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Systemic Therapies for Advanced Gastroesophageal Cancers: An Evolving Treatment Landscape

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Disclosures

- Employment – GlaxoSmithKline (IF)
- Stock – GlaxoSmithKline (IF)

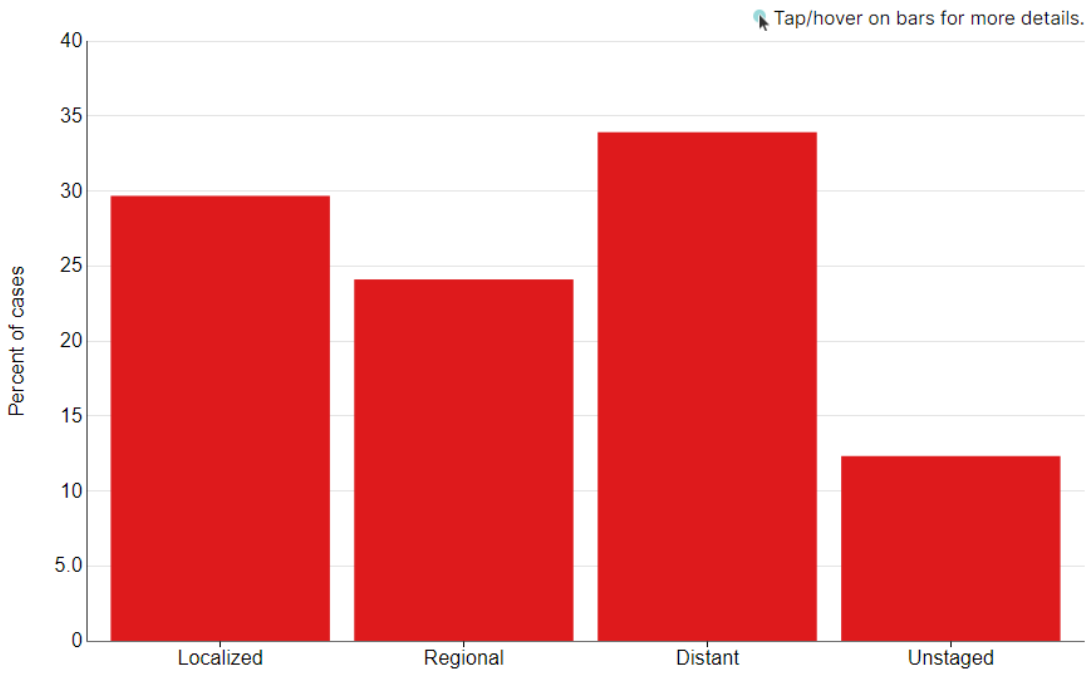
Learning objectives

- Understand the importance of timely biomarker testing to guide treatment decision-making in advanced gastroesophageal cancers
- Review guideline-recommended systemic therapy options for HER2-negative and HER2-positive gastroesophageal cancers
- Explore emerging molecularly informed approaches in the management of advanced gastroesophageal cancers

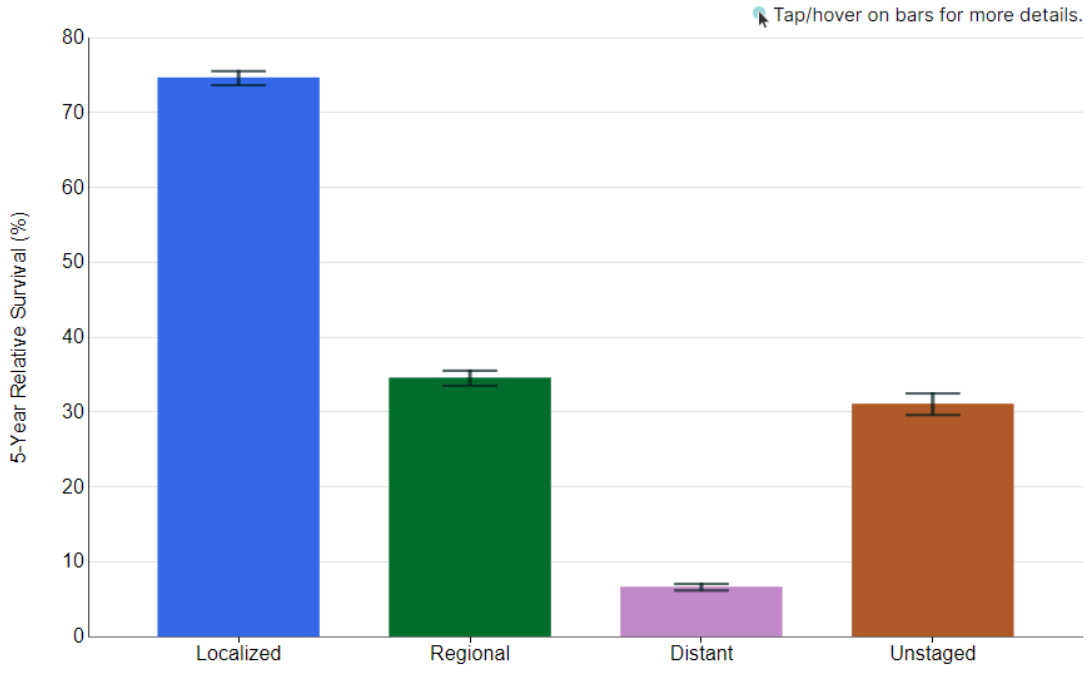
Overview of Advanced GE Cancers

Prognosis for advanced GE cancers is dismal

Incidence

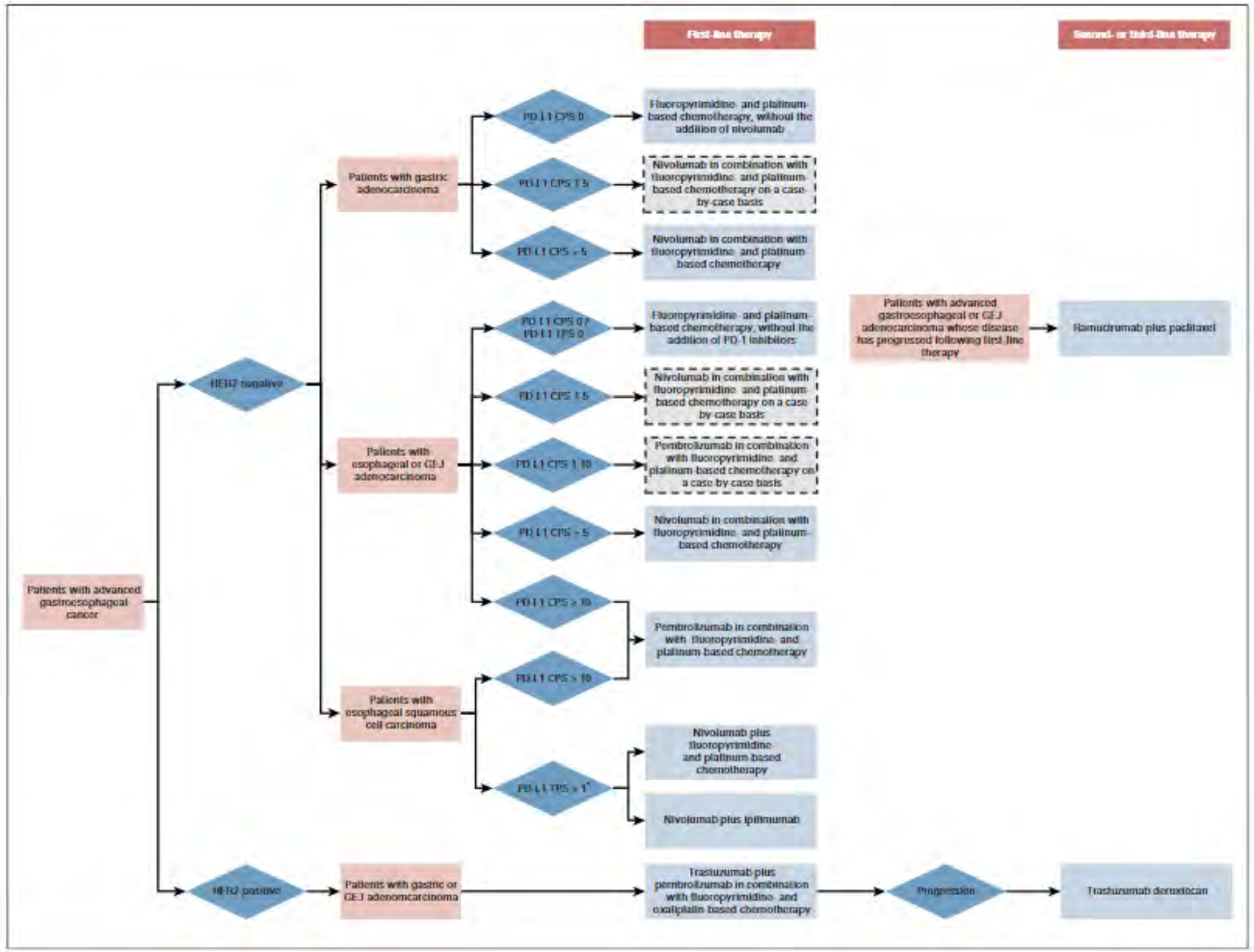


5-year survival



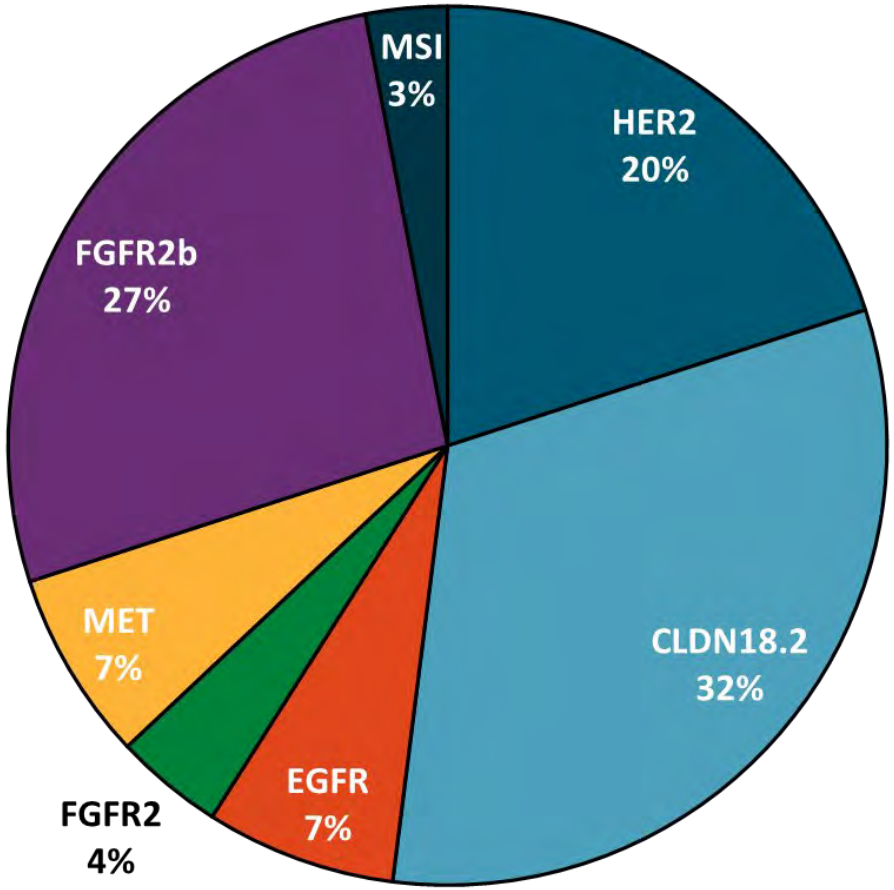
ACS Facts and Figures 2023; NCI SEER*Explorer

Treatment for advanced GE cancers is rapidly evolving



ASCO guidelines, Shah *JCO* 2023

Timely biomarker testing is essential



- At minimum:
  - HER2/ERBB2
  - PD-L1
  - MMR/MSI
- Also consider:
  - FGFR2b
  - CLDN18.2
  - And others

- Courtesy of Samuel Klempner, MD

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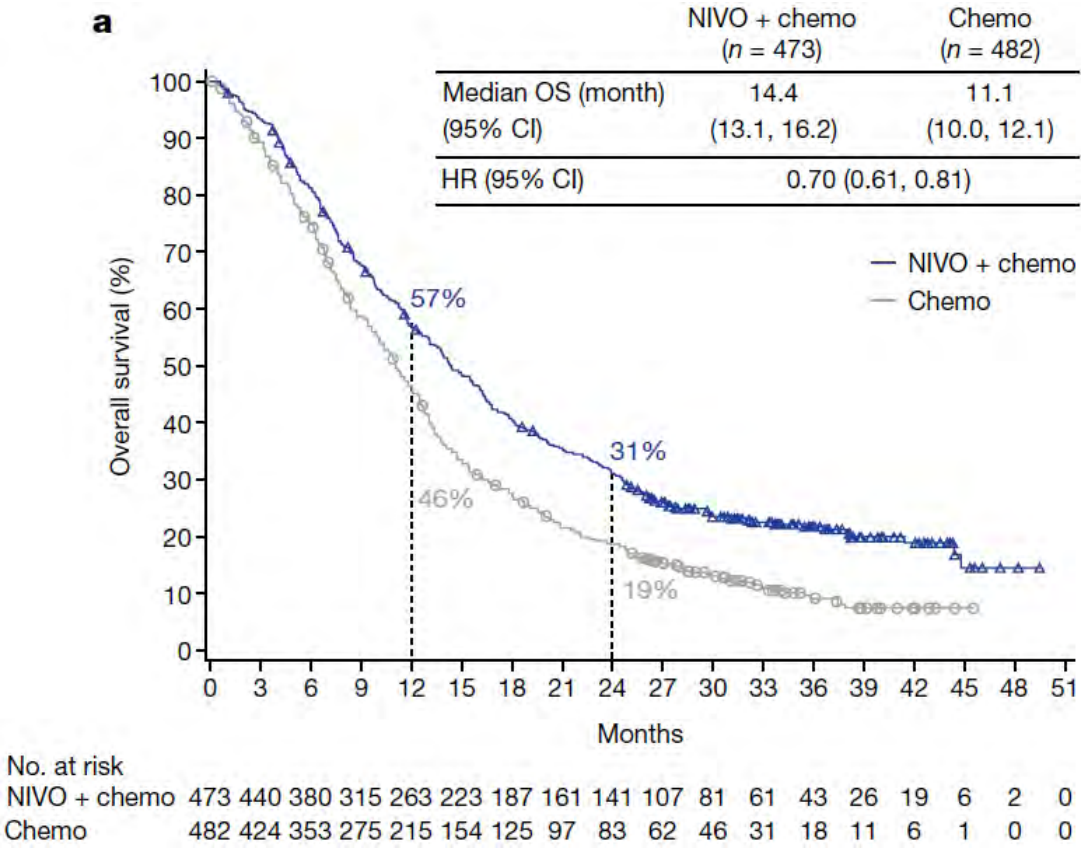
Approach to HER2-Negative GE Cancers

1L: Fluoropyrimidine + platinum +/- nivolumab (CheckMate 649)

Primary outcome:
OS in CPS ≥5

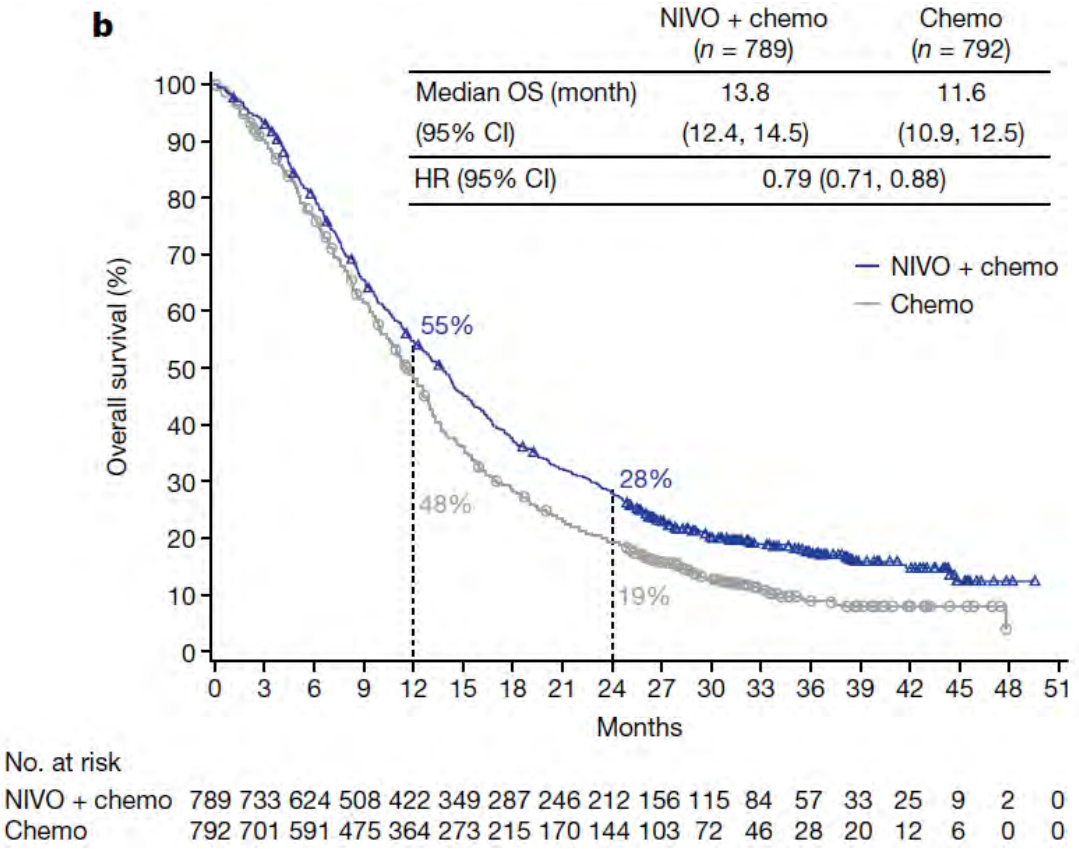


Chemo backbone:
- FOLFOX
- CAPOX

Janjigian *Lancet* 2021, Shitara *Nature* 2022

1L: Fluoropyrimidine + platinum +/- nivolumab (CheckMate 649)

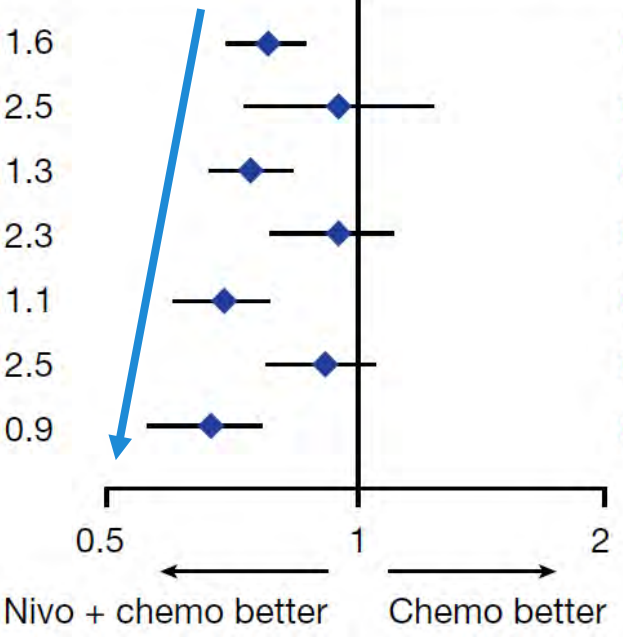
Secondary outcome: OS in all randomized pts



1L: Fluoropyrimidine + platinum +/- nivolumab (CheckMate 649)

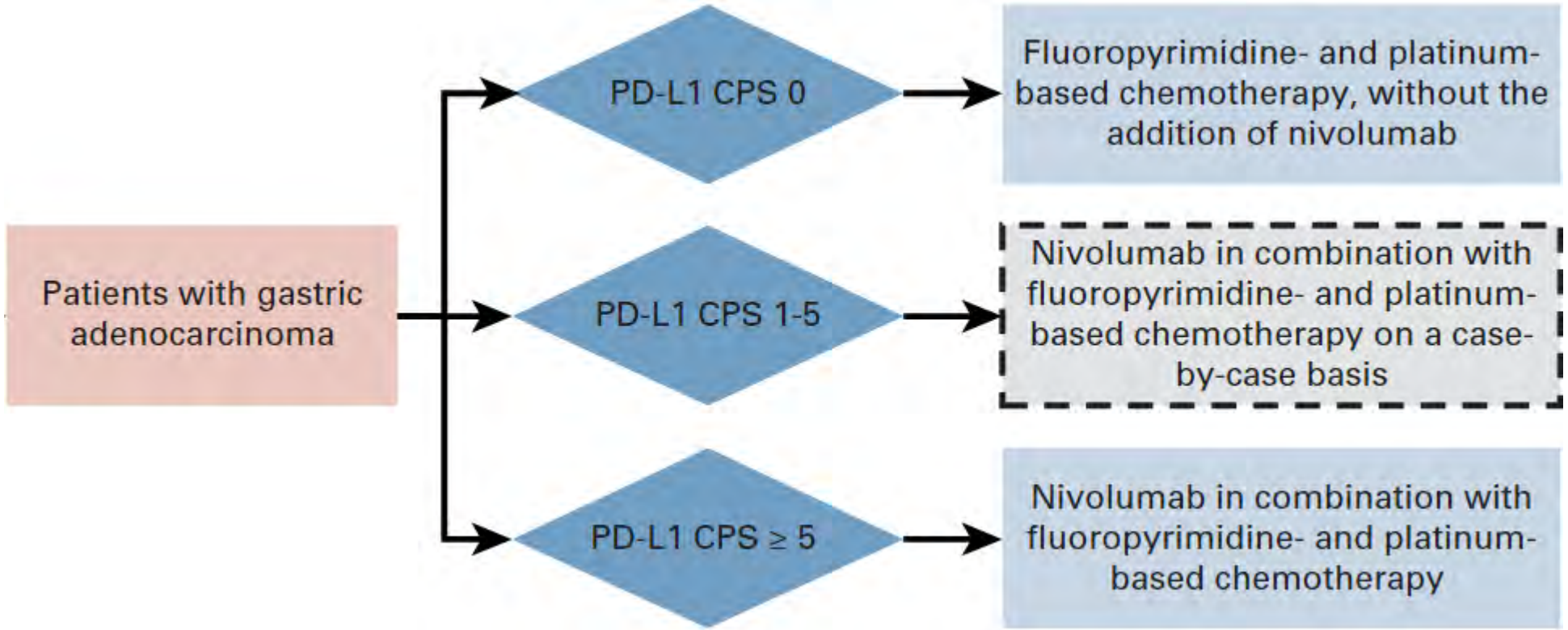
a

Population	Median overall survival (month) Nivolumab plus chemotherapy	Chemotherapy	Unstratified HR for death (95% CI)
Overall (*n* = 1,581)	13.8	11.6	0.78 (0.70, 0.87)
PD-L1 CPS <1 (*n* = 265)	13.1	12.5	0.95 (0.73, 1.24)
PD-L1 CPS ≥1 (*n* = 1,297)	13.8	11.3	0.74 (0.66, 0.84)
PD-L1 CPS <5 (*n* = 607)	12.4	12.3	0.94 (0.79, 1.11)
PD-L1 CPS ≥5 (*n* = 955)	14.4	11.1	0.69 (0.60, 0.79)
PD-L1 CPS <10 (*n* = 795)	12.4	12.5	0.91 (0.78, 1.06)
PD-L1 CPS ≥10 (*n* = 767)	15.0	10.9	0.66 (0.56, 0.77)



OS benefit persists after excluding patients with dMMR/MSI-H disease

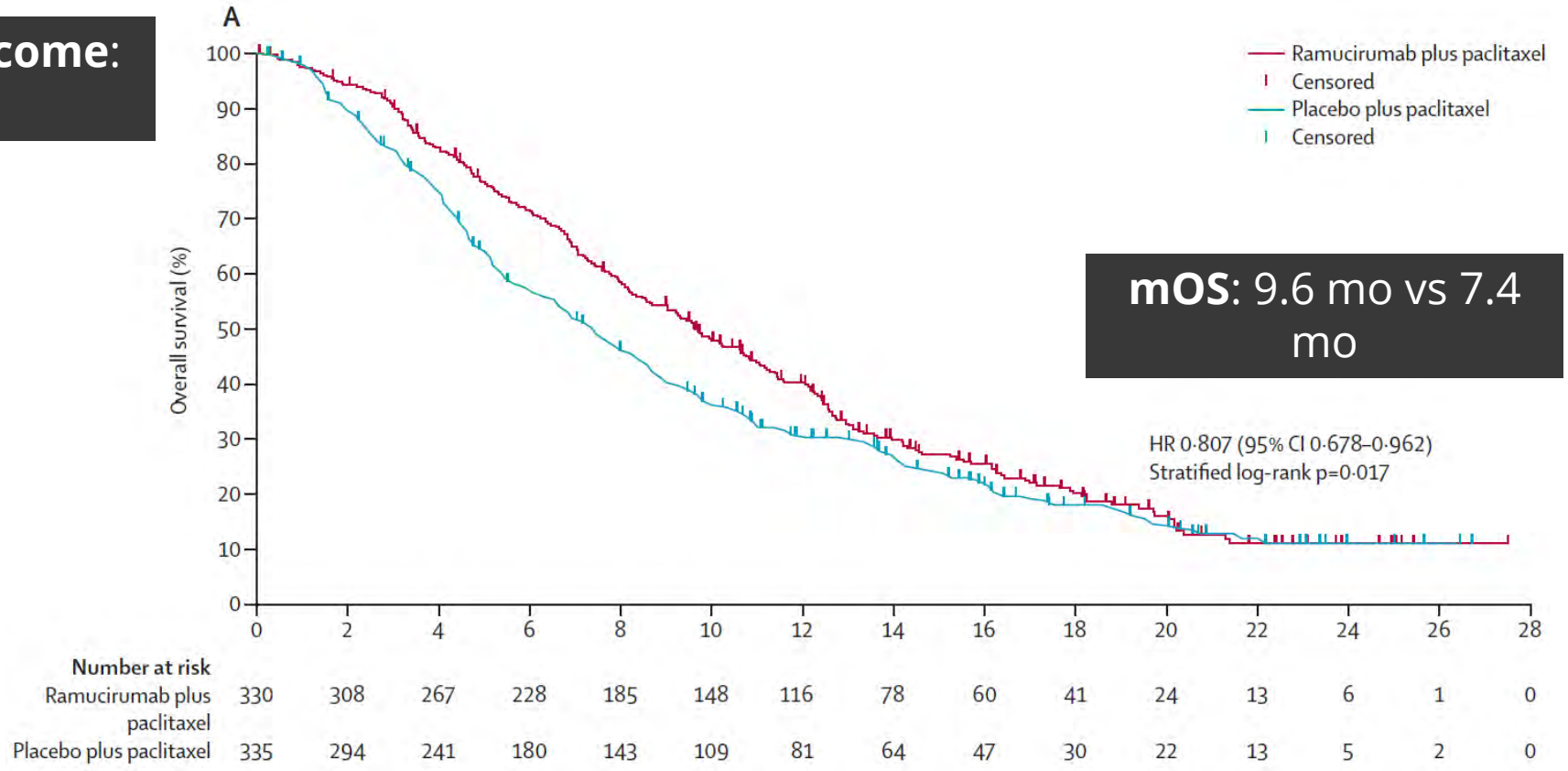
1L: Fluoropyrimidine + platinum +/- nivolumab (CheckMate 649)



- ASCO guidelines, Shah *JCO* 2023

2L: Paclitaxel + ramucirumab (RAINBOW)

Primary outcome: OS



mOS: 9.6 mo vs 7.4 mo

Subsequent therapies

Second-Line or Subsequent Therapy
- Dependent on prior therapy and PS

Preferred Regimens
- Ramucirumab and paclitaxel (category 1)[43]
- Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[44]
- Docetaxel (category 1)[37,38]
- Paclitaxel (category 1)[33,34,45]
- Irinotecan (category 1)[45-48]
- Fluorouracil[a,i] and irinotecan[46,49,50]
- Trifluridine and tipiracil for third-line or subsequent therapy (category 1)[51]

Other Recommended Regimens
- Ramucirumab (category 1)[52]
- Irinotecan and cisplatin[20,53]
- Fluorouracil and irinotecan + ramucirumab[a,i,54]
- Irinotecan and ramucirumab[55]
- Docetaxel and irinotecan (category 2B)[56]

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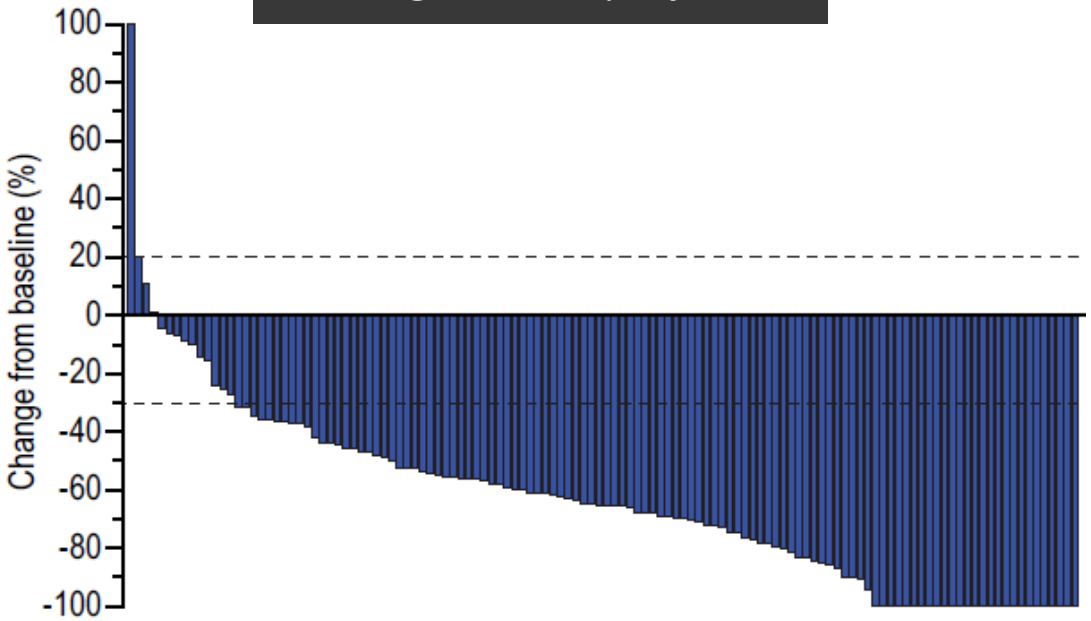
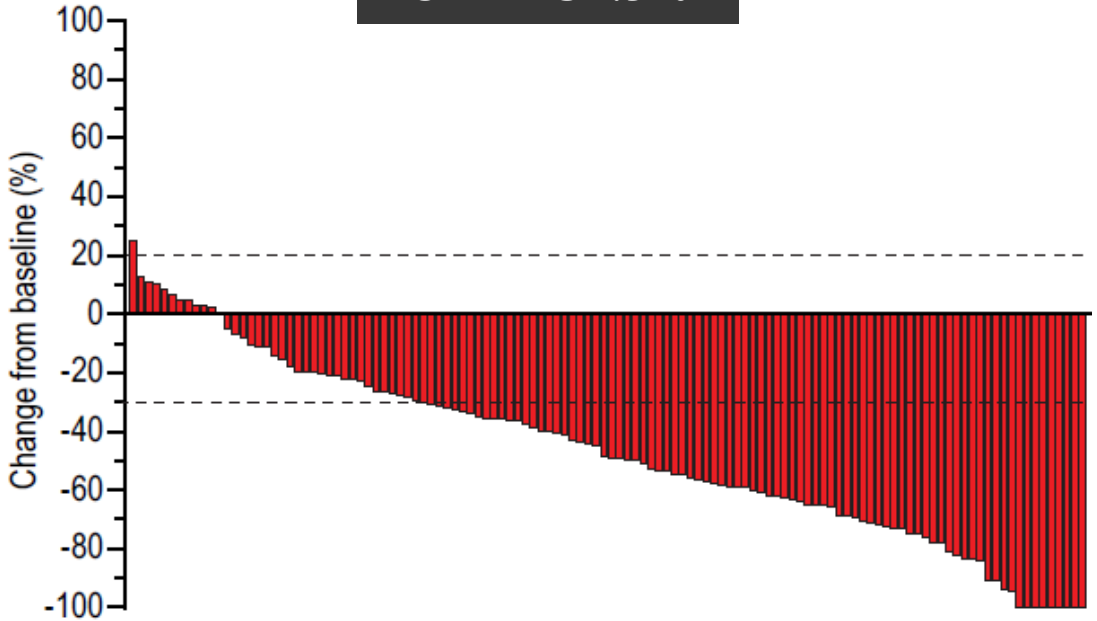
Approach to HER2-Positive GE Cancers

1L: Fluoropyrimidine + platinum + trastuzumab + pembrolizumab (KEYNOTE 811)

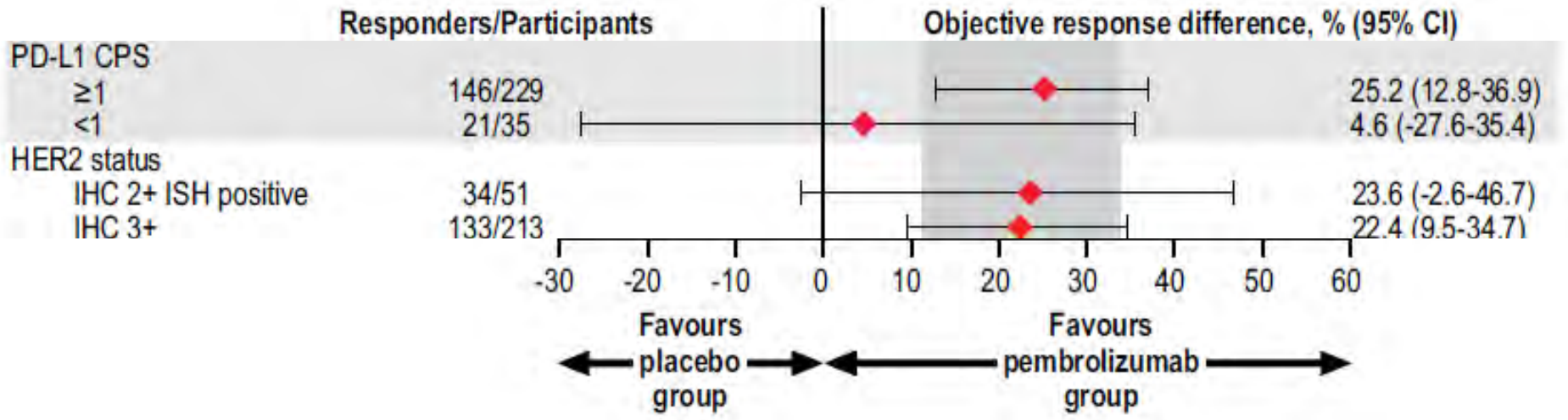
Pembrolizumab group
ORR = 74.4%

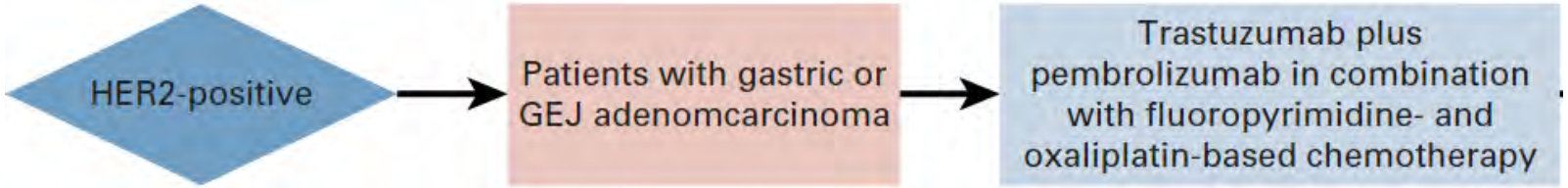


Placebo group
ORR = 51.9%



1L: Fluoropyrimidine + platinum + trastuzumab + pembrolizumab (KEYNOTE 811)



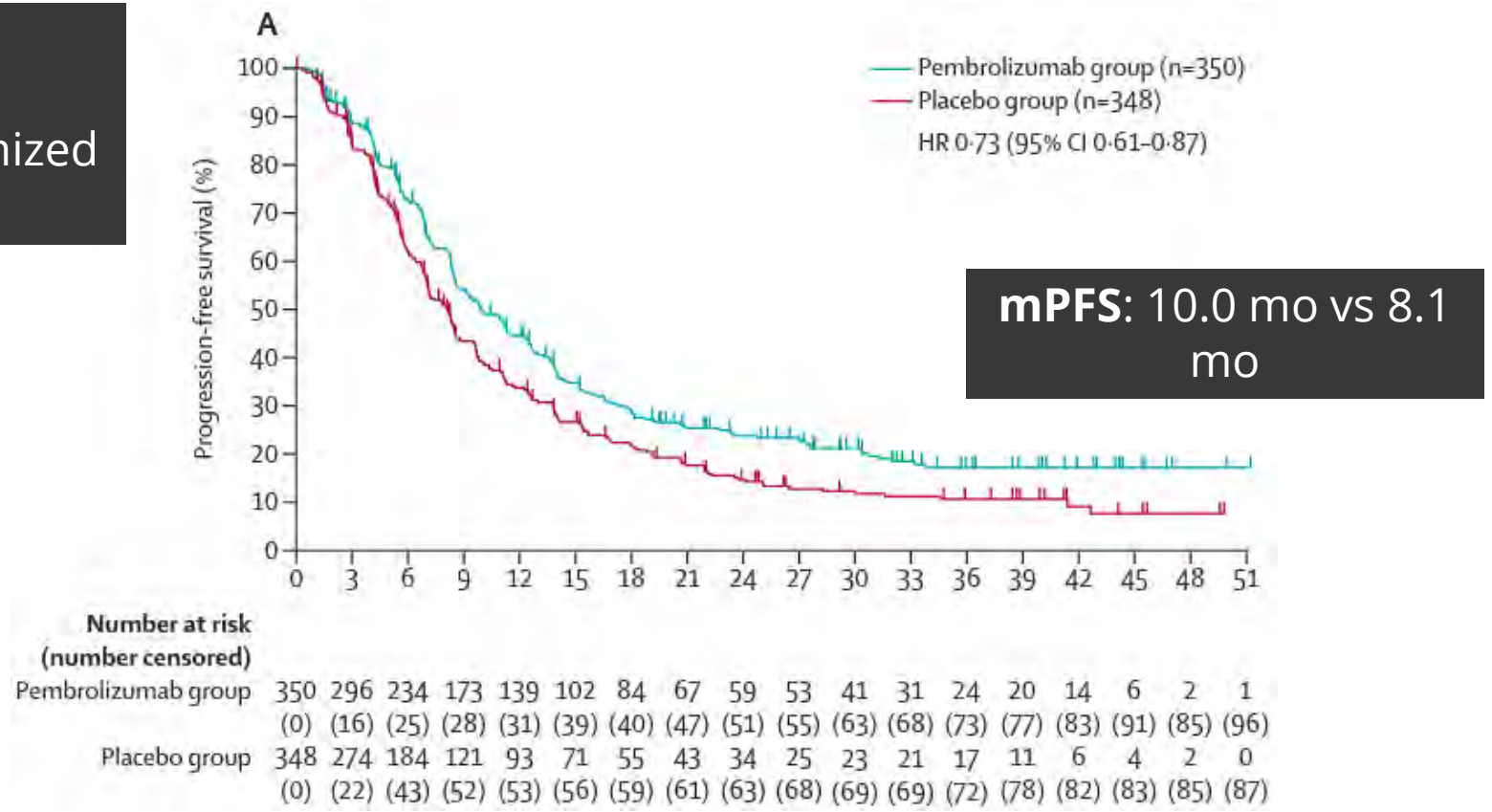


HER2 loss on IHC occurs in 20-60% of patients after trastuzumab

Janjigian *Nature* 2021; ASCO guidelines, Shah *JCO* 2023

1L: Fluoropyrimidine + platinum + trastuzumab + pembrolizumab (KEYNOTE 811)

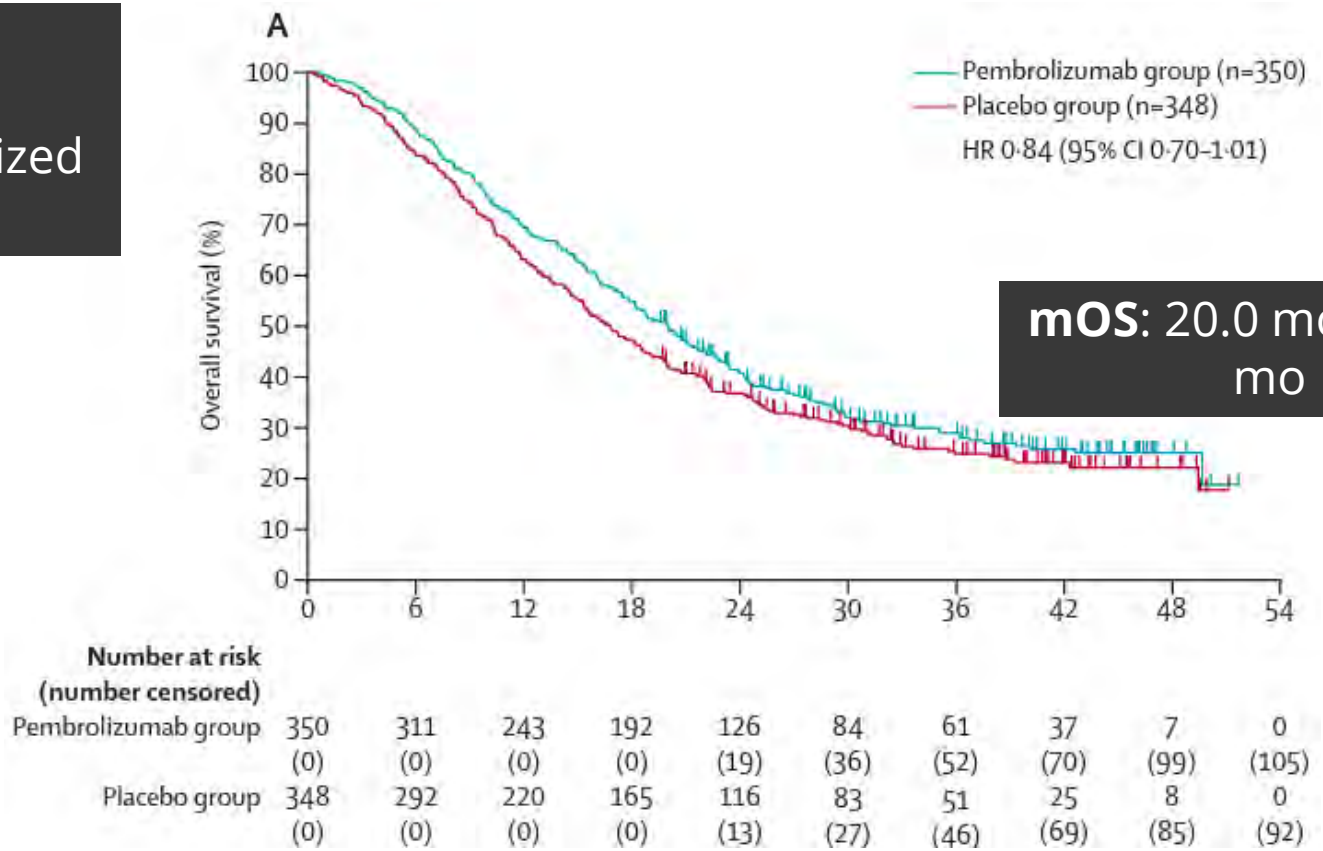
Co-primary outcome:
PFS in all randomized pts



mPFS: 10.0 mo vs 8.1 mo

1L: Fluoropyrimidine + platinum + trastuzumab + pembrolizumab (KEYNOTE 811)

Co-primary outcome:
OS in all randomized pts



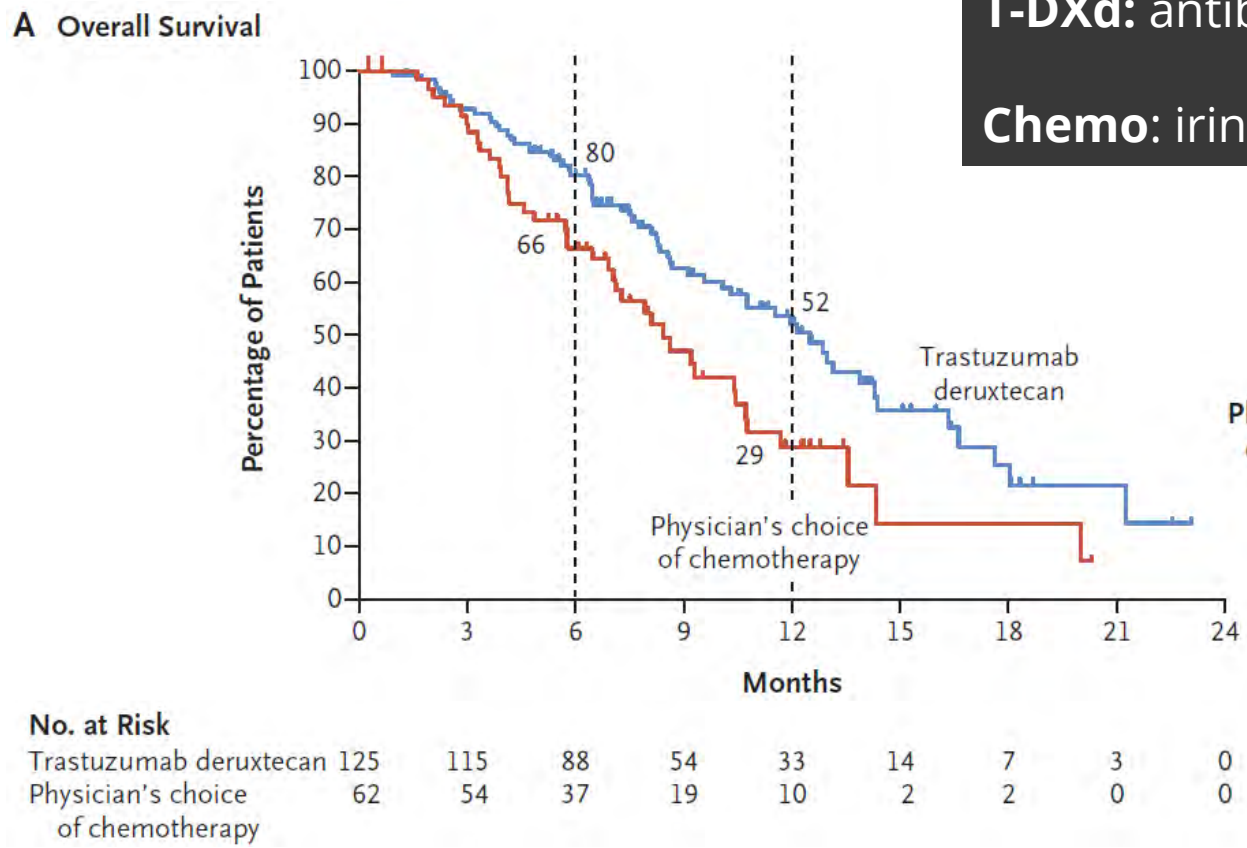
mOS: 20.0 mo vs 16.8 mo

HER2 loss on IHC occurs in 20-60% of patients after trastuzumab

2L: Trastuzumab deruxtecan (DESTINY-Gastric01 and Gastric02)

T-DXd: antibody-drug conjugate

Chemo: irinotecan or paclitaxel



	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI)
		mo
Trastuzumab Deruxtecan	62/125	12.5 (9.6–14.3)
Physician's Choice of Chemotherapy	39/62	8.4 (6.9–10.7)

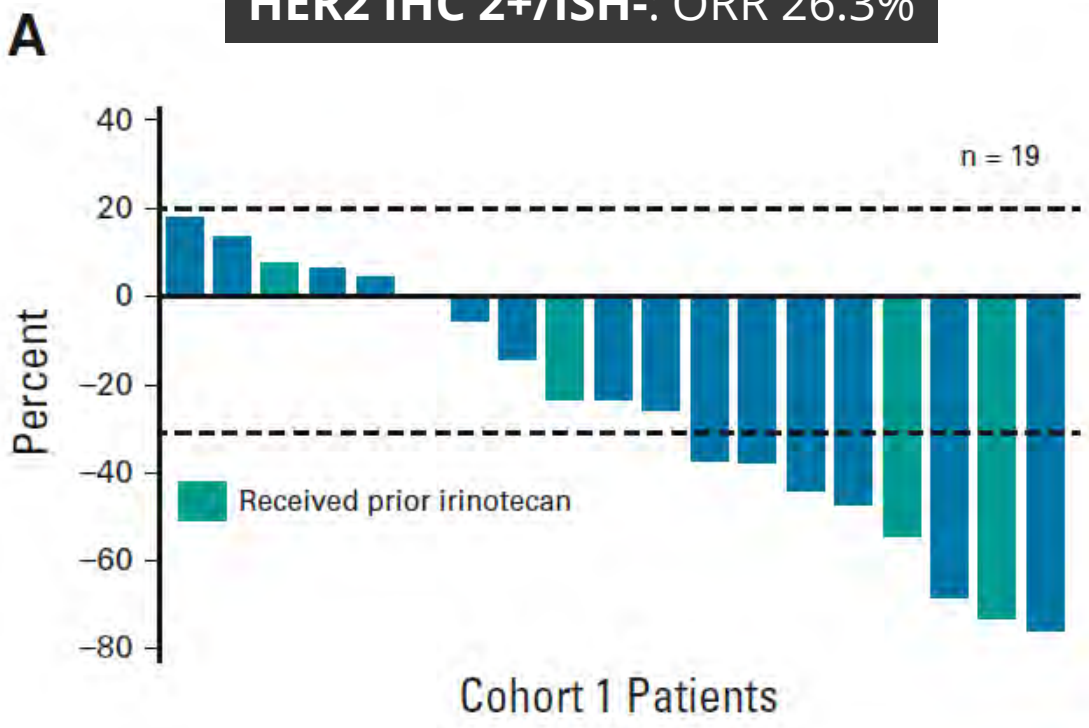
Hazard ratio for death, 0.59 (95% CI, 0.39–0.88)
P=0.01

Consider starting at 5.4 mg/kg -> 6.4 mg/kg
Pneumonitis in 6-10% can be life-threatening

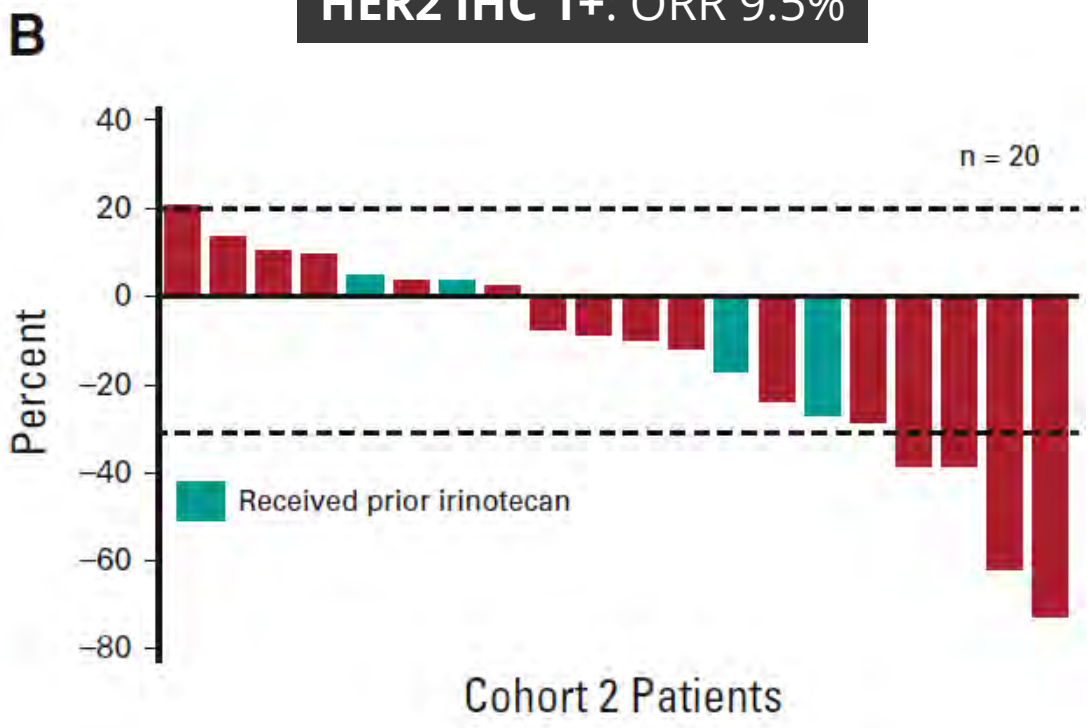
Shitara *NEJM* 2020

Trastuzumab deruxtecan in HER2-low disease

HER2 IHC 2+/ISH-: ORR 26.3%



HER2 IHC 1+: ORR 9.5%



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- Docetaxel and irinotecan (category 2B)[56]

No clear role for trastuzumab beyond progression

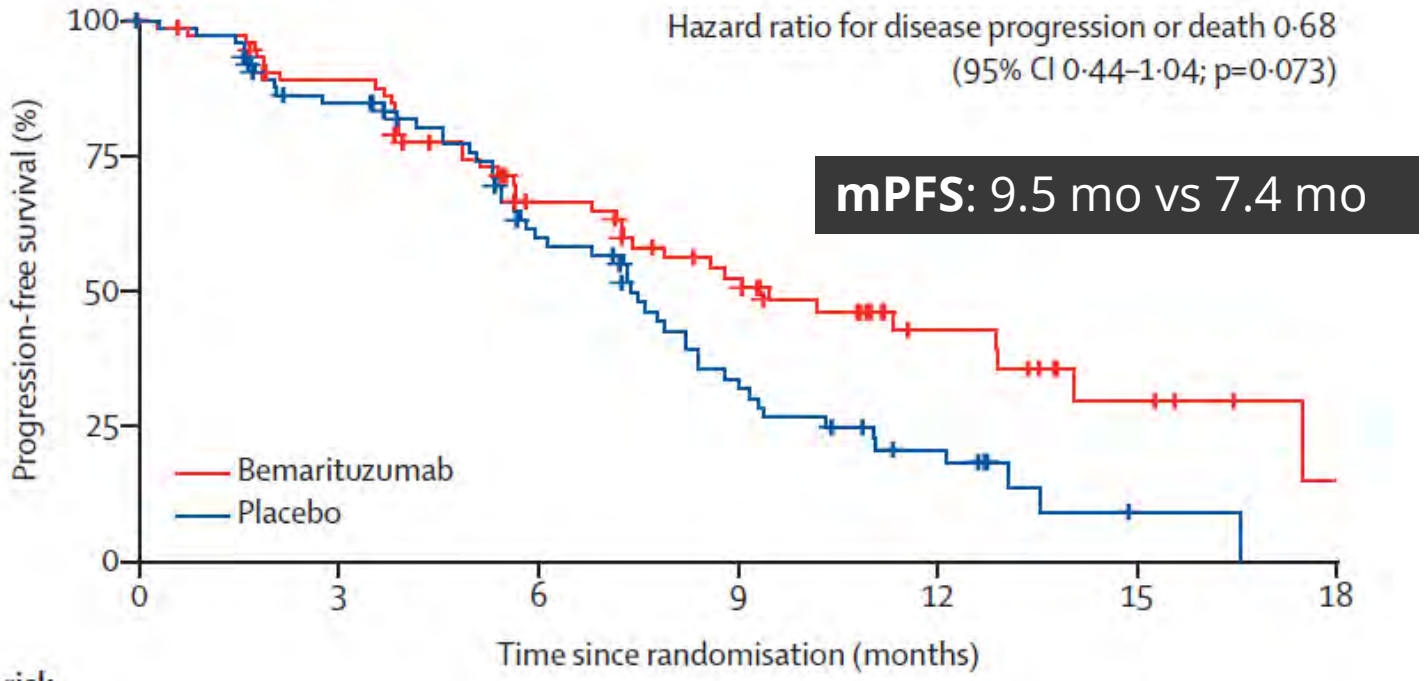
Additional Molecularly Informed Approaches

1L bemarituzumab in FGFR2b-positive tumors (FIGHT)

Primary outcome: PFS

Bemarituzmab: anti-FGFR2b mAb

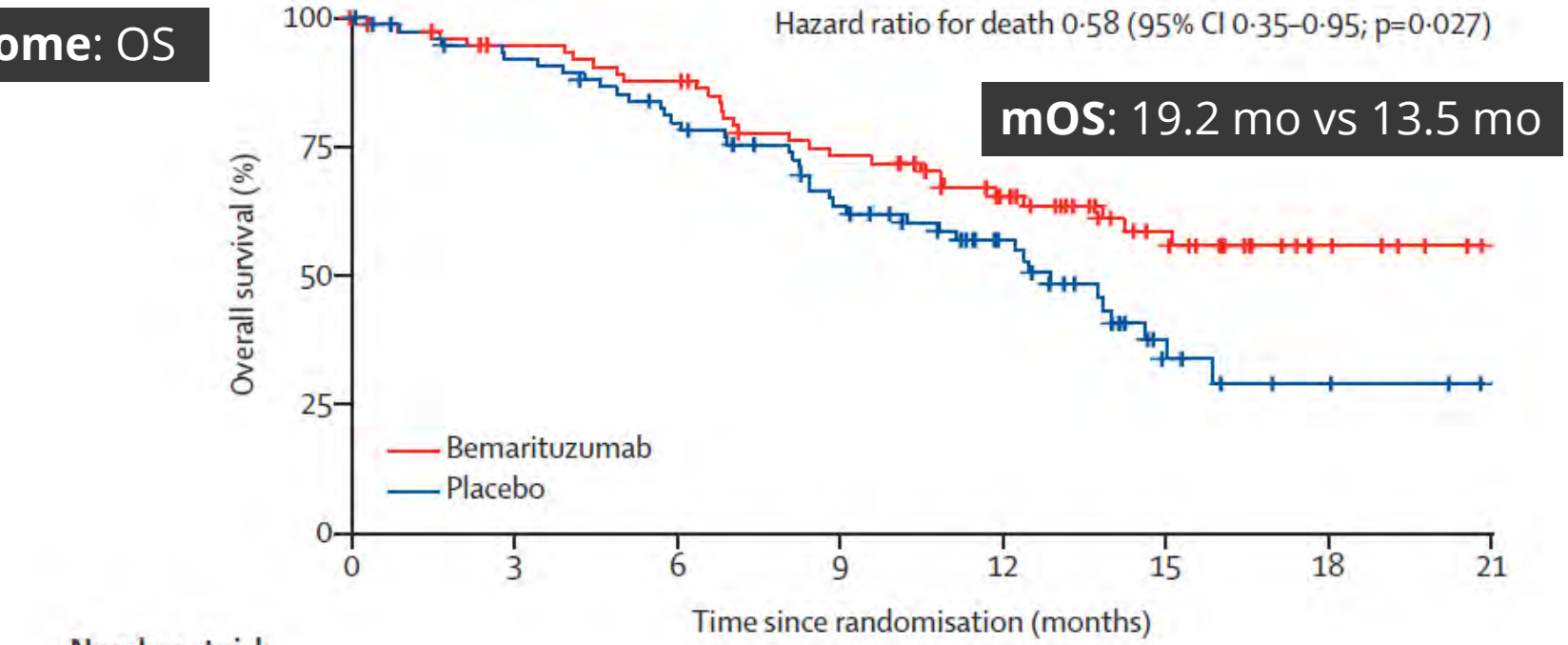
Chemo backbone: FOLFOX



Number at risk (number censored)							
Bemarituzumab	77 (0)	62 (7)	40 (14)	28 (18)	12 (30)	5 (34)	1 (37)
Placebo	78 (0)	59 (8)	37 (14)	19 (17)	9 (20)	1 (25)	0 (25)

1L bemarituzumab in FGFR2-positive tumors (FIGHT)

Secondary outcome: OS



mOS: 19.2 mo vs 13.5 mo

Number at risk (number censored)								
Bemarituzumab	77 (0)	68 (5)	63 (5)	50 (8)	38 (15)	21 (29)	6 (43)	0 (49)
Placebo	78 (0)	68 (4)	57 (6)	42 (10)	27 (21)	10 (30)	4 (34)	1 (37)

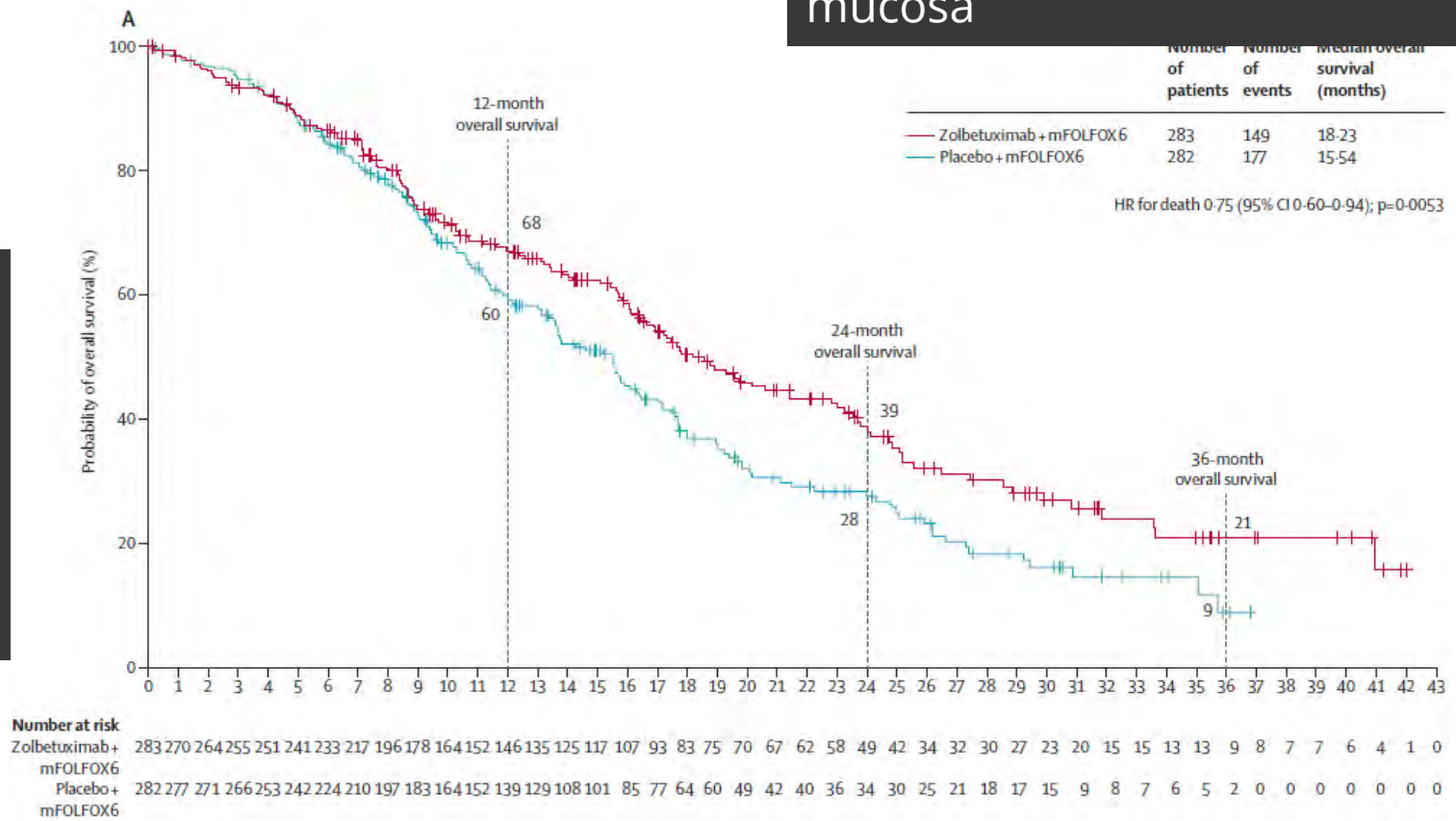
AE: neutropenia, anemia, stomatitis, and corneal events*

CLDN18.2-positive tumors (SPOTLIGHT)

CLDN18.2:
- Structural component of intercellular tight junctions
- Not routinely expressed outside gastric mucosa

Zolbetuximab: anti-CLDN18.2 mAb

Chemo backbone: FOLFOX

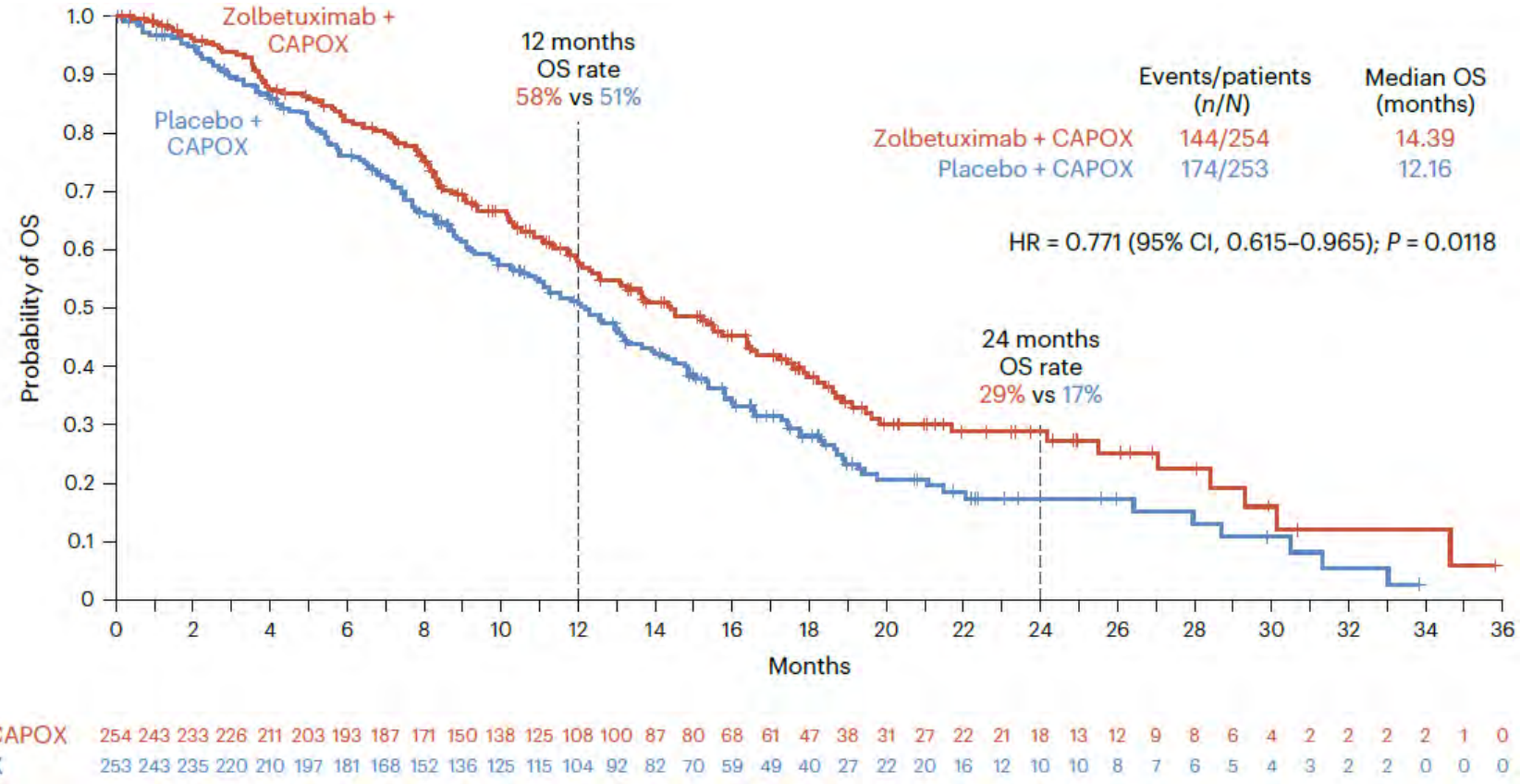


Shitara *Lancet* 2023

CLDN18.2-positive tumors (GLOW)

Zolbetuximab: anti-CLDN18.2 mAb

Chemo backbone: CAPOX



AE: nausea, vomiting, decreased appetite

Shah *Nature Med* 2023

Additional tumor-agnostic approvals

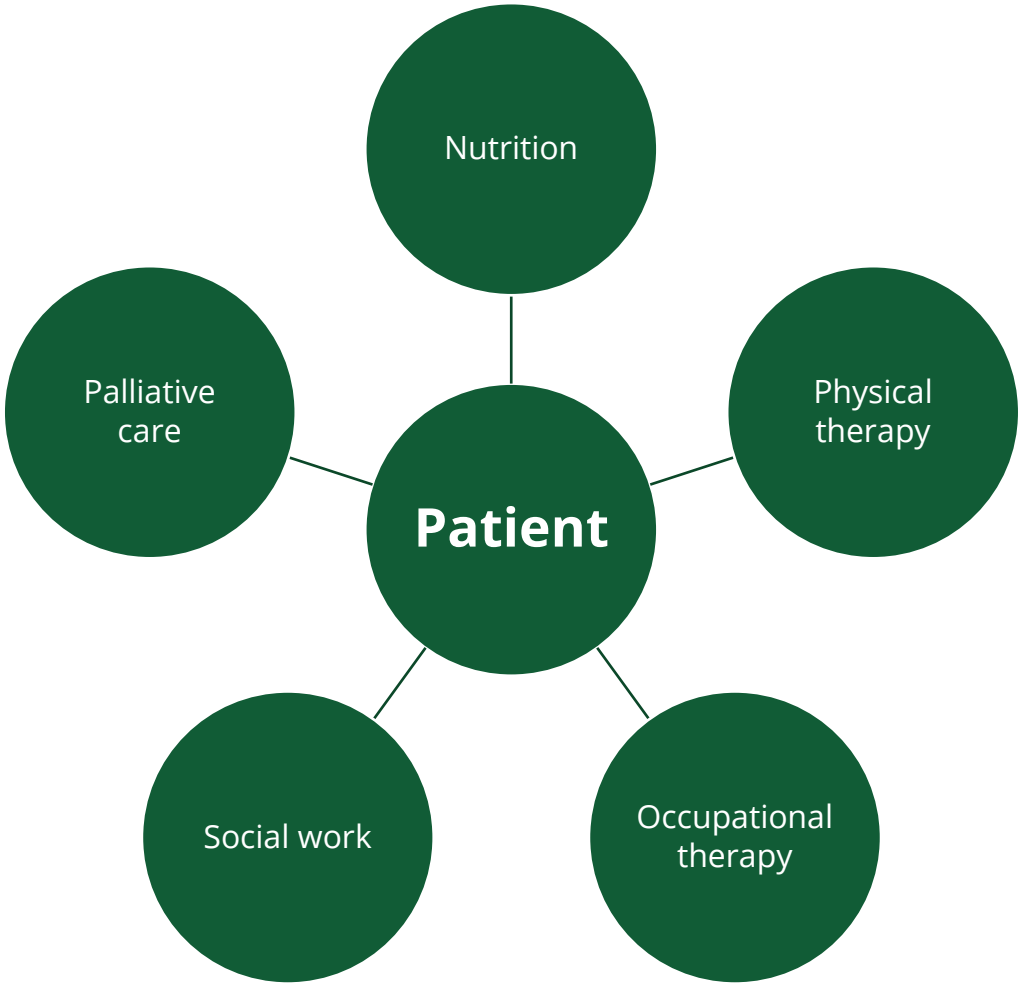
- BRAF V600E alterations -> dabrafenib/trametinib
- NTRK fusions -> entrectinib, larotrectinib
- RET fusions -> selpercatinib

Final Thoughts

Multidisciplinary supportive care is crucial

Only **38-55%** of patients in 1L phase III trials get to 2L therapy

- Physical symptom burden
- Malnutrition
- Malignant ascites
- Declining performance status



Take-home messages

- Timely biomarker testing is of utmost importance to guide treatment decision-making in advanced gastroesophageal cancers
- First-line systemic therapy has rapidly evolved in recent years and now includes the integration of immune checkpoint inhibitors for both HER2-negative and HER2-positive disease
- Additional advances in systemic therapy have centered around targeted therapy approaches, including for HER2, FGFR2, and CLDN18.2-positive disease
- Multidisciplinary supportive care is critical for all patients with advanced gastroesophageal cancer

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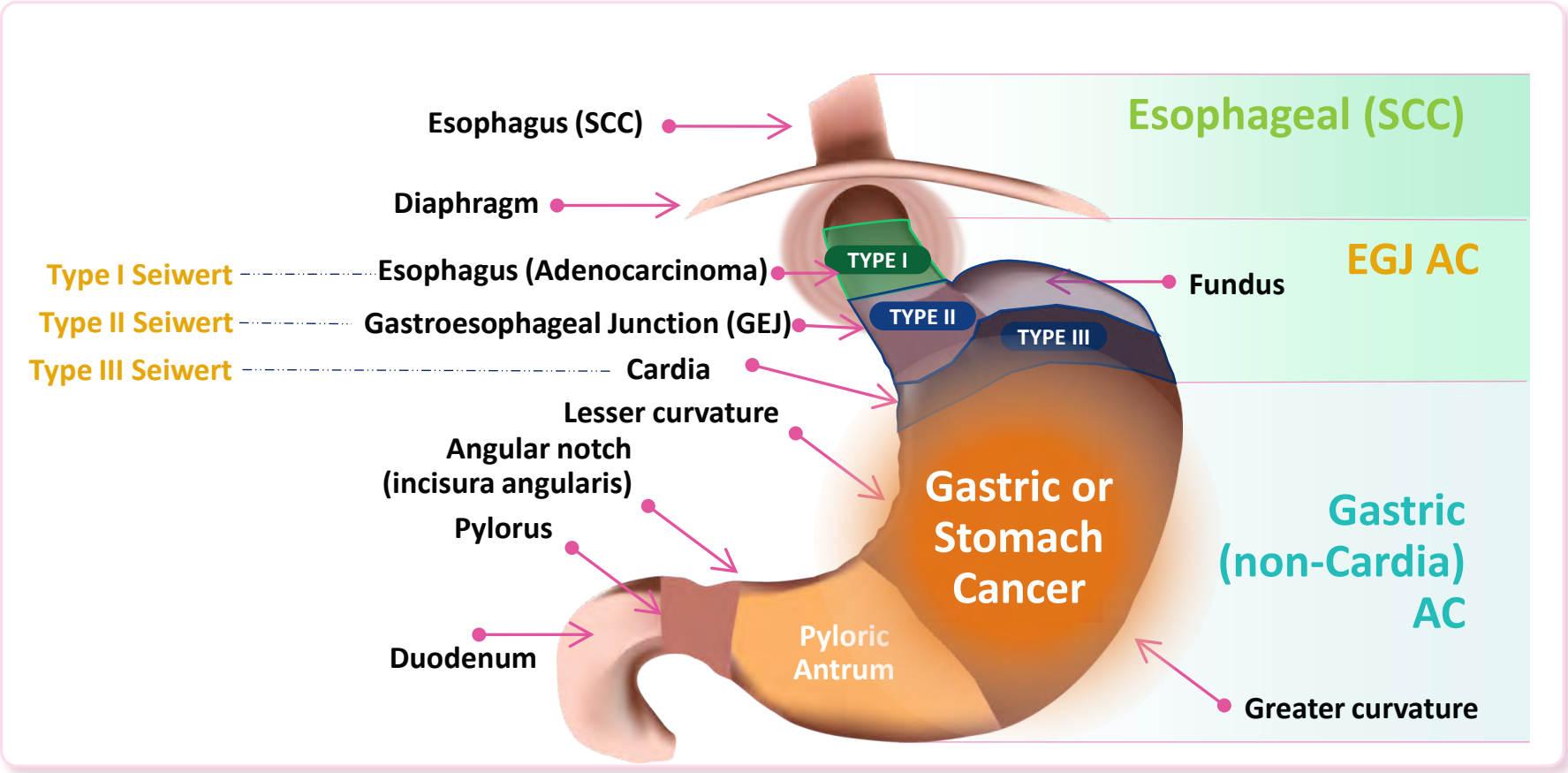
Current Management of localized Gastric Cancer: Surgery to Molecular-Directed Therapy

Mitchell C. Posner M.D., FACS
Thomas D. Jones Professor and Vice Chairman
Chief, Section of General Surgery and Surgical Oncology
Physician-in-Chief, University of Chicago Medicine
Comprehensive Cancer Center

Disclosures

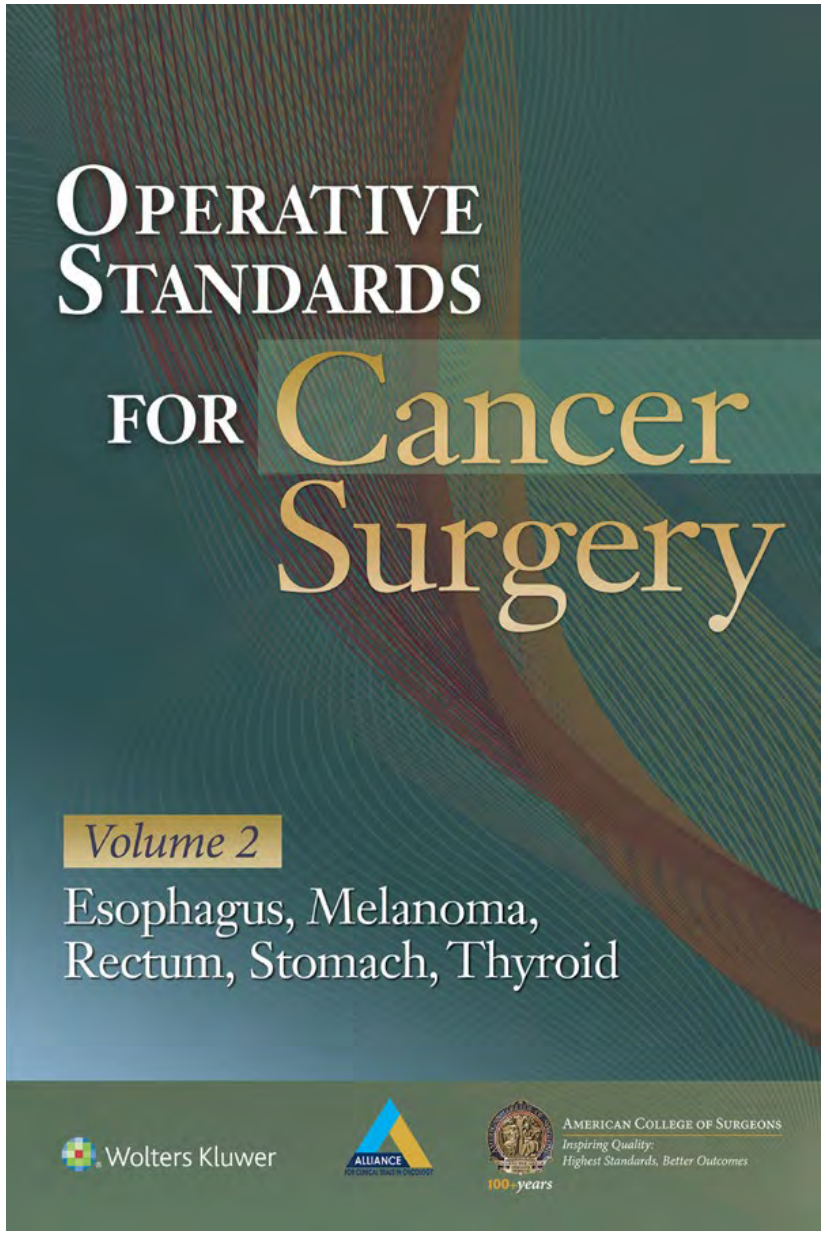
- Nothing to disclose

Gastroesophageal Cancer



Esophageal vs. Gastric Adenocarcinoma
7th edition 2010 AJCC/UICC Staging

Sehdev A, Catenacci DVT. Gastroesophageal Adenocarcinoma: Focus on Epidemiology, Classification and Staging. *Discov Med* 2013


Operative Standards for Cancer Surgery
Volume 2
Esophagus, Melanoma, Rectum, Stomach, Thyroid
Wolters Kluwer
ALLIANCE
American College of Surgeons
Inspiring Quality:
Highest Standards, Better Outcomes
100+ years

Surgical Issues

Surgical Rx Gastric Cancer

- Intraoperative staging
- Resection of the primary tumor
  - Partial & total gastrectomy
  - Total vs. Proximal for GEJ tumors
  - MIS gastrectomy
- Assessment of surgical margins
- Regional lymphadenectomy
- Reconstruction of the GI tract

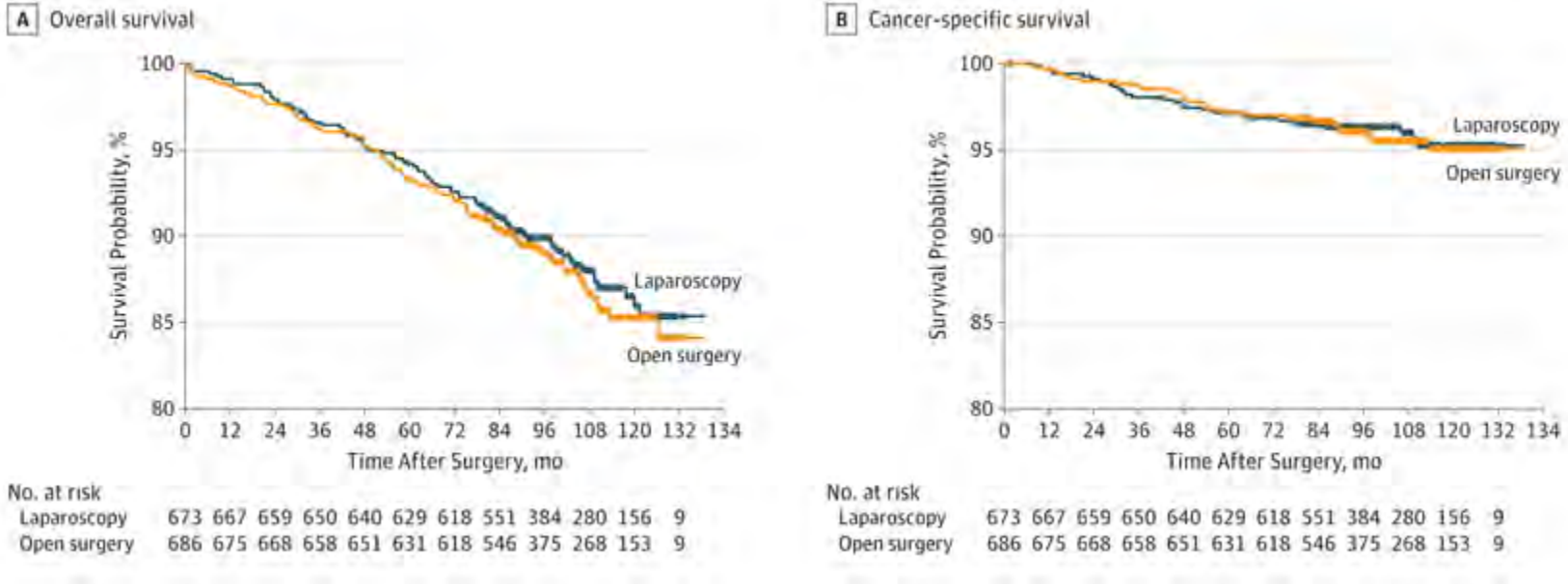
Key Questions:

Surgical Rx Gastric Cancer

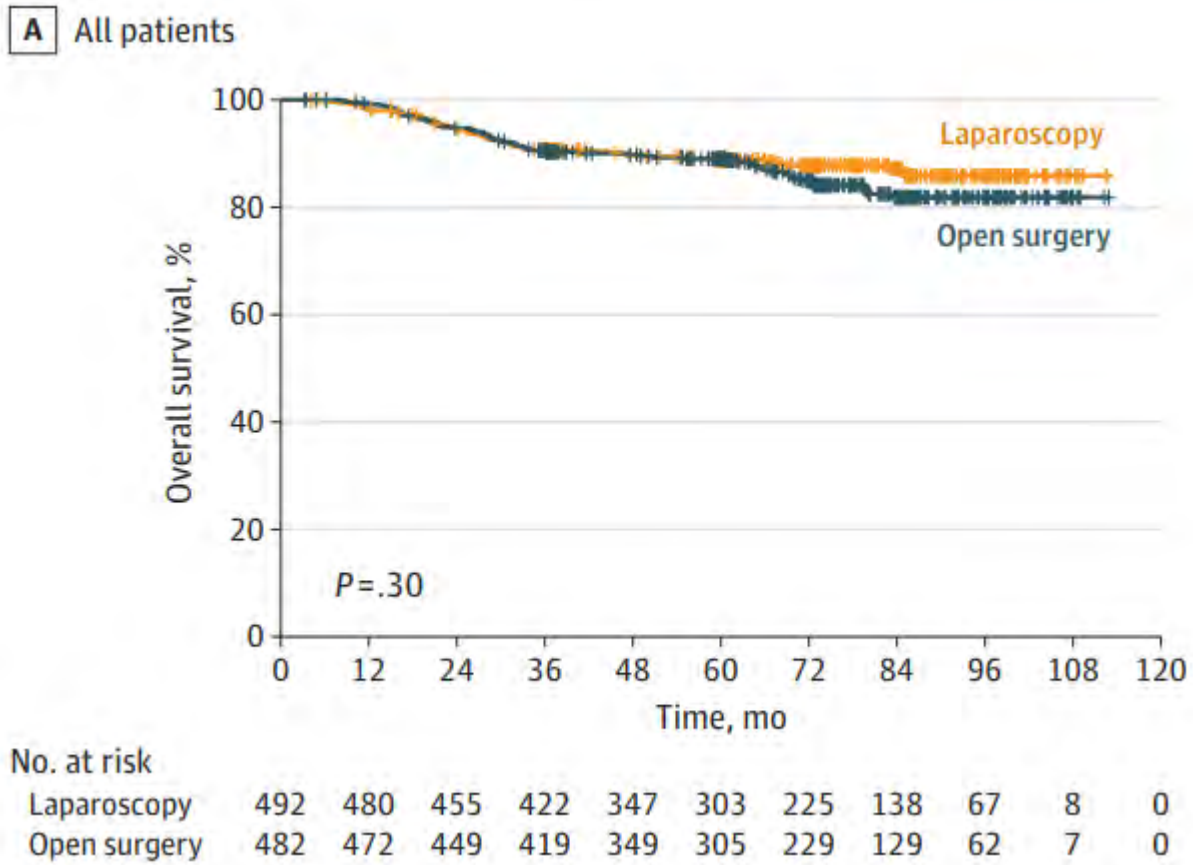
- In patients with localized and resectable gastric cancer, what is the optimal extent of lymph node dissection—D1 versus D2 versus D3—and what are the optimal indictors for morbidity, mortality, and long-term outcomes in gastrectomy?
- For gastroesophageal junction (GEJ) cancers, does an “esophageal” or “gastric” surgical approach offer better perioperative and oncologic outcomes?

Effect of Laparoscopic Distal Gastrectomy vs Open Distal Gastrectomy on Long-term Survival Among Patients With Stage I Gastric Cancer

The KLASS-01 Randomized Clinical Trial

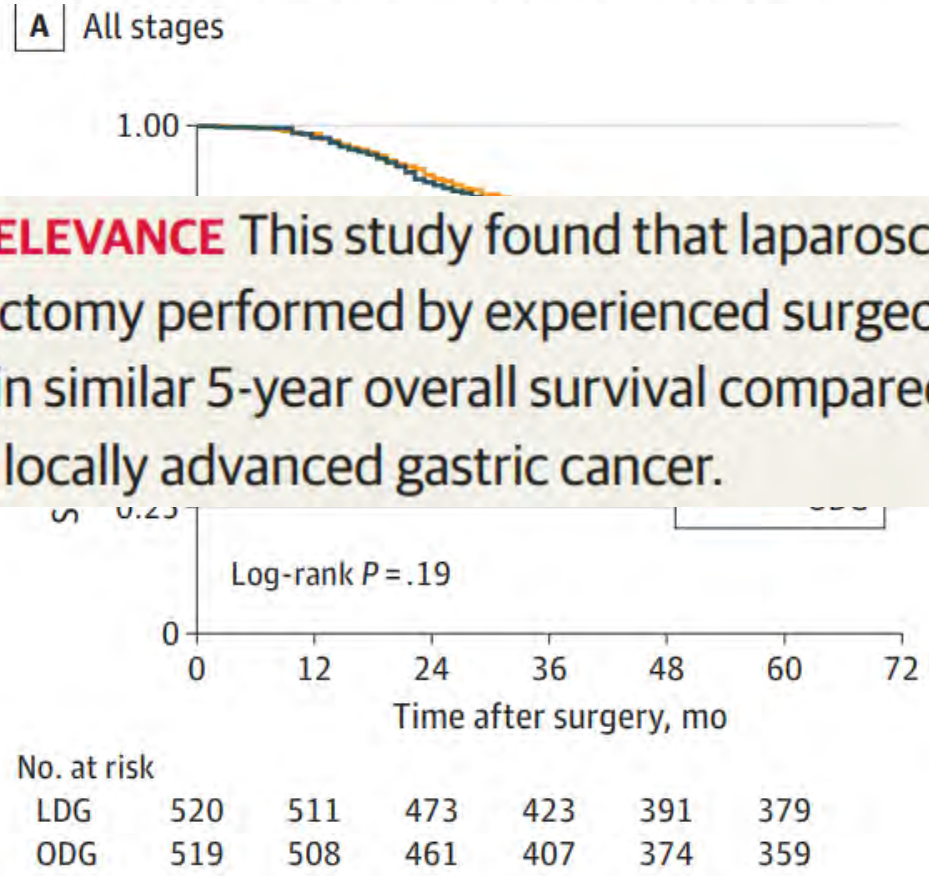


Long-Term Outcomes of Laparoscopic Distal Gastrectomy for Locally Advanced Gastric Cancer: The KLASS-02-RCT Randomized Clinical Trial



Laparoscopic vs Open Distal Gastrectomy for Locally Advanced Gastric Cancer

Five-Year Outcomes From the CLASS-01 Randomized Clinical Trial



CONCLUSIONS AND RELEVANCE This study found that laparoscopic distal gastrectomy with D2 lymphadenectomy performed by experienced surgeons in high-volume specialized institutions resulted in similar 5-year overall survival compared with open distal gastrectomy among patients with locally advanced gastric cancer.

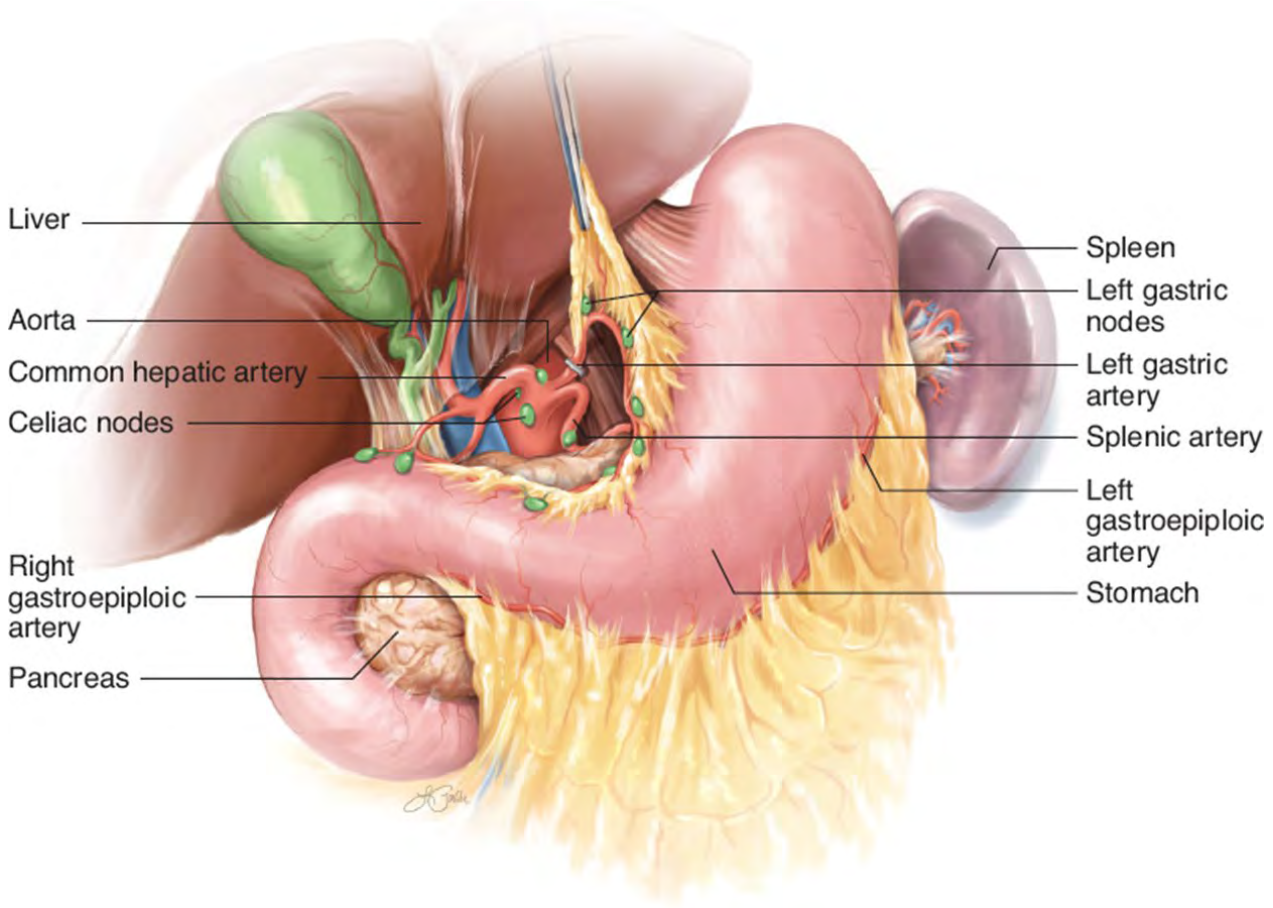
Huang C et al *JAMA Surg* 2022

Resection of the primary tumor

Surgical Rx Gastric Cancer

- MIS gastrectomy
  - **recommendation: Minimally invasive surgery is a suitable alternative to open surgery for cases including but not limited to early and distal gastric cancer. Minimally invasive gastrectomy for advanced gastric cancer requiring total gastrectomy when a surgeon's expertise is adequate. Robotic surgery for gastric cancer has been suggested to be noninferior to laparoscopic surgery**
    - **Randomized controlled trials, large retrospective studies**
    - **Strong recommendation, high-quality evidence**

Regional Lymphadenectomy
D2 Lymph Node Dissection



Regional Lymphadenectomy

Surgical Rx Gastric Cancer

- Regional Lymphadenectomy
  - **Recommendation: At least 16 regional lymph nodes should be removed and examined at gastrectomy. A D2 dissection is the minimum lymph node dissection that would enable routine resection and assessment of at least 16 regional nodes**
    - **Prospective trials and meta-analyses**
    - **strong recommendation, high quality evidence**

Key Questions:

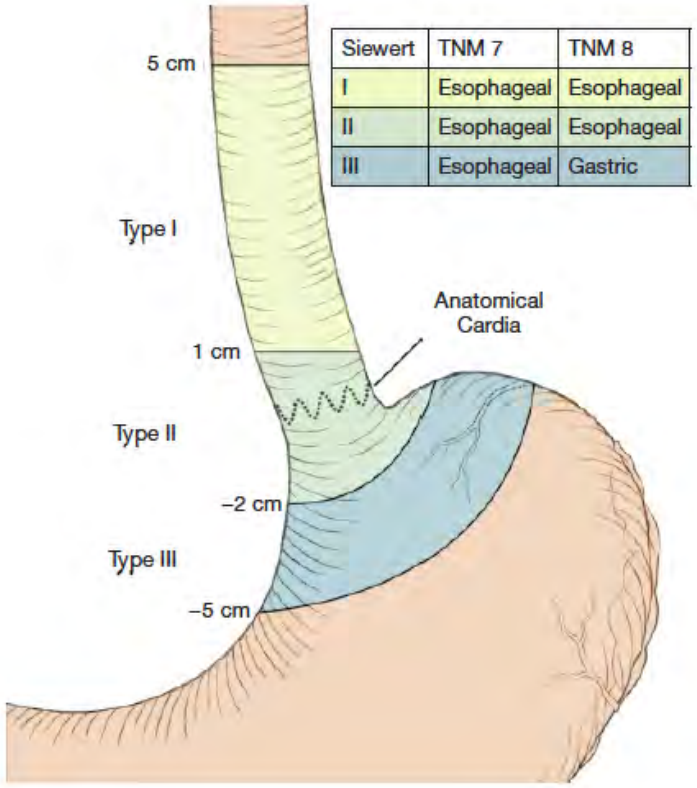
Surgical Rx Gastric Cancer

- In patients with localized and resectable gastric cancer, what is the optimal extent of lymph node dissection—D1 versus D2 versus D3—and what are the optimal in lo

D2 lymph node dissection preserving the pancreas and spleen should be considered standard for optimal staging and treatment (GRADE, 2A). Extended lymph node dissections beyond D2 should not be routinely performed, because they have been shown to lead to increased morbidity with no improvement in outcomes.

In patients with T1 tumors, advanced age, poor functional status, or multiple comorbidities, D1 or D1+ dissections may be considered.

Gastroesophageal Junction Classification



Siewert	TNM 7	TNM 8
I	Esophageal	Esophageal
II	Esophageal	Esophageal
III	Esophageal	Gastric

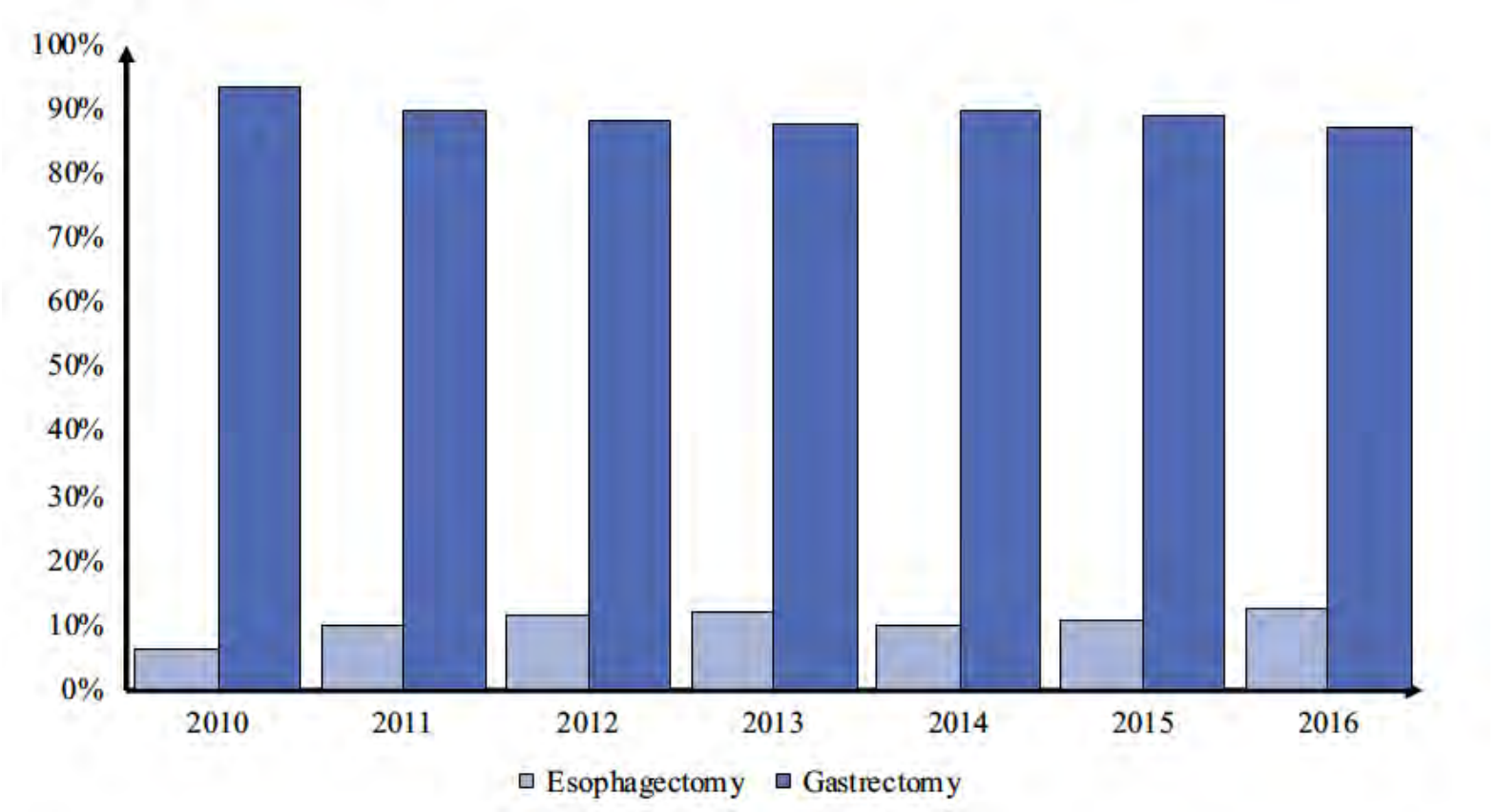
Key Questions:

Surgical Rx Gastric Cancer

- For gastroesophageal junction (GEJ) cancers, does an “esophageal” or “gastric” surgical approach offer better perioperative and oncologic outcomes?

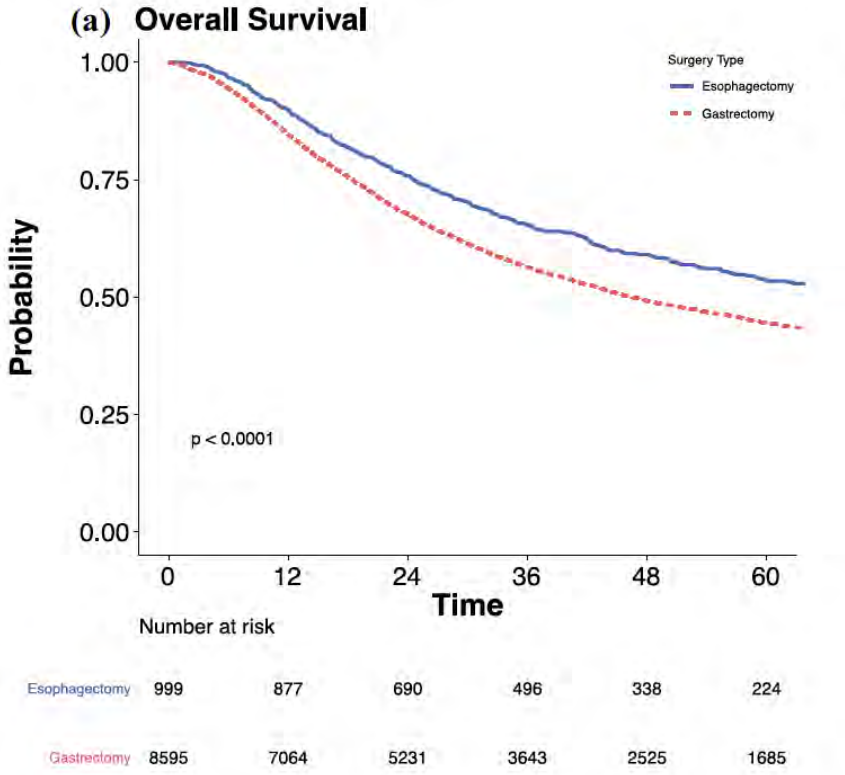
The proximal and distant extent of the tumor greatly influences choice of operation. OS rates appear comparable for esophagectomy and gastrectomy. There are no statistically significant differences between R0 resection, lymph node yield, and perioperative results. Type I cancers be treated with esophagectomy and type III cancers be treated with extended gastrectomy. For type II cancers either an esophageal or a gastric surgical approach is reasonable.

Trends Esophagectomy vs. Gastrectomy
GEJ Adenocarcinoma – Siewert Type II



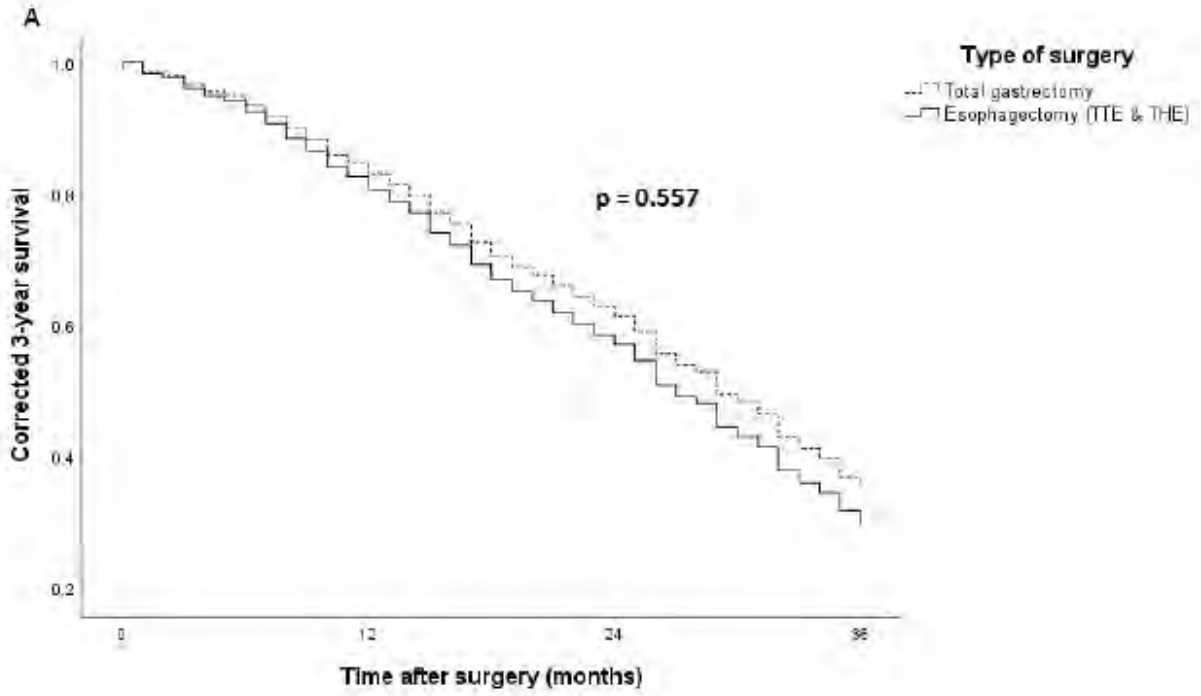
Kamarajah SK, *Ann Surg Oncol* 2021

Esophagectomy vs. Gastrectomy
Overall Survival Siewert Type II



Kamarajah SK, *Ann Surg Oncol* 2021

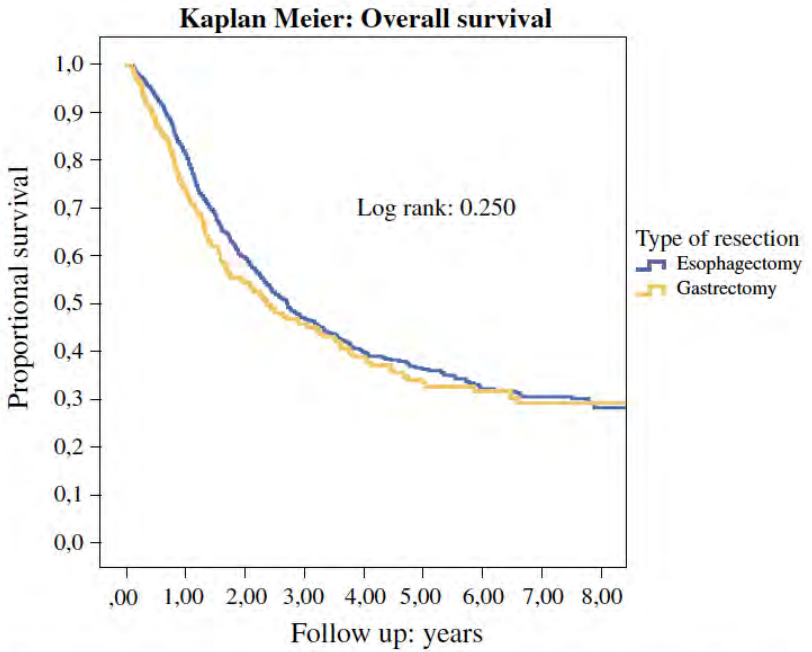
Esophagectomy vs. Gastrectomy
3 year Overall Survival



Numbers at risk				
Esophagectomy	790	602	433	295
Total gastrectomy	81	59	42	24

Jezerskyte E, *Ann Surg* 2021

Esophagectomy vs. Gastrectomy Overall Survival



Numbers at risk	0	1	2	3	4	5	6	7	8
Esophagectomy	939	760	477	312	209	149	97	59	30
Gastrectomy	257	188	130	90	60	45	32	17	9

FIG. 1 Overall survival of patients with a resectable adenocarcinoma of the GEJ treated with an esophagectomy or gastrectomy

Esophagectomy vs. Gastrectomy Overall Survival

Study or Subgroup	Oesophagectomy Events	Total	Gastrectomy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Blank 2018	13	56	37	186	2.6%	1.22 [0.59, 2.49]
Chen 2022	2917	6599	107	504	22.3%	2.94 [2.36, 3.66]
Kamarajah 2021	224	999	1685	8595	54.7%	1.19 [1.01, 1.39]
Parry 2014	49	155	4	21	1.0%	1.96 [0.63, 6.15]
Reddavid 2019	7	121	5	49	1.3%	0.54 [0.16, 1.79]
Siewert 2000	12	33	72	173	2.9%	0.80 [0.37, 1.73]
Tosolini 2019	36	91	84	179	6.9%	0.74 [0.44, 1.24]
Voron 2019	14	119	9	64	2.1%	0.81 [0.33, 2.00]
Xing 2020	17	28	24	28	1.9%	0.26 [0.07, 0.95]
Zheng 2010	100	284	19	47	4.2%	0.80 [0.43, 1.51]
Total (95% CI)		**8485**		**9846**	**100.0%**	**1.49 [1.34, 1.67]**
Total events	3389		2046			

Heterogeneity: Chi² = 70.44, df = 9 (P < 0.00001); I² = 87%
Test for overall effect: Z = 7.06 (P < 0.00001)

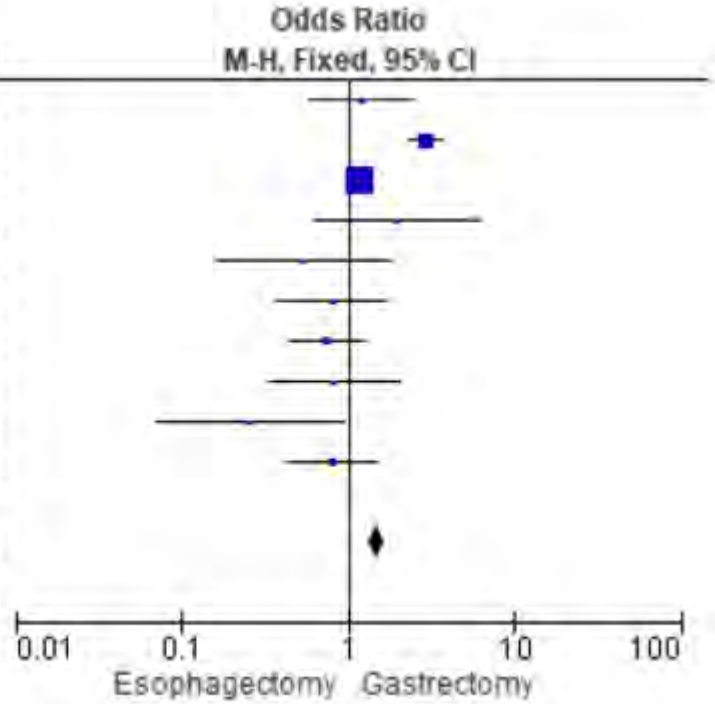
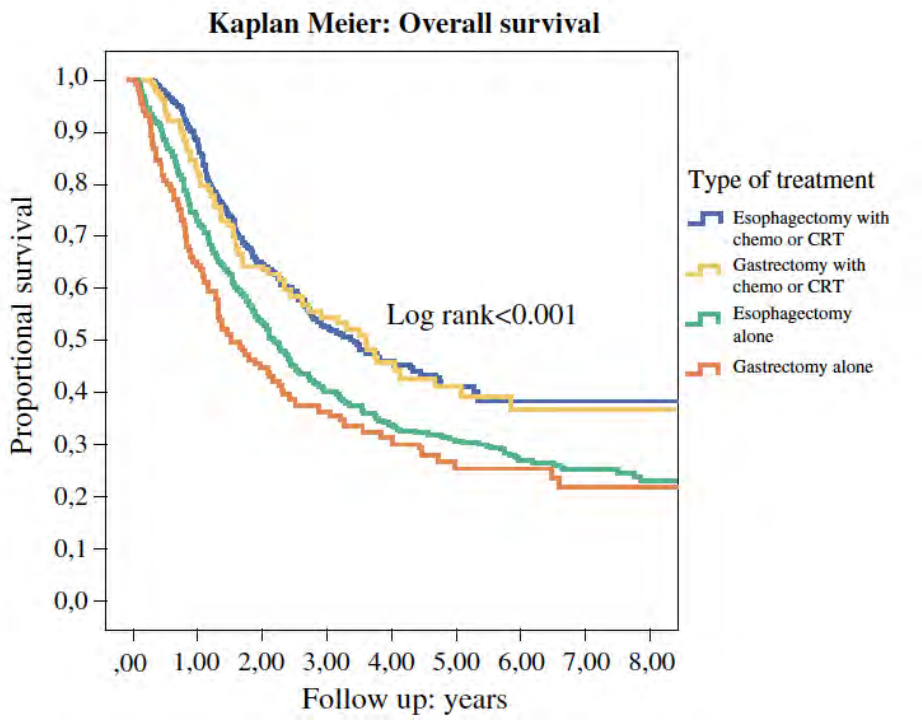


Fig. 11 Five-year overall survival

Esophagectomy vs. Gastrectomy
Surgery vs. Surgery + CRT or C



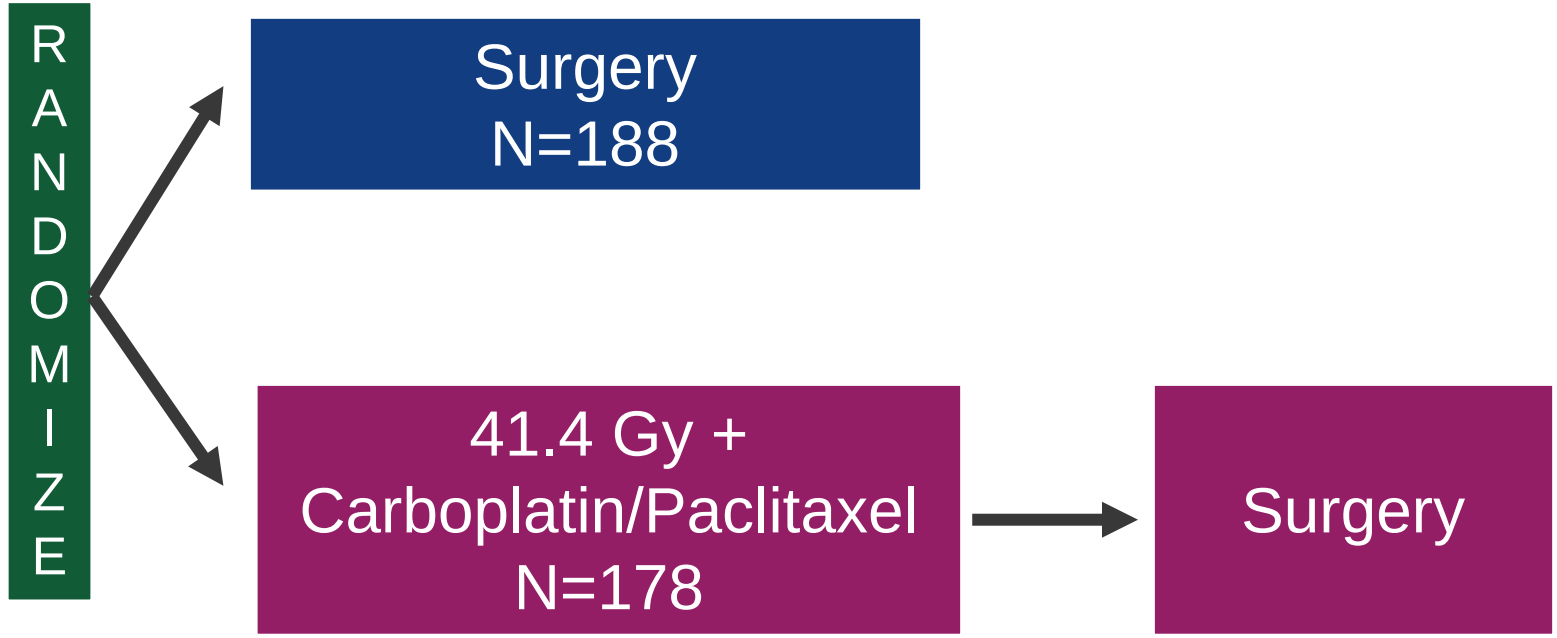
Koeter M, *Ann Surg Oncol* 2016

Neoadjuvant Chemoradiotherapy: CROSS Trial

366 Esophageal and GEJ Cancer Patients

75% adeno

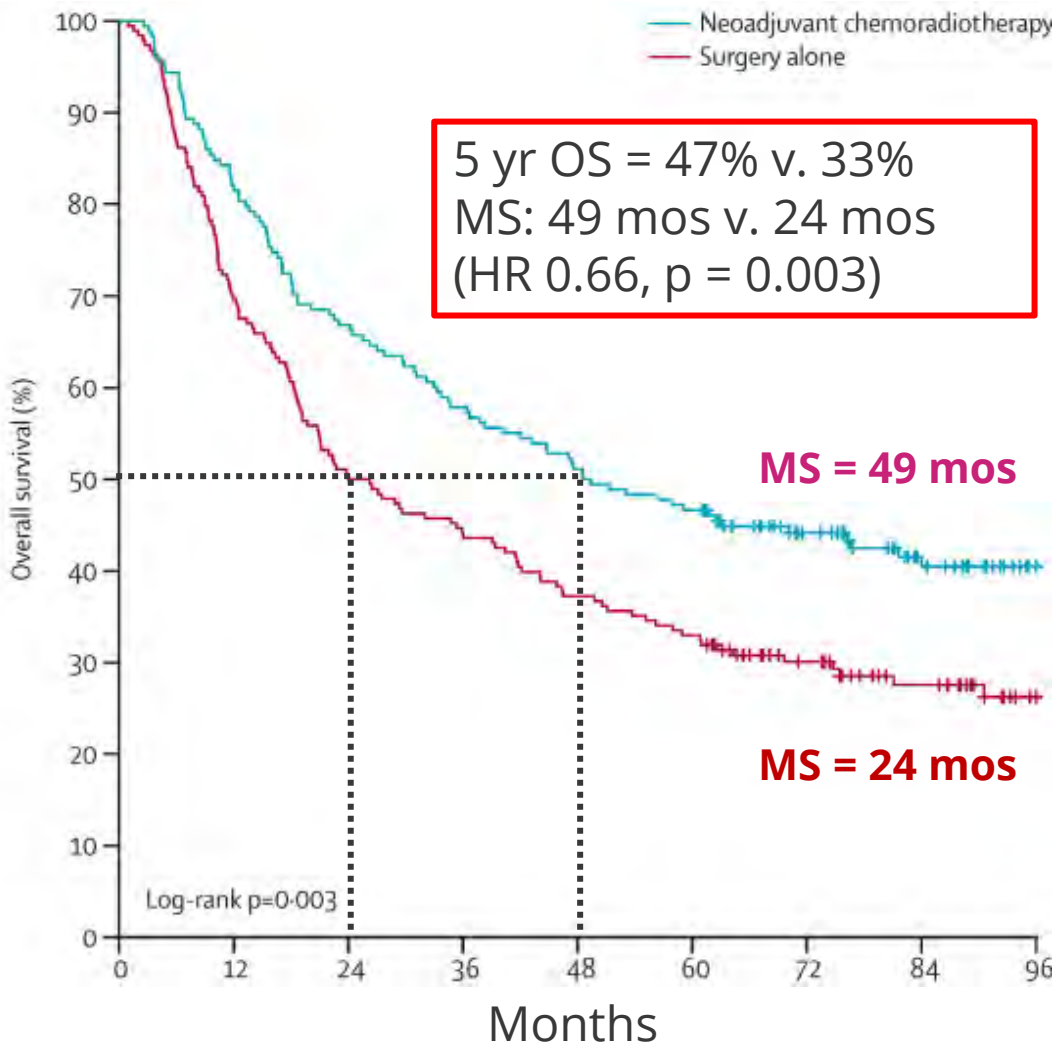
Primary Endpoint: Median OS

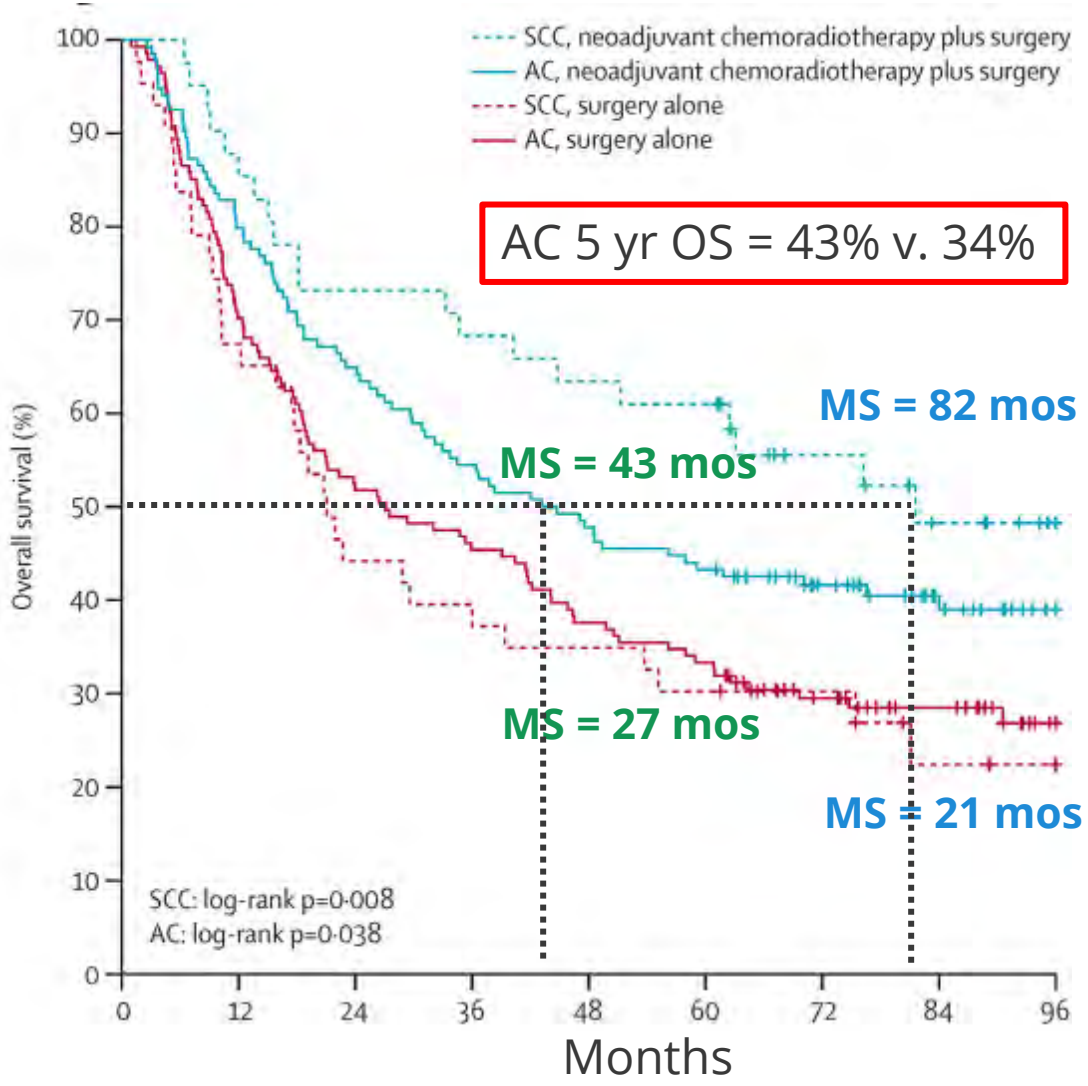


- pCR: 49% in SCC group and 23% in AC group
- R0 resection rate: 88% v. 59% for ITT groups

Van Hagen, *N Engl J Med* 2012

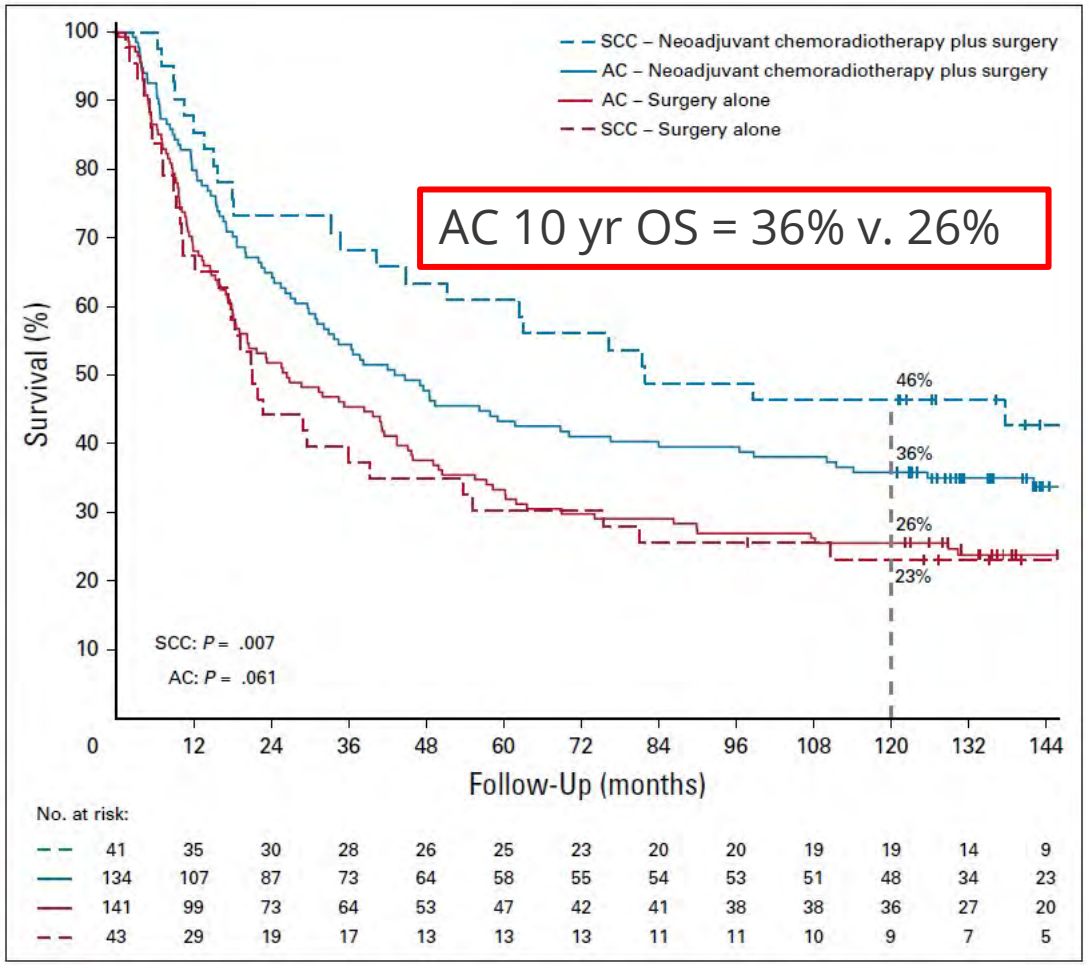
Neoadjuvant Chemoradiotherapy: CROSS Trial





Shapiro, *Lancet Oncol*, 2015

Neoadjuvant Chemoradiotherapy: CROSS Trial



Neoadjuvant Chemoradiotherapy: CROSS Trial

Patterns of Failure

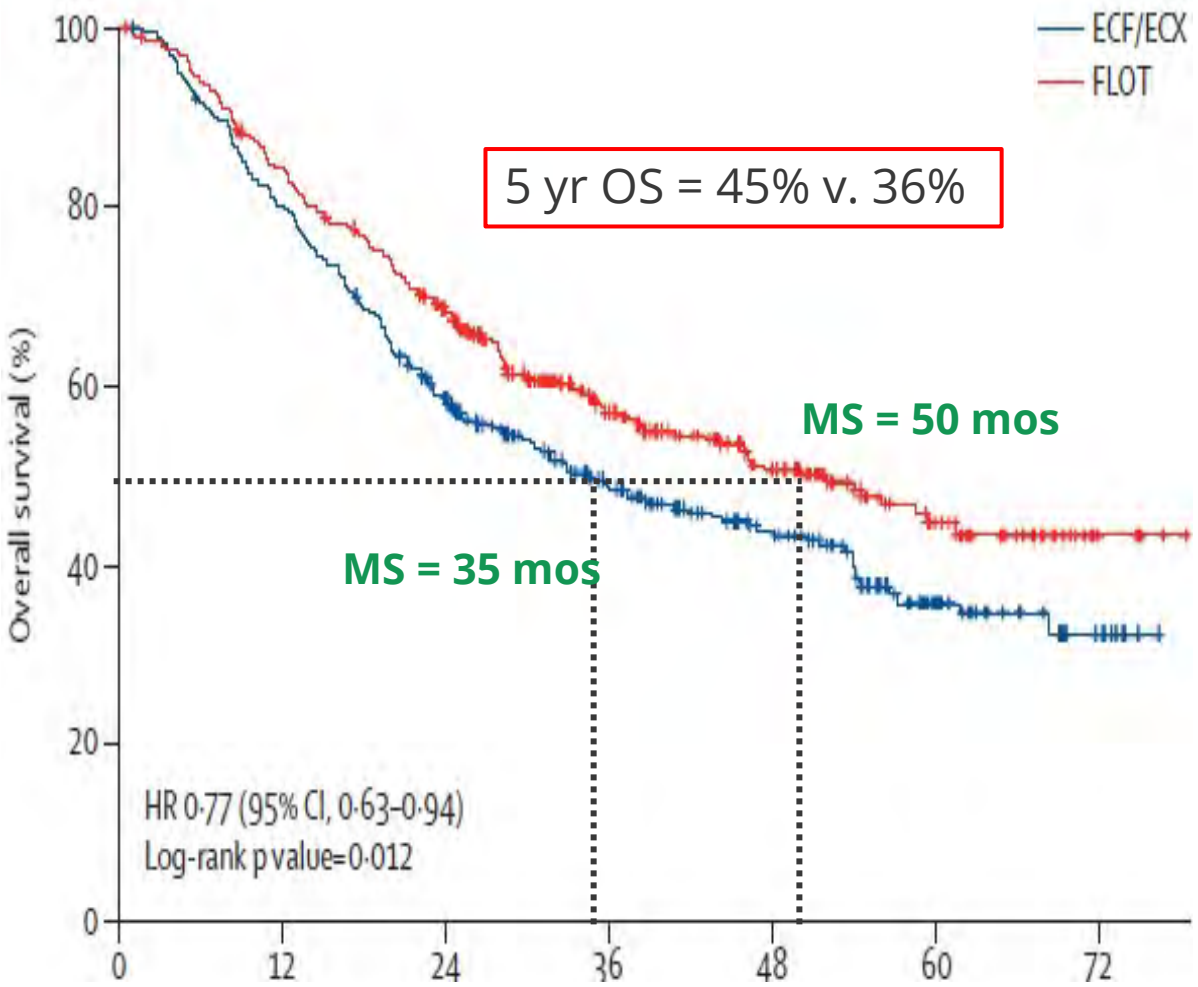
	Pre-op CRT	S Alone	P value
LRR	14%	34%	<.001
Peritoneal carcinomatosis	4%	14%	<.001
Hematogenous spread	29%	35%	.025

At 10 years, risk of distant relapse (with or without locoregional relapse) was lower in the CRT arm (HR, 0.61; 95%CI, 0.45 to 0.84)

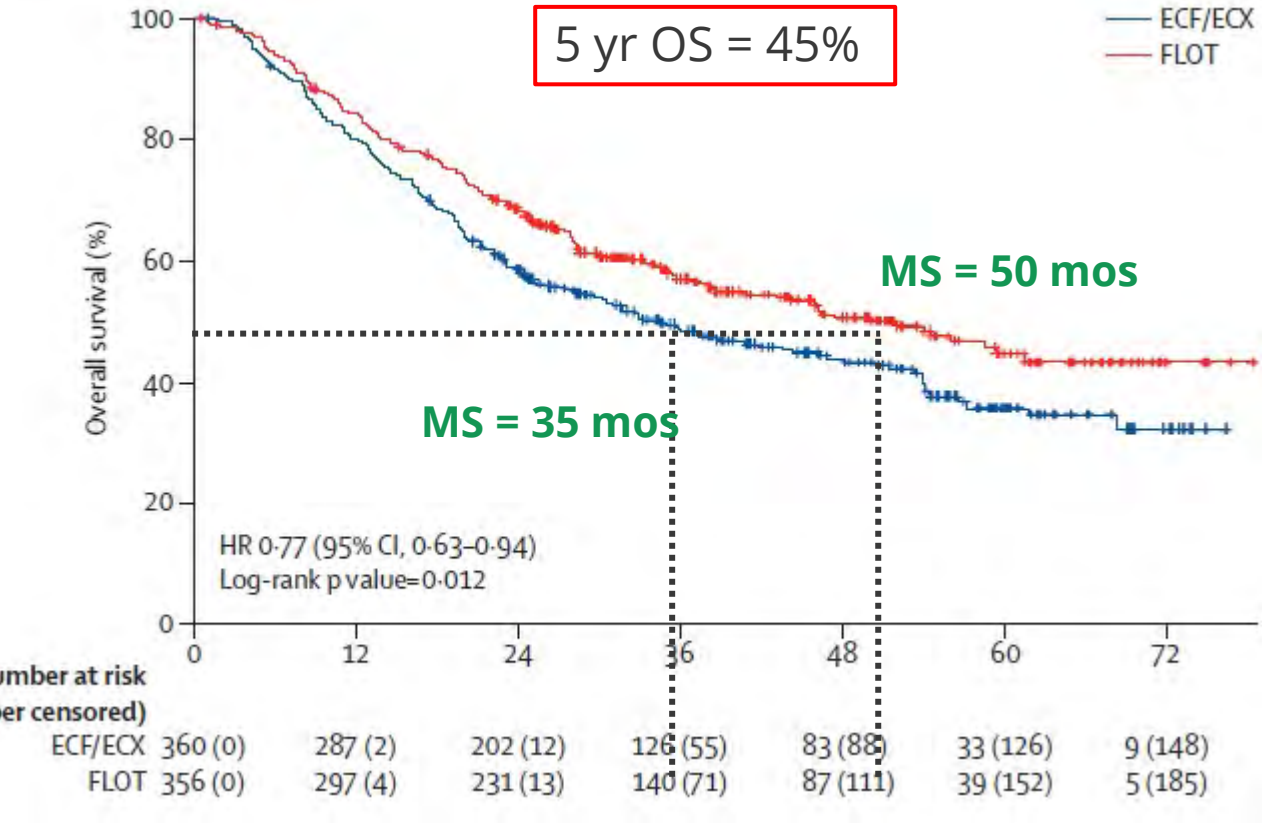
Oppedijk, *J Clin Oncol*, 2014; Eyck BM, *J Clin Oncol*, 2021

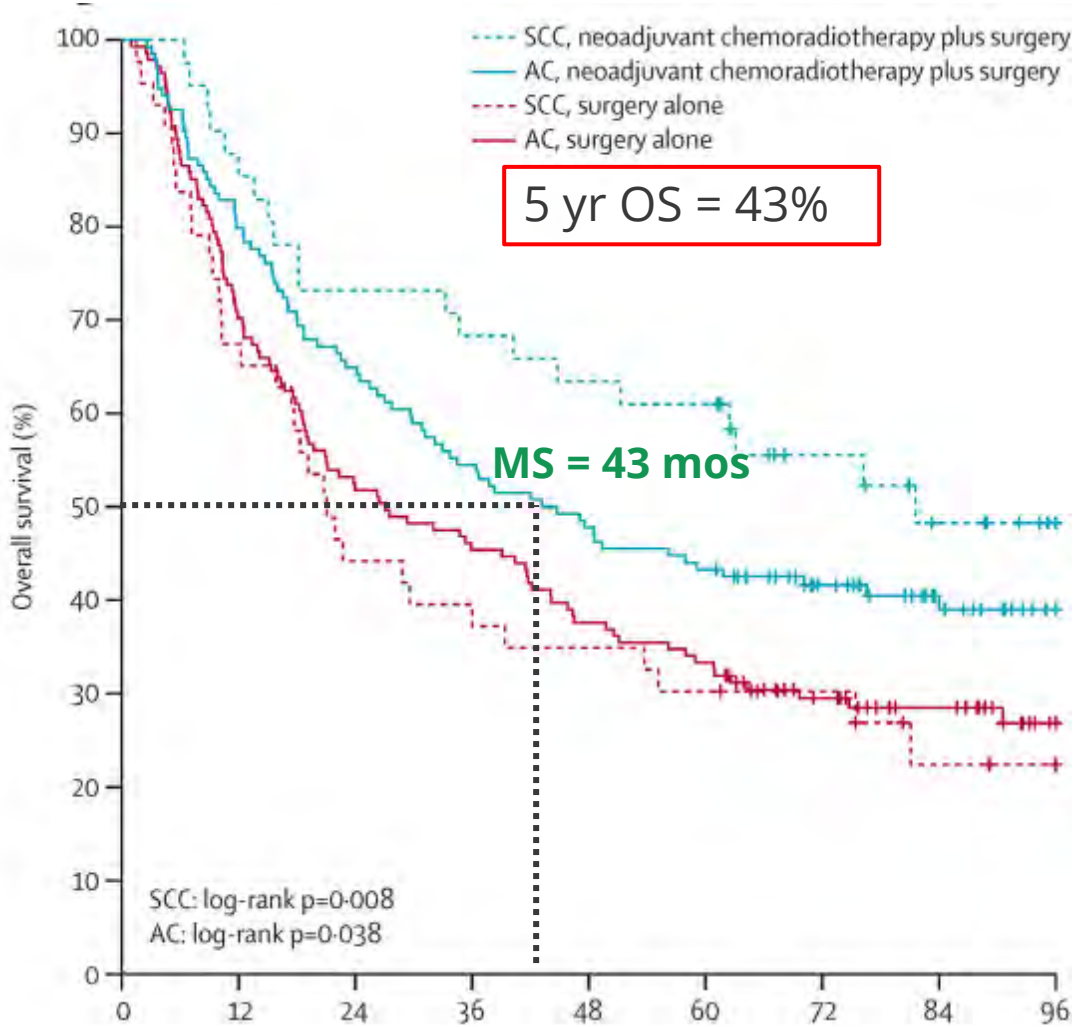
Neoadjuvant Chemotherapy: FLOT4 Trial

- Modern trial
- Perioperative FLOT4 v. ECF/ECX
- 716 pts with GEJ and gastric cancers randomized
- R0 resection: 85% v. 78%



Survival: FLOT4 Trial v. CROSS

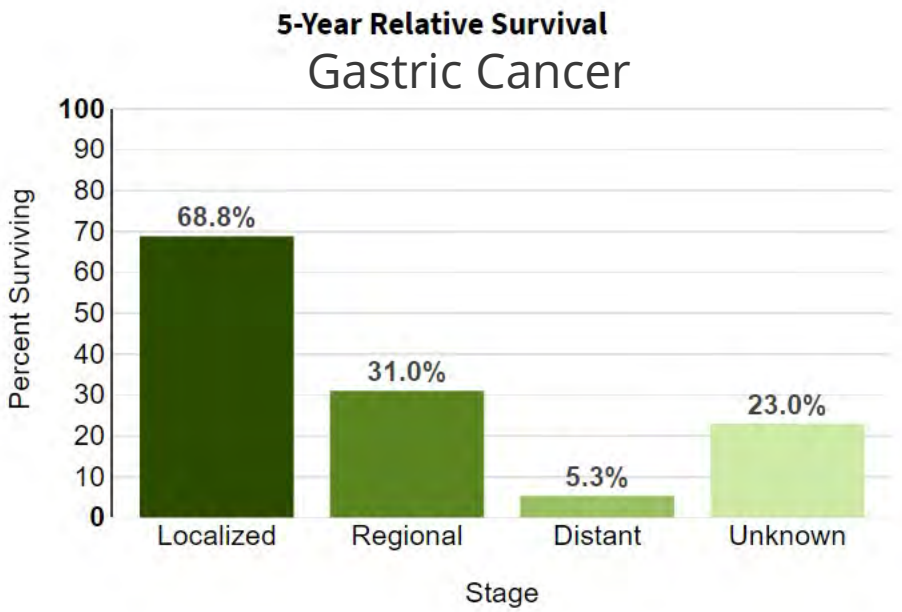


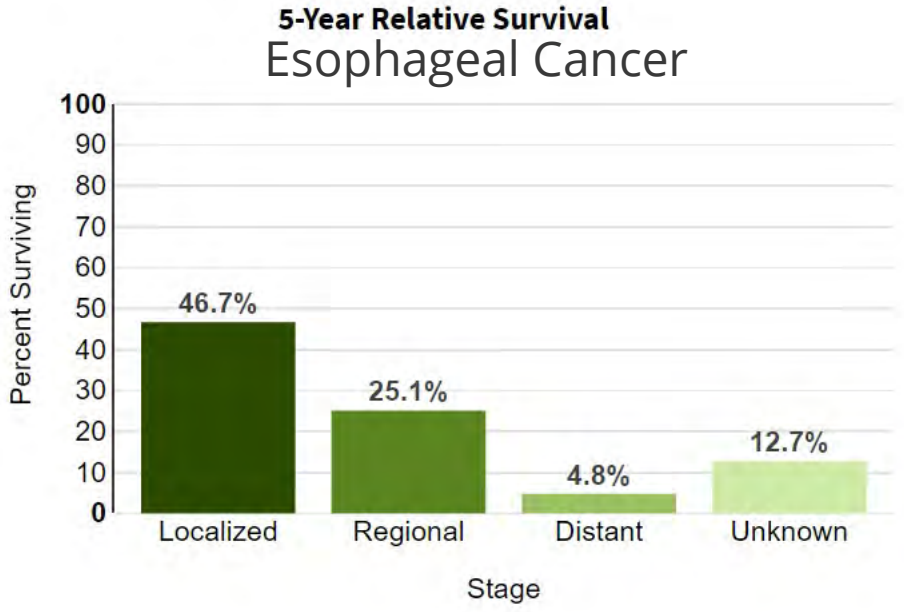


Van Hagen *NEJM*, 2012; Shapiro, *Lancet Oncol*, 2015

Comparison of CROSS v. FLOT

	CROSS	FLOT
Location		
Esophagus	74%	0%
GE junction	22%	56% (33% Siewerts 2-3)
Stomach	0%	44%





Neoadjuvant Chemo v. Chemoradiotherapy: NEOAegis

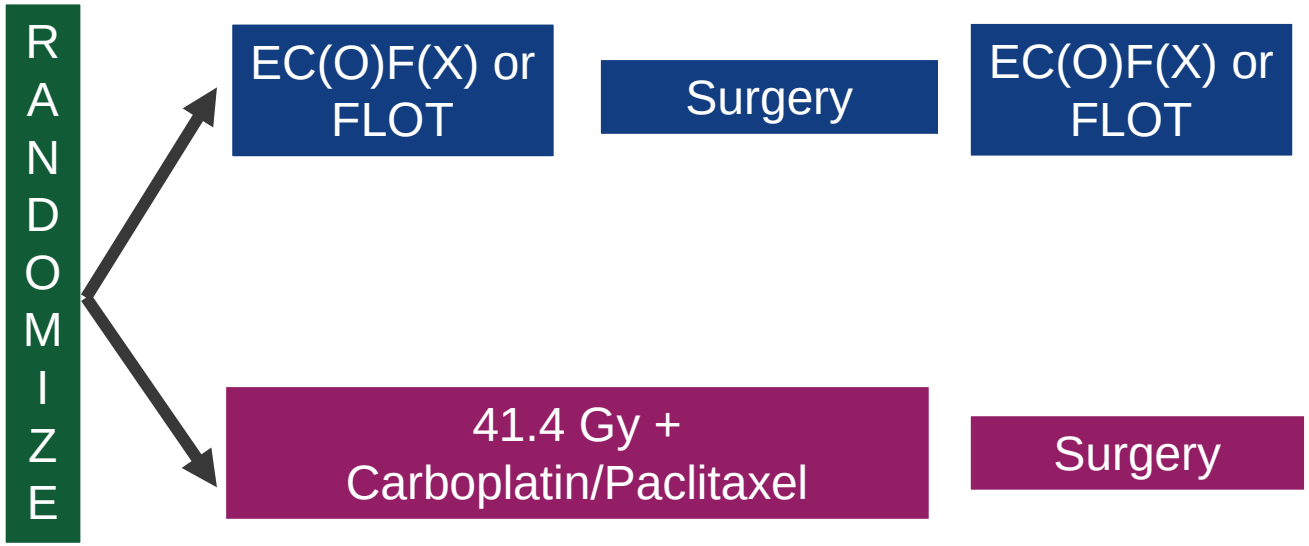
Neoadjuvant trial in Adenocarcinoma of the Esophagus and EG Junction International Study

377 Esophageal and GEJ Cancer Patients

100% adeno

Primary Endpoint: OS

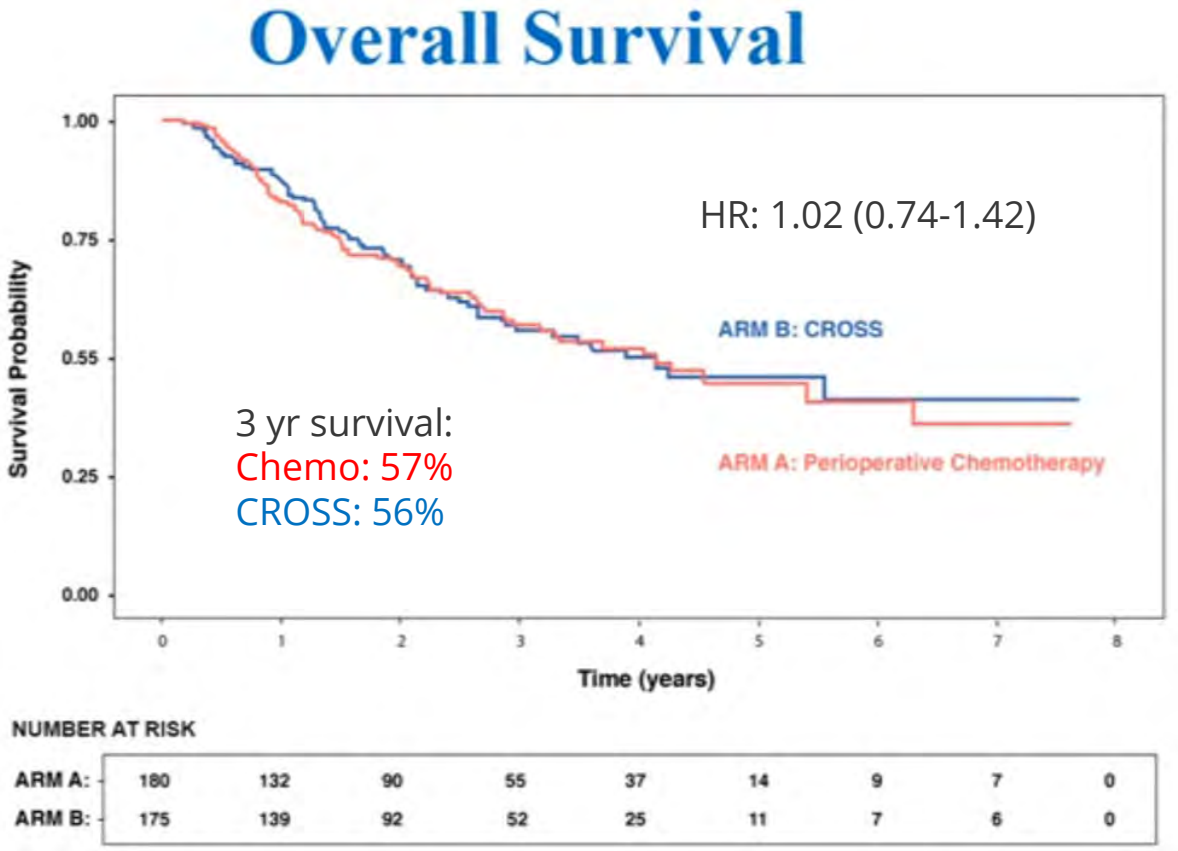
Non-inferiority



	Peri-op Chemo	CROSS	p-value
pCR	5%	16%	0.001
R0	82%	95%	<0.001
LN negative	44.5%	60%	0.004

Reynolds JV, *Proc ASCO*, 2021

Neoadjuvant Chemo v. Chemoradiotherapy: NEOAegis

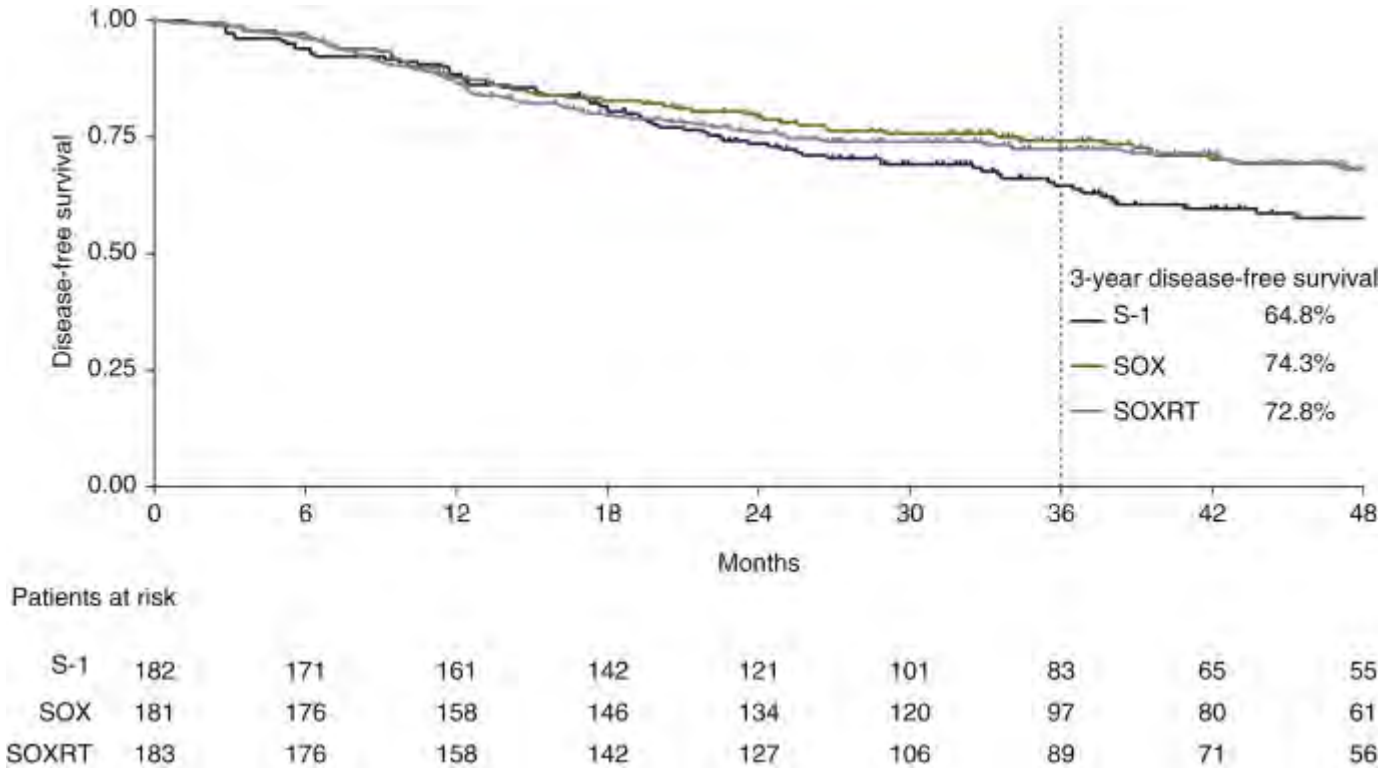


Conclusion

- No evidence that peri-operative chemotherapy is unacceptably inferior to multimodal therapy, notwithstanding greater proxy markers of local tumor response in the CROSS arm
- No significant difference in severity of complications or post-op mortality, no negative effects of pre-op chemoradiation
- Data support equipoise

Reynolds JV, *Proc ASCO*, 2021

A randomized phase III trial comparing adjuvant single-agent S1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: the ARTIST 2 trial

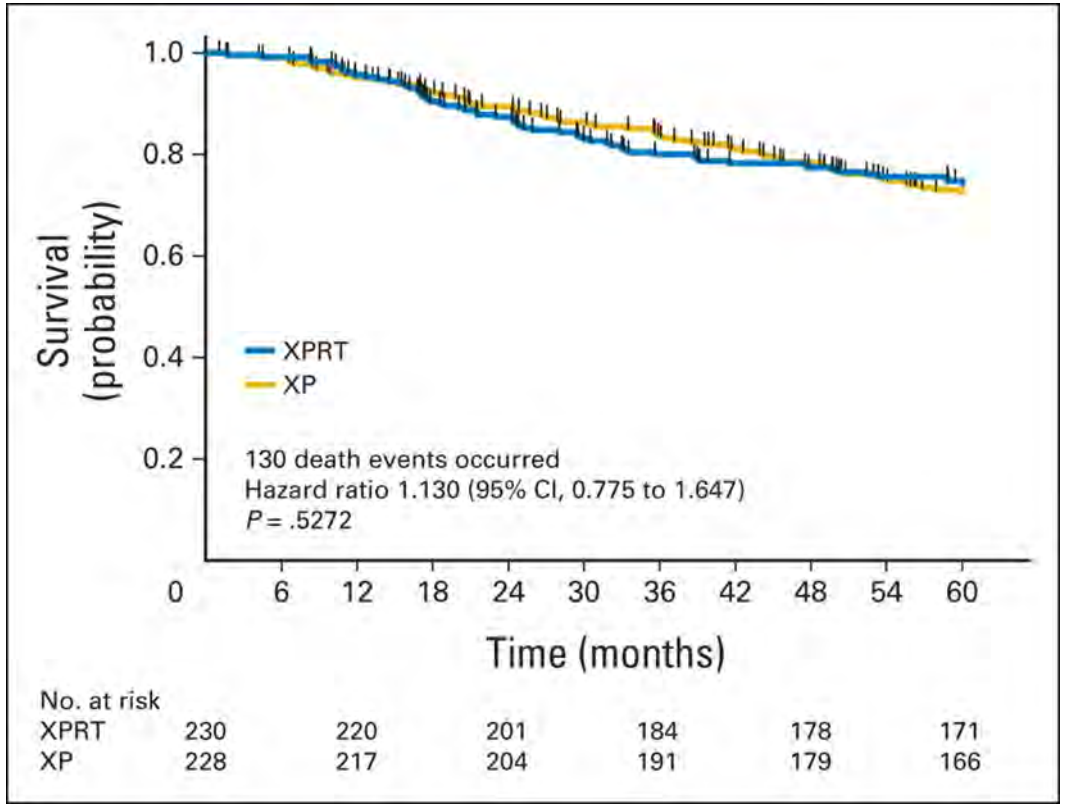


Patients at risk

S-1	182	171	161	142	121	101	83	65	55
SOX	181	176	158	146	134	120	97	80	61
SOXRT	183	176	158	142	127	106	89	71	56

Park SH et al; *Ann Onc* 2021

Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses



UGT1A1 genotype guided irinotecan dosing 'gFOLFIRINOX' for Gastric/GEJ cancer
R0 Analysis: Surgical and pathology results

Surgical Results	CRT CROSS[5] (n=134 (AC))	ECF/ECX[4] (n=360)	FLOT[4] (n=356)	gFOLFIRINOX (n=36)
Proceeded to surgery		341 (95%)	345 (97%)	**35 (97%)**
Resection rate	122 (91%)*	314 (87%)	336 (94%)	**35 (97%)**
Rate of margin-free R0 resection ITT	**110 (82%)***	**279 (78%)**	**301 (85%)**	**32[#] (89%)**
Type of surgery esophagogastrectomy gastrectomy (total & partial)	134 (100%)	98 (27%) 200 (56%)	109 (31%) 208 (58%)	23 (66%) 12 (34%)
Mean # of LN removed (25%; 75% Quartile)	15	25 (19; 33)	24 (18; 32)	**24 (19; 28)**
ypT-stage **≤T1** T2 T3 T4 Tx	Not reported	 53 (15%) 44 (12%) 175 (49%) 47 (13%) 41 (11%)	 88 (25%) 44 (12%) 165 (46%) 37 (10%) 22 (6%)	 **12 (33%)** 4 (11%) 17 (47%) 3 (8%) --
ypN-stage **N0** N1 N2 N3 Nx	Not reported	 146 (41%) 44 (12%) 54 (15%) 73 (20%) 43 (12%)	 174 (49%) 55 (16%) 47 (13%) 57 (16%) 23 (7%)	 **19 (53%)** 5 (14%) 6 (17%) 6 (17%) --

JAMA Netw Open. 2020 Feb 5;3(2):e1921290

Adjuvant Immunotherapy: Checkmate 577

794 Resected Esophageal and GEJ Cancer Patients with residual disease after neadjuvant CRT

71% adeno, 29% SCC

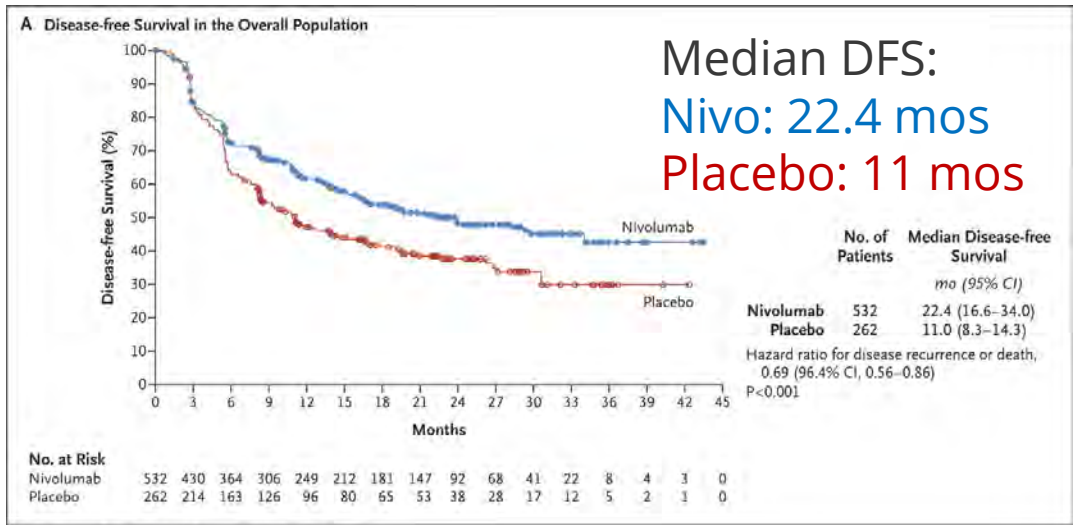
Primary Endpoint: DFS

RANDOMIZE

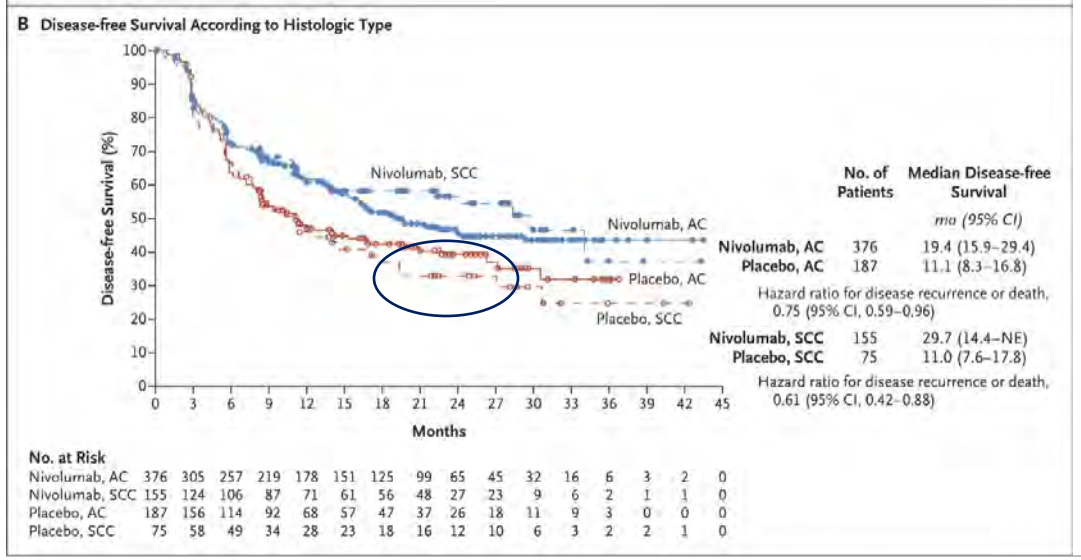
Adjuvant Nivolumab x 6 mos

Placebo

Subgroup	Median Disease-free Survival, months		Unstratified Hazard Ratio (95% CI)
	Nivolumab	Placebo	
PD-L1 CPS expression			
≥5 (n = 371)	29.4	10.2	0.62 (0.46–0.83)
<5 (n = 295)	16.3	11.1	0.89 (0.65–1.22)



Median DFS:
Nivo: 22.4 mos
Placebo: 11 mos



Kelly RJ, *NEJM*, 2021

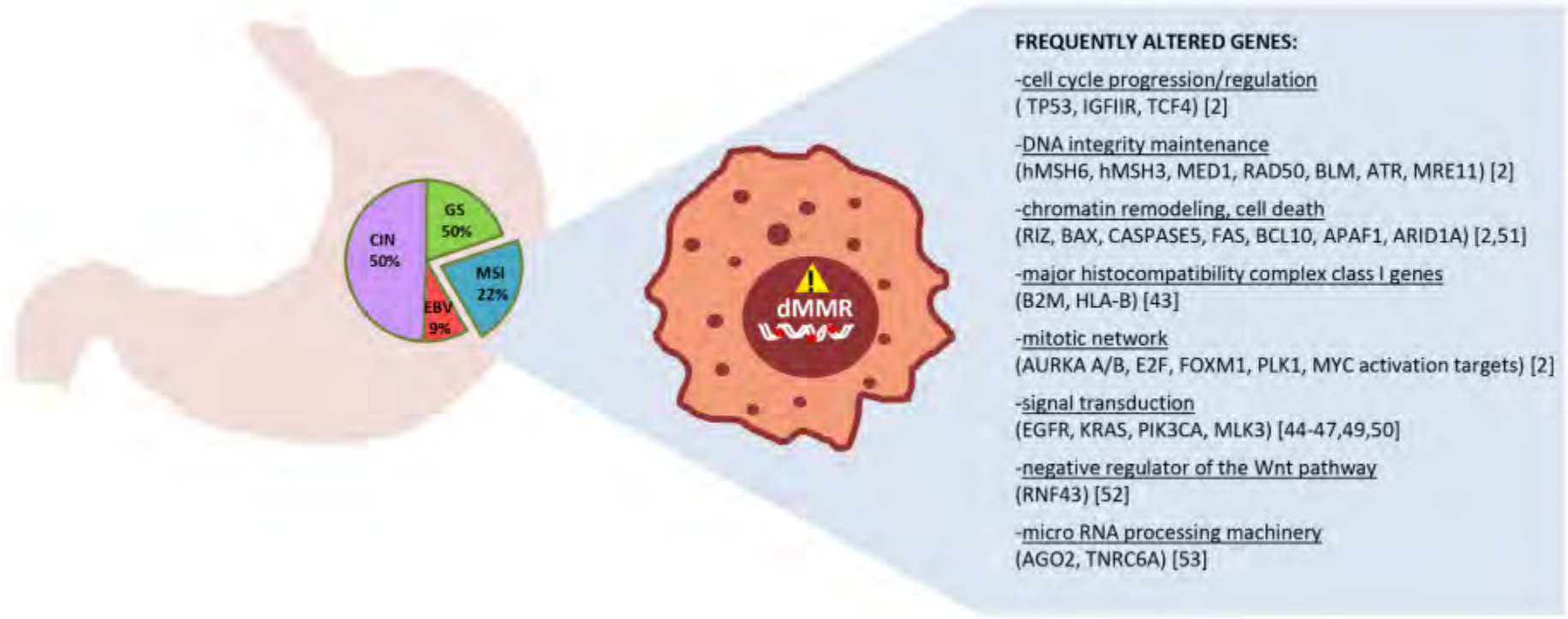
Conclusions

- Adherence to operative standards, not unlike chemotherapy and RT standards, are essential for an optimal outcome
- Choice of operative approach (open, MIS, robotic) does not affect oncologic outcomes
- Peri-operative FLOT addresses the highest risk for recurrence in gastroesophageal adenocarcinomas – distant spread

Conclusions

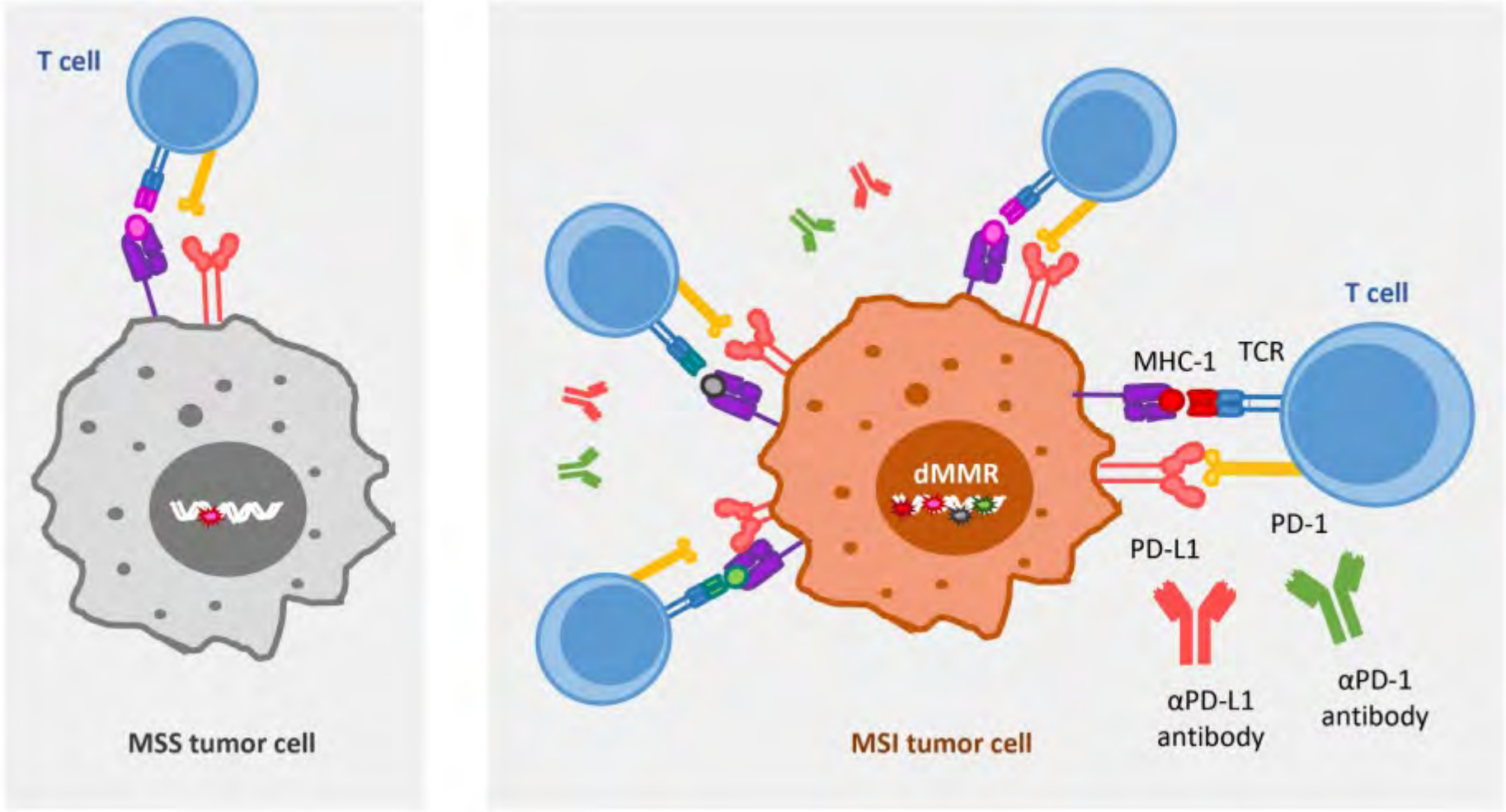
- Incorporating chemoradiotherapy into neoadjuvant regimen can improve local control parameters
- Total neoadjuvant therapy, chemotherapy + CRT addresses micrometastatic disease and local control
- Addition of adjuvant Nivolumab may address the need for more systemic control

MSI in Gastric Cancer



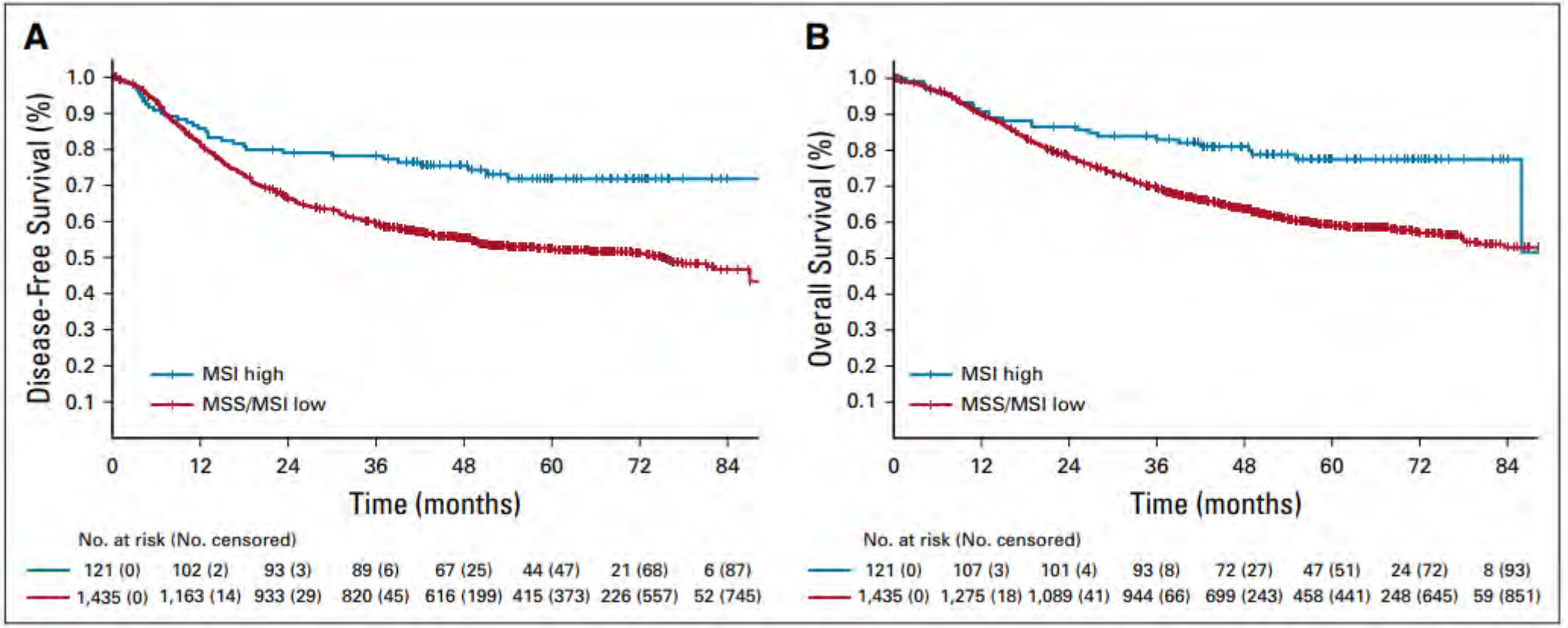
Puliga E et al, *Cancer Treat Reviews*, 2021

MSI in Gastric Cancer



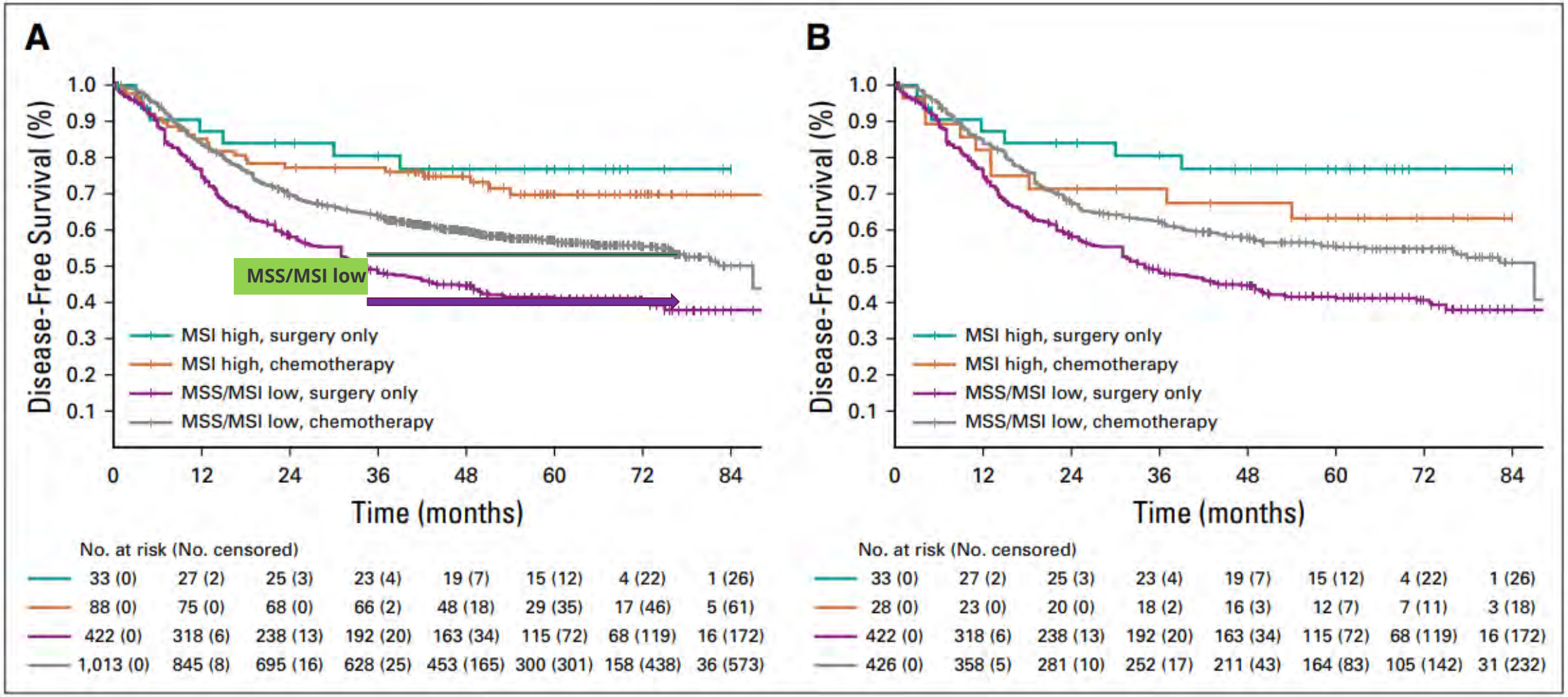
Puliga E et al, *Cancer Treat Reviews*, 2021

MSI Biomarker in Gastric Cancer Prognostic



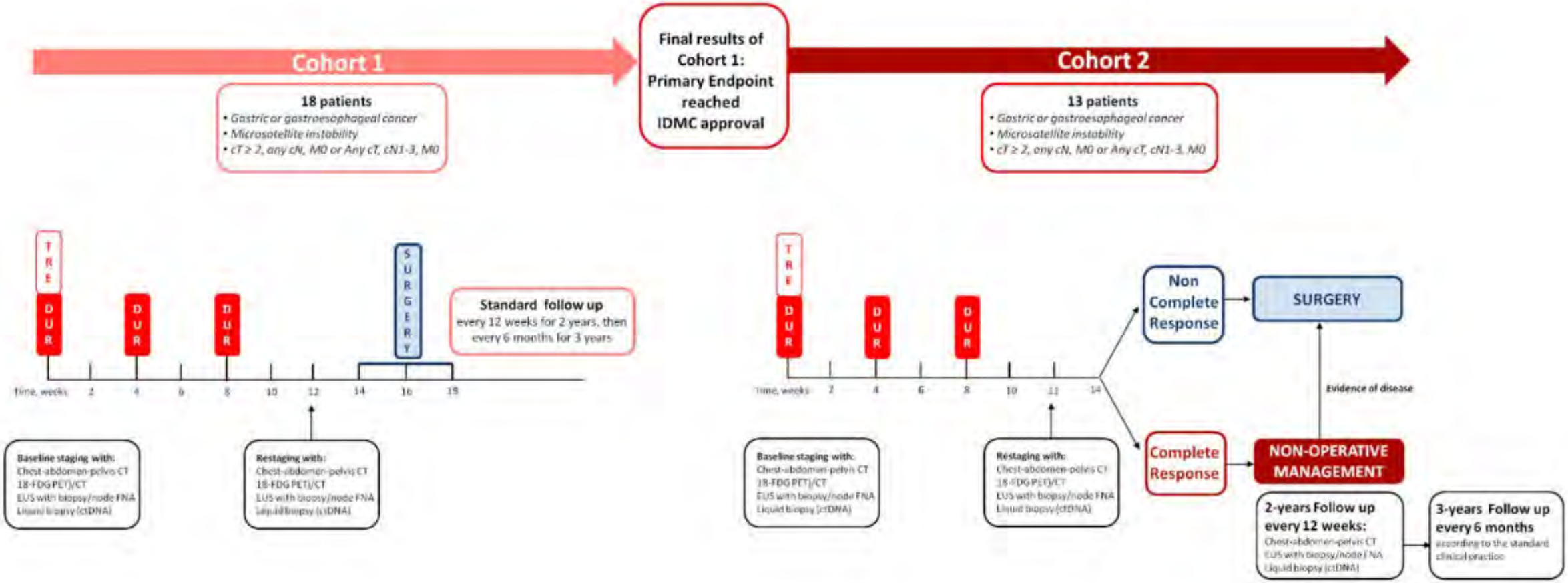
Pietrantonio F et al, *JCO*, 2019

MSI Biomarker in Gastric Cancer Predictive



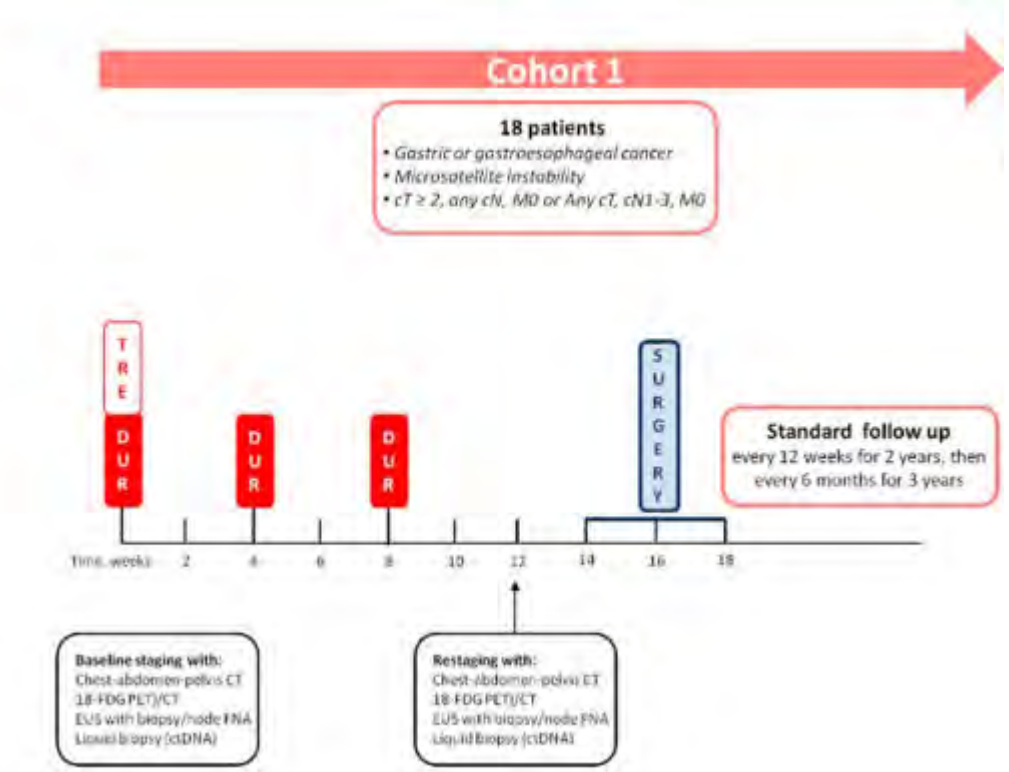
Pietrantonio F et al, *JCO*, 2019

TremelImumab and Durvalumab Combination for the Non-OperatIve Management (NOM) of Microsatellite InstabiliTY (MSI)-High Resectable Gastric or Gastroesophageal Junction Cancer: The Multicentre, Single-Arm, Multi-Cohort, Phase II INFINITY Study



Raimondi A et al, *Cancers*, 2021

TremelImumab and Durvalumab Combination for the Non-OperatIve Management (NOM) of Microsatellite InstabiliTY (MSI)-High Resectable Gastric or Gastroesophageal Junction Cancer: The Multicentre, Single-Arm, Multi-Cohort, Phase II INFINITY Study



- 18 patients MSI/dMMR resectable cT2-4 any N gastric or GEJ cancer
- 15 evaluable pts → 14 pts resected
- pCR 60% (major/complete response 80%)
- All pts with pCR had negative ctDNA pre-surgery

Conclusions

- Surgery: dealer's choice
- Neoadjuvant therapy: dealer's choice
- Immunotherapy: promising
- Individualized approach: the future and a necessity

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Thank You