Differentiating Biomarker-Driven First-Line Treatment Strategies in Metastatic Gastric/GEJ Cancers

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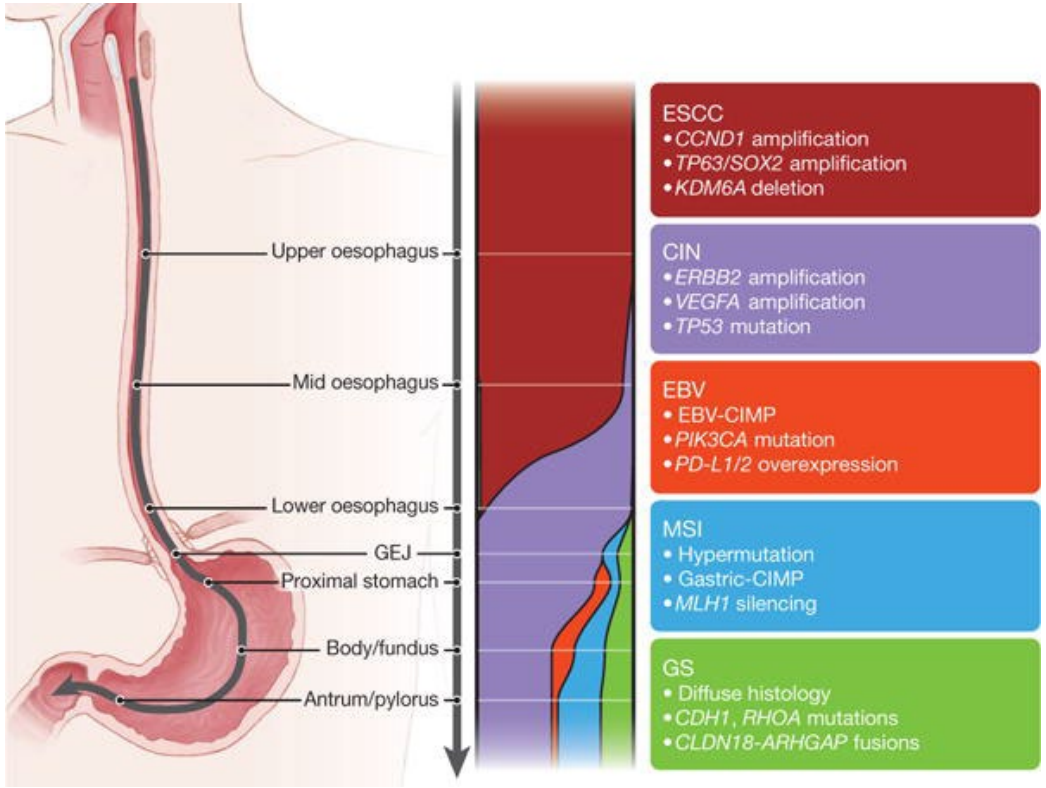
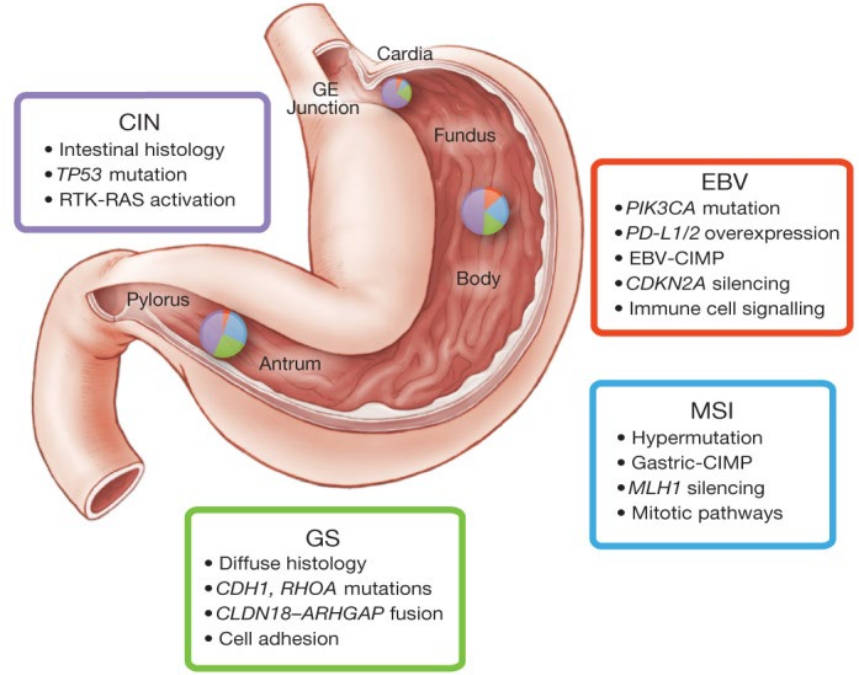
TOTAL CME

Biomarkers in Gastric/Gastroesophageal Junction Cancers

Anatomic and Molecular Heterogeneity



164 esophageal tumors, 359 gastric adenocarcinomas and 36 additional adenocarcinomas at the GEJ



EBV, Epstein Barr virus; CIN, chromosomal instability; GS, genomically stable; MSI, microsatellite unstable.

Cancer Genome Atlas Research Network. *Nature*. 2017;541(7636):169-175. Cancer Genome Atlas Research Network. *Nature*. 2014;513(7517):202-209.

Relevant Biomarkers in Advanced Gastric/GEJ Cancers

Current:

- Microsatellite status (PCR or IHC for MMR protein expression)*
- HER2 status (IHC and FISH as needed; NGS)
- PD-L1 expression

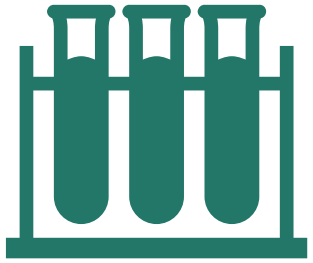
Under Investigation:

- Claudin 18.2, FGFR2b

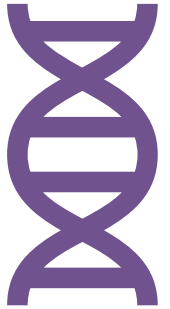
** Microsatellite status should be determined regardless of stage.*

Testing for Microsatellite Instability

Immunohistochemistry: expression of mismatch repair (MMR) proteins

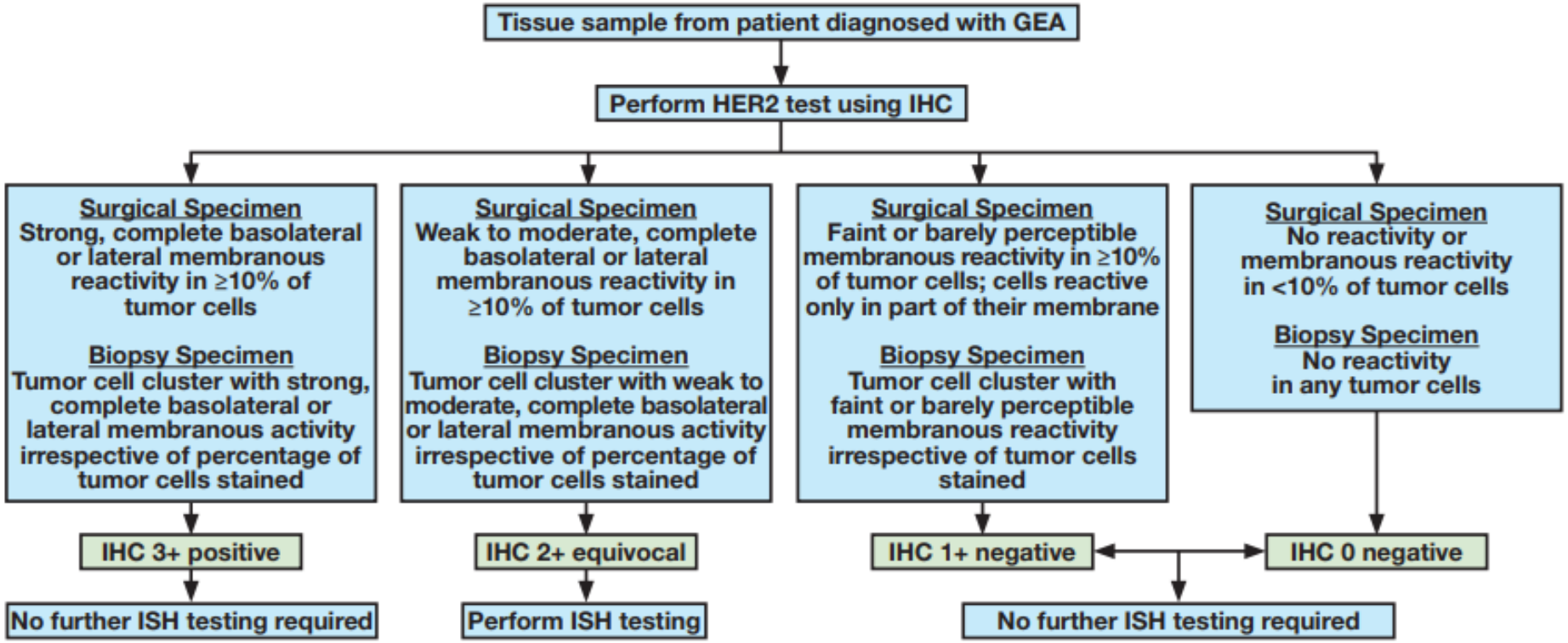


PCR-based assays for microsatellite instability (MSI)



Next-generation sequencing (NGS)

ASCO/CAP/ASCP Guidelines for HER2 Status Assessment in Gastroesophageal Adenocarcinoma



Bartley AN, et al. *J Clin Oncol*. 2017;35(4):446-464.

PD-L1 Testing in Upper Gastric/GEJ Tumors

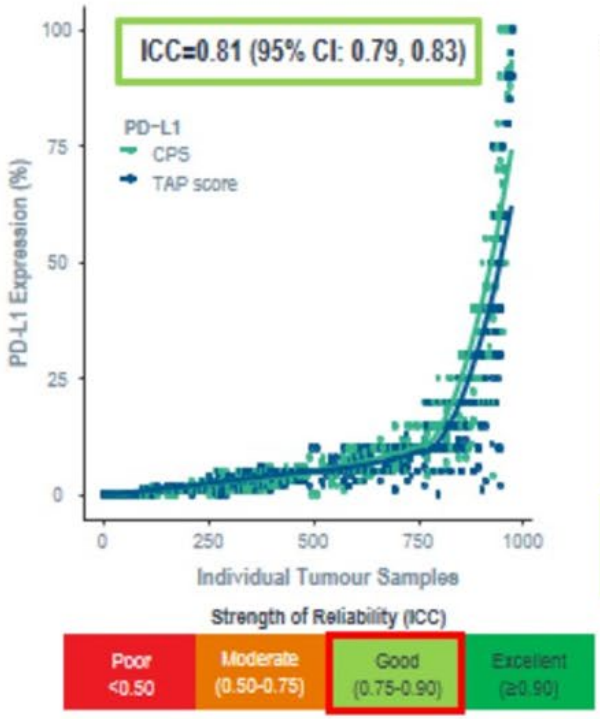
PD-L1 tumor-positive score (TPS):
% of viable tumor cells with partial or complete membrane staining in at least 100 viable tumor cells examined

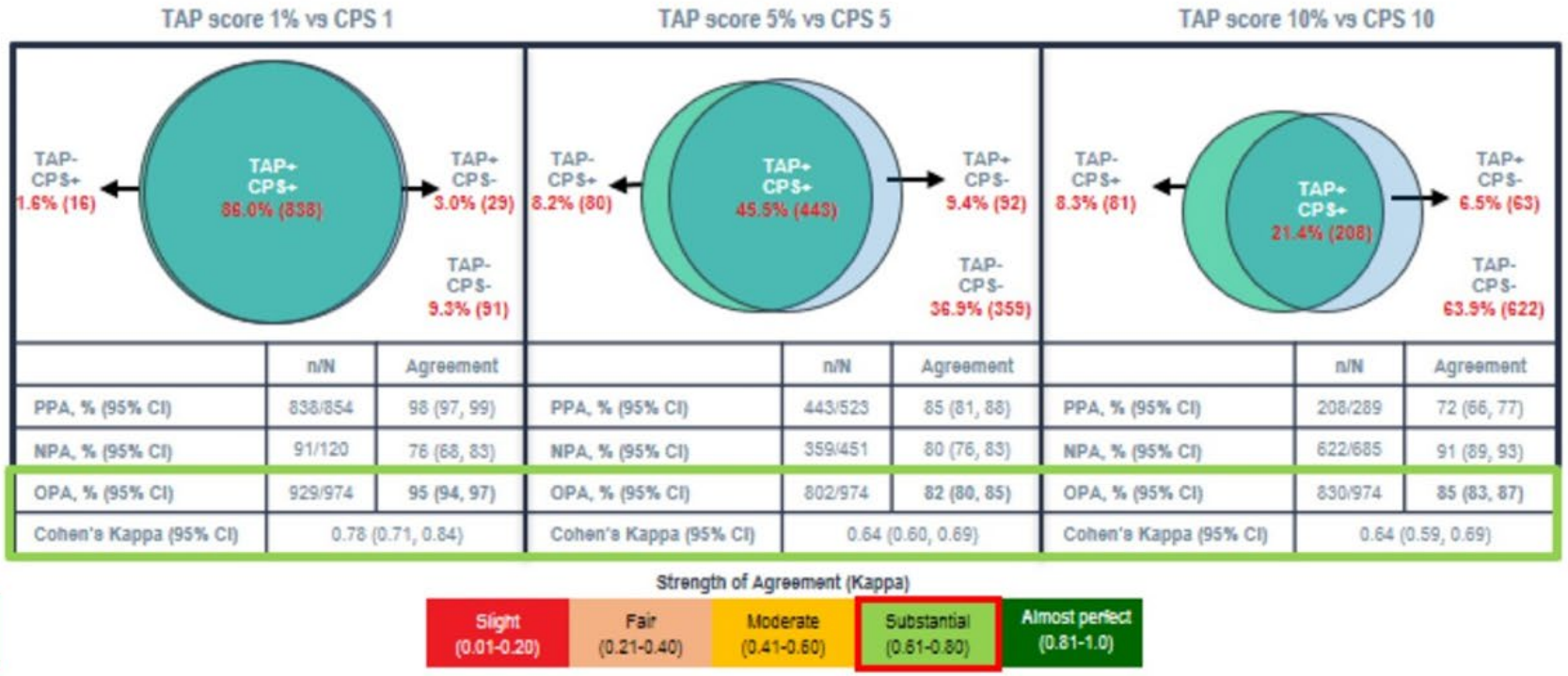
PD-L1 combined positive score (CPS):
# of PD-L1-positive tumor cells, lymphocytes, and macrophages divided by the total number of viable tumor cells multiplied by 100; at least 100 viable tumor cells must be present

PD-L1 tumor area positivity (TAP) (%):
Ratio of the area occupied by PD-L1-positive tumor cells and immune cells to the total tumor area (no cell counting; visual estimation)

Commercial PD-L1 immunohistochemistry (IHC): the Ventana PD-L1 SP263 assay (SP263), the Dako PD-L1 IHC 22C3 pharmDx assay (22C3), and the Dako PD-L1 IHC 28-8 pharmDx assay (28-8).

Concordance Between PD-L1 CPS and TAP Scores





	n/N	Agreement
PPA, % (95% CI)	838/854	98 (97, 99)
NPA, % (95% CI)	91/120	76 (68, 83)
OPA, % (95% CI)	929/974	95 (94, 97)
Cohen's Kappa (95% CI)	0.78 (0.71, 0.84)	

	n/N	Agreement
PPA, % (95% CI)	443/523	85 (81, 88)
NPA, % (95% CI)	359/451	80 (76, 83)
OPA, % (95% CI)	802/974	82 (80, 85)
Cohen's Kappa (95% CI)	0.64 (0.60, 0.69)	

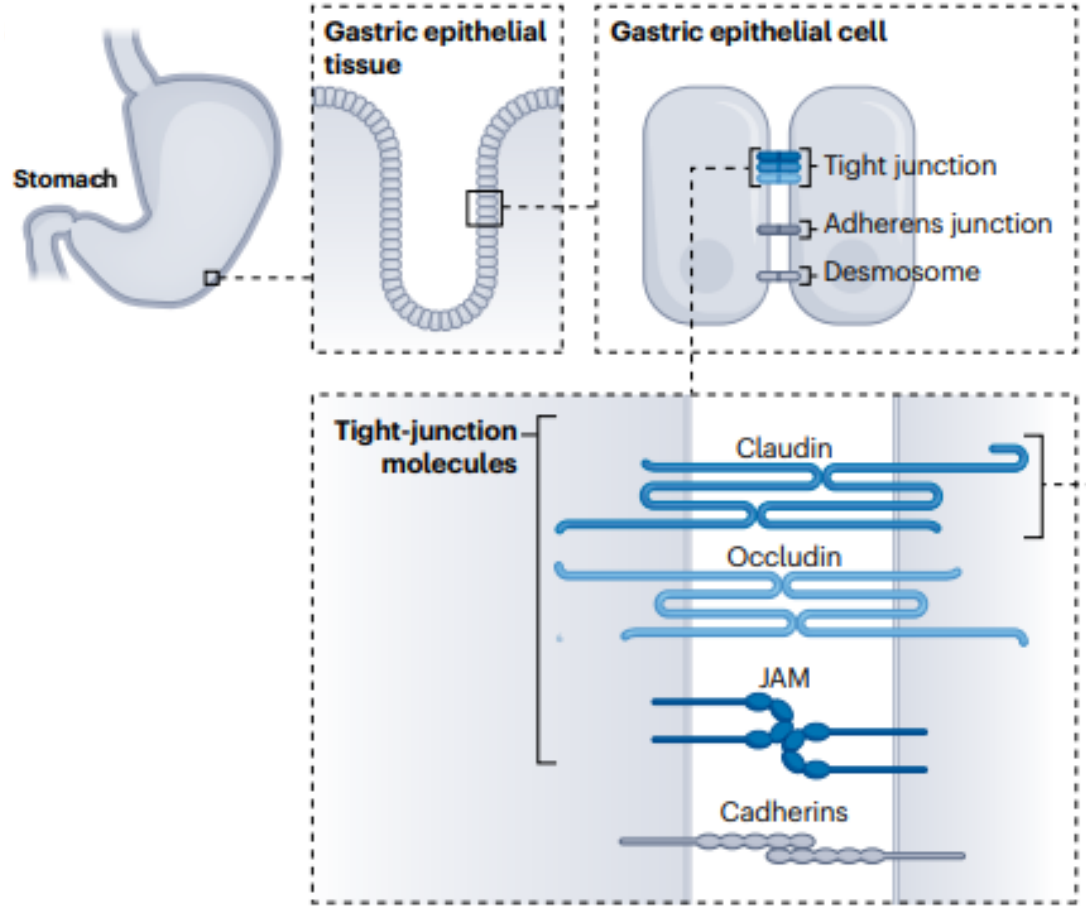
	n/N	Agreement
PPA, % (95% CI)	208/289	72 (66, 77)
NPA, % (95% CI)	622/685	91 (89, 93)
OPA, % (95% CI)	830/974	85 (83, 87)
Cohen's Kappa (95% CI)	0.64 (0.59, 0.69)	

Abbreviations: CI, confidence interval; CPS, combined positive score; GC/GEJC, gastric or gastro-oesophageal junction adenocarcinoma; NPA, negative percent agreement; PPA, positive percent agreement; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity.

Moehler M, et al. ESMO GI 2024. Abstract 397MO.

Claudin 18.2: A Novel Cancer Biomarker

Zolbetuximab with chemotherapy is now FDA-approved as first-line treatment of CLDN 18.2+/HER2- advanced gastric/GEJ adenocarcinoma.



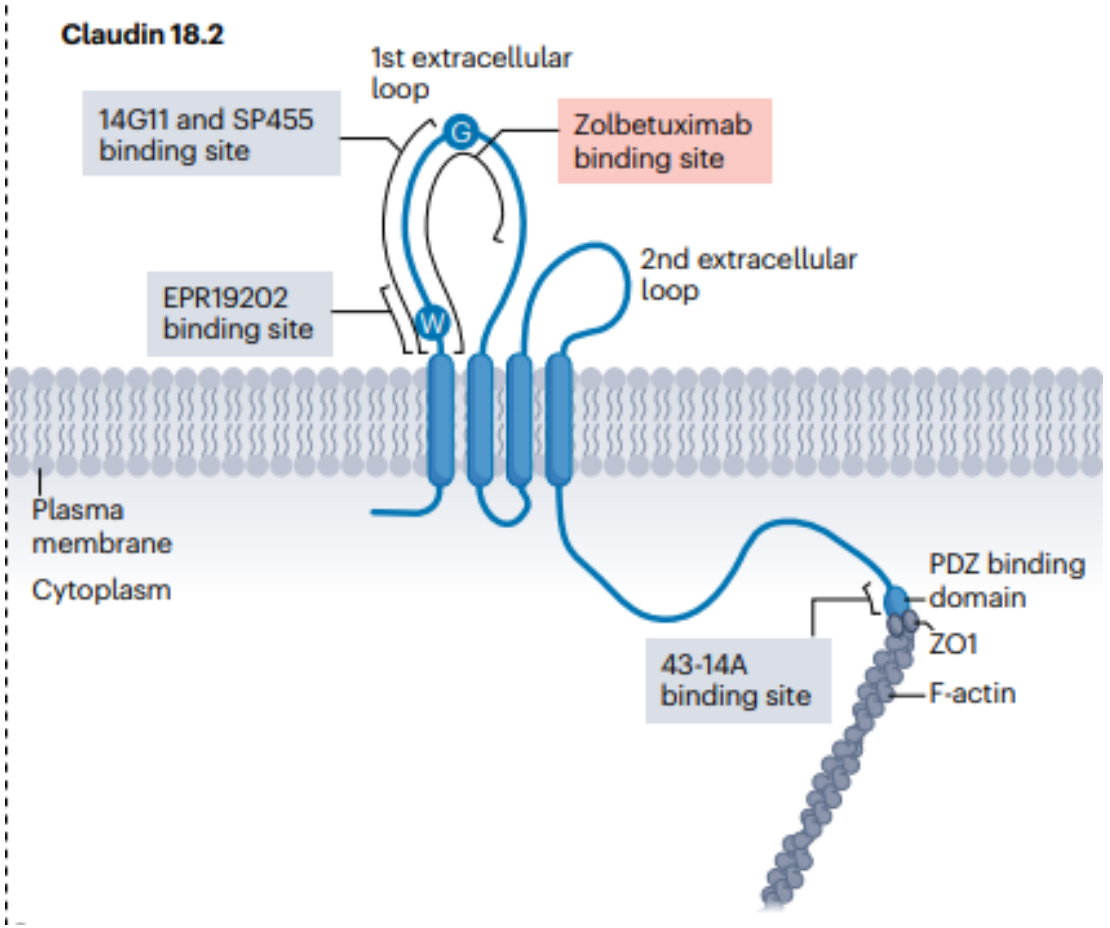


Figure adapted from Nakayama I, et al. *Nat Rev Clin Oncol*. 2024;21(5):354-369.

Emerging Information on Biomarker Overlap: Clinical Decision Challenge

	CLDN 18.2+	CLDN 18.2 -
HER2+	**15%-21%**	**14%-34%**
dMMR/MSI-H	**5%-14%**	**6%-17%**
PD-L1 ≥ 1	**26%-79%**	**21%-71%**
PD-L1 ≥ 5	**18%-42%**	**21%-52%**

Treatment selection will depend on :

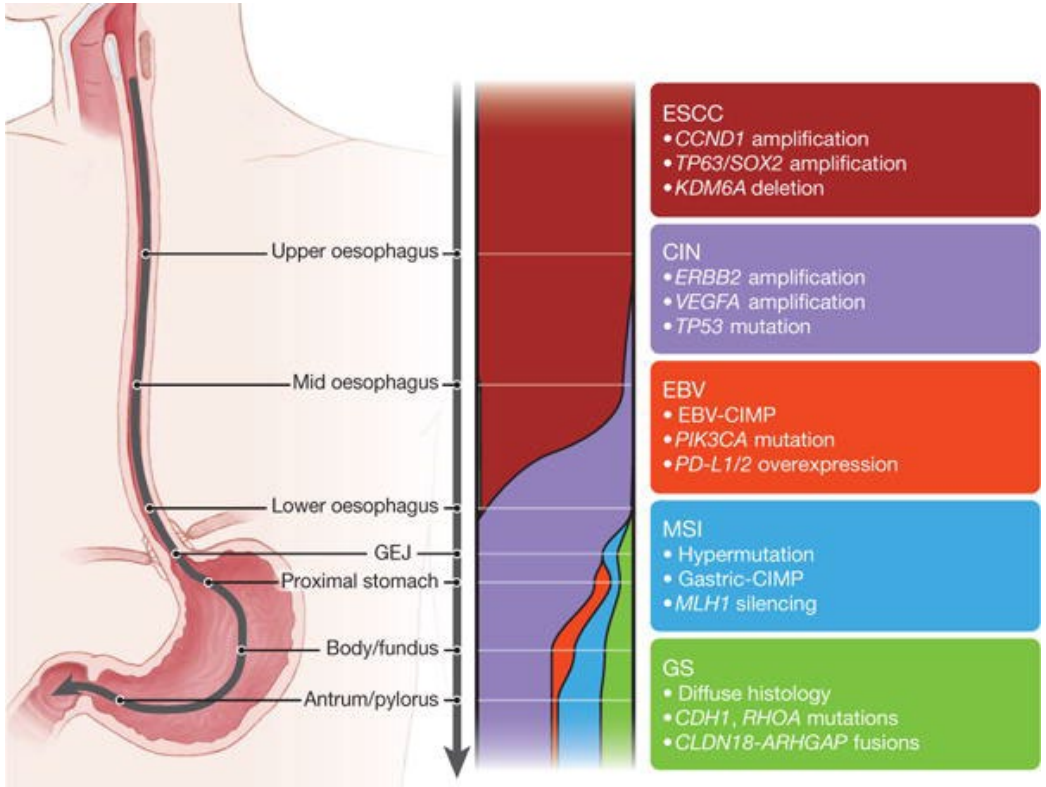
- Efficacy
- Toxicity profile
- Turnaround time for testing results
- Tissue availability

Sequential **testing will be a challenge given disease-related symptomatic burden.**

Reflex **IHC testing for all relevant biomarkers will be essential.**

Kubota Y, et al. *ESMO Open.* 2023;8(1):100762. Pellino A, et al. *J Pers Med*. 2021;11(11):1095. Jia K, et al. *BMC Med*. 2022;20(1):223.

Growing Number of New Treatments Are Biomarker Based



Established Biomarkers

- **HER2** 10%-20%
- **MSI/MMR IHC** 5%-10%
- **PD-L1** 40%-60%

Emerging Biomarkers

- **FGFR2b** ~30%
- **Claudin 18.2** 30%-40%

Cancer Genome Atlas Research Network. *Nature*. 2017;541(7636):169-175. Cancer Genome Atlas Research Network. *Nature*. 2014;513(7517):202-209.

HER2-Negative Gastric/Gastroesophageal Junction Cancers

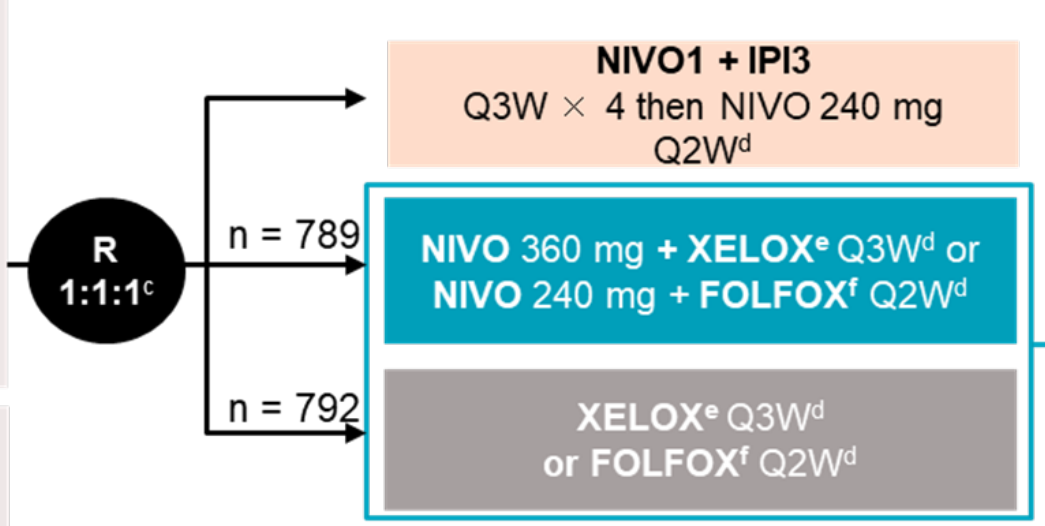
CheckMate 649: Phase 3 Global Study of Nivolumab & Chemo vs Chemo in First-Line Esophagogastric Adenocarcinomas

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)

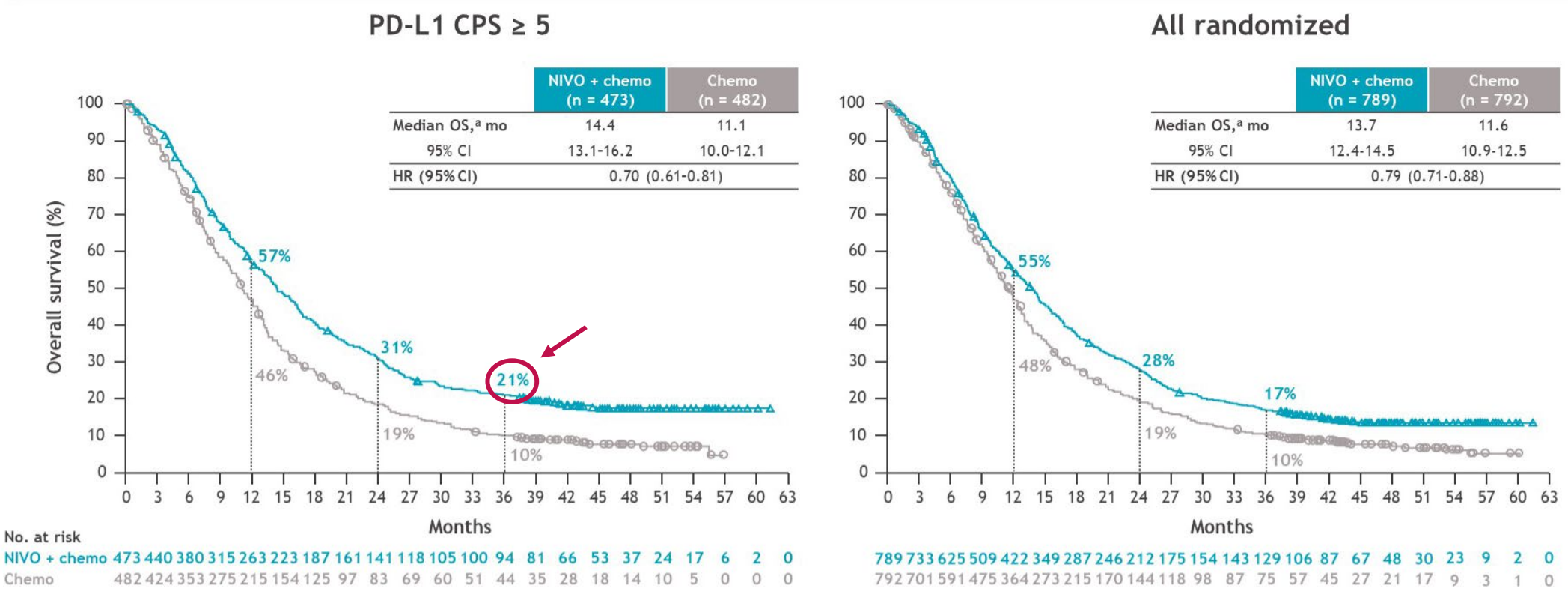
Secondary endpoints:

- **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]

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

Janjigian YY, et al. *Lancet*. 2021;398(10294):27-40. Moehler M, et al. ESMO 2020. Abstract LBA6.

CheckMate 649: Overall Survival With 36-Month Follow-Up



- Clinically meaningful improvement in OS with NIVO + chemo vs chemo was maintained with longer follow-up in PD-L1 CPS ≥ 5 and all randomized populations

Janjigian YY, et al. *J Clin Oncol*. 2024;42(17):2012-2020.

CheckMate 649: Subgroup Analyses

Population*	Median overall survival, months		Unstratified hazard ratio for death (95% CI)	Interaction test p value
	Nivolumab plus chemotherapy	Chemotherapy alone		
Overall (N=1581)	13·8	11·6	0·79 (0·70–0·89)	
PD-L1 CPS <1 (n=265)	13·1	12·5	0·92 (0·70–1·23)	
PD-L1 CPS ≥1 (n=1296)	14·0	11·3	0·76 (0·67–0·87)	0·2041
PD-L1 CPS <5 (n=606)	12·4	12·3	0·94 (0·78–1·13)	
PD-L1 CPS ≥5 (n=955)	14·4	11·1	0·70 (0·60–0·81)	0·0107†

Overall Survival

Population‡§	Objective response rate, %		Unweighted objective response rate difference,‖ % (95% CI)
	Nivolumab plus chemotherapy	Chemotherapy alone	
Overall (N=1211)	58	46	12 (6–17·5)
PD-L1 CPS <1 (n=178)	51	41	9 (–5 to 23)
PD-L1 CPS ≥1 (n=1019)	60	46	13 (7–19)
PD-L1 CPS <5 (n=428)	55	46	9 (–0·6 to 18)
PD-L1 CPS ≥5 (n=769)	60	45	15 (7·5–21)

Objective Response Rate

NCCN category 1 recommendation:
Nivolumab should be reserved for those with PD-L1 CPS ≥ 5 tumors

Janjigian YY, et al. *Lancet*. 2021;398(10294):27-40. Moehler M, et al. ESMO 2020. Abstract LBA6.

CheckMate 649: Safety Summary

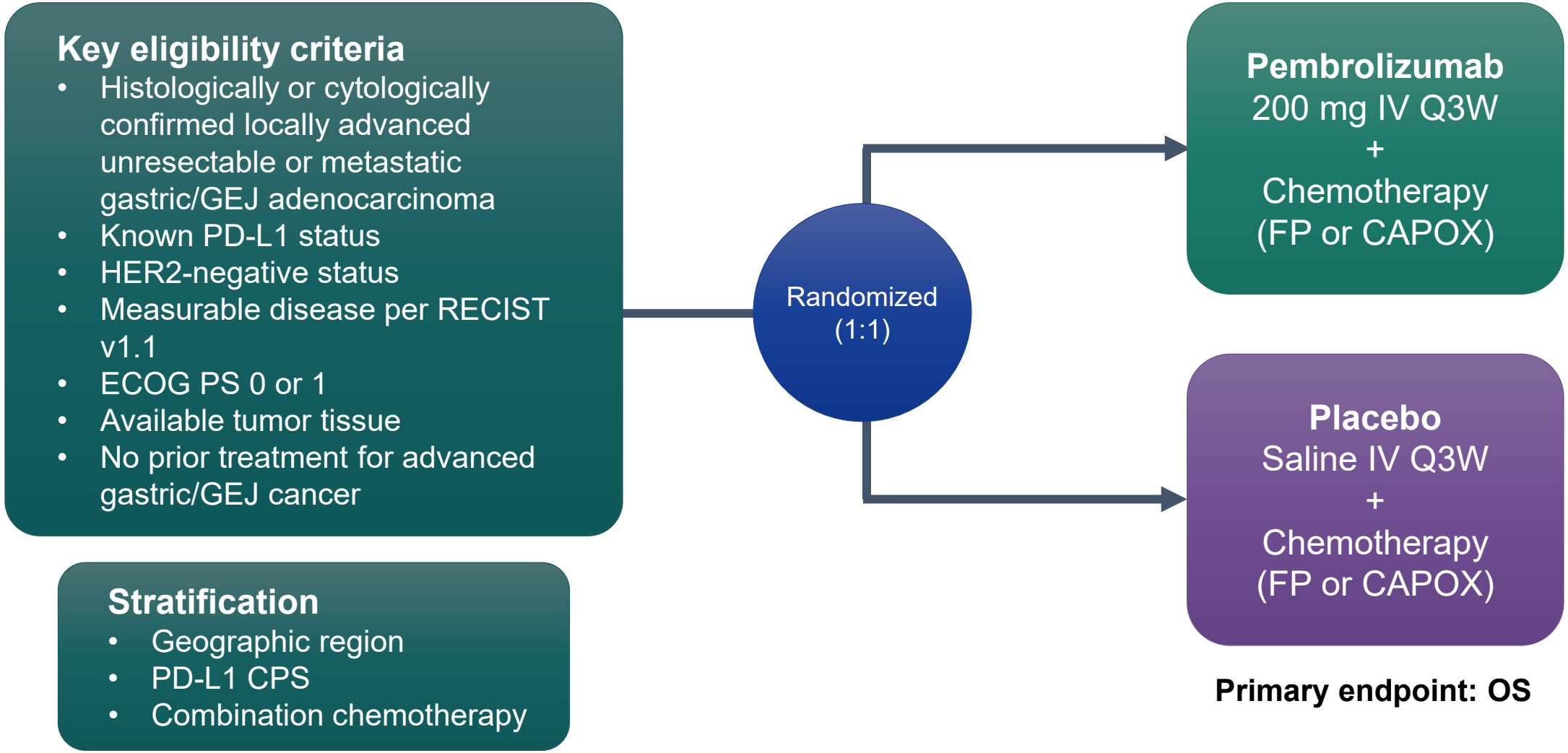
Adverse Event, n (%)	Nivo + CT (n = 782)		CT (n = 767)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any TRAE	739 (95)	473 (60)	682 (89)	346 (45)
Serious TRAE	176 (23)	134 (17)	95 (12)	78 (10)
TRAEs leading to d/c	331 (42)	147 (19)	198 (26)	73 (10)
Treatment-related deaths	16 (2)*		4 (<1)†	
Potential immunologic TRAE				
▪ Endocrine	109 (14)	6 (< 1)	3 (<1)	0
▪ GI	265 (34)	43 (5)	208 (27)	25 (3)
▪ Hepatic	211 (27)	32 (4)	140 (18)	18 (2)
▪ Pulmonary	41 (5)	14 (2)	4 (<1)	1 (<1)
▪ Renal	28 (4)	7 (<1)	9 (1)	2 (<1)
▪ Skin	219 (28)	28 (4)	109 (14)	9 (1)

*Due to pneumonitis (n = 4), febrile neutropenia or neutropenic fever (n = 2), acute cerebral infarction or stroke (n = 2), and disseminated intravascular coagulation, GI bleeding, GI toxicity, infection, intestinal mucositis, mesenteric thrombosis, pneumonia, and septic shock (n = 1 each).
†Due to asthenia and severe hyporexia, diarrhea, pneumonitis, and pulmonary thromboembolism (n = 1 each).

- **Most common grade 3/4 TRAEs:**
  - Nivo + CT: neutropenia (16%), neutrophil count decreased (11%), anemia (6%), increased lipase (6%)
  - CT: neutropenia (13%), neutrophil count decreased (9%), diarrhea (3%), peripheral neuropathy (3%), anemia (3%), vomiting (3%)
- Most TRAEs with potential immunologic etiology emerged within first 6 mo of treatment across all organ categories

Janjigian YY, et al. *J Clin Oncol*. 2024;42(17):2012-2020.

KEYNOTE-859: Phase 3 Study of Pembrolizumab + Chemotherapy in G/GEJ Adenocarcinoma

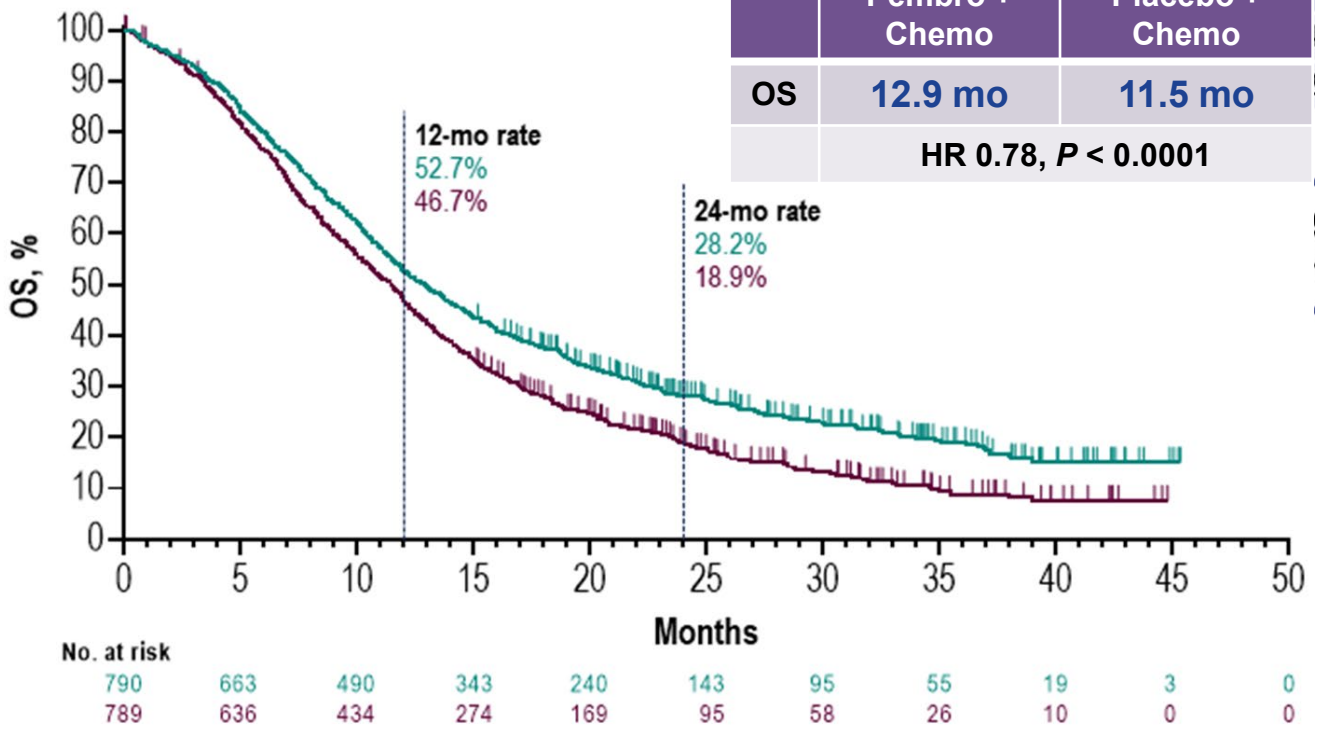


Tabernero J, et al. *Future Oncol*. 2021;17(22):2847-2855.

KEYNOTE-859: Efficacy Outcomes (ITT Population)

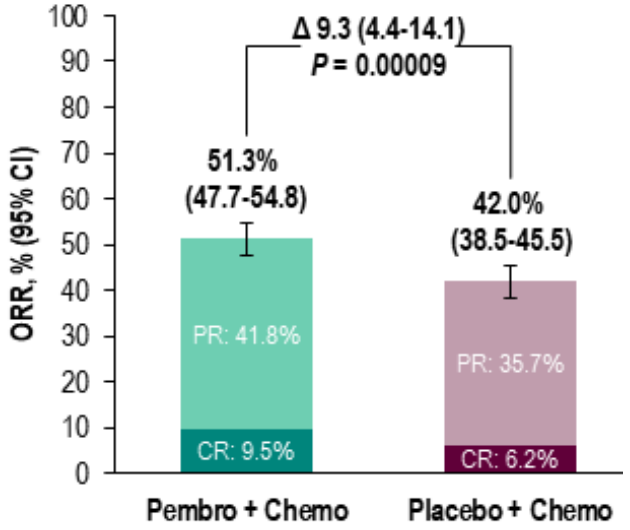
Overall Survival

	Pembro + Chemo	Placebo + Chemo
OS	12.9 mo	11.5 mo
	HR 0.78, *P* < 0.0001	

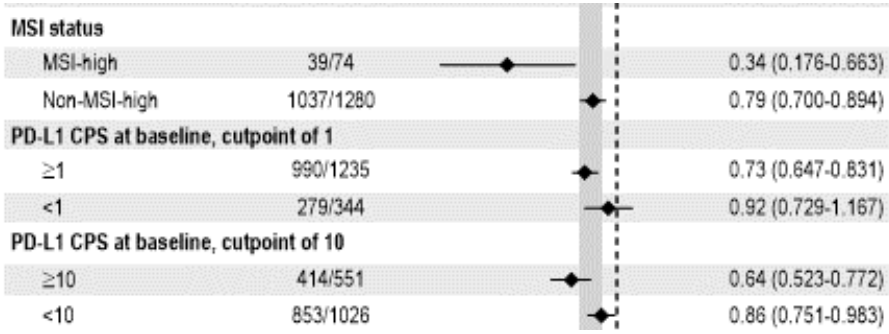


No new safety signals

Overall Response Rate



Overall Survival in Subgroups



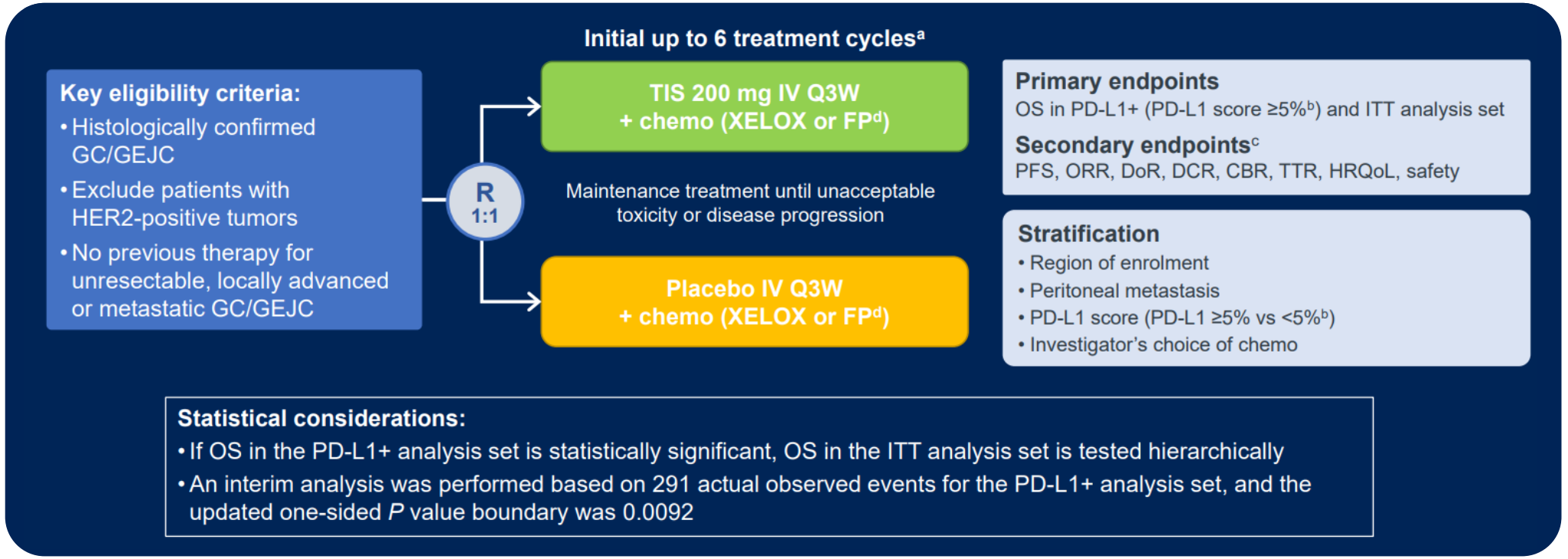
Rha SY, et al. *Lancet Oncol*. 2023;24(11):1181-1195.

RATIONALE-305: Phase 3 Study of Tislelizumab vs Placebo + Chemo in First-Line for Advanced G/GEJ Adenocarcinoma

BeiGene's Biologics License Application for TEVIMBRA® (tislelizumab) for First-Line Gastric or Gastroesophageal Junction Cancers Accepted by FDA

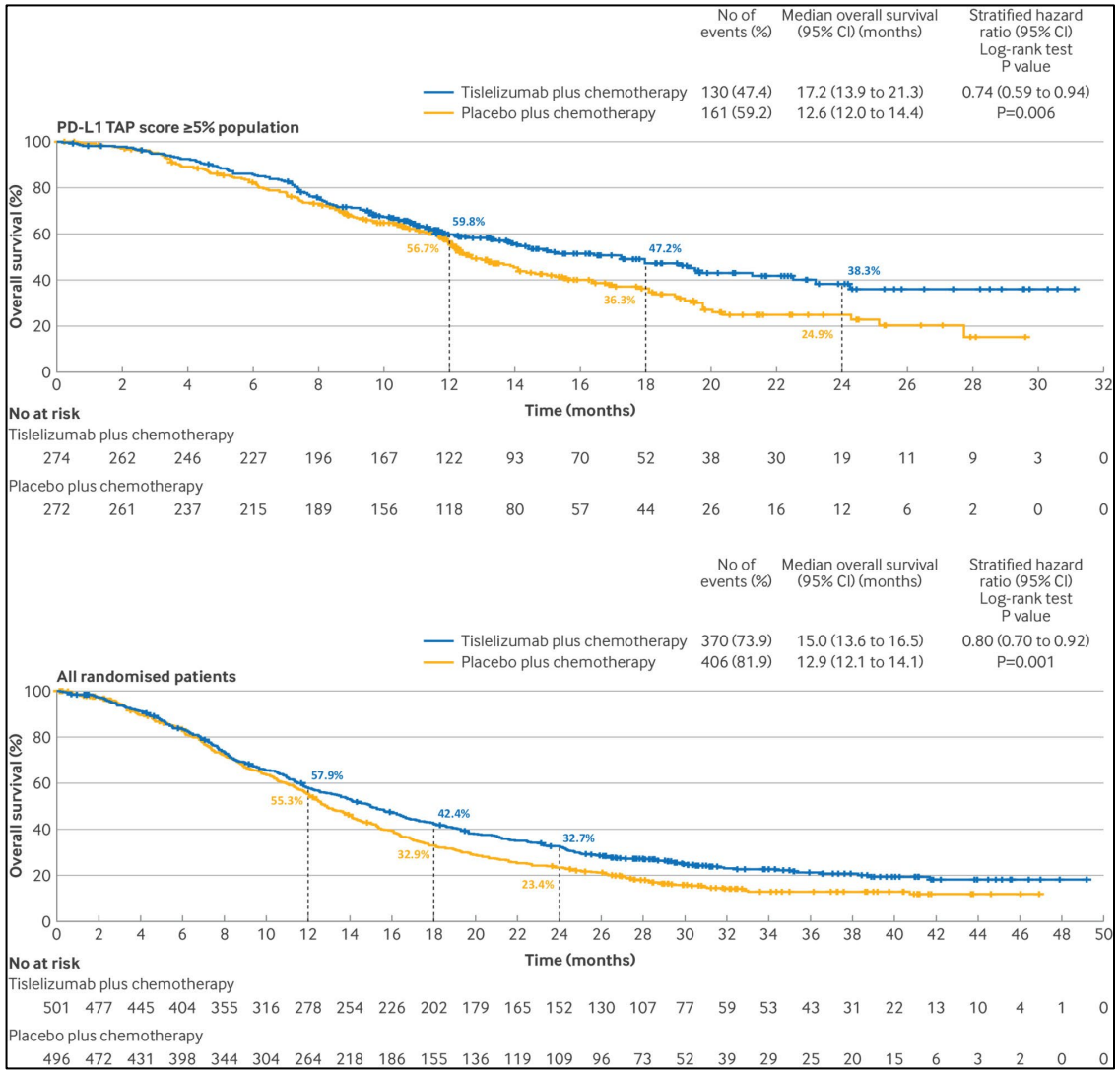
Feb 27, 2024 6:00 AM

Application based on results from global Phase 3 RATIONALE-305 trial demonstrating TEVIMBRA plus chemotherapy significantly improved overall survival in advanced gastric/GEJ cancer



Moehler MH, et al. *J Clin Oncol*. 2023;41(4_suppl):286.

RATIONALE-305: Efficacy Results



	PD-L1 TAP ≥ 5		All randomized patients	
	Chemo + Tisle	Chemo + Placebo	Chemo + Tisle	Chemo + Placebo
OS (mo)	17.2	12.6	15.0	12.9
	HR 0.74		HR 0.80	
PFS (mo)	7.2	5.9	6.9	6.2
	HR 0.67		HR 0.78	
Confirmed ORR (%)	50	43	47	41
DCR (%)	88	83	87	83
Median DOR (mo)	9.0	7.1	8.6	7.2

Qiu MZ, et al. *BMJ*. 2024;385:e078876.

Rationale-305: Safety Summary

Table 2 | Treatment related adverse events with an incidence ≥10% by preferred term and worst grade (safety population). Values are number (percentage) of patients by worst grade of event

	Tislelizumab plus chemotherapy (n=498)				Placebo plus chemotherapy (n=494)			
Adverse events	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1-2**	**Grade 3**	**Grade 4**	**Grade 5**
Any event	215 (43)	231 (46)	26 (5)	11 (2)	230 (47)	217 (44)	25 (5)	4 (<1)
Nausea	224 (45)	13 (3)	0 (0)	0 (0)	223 (45)	9 (2)	0 (0)	0 (0)
Decreased appetite	168 (34)	14 (3)	0 (0)	0 (0)	169 (34)	16 (3)	0 (0)	0 (0)
Decreased platelet count	118 (24)	41 (8)	15 (3)	0 (0)	126 (26)	46 (9)	11 (2)	0 (0)
Decreased neutrophil count	109 (22)	54 (11)	5 (1)	0 (0)	103 (21)	53 (11)	4 (<1)	0 (0)
Vomiting	150 (30)	11 (2)	0 (0)	0 (0)	150 (30)	12 (2)	0 (0)	0 (0)
Anaemia	133 (27)	25 (5)	0 (0)	0 (0)	126 (26)	35 (7)	2 (<1)	0 (0)
Increased aspartate aminotransferase	132 (27)	12 (2)	1 (<1)	0 (0)	133 (27)	4 (<1)	0 (0)	0 (0)
Decreased white blood cell count	104 (21)	14 (3)	1 (<1)	0 (0)	126 (26)	8 (2)	0 (0)	0 (0)
Increased alanine aminotransferase	105 (21)	8 (2)	0 (0)	0 (0)	93 (19)	4 (<1)	0 (0)	0 (0)
Diarrhoea	99 (20)	12 (2)	0 (0)	0 (0)	115 (23)	11 (2)	0 (0)	0 (0)
Peripheral sensory neuropathy	105 (21)	1 (<1)	0 (0)	0 (0)	113 (23)	3 (<1)	0 (0)	0 (0)
Palmar-plantar erythrodysaesthesia syndrome	80 (16)	15 (3)	0 (0)	0 (0)	83 (17)	10 (2)	0 (0)	0 (0)
Asthenia	66 (13)	10 (2)	0 (0)	0 (0)	64 (13)	7 (1)	0 (0)	0 (0)
Fatigue	66 (13)	9 (2)	0 (0)	0 (0)	55 (11)	6 (1)	0 (0)	0 (0)
Neutropenia	41 (8)	32 (6)	1 (<1)	0 (0)	46 (9)	32 (7)	2 (<1)	0 (0)
Hypoaesthesia	68 (14)	1 (<1)	0 (0)	0 (0)	67 (14)	0 (0)	0 (0)	0 (0)
Increased blood bilirubin	54 (11)	6 (1)	1 (<1)	0 (0)	55 (11)	3 (<1)	0 (0)	0 (0)
Thrombocytopenia	45 (9)	14 (3)	1 (<1)	0 (0)	42 (9)	12 (2)	2 (<1)	0 (0)
Decreased weight	58 (12)	0 (0)	0 (0)	0 (0)	53 (11)	0 (0)	0 (0)	0 (0)
Hypothyroidism	54 (11)	1 (<1)	0 (0)	0 (0)	12 (2)	0 (0)	0 (0)	0 (0)

Data cut-off was 28 February 2023.
Data are shown for all grade incidence of ≥10% in either treatment arm (see also supplementary appendix table S11).
Treatment related adverse events are sorted by decreasing frequency for all grade events in the tislelizumab plus chemotherapy arm. Patients with two or more adverse events in the same preferred term are counted only once for that preferred term. Adverse events were graded based on National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 and coded using Medical Dictionary for Regulatory Activities version 24.0.

No unexpected safety signals; similar safety profile to other anti-PD-1 and chemotherapy combinations in this patient population

Qiu MZ, et al. *BMJ*. 2024;385:e078876.

Key Takeaways

- All advanced gastroesophageal adenocarcinomas should be tested for PD-L1 expression
- Chemotherapy with anti-PD-1 agents is standard first-line treatment for patients with PD-L1-positive tumors
- Pembrolizumab and nivolumab are approved
- Tislelizumab is under review at the FDA
- Similar efficacy trends across anti-PD-1 agents, with limited activity observed in patients with PD-L1 CPS <1 tumors
- No concerning safety signals when anti-PD-1 agents are added to chemotherapy

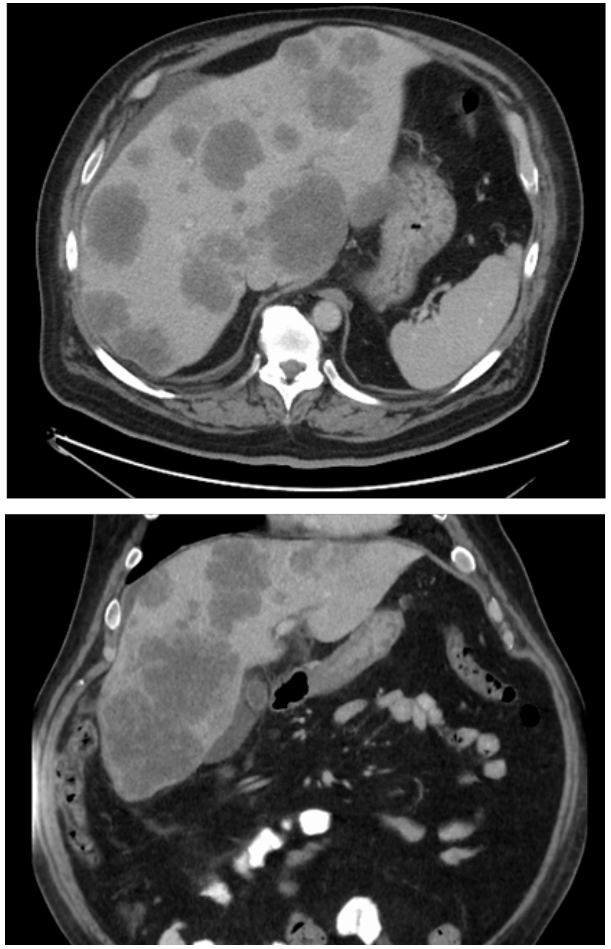
HER2-Positive Gastric/Gastroesophageal Junction Cancers

HER2+ Gastroesophageal Adenocarcinomas

- 15%-20% of gastroesophageal adenocarcinomas (GEA) are HER2+
- HER2 testing is indicated for locally advanced and inoperable, recurrent, or metastatic tumors
- No data to support targeting this pathway in early-stage disease
- In advanced disease, HER2 expression can change over time
- Concurrent alterations in other signaling cascades and changes in HER2 expression can affect therapeutic options

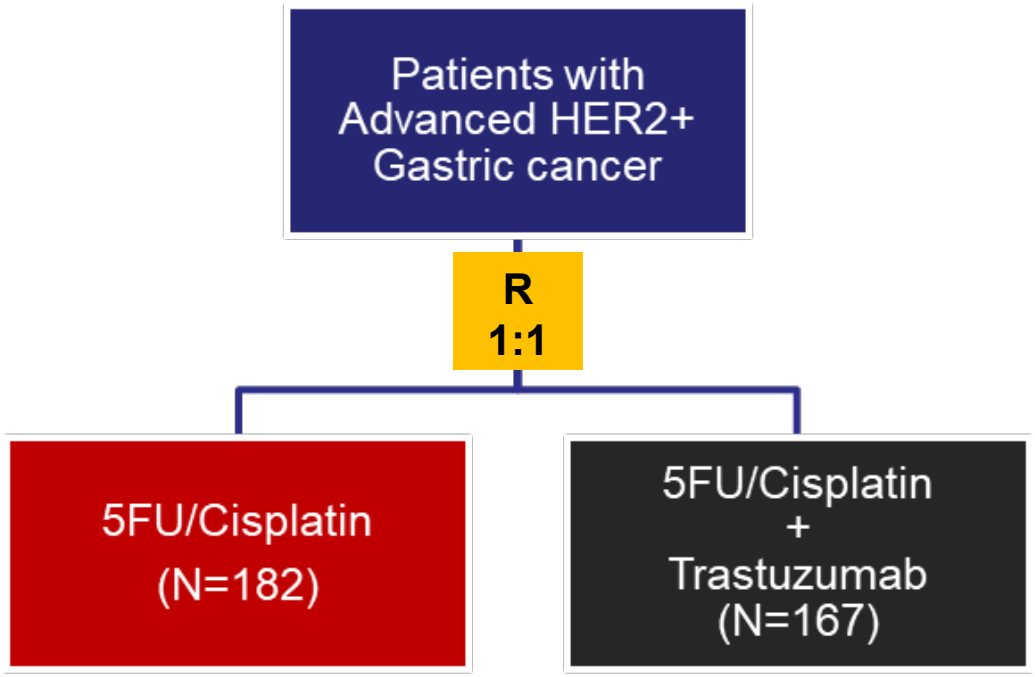
HER2+ GEA Case Presentation

- **PRESENTATION**: 69-year-old man presented with a 3-month history of progressive dysphagia
- **EGD**: Partially obstructing, malignant esophageal tumor was found in the GEJ extending to gastric cardia
- **PATHOLOGY**: Invasive adenocarcinoma, with moderately differentiated features
- No loss of nuclear expression of MMR proteins; PD-L1 CPS 5%, HER2 IHC 3+
- **IMAGING**: Multiple liver lesions and enlarged retroperitoneal lymph nodes consistent with metastatic disease

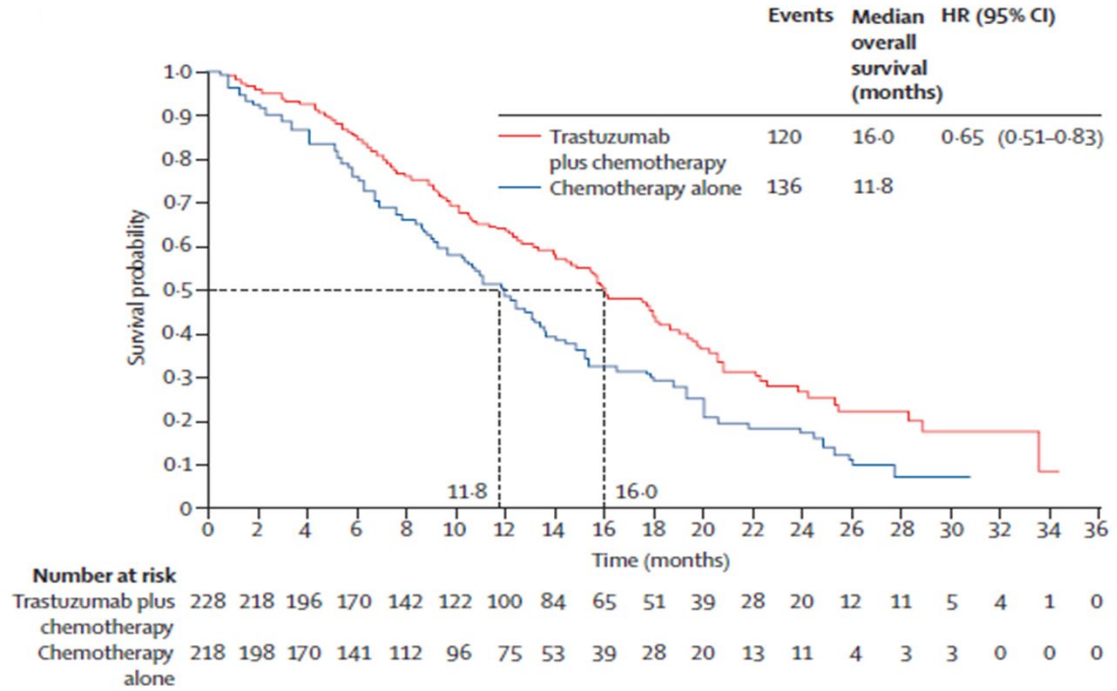


ToGA Trial: Trastuzumab in First Line

ToGA Trial Design



HER2 IHC 3+ or IHC 2+/FISH+



Bang YJ, et al. *Lancet*. 2010;376(9742):687-697.

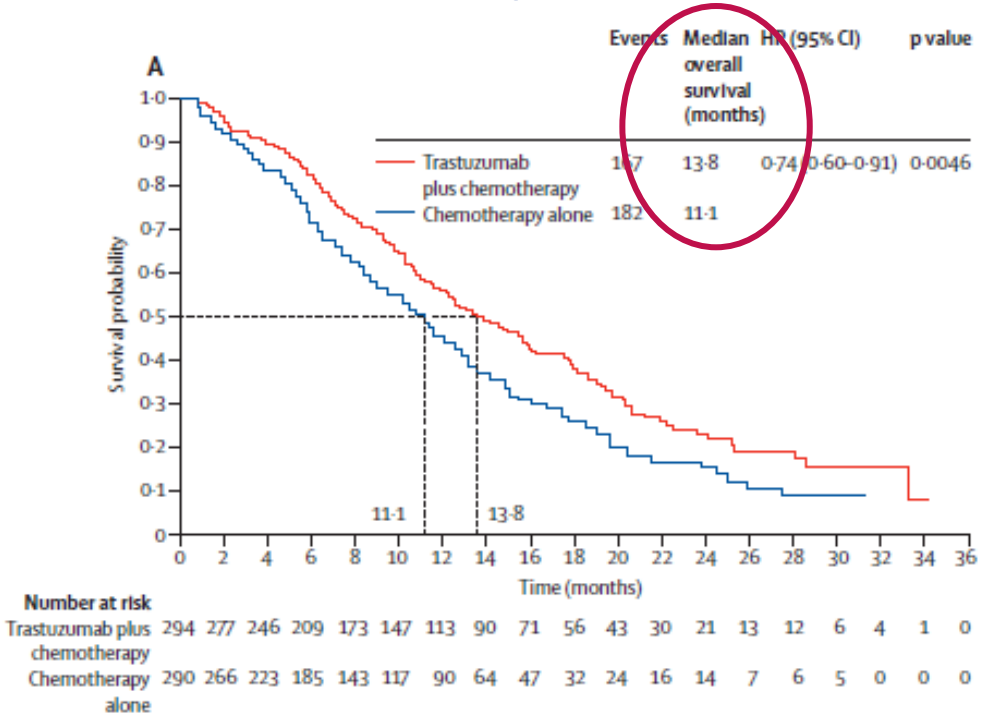
Efforts to Target HER2 in Upper GI Cancers

	Study	N	Treatment Arms	OS (mo)	HR p	
1st Line	TOGA[1]	584	5FU/cis 5FU/cis + Trastuzumab	11.1 13.8	HR 0.74 p < 0.001	✓
	LOGIC[2]	545	XELOX XELOX + Lapatinib	10.5 12.2	HR = 0.91 p = 0.34	⊘
	JACOB[3]	780	5FU/cis + trastuzumab 5FU/cis + trastuzumab + pertuzumab	14.2 17.5	HR = 0.84 p = 0.0565	⊘
2nd Line	TyTAN[4]	261	Paclitaxel Paclitaxel + lapatinib	8.9 11.0	HR = 0.54 p = 0.21	⊘
	GATSBY[5]	415	T-DM1 Taxane	7.9 8.6	HR = 1.14 p =0.31	⊘
	T-ACT[6] (Phase 2)	91	Paclitaxel Paclitaxel + Trastuzumab	9.95 10.20	HR = 1.23 p = 0.199	⊘

1. Bang YJ, et al. *Lancet*. 2010;376(9742):687-697. 2. Hecht JR, et al. *J Clin Oncol*. 2016;34(5):443-451.
3. Tabernero J, et al. *Gastric Cancer*. 2023;26(1):123-131. 4. Satoh T, et al. *J Clin Oncol*. 2014;32(19):2039-2049.
5. Shah MA, et al. *Gastric Cancer*. 2019;22(4):803-816. 6. Makiyama A, et al. *J Clin Oncol*. 2020;38(17):1919-1927.

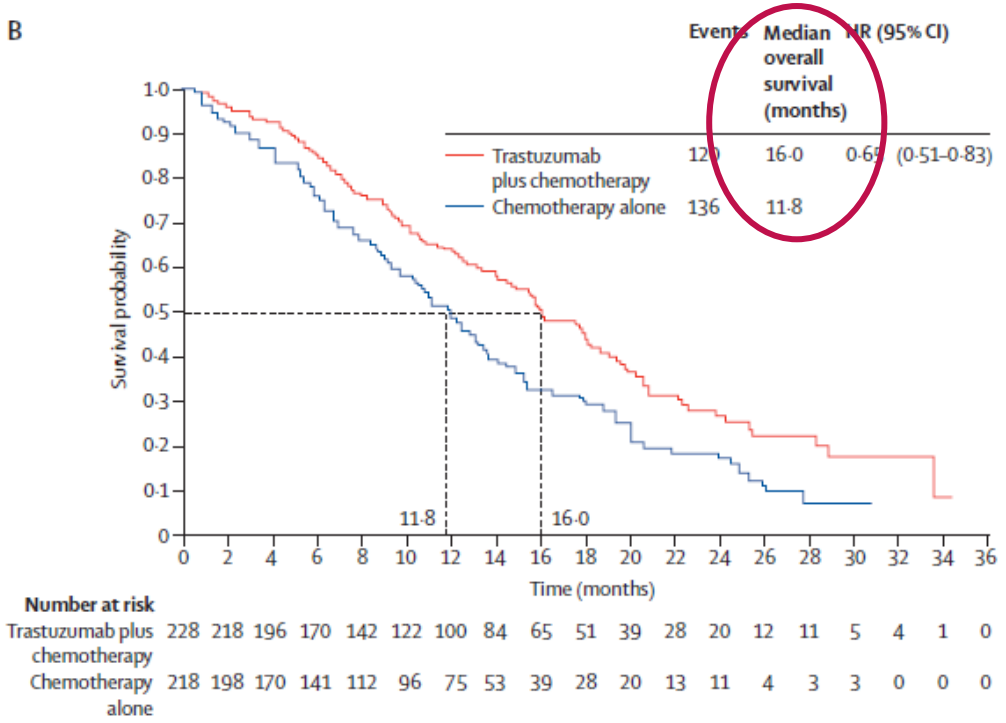
Lesson From ToGA Trial: Biomarker Selection Matters

ITT subjects



* Included patients with FISH+/IHC 0 and FISH+/IHC 1+ tumors

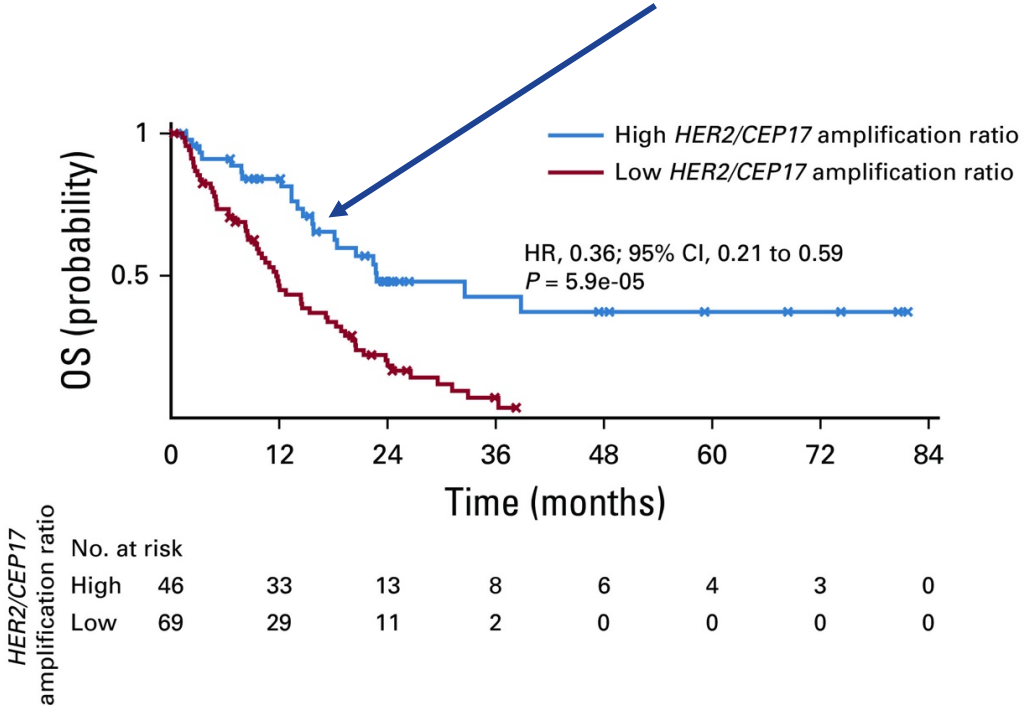
IHC 3+ or IHC 2+/FISH+

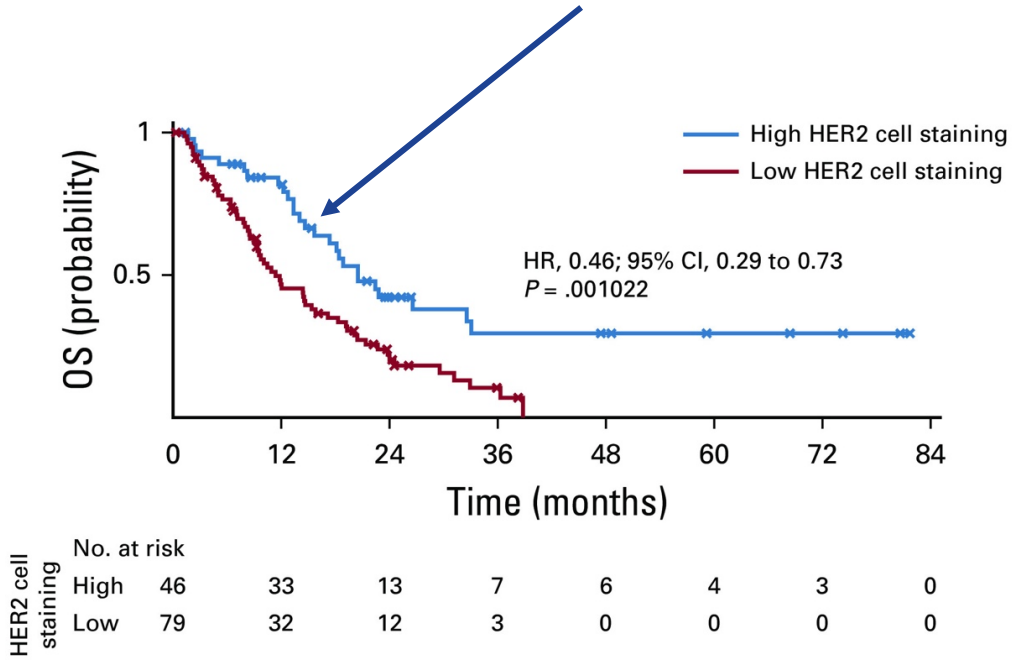


Bang YJ, et al. *Lancet*. 2010;376(9742):687-697.

Level of HER2 Expression and Amplification Matters

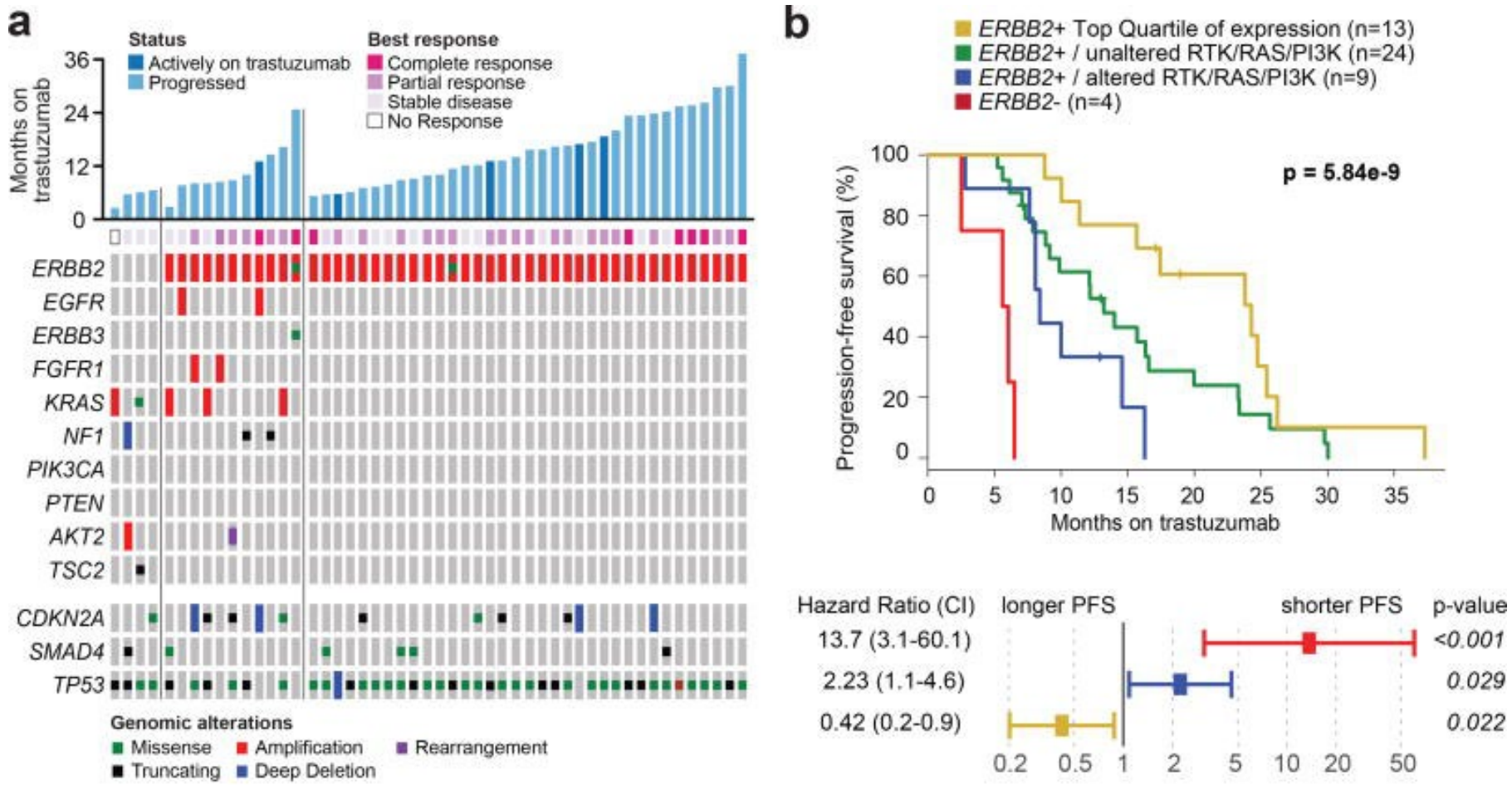
Higher OS probability with higher amplification ratio and higher HER2 cell staining





Haffner I, et al. *J Clin Oncol*. 2021;39(13):1468-1478.

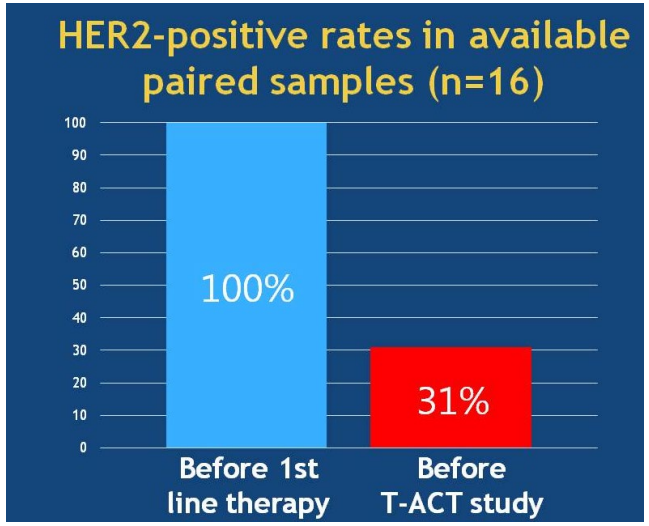
Genomic Biomarkers and Anti-HER2 Efficacy: Concurrent Alterations Matter



Janjigian YY, et al. *Cancer Discov*. 2018;8(1):49-58.

HER2 Expression Can Change Over Time: Repeat Testing Needed

T-ACT Trial



Before 1st line therapy			Before T-ACT trial		
HER2 status	IHC	FISH	HER2 status	IHC	FISH
+	3	-	+	3	+
+	3	-	+	3	+
+	3	-	+	3	+
+	3	-	+	2	+
+	3	-	+	2	+
+	3	-	-	1	+
+	3	-	-	1	-
+	3	-	-	1	+
+	3	-	-	1	-
+	2	+	-	1	+
+	3	-	-	0	-
+	3	-	-	0	-
+	3	-	-	0	-
+	3	-	-	0	-
+	2	+	-	0	-
+	2	+	-	0	-

Definition of HER2 positive: IHC3+ or IHC2+ with FISH positive

GASTHER3 Study

14/43 patients with loss of HER2 expression after trastuzumab

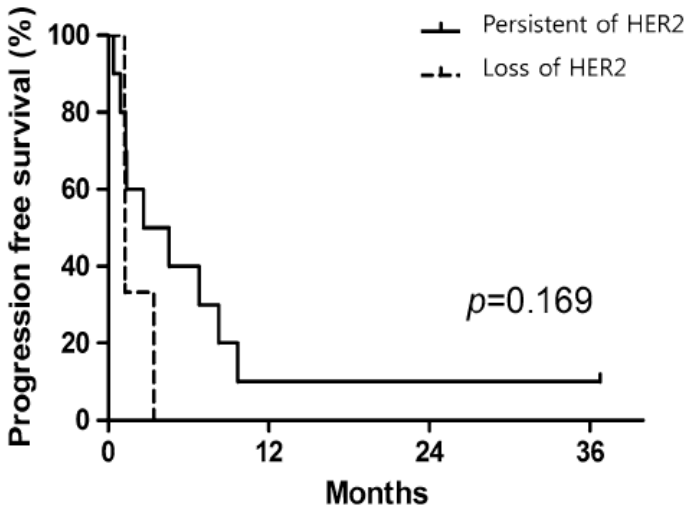


Fig. 3 Impact of HER2 status changes on progression-free survival in patients treated with second-line T-DM1 therapy

HER2 Post Trastuzumab

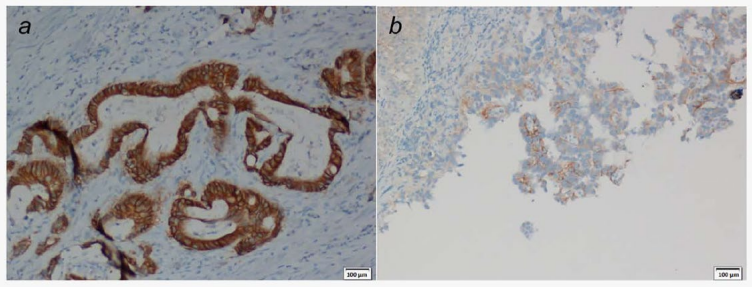
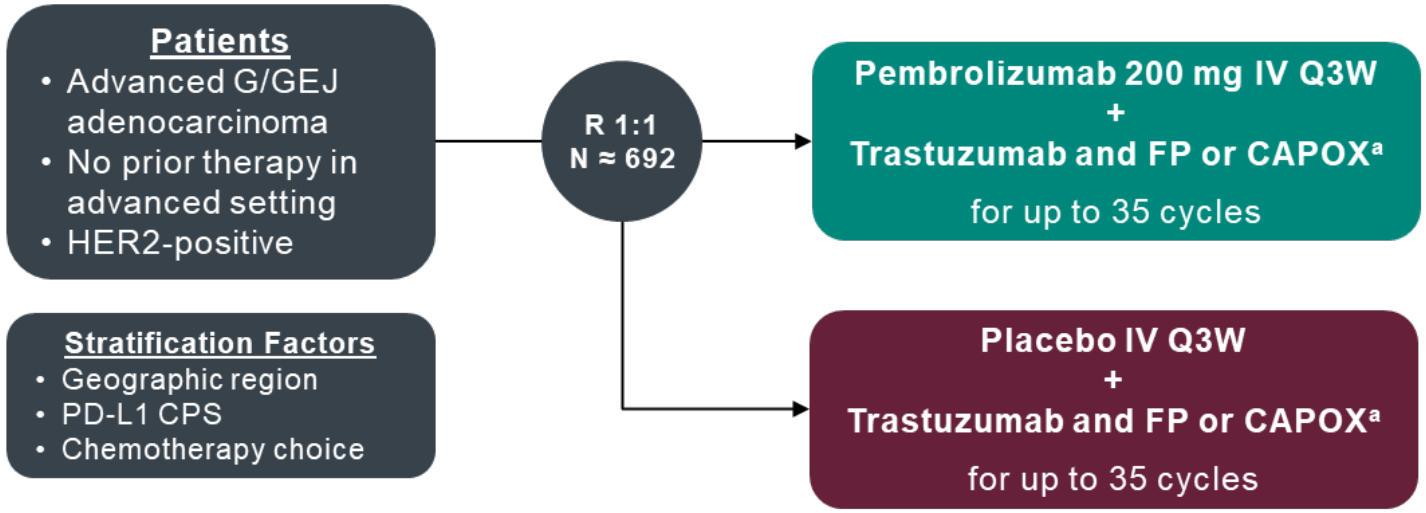


Table 2. Change in HER2 status after trastuzumab-based chemotherapy

Pretreatment tumor HER2 status ($N = 22$)			Post–treatment tumor HER2 status ($N = 22$)		
	N	%		*N*	%
Positive	22	100	Positive	13	59
			Negative	6	27
			Not assessable	3	14
Overexpressed	22	100	Overexpressed	15	68
			Loss of HER2 overexpression	7	32

Sukawa Y, et al. *J Clin Oncol*. 2018;36(15_suppl):4029. Seo S, et al. *Gastric Cancer*. 2019;22(3):527-535.
Pietrantonio et al, *Int J Cancer*. 2016;139(12):2859-2864.

Pembrolizumab for HER2+ GEA in First Line: KEYNOTE-811 Study Design



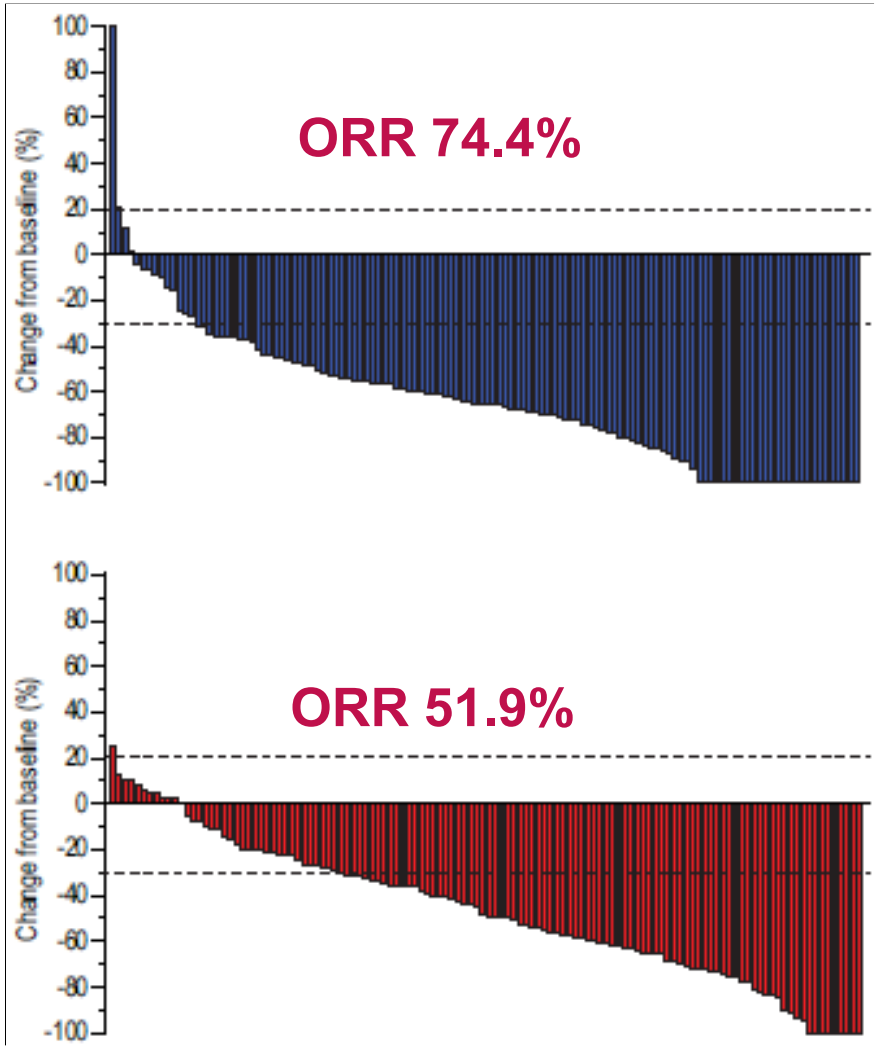
Dual Primary End Points
- OS
- PFS (RECIST v1.1 per BICR)

Secondary End Points
- ORR (RECIST v1.1 per BICR)
- DOR (RECIST v1.1 per BICR)
- Safety

[a]Trastuzumab dose: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP dose: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX dose: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100).

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

KEYNOTE-811: First Interim Analysis Results



	Pembro (N = 133)	Placebo (N = 131)
ORR	74.4%	51.9% *P* = 0.00006
CR	11%	4%
DCR	96.2%	89.3%
DOR	10.6 mo	9.5 mo

5/5/2021: pembrolizumab received accelerated FDA approval in this setting

Does PD-L1 expression matter?

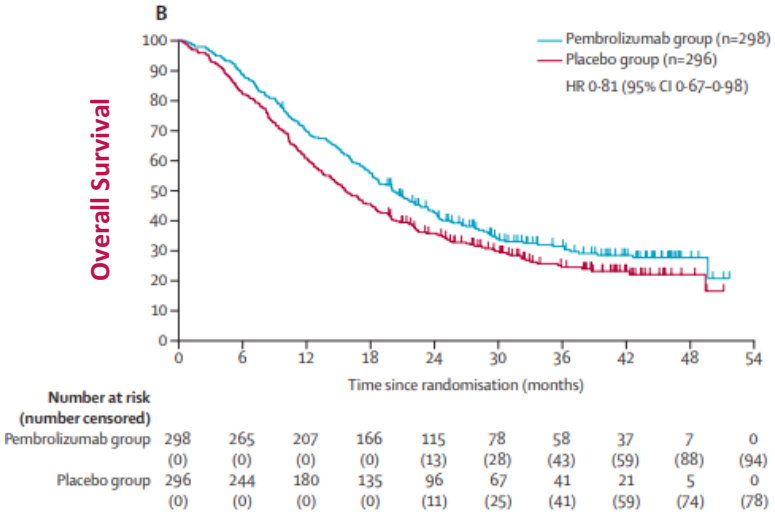
Janjigian YY, et al. *Nature*. 2021;600(7890):727-730.

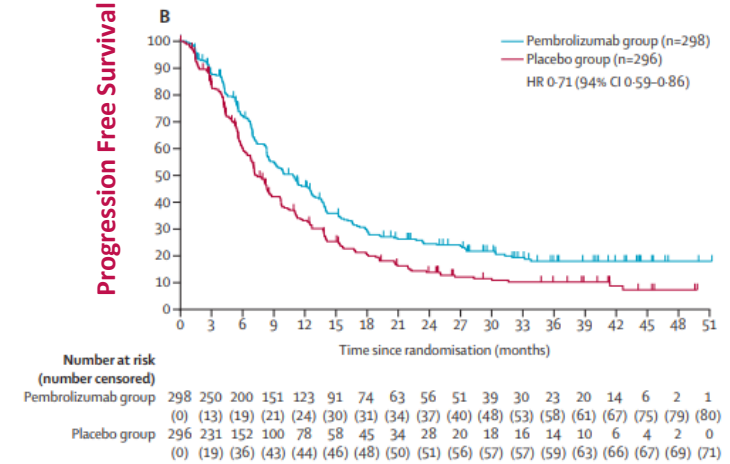
Updated Efficacy Results: Third Interim Analysis

- Median follow-up time: 38.4 mo
- 85% of patients w/ PD-L1 CPS ≥ 1 tumors
- 39% of patients in the pembrolizumab group and 47% in the placebo group received second-line treatment
- **FDA restriction to PD-L1 CPS ≥ 1 tumors**

	Pembrolizumab	Placebo	
OS (all)	20 mo	16.8 mo	HR 0.84
OS (PD-L1 CPS ≥ 1)	20 mo	15.7 mo	HR 0.81
PFS	10 mo	8.1 mo	
ORR	72.6%	60.1%	
DOR	11.3 mo	9.5 mo	

Patients with PD-L1 CPS ≥ 1 tumors





Janjigian YY, et al. *Lancet.* 2023;402(10418):2197-2208.

KEYNOTE-811: Safety Profile

	Pembrolizumab group (N=350)		Placebo group (N=346)	
	Any	Grade ≥3	Any	Grade ≥3
Any adverse event	347 (99%)	248 (71%)	346 (100%)	225 (65%)
Any treatment-related adverse event*	341 (97%)	204 (58%)	334 (97%)	176 (51%)
Serious	88 (25%)	76 (22%)	79 (23%)	66 (19%)
Led to death	4 (1%)	4 (1%)	3 (1%)	3 (1%)
Led to discontinuation of any drug	124 (35%)	59 (17%)	108 (31%)	44 (13%)
Any adverse event of interest†	132 (38%)	36 (10%)	83 (24%)	12 (3%)

(Table 2 continues on next page)

No new **unexpected** safety signals

In the experimental group, the most common treatment-related AEs were:

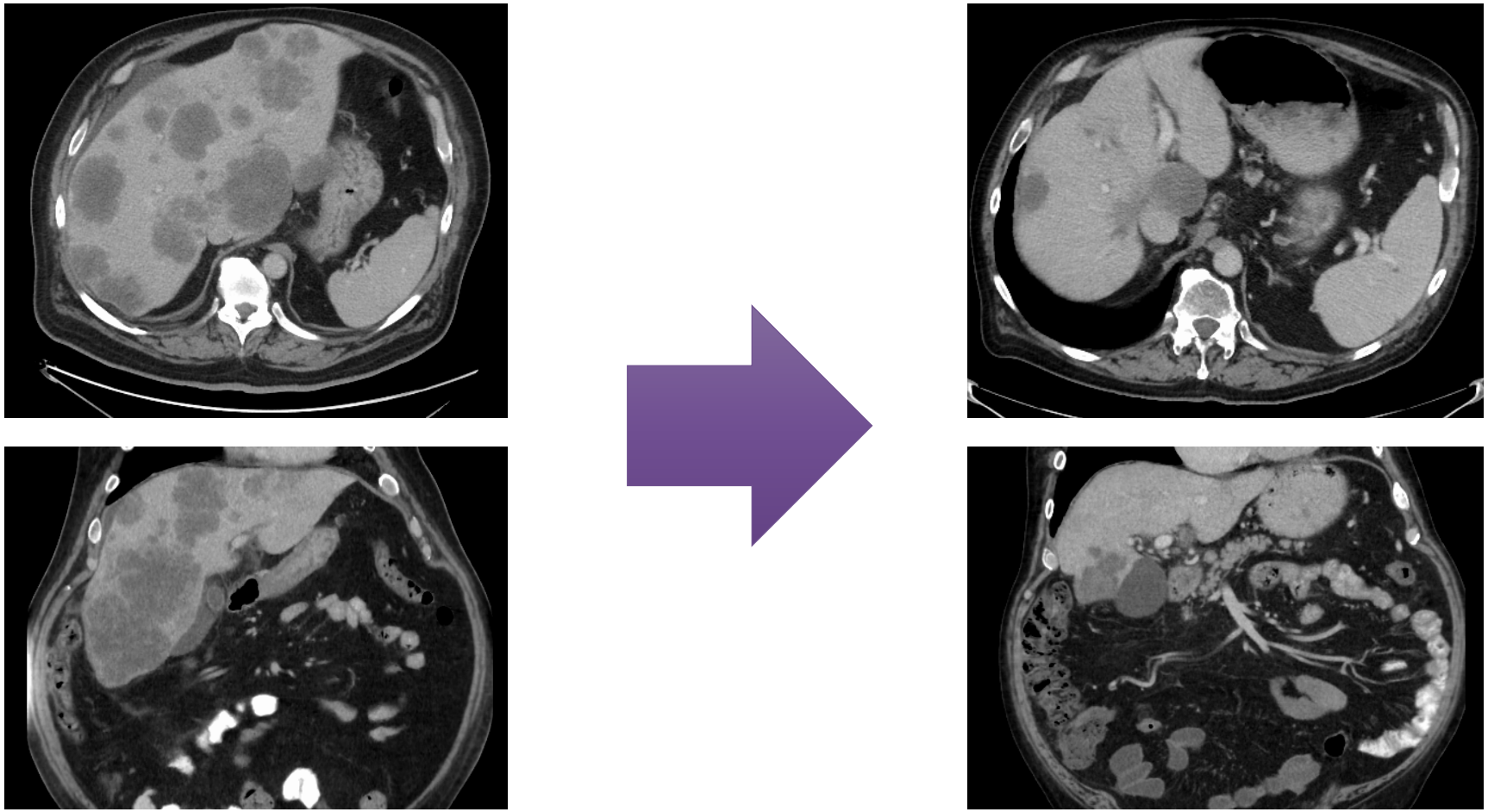
- Infusion reactions
- Hypothyroidism
- Pneumonitis
- Colitis

Grade ≥ 3 immune-mediated adverse events occurred in 36 (10%) patients in the pembrolizumab group.

On May 1, 2024, Merck announced that KEYNOTE-811 met the dual primary endpoint of overall survival.

Janjigian YY, et al. *Lancet.* 2023;402(10418):2197-2208.

After 6 Months of FOLFOX/Trastuz/ Pembrolizumab



HER2+ Gastroesophageal Adenocarcinoma Key Takeaways

- All advanced HER2+ gastroesophageal adenocarcinomas should be treated with trastuzumab-containing regimens in the first-line setting
- Pembrolizumab should be added if tumors also have PD-L1 CPS ≥ 1
- KEYNOTE-811 regimen produces significant response rates and OS benefits with no unexpected safety signals

Novel Biomarker-Based Therapies

Zanidatamab: Bispecific HER2-Directed Ab

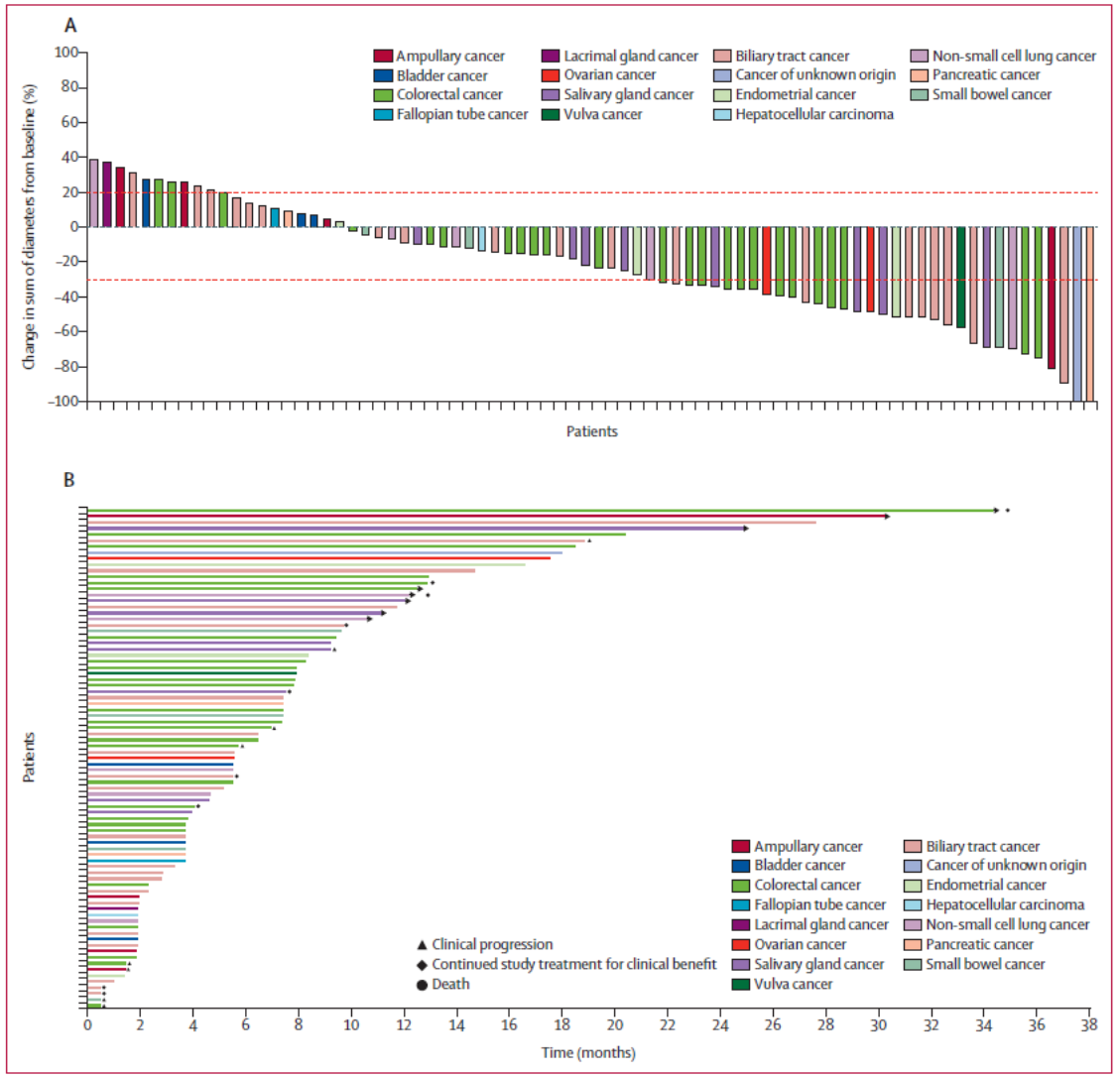
Simultaneously binds two HER2 epitopes:

- ECD4 – trastuzumab binding domain
- ECD2 – pertuzumab binding domain

Multiple mechanisms of action:

- Improved binding, clustering & receptor internalization
- Inhibition of ligand-dependent & independent proliferation
- Potent activation of ADCC

Single-Agent Activity Across Tumor Types



Meric-Bernstam F, et al. *Lancet Oncol*. 2022;23(12):1558-1570.

Phase 2 Study of Zanidatamab + Chemo in First Line for HER2+ GEA

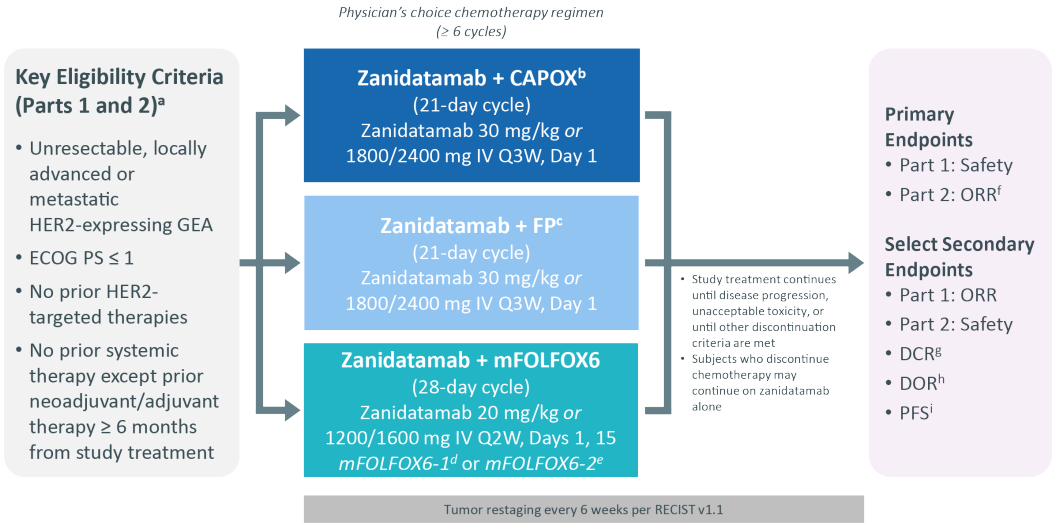
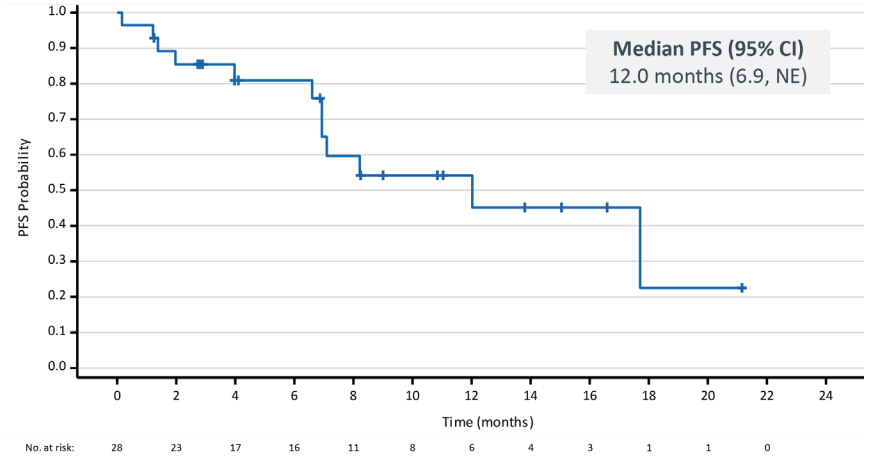
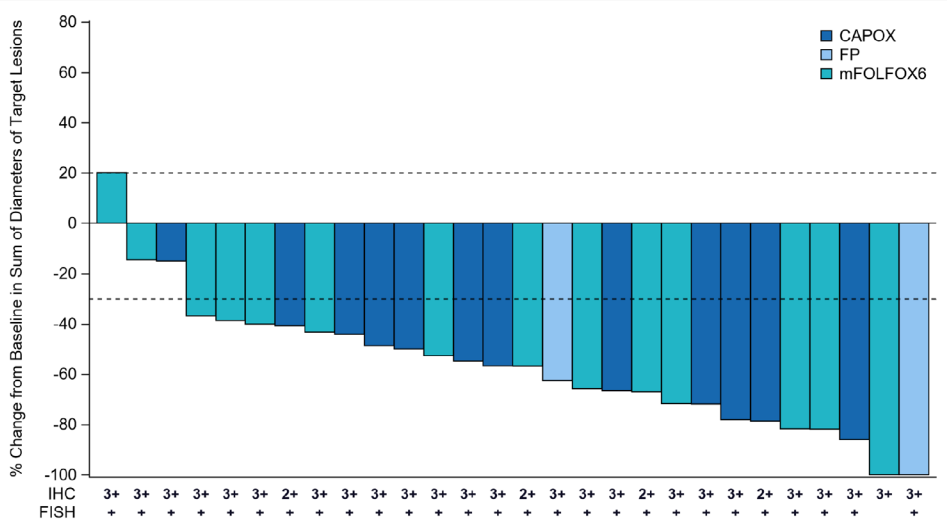


Figure 5: Progression-free Survival



NE = not estimable; PFS = progression-free survival.

Figure 3: Change in Target Lesion Size



HER2-positive subjects[a]	Zanidatamab + CAPOX (n = 12)	Zanidatamab + FP (n = 2)	Zanidatamab + mFOLFOX6 (n = 14)	Total (N = 28)
cORR,[b] % (95% CI)	92 (61.5, 99.8)	100 (15.8, 100)	57 (28.9, 82.3)	75 (55.1, 89.3)
CR, n (%)	0	0	1 (7)	1 (4)
PR, n (%)	11 (92)	2 (100)	7 (50)	20 (71)
SD, n (%)	1 (8)	0	3 (21)	4 (14)
PD, n (%)	0	0	3 (21)	3 (11)
DCR, % (95% CI)	100 (73.5, 100)	100 (15.8, 100)	79 (49.2, 95.3)	89 (71.8, 97.7)
Median DOR (range), months	NR (2.7, 15.2+)	NR (6.8, 12.5+)	16.4 (1.4, 19.8+)	16.4 (1.4, 19.8+)

[a]HER2-positive was defined as IHC 3+ or IHC 2+/FISH+. [b]cORR included a baseline scan and a confirmatory scan obtained ≥ 4 weeks following initial documentation of objective response; the efficacy-evaluable population was defined as all HER2-positive subjects who had ≥ 1 evaluable post-baseline disease assessment or discontinued study treatment due to death or clinical progression. + = indicates that the subject is in response at the time of data extraction.
5-FU = 5-fluorouracil; CAPOX = capecitabine plus oxaliplatin; CR = complete response; DCR = disease control rate; DOR = duration of response; FP = 5-FU and cisplatin; mFOLFOX6 = 5-FU plus oxaliplatin and leucovorin; NR = not reached; ORR = objective response rate (CR + PR); PD = progressive disease; PR = partial response; SD = stable disease.

Ku GY, et al. *Ann Oncol*. 2022;33(suppl_7):S1100.

HERIZON-GEA-01: Phase 3 Study of Zanidatamab & Chemo +/- Tislelizumab in First Treatment of HER2+ mGEA

Key eligibility requirements

- Unresectable, locally advanced or metastatic GEA
- HER2-positive (IHC 3+ or IHC 2+/ISH+) per central testing of new or archival tumor tissue
- No prior therapy in the advanced/metastatic setting
- Prior treatment with HER2-targeted agents or checkpoint inhibitors in adjuvant setting is also not permitted
- Any PD-L1 status

Stratification factors:

- By geographic region, HER2 status, and ECOG performance status

R (1:1:1)

21-day treatment cycles

Arm A: Trastuzumab + chemotherapy (CAPOX or FP)

Arm B: Zanidatamab + chemotherapy (CAPOX or FP)

Arm C: Zanidatamab + chemotherapy (CAPOX or FP) + tislelizumab

Safety and survival follow-up

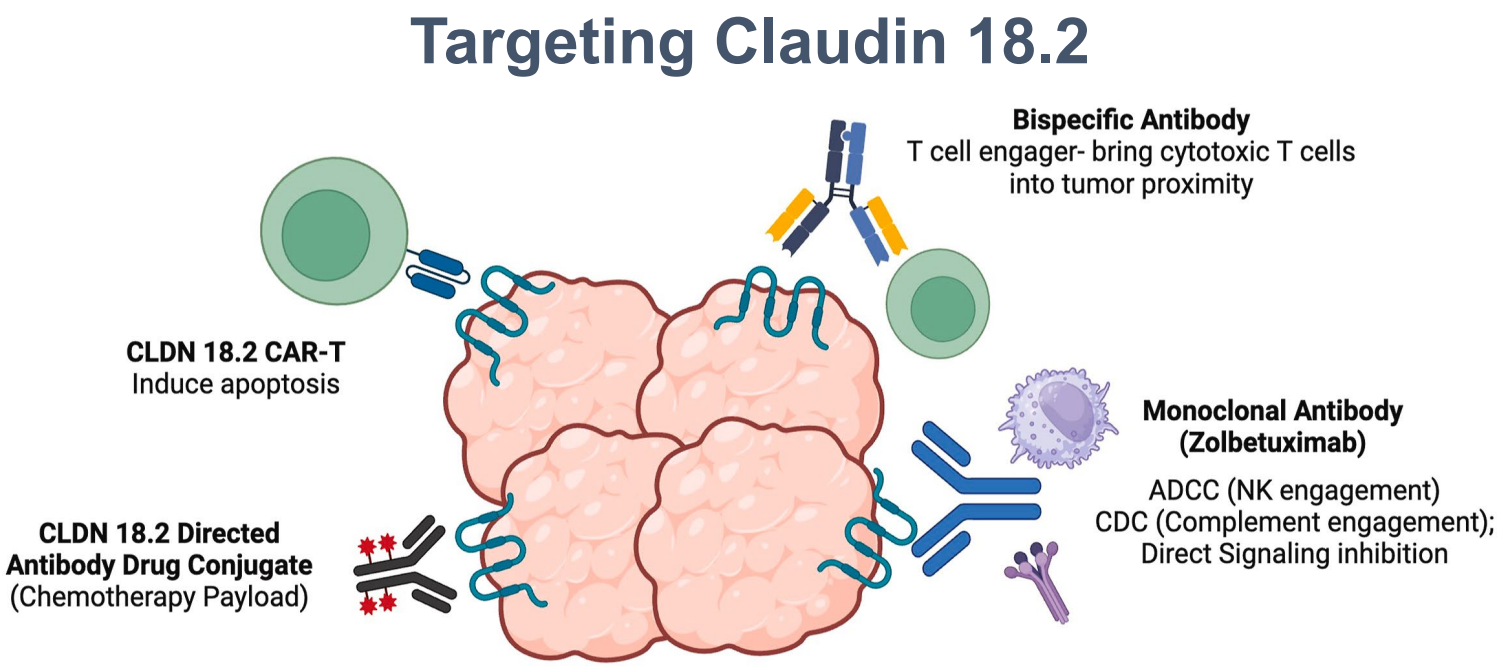
Primary endpoints

- PFS
- OS

Tabernero J, et al. *Future Oncol*. 2022;18(29):3255-3266.

Targeting Claudin 18.2

Zolbetuximab with chemotherapy is now FDA-approved as first-line treatment of CLDN 18.2+/HER2- advanced gastric/GEJ adenocarcinoma.



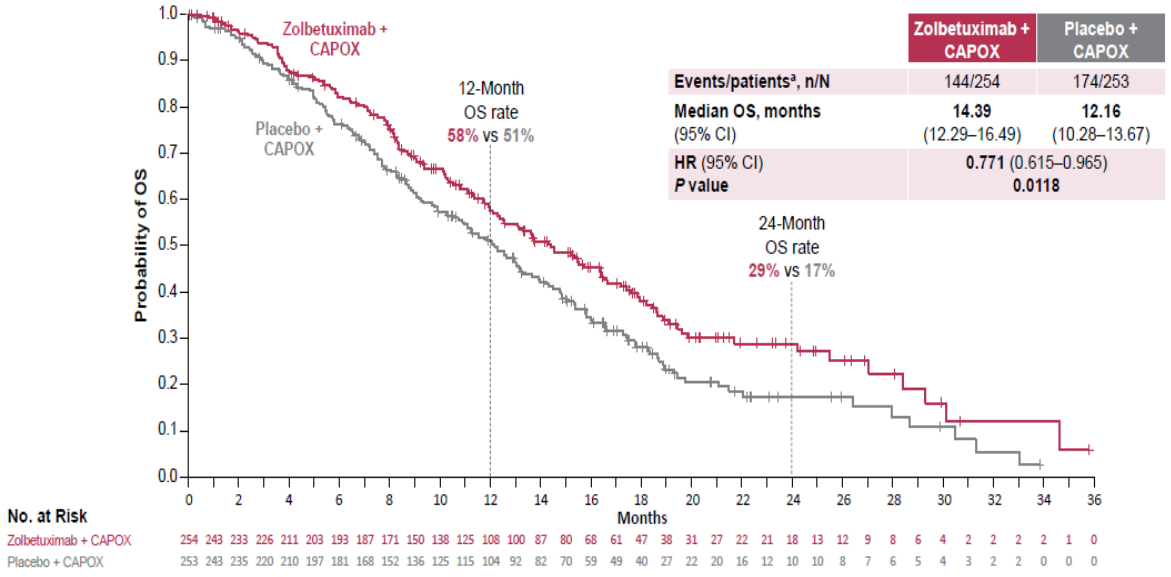
Threshold for claudin 18.2 positivity differs across ongoing studies.

In phase 3 SPOTLIGHT and GLOW studies, CLDN 18.2 positive was defined as **>75% of tumor cells showing moderate to strong membranous CLDN 18.2** staining with IHC using VENTANA 43–14A clone.

Figure adapted from Mehlhaff E, et al. *Hematol Oncol Clin North Am*. 2024;38(3):659-675. Shah MA, et al. *Nat Med*. 2023;29(8):2133-2141. Shitara K, et al. *Lancet*. 2023;401(10389):1655-1668.

Zolbetuximab for Claudin 18.2+ Advanced GEA

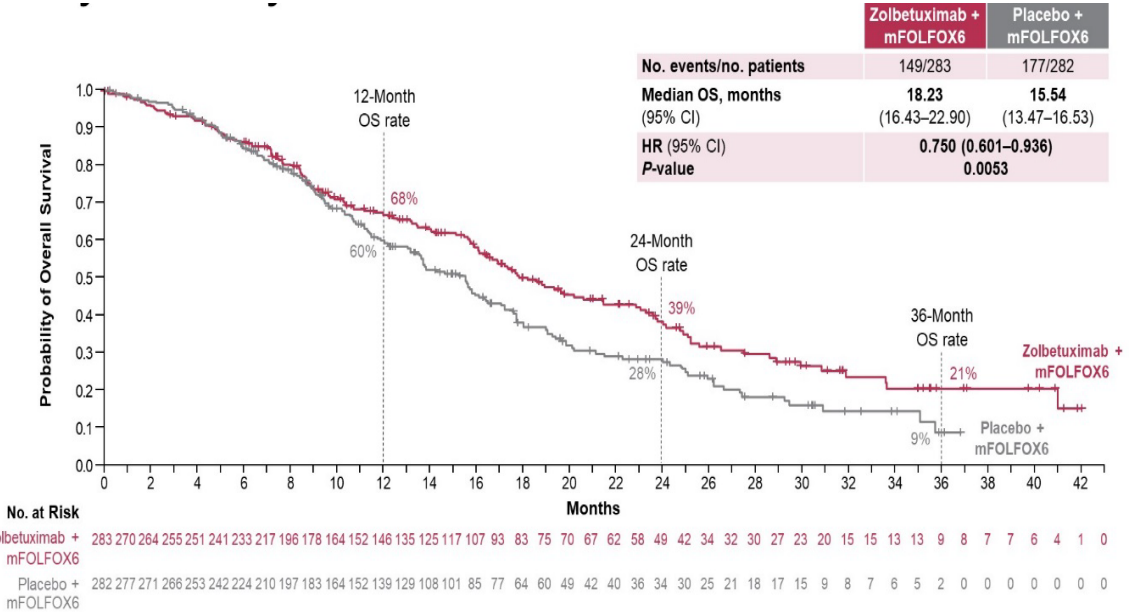
GLOW: Phase 3 Study of Zolbetuximab + CAPOX in 1L Claudin 18.2+ (CLDN 18.2)/HER2- Locally Advanced or Metastatic G/GEJ Adenocarcinoma[1]



	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[a], n/N	144/254	174/253
Median OS, months (95% CI)	14.39 (12.29–16.49)	12.16 (10.28–13.67)
HR (95% CI)	0.771 (0.615–0.965)	
P value	0.0118	

Median PFS 8.21 months vs 6.80 months; HR = 0.687; 95% CI 0.544–0.866; *P* = 0.0007

SPOTLIGHT: Phase 3 Study of Zolbetuximab + mFOLFOX6 in 1L Claudin 18.2+ (CLDN 18.2)/HER2- Locally Advanced or Metastatic G/GEJ Adenocarcinoma[2]



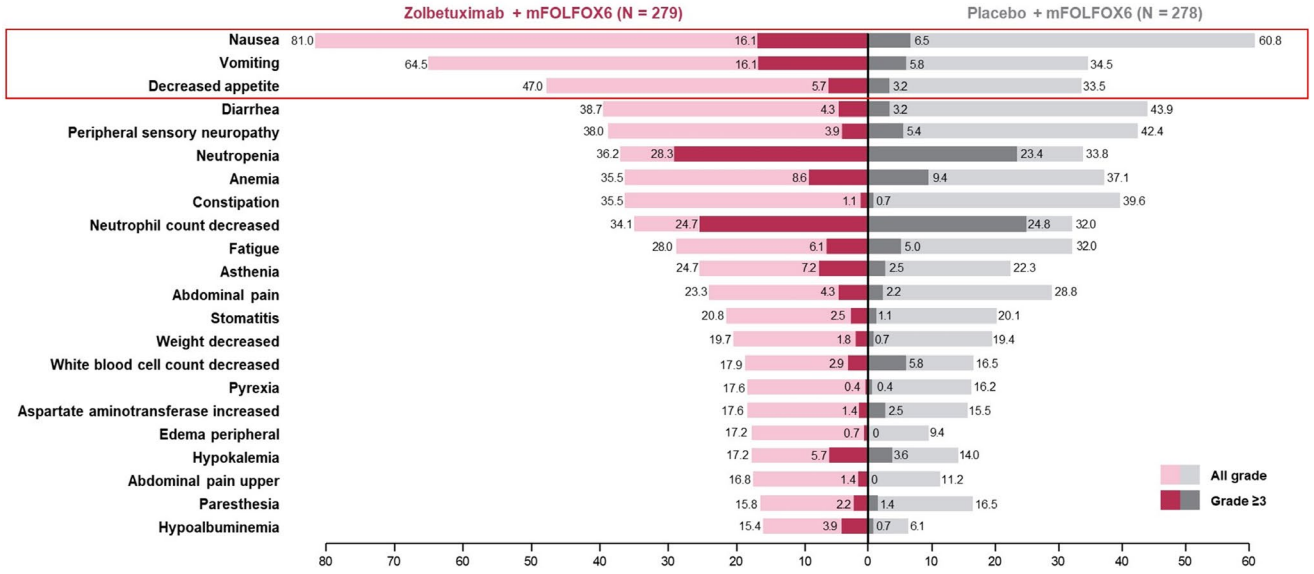
	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	149/283	177/282
Median OS, months (95% CI)	18.23 (16.43–22.90)	15.54 (13.47–16.53)
HR (95% CI)	0.750 (0.601–0.936)	
P-value	0.0053	

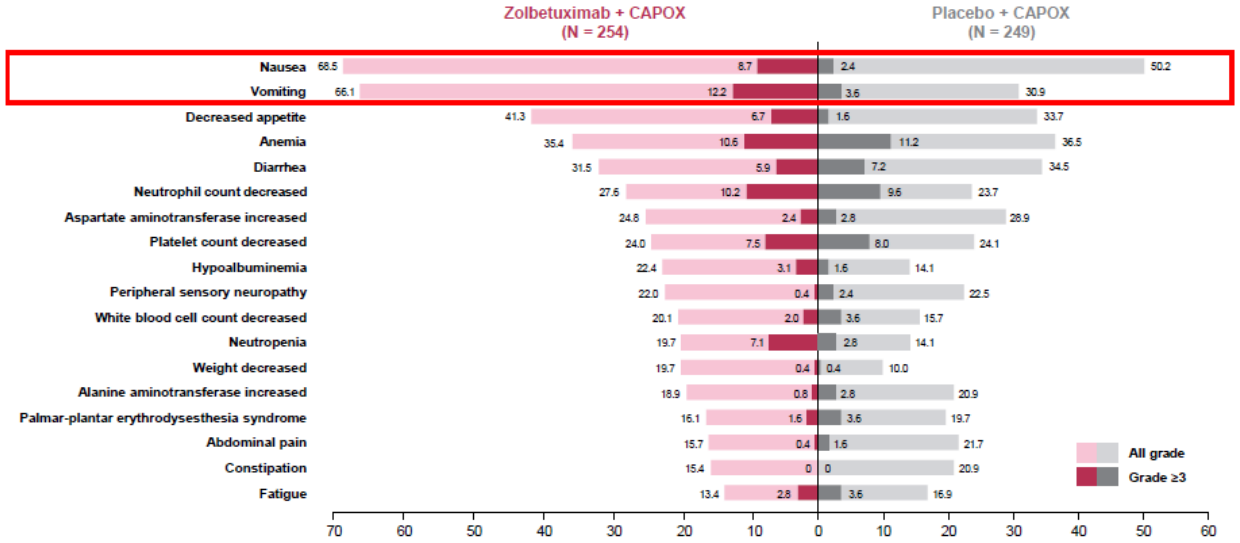
Median PFS 10·61 months vs 8·67 months; HR 0.75; 95% CI 0.60-0.94; *P* = 0.0066

- PFS was the primary endpoint and was statistically significantly improved by zolbetuximab in both studies
- OS was a secondary endpoint and was improved in both studies by the addition of zolbetuximab to CAPOX or mFOLFOX6

1. Shah MA, et al. *Nat Med*. 2023;29(8):2133-2141. 2. Shitara K, et al. *Lancet*. 2023;401(10389):1655-1668.

GLOW and SPOTLIGHT: Adverse Events

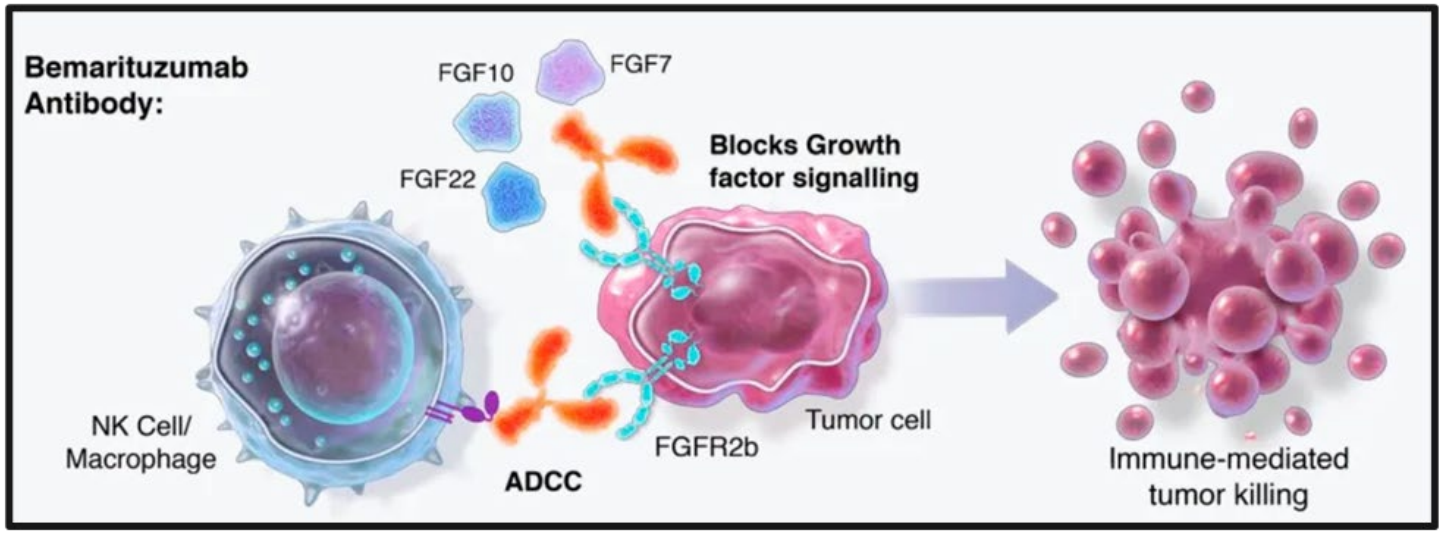




1. Shah MA, et al. *Nat Med*. 2023;29(8):2133-2141. 2. Shitara K, et al. *Lancet*. 2023;401(10389):1655-1668.

Targeting FGFR2b: Bemarituzumab Against FGFR2b-Positive GEA

- First-in-class, humanized, IgG1 monoclonal antibody directed against fibroblast growth factor receptor 2b (FGFR2b)
- Antitumor activity via blockade of FGFR2-dependent signaling and antibody-dependent cell-mediated cytotoxicity

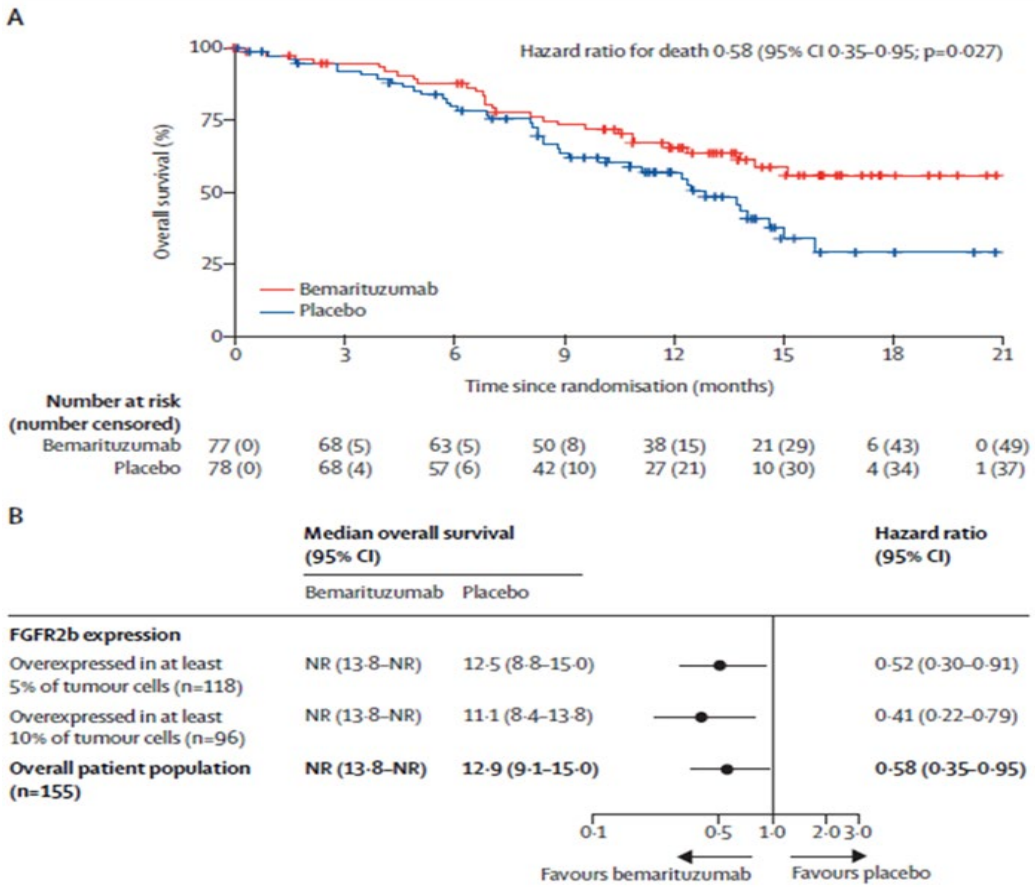


- Currently investigated in phase 3 trials:
  1. FORTITUDE-101 in combination with mFOLFOX6 (NCT05052801)
  2. FORTITUDE-102 in combination with mFOLFOX6 + nivolumab (NCT05111626)

Wainberg ZA, et al. *Lancet Oncol*. 2022;23(11):1430-1440.

Bemarituzumab Efficacy and Safety: FIGHT Trial

Overall Survival



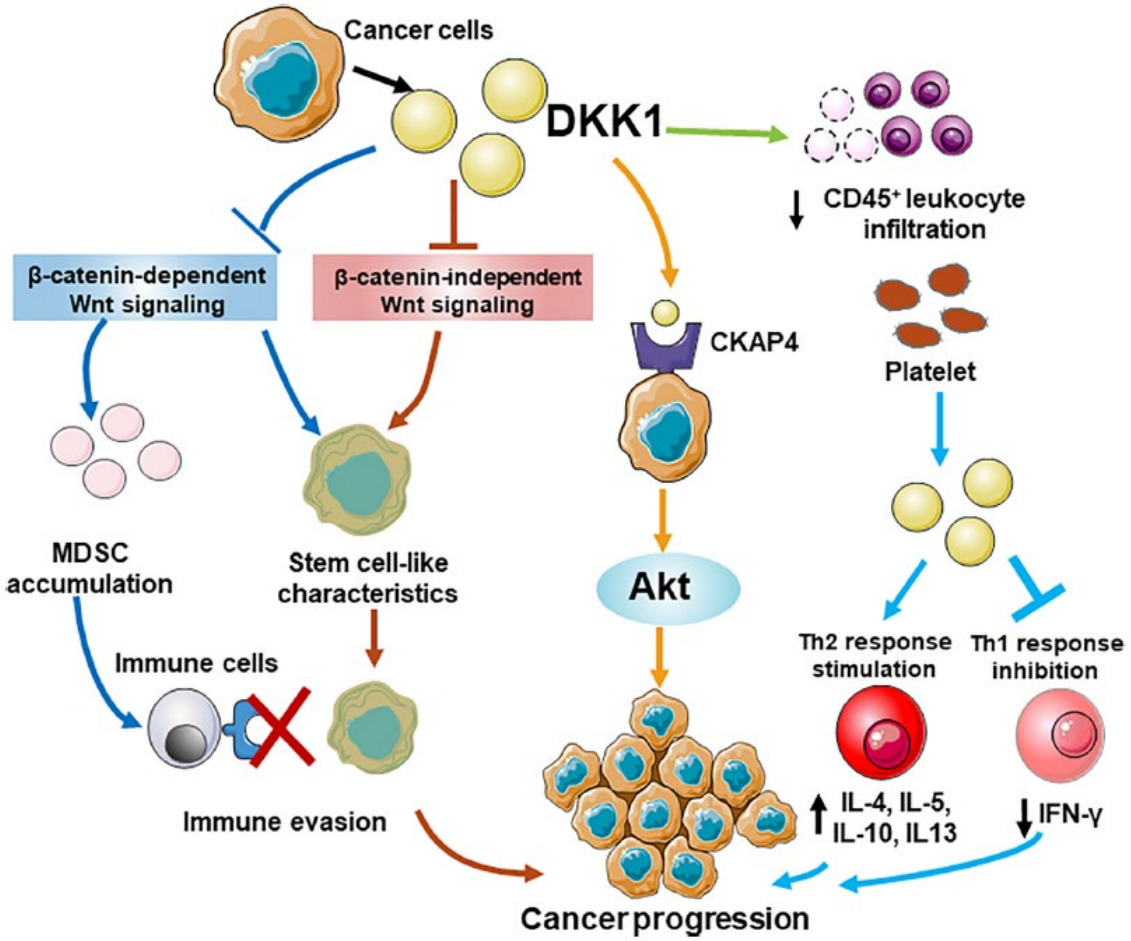
Safety Analyses

- **Grade ≥3 adverse events occurring with higher incidence in the bemarituzumab-containing arm vs placebo were the following:**
  - Decreased neutrophil count (23 [30%] of 76 in the bemarituzumab arm vs 27 [35%] of 77 in the placebo arm)
  - Cornea disorder (18 [24%] vs none)
  - Neutropenia (10 [14%] vs 7 [9%])
  - Stomatitis (7 [9%] vs 1 [1%])
  - Anemia (6 [8%] vs 10 [13%])
- **All-grade corneal events (adverse events of special interest) occurred in 51 (67%) patients in the bemarituzumab group and 8 (10%) in the placebo group**
  - Grade 3 corneal events: 18 (24%) patients in the bemarituzumab group

Improved OS in FGFR2b+ GEA with addition of bemarituzumab to mFOLFOX6 from the phase 2 FIGHT trial

Wainberg ZA, et al. *Lancet Oncol*. 2022;23(11):1430-1440.

DKK1 and DKN-01 Antibody



DKK1

- Modulates Wnt signaling
- Promotes proliferation, metastasis, and angiogenesis
- Suppresses antitumor immune responses
- Activates Akt signaling through CKAP4 receptor

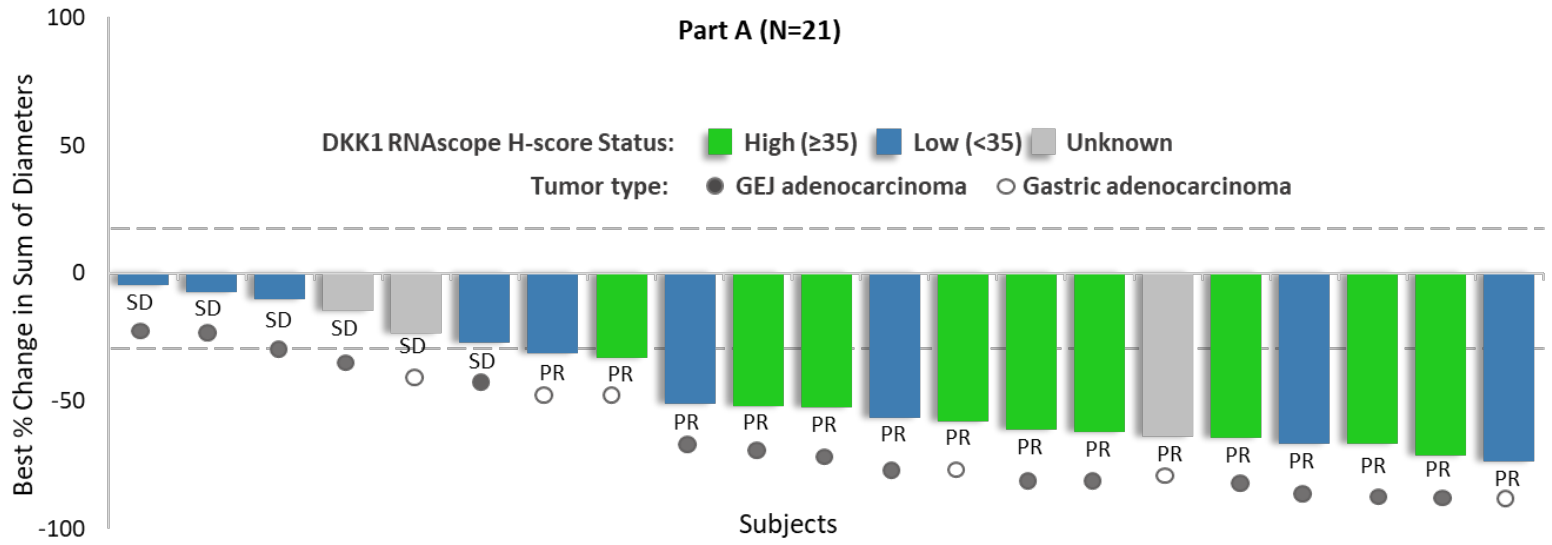
DKN-01

- Humanized monoclonal ab against DKK1
- In vivo, DKN-01 downregulates Akt activity and upregulates PD-L1 expression

Adapted from: Klempner SJ, et al. *Ann Oncol*. 2022;33(suppl_7):S1103-S1104.

DKN-01 in Combination With Tislelizumab and Chemotherapy as a First-Line Therapy in Advanced GEA: DisTinGuish Trial

- Tumoral DKK1 mRNA expression: assessed by a chromogenic in situ hybridization RNAscope assay and assigned an H-score (0-300)
- High score ≥ 35
- Primary efficacy endpoint: objective response rate (ORR)

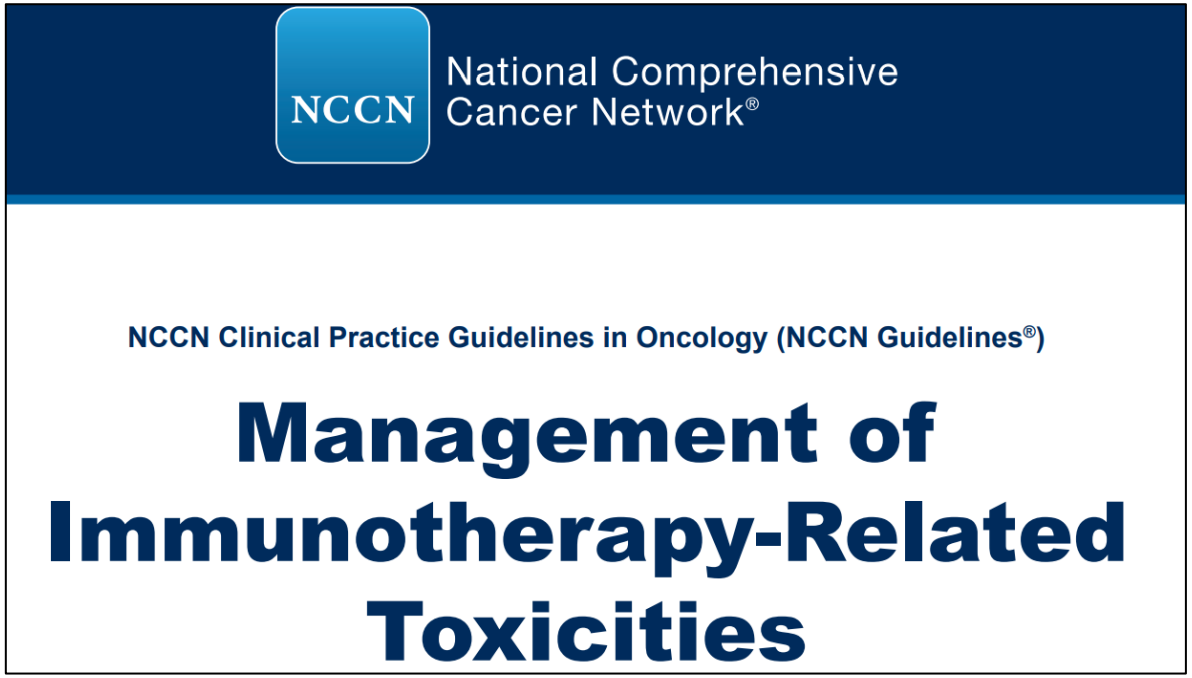


- ORR 68.2% (15 PR, 6 SD, 1 NE)
- DCR 96%
- DKK1-high mITT ORR 90%
- DKK1-low mITT ORR 55.6%
- Median PFS 10.7 mo
- Median PFS in DKK1-high 11.9 mo
- OS not reached

Klempner SJ, et al. *Ann Oncol*. 2022;33(suppl_7):S1103-S1104.

Monitoring and Managing Adverse Events

TOTAL CME



Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

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NCCN Guidelines. Version 1.2024. Schneider BJ, et al. *J Clin Oncol*. 2021;39(36):4073-4126.

Zolbetuximab: GI-Associated Toxicities

Zolbetuximab with chemotherapy is now FDA-approved as first-line treatment of CLDN 18.2+/HER2- advanced gastric/GEJ adenocarcinoma.

- The most frequent treatment-emergent adverse events (TEAEs) ≥20% for zolbetuximab in combination with chemotherapy were nausea, vomiting, decreased appetite, neutropenia, and decreased weight
- GI toxicities (nausea and vomiting in particular) are thought to be on-target effects of zolbetuximab, given normal expression of claudin 18.2 in gastric mucosa
- Management strategies include antiemetics, dose interruptions, and infusion rate adjustments
- Consensus guidance for management of nausea/vomiting in patients treated with zolbetuximab + chemotherapy (RAND/UCLA modified Delphi panel study) are under development

Shah MA, et al. *Nat Med*. 2023;29(8):2133-2141. Shitara K, et al. *Lancet*. 2023;401(10389):1655-1668.
Klempner SJ, et al. ESMO GI 2024. Abstract 506P.

Summary

Zolbetuximab with chemotherapy is now FDA-approved as first-line treatment of CLDN 18.2+/HER2- advanced gastric/GEJ adenocarcinoma.

- Gastroesophageal adenocarcinomas are a group of heterogeneous disorders
- Personalized approaches are key for best patient outcomes
- Reflex testing for MMR protein expression, HER2, and PD-L1 are current standard of care
- Claudin 18.2 is an emerging biomarker, given expected approval of zolbetuximab in the first-line setting
- Biomarker overlap will challenge clinical decision-making in practice
- Both efficacy and safety of treatments will need to be considered for best treatment selection