Taking personalized care to the next level in Upper GI cancers – recent updates

Mridula Krishnan, MD

Assistant professor of Medicine

University of Nebraska medical center

- No disclosures

Objectives

- Describe the genomic landscape of Gastroesophageal adenocarcinoma's
- Novel targets in upper Gastrointestinal cancers – targets beyond PD1
- What is Zolbetuximab

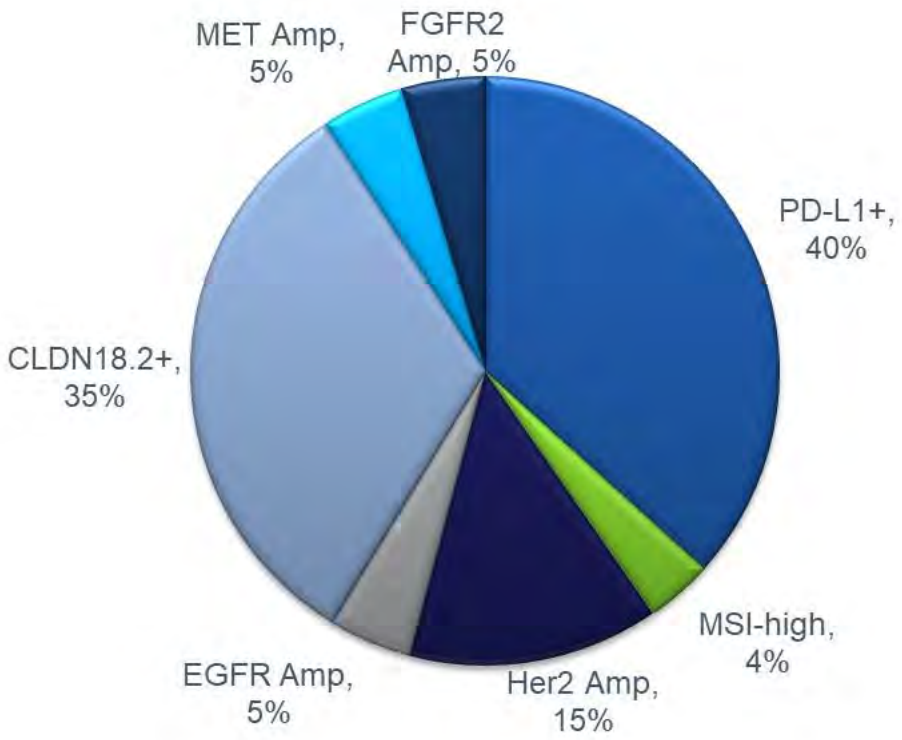
Background

Advanced GE adenocarcinoma – moving towards more targeted therapeutic approach with newer driver mutations/targets

Why do we need novel therapies?

- Low path CR rate even with neoadjuvant therapy
- Recurrence (approximately half of the patients will develop locoregional/distant metastasis after surgery)

Key Biomarkers for Treatment in Gastroesophageal Cancer



KEY MARKERS IN ADVANCED DISEASE

- **HER2** positive – 15%-20% of patients, improved survival with non-chemo antibody trastuzumab
- **MSI** high – 3%-5% of patients, high response rates to immunotherapies
- **PD-L1** positive – 30%-50% of patients, identifies those more likely to benefit from immune therapies, likely gradation within PD-L1+
- **CLDN18.2** high – 30%-35% of patients, response predictor for zolbetuximab

INVESTIGATIONAL BIOMARKERS

- **FGFR2** amp – 5%-10% of patients, multiple trials of inhibitors
- **FGFR2** high- May be up to 30% of HER2 negative
- **EGFR** amp – 5%-7%, may predict response to EGFR drugs like cetuximab

Immunotherapy in advanced/metastatic gastric and esophageal adenocarcinomas

- Nivolumab with chemotherapy is approved in the United states for treatment irrespective of PDL1 status (Checkmate 649)
- Pembrolizumab, trastuzumab and chemotherapy approved for HER 2 positive disease (Keynote 811)
- Pembrolizumab – agnostic approval TMB >10mut/Mb or MSI high tumors

Novel targets in upper GI cancers – targets beyond PD1

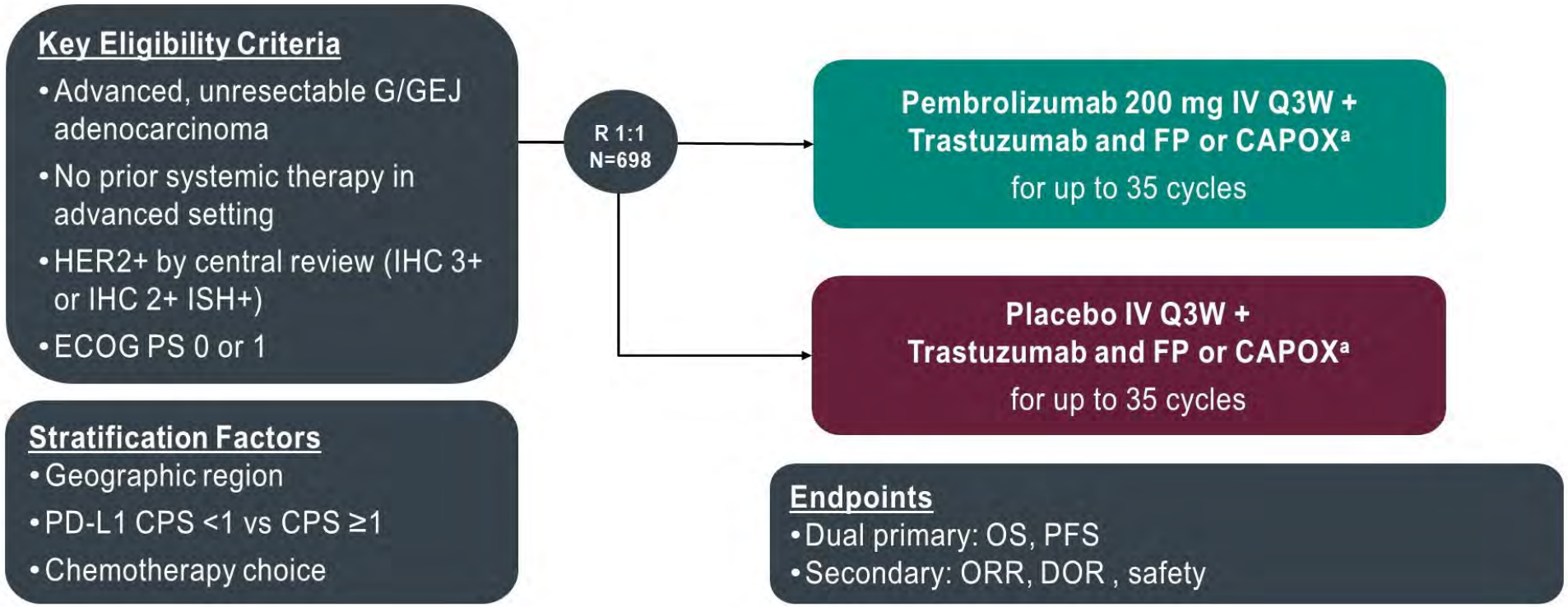
- HER 2
- CLDN18.2
- FGFR
- Mismatch repair
- Other Biomarkers

HER 2 targeting

- Heterogeneity is the crux of the problem

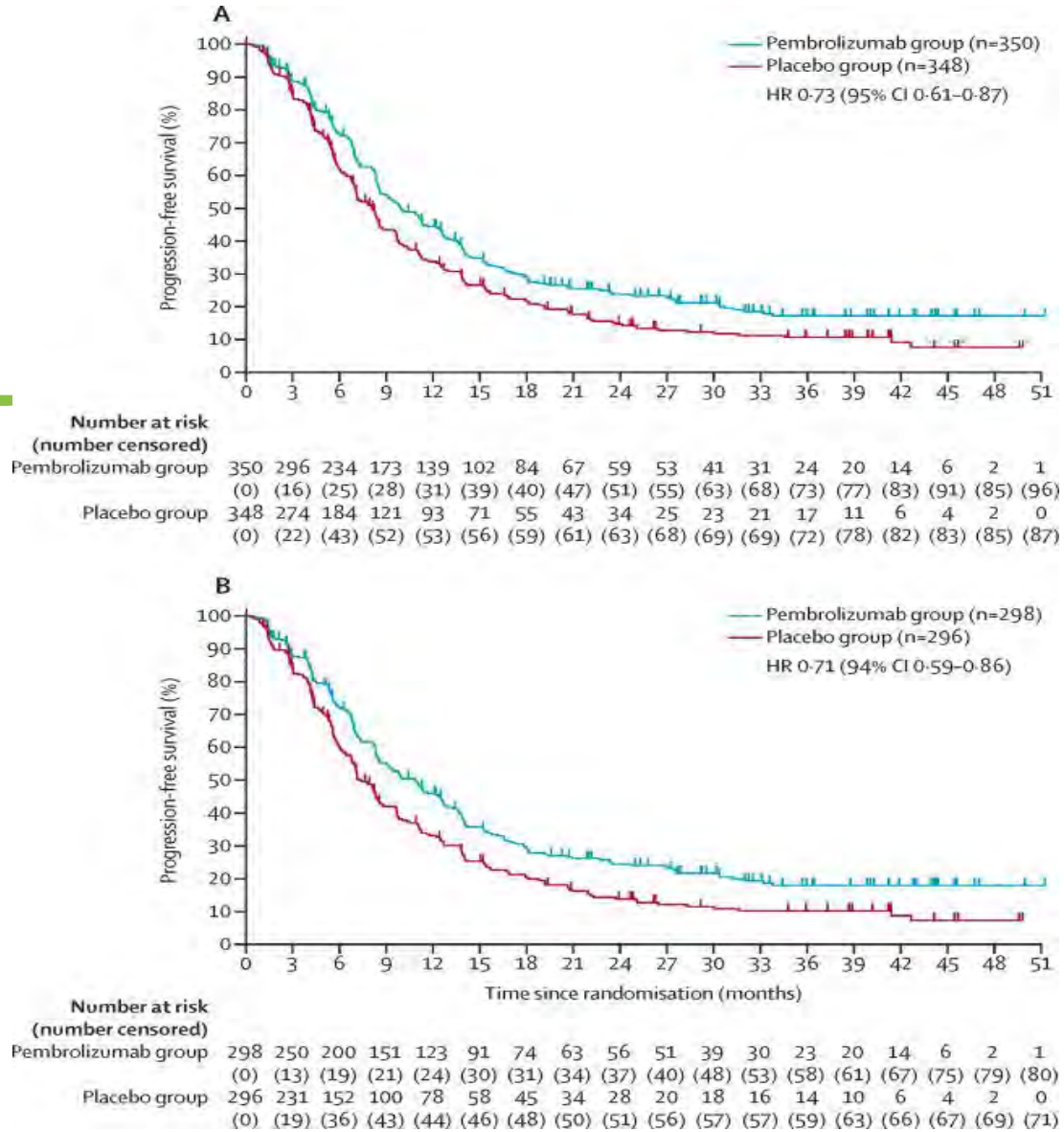
KEYNOTE-811 Study Design (NCT03615326)

Phase 3 Randomized, Placebo-Controlled



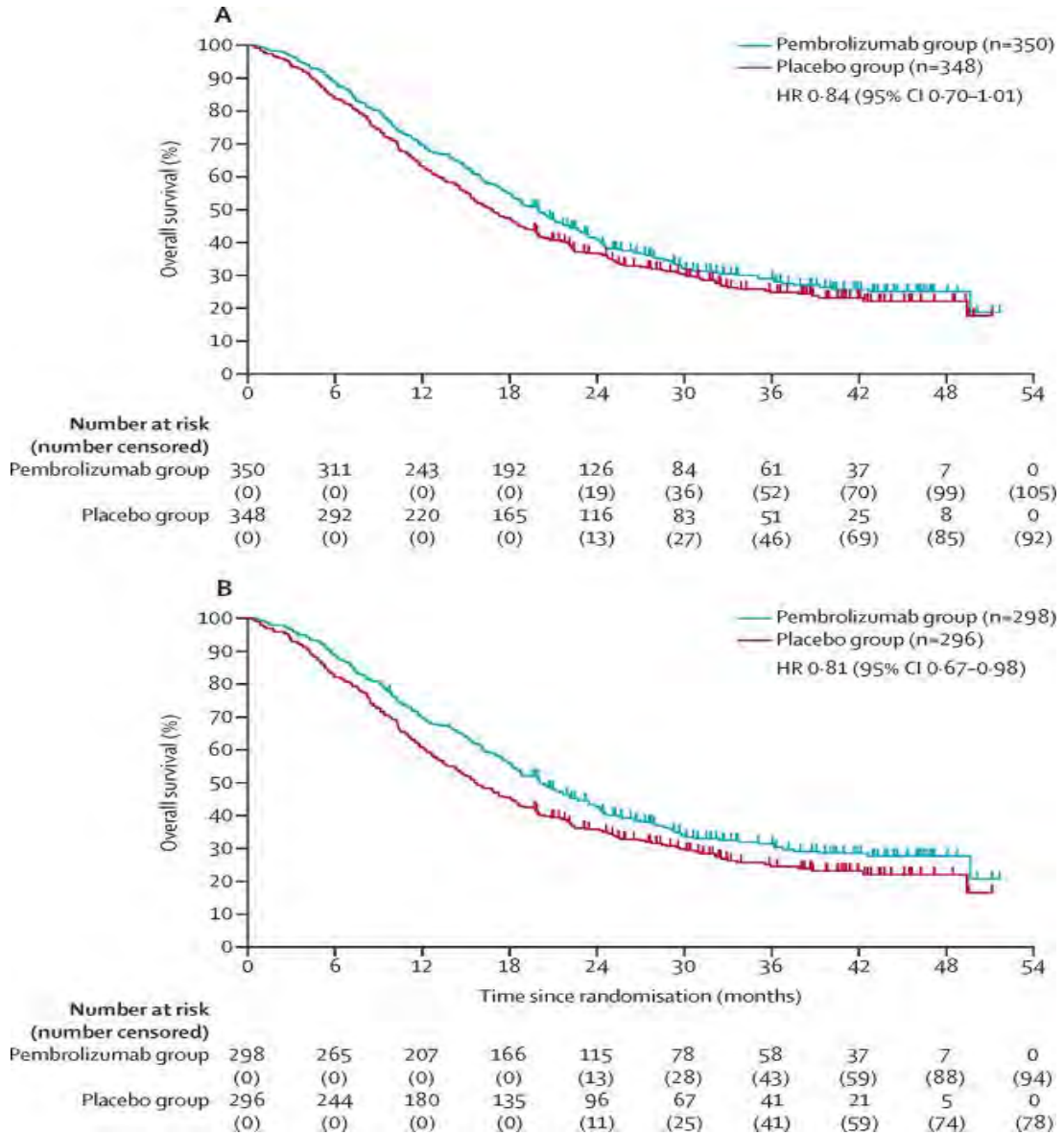
[a]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W. PFS, ORR, DOR per RECIST by BICR.

PFS



Janjigian, Yelena Y., et al. *The Lancet* 402.10418 (2023): 2197-2208.

OS



Janjigian, Yelena Y., et al. *The Lancet* 402.10418 (2023): 2197-2208.

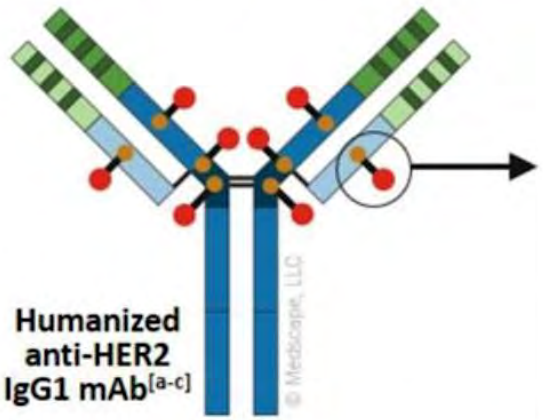
Trastuzumab Deruxtecan

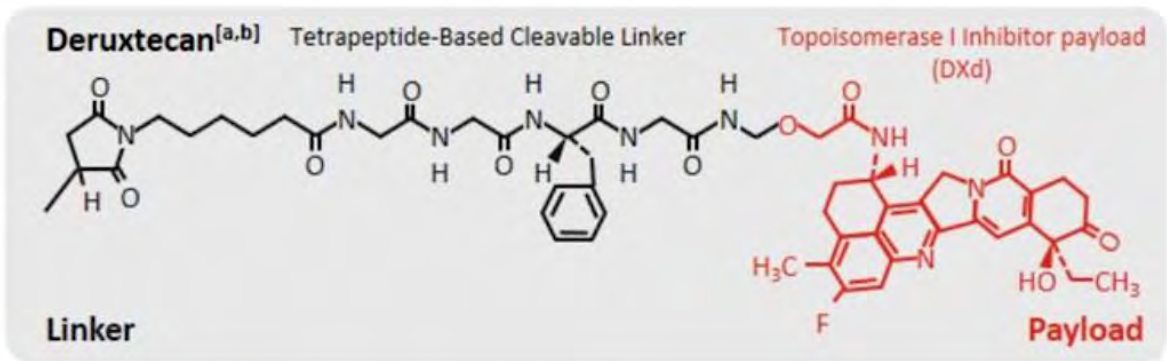
Novel ADC Designed to Deliver an Optimal Antitumor Effect

Trastuzumab deruxtecan is an ADC composed of 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker

Payload MOA: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload



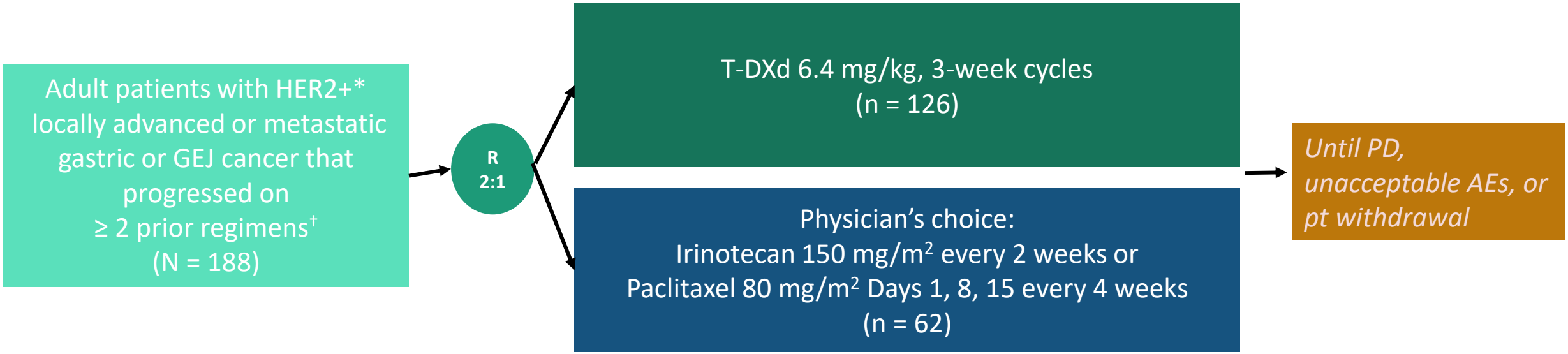


The clinical relevance of these features is under investigation.

a. Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019;67:173-185; b. Ogitani Y, et al. *Clin Cancer Res*. 2016;22):5097-5108; c. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142; d. Ogitani Y, et al. *Cancer Sci*. 2016;107:1039-1046.

DESTINY-Gastric01: Study Design

- Multicenter, open-label, randomized phase II study



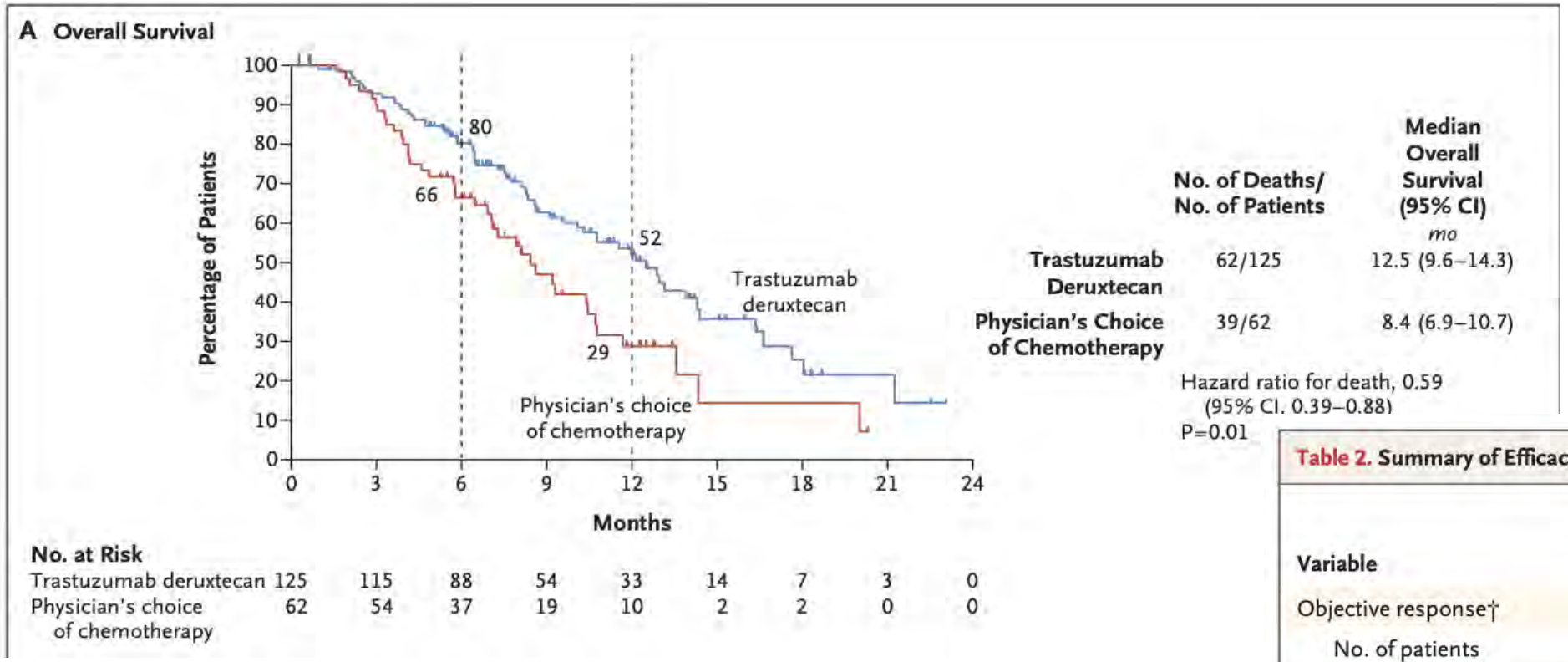
Primary endpoint: ORR by ICR (RECIST v1.1)
Secondary endpoints: OS (key), DoR, PFS, DCR, confirmed ORR, safety

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

*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.

Shitara. ASCO 2020. Abstr 4513. Shitara. N Engl J Med 2020; 382:2419-2430

Improved ORR and OS



	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

Table 2. Summary of Efficacy.*

Variable	Trastuzumab Deruxtecan (N=119)	Physician's Choice of Chemotherapy (N=56)
Objective response†		
No. of patients	61	8
Percent of patients (95% CI)	51 (42–61)	14 (6–26)
Best response — no. (%)		
Complete response	11 (9)	0
Partial response	50 (42)	8 (14)
Stable disease	42 (35)	27 (48)
Progressive disease	14 (12)	17 (30)
Could not be evaluated	2 (2)	4 (7)

Shitara, NEJM 2020

Summary of Trastuzumab deruxtecan

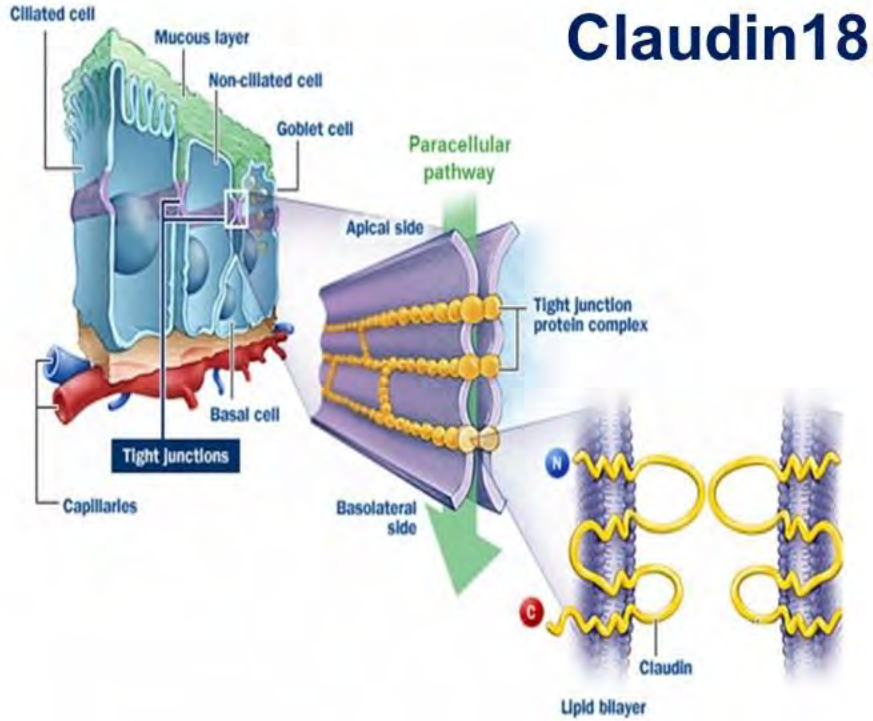
- FDA approved as 2L and beyond for HER2+ gastric/GEJ cancers
- DESTINY-Gastric02
  - Phase II study (n=79) from **Europe** and the **United States** who had progressed on one trastuzumab-containing regimen.
  - ORR: 42%
  - Median PFS: 5.6 months
- DESTINY-Gastric04 ongoing (second line ram/taxol versus T-DXd)

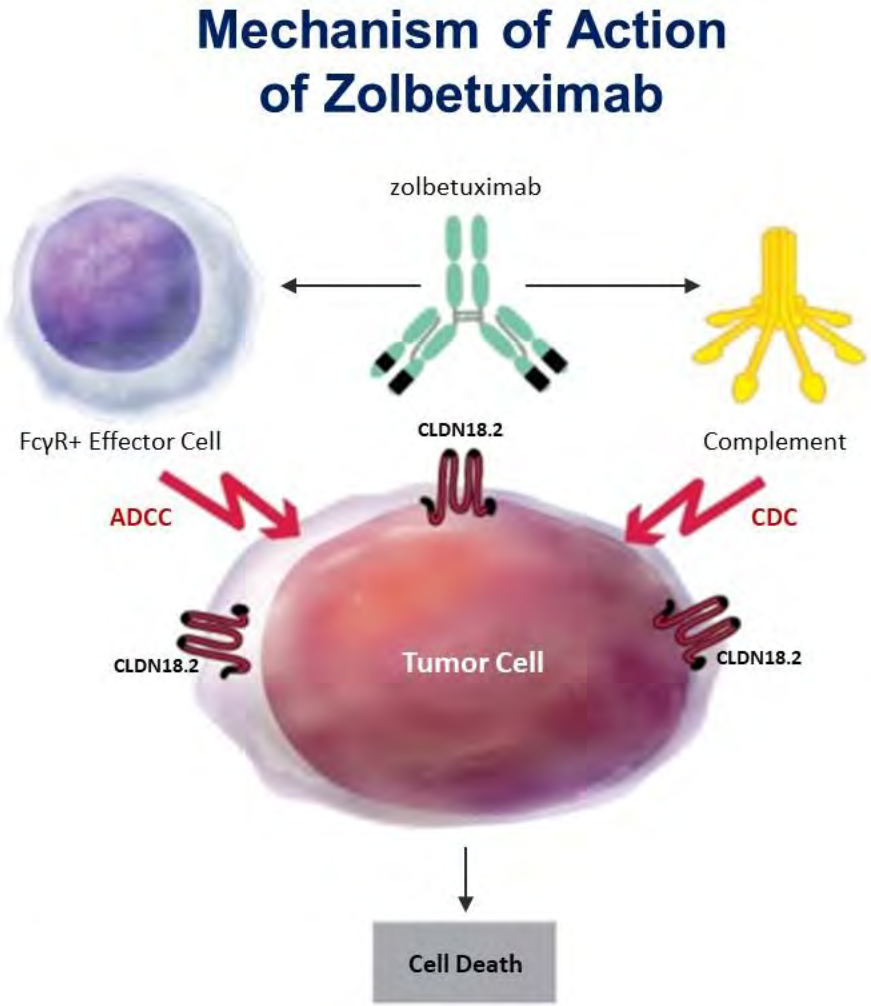
Ku G et al. ESMO 2022;Abstract 1205MO. Van-Cutsem E et al. *Lancet Oncol* 2023;24(7):744-56.

Other novel therapies in the HER 2 space

- Zanidatamab– bispecific antibody – targets 2 HER2 epitopes (dual HER 2 binding)
- Ongoing phase 3 study HERIZON GEA 01 – Zanidatamab + chemo +/- Tislelizumab for HER 2 + GE adenocarcinoma
- Most common toxicity - diarrhea

Claudin18.2
A Novel Target





- 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

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

Zolbetuximab

- IgG1 monoclonal Ab against Claudin 18.2
- Activate immune response both complement and T cell mediated

SPOTLIGHT STUDY

Global, randomized, double-blind phase III trial

Primary endpoint: PFS

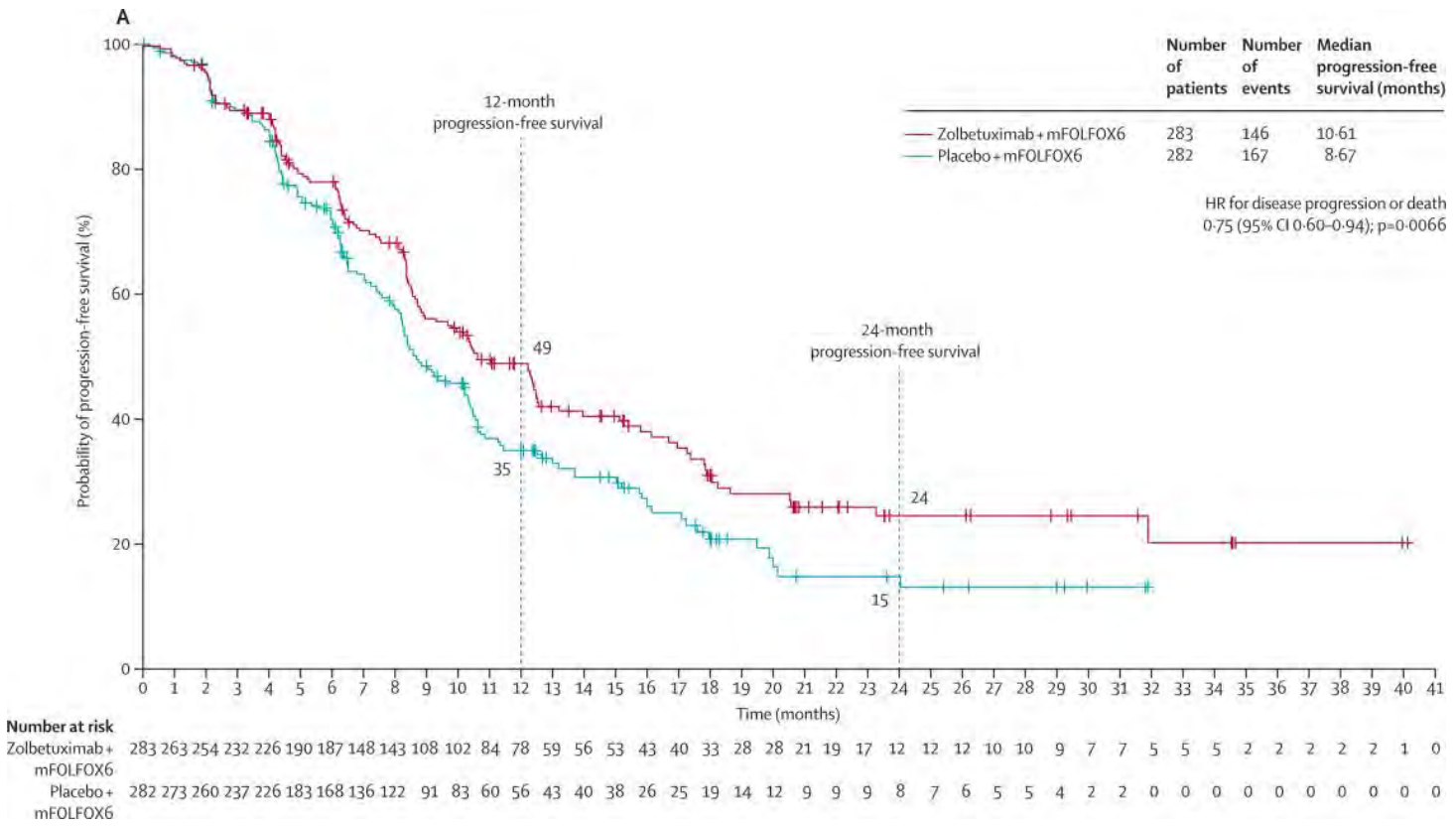
Stratified by region (Asia vs non-Asia), organs w/mets (0-2 vs ≥3), prior gastrectomy (yes vs no)

Patients with previously untreated locally advanced or metastatic gastric/GEJ adenocarcinoma; CLDN18.2+*; HER2 negative; ECOG PS 0-1

(N = 565)

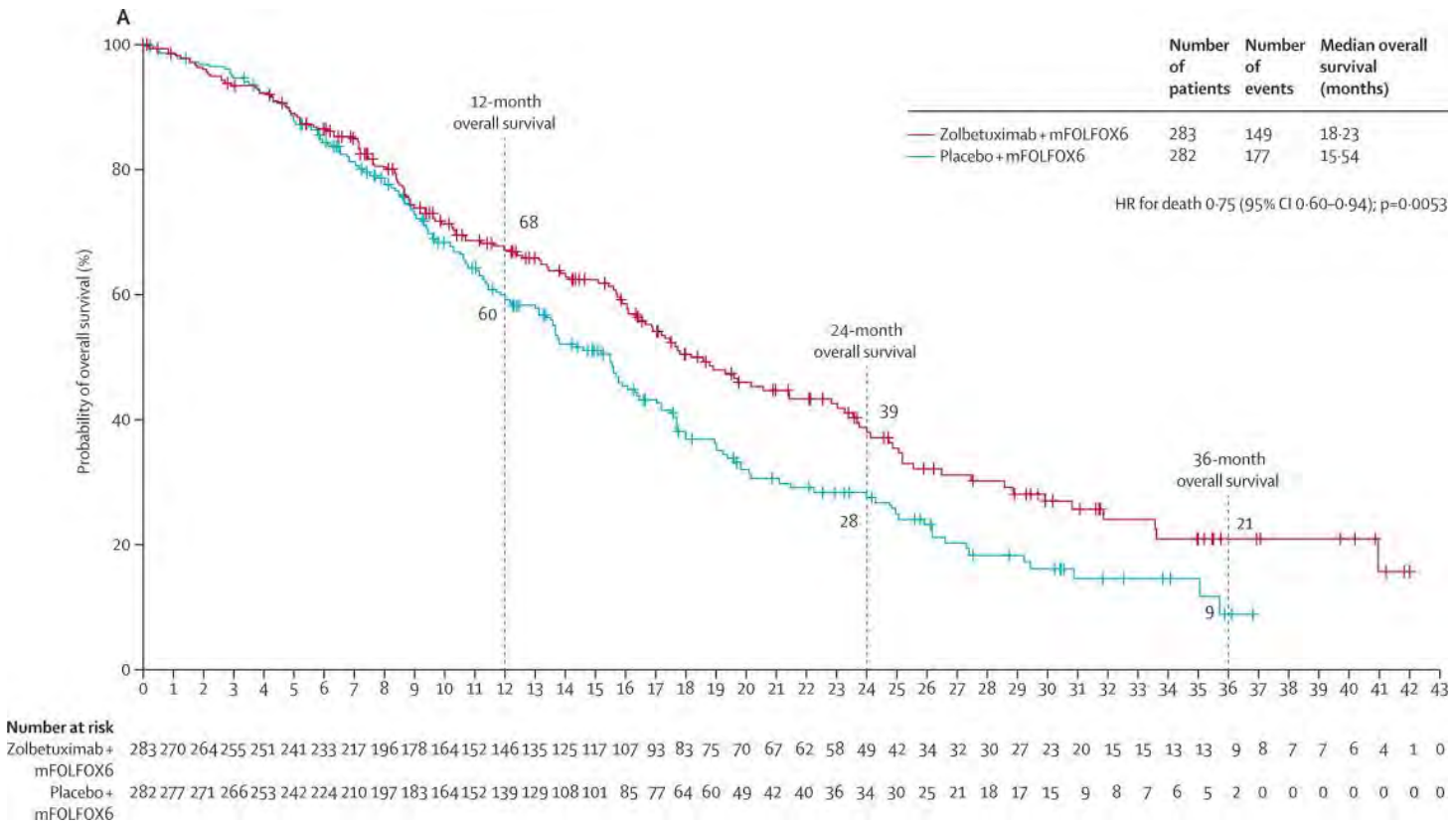
Zolbetuximab 600† mg/m^2 IV Q3W + **mFOLFOX6** IV Q2W 4 cycles (42 days/cycle) (n = 283)	**Zolbetuximab** 600 mg/m^2 IV Q3W + **5-FU + folinic acid** IV Q2W Cycles 5+
Placebo IV Q3W + **mFOLFOX6** IV Q2W 4 cycles (42 days/cycle) (n = 282)	**Placebo** IV Q3W + **5-FU + folinic acid** IV Q2W Cycles 5+

PFS



Shitara, Kohei, et al. *Lancet* 401.10389 (2023): 1655-1668.

OS



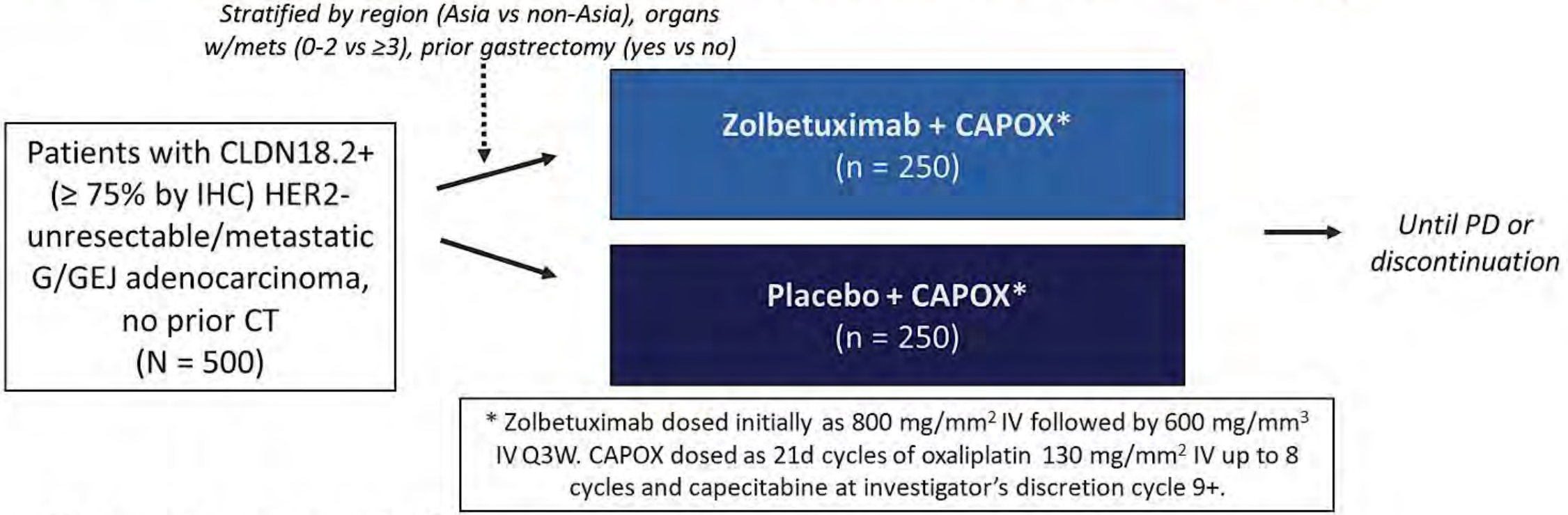
Shitara, Kohei, et al. *Lancet* 401.10389 (2023): 1655-1668.

GLOW study

- Similar design to SPOTLIGHT – used CAPOX for chemotherapy
- patient populations in GLOW and SPOTLIGHT were different, with more Asian patients in GLOW and non-Asiatic in SPOTLIGHT.

GLOW: Study Design

- Global, double-blind, placebo-controlled, randomized phase III study



Primary endpoint: IRC-assessed PFS

Secondary endpoints: OS, ORR, DOR, safety, PK, QoL

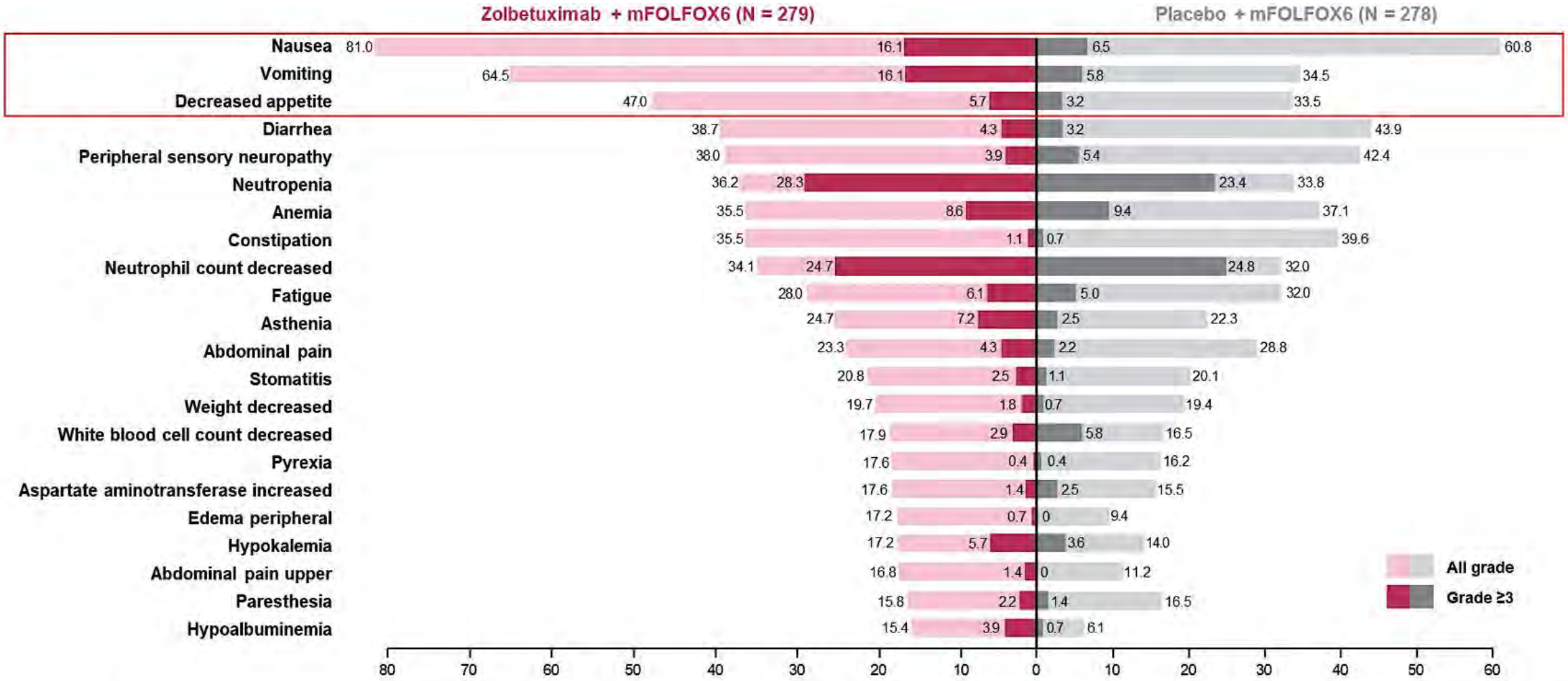
Shah, M Nature Med 2023

SPOTLIGHT and GLOW

	SPOTLIGHT (n=550)	GLOW (n=500)
Control	FOLFOX	CapeOX
Countries	Global	Global (~50% from China)
CPS≥5	13%	22%
mPFS	10.6 vs 8.7 **+1.9** **HR 0.75**	8.2 vs 6.8 **+1.4** **HR 0.69**
mOS	18.2 vs 15.5 **+2.7** **HR 0.75**	14.4 vs 12.2 **+2.2** **HR 0.77**
ORR	61% vs 62% -1%	54% vs 49% +5%
Nausea Vomiting	81% vs 61% 65% vs 35%	69% vs 50% 66% vs 31%
Discontinuation of zolbe/pbo by AE	14% vs 2%	7% vs 4%

Courtesy of Manish Shah, GI ASCO 2024

Nausea, Vomiting and Anorexia are Key AEs

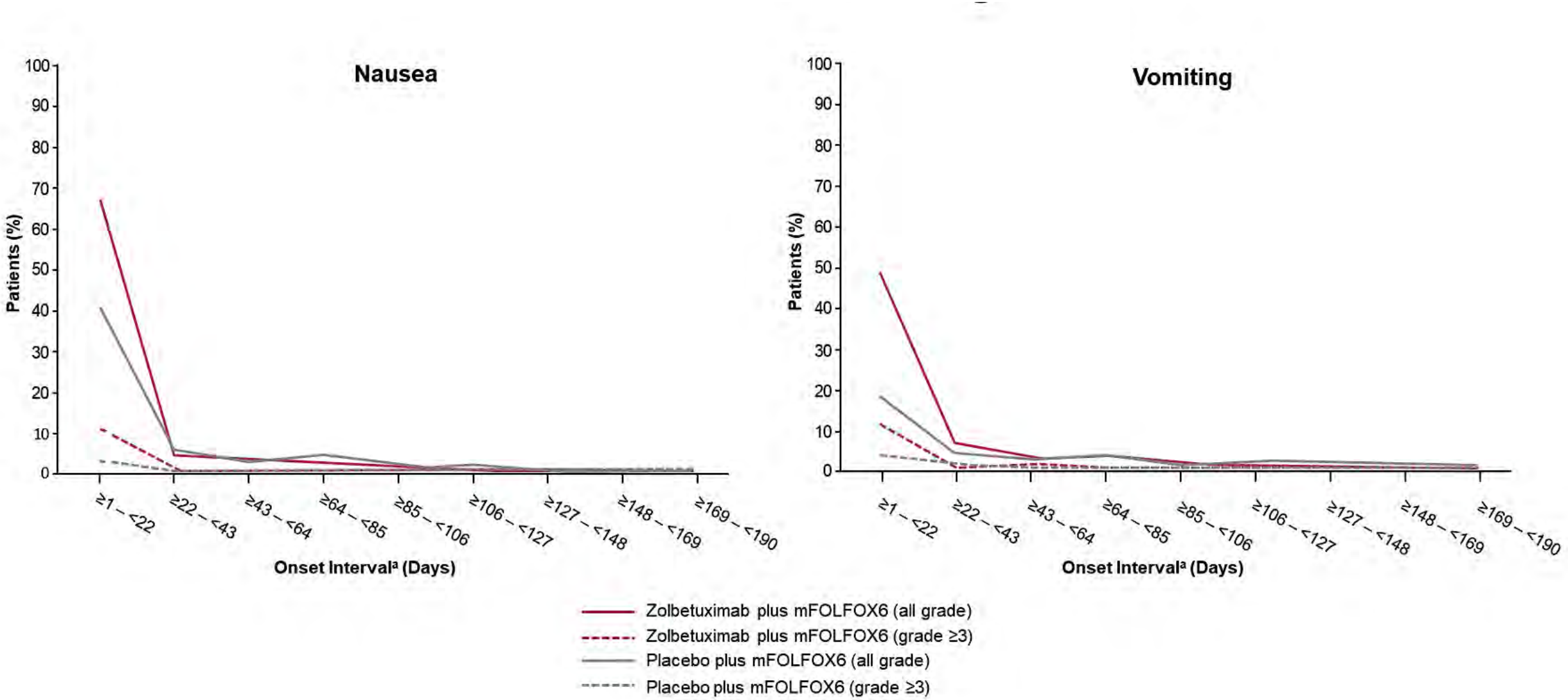


- The most common TEAEs with zolbetuximab + mFOLFOX6 were nausea and vomiting as on-target effects

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

Shitara, GI ASCO 2023

Nausea/Vomiting Peak with 1st Dose

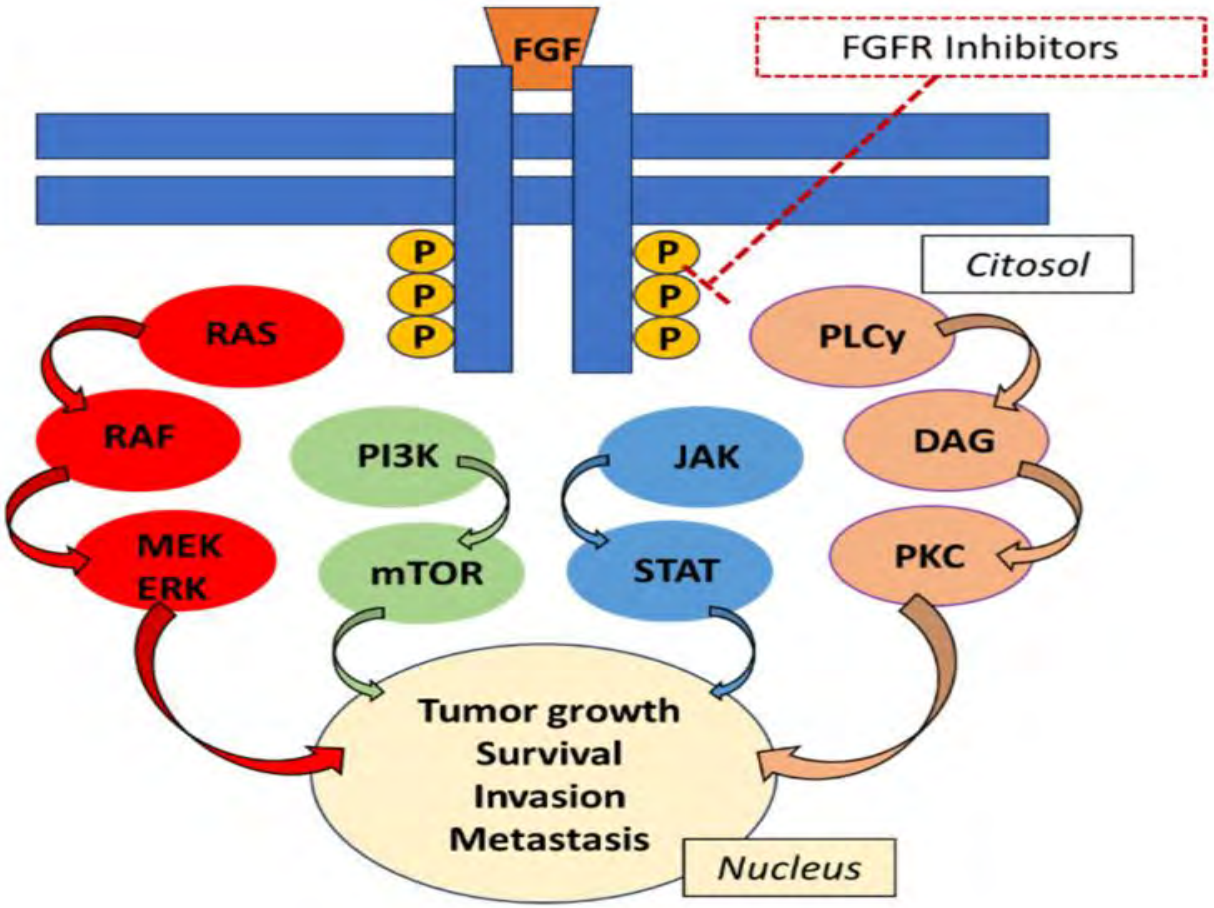


Shitara, GI ASCO 2023

FDA Approval October 18 2024

- FDA now approved Zolbetuximab for HER2-negative ($HER2^-$), CLDN18.2-positive ($CLDN18.2^+$) advanced gastric or gastroesophageal junction (GEJ)
- The FDA also approved the VENTANA CLDN18 (43-14A) RxDx Assay as a companion diagnostic device to help identify patients who may be eligible for zolbetuximab treatment

FGFR



Ratti, Margherita, et al. *Biomedicines* 11.10 (2023): 2650.

FGFR overexpression in gastric cancer

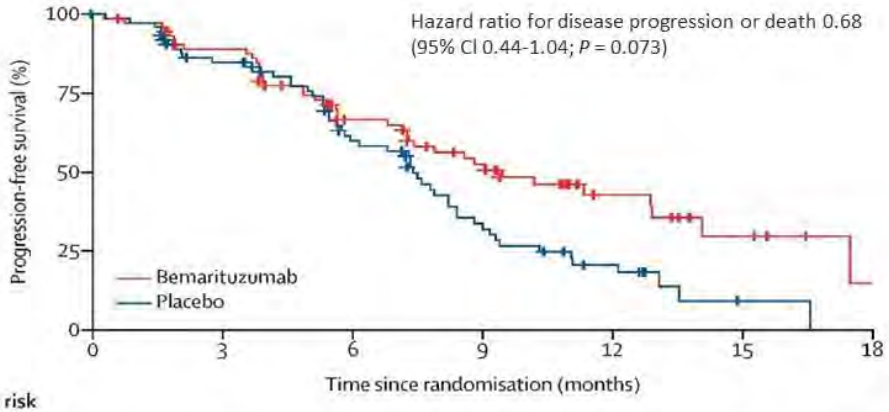
- FGFR 2 amplification is most common
- Bemarituzumab is a first-in-class IgG mAb
- Bemartizumab – also has immunomodulatory properties

FIGHT

- Phase II trial
- First line trial
- Evaluated the activity of bemarituzumab in combination with chemotherapy versus chemotherapy alone
- FGFR2b amplification in 30%
- highest improvement of outcomes in patients with FGFR2b hyperexpression (> 10% of tumor cells).

FIGHT Outcomes

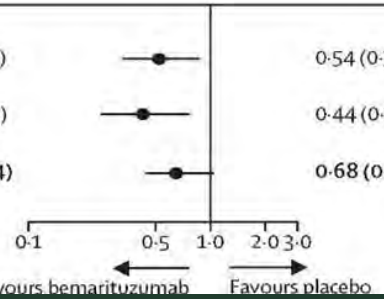
PFS



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)

B

	Median progression-free survival (95% CI)		Hazard ratio (95% CI)
	Bemarituzumab	Placebo	
FGFR2b expression			
Overexpressed in at least 5% of tumour cells (n=118)	10·2 (6·8–14·1)	7·3 (5·5–8·2)	0·54 (0·33–0·87)
Overexpressed in at least 10% of tumour cells (n=96)	14·1 (6·8–NR)	7·3 (5·4–8·2)	0·44 (0·25–0·77)
Overall patient population (n=155)	**9·5 (7·3–12·9)**	**7·4 (5·8–8·4)**	**0·68 (0·44–1·04)**



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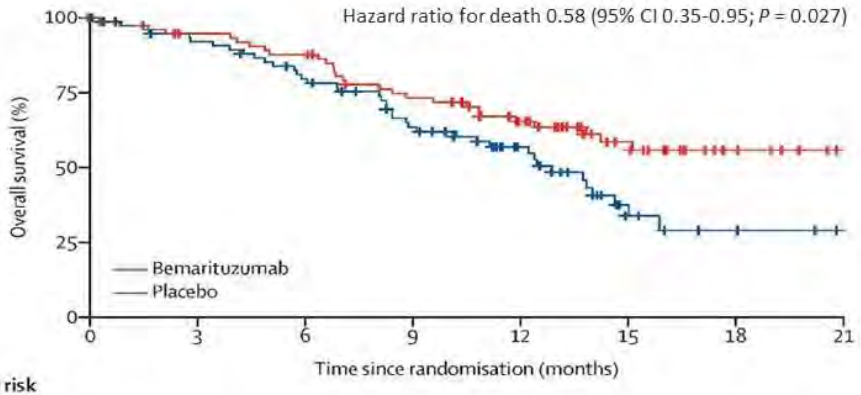
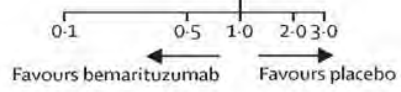


Number at risk (number censored)								
Bemarituzumab	77 (0)	68 (5)	63 (5)	50 (8)	38 (15)	21 (29)	6 (43)	0 (49)
Placebo	78 (0)	68 (4)	57 (6)	42 (10)	27 (21)	10 (30)	4 (34)	1 (37)

B

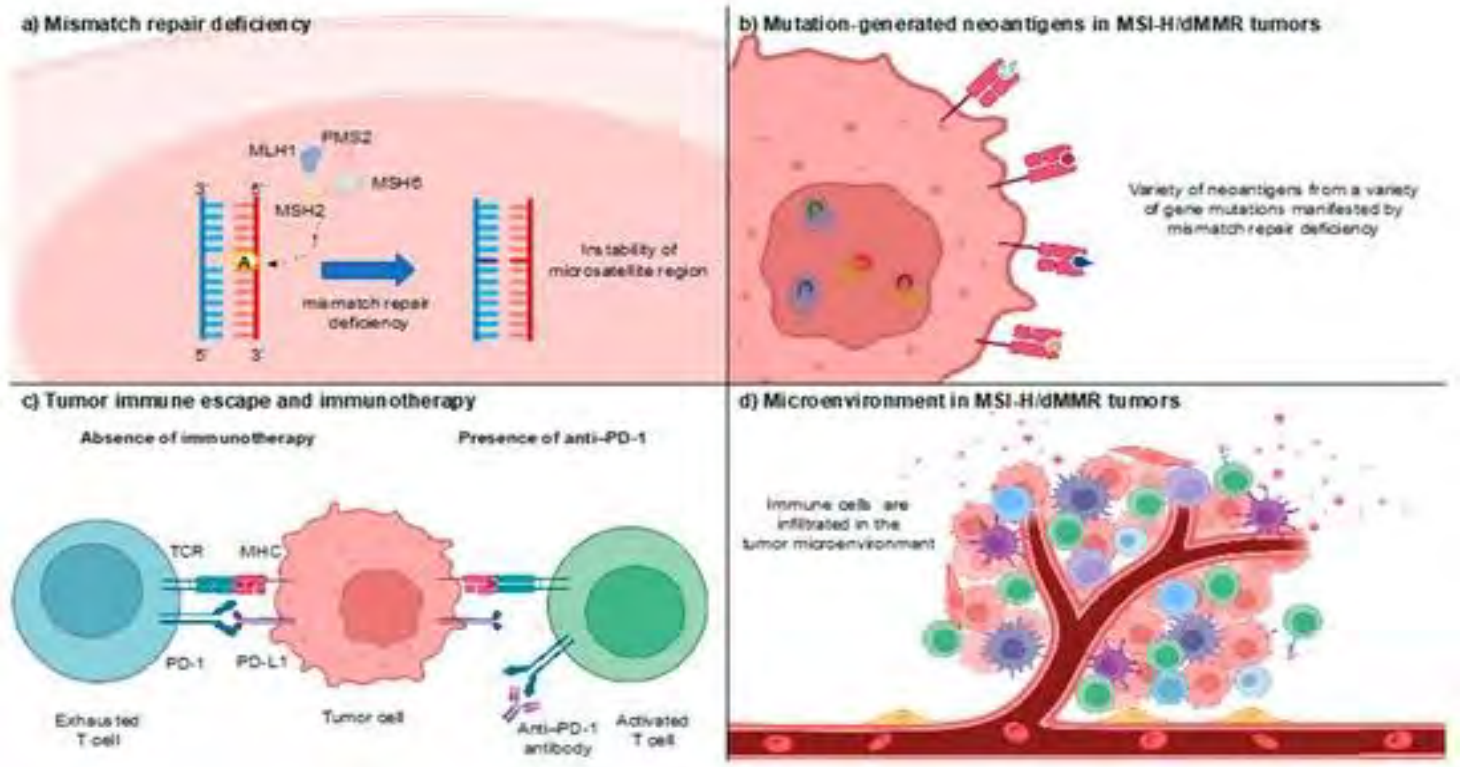
	Median overall survival (95% CI)		Hazard ratio (95% CI)
	Bemarituzumab	Placebo	
FGFR2b expression			
Overexpressed in at least 5% of tumour cells (n=118)	NR (13·8–NR)	12·5 (8·8–15·0)	0·52 (0·30–0·91)
Overexpressed in at least 10% of tumour cells (n=96)	NR (13·8–NR)	11·1 (8·4–13·8)	0·41 (0·22–0·79)
Overall patient population (n=155)	**NR (13·8–NR)**	**12·9 (9·1–15·0)**	**0·58 (0·35–0·95)**



Future of FGFR 2 in Upper GI cancers?

- Phase III FORTITUDE-101 trial (NCT05052801) with bemarituzumab plus chemotherapy in the 1L setting for HER2- and FGFR2b+ GEA is recruiting
- Also being studied with ICI

MMR deficiency

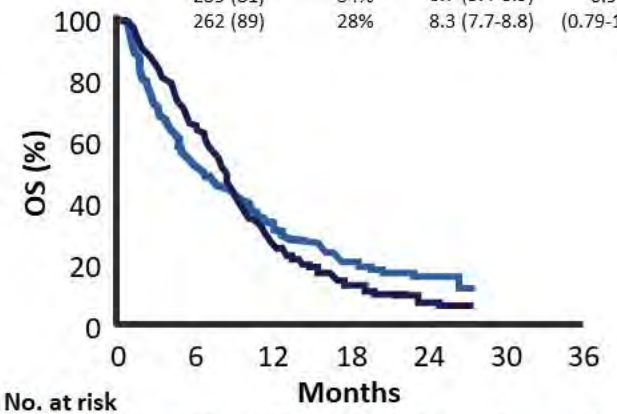


Shimozaki, Keitaro, et al. *Cells* 12.7 (2023): 1049.

PD-1 Inhibitors in MSI-H/dMMR Gastric Cancer

KEYNOTE-061: 2L Pembrolizumab vs Chemo

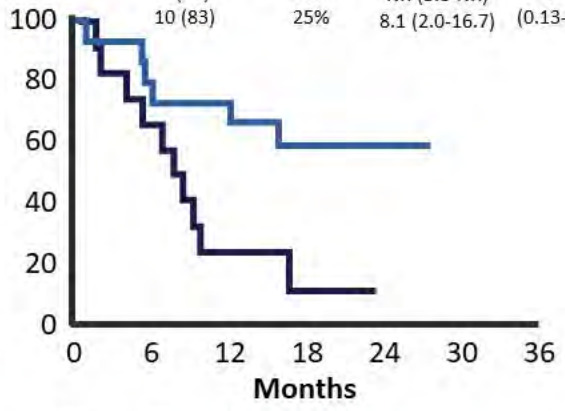
	Events n (%)	12-Mo Rate	Median, Mo (95% CI)	HR (95% CI)
Pembro	239 (81)	34%	6.7 (5.4-8.9)	0.94
Chemo	262 (89)	28%	8.3 (7.7-8.8)	(0.79-1.12)



No. at risk							
Pembro 296	155	101	53	16	0	0	
Chemo 296	191	83	36	12	0	0	

KEYNOTE-061: Pembrolizumab vs Chemo in MSI-H

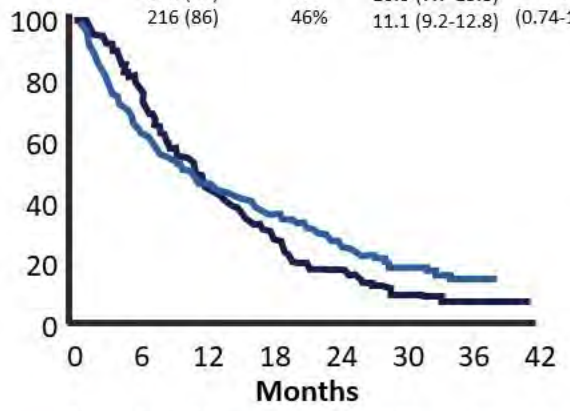
	Events n (%)	12-Mo Rate	Median, Mo (95% CI)	HR (95% CI)
Pembro	6 (40)	73%	NR (5.6-NR)	0.42
Chemo	10 (83)	25%	8.1 (2.0-16.7)	(0.13-1.31)



15	12	11	6	3	0	0	
12	8	3	1	0	0	0	

KEYNOTE-062: 1L Pembrolizumab vs Chemo

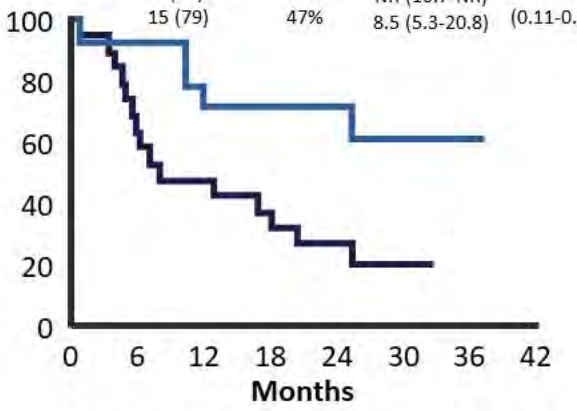
	Events n (%)	12-Mo Rate	Median, Mo (95% CI)	HR (95% CI)
Pembro	201 (79)	47%	10.6 (7.7-13.8)	0.91
Chemo	216 (86)	46%	11.1 (9.2-12.8)	(0.74-1.10)



256	162	120	94	59	23	4	0	
250	192	114	75	38	15	2	0	

KEYNOTE-062: Pembrolizumab vs Chemo in MSI-H

	Events n (%)	12-Mo Rate	Median, Mo (95% CI)	HR (95% CI)
Pembro	5 (36)	79%	NR (10.7-NR)	0.29
Chemo	15 (79)	47%	8.5 (5.3-20.8)	(0.11-0.81)



14	13	11	10	9	4	2	0	
19	13	9	7	4	3	0	0	

Response	Keynote-059 (3L+) Pembro (n = 7)	KEYNOTE-061 (2L) Pembro (n = 15)	KEYNOTE-061 (2L) Chemo (n = 12)	KEYNOTE-062 (1L) Pembro (n = 14)	KEYNOTE-062 (1L) Chemo (n = 19)
ORR, n (%)	4 (57)	7 (47)	2 (17)	8 (57)	7 (37)
Median DOR, mo (range)	Not reached (20.0+ to 26.8+)	Not reached (5.5 to 26.0+)	Not reached (2.2+ to 12.2+)	21.2 (1.4+ to 33.6+)	7.0 (2.0 to 30.4+)

MSI-H or dMMR is strongly associated with improved outcomes with immune checkpoint inhibitor therapy. Activity is independent of the line of therapy.

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

Sequencing novel therapies – summary

- How do we sequence these therapies and how do we use Zolbetuximab now with the approval in HER 2 negative patients ?
- Still pending antibody to test for Claudin Expression
- In patients claudin 18.2+, PDL1 + -> longer term data with PDL1 tail end of the curve (however minority of patients 10% or so)
- Nausea/vomiting with zolbetuximab is very different (s/p gastrectomy – it is better)
- Concern in the practical setting – despite maximizing antiemetic prophylaxis
- Recommendation – stop and slow it down in half rate

Conclusion

- Targeted therapy is the future of this disease
- Critical to test for Claudin 18.2, HER 2, MSI, PDL1 in all GE adenocarcinomas
- Planning ahead FGFR testing