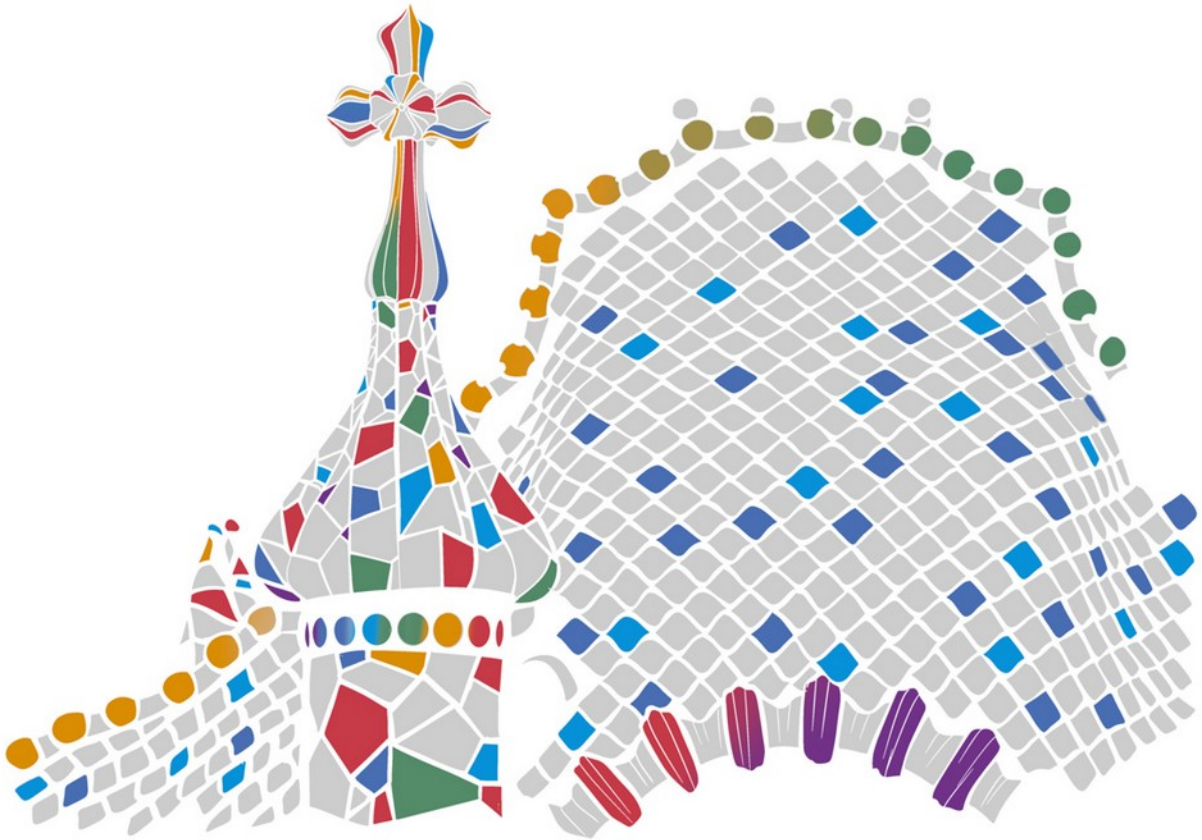
DIGESTIVE CANCERS EUROPE

8TH ANNUAL MASTERCLASS
29 JUNE – 01 JULY 2023
BARCELONA



Latest Update on Eso-Gastric Cancers

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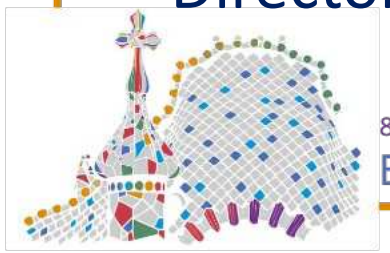
Germany

Disclosure of Interest

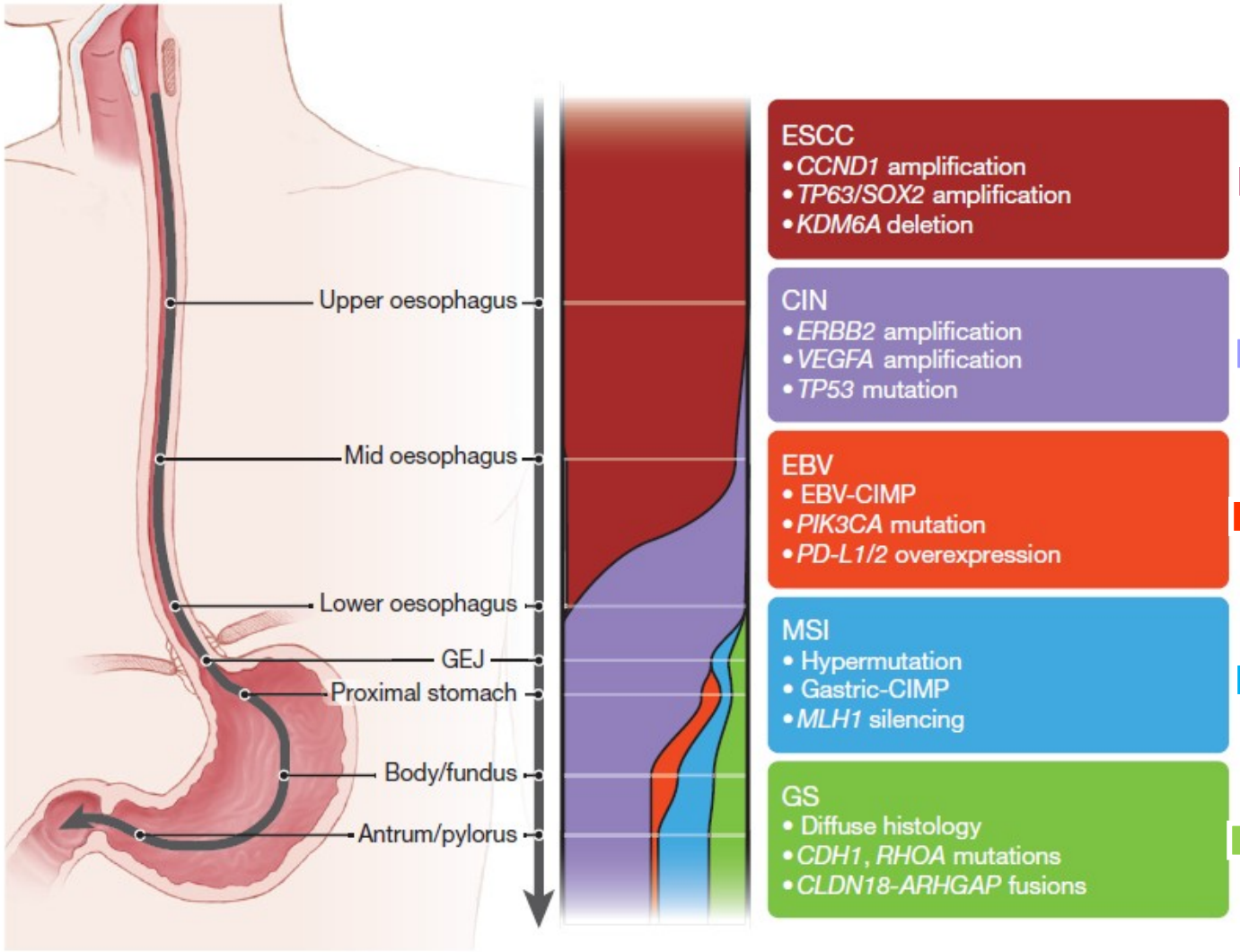
Personal honoraria: Amgen, Art tempi, Astellas, Astra Zeneca, Bayer, Biontech, BMS, Daiichi Sankyo, Eli Lilly, Elsevier, Falk Foundation, Incyte, MedUpdate, Merck, MSD, Novartis, Roche, Servier, Springer-Nature, StreamedUp!

Research support: Astra Zeneca, BMS, Gilead, MSD

Employment and leadership: University Hospital Leipzig (Cancer Center Director and Head of Department of Oncology)



BIOLOGY OF ESOPHAGO-GASTRIC CANCER



ESCC - Similarities with Head-Neck Cancer

CIN – Moderately immunogenic
HER2 / VEGF amplifications

EBV - Immunogenic
Immune infiltrates, PD-L1 high

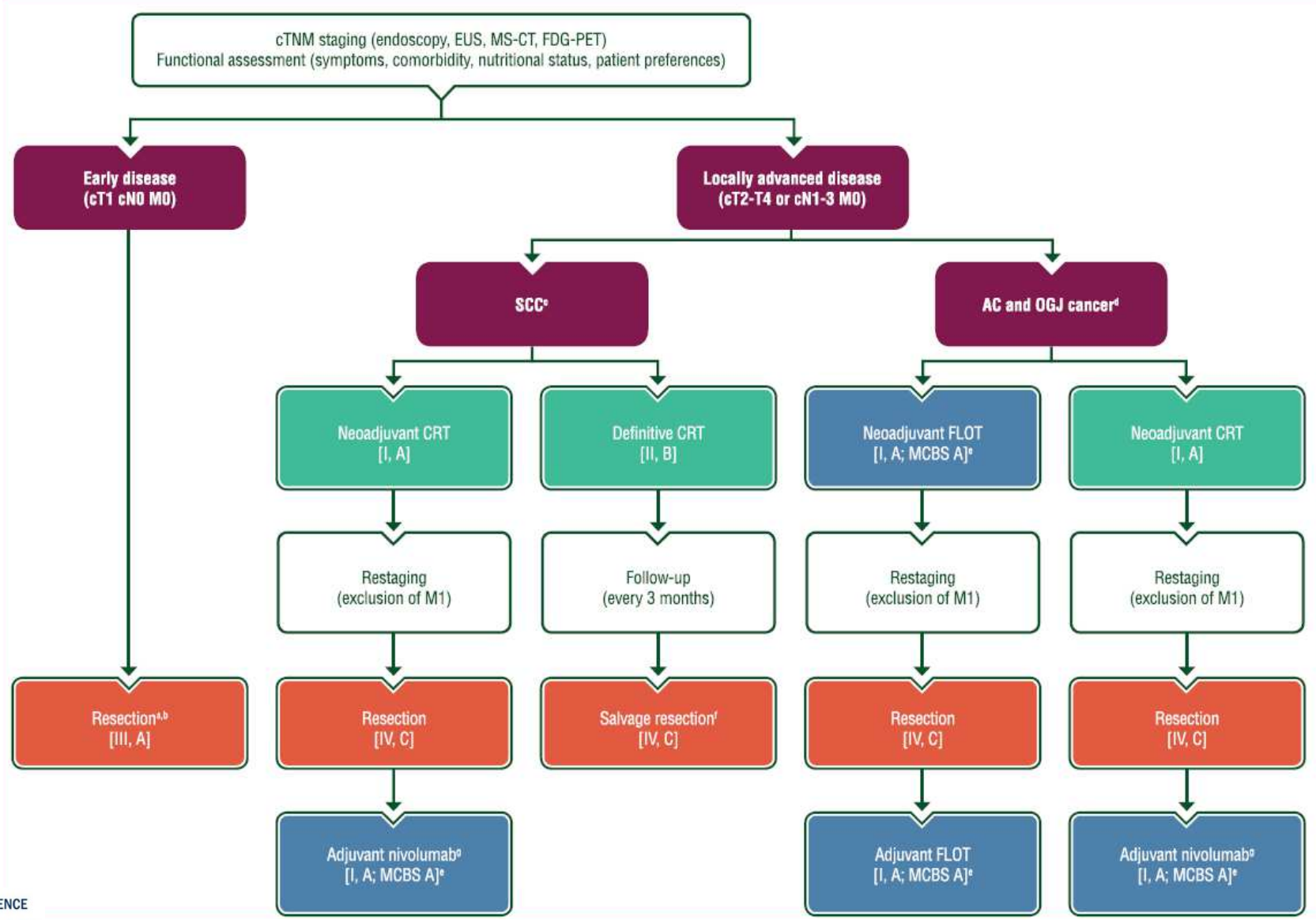
MSI - Immunogenic
High mutational burden

Genomic stable (silent)
Lower mutational burden

Gradations of molecular subclasses of gastroesophageal carcinoma

The Cancer Genome Atlas Research Network. Nature. 2017;541:169-175

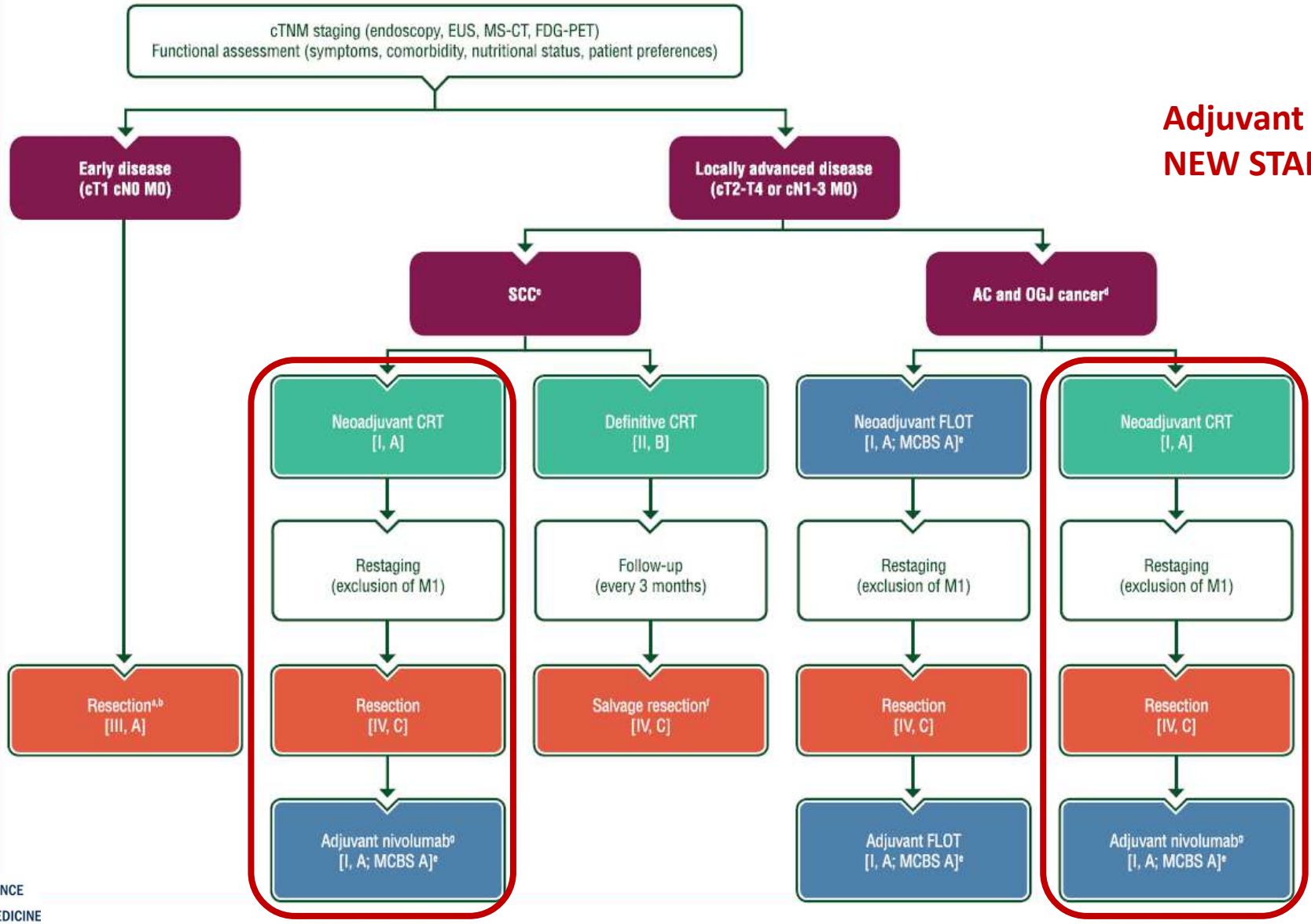
LOCALIZED ESOPHAGEAL CANCER – ESMO GUIDELINES 2022



GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Obermannová R, et al. *Ann Oncol* 2022

LOCALIZED ESOPHAGEAL CANCER – ESMO GUIDELINES 2022



Adjuvant Nivolumab
NEW STANDARD OF CARE!

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Obermannová R, et al. *Ann Oncol* 2022

LOCALIZED ESOPHAGEAL CANCER – CHECKMATE-577

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])

N = 794 → R 2:1

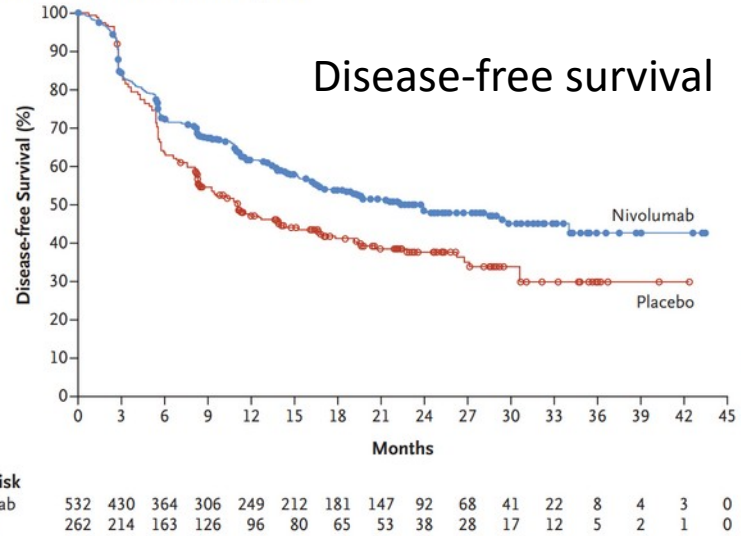
- n = 532 → **Nivolumab** 240 mg Q2W × 16 weeks then 480 mg Q4W
- n = 262 → **Placebo** Q2W × 16 weeks then Q4W

Total treatment duration of up to 1 year[d]

Primary endpoint:
- DFS[e]

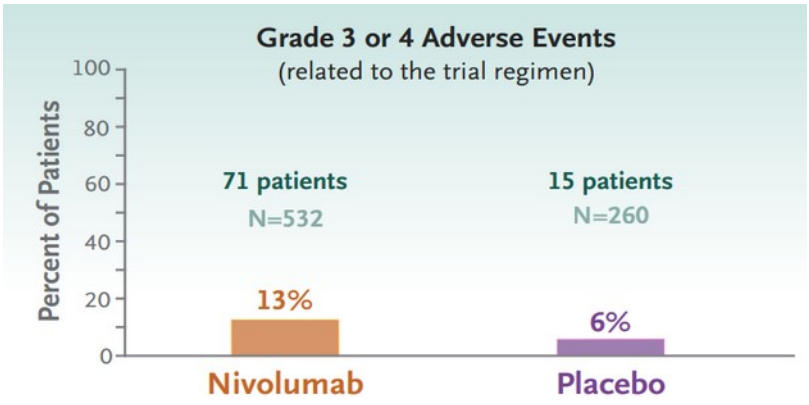
Secondary endpoints:
- OS[f]
- OS rate at 1, 2, and 3 years

- Median follow-up was 24.4 months (range, 6.2-44.9)[g]



	No. of Patients	Median Disease-free Survival
		mo (95% CI)
Nivolumab	532	22.4 (16.6–34.0)
Placebo	262	11.0 (8.3–14.3)

Hazard ratio for disease recurrence or death, 0.69 (96.4% CI, 0.56–0.86)
P<0.001

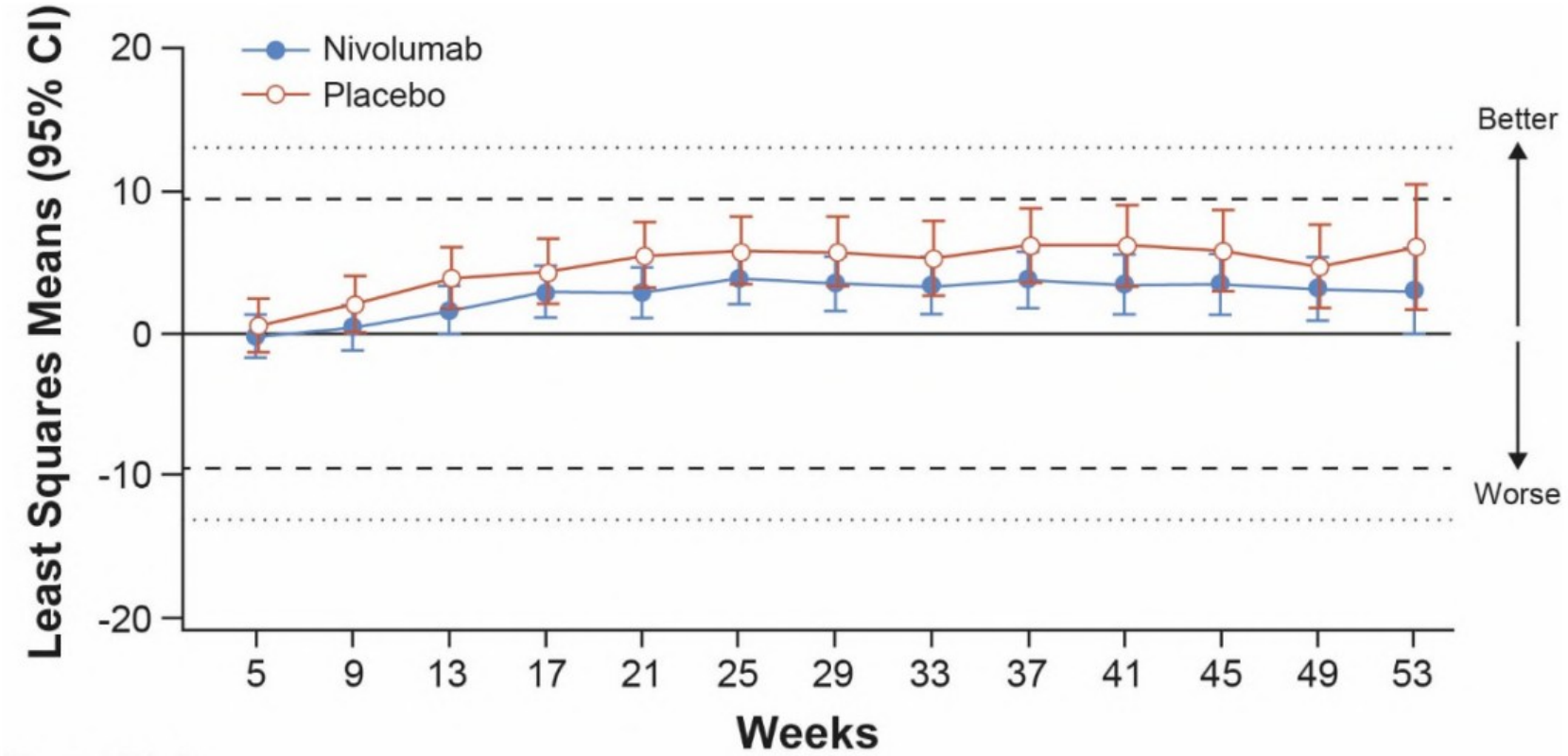


- Nivolumab showed a 26% reduction in the risk of distant recurrence or death versus placebo
- Distant (29% versus 39%) and locoregional (12% versus 17%) recurrences were less frequent with Nivolumab versus placebo
- Adverse events in the Nivolumab group occurred early (median time to onset, 6–13 weeks) and resolved for most patients

Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203

LOCALIZED ESOPHAGEAL CANCER – CHECKMATE-577

Quality of Life (FACT-E)

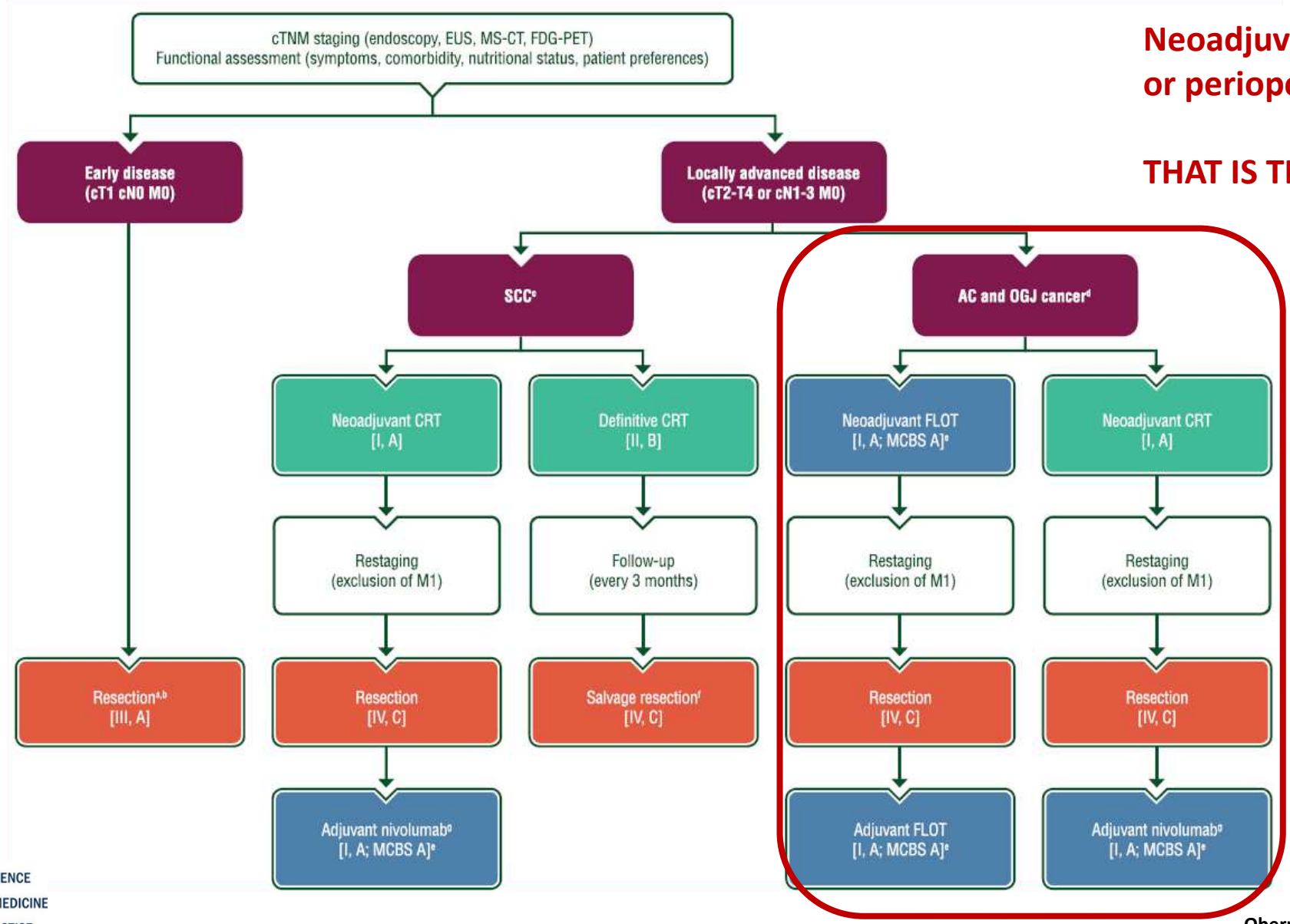


No. at Risk

Nivolumab	439	410	375	319	303	289	274	272	257	251	232	217	45
Placebo	227	217	200	174	168	154	136	134	124	106	99	96	20

Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203. *Supplement*

LOCALIZED ESOPHAGEAL CANCER – ESMO GUIDELINES 2022



Neoadjuvant RADIOCHEMO or perioperative CHEMO

THAT IS THE QUESTION!

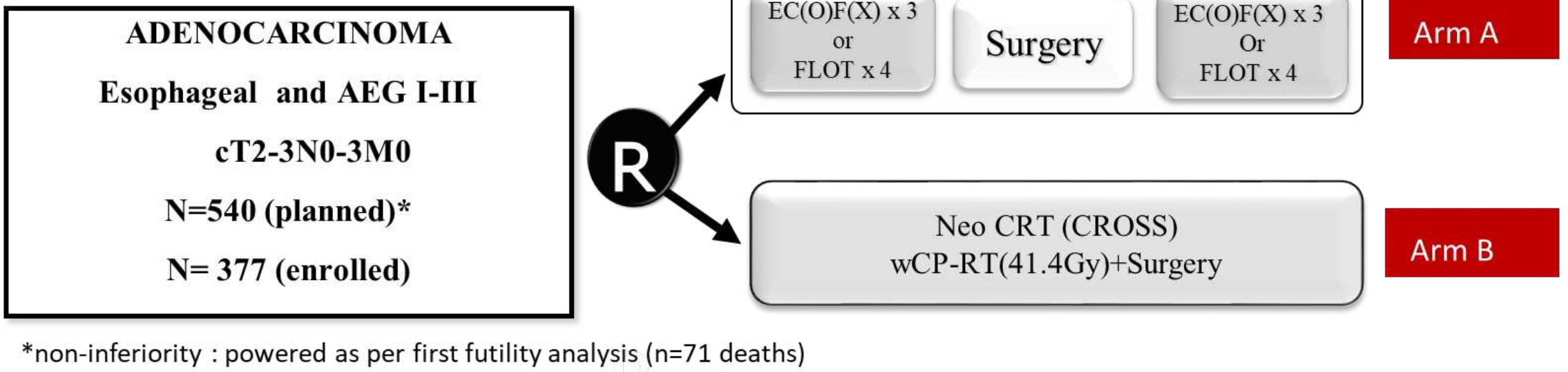
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Obermannová R, et al. *Ann Oncol* 2022

ESOPHAGEAL AND AEG I-III – RCTX VERSUS CTX?

Phase III: Neo-AEGIS: 3-year Follow-Up

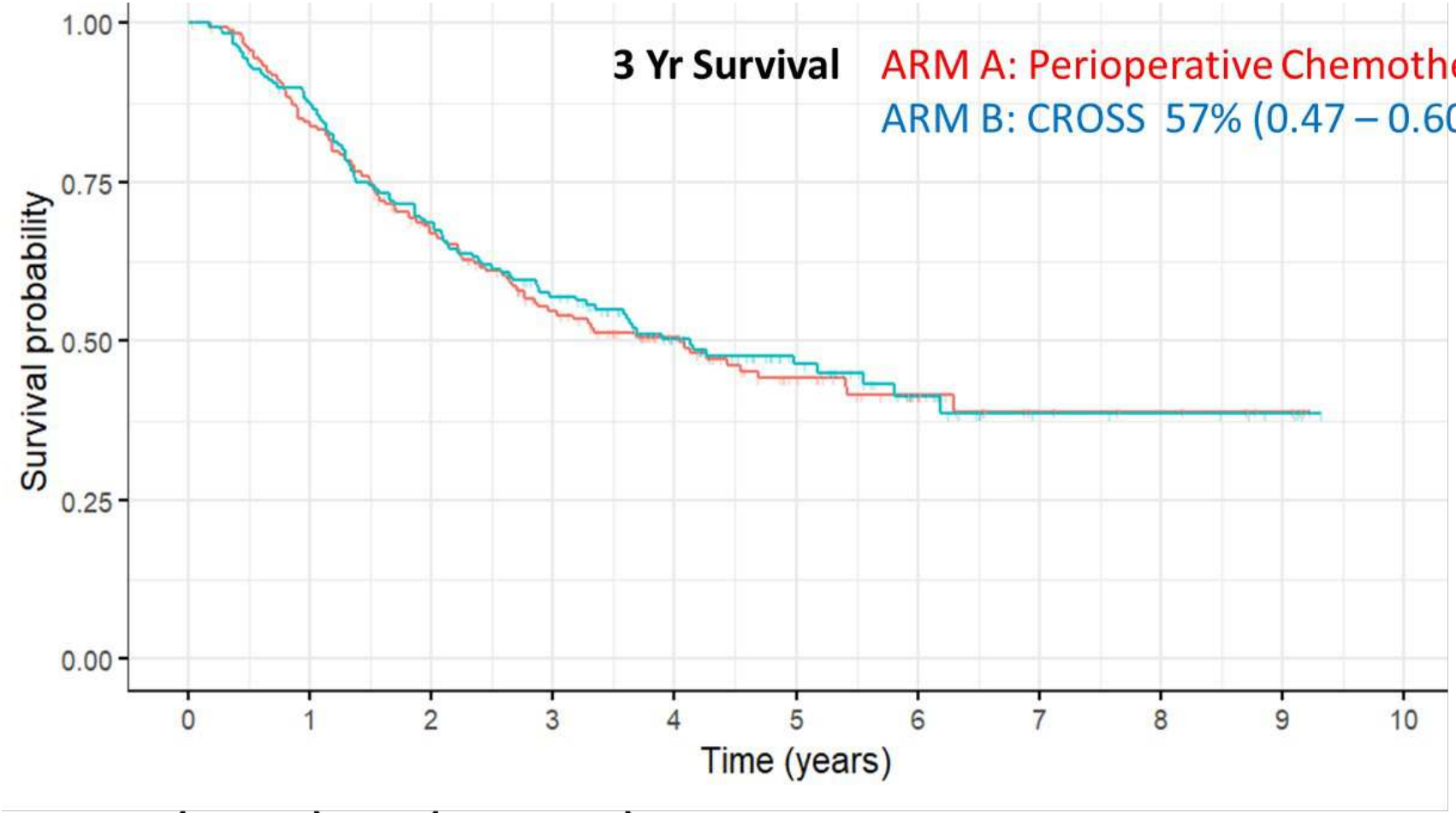
Update ASCO GI 2023



*non-inferiority : powered as per first futility analysis (n=71 deaths)

Lowery M et al., ASCO-GI 2023, abstract 295

ESOPHAGEAL AND AEG I-III – NEO-AEGIS



HR (95% CI) 1.03 (0.77- 1.38)

Median follow-up of 34.2 (0.43-111.8) mo

Lowery M et al., ASCO-GI 2023, abstract 295

NEW DATA EXPECTED

ESOPEC recruitment finished

N=438

T1N1M0
or
T2–4aN0–1M0

R A N D O M

Perioperative CTX: FLOT* 4 x pre and post
RESECTION

*FLOT = 5-FU Leucovorin, Oxaliplatin, Docetaxel

Primary endpoint: Overall Survival
Assumption: 3-year-OS-rate
55% CROSS vs. 68% FLOT)

Neoadjuvant Radio-CTX – CROSS Regime
RESECTION

Hoeppner J, Lordick F. et al. *BMC Cancer* 2016; 16: 503

WHAT DOES IT MEAN FOR THE PATIENT WITH ESOPHAGEAL CANCER

A. Treatment in an experienced high volume center

B. Shared decision making about options

- operative or non-operative treatment
- perioperative chemotherapy or chemoradiotherapy

C. Access to immunotherapy

- in-label post chemorad and surgery
- or within a clinical trial

PREDICTIVE MARKERS IN ESOPHAGO-GASTRIC CANCER

Validated in phase III

HER2 (IHC and ISH)

PD-L1 (TPS and CPS)

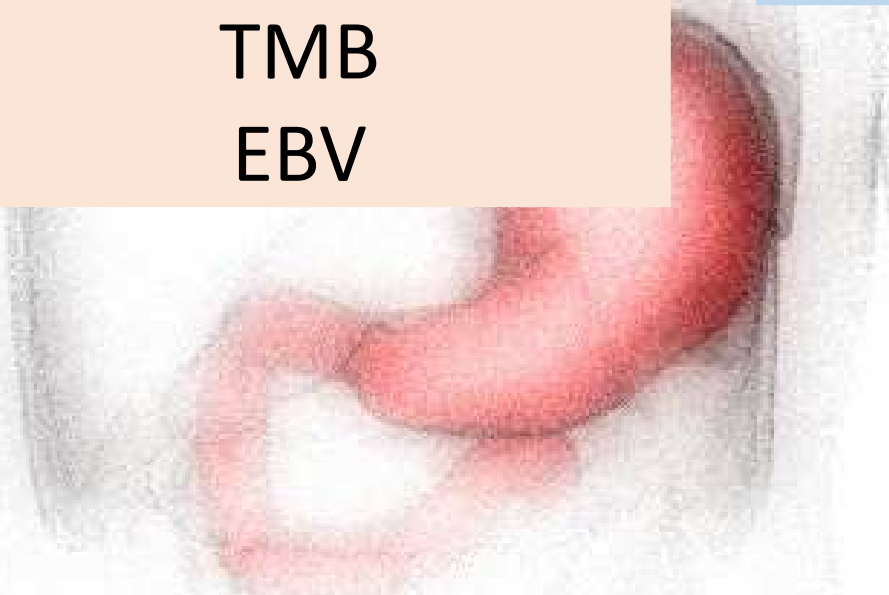
CLAUDIN 18.2

Evidence Phase II-III

dMMR / MSI
TMB
EBV

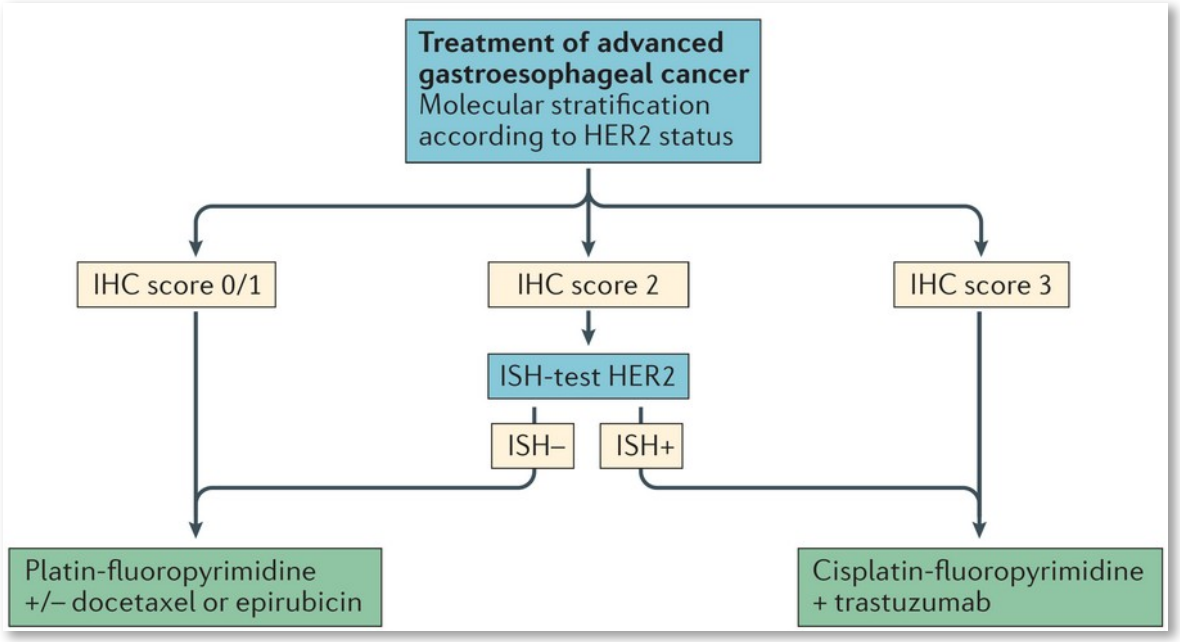
Promising in phase II

FGFR2B



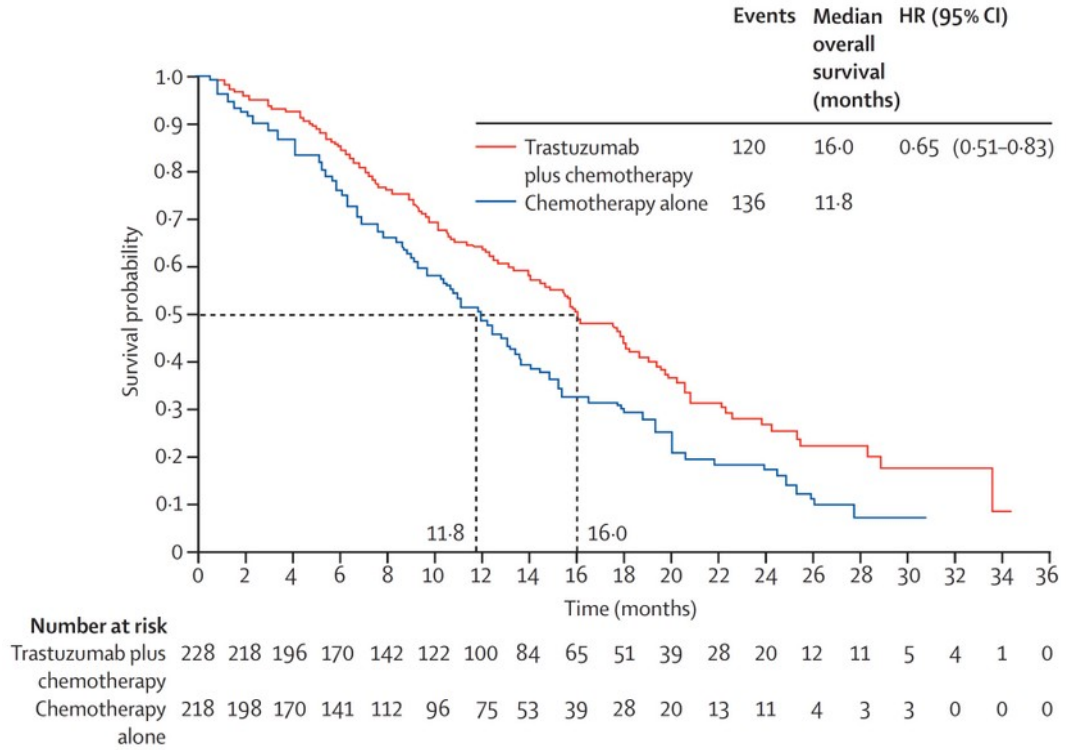
HER2 – HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR-2

HER2 test algorithm for treatment selection



TOGA – HER2 IHC 3+ or IHC2+ and FISH+

Trastuzumab + Chemo vs Chemo



Lordick F, Janjigian YY. *Nat Rev Clin Oncol.* 2016 Jun;13(6):348-60

Bang YJ et al.. *Lancet. 2010 Aug 28;376(9742):687-97*

TARGET HETEROGENEITY – HER2 VARIANZ STUDY

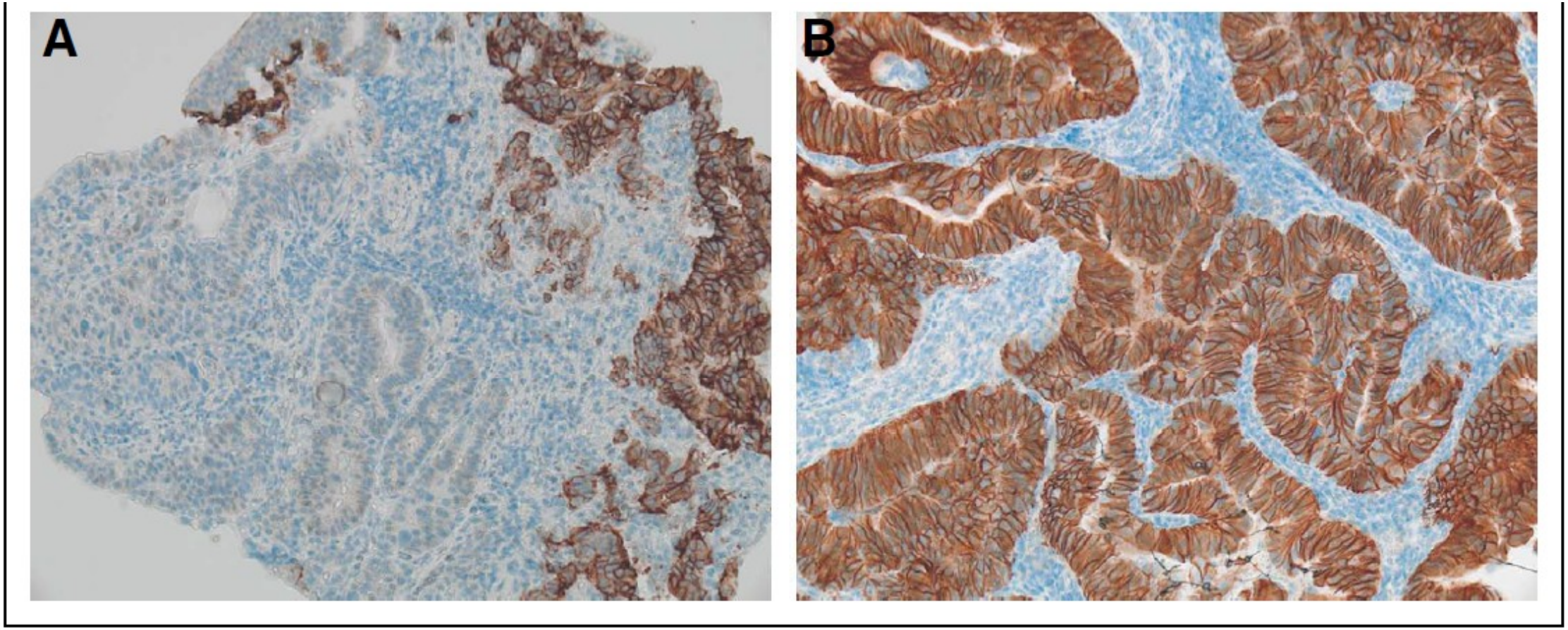
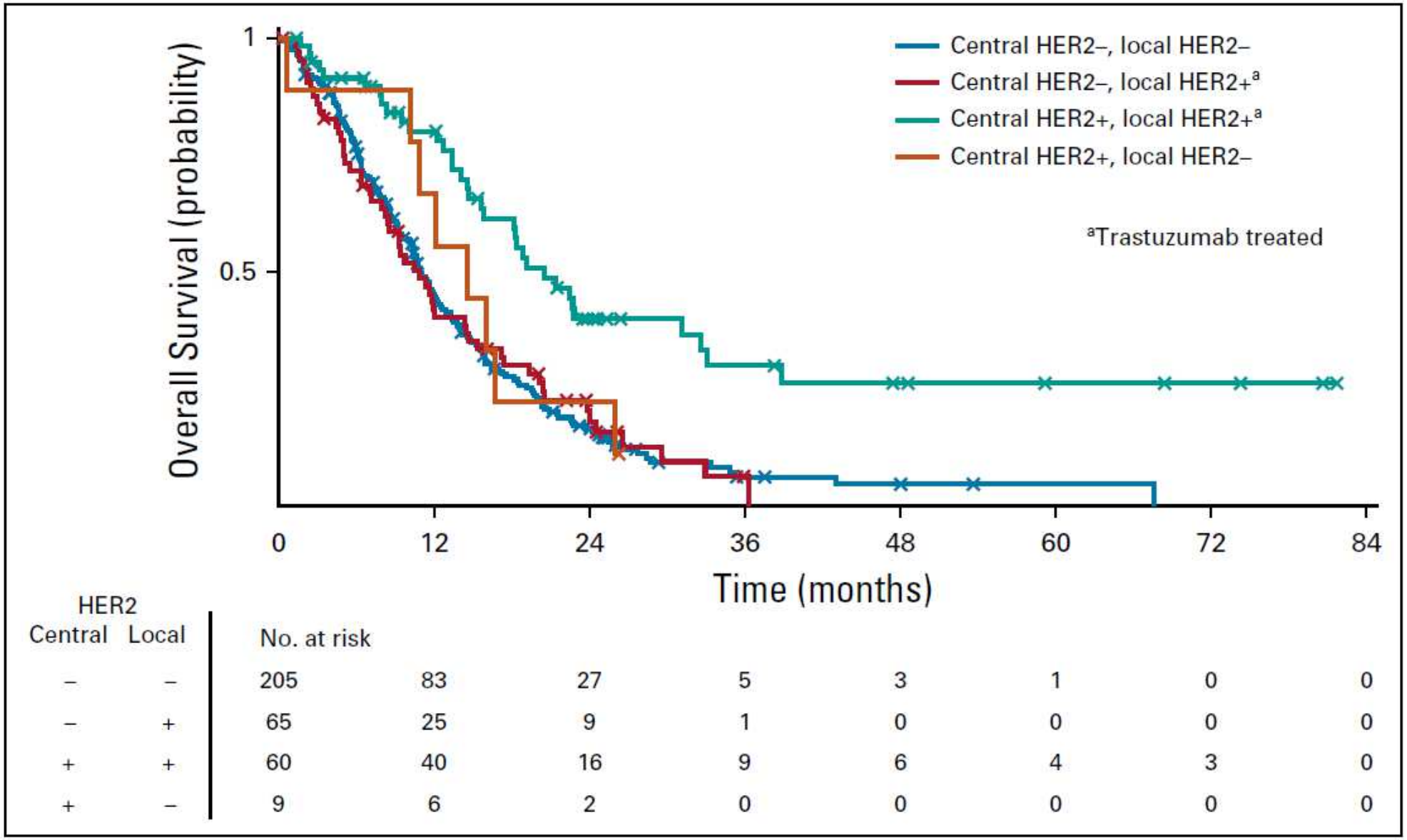


FIG A1. HER2 staining examples in the VARIANZ study. (A) Example of intratumoral heterogeneity: unstained HER2 negative tumor cells on the left side, some normal stomach glands in the middle, and strongly staining HER2-positive tumor cells on the right side, (B) example of homogenously HER2-positive staining tumor cells. HER2, human epidermal growth factor receptor 2.

Haffner I.…Lordick F. *J Clin Oncol.* 2021 May 1;39(13):1468-1478

HER2 VARIANZ STUDY

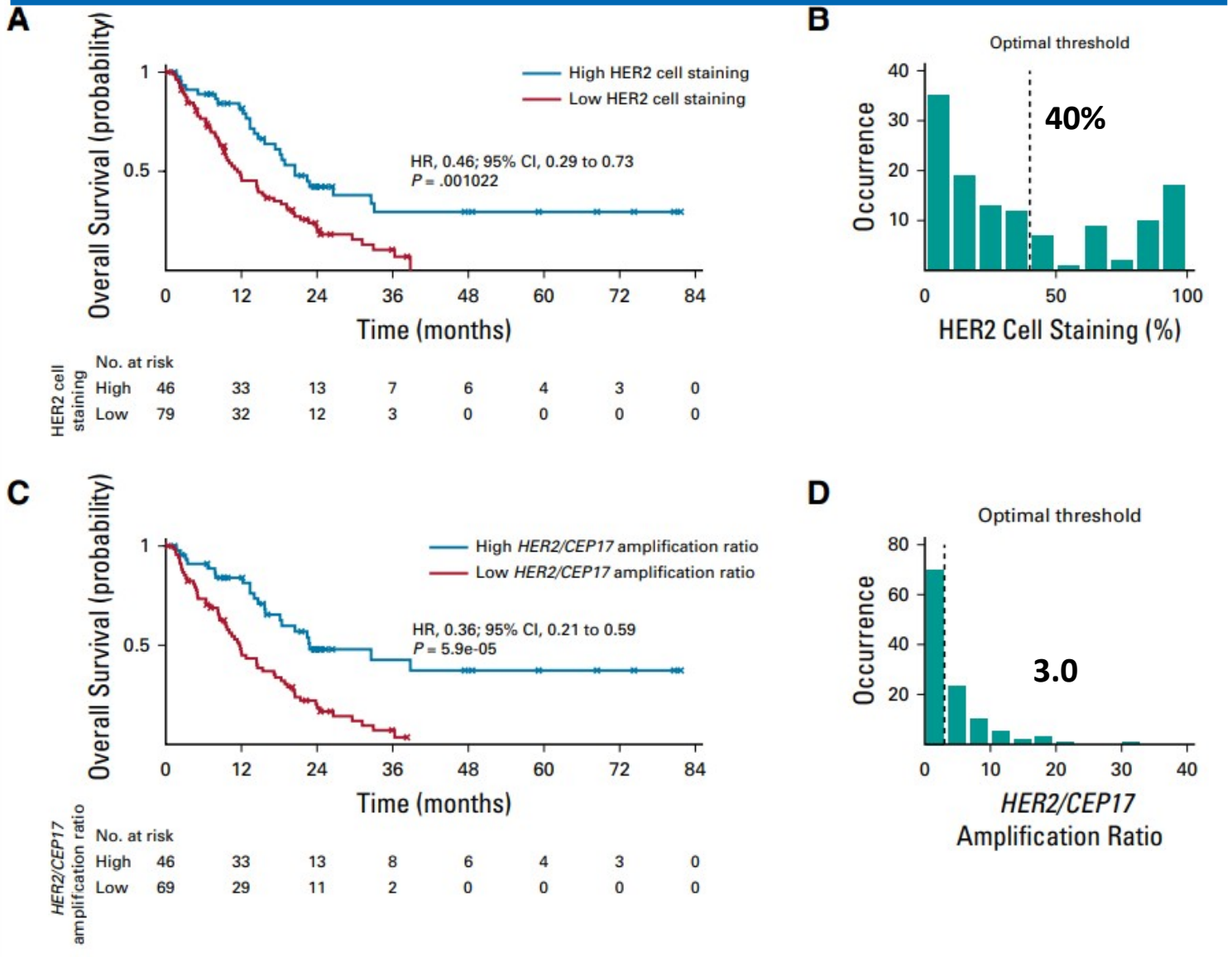


HER2 Central	HER2 Local	No. at risk						
–	–	205	83	27	5	3	1	0	0
–	+	65	25	9	1	0	0	0	0
+	+	60	40	16	9	6	4	3	0
+	–	9	6	2	0	0	0	0	0

Haffner I.…Lordick F. *J Clin Oncol.* 2021 May 1;39(13):1468-1478

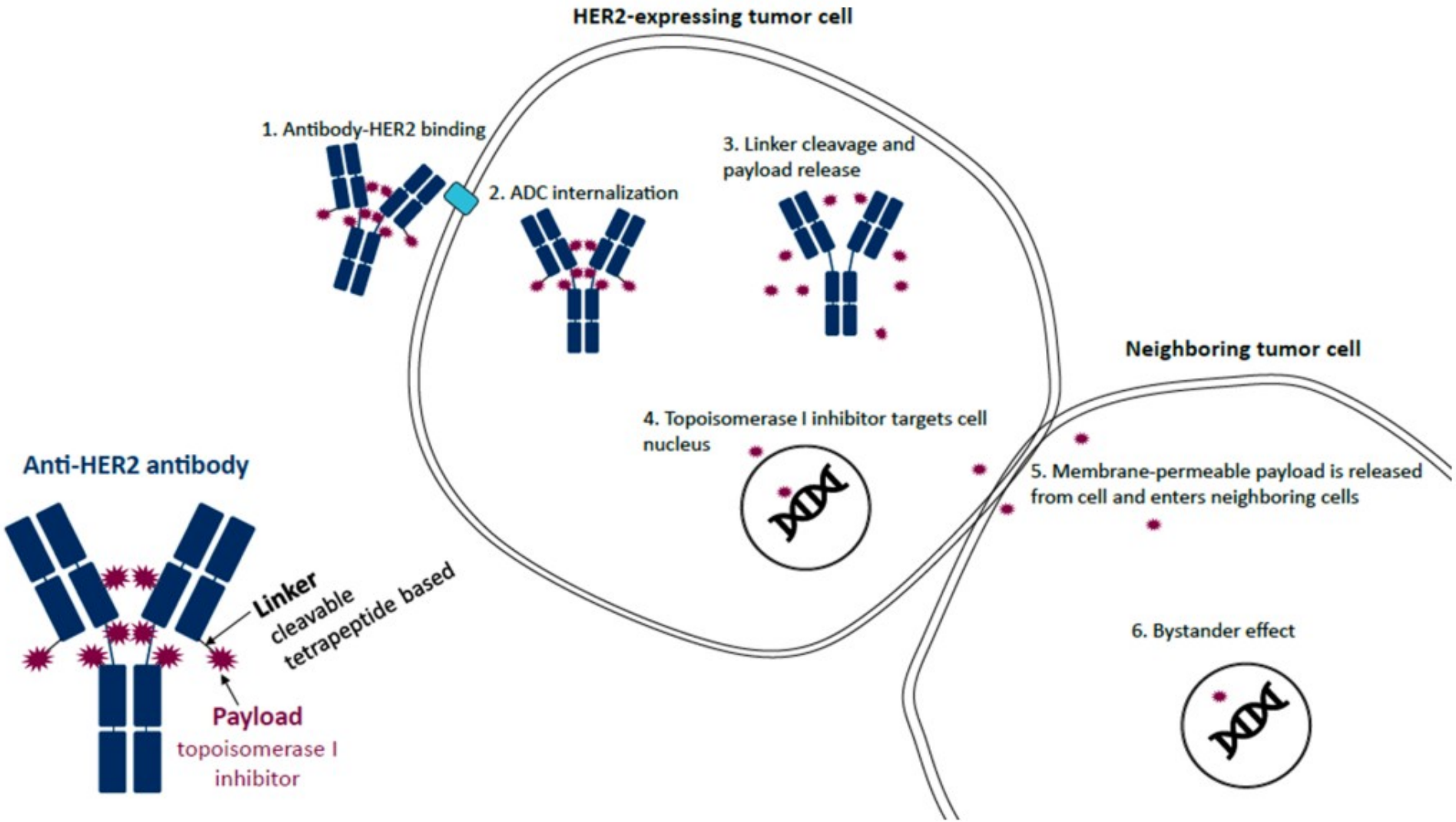
HER2 VARIANZ STUDY

Calculation of optimized HER2 threshold for prediction of survival



Haffner I.…Lordick F. *J Clin Oncol.* 2021 May 1;39(13):1468-1478

TRASTUZUMAB DERUXTECAN – T-DXD - ANTIBODY DRUG CONJUGATE



Swain SM et al. *Cancer Treat Rev.* 2022;106:102378

DESTINY GASTRIC-01

- Multicenter, open-label, randomized phase II study

Stratified by region (Japan vs Korea), ECOG PS (0 vs 1), HER2 status (IHC 3+ vs IHC 2+/ISH+)

Adult patients with HER2+* locally advanced or metastatic gastric or GEJ cancer that progressed on ≥ 2 prior regimens† (N = 188)

Randomized 2:1

T-DXd 6.4 mg/kg, 3-week cycles (n = 126)

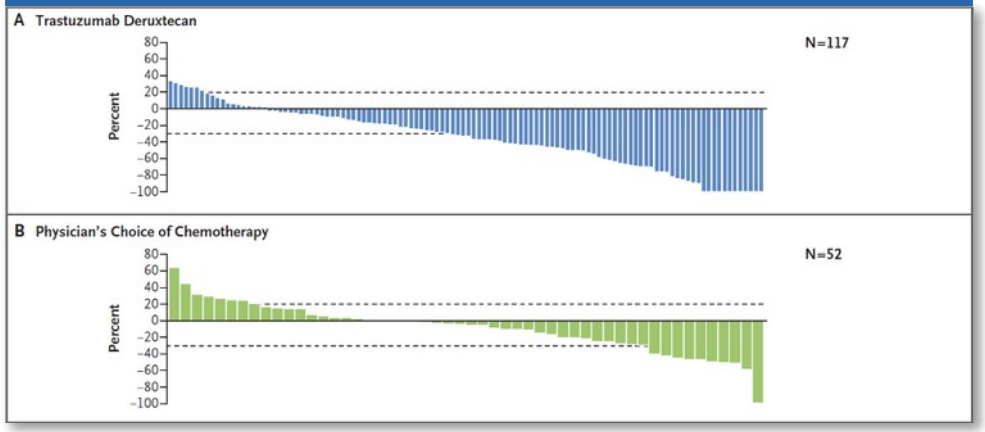
Physician's choice:
Irinotecan 150 mg/m² every 2 weeks or
Paclitaxel 80 mg/m² Days 1, 8, 15 every 4 weeks
(n = 62)

Until PD, unacceptable AEs, or pt withdrawal

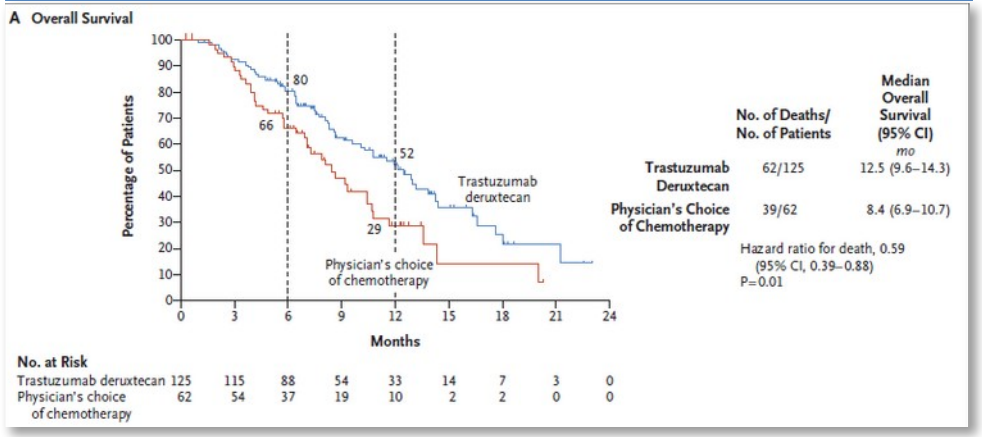
*HER2+ based on IHC 3+ or IHC 2+/ISH+ according to ASCO/CAP guidelines.
†Prior regimens included fluoropyrimidine, a platinum agent, and trastuzumab or approved biosimilar.

- Primary endpoint: ORR by ICR (RECIST v1.1)
- Secondary endpoints: OS (key), DoR, PFS, DCR, confirmed ORR, safety

Objective confirmed overall response rate 43% vs 12%



Overall survival (median) 12.5 vs 8.4 months

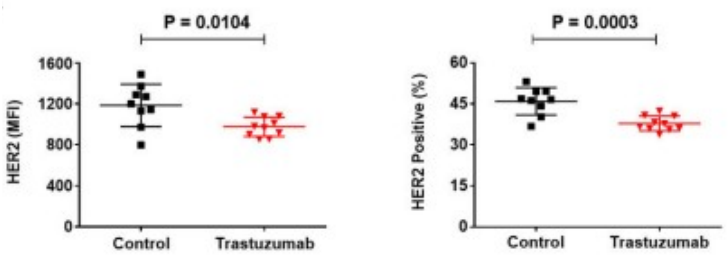


Shitara K et al. *NEJM* 2020;382:2419-30

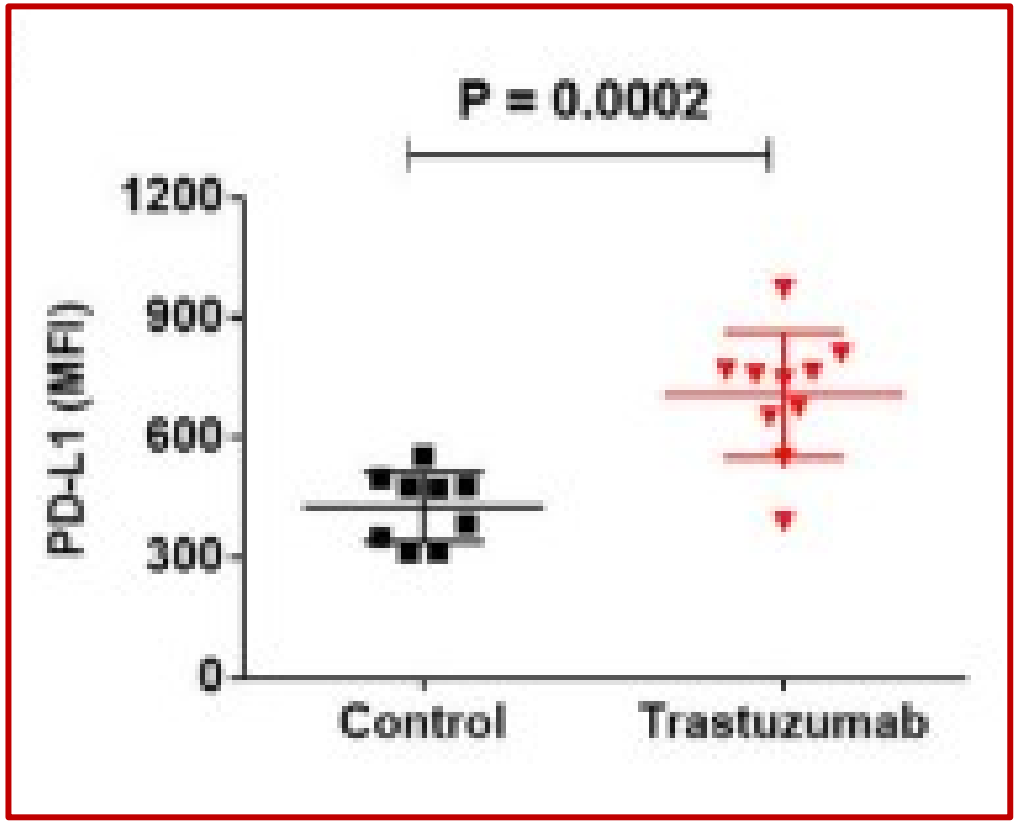
TRASTUZUMAB UPREGULATES PD-L1 EXPRESSION

Published in final edited form as:
Cancer Lett. 2018 August 28; 430: 47–56. doi:10.1016/j.canlet.2018.05.009.

Trastuzumab upregulates PD-L1 as a potential mechanism of trastuzumab resistance through engagement of immune effector cells and stimulation of IFNγ secretion



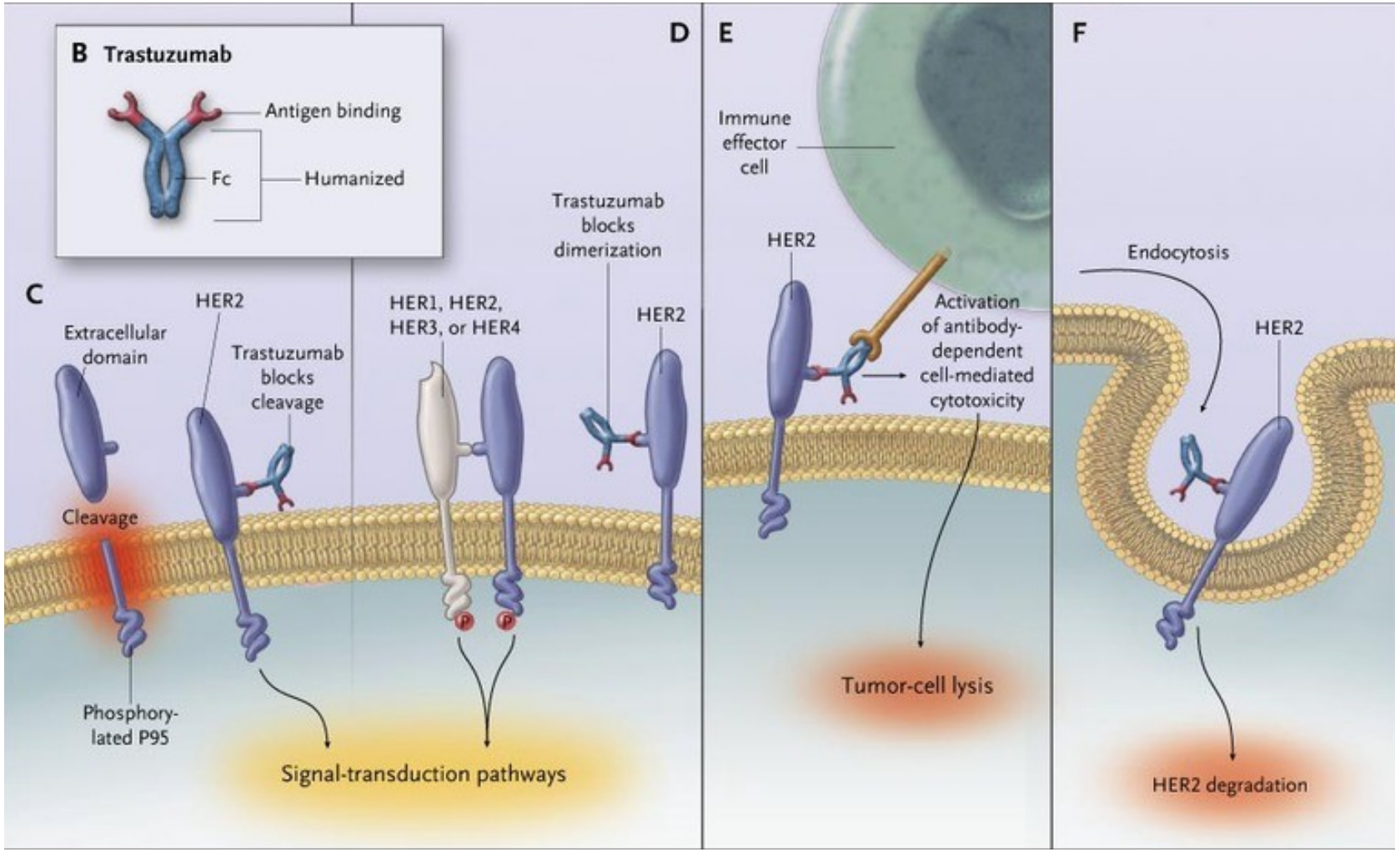
Upregulation of MHC-I, T-cell co-stimulatory molecules, and PD-L1 and downregulation of HER2 by trastuzumab in HER2-overexpressing tumors in vivo. Syngeneic B16-BL6 melanoma cells transduced to overexpress human HER2 were transplanted in hmHER2 transgenic mice. When the tumors became palpable, the mice were treated with 100 μg/ mouse of trastuzumab (n=10) or control antibody bevacizumab (n=9) via intraperitoneal injection. The tumors were harvested 48 h after the treatment, and single tumor cell suspensions were prepared and subjected to multicolor flow cytometry analysis after staining or not with fluorescence-labeled anti-human HER2 antibody (A), anti-human IgG antibody (B), anti-mouse H-2Kb or H-2Db antibody (C), anti-mouse CD80 or CD86 antibody (D), or anti-mouse PD-L1 antibody (E). Analyses of the MFI values in (C), (D), and (E) were gated for HER2-positive cells onl



Chaganti BKR et al. *Cancer Lett.* 2018 Aug 28;430:47-56

HER2-TARGETED AND IMMUNE THERAPY – POTENTIAL SYNERGY

HER2-antibody mode of action favors combination with immune stimulating therapy



Hudis C et al. *N Engl J Med* 2007; 357:39-51

TRASTUZUMAB + PD-L1 BLOCKADE (KN-811) YIELDS HIGH RESPONSE RATES

Summary of confirmed objective response in the efficacy population

Variable	Pembrolizumab Group (N=133)	Placebo Group (N=131)
Objective response — % (95% CI)*	74.4 (66.2–81.6)	51.9 (43.0–60.7)
Disease control — % (95% CI)†	96.2 (91.4–98.8)	89.3 (82.7–94.0)
Best overall response — no. (%)		
Complete response	15 (11.3)	4 (3.1)
Partial response	84 (63.2)	64 (48.9)
Stable disease	29 (21.8)	49 (37.4)
Progressive disease	5 (3.8)	7 (5.3)
Not evaluable‡	0 (0.0)	2 (1.5)
Not assessed‡	0 (0.0)	5 (3.8)

*"In KEYNOTE-811, **84.1% of participants had a PD-L1 combined positive score of ≥1**. We observed **a greater difference in objective response rate in participants with PD-L1 combined positive score ≥1"***

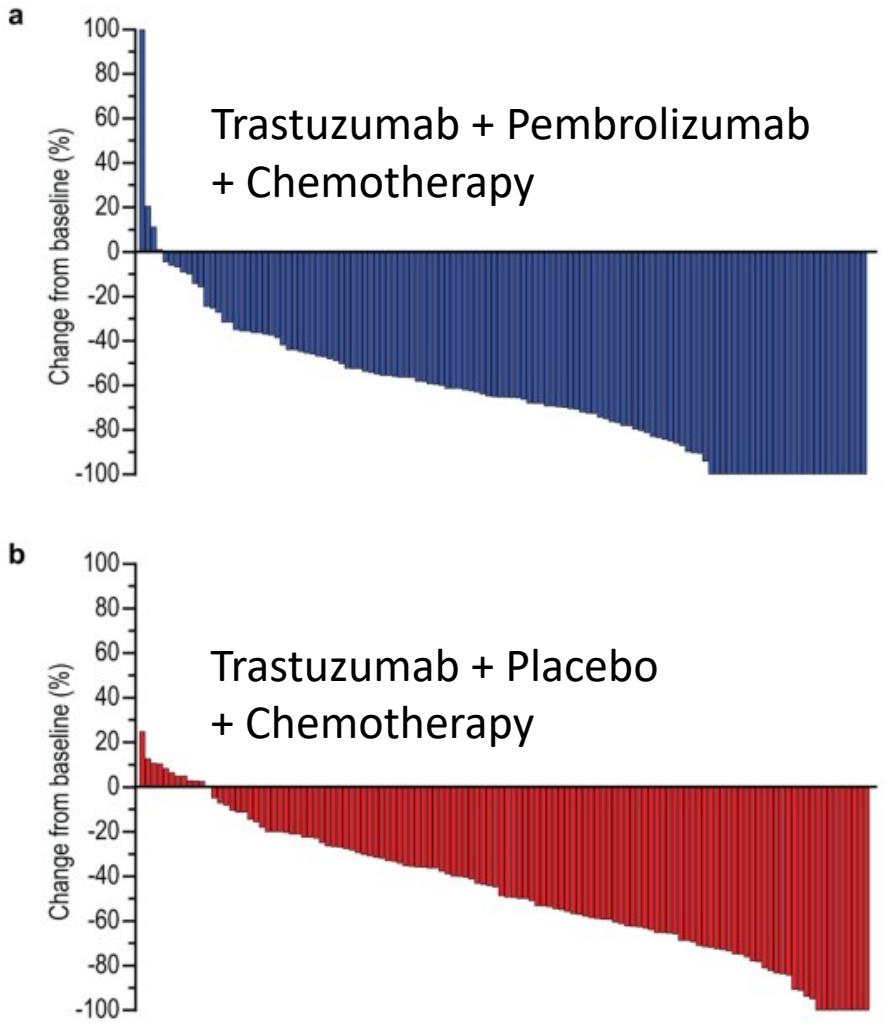


Fig. 1. Best percentage change from baseline in the size of target lesions among particip the efficacy population.

Janjigian Y et al. *Nature*. 2021 Dec;600(7890):727-730

WHAT DOES IT MEAN FOR THE PATIENT WITH GASTRIC CANCER?

A. Treatment in center with accurate biomarker assessment

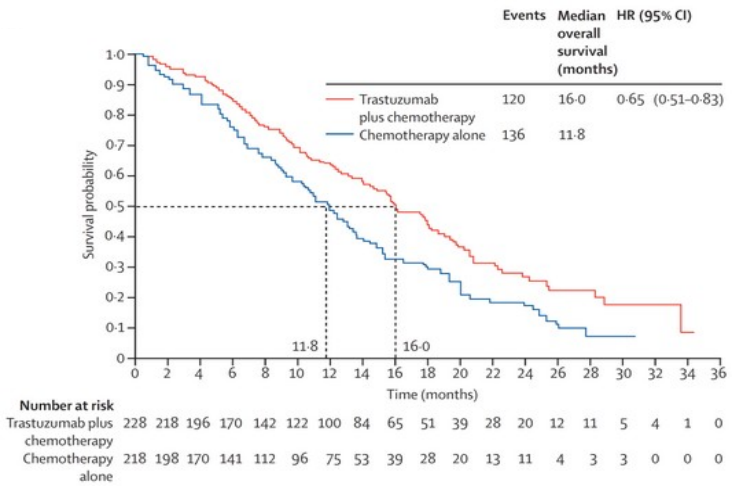
B. Careful planning of treatment sequences and options

C. Access to optimal HER2-targeted therapy

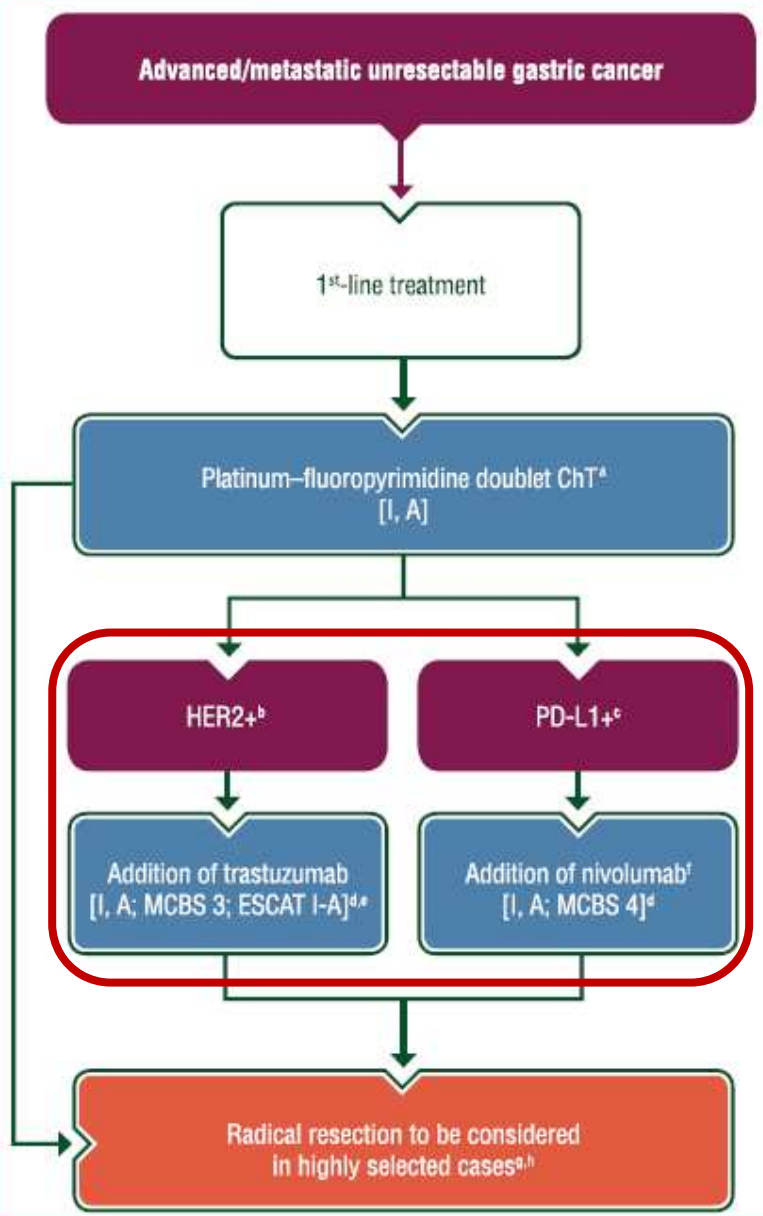
- in-label, e.g. trastuzumab-deruxtecan
- or within a clinical trial

1ST-LINE STAGE 4 GASTRIC / EGJ CANCER – ESMO 2022

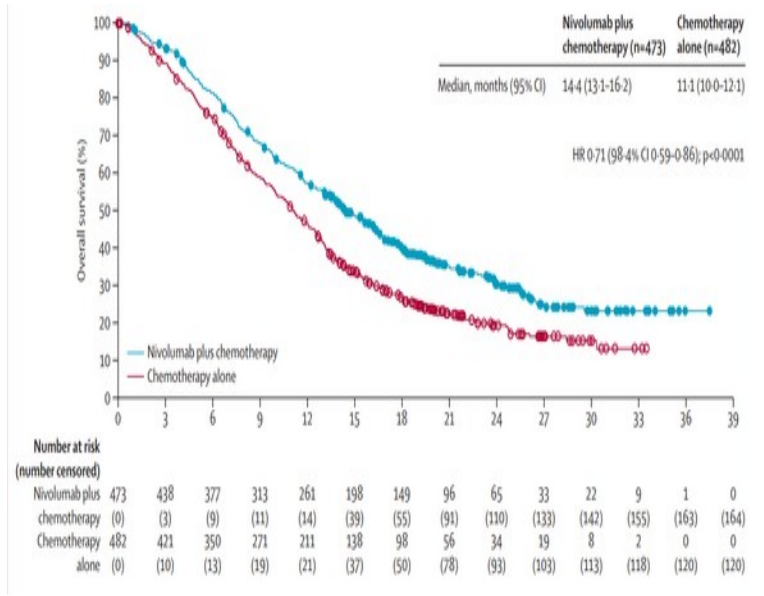
ToGA: Trastuzumab + Chemo vs Chemo



Bang YJ et al.. *Lancet. 2010 Aug 28;376(9742):687-97*



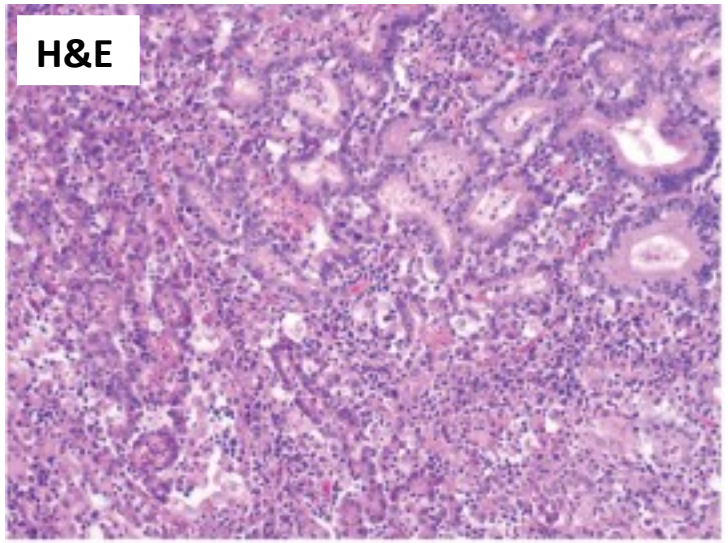
CHECKMATE-649, PD-L1 CPS ≥ 5

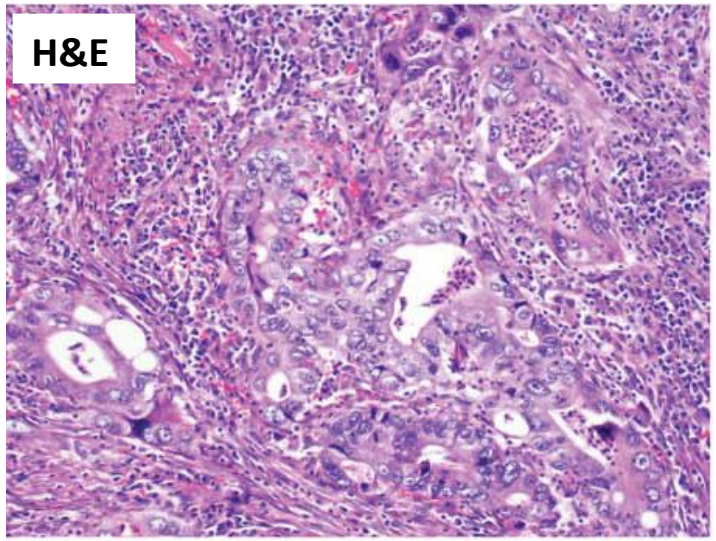


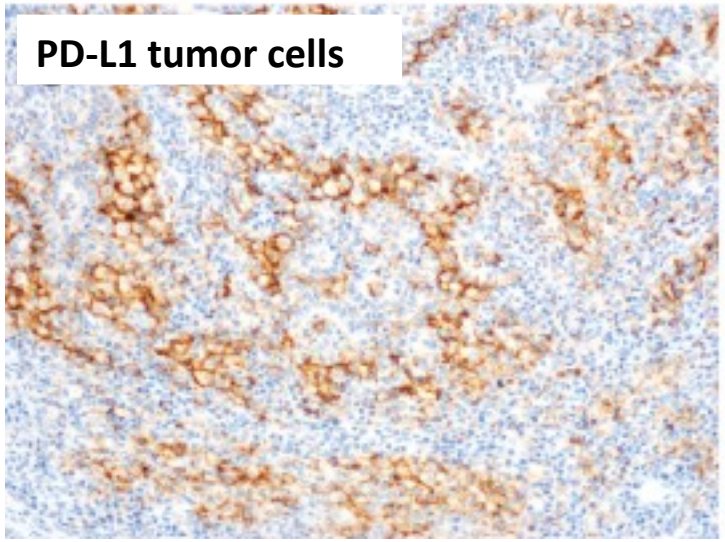
Janjigian Y, et al. *Lancet*. 2021 Jul 3;398(10294):27-40

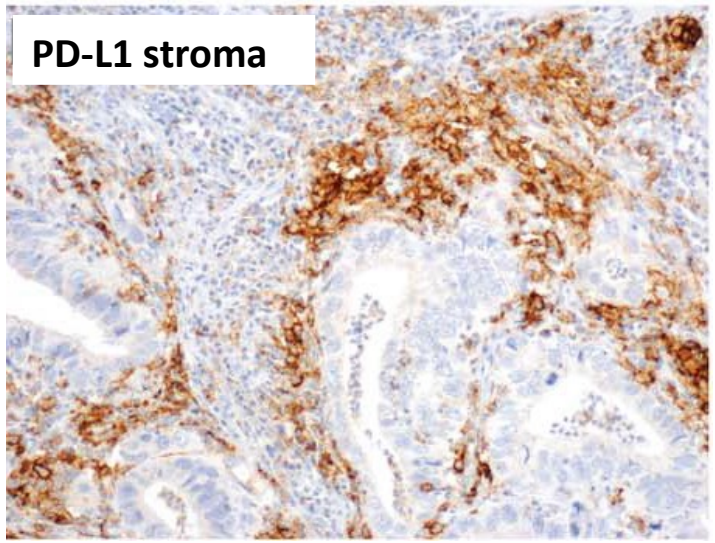
Lordick F, et al. *Ann Oncol* 2022,

PD-L1 EXPRESSION









Data from patients treated at Johns-Hopkins; IHC using (5H1 clone)

12% of resections showed **tumour cell membranous PD-L1 expression** and **44%** showed expression within the **immune stroma**

CPS – Combined Positive Score

$$\text{CPS} = \frac{\text{No. PD-L1–stained cells (tumor cells, lymphocytes, macrophages)}}{\text{Total No. of viable tumor cells}} \times 100$$

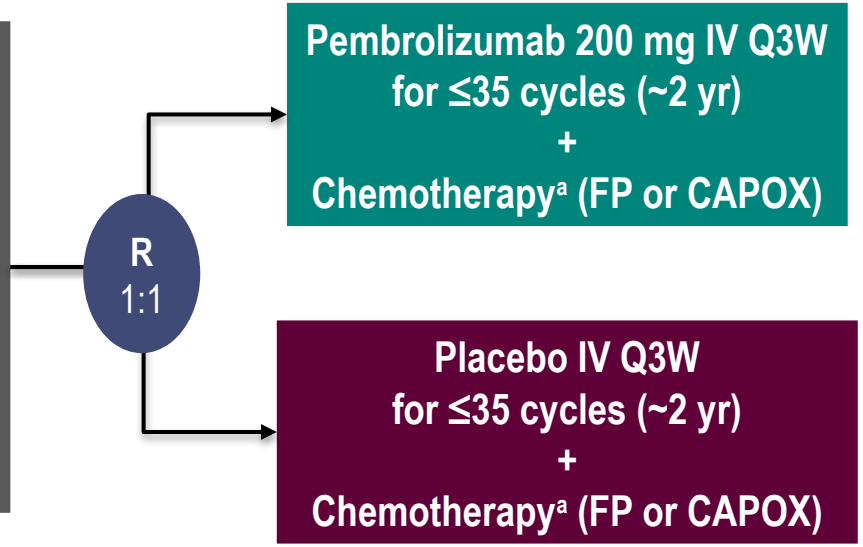
Thompson ED et al. *Gut.* 2017 May;66(5):794-801

KEYNOTE-859 Study Design

Randomized, Double-Blind, Phase 3 Trial

Key Eligibility Criteria

- Histologically or cytologically confirmed adenocarcinoma of the stomach or GEJ
- Locally advanced unresectable or metastatic disease
- No prior treatment
- Known PD-L1 status (assessed centrally using PD-L1 IHC 22C3)
- HER2-negative status (assessed locally)
- ECOG PS 0 or 1



Stratification Factors

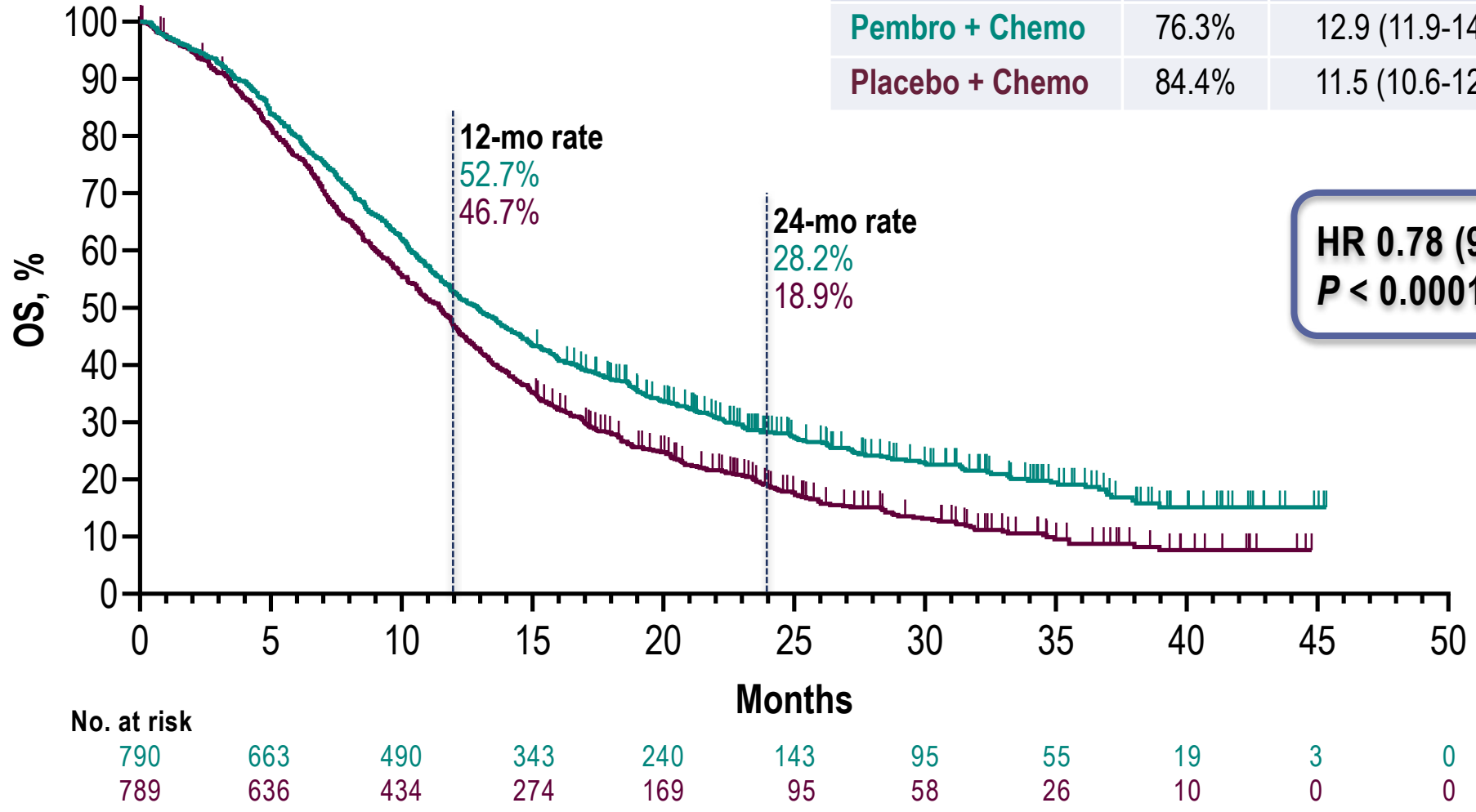
- Geographic region (Europe/Israel/North America/ Australia vs Asia vs rest of world)
- PD-L1 CPS (<1 vs ≥1)
- Choice of chemotherapy[a] (FP vs CAPOX)

- **Primary End Point:** OS
- **Secondary End Points:** PFS,[b] ORR,[b] DOR,[b] and safety

[a] FP: 5-fluorouracil 800 mg/m^2/day IV continuous on days 1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 orally twice daily on days 1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W. Cisplatin and oxaliplatin could have been limited to 6 cycles as per local country guidelines.
[b] Assessed per RECIST v1.1 by blinded, independent central review.
ClinicalTrials.gov number, NCT03675737.

OS, ITT Population

	Pts w/ Event	Median, mo (95% CI)
Pembro + Chemo	76.3%	12.9 (11.9-14.0)
Placebo + Chemo	84.4%	11.5 (10.6-12.1)

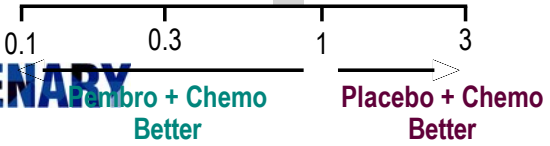


HR 0.78 (95% CI, 0.70-0.87)
***P* < 0.0001**

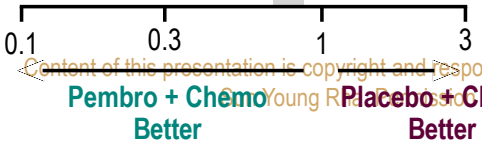
Data cutoff date: October 3, 2022.

OS in Key Subgroups, ITT Population

Subgroup	No. Events/ No. Participants	Hazard Ratio (95% CI)
Overall	1269/1579	0.78 (0.695-0.868)
Age		
<65 years	799/965	0.76 (0.664-0.878)
≥65 years	470/614	0.77 (0.639-0.918)
Sex		
Female	426/508	0.76 (0.625-0.916)
Male	843/1071	0.77 (0.674-0.884)
Geographic region		
Asia	390/525	0.71 (0.581-0.865)
W Eur/Isr/N Am/Australia	332/403	0.80 (0.648-0.999)
Rest of world	547/651	0.80 (0.678-0.949)
ECOG performance status		
0	439/582	0.73 (0.602-0.879)
1	830/997	0.77 (0.675-0.886)
Primary tumor location		
GEJ	276/334	0.74 (0.582-0.941)
Stomach	992/1243	0.77 (0.681-0.874)
Histologic subtype		
Diffuse	528/619	0.76 (0.639-0.900)
Indeterminate	309/401	0.69 (0.550-0.865)
Intestinal	430/557	0.81 (0.672-0.982)



Subgroup	No. Events/ No. Participants	Hazard Ratio (95% CI)
Overall	1269/1579	0.78 (0.695-0.868)
Disease status		
Metastatic	1225/1520	0.77 (0.686-0.860)
Liver metastases		
No	756/953	0.73 (0.631-0.840)
Yes	512/625	0.83 (0.700-0.990)
Prior gastrectomy/esophagectomy		
No	1022/1235	0.79 (0.703-0.899)
Yes	238/334	0.69 (0.538-0.897)
MSI status		
MSI-high	39/74	0.34 (0.176-0.663)
Non-MSI-high	1037/1280	0.79 (0.700-0.894)
PD-L1 CPS at baseline, cutpoint of 1		
≥1	990/1235	0.73 (0.647-0.831)
<1	279/344	0.92 (0.729-1.167)
PD-L1 CPS at baseline, cutpoint of 10		
≥10	414/551	0.64 (0.523-0.772)
<10	853/1026	0.86 (0.751-0.983)
Chemotherapy choice at randomization		
CAPOX	1076/1363	0.76 (0.675-0.858)
FP	193/216	0.82 (0.617-1.087)

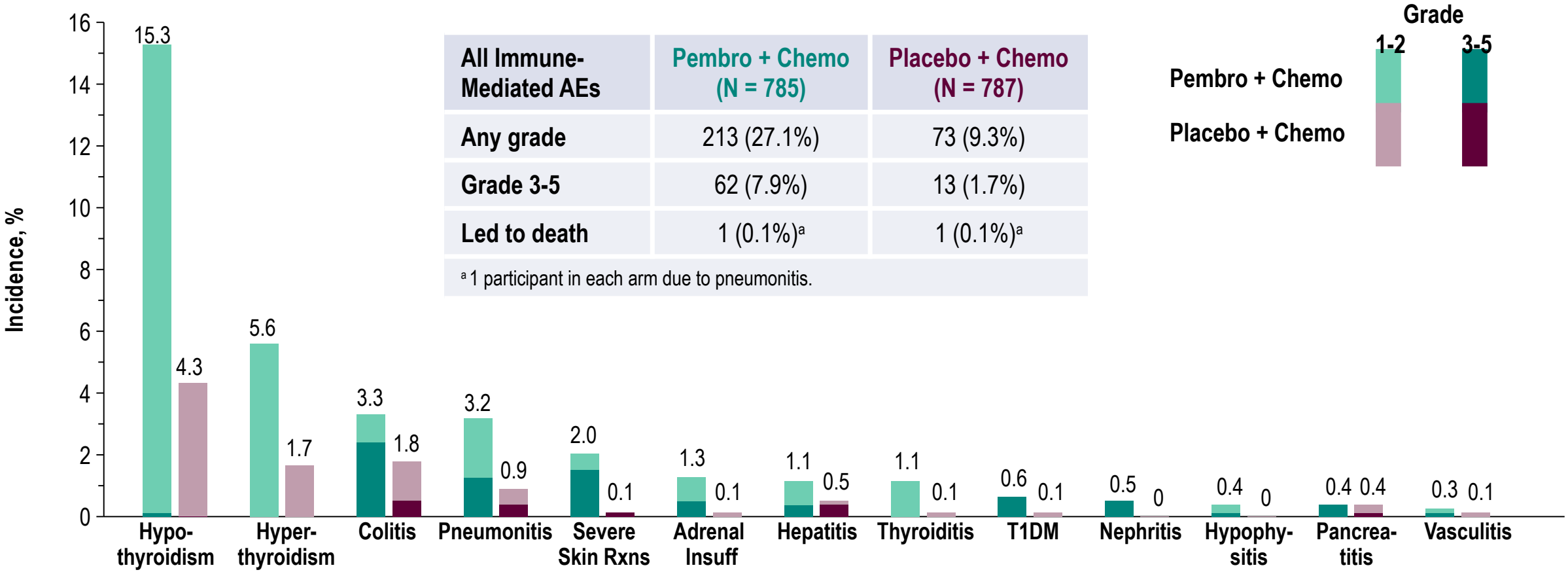


Data cutoff date: October 3, 2022.

Immune-Mediated Adverse Events

All Immune-Mediated AEs	Pembro + Chemo (N = 785)	Placebo + Chemo (N = 787)
Any grade	213 (27.1%)	73 (9.3%)
Grade 3-5	62 (7.9%)	13 (1.7%)
Led to death	1 (0.1%)[a]	1 (0.1%)[a]

[a] 1 participant in each arm due to pneumonitis.



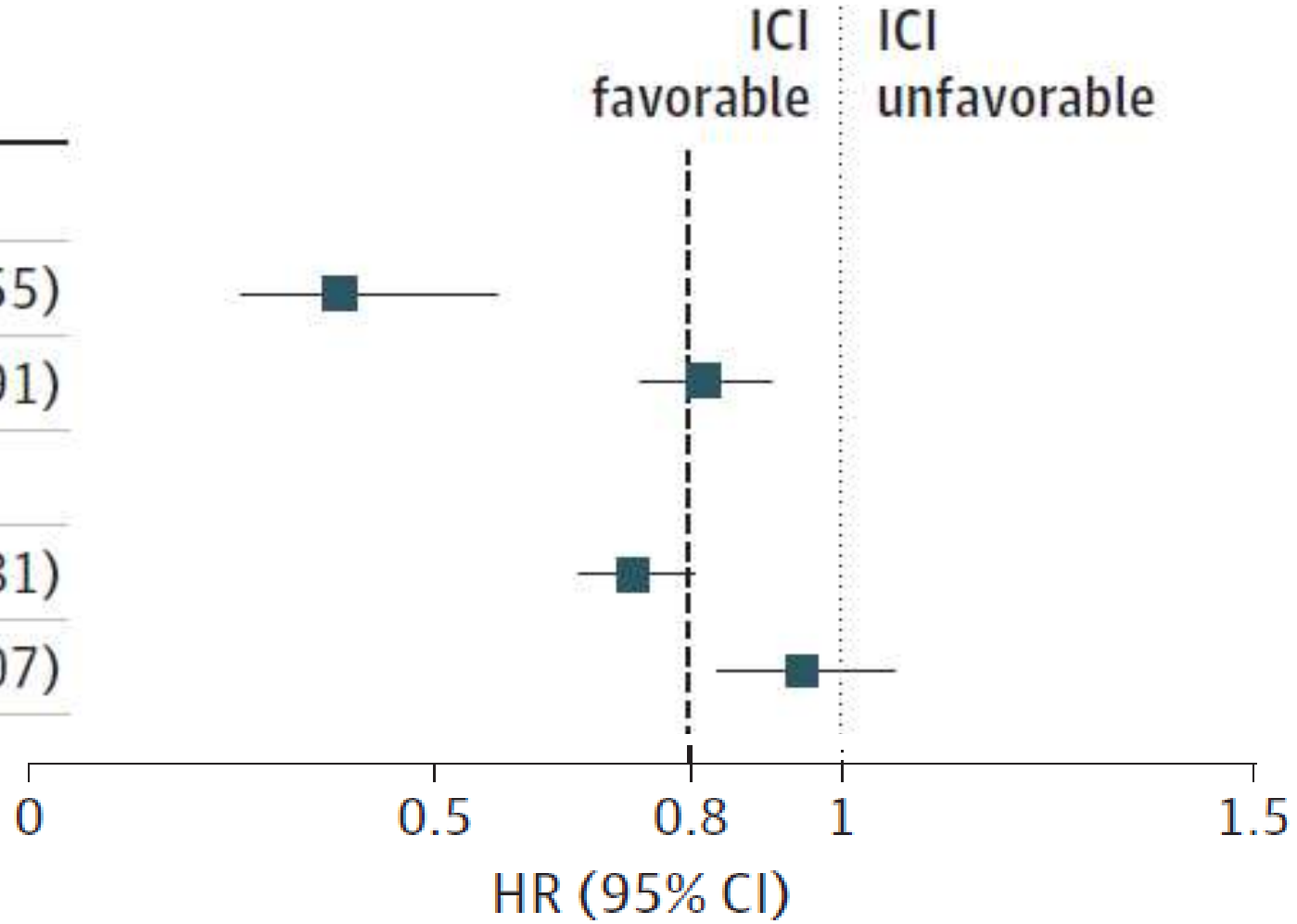
Immune-Mediated Adverse Events with Incidence ≥2 Participants

Insuff, insufficiency; rxns, reactions; T1DM, type 1 diabetes mellitus.
Events were considered regardless of attribution to treatment by the investigator. Related terms were included in addition to the specific terms listed.
Data cutoff date: October 3, 2022.

PD-L1 SCORING IN ADENOCARCINOMA

Systematic Review on 6099 study patients

Variable	HR (95% CI)
MSI	
High	0.35 (0.22-0.55)
Low	0.82 (0.74-0.91)
PD-L1 CPS	
High	0.73 (0.66-0.81)
Low	0.95 (0.84-1.07)



Yoon et al. *JAMA Oncol.* 2022 Aug 25. doi: 10.1001/jamaoncol.2022.3707

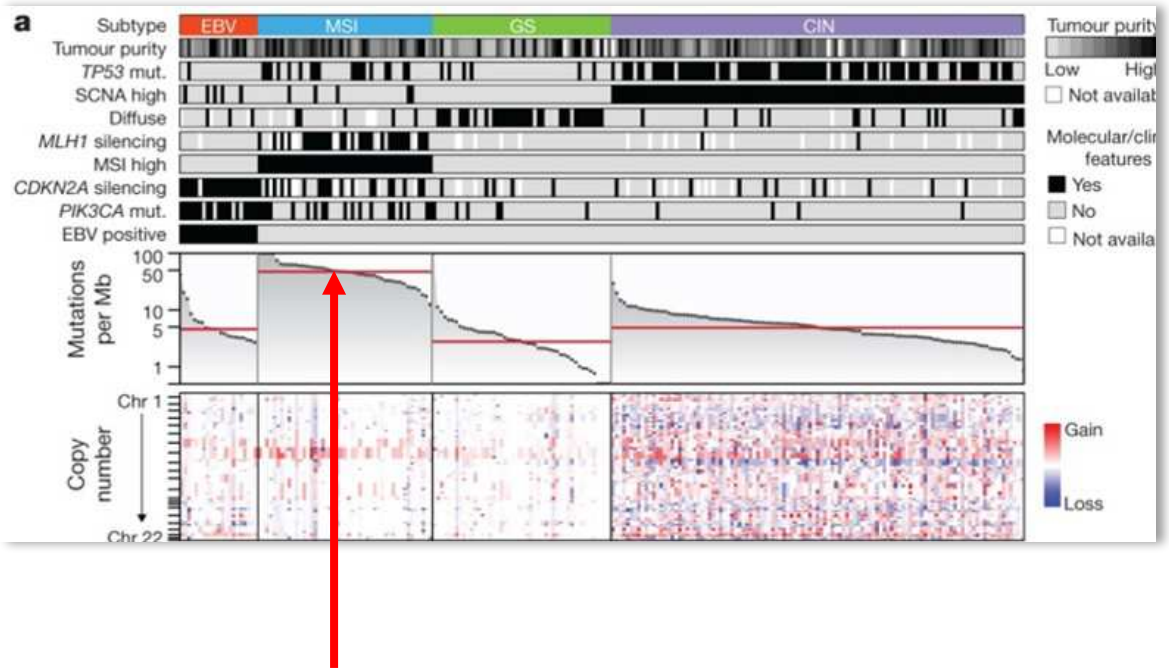
WHAT DOES IT MEAN FOR THE PATIENT WITH GASTRIC CANCER?

A. Immunotherapy is effective – especially for PD-L1-pos tumors

B. Testing is key! Not very easy….

C. Benefit must be weighed against potential side effects

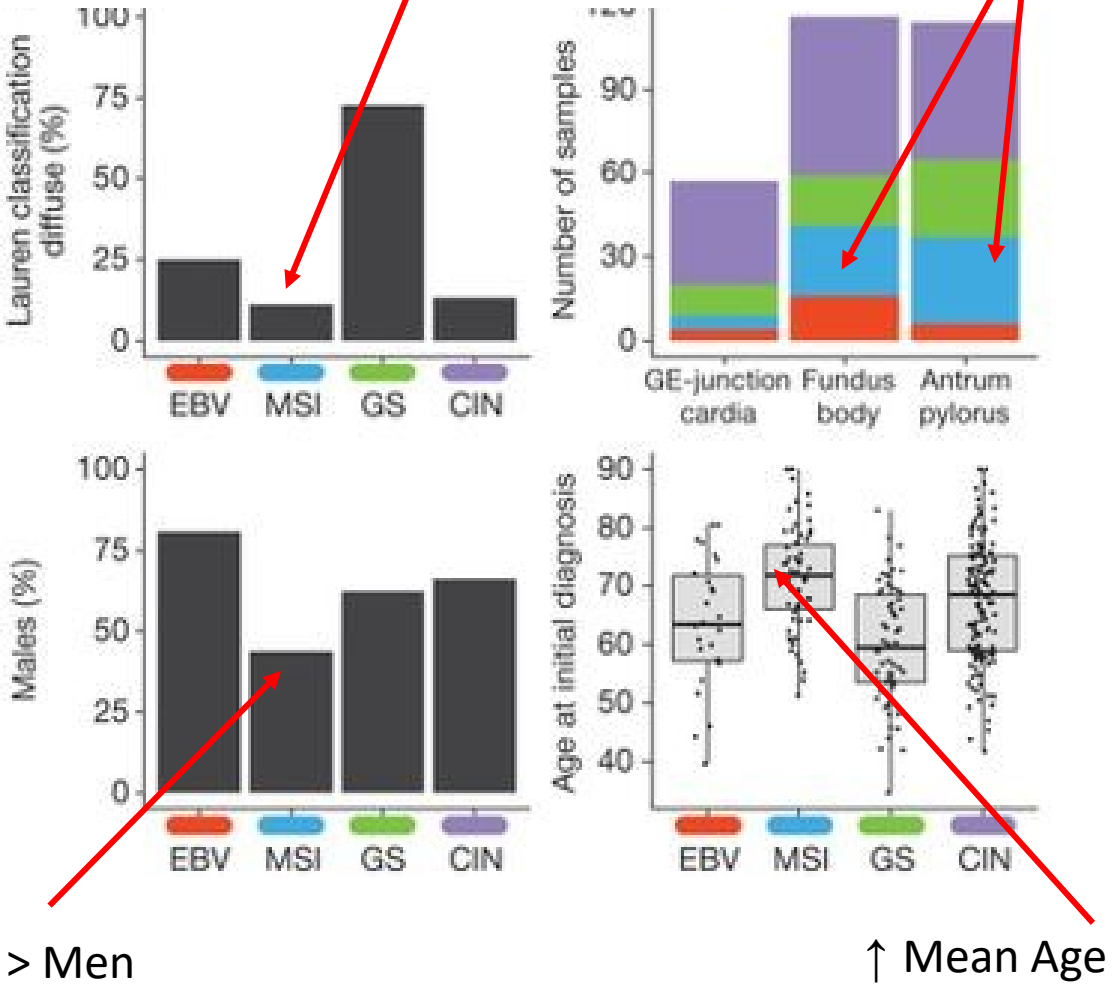
GASTRIC CANCER – MSI SUBTYPE



High Tumor Mutational Burden (TMB)

Intestinal > diffuse

Distal>proximal

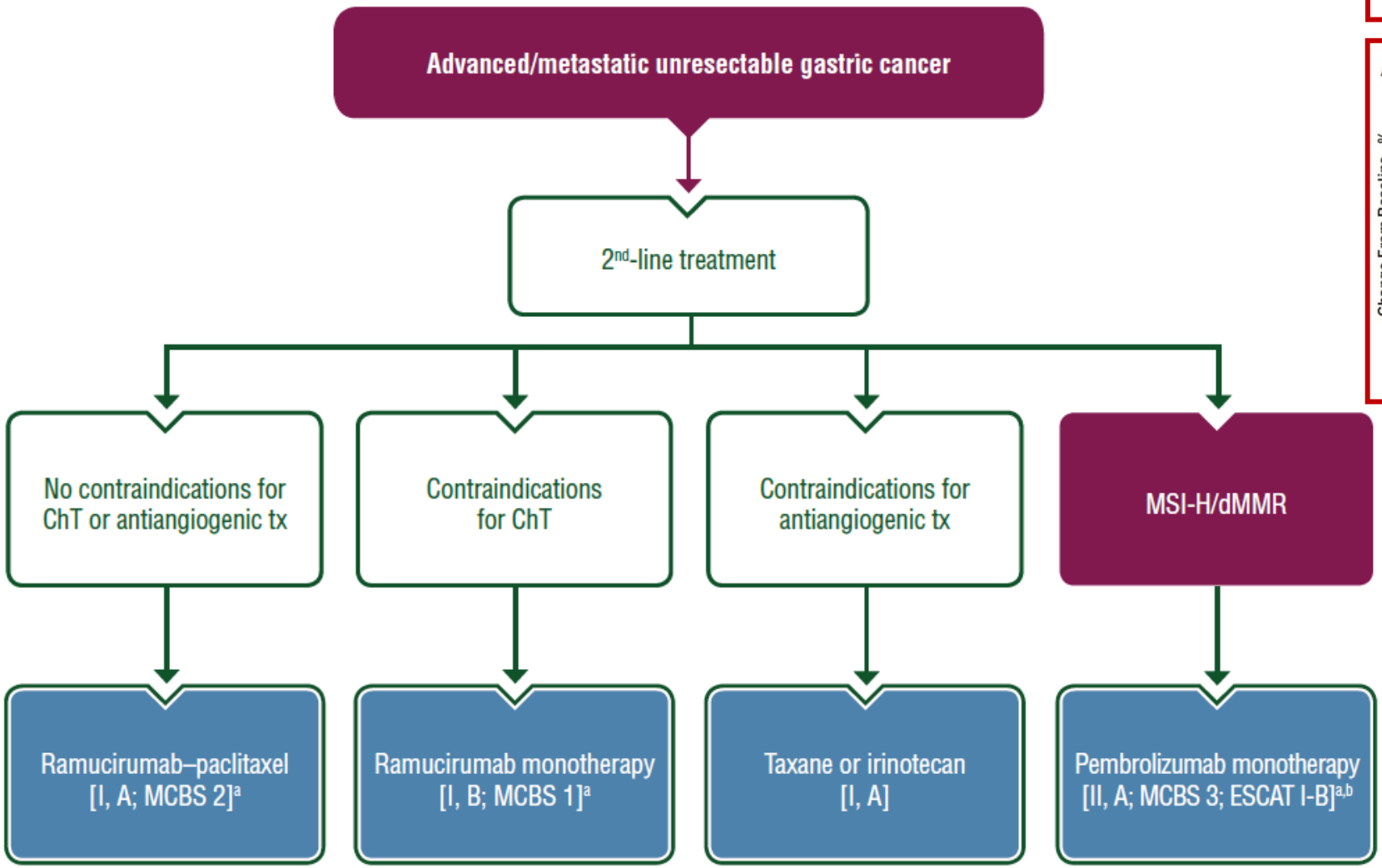


Women > Men

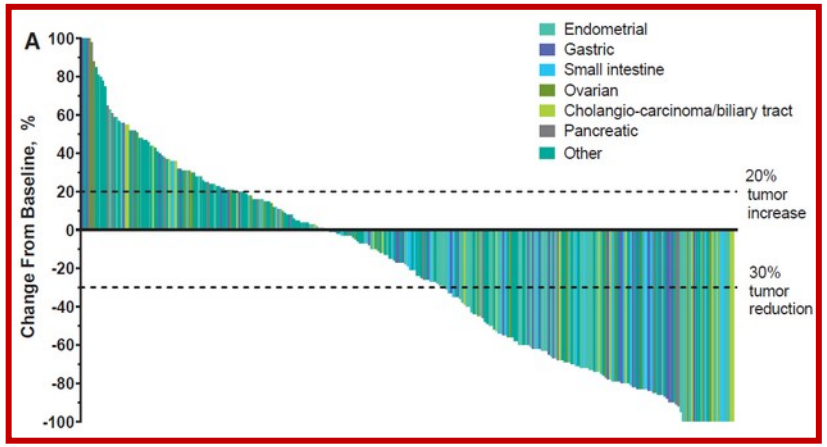
↑ Mean Age

TCGA *Nature*. 2014 Sep 11;513(7517):202-9

2ND-LINE STAGE 4 GASTRIC / EGJ CANCER – ESMO 2022



KEYNOTE-158 – Pembrolizumab in MSI-GC

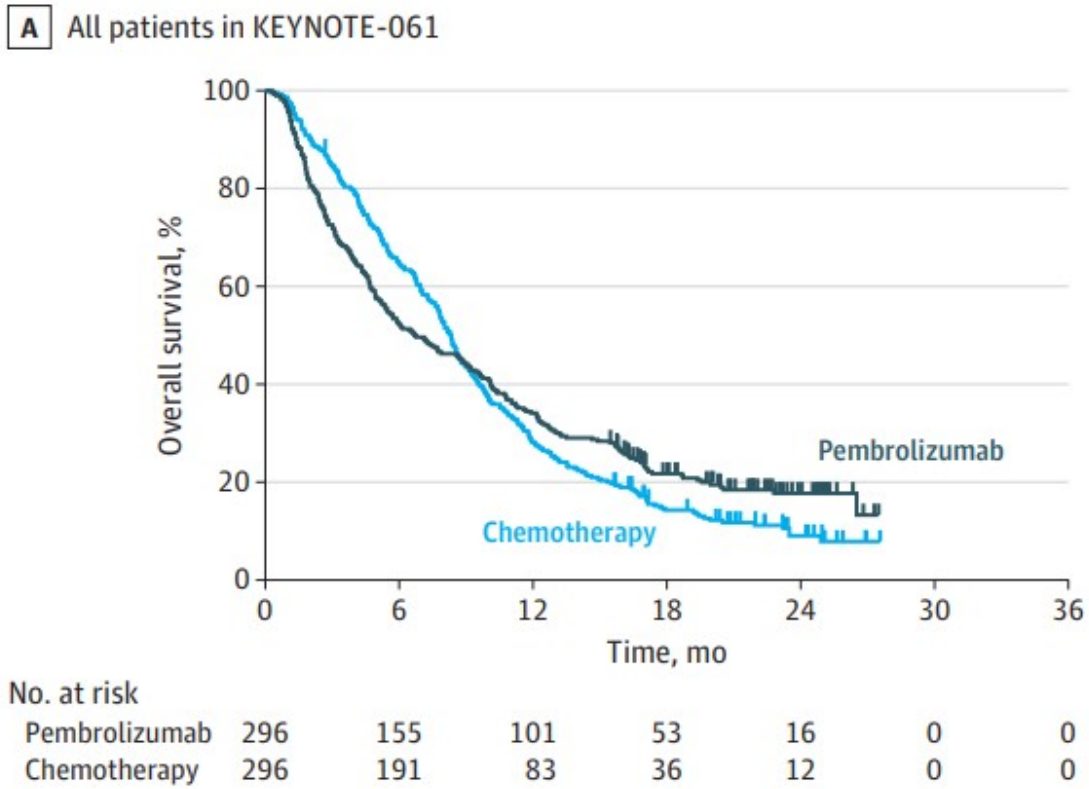


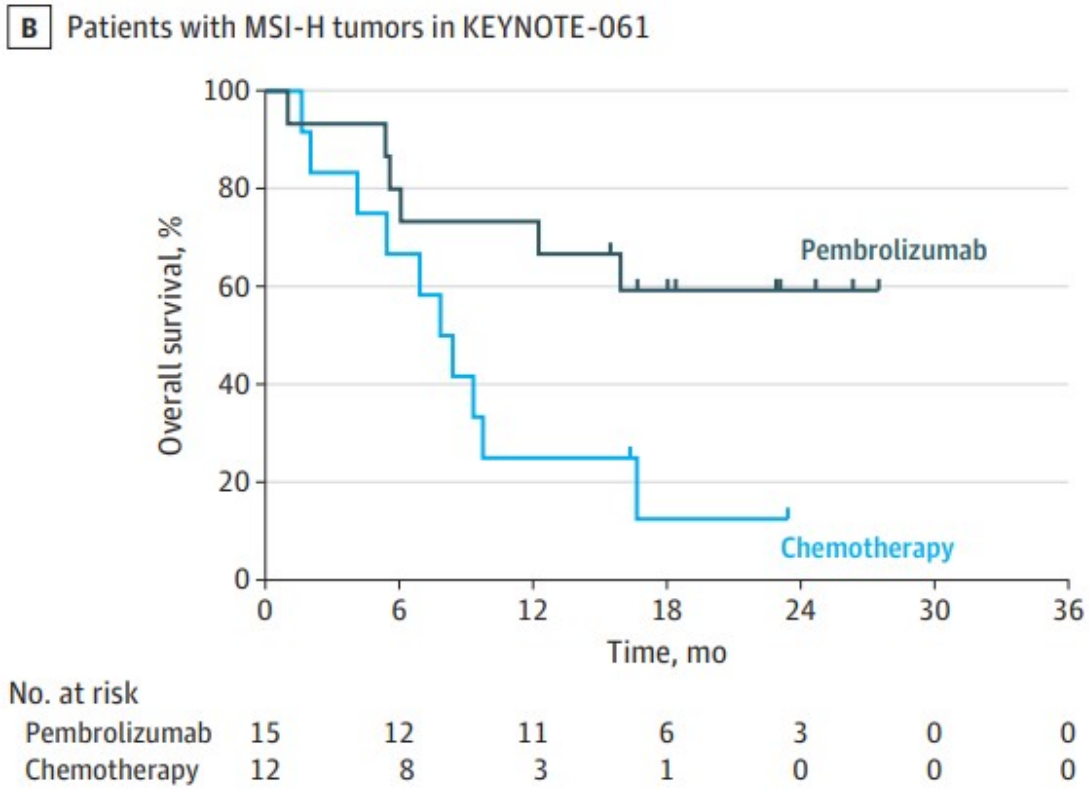
Marabelle A et al *J Clin Oncol.* 2020 Jan 1;38(1):1-10

Lordick F, et al. *Ann Oncol* 2022,

KEYNOTE-061 – MICROSATELLITE INSTABILITY GC

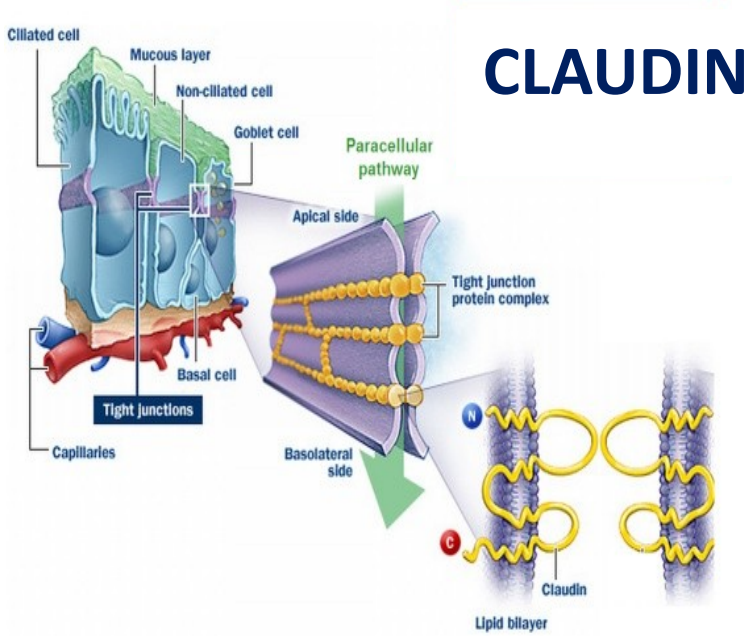
2nd-line mGC, Pembrolizumab vs Paclitaxel, MSS and MSI-H cancers





Chao J et al. *JAMA Oncol.* 2021;7(6):895-902

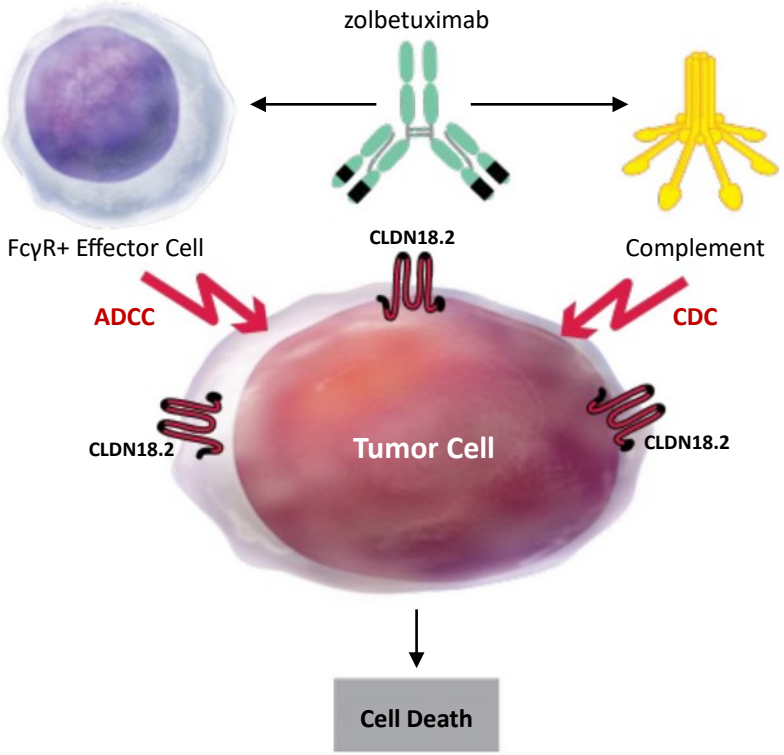
CLAUDIN18.2 – A NOVEL TARGET



CLAUDIN 18.2

- Member of the claudin family
- Major structural component of tight junctions
- Seals intercellular space in epithelial sheets
- Not expressed in any healthy tissues, except: stomach mucosa, but with limited accessibility

Mechanism of Action of Zolbetuximab



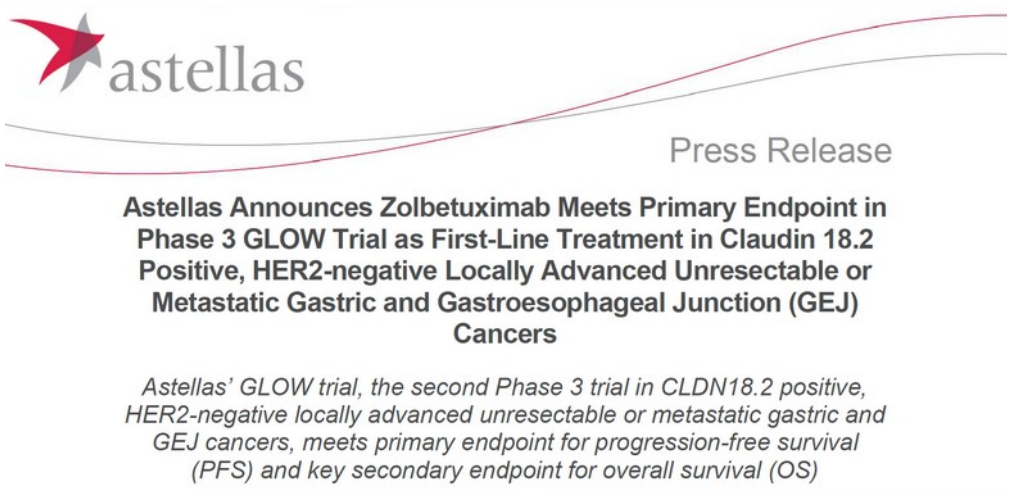
Sahin U et al. *Ann Oncol.* 2021 May;32(5):609-619

CLAUDIN18.2 ZOLBETUXIMAB– 2 POSITIVE PHASE-3 STUDIEN

SPOTLIGHT

https://www.astellas.com/en/news/26821

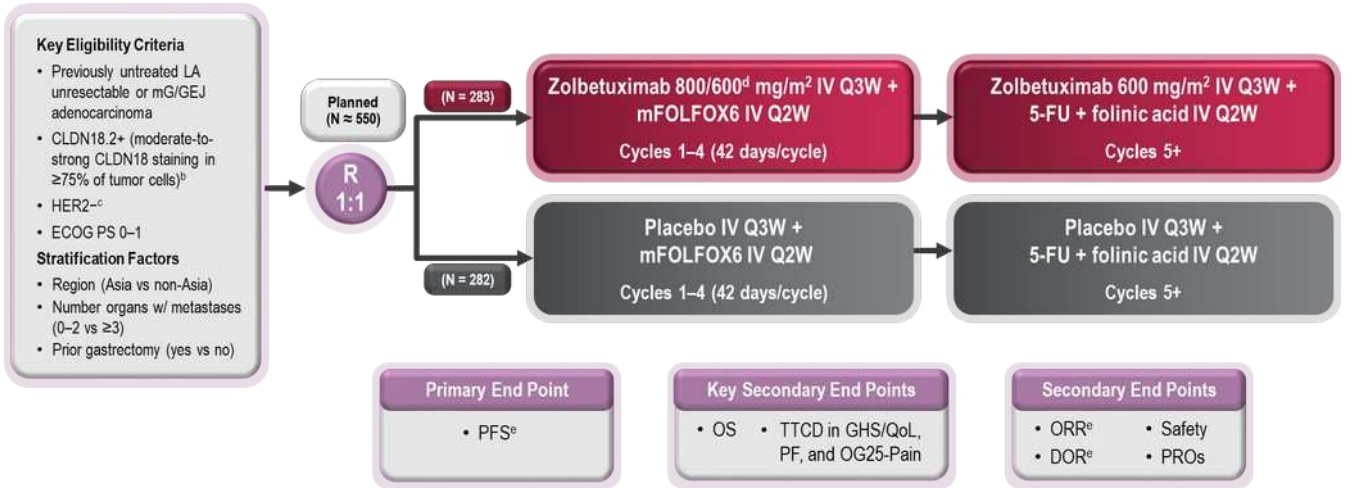
GLOW

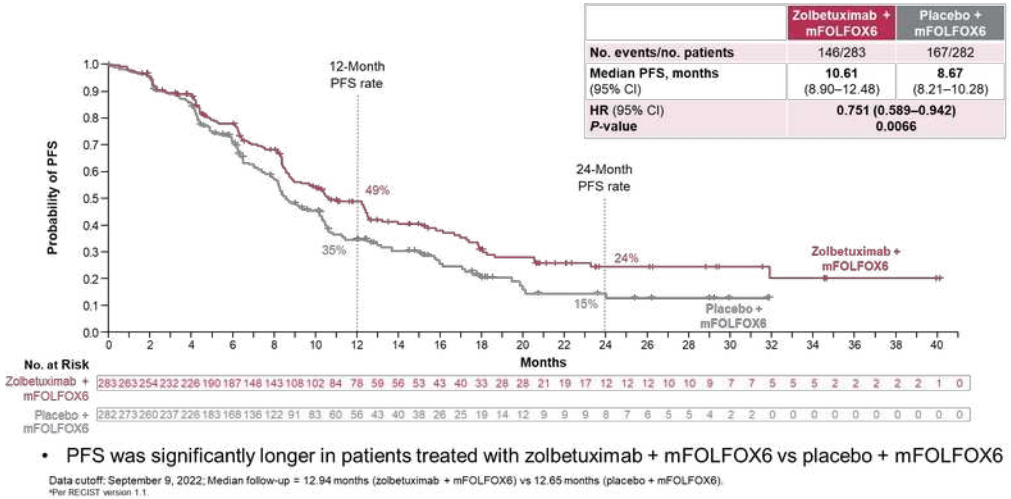


https://www.astellas.com/en/news/26891

SPOTLIGHT PHASE III – STUDY DESIGN AND PRIMARY ENDPOINT (PFS)

Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial





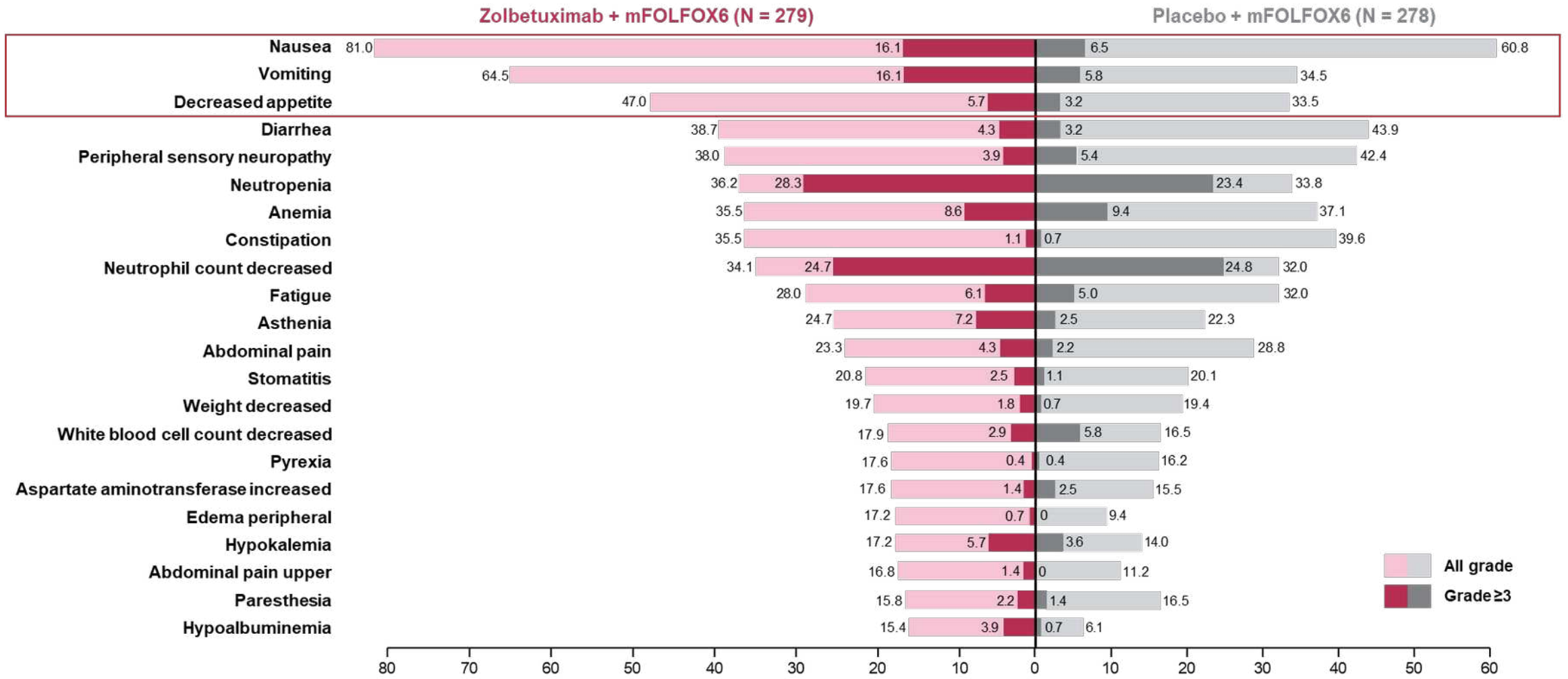
- PFS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

Data cutoff: September 9, 2022; Median follow-up = 12.94 months (zolbetuximab + mFOLFOX6) vs 12.65 months (placebo + mFOLFOX6).
[e]Per RECIST version 1.1.

[a]Study was conducted at 215 sites in 20 countries across Australia, Asia, Europe, N. America, and S. America; [b]By central IHC using the analytically validated VENTANA CLDN18 (43-14A) RxDx Assay; [c]By central or local HER2 testing; [d]800 mg/m² at cycle 1 day 1 followed by 600 mg/m² on cycle 1 day 22 and days 1 and 22 of subsequent cycles; [e]Per RECIST v1.1 by independent review committee.

Shitara K et al. *Lancet.* 2023

SPOTLIGHT – TEAES IN ≥15%

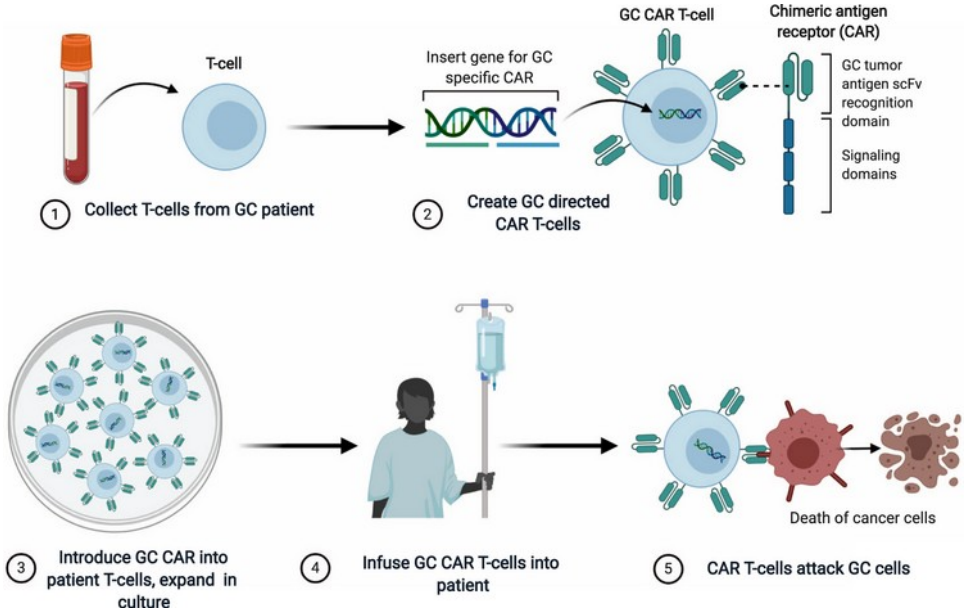


- The most common TEAEs with zolbetuximab + mFOLFOX6 were nausea and vomiting as on-target effects

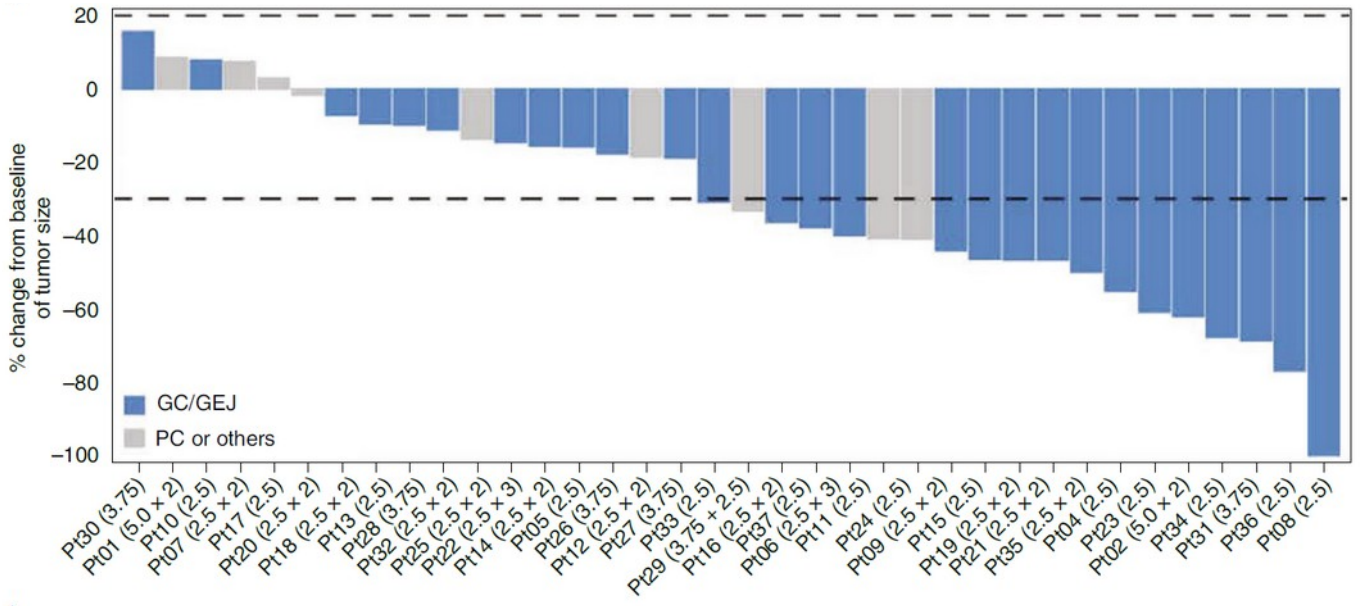
[a]Preferred terms were defined according to the Medical Dictionary for Regulatory Activities terminology version 25.0.

Shitara K et al. *Lancet.* 2023

CAR-T CELL THERAPY IN CLAUDIN18.2 POSITIVE TUMORS



Claudin 18.2-directed CAR-T therapy



Olnes MJ, Martinson HA. *Cancer Gene Ther*. 2021 Sep;28(9):924-934
Qi C et al. *Nat Med*. 2022 Jun;28(6):1189-1198

WHAT DOES IT MEAN FOR THE PATIENT WITH GASTRIC CANCER?

A. Biomarlers become increasingly important

B. Novel technologies are entering the field (ADCs, Bispecifics, CAR-T)

C. Stay tuned and ask for access to research and studies

Thank you for your kind attention

CANCER CENTER
CENTRAL GERMANY
United to beat cancer