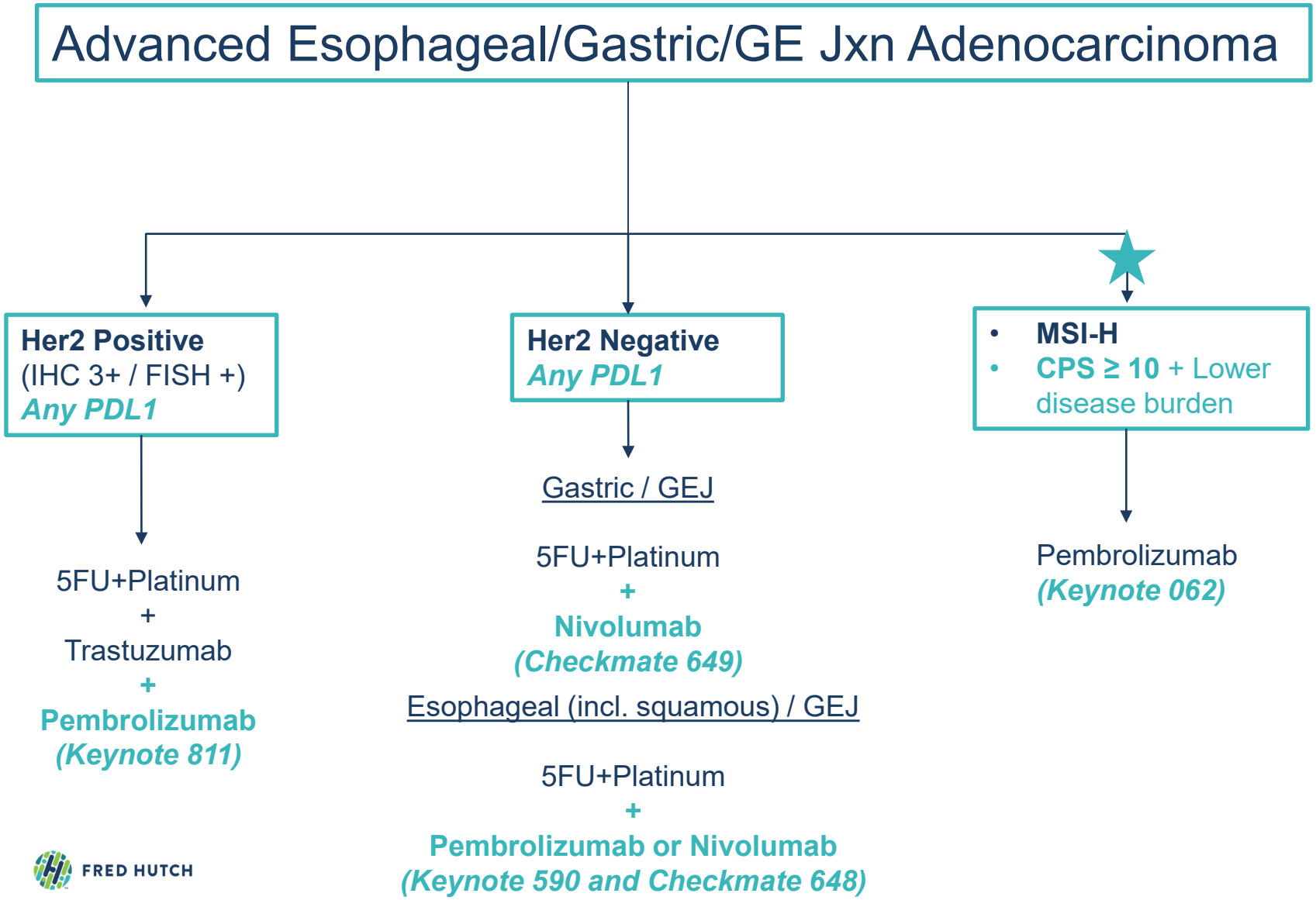
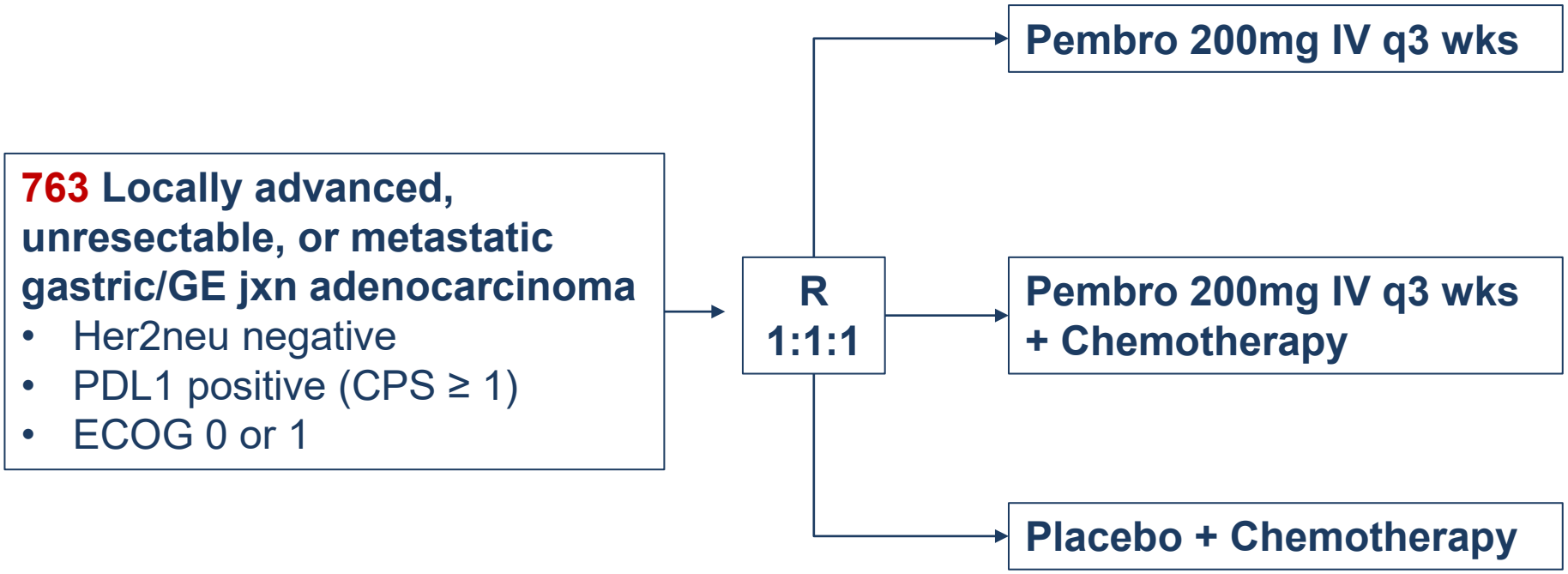
Initial Treatment - 2021



First-line pembrolizumab – Keynote 062



Primary endpoints = noninferiority OS (pembro vs. chemo) ; superiority OS (pembro+chemo vs. chemo)
Chemotherapy = 5-FU or capecitabine + cisplatin

Tabernero, J. et al. 2019. ASCO Annual Meeting

First-line pembrolizumab – Keynote 062

Pembro versus Chemotherapy

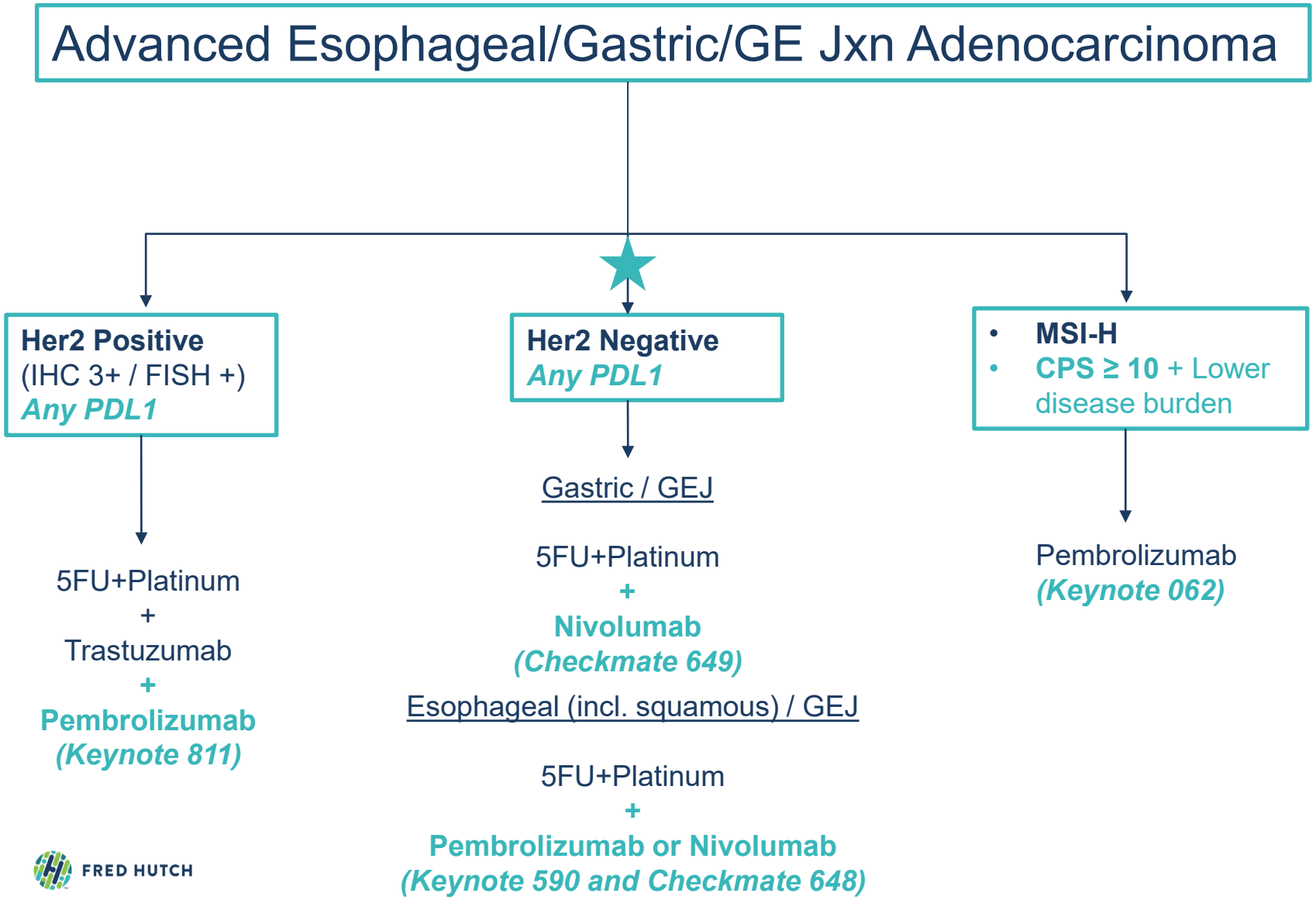
- Noninferior OS Pembro vs. Chemo (10.6 months vs. 11.1 months) HR 0.91, p=NS
- Superior OS in CPS ≥ 10 subgroup (17.4 vs. 10.8 months) HR = 0.69
- Lower Grade 3 or higher AEs (17% P, 71% pembro +chemo, 68% chemo)

Pembro + Chemo versus Chemo

- OS ***not*** superior Pembro + chemo vs. chemo (12.5 mo vs. 11.1 mo) HR 0.85
- ORR slightly better in pembro + chemo vs. chemo alone (48.6% vs. 36.8%
- OS not superior in CPS ≥ 10 subgroup (12.3 mo vs. 10.8 mo) HR 0.85

Tabernero, J. et al. 2019. ASCO Annual Meeting

Initial Treatment - 2021



First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial

Yelena Y Janjigian, Kohei Shitara*, Markus Moehler, Marcelo Garrido, Pamela Salman, Lin Shen, Lucjan Wyrwicz, Kensei Yamaguchi, Tomasz Skoczylas, Arinilda Campos Bragagnoli, Tianshu Liu, Michael Schenker, Patricio Yanez, Mustapha Tehfe, Ruben Kowalyszyn, Michalis V Karamouzis, Ricardo Bruges, Thomas Zander, Roberto Pazo-Cid, Erika Hitre, Kynan Feeney, James M Cleary, Valerie Poulart, Dana Cullen, Ming Lei, Hong Xiao, Kaoru Kondo, Mingshun Li, Jaffer A Ajani*

Janjigian, Y. et al. The Lancet. Pub online June 5, 2021

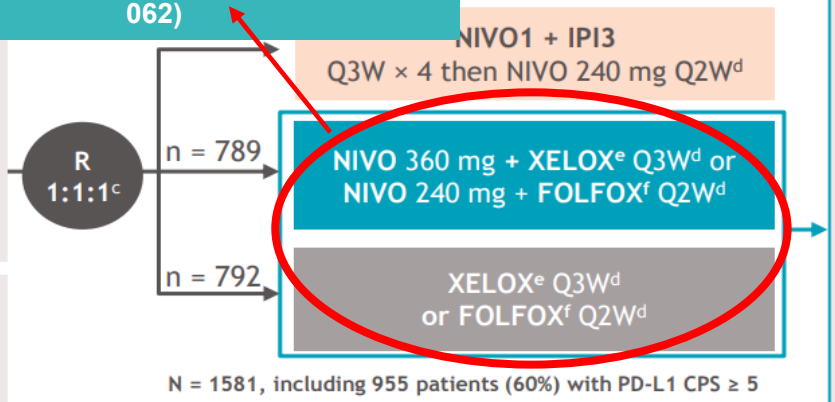
CheckMate 649 study design

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

Use of oxaliplatin based therapies (as opposed to cisplatin with KEYNOTE-062)

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)



N = 1581, including 955 patients (60%) with PD-L1 CPS ≥ 5

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

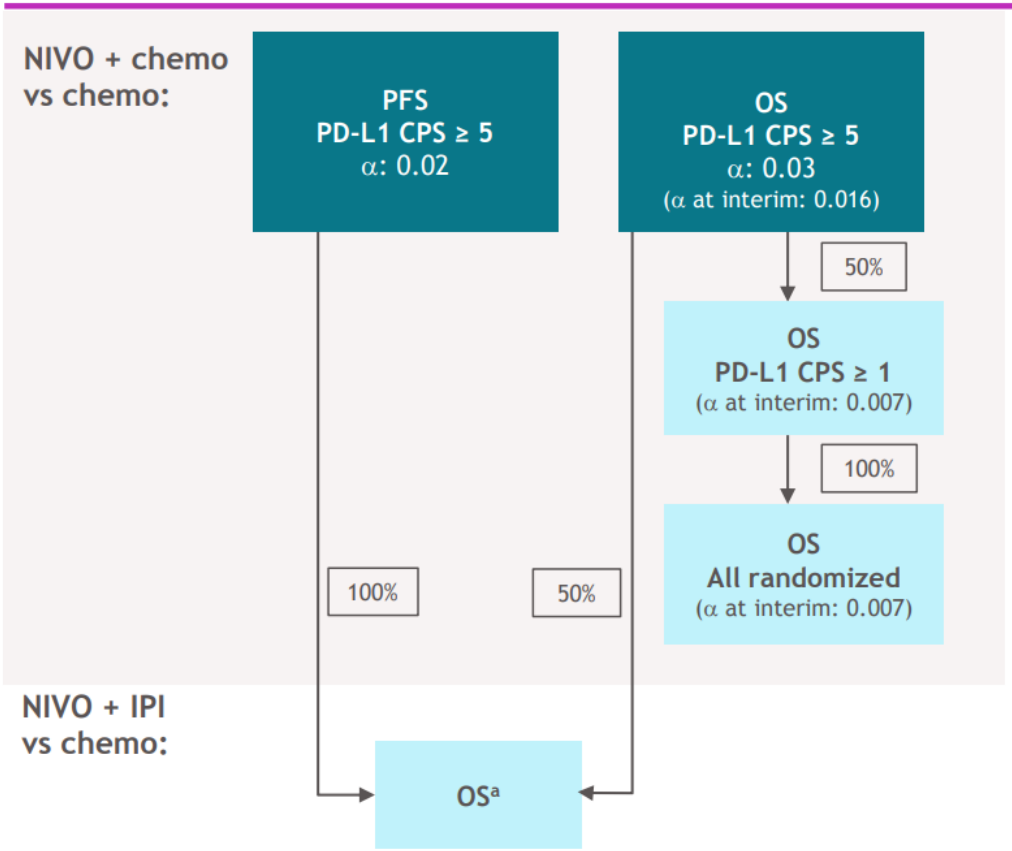
Secondary endpoints:
- OS (PD-L1 CPS ≥ 1 or all randomized)
- OS (PD-L1 CPS ≥ 10)
- PFS[g] (PD-L1 CPS ≥ 10, 1, or all randomized)
- ORR[g]

- 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.

Moehler M, et al. Abstract LBA6. ESMO 2020 Virtual Congress

Statistical considerations



- Overall α is split between the 2 primary endpoints
- If OS in the PD-L1 CPS ≥ 5 population is statistically significant, OS in PD-L1 CPS ≥ 1, followed by OS in all randomized patients, is tested hierarchically
- Final PFS and pre-specified interim OS analyses: after a minimum follow-up of 12 months

Primary endpoint
Secondary endpoint
% Fraction of α transmitted to next endpoint

[a]Hierarchical testing of OS in the PD-L1 CPS ≥ 5 population, followed by all randomized patients, is planned for the final analysis.

Moehler M, et al. Abstract LBA6. ESMO 2020 Virtual Congress

	Patients with a PD-L1 CPS of five or more		All randomly assigned patients	
	Nivolumab plus chemotherapy (n=473)	Chemotherapy alone (n=482)	Nivolumab plus chemotherapy (n=789)	Chemotherapy alone (n=792)
Median age, years	63 (54–69)	62 (54–68)	62 (54–69)	61 (53–68)
<65	266 (56%)	286 (59%)	473 (60%)	488 (62%)
≥65	207 (44%)	196 (41%)	316 (40%)	304 (38%)
Sex				
Men	331 (70%)	349 (72%)	540 (68%)	560 (71%)
Women	142 (30%)	133 (28%)	249 (32%)	232 (29%)
Race				
Asian	119 (25%)	117 (24%)	186 (24%)	189 (24%)
White	328 (69%)	327 (68%)	556 (70%)	541 (68%)
American Indian or Alaska Native	10 (2%)	10 (2%)	12 (2%)	14 (2%)
Black or African American	2 (<1%)	7 (1%)	7 (1%)	11 (1%)
Other	14 (3%)	21 (4%)	28 (4%)	36 (5%)
Not reported	0	0	0	1 (<1%)
Region				
Asia	117 (25%)	111 (23%)	178 (23%)	178 (22%)
USA and Canada	67 (14%)	70 (15%)	131 (17%)	132 (17%)
Rest of world	289 (61%)	301 (62%)	480 (61%)	482 (61%)
ECOG performance status*				
0	194 (41%)	203 (42%)	326 (41%)	336 (42%)
1	279 (59%)	278 (58%)	462 (59%)	452 (57%)
2	0	0	1 (<1%)	3 (<1%)
Not reported	0	1 (<1%)	0	1 (<1%)
Primary tumour location at initial diagnosis				
Gastric cancer	333 (70%)	334 (69%)	554 (70%)	556 (70%)
Gastro-oesophageal junction cancer	84 (18%)	86 (18%)	132 (17%)	128 (16%)
Oesophageal adenocarcinoma	56 (12%)	62 (13%)	103 (13%)	108 (14%)
Tumour cell PD-L1 expression				
<1%†	363 (77%)	362 (75%)	663 (84%)	664 (84%)
≥1%	110 (23%)	120 (25%)	126 (16%)	127 (16%)
Previous surgery				
Yes	97 (21%)	105 (22%)	160 (20%)	176 (22%)
No	376 (79%)	377 (78%)	629 (80%)	616 (78%)
Disease stage				
Metastatic	454 (96%)	461 (96%)	757 (96%)	756 (95%)
Locally advanced	16 (3%)	20 (4%)	27 (3%)	34 (4%)
Locally recurrent	3 (1%)	1 (<1%)	5 (1%)	2 (<1%)
Organs with metastases				
1	98 (21%)	105 (22%)	164 (21%)	183 (23%)
≥2	361 (76%)	362 (75%)	602 (76%)	583 (74%)

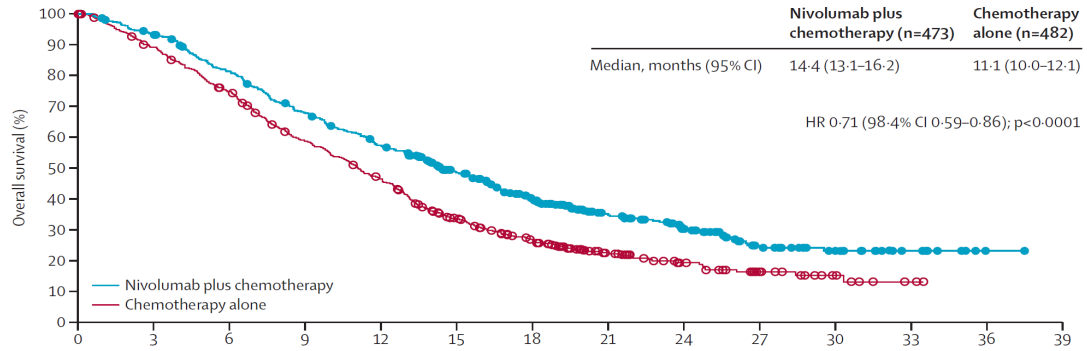
(Table 1 continues on next page)

	Patients with a PD-L1 CPS of five or more		All randomly assigned patients	
	Nivolumab plus chemotherapy (n=473)	Chemotherapy alone (n=482)	Nivolumab plus chemotherapy (n=789)	Chemotherapy alone (n=792)
(Continued from previous page)				
Site of metastases				
Liver	191 (40%)	217 (45%)	301 (38%)	314 (40%)
Peritoneum	101 (21%)	96 (20%)	188 (24%)	188 (24%)
CNS	1 (<1%)	0	1 (<1%)	0
Signet ring cell carcinoma‡				
Yes	72 (15%)	69 (14%)	145 (18%)	136 (17%)
No	401 (85%)	413 (86%)	644 (82%)	656 (83%)
Lauren classification				
Intestinal type	171 (36%)	176 (37%)	272 (34%)	267 (34%)
Diffuse type	137 (29%)	141 (29%)	254 (32%)	273 (34%)
Mixed	37 (8%)	30 (6%)	58 (7%)	48 (6%)
Unknown	128 (27%)	135 (28%)	205 (26%)	204 (26%)
Microsatellite instability status				
Microsatellite stable	423 (89%)	423 (88%)	695 (88%)	682 (86%)
Microsatellite instability-high	18 (4%)	16 (3%)	23 (3%)	21 (3%)
Not reported or invalid	32 (7%)	43 (9%)	71 (9%)	89 (11%)
Chemotherapy regimen§				
FOLFOX	237/468 (51%)	242/465 (52%)	422/782 (54%)	406/767 (53%)
XELOX	231/468 (49%)	223/465 (48%)	360/782 (46%)	361/767 (47%)

Data are median (IQR) or n (%). PD-L1=programmed cell death ligand 1. CPS=combined positive score. ECOG=Eastern Cooperative Oncology Group. FOLFOX=leucovorin, fluorouracil, and oxaliplatin. XELOX=capecitabine and oxaliplatin. *Based on case report form. All randomly assigned patients had ECOG performance status of 0 or 1 based on interactive response technology. †Includes indeterminate tumour cell PD-L1 expression. ‡Per WHO histological classification. §Patients who received at least one dose of the assigned treatment.

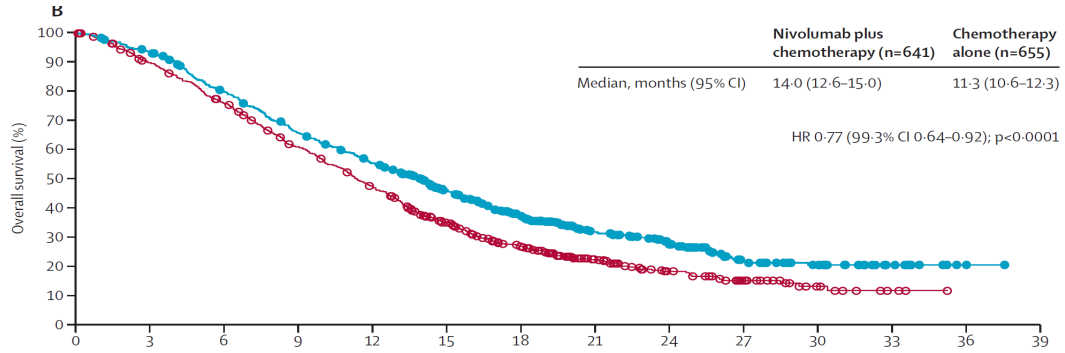
Table 1: **Baseline characteristics**

Checkmate 649 – Overall Survival



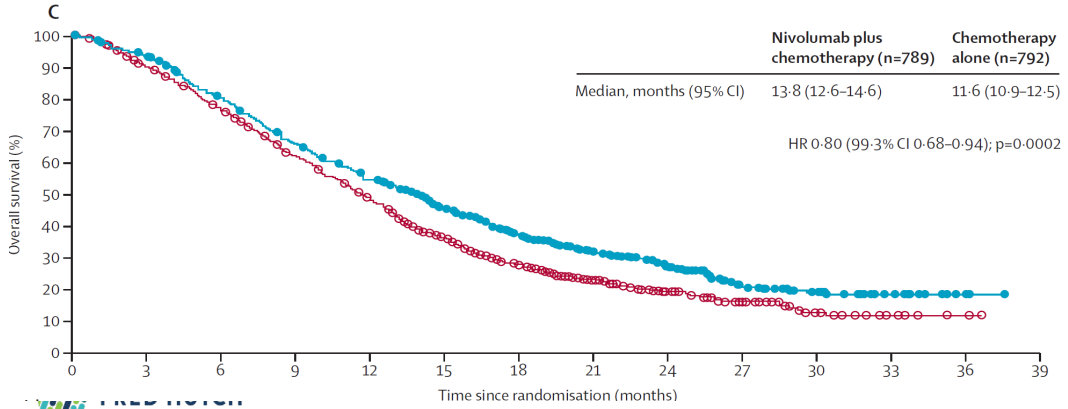
CPS 5 or higher

Median OS 14.4 vs 11.1 mo



CPS 1 or higher

Median OS 14.0 vs 11.3 mo

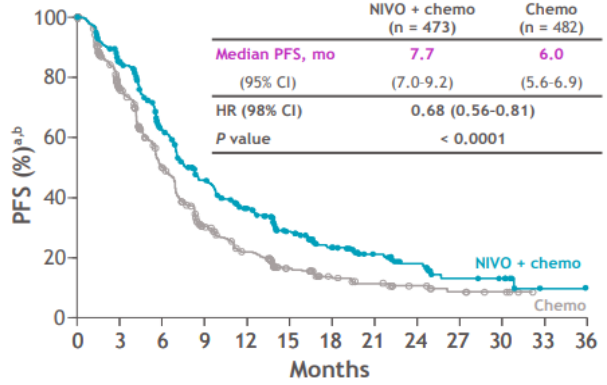


All pts, regardless of CPS

Median OS 13.8 vs 11.6 mo

Progression-free survival

Primary endpoint (PD-L1 CPS ≥ 5)



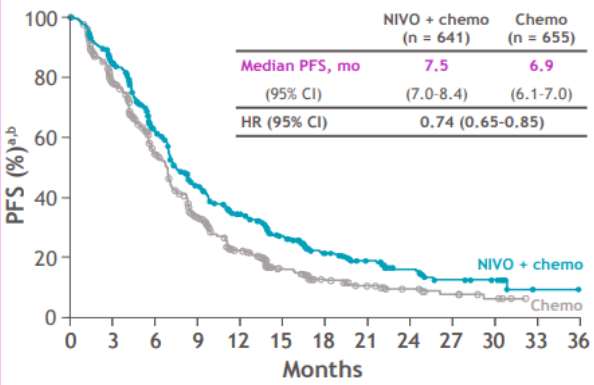
	NIVO + chemo (n = 473)	Chemo (n = 482)
Median PFS, mo	7.7	6.0
(95% CI)	(7.0-9.2)	(5.6-6.9)
HR (98% CI)	0.68 (0.56-0.81)	
P value	< 0.0001	

No. at risk

NIVO + chemo	473	384	258	181	132	89	60	39	23	10	8	1	0
Chemo	482	325	200	109	72	41	25	18	12	7	4	0	0

12-mo rate: NIVO + chemo, 36%; chemo, 22%

PD-L1 CPS ≥ 1

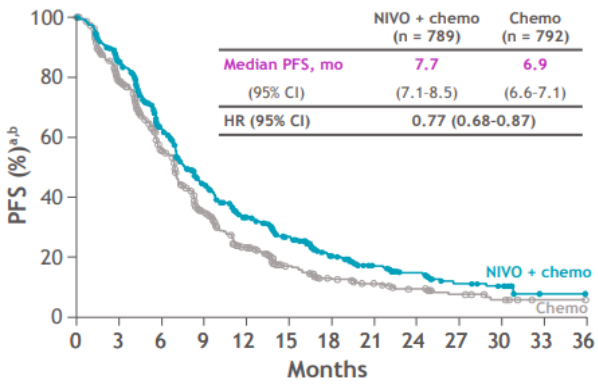


	NIVO + chemo (n = 641)	Chemo (n = 655)
Median PFS, mo	7.5	6.9
(95% CI)	(7.0-8.4)	(6.1-7.0)
HR (95% CI)	0.74 (0.65-0.85)	

NIVO + chemo	641	522	351	234	167	113	71	46	27	13	10	1	0
Chemo	655	452	291	167	99	53	31	21	13	8	4	0	0

NIVO + chemo, 34%; chemo, 22%

All randomized



	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)	

NIVO + chemo	789	639	429	287	197	136	83	51	31	15	11	1	0
Chemo	792	544	351	202	120	65	38	28	18	12	6	1	0

NIVO + chemo, 33%; chemo, 23%

- Superior PFS, 32% reduction in the risk of progression or death with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5
- PFS benefit with NIVO + chemo versus chemo in PD-L1 CPS ≥ 1 and all randomized patients

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

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Treatment-Related Adverse Events

- No new safety signals w/ chemo + nivo
- Most common TRAE ≥25% = diarrhea, nausea, and CIPN
- Grade 3-4 immunological AE's ≤5%

Treatment-related adverse events

Patients, n (%)	All treated[a]			
	NIVO + chemo (n = 782)[b]		Chemo (n = 767)[b]	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAEs[c]	738 (94)	462 (59)	679 (89)	341 (44)
Serious TRAEs[c]	172 (22)	131 (17)	93 (12)	77 (10)
TRAEs leading to discontinuation[c]	284 (36)	132 (17)	181 (24)	67 (9)
Treatment-related deaths	12[d] (2)		4[e] (< 1)	

Treatment-related adverse events with potential immunologic etiology

Select TRAEs[b,c], n (%)	All treated[a]			
	NIVO + chemo N = 782		Chemo N = 767	
	Any grade	Grade 3-4[d]	Any grade	Grade 3-4
Endocrine	107 (14)	5 (<1)	3 (<1)	0
Gastrointestinal	262 (34)	43 (5)	207 (27)	25 (3)
Hepatic	203 (26)	29 (4)	134 (17)	16 (2)
Pulmonary	40 (5)	14 (2)	4 (<1)	1 (<1)
Renal	26 (3)	6 (<1)	8 (1)	1 (<1)
Skin	214 (27)	26 (3)	105 (14)	6 (<1)

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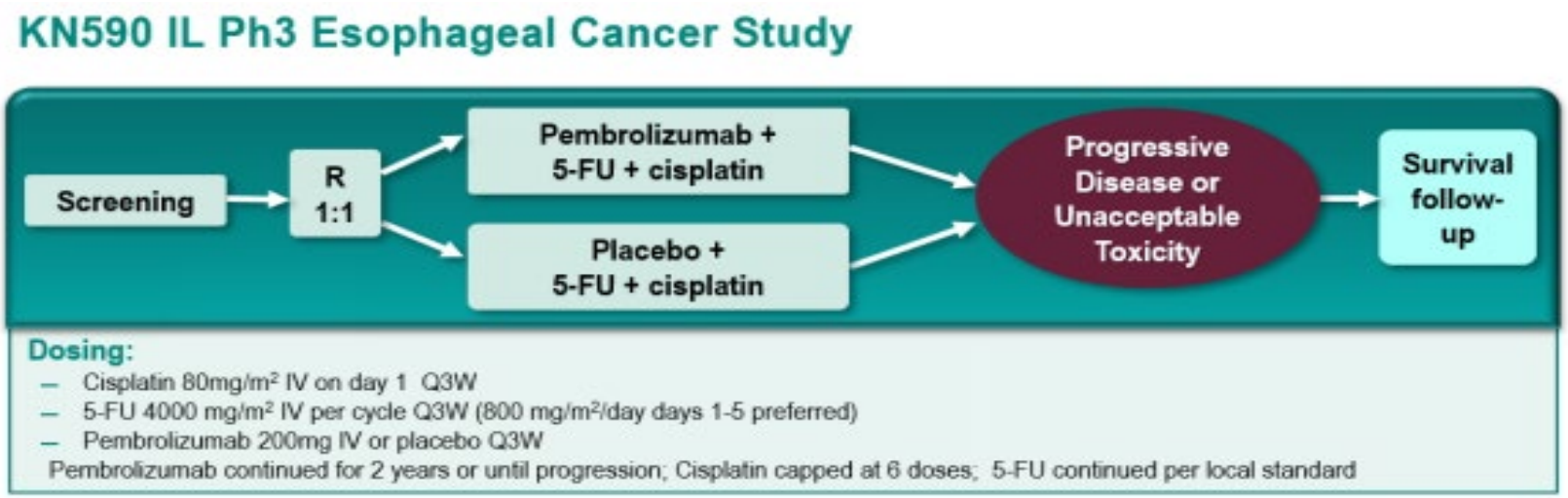
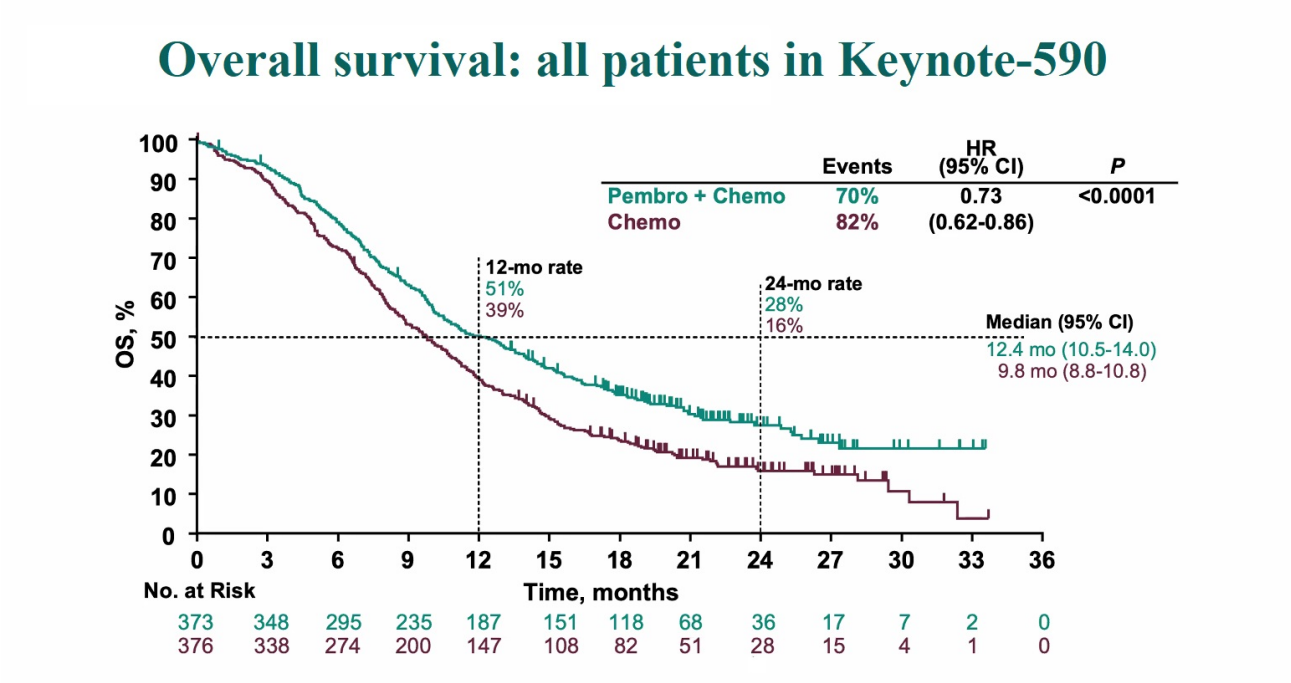
Keynote 590 Schema

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



Keynote 590 Results

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



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

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

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*

Median PFS (months)			
	C	C + Pem	
All patients	6.3	5.8	HR 0.65
Squamous cell CPS ≥ 10			
Squamous cell	6.3	5.8	HR 0.51
Any histology, CPS ≥ 10	7.5	5.5	HR 0.51
Adenocarcinoma	*6.3*	*5.7*	*HR 0.63*

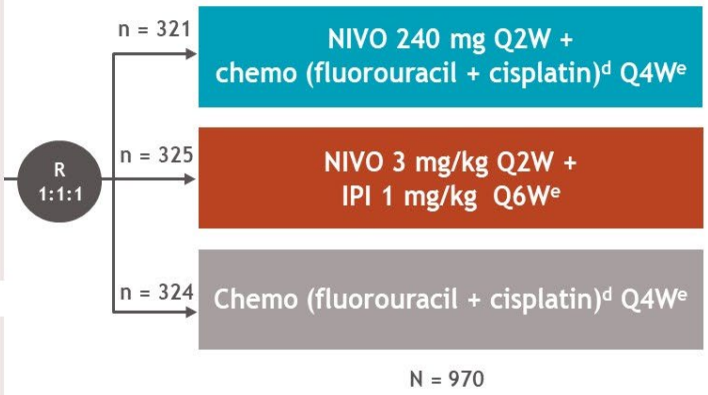
First-line Nivolumab in Squamous Cell

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)

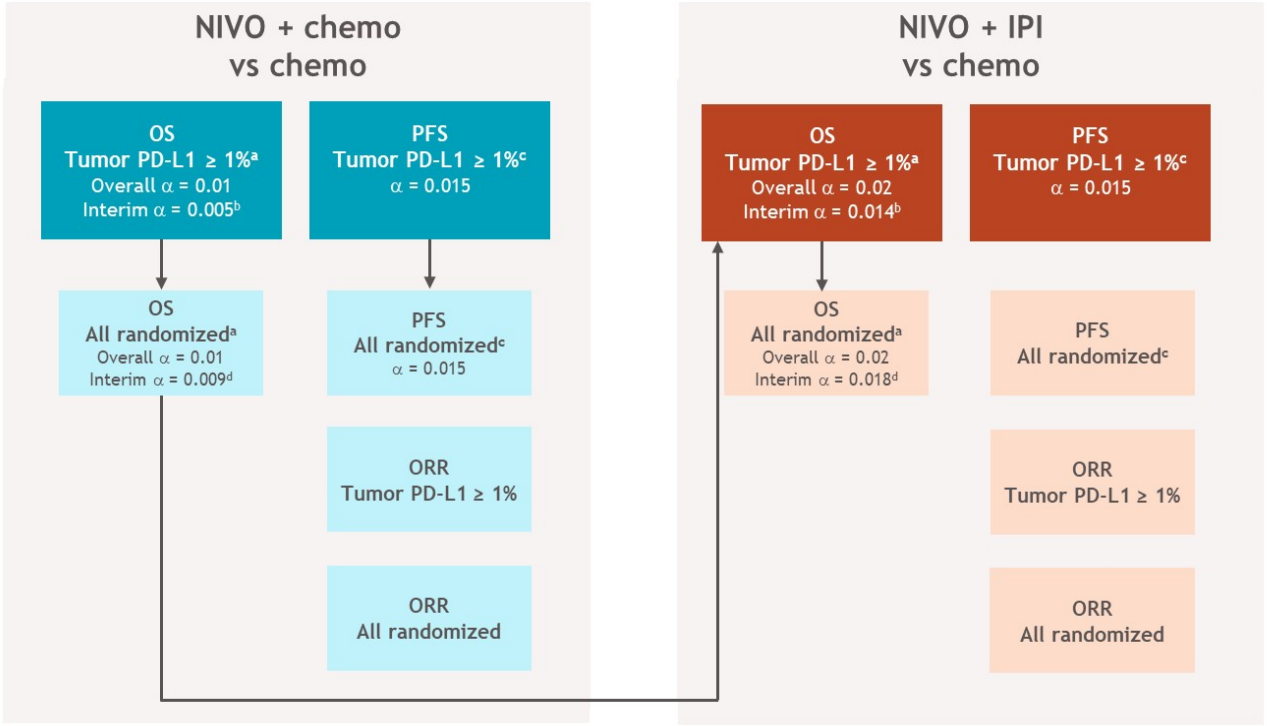
- At data cutoff (January 18, 2021), the minimum follow-up was 12.9 months[g]

[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.

First-line Nivolumab in Squamous Cell

CheckMate 648

Statistical testing



- All 4 primary endpoints in top row were tested first and in parallel[e]
- Secondary endpoints were tested hierarchically only if corresponding primary endpoints above were significant[e]
- 100% of α was passed from successful hypotheses to next endpoint(s) as indicated by arrows

[a]Study designed to detect an OS HR of 0.6 and 0.68 in patients with tumor cell PD-L1 ≥ 1% (90% power with 313 patients) and all randomized patients (94% power with 626 patients), respectively, with a type I error of 1% (2 sided); [b]OS in patients with tumor cell PD-L1 ≥ 1% used the O'Brien-Fleming alpha spending function; [c]Study designed to detect a PFS HR of 0.62 and 0.72 in patients with tumor cell PD-L1 ≥ 1% (90% power with 313 patients) and all randomized patients (90% power with 626 patients), respectively, with a type I error of 1.5% (2 sided); [d]OS in all randomized patients used the Pocock alpha spending function; [e]The type I error across the primary and secondary endpoints were controlled using the Bonferroni-based graphical approach by Maurer and Bretz (2013).[1] 1. Maurer W, Bretz F. *Stat Biopharm Res* 2013;5:311-320.

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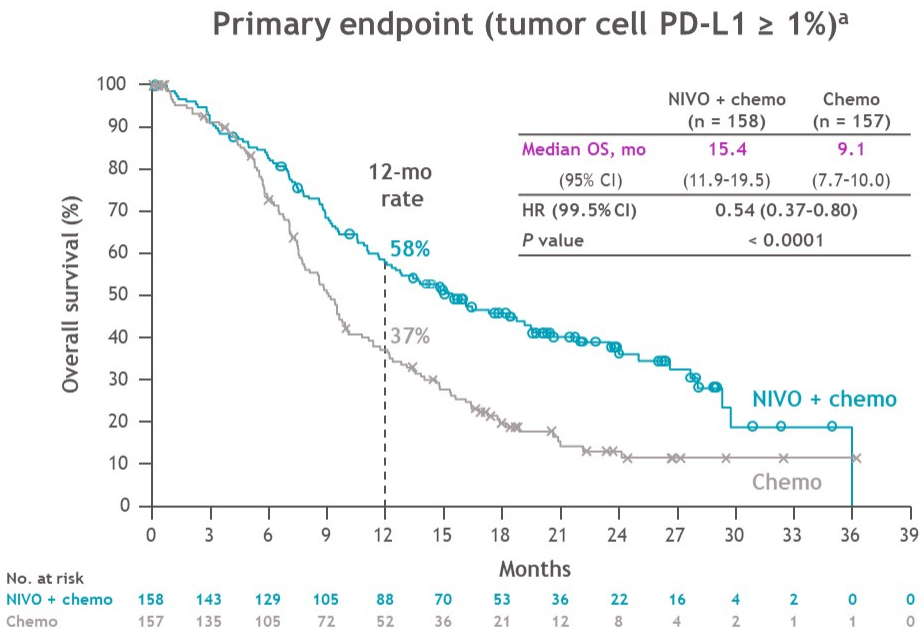
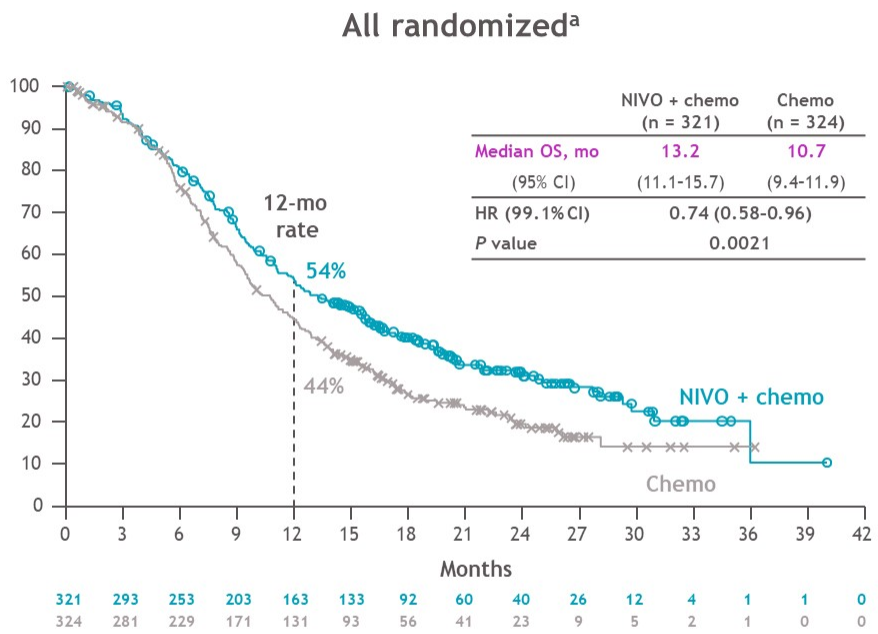
First-line Nivolumab in Squamous Cell

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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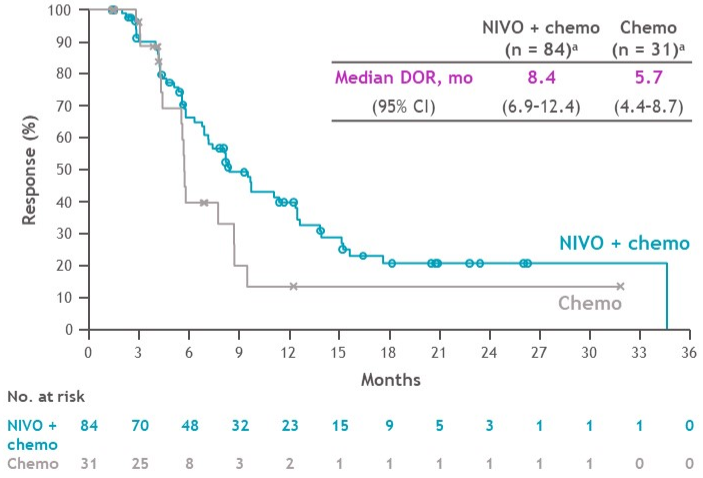
First-line Nivolumab in Squamous Cell

CheckMate 648

Response and duration of response: NIVO + chemo vs chemo

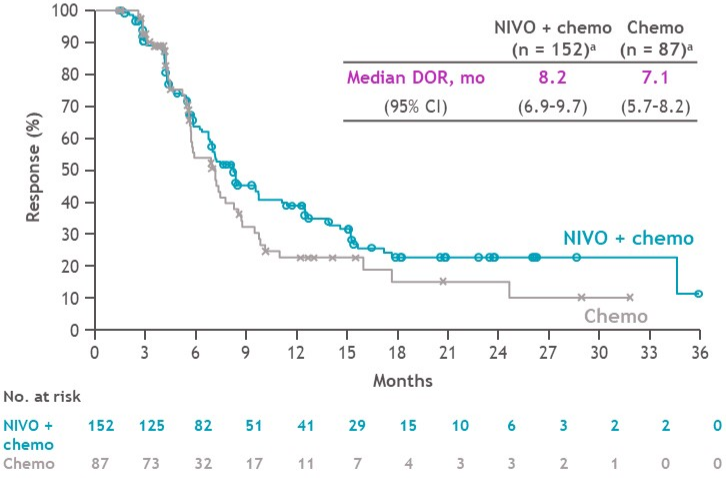
Tumor cell PD-L1 ≥ 1%

Response per BICR	NIVO + chemo (n = 158)	Chemo (n = 157)
ORR, % (95% CI)	53 (45-61)	20 (14-27)
CR	16	5
PR	37	15
SD	25	46
PD	14	15



All randomized

Response per BICR	NIVO + chemo (n = 321)	Chemo (n = 324)
ORR, % (95% CI)	47 (42-53)	27 (22-32)
CR	13	6
PR	34	21
SD	32	46
PD	13	12



[a]Number of responders.

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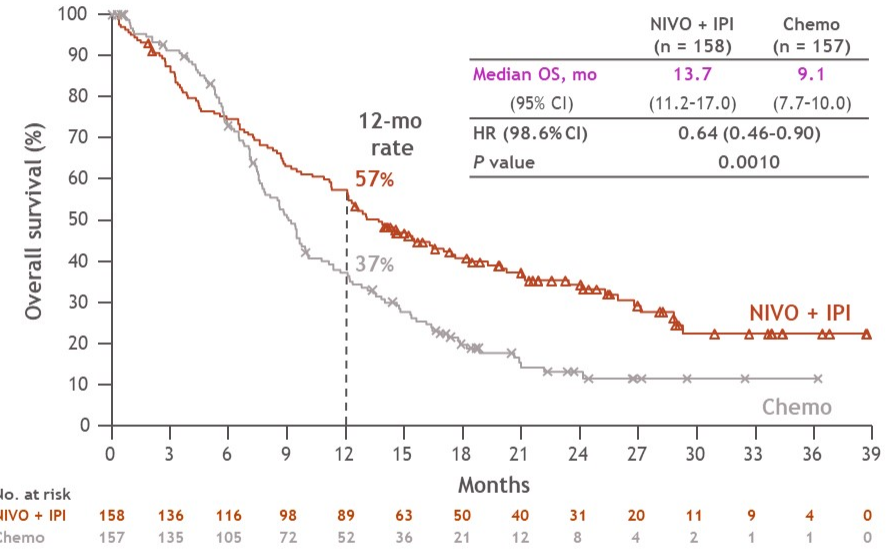
First-line Nivolumab in Squamous Cell

CheckMate 648

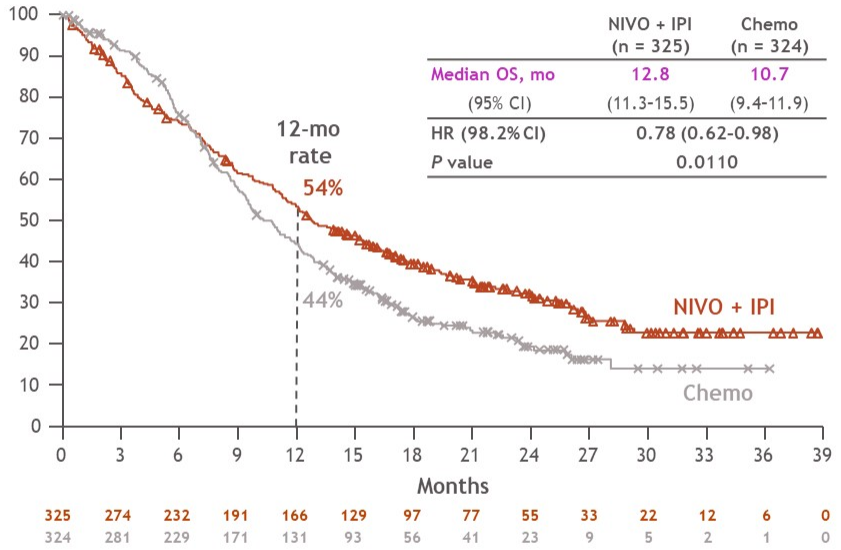
Overall survival: NIVO + IPI vs chemo

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	

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	

- 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.

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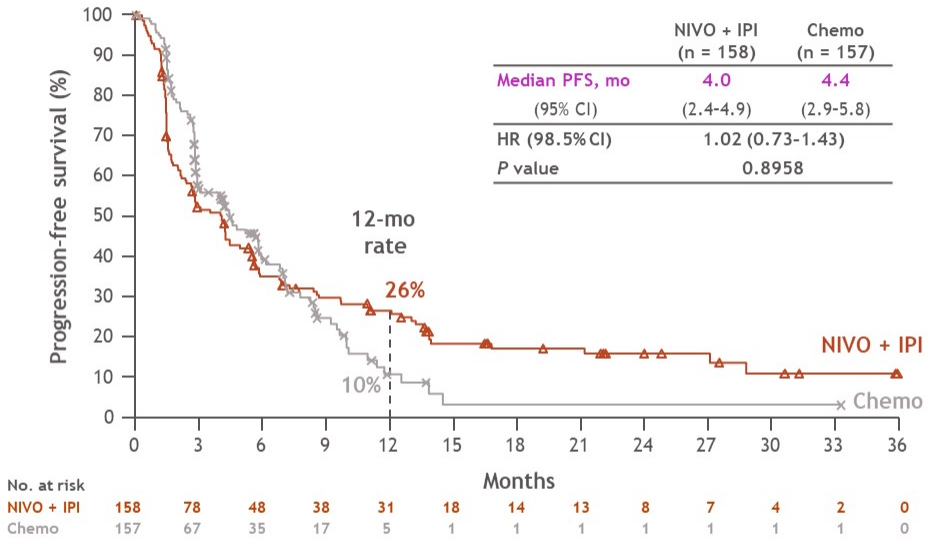
First-line Nivolumab in Squamous Cell

CheckMate 648

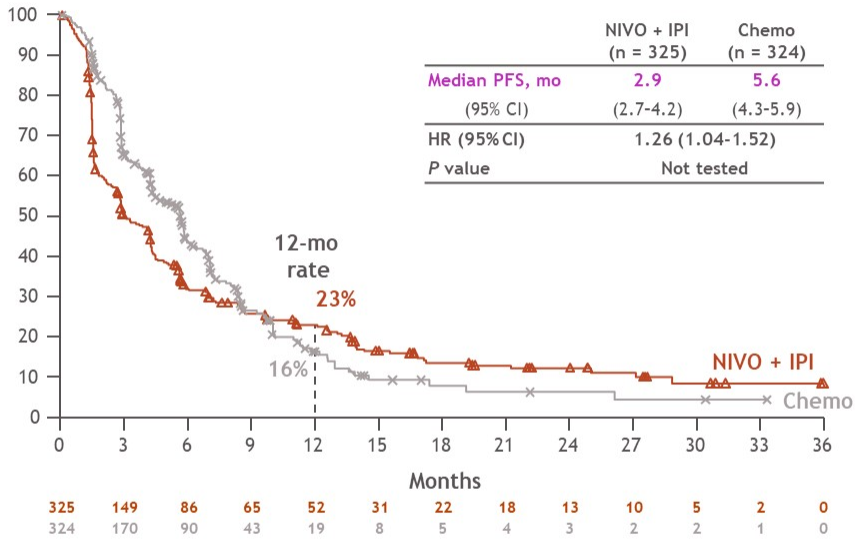
Progression-free survival: NIVO + IPI vs chemo

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



	NIVO + IPI (n = 158)	Chemo (n = 157)
Median PFS, mo	4.0	4.4
(95% CI)	(2.4-4.9)	(2.9-5.8)
HR (98.5% CI)	1.02 (0.73-1.43)	
P value	0.8958	

All randomized (per BICR)[a]



	NIVO + IPI (n = 325)	Chemo (n = 324)
Median PFS, mo	2.9	5.6
(95% CI)	(2.7-4.2)	(4.3-5.9)
HR (95% CI)	1.26 (1.04-1.52)	
P value	Not tested	

- Primary endpoint of PFS per BICR not met in patients with tumor cell PD-L1 ≥ 1%
- PFS per BICR not hierarchically tested in all randomized patients
- Directionally improved PFS per INV[b] with HR of 0.83 (95% CI, 0.64-1.07) in tumor cell PD-L1 ≥ 1% and 1.01 (95% CI, 0.85-1.21) in all randomized populations

[a]Minimum follow-up 12.9 months; [b]Exploratory analysis.

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First-line Nivolumab in 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.

Checkmate 648, 649 and Keynote 590 Takeaways

FOLFOX/XELOX + Nivo in advanced GEJ/gastric

- *Any CPS*

5-FU/Platinum + Pembro (FOLFOX + q6 wk pembro) or FOLFOX + nivo in SCC esophagus

- *Any CPS*

Consider Nivo + Ipi alone in patients who are not fit for chemo and/or low disease burden

Remaining/Evolving Questions: What to do in ≥2L advanced disease after progression on 1L ICI + chemo? Can we rechallenge with ICI?

Second Line Therapy

For patients who retain good PS

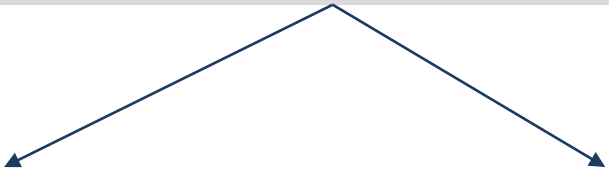
- Paclitaxel (+ Ramucirumab)
- Irinotecan
- Ramucirumab
- TAS-102
- *Pembrolizumab (CPS ≥ 10)*

How to choose ?

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

WJOG 4007: 2nd Line Irinotecan vs. Paclitaxel

Advanced Gastric Cancer without Severe Peritoneal Metastases – After Progression through 5-FU + Platinum (n=223)

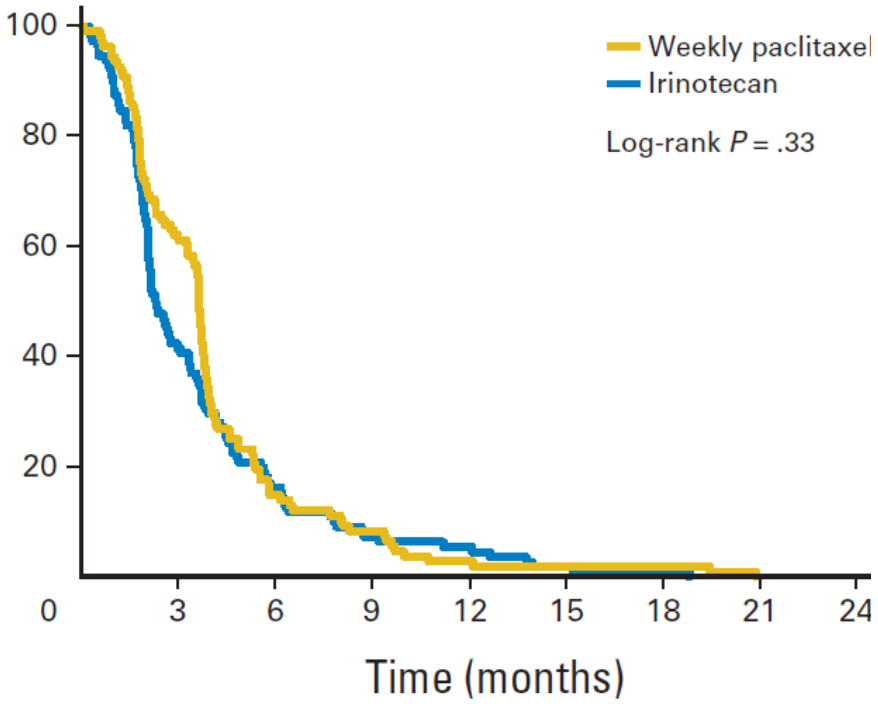


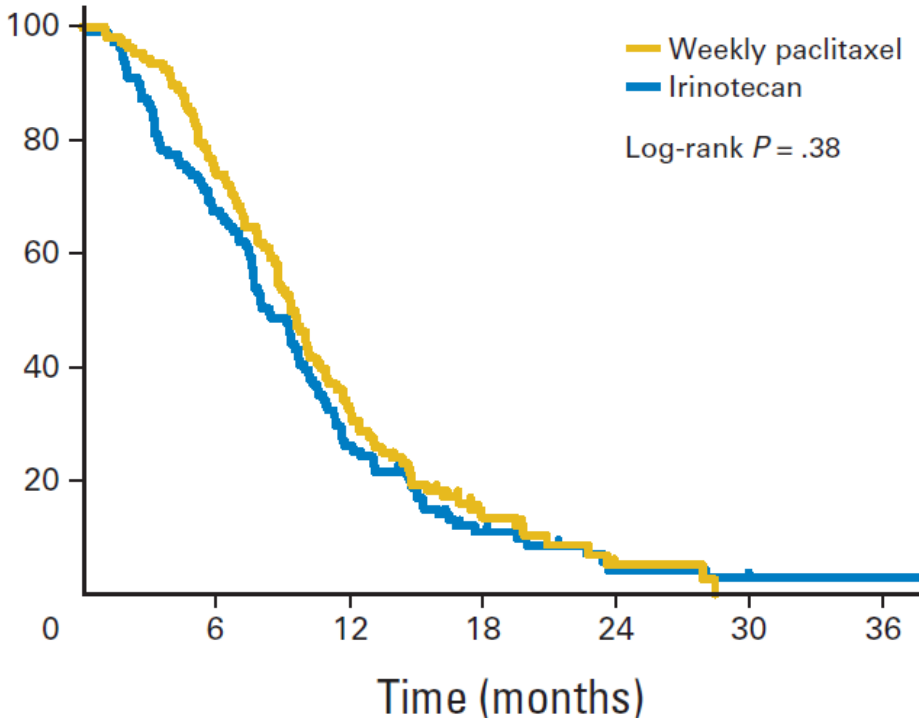
Weekly Paclitaxel 80mg/m2 Days 1, 8, 15 q28 days (n=111)

Irinotecan 150 mg/m2 Days 1,15 q28 days (n=112)

Hironaka S et al. J Clin Oncol, 2013; 31: 4438-4444.

WJOG 4007: 2nd Line Irinotecan vs. Paclitaxel





PFS: 3.6 mo (paclitaxel) vs. 2.3 mo (irinotecan)

OS: 9.5 mo (paclitaxel) vs. 8.4 mo (irinotecan)

Versus 5.2 mo in docetaxel arm of Cougar-2 study

Hironaka S et al. J Clin Oncol, 2013; 31: 4438-4444.

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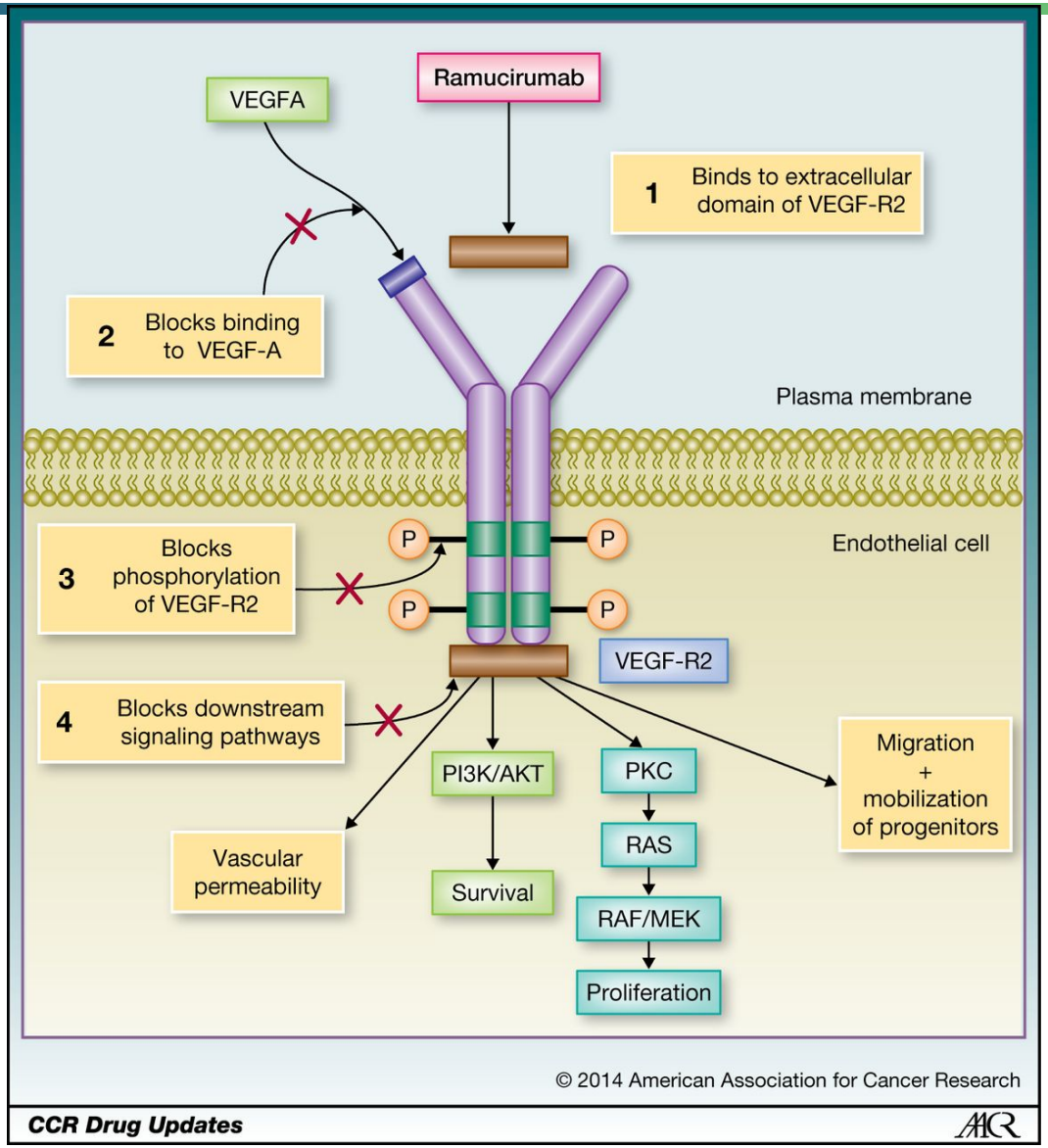
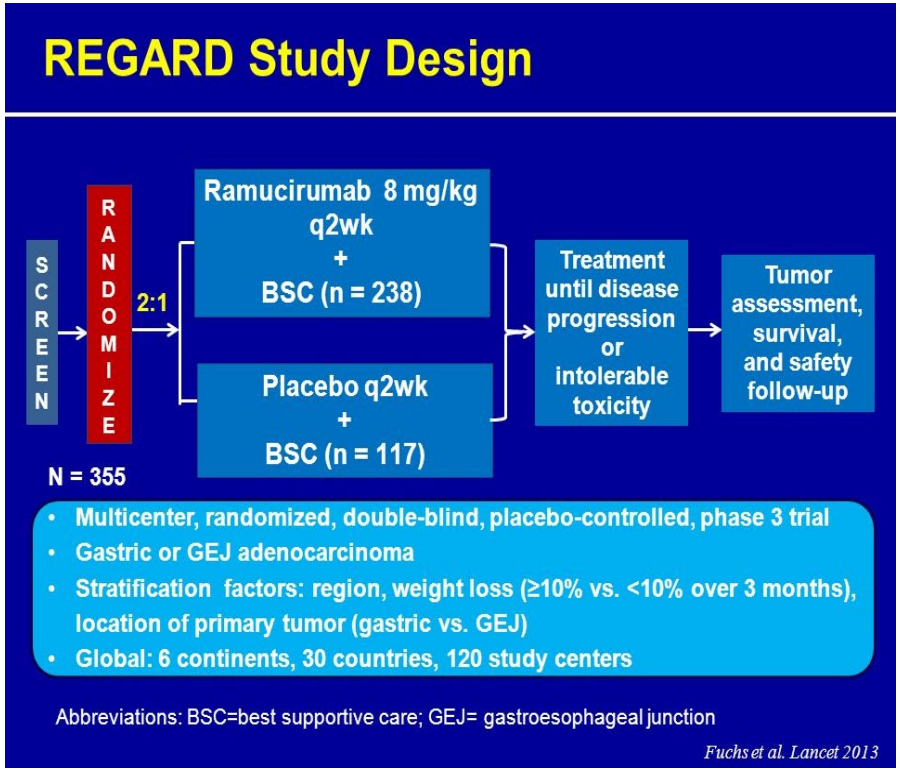
Ramucirumab and VEGF Pathway

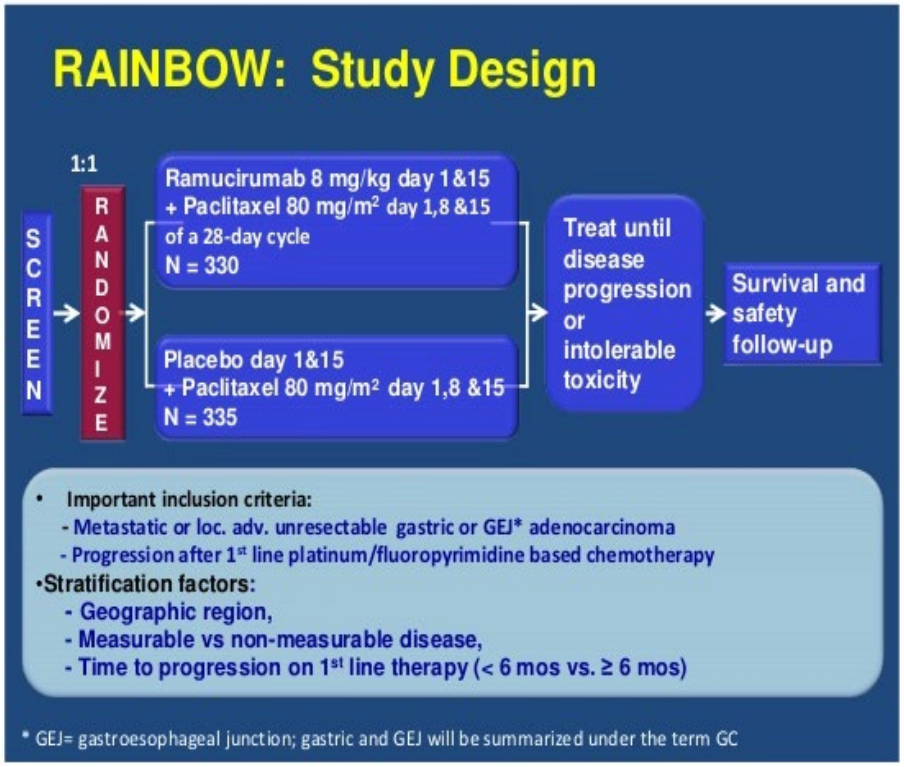


Javle, M et al. Clinical Cancer Research. 2014. 20(23)

REGARD and RAINBOW

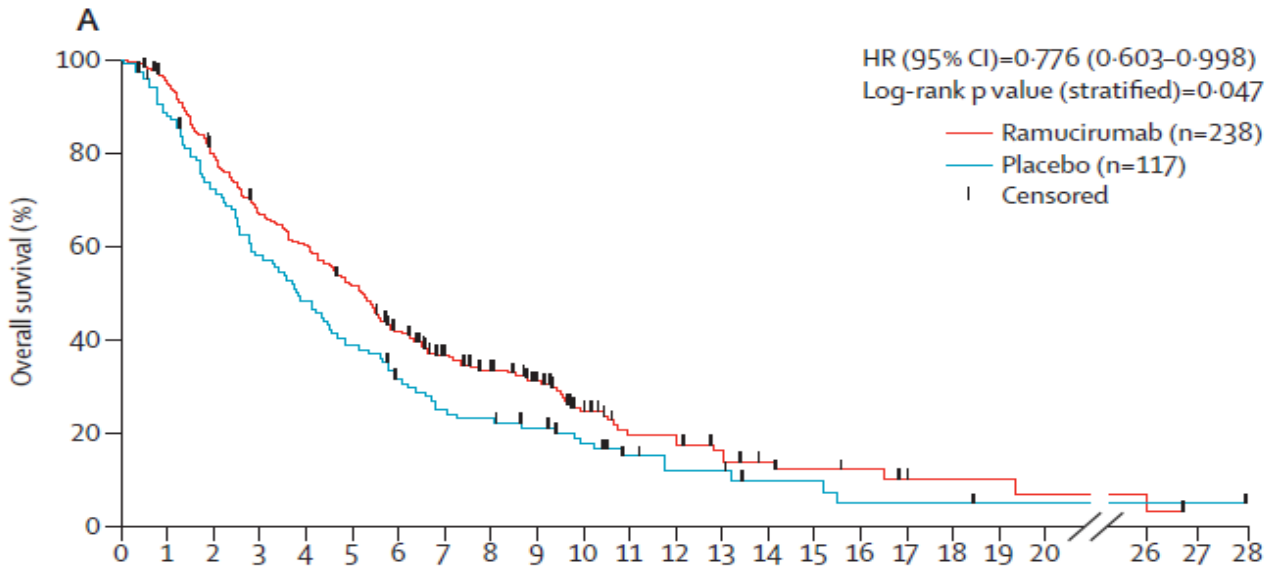


Fuchs, C et al. *Lancet*. Oct 3, 2013



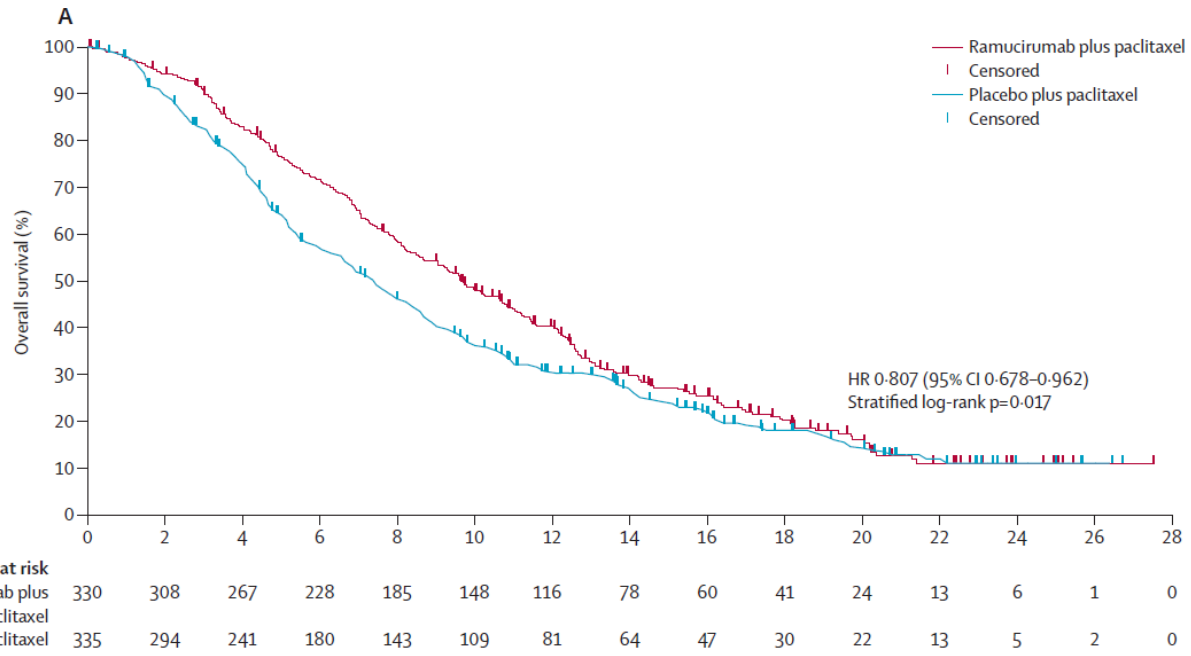
Wilke, H et al. Lancet Oncology. 2014, 15(11): 1224-35.

Ramucirumab: REGARD Study



	Ram	Placebo	P
PFS	2.1 mo	1.3 mo	<0.001
OS	**5.2 mo**	**3.8 mo**	**0.047**

Ramucirumab: RAINBOW



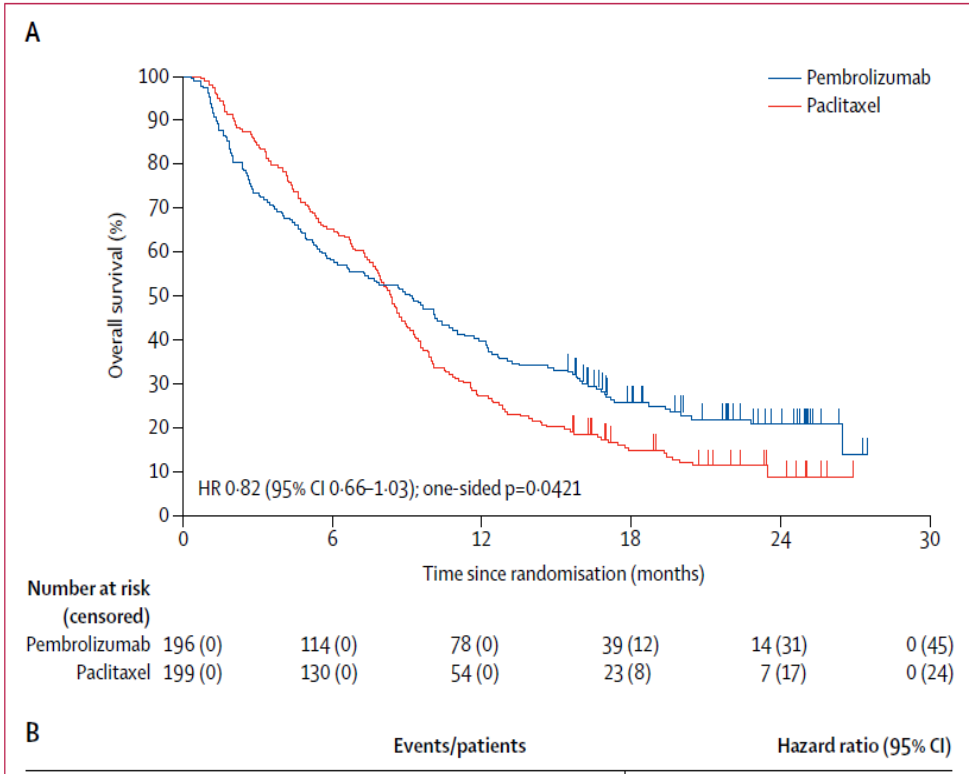
Endpoint	Ram + Paclitaxel	Placebo + Paclitaxel	Δ	p value
RR	28%	16%	12%	0.0001
DCR	80%	64%	16%	<0.0001
PFS	4.4 mo	2.86 mo	1.5	<0.0001
OS	9.63 mo	7.36 mo	2.3	0.0169

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

Second-line Pembrolizumab: Keynote 061

592 pts with advanced gastric cancer randomized to paclitaxel weekly versus pembro 200mg IV q3 wks. Trial amended to include only PDL1 CPS ≥1 pts.



- **Pembro did not significantly prolong OS** (9.1 vs 8.3 mo, HR 0.82, 95% CI 0.66-1.03). ORR was similar (16 versus 14 %)
- P threshold 0.0135 for superiority
- **Pembro toxicity profile favorable** (14% vs. 35% grade ≥ 3 AE)
- Potentially greater effect in CPS ≥10 and MSI-h

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Shitara, K. et al. Lancet. 2018; 392: 123-133.

Second-line Pembrolizumab: Keynote 061

Efficacy Outcomes.

	Pembrolizumab CPS ≥1 n = 196	Paclitaxel CPS ≥1 n = 199	Pembrolizumab CPS ≥5 n = 95	Paclitaxel CPS ≥5 n = 91	Pembrolizumab CPS ≥10 n = 53	Paclitaxel CPS ≥10 n = 55
OS, deaths, n (%)	176 (89.8)	190 (95.5)	84 (88.4)	86 (94.5)	44 (83.0)	51 (92.7)
OS, months, median (95% CI)	9.1 (6.2-10.7)	8.3 (7.6-9.0)	10.4 (6.7-15.5)	8.3 (6.8-9.4)	10.4 (5.9-18.3)	8.0 (5.1-9.9)
HR (95% CI)	0.81 (0.66-1.00)	—	0.72 (0.53-0.99)	—	0.69 (0.46-1.05)	—
P	0.03	—	0.02	—	0.04	—
PFS, months, median (95% CI)	1.5 (1.4-2.0)	4.1 (3.2-4.3)	1.6 (1.4-2.8)	4.0 (2.8-4.4)	2.7 (1.4-4.3)	4.0 (2.7-4.4)
HR (95% CI)	1.25 (1.02-1.54)	—	0.98 (0.71-1.34)	—	0.79 (0.51-1.21)	—
ORR, % (n)	16.3 (32)	13.6 (27)	20.0 (19)	14.3 (13)	24.5 (13)	9.1 (5)
DOR, months, (range)	19.1 (1.4+ to 47.1+)	5.2 (1.3+ to 16.8)	32.7 (4.1 to 47.1+)	4.8 (1.3+ to 15.3)	NR (4.1 to 47.1+)	6.9 (2.6 to 6.9)

Fewer drug-related AEs with Pembrolizumab

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Fuchs, C et al. ASCO 2020

Second-line Pembrolizumab: Keynote 181

401 pts with SCC and 222 pts with CPS ≥10

628 patients with advanced or metastatic **squamous cell cancer** of the esophagus or **adenocarcinoma** of the esophagus / GE jxn
- Progressed on 1L therapy
- ECOG 0 or 1

R
1:1

Pembrolizumab 200mg q3wk

Investigator choice chemo
- Paclitaxel 80mg/m2 D 1,8,15 q28d
- Docetaxel 75mg/m2 q3wk
- Irinotecan 180mg/m2 q2wk

Primary endpoints: OS in SCC, CPS ≥10, and total population

Kojima, T. et al. 2019 GI Cancers Symposium

Pembro approved in July 2019 for 2nd line treatment of SCC esophagus with CPS ≥ 10 based on results from Keynote 181

Key Results

- Pembrolizumab was superior to chemo for OS in CPS ≥10 (9.3 vs. 6.7 mo; HR 0.69; 95% CI 0.52-0.93; *P*=0.0074).
- SCC subgroup: Improvement in OS with pembrolizumab vs chemo, (8.2 mo vs 7.1 mo; HR 0.78; 95% CI 0.63, 0.96; *P*=0.0095).
- Fewer any-grade (64% vs 86%) or grade 3-5 (18% vs 41%) drug-related AEs with pembrolizumab vs chemo.

What didn't work?

CMET Inhibitors -- (RILOMET 1 – worse survival in Txarm)

EGFR Inhibitors – Cetuximab, Panitumumab (REAL3, E1206/CALGB 80403)

mTOR inhibitors – Everolimus vs. BSC

Napabucasin (BRIGHTER trial)

Take-home points: Metastatic Gastric/Eso

- 2 drug combinations (5-FU+platinum) represents a standard of care worldwide in 1st line therapy
- Trastuzumab in 1st line for Her2 positive tumors (can add pembro); Trastuzumab-deruxtecan in subsequent line
- Nivolumab + chemo in 1st line gastric/GEJ adeno (any CPS)
- Pembro/Nivo + chemo in 1st line esophagus (any CPS)
- Nivo + Ipi – non chemo option in select patients
- In 2nd line, irinotecan, paclitaxel (+ramucirumab) viable options; nivo or pembro if no prior checkpoint inhibitor

THANK YOU

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Extra Slides

The Dutch Gastric Cancer Group: D1 vs. D2

	D2	D1
N stage		
N0	**144 (44%)**	**171 (45%)**
N1	113 (34%)	138 (36%)
N2	47 (14%)	50 (13%)
N3	27 (8%)	21 (6%)

- High rates of over and under dissection
- Higher than anticipated number of node negative cases

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

Neoadjuvant ChemoRT: Randomized Trials

Citation	# Pts	Preoperative Treatment	Path CR	Survival
Walsh, TN *NEJM* 1996	113 (adeno only)	Cis/5-FU/RT (40 Gy)	25%	16 vs. 11 months (p=0.01)
Bosset, JF *NEJM* 1997	282 (SCC only)	Cis/RT (37 Gy)	26%	18.6 months both groups
Urba, SG *JCO* 2001	100 (75% adeno)	Cis/5FU/ Vinblastine/RT (45 Gy)	28%	17.6 vs. 16.9 months (p=0.15)
Burmeister, BH *Lancet Oncol* 2005	256 (60% adeno)	Cis/5FU/RT (35 Gy)	16%	21.7 vs. 18.5 months (p=NS)
Tepper, J *JCO* 2008	56 (75% adeno)	Cis/5FU/RT (50.4 Gy)	40%	4.48 years vs 1.79 years (p=0.02)
Van Hagen, P *NEJM* 2012	363 (75% adeno)	Paclitaxel/Carbo/RT (41.4 Gy)	32.6%	49 vs. 24 months (p=0.011)

Siewert Classification

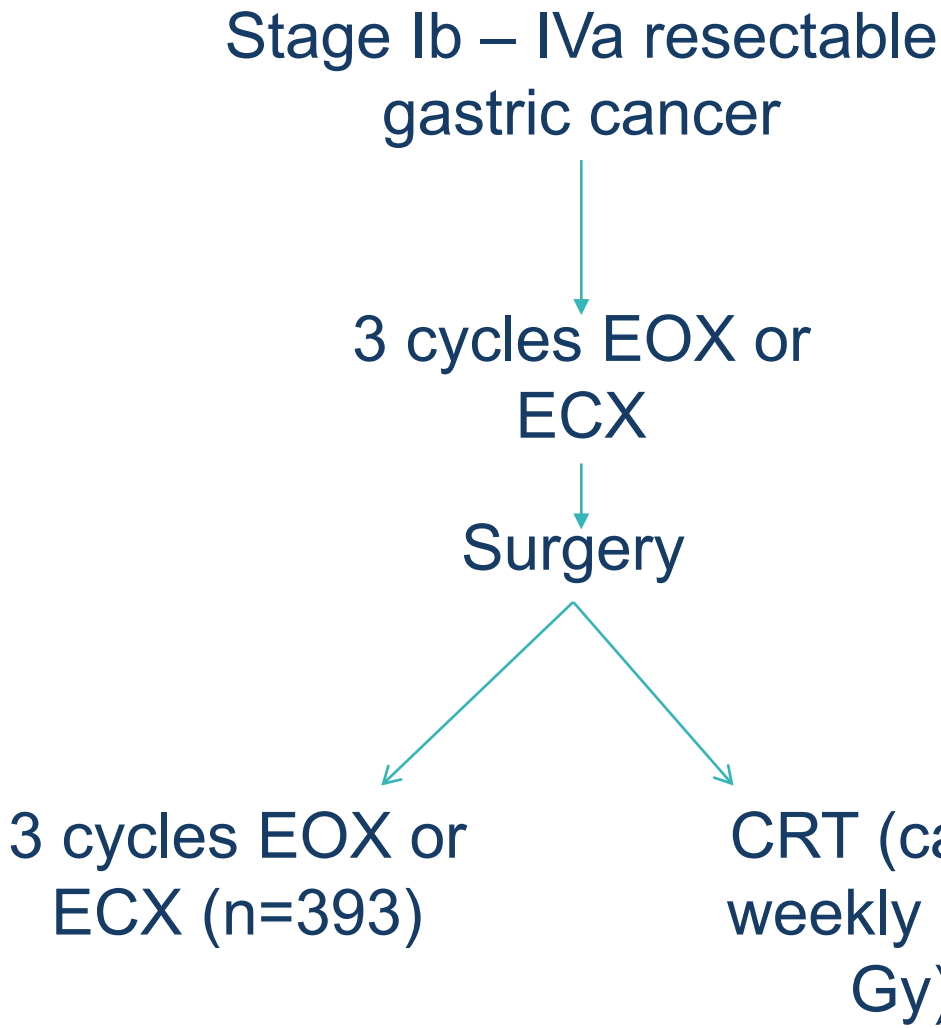
	Type 1 (n= 494)	Type II (n= 414)	Type III (n= 438)
Mean age at presentation	60.1 ± 10.3	60.7 ± 11.4	62.7 ± 12.0
Male: Female Ratio	9.9 : 1	4.8 : 1	2.1 : 1
Associated Barrett's	76.9%	9.8%	2.0%
Prevalence of Grade 3/4 tumors	52.6%	58.7%	72.6%
Intestinal type histology	81.1%	41.3%	39.1%

Siewert R et al. *J Surg Onc*. 90; 139-46, 2005

Chemo (PeriOp vs. PostOp) vs. ChemoRT

Citation	# Pts	Treatment	3 or 5 year OS in Treatment Arm
MacDonald, JS 2001 (INT-0116)	**556**	**Arm A: Surgery alone** **Arm B: Surgery → 5-FU/LV + RT**	**50%**
Fuchs, CS 2011 (CALGB 80101)	546	Arm A: Surgery → 5-FU/LV/RT Arm B: Surgery → ECF/RT	52%
Cunningham, D 2006 (MAGIC)	**503**	**Arm A: Surgery alone** **Arm B: ECF(3) → surgery → ECF(3)**	**36%**
Sasako, M 2011 (ACTS-GC)	1,059	Arm A: Surgery (D2) Arm B: Surgery → S1 x 1 year	71.7%
Bang, Y. 2011 (CLASSIC)	**1,035**	**Arm A: Surgery (D2)** **Arm B: Surgery (D2) →XELOX x 8 cycles**	**83%**

CRITICS Trial: (MAGIC vs. MacDonald?)



KEY RESULTS

5-year survival: 41.3 % (chemo) vs. 40.9% (RT), p=0.99

87% underwent D2 dissection

Poor postoperative treatment compliance in both arms

Cats, A. et al. Lancet Oncology. 2018, 19(5): 616-628

2nd Line Therapy --- Cougar-2 Study

Advanced Esophagogastric Cancer (n=168)

Progression within 6 mo of 5FU/platinum

ECOG 0-2

→ Docetaxel 75mg/m2 q3w X 6 cycles

→ Active symptom control

OS (primary endpoint),
HRQOL (secondary endpoint)

Ford H et al. Lancet Oncology 2014; 15: 78-86

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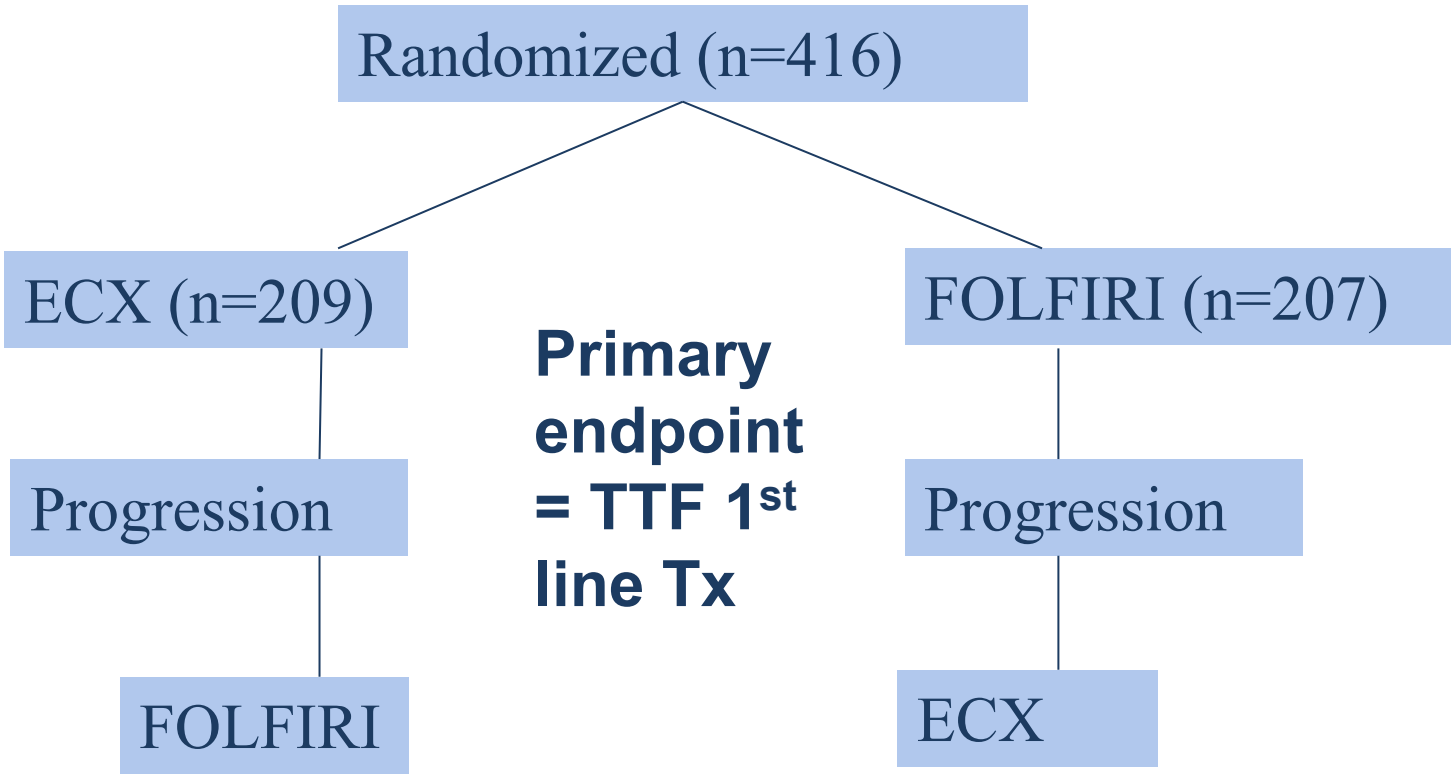
2 Drugs vs. 3 Drugs



TTF = Time between randomization and treatment d/c, progression, death

Guimbaud, R et al. J Clin Oncol. 2014, Nov 1; 32(21): 3250-6.

2 Drugs vs. 3 Drugs

Table 3. Maximum Severity Grade for Toxicities

	ECX Arm		FOLFIRI Arm		
Toxicity and Grade	No.	%	No.	%	*P**
First-line	200		203		
Nonhematologic					.81
Grade 0 to 2	85	42.5	90	44.3	
Grade 3 to 4	107	53.5	108	53.2	
Missing	8	4.0	5	2.5	
Hematologic					< .001
Grade 0 to 2	60	30.0	120	59.1	
Grade 3 to 4	129	64.5	78	38.4	
Missing	11	5.5	5	2.5	
Overall					< .001
Grade 0 to 2	25	12.5	58	28.6	
Grade 3 to 4	167	83.5	140	69.0	
Missing	11	5.5	5	2.5	

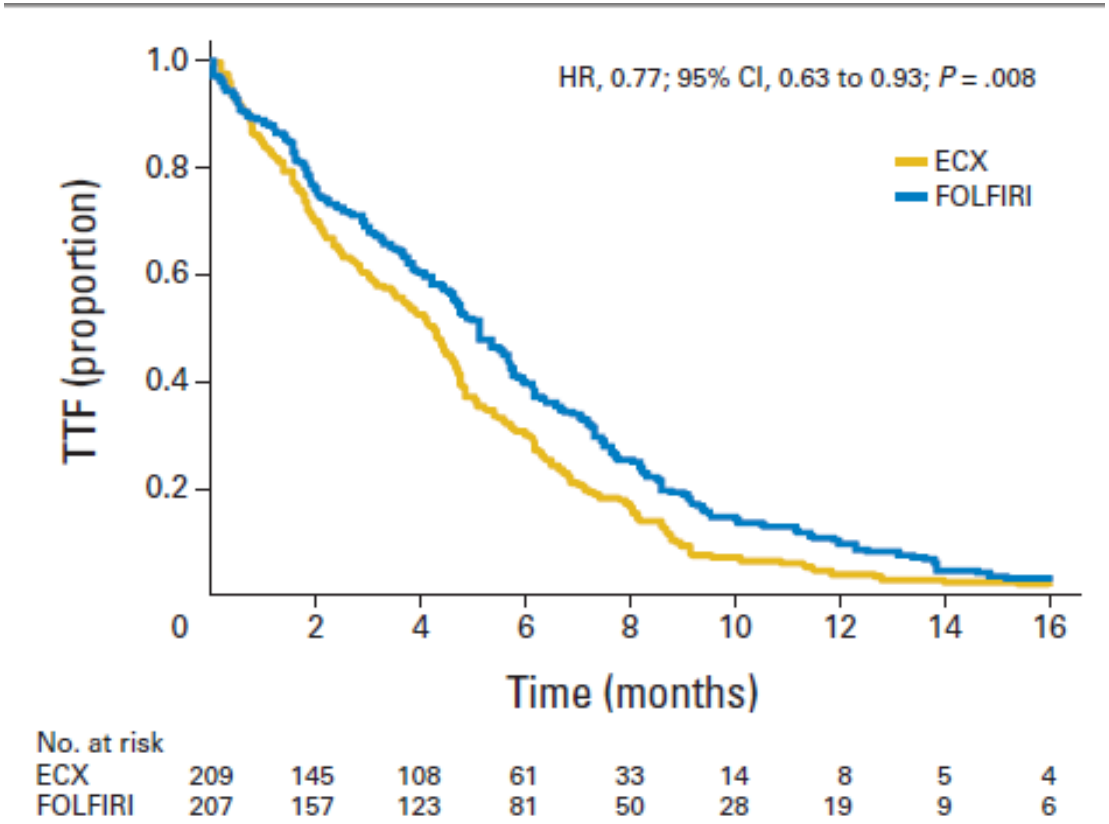
Guimbaud, R et al. J Clin Oncol. 2014, Nov 1; 32(21): 3250-6.

2 Drugs vs. 3 Drugs

TTF:
4.24 mo (ECX)
5.08 mo (FOLFIRI)
P=0.008

PFS:
5.29 mo (ECX)
5.75 mo (FOLFIRI)
P=0.96

OS:
9.49 mo (ECX)
9.72 mo (FOLFIRI)
P=0.95



In U.S., most typical 2-drug first-line regimen is FOLFOX

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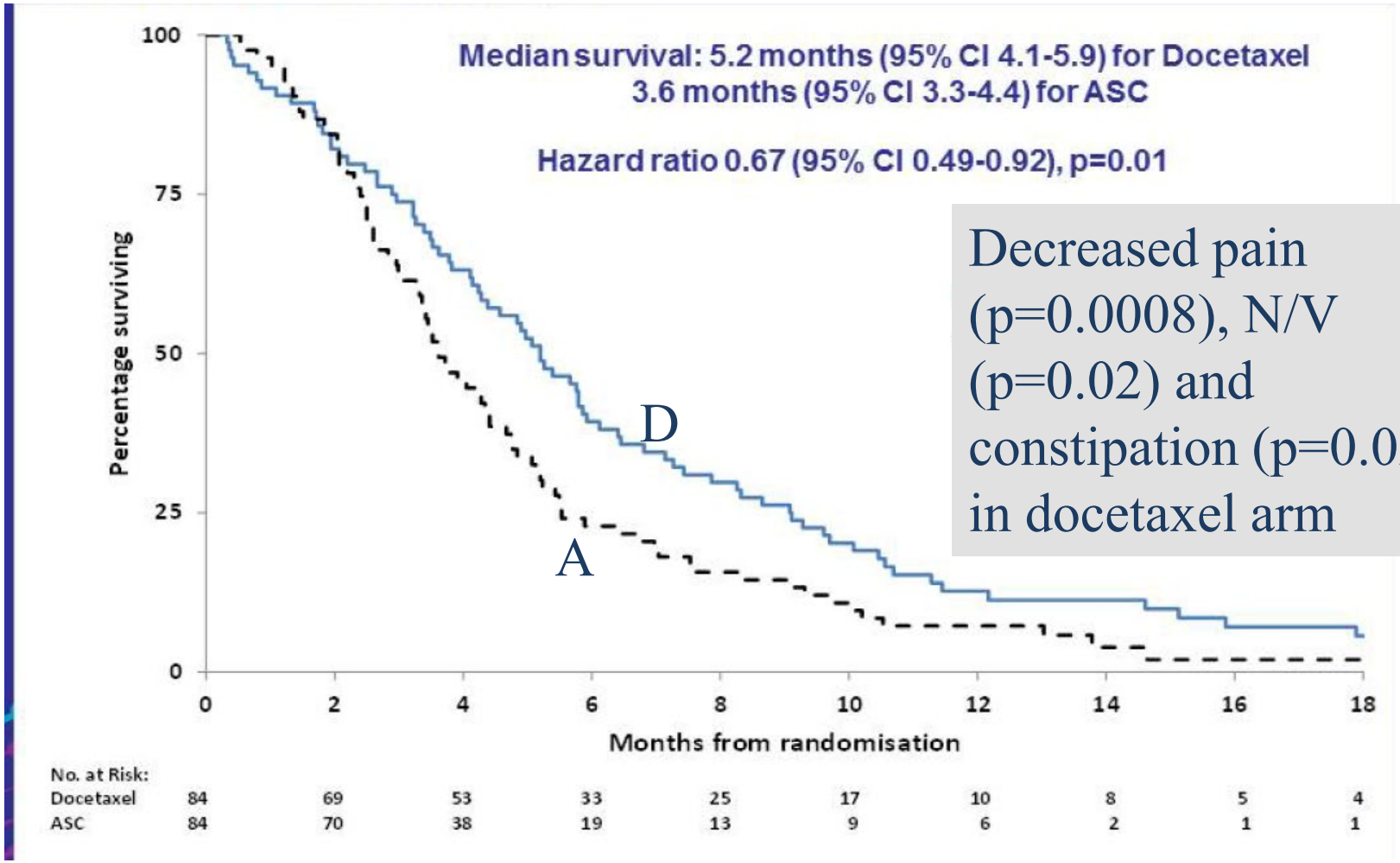
2nd Line Therapy --- Cougar-2 Study



Decreased pain (p=0.0008), N/V (p=0.02) and constipation (p=0.02) in docetaxel arm

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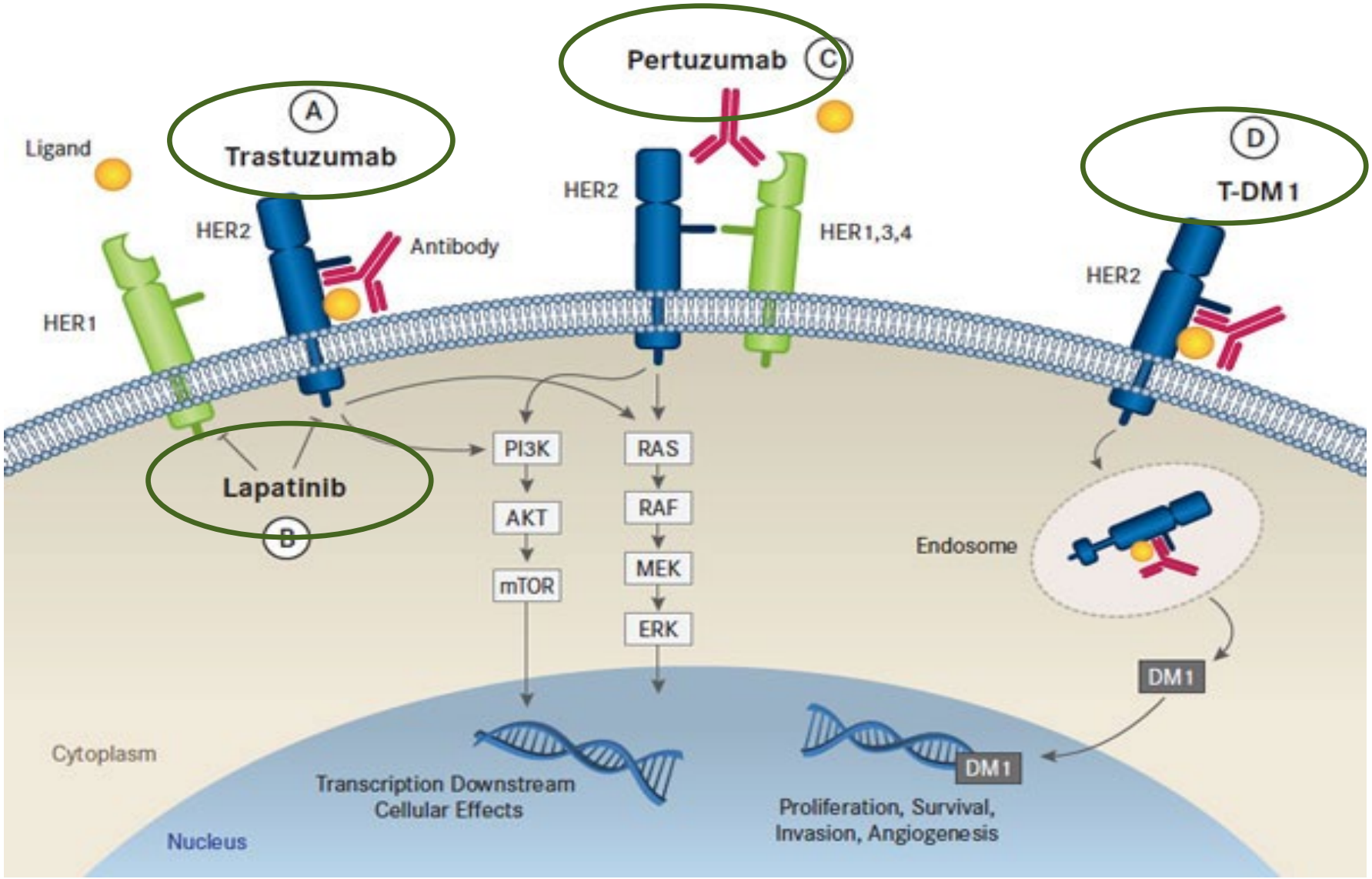
Ford H et al. Lancet Oncology 2014; 15: 78-86

Anti-Her2 agents – Mechanism of Action



Immune Checkpoint Inhibitors

Study	Drug	Population	N	RR	OS
Keynote 012	Pembro 10mg/kg q2 wks	Refractory PDL1+	39	22%	11.4 mo
Attraction-2	Nivolumab 3mg/kg q2 wks vs. Placebo	Refractory any PDL1	493	11.2%	5.32 vs. 4.14 mo (HR 0.63, p<0.0001)
Keynote 059 (cohort 1)	Pembro 200mg q3 wk	Refractory any PDL1	259	11.2% *PDL1+ 15.5%* *PDL1- 5.5%*	NR
Checkmate 032	• Nivo 3mg/kg q2 • Nivo 1mg/kg + Ipi 3mg/kg • Nivo 3mg/kg + Ipi 1mg/kg	Refractory any PDL1	160	16% Overall 14% N3 26% N1+I3 10% N3+I1	 5.0 mo 6.9 mo 4.8 mo

Muro, K et al. *Lancet Oncology*. 17(7), 2016.
Al-Batran, S. et al. ACSO 2017 Annual Meeting
Janjigian, E. et al. ASCO 2016
Fuchs, CS et al. ASCO 2017.

Pembrolizumab – Keynote 059

Advanced gastric cancer, progressed after 2 or more prior therapies

Table 1. Objective Tumor Response

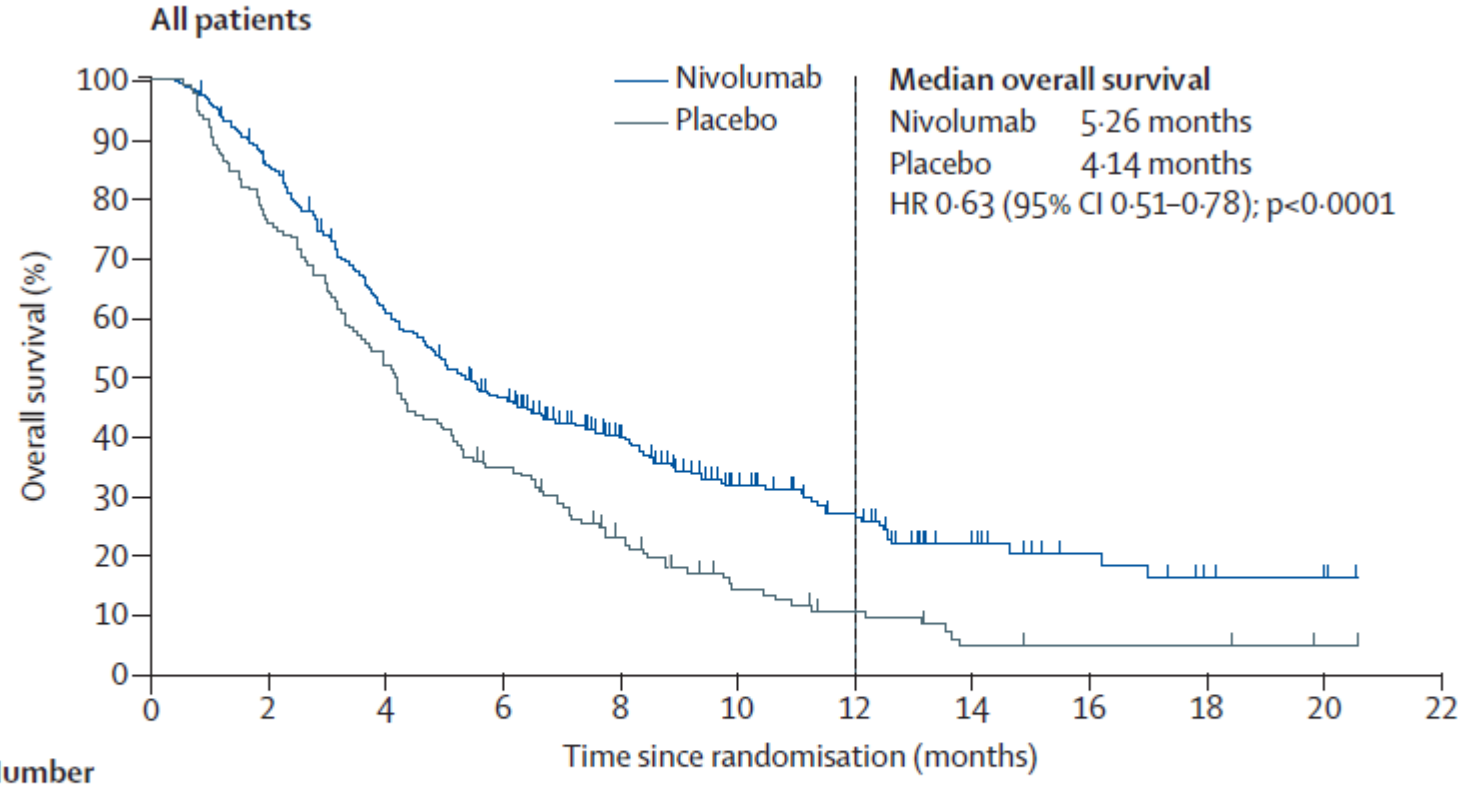
Best Overall Response[a]	Participants (n = 259) No.	% (95% CI)
Objective response (CR+PR)	30	11.6 (8.0-16.1)
Disease control (CR+PR+SD ≥2 mo)	70	27.0 (21.7-32.9)
CR	6	2.3 (0.9-5.0)
PR	24	9.3 (6.0-13.5)
SD	42	16.2 (11.9-21.3)
Progressive disease	145	56.0 (49.7-62.1)
Nonevaluable	7	2.7 (1.1-5.5)
No assessment[b]	35	13.5 (9.6-18.3)
Duration of response, median (range), mo	8.4 (1.6+ to 17.3+)[c]	

15.5% PDL1 +

6.4% PDL1 -

Fuchs, C et al. JAMA Oncology. 2018, 4(5): e180013

Nivolumab vs. BSC: ATTRACTION 2 Trial



Number at risk (censored)												
Nivolumab	330 (0)	275 (6)	192 (10)	141 (16)	94 (45)	56 (65)	38 (75)	19 (88)	10 (96)	5 (99)	3 (101)	0 (104)
Placebo	163 (0)	121 (3)	82 (4)	53 (6)	32 (10)	16 (15)	10 (17)	4 (18)	3 (19)	3 (19)	1 (21)	0 (22)

Kang, Y et al. Lancet. 2017, 390: 2461-2471.

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