Recent FDA Approved Therapies for Advanced Gastric Cancer, Based on What Studies?

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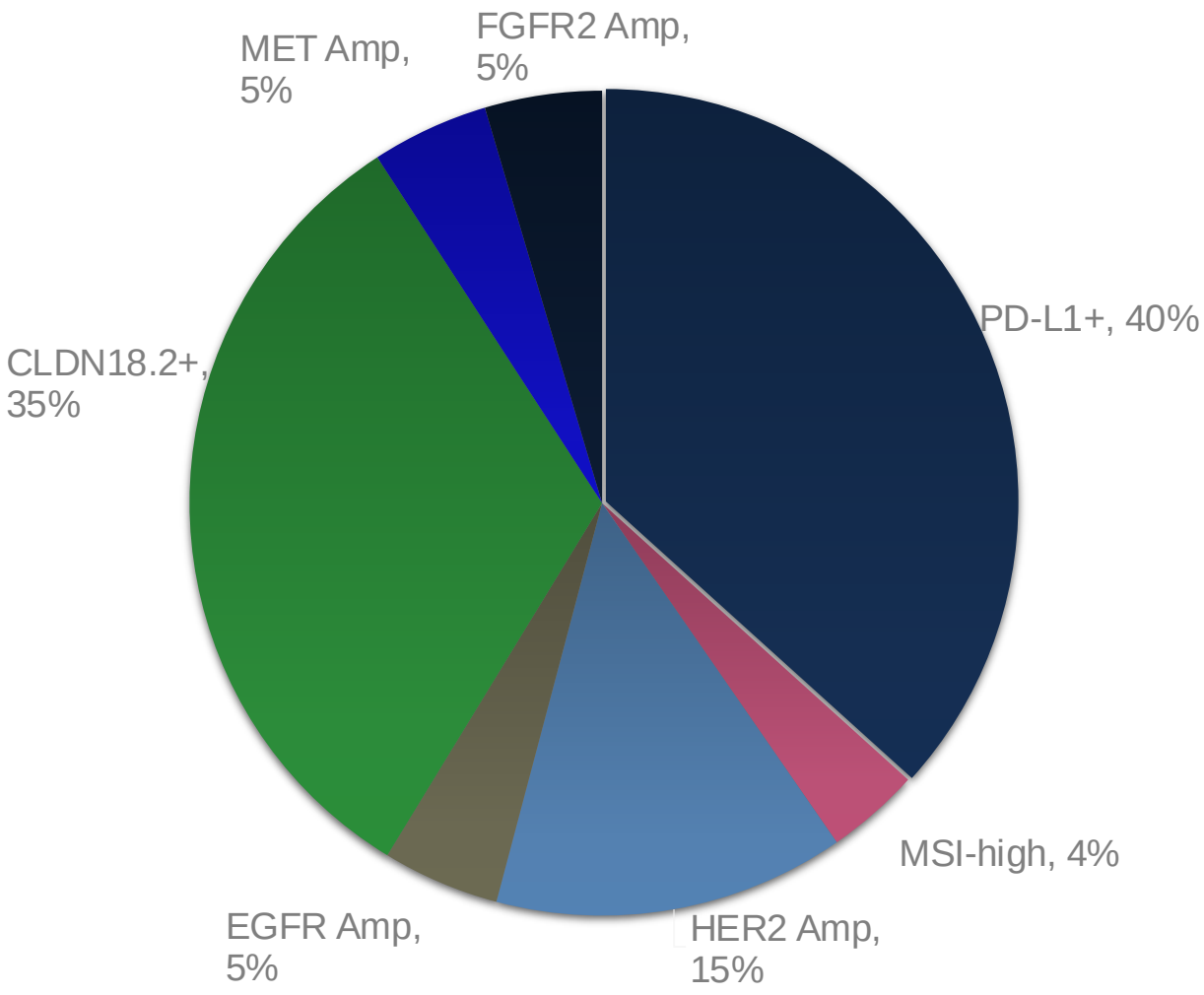
Manish A. Shah, MD FASCO
Weill Cornell Medicine/ New York-Presbyterian
mas9313@med.cornell.edu

Key Biomarkers in Gastroesophageal Cancer



AMP = amplification; CPS = combined positive score; EGFR = epidermal growth factor receptor; FGFR2 = fibroblast growth factor receptor 2; HER = human epidermal growth factor receptor

Key markers in advanced disease

HER2 positive: 15%-20% of patients; improved survival with chemo + HER2-targeting trastuzumab

MSI high: 3%-5% of patients, high response rates to immunotherapies ± chemo

PD-L1 positive: 30%-50% of patients; identifies those more likely to benefit from immunotherapy; likely gradation within PD-L1+ (CPS)

CLDN18.2 high: 30%-35% of patients; response predictor for CLDN18.2-targeting agent

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 agents

Tumor agnostic

Mismatch repair deficiency (or MSI-H)

Tumor mutation burden

NTRK fusion

Kuwata T. *Pathol Int*. 2024; online ahead of print.

Practice-Changing Advances Seen With Immunotherapy in Gastroesophageal Adenocarcinoma

Addressing Gaps and Improving Outcomes With Immunotherapy

- Previously, 1L chemotherapy resulted in disease progression and death within 1 year in most patients with gastroesophageal adenocarcinoma
- Anti-PD-1 (immune-based) therapies have demonstrated superior OS vs chemotherapy in numerous phase 3 RCTs and have become new standard of care

Approvals in Adenocarcinoma

- **Nivolumab/Pembrolizumab + chemotherapy** approved in the United States for 1L treatment, CPS > 0[1]
- **Pembrolizumab + trastuzumab and chemotherapy** approved in the United States for HER2+ disease[2]
- **Nivolumab** approved in Asia irrespective of PD-L1 status for ≥3L treament[3]
- **Pembrolizumab** approval for ≥3L treatment in the United States withdrawn (announced in July 2021)[4]
- **Pembrolizumab** approved in TMB ≥10 mut/Mb (United States) or MSI-H tumors (United States and Japan)[2,5]

1. FDA ODAC meeting, Sept 26, 2024
2. Keytruda (pembrolizumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125514s143lbl.pdf.
3. Högner A, Thuss-Patience P. *Pharmaceuticals (Basel)*. 2021;14:151.
4. https://www.cancernetwork.com/view/merck-to-withdraw-indication-for-pembrolizumab-in-third-line-gastric-cancer.
5. https://www.ajmc.com/view/phase-3-data-for-pembrolizumab-in-hepatocellular-carcinoma-show-significant-improvements-in-os-pfs.

Overview of Select Trials of Immunotherapy in Upper GI Cancers: Increasing Complexity

Parameter	CheckMate -649[2]	KEYNOTE-859[3]	Rationale-05
Disease location	Gastric, GEJ, esophagus	Gastric, GEJ	Gastric, GEJ
Histology	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma
Agent	Nivolumab + chemo vs chemo	Pembrolizumab + chemo vs chemo	Tislelizumab + chemotherapy vs chemo
Setting	1L advanced	1L advanced	1L advanced
ORR, %	60 vs 45 (CPS ≥5)	51.3 vs 42	50 vs 43 (TAP ≥5)
PFS HR	0.68 (CPS ≥5)	0.76	0.67 (TAP ≥5)
OS Δ, mo	3.3 (CPS ≥5), 2.7 (CPS ≥1), 2.2 (all patients)	1.4	4.6 mo (TAP ≥5)

[a] Results from prespecified interim analysis of the first 264 patients.

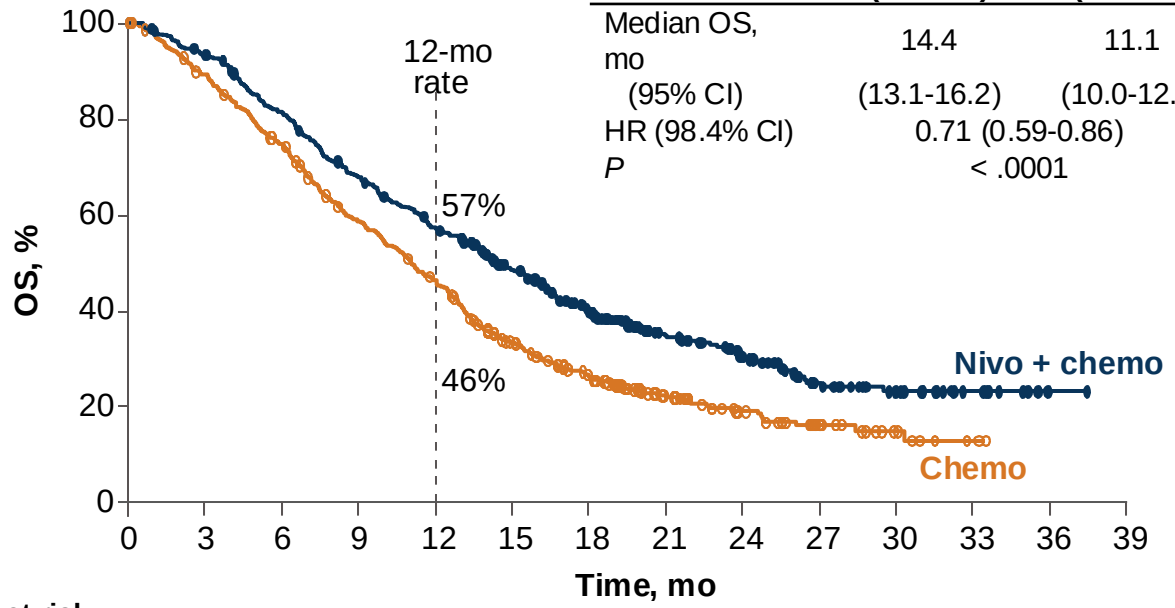
1. Janjigian YY et al. *Lancet*. 2021;398:27-40. 2. Rha SY et al. ESMO 2023. Abstract VP1-2023. 3. Xu R-H, et al. Oral presentation at ESMO 2023. Abstract LBA80.

CheckMate -649 Global Phase 3 Trial: Nivolumab Plus Chemotherapy Improved Survival[1,2]

- **FDA-approved April 2021**

PD-L1 CPS ≥5

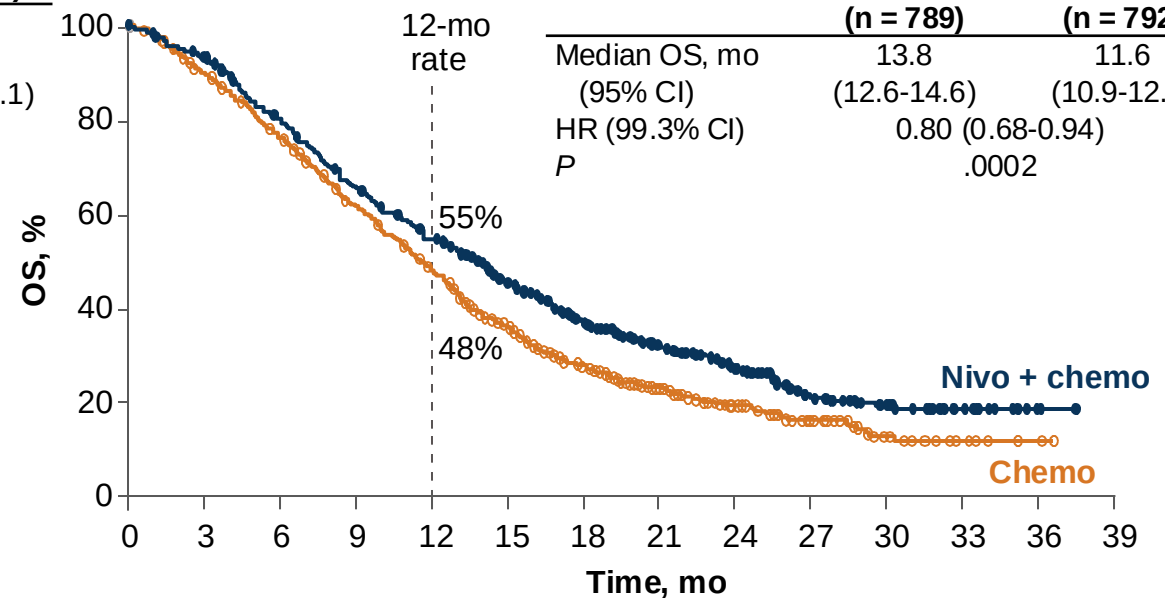
	Nivo + Chemo (n = 473)	Chemo (n = 482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (98.4% CI)	0.71 (0.59-0.86)	
P	< .0001	



No. at risk														
Nivo + chemo	473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemo	482	421	350	271	211	138	98	56	34	19	8	2	0	0

All randomized

	Nivo + Chemo (n = 789)	Chemo (n = 792)
Median OS, mo	13.8	11.6
(95% CI)	(12.6-14.6)	(10.9-12.5)
HR (99.3% CI)	0.80 (0.68-0.94)	
P	.0002	



Nivo + chemo	789	731	621	506	420	308	226	147	100	49	34	14	2	0
Chemo	792	697	586	469	359	239	160	94	59	35	15	7	2	0

- Grade 3-4 TRAEs were reported in 59% of patients in the nivolumab + chemo arm and 44% of patients in the chemo arm
- Treatment-related deaths occurred in 16 (2%) and 4 (1%) of patients in the nivolumab + chemo and chemo arms, respectively

Adapted with permission from Yelena Y. Janjigian, MD.

1. Opdivo (nivolumab) Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125554Orig1s121lbl.pdf.
2. Janjigian YY et al. *Lancet*. 2021;398:27-40.

KEYNOTE-859: Study Design[1]

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

R
1:1

Pembrolizumab 200 mg IV Q3W
for ≤35 cycles (~2 y)
+ Chemotherapy (FP or CAPOX)

Placebo IV Q3W
for ≤35 cycles (~ 2 y)
+ Chemotherapy (FP or CAPOX)

Stratification Factors

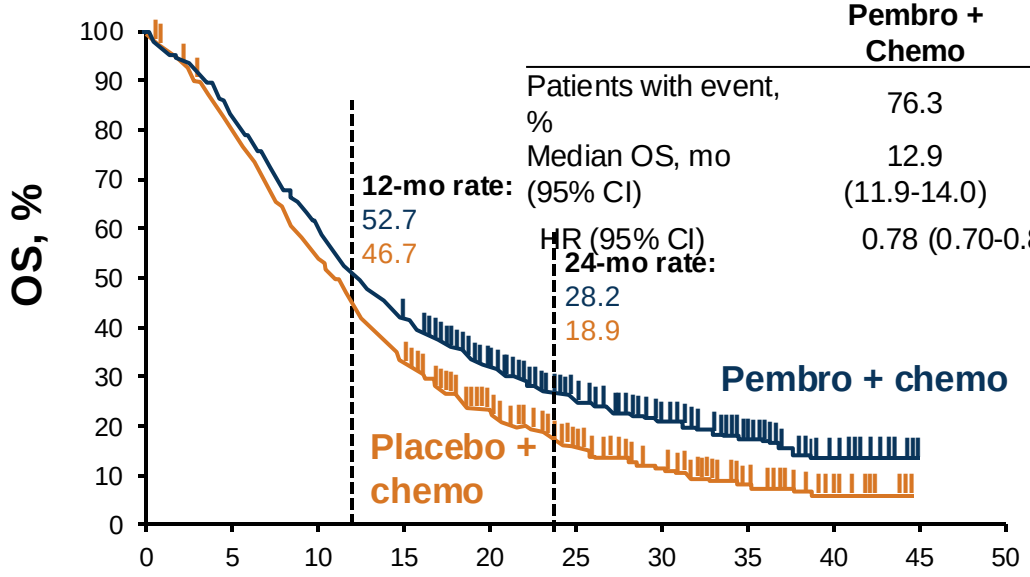
- Geographic region (EU/Israel/North America/Australia vs Asia vs rest of the world)
- PD-LI CPS (<1 vs >1)
- Choice of chemotherapy (FP vs CAPOX)

- **Primary endpoint**: OS
- **Secondary endpoints**: PFS, ORR, DOR, safety

1. Rha SY et al. ESMO 2023. Abstract VP1-2023.

KEYNOTE-859: 1L Pembrolizumab + Chemotherapy Improves Survival for Advanced G/GEJ Cancer[1]

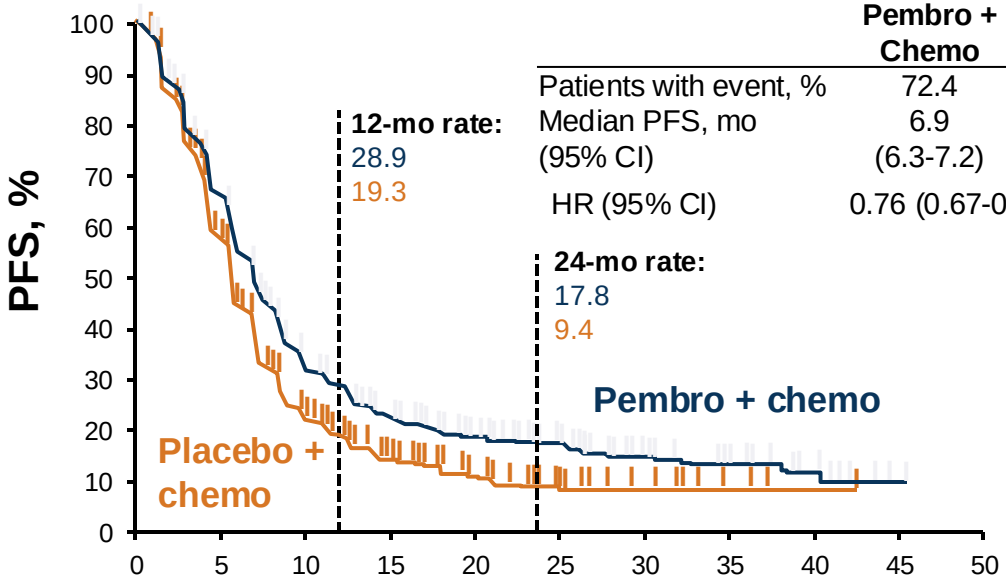
ITT Population OS



	Pembro + Chemo	Placebo + Chemo
Patients with event, %	76.3	84.4
Median OS, mo (95% CI)	12.9 (11.9-14.0)	11.5 (10.6-12.1)
HR (95% CI)	0.78 (0.70-0.87); *P* < .0001	

No. at Risk											
Pembro + chemo	790	663	490	343	240	143	95	55	19	3	0
Placebo + chemo	789	636	434	274	169	95	58	26	10	0	0

ITT Population PFS



	Pembro + Chemo	Placebo + Chemo
Patients with event, %	72.4	77.1
Median PFS, mo (95% CI)	6.9 (6.3-7.2)	5.6 (5.5-5.7)
HR (95% CI)	0.76 (0.67-0.85); *P* < .0001	

No. at Risk											
Pembro + chemo	790	461	199	131	94	63	36	22	9	1	0
Placebo + chemo	789	407	130	71	41	19	11	3	1	0	0

In addition to higher ORR (51.3% vs 42.0%), responses were also more durable in pembrolizumab arm (median DOR, 8.0 vs 5.7 months)

1. Rha SY et al. ESMO 2023. Abstract VP1-2023.

Rationale 305

Phase 3

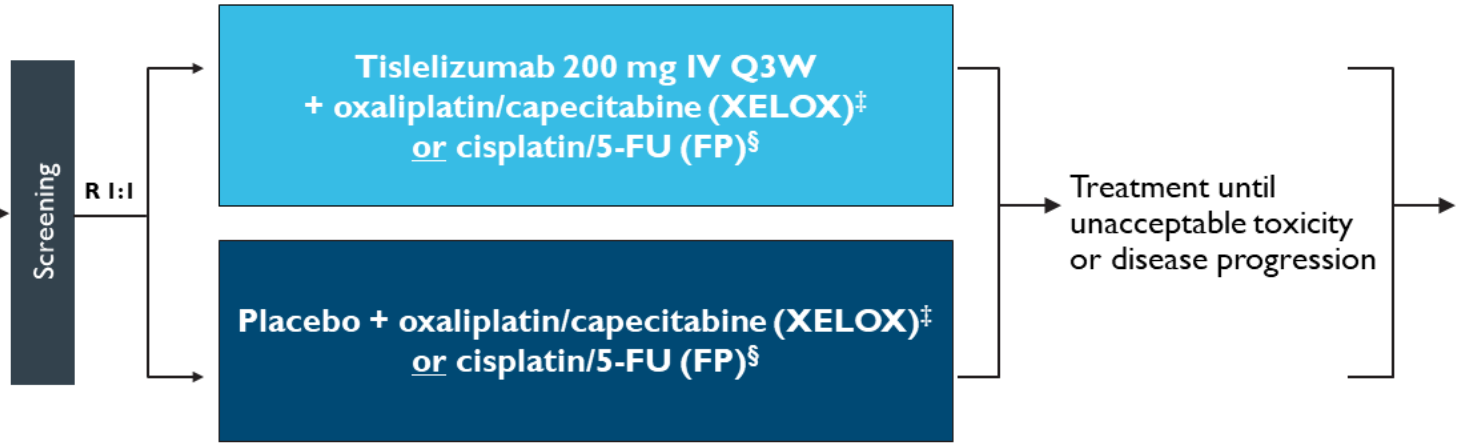
Study Identifier: RATIONALE-305, BGB-A317-305, NCT03777657

Primary Endpoint: OS in PD-L1+ (PD-L1 score ≥5%*) and ITT analysis set
Key Secondary Endpoints: PFS, ORR, DoR, DCR, CBR, HRQoL, safety

Key eligibility criteria

- Histologically confirmed GC/GEJC
- HER2/neu-negative disease
- Measurable disease
- ECOG PS ≤1
- No previous therapy for locally advanced unresectable or metastatic GC/GEJC†
- No prior therapy with drug specifically targeting T cell co-stimulation or checkpoint pathways

Treatment



Follow-up

Safety and survival

Stratification Factors

- Regions of enrollment
- Peritoneal metastasis
- PD-L1 score (PD-L1 ≥5% vs <5%)
- Investigator's choice of chemo

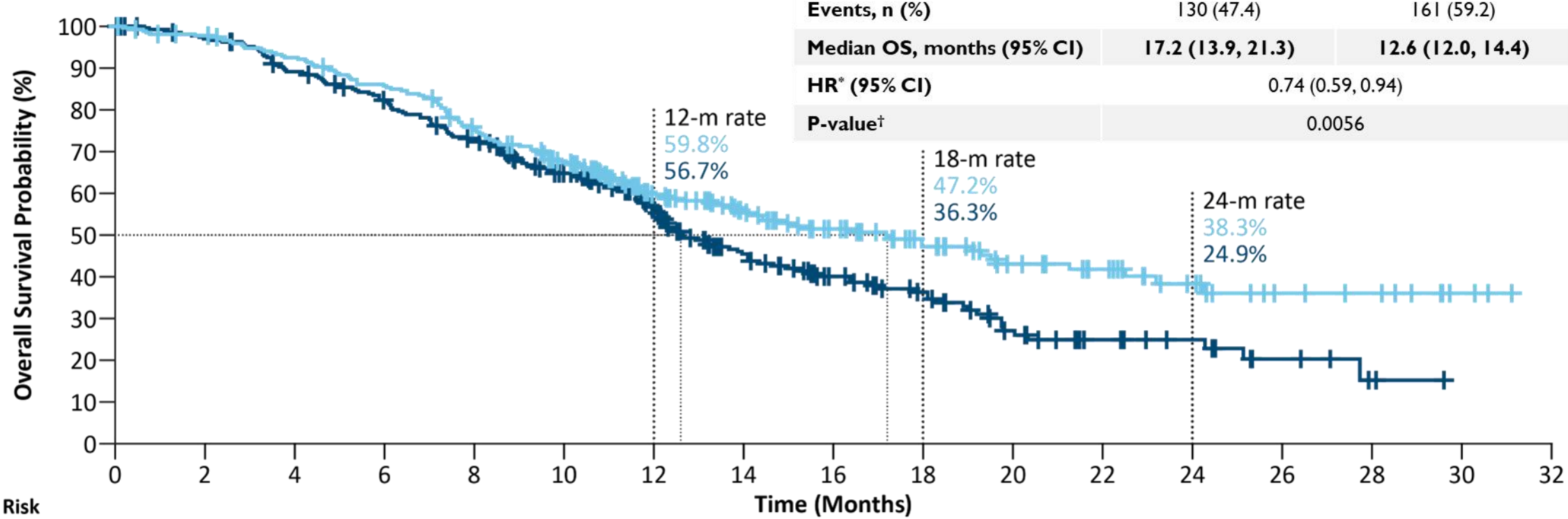
Statistical considerations:

- If OS in the PD-L1+ analysis set is statistically significant, OS in the ITT analysis set is tested hierarchically
- An interim analysis was performed based on 291 actual observed events for the PD-L1+ analysis set and the updated one-sided *P* value boundary was 0.0092
- Final analysis (cutoff date: 28 February 2023) based on 776 OS events (ITT)

RATIONALE-305: Interim Analysis

Tislelizumab plus chemotherapy demonstrated statistically significant improvement in OS vs placebo plus chemotherapy

	Tislelizumab + chemo	Placebo + chemo
Events, n (%)	130 (47.4)	161 (59.2)
Median OS, months (95% CI)	**17.2 (13.9, 21.3)**	**12.6 (12.0, 14.4)**
HR* (95% CI)	0.74 (0.59, 0.94)	
P-value†	0.0056	



Number at Risk																	
TIS+chemo	274	262	246	227	196	167	122	93	70	52	38	30	19	11	9	3	0
Placebo+chemo	272	261	237	215	189	156	118	80	57	44	26	16	12	6	2	0	0

Data cutoff: October 08, 2021.

*Primary OS analysis: Stratified by regions (east Asia vs rest of the world) and presence of peritoneal metastasis. †One-sided stratified log-rank test. 116 (42.3%) patients and 147 (54.0%) patients in tislelizumab plus chemotherapy arm and placebo plus chemotherapy arm received subsequent anticancer systemic therapies, respectively. Of those, 19 (6.9%) patients and 38 (14.0%) patients received immunotherapy.

CI=confidence interval, HR=hazard ratio, OS=overall survival, m=month

Moehler M et al. ASCO-GI 2023 abstract no. 286 Jan19-21, 2023

FDA ODAC Meeting – September 24, 2024

Intended to harmonize biomarker testing across platforms

Benefit of immunotherapy is greater for higher PD-L1 expressing tumors

Here are the FDA slides used for discussion

Gastric Cancer Applications

	Nivolumab CheckMate-649 April 16, 2021	Pembrolizumab Keynote-859 November 16, 2023	Tislelizumab Rationale-305 Under review
Intent to Treat	**N = 1581**	**N=1579**	**N=997**
Median OS - ICI + Chemo arm, mos (95% CI) - Chemo arm, mos (95% CI)	 13.8 (12.6, 14.6) 11.6 (10.9, 12.5)	 12.9 (11.9, 14.0) 11.5 (10.6, 12.1)	 15.0 (13.6, 16.5) 12.9 (12.1, 14.1)
OS HR (95% CI)	**0.80** (0.71, 0.90)	**0.78** (0.70, 0.87)	**0.80** (0.70, 0.92)
Pre-specified analysis for PD-L1 group 1	**CPS ≥ 1 N = 1296**	**CPS ≥ 1 N = 1235**	**TAP ≥ 5 N = 576**
Median OS - ICI + Chemo arm, mos (95% CI) - Chemo arm, mos (95% CI)	 14.0 (12.6, 15.0) 11.3 (10.6, 12.3)	 13.0 (11.6, 14.2) 11.4 (10.5, 12.0)	 17.2 (13.9, 21.3) 12.6 (12.0, 14.4)
OS HR (95% CI)	**0.77** (0.68, 0.88)	**0.74** (0.65, 0.84)	**0.74** (0.59, 0.94)
Pre-specified analysis for PD-L1 group 2	**CPS ≥ 5 N = 955**	**CPS ≥ 10 N = 551**	NA
Median OS - ICI + Chemo arm, mos (95% CI) - Chemo arm, mos (95% CI)	 14.4 (13.1, 16.2) 11.1 (10.0, 12.1)	 15.7 (13.8, 19.3) 11.8 (10.3, 12.7)	NA
OS HR (95% CI)	**0.71** (0.61, 0.83)	**0.65** (0.53, 0.79)	NA

Adapted from slide made by Dr. Vaibhav Kumar

Abbreviations: CPS combined positive score; TAP tumor area positivity; ICI immune checkpoint inhibitor; mos months; OS overall survival

Gastric Cancer Applications

Pre-Specified PD-L1 groups

	Nivolumab CheckMate-649 April 16, 2021		Pembrolizumab Keynote-859 November 16, 2023		Tislelizumab Rationale-305 Under review	
Pre-specified analysis for PD-L1 group 1	**CPS ≥ 1 N = 1296**	**CPS < 1 N = 265**	**CPS ≥ 1 N = 1235**	**CPS < 1 N = 344**	**TAP ≥ 5 N = 576**	**TAP < 5 N = 451**
Median OS - ICI + Chemo arm, mos - Chemo arm, mos	 14.0 11.3	 13.1 12.5	 13.0 11.4	 12.7 12.2	 17.2 12.6	 14.1 12.9
OS HR (95% CI)	**0.77** (0.68, 0.88)	**0.85** (0.63, 1.15)	**0.74** (0.65, 0.84)	**0.92 (0.73, 1.17)**	**0.74** (0.59, 0.94)	**0.91** (0.74, 1.12)
Pre-specified analysis for PD-L1 group 2	**CPS ≥ 5 N = 955**	**CPS < 5 N = 606**	**CPS ≥ 10 N = 551**		NA	
Median OS - ICI + Chemo arm, mos (95% CI) - Chemo arm, mos (95% CI)	 14.4 11.1	 12.4 12.3	 15.7 11.8		NA	
OS HR (95% CI)	**0.71** (0.61, 0.83)	**0.94** (0.78, 1.14)	**0.65** (0.53, 0.79)		NA	

Abbreviations: CPS combined positive score; TAP tumor area positivity; ICI immune checkpoint inhibitor; mos months; OS overall survival

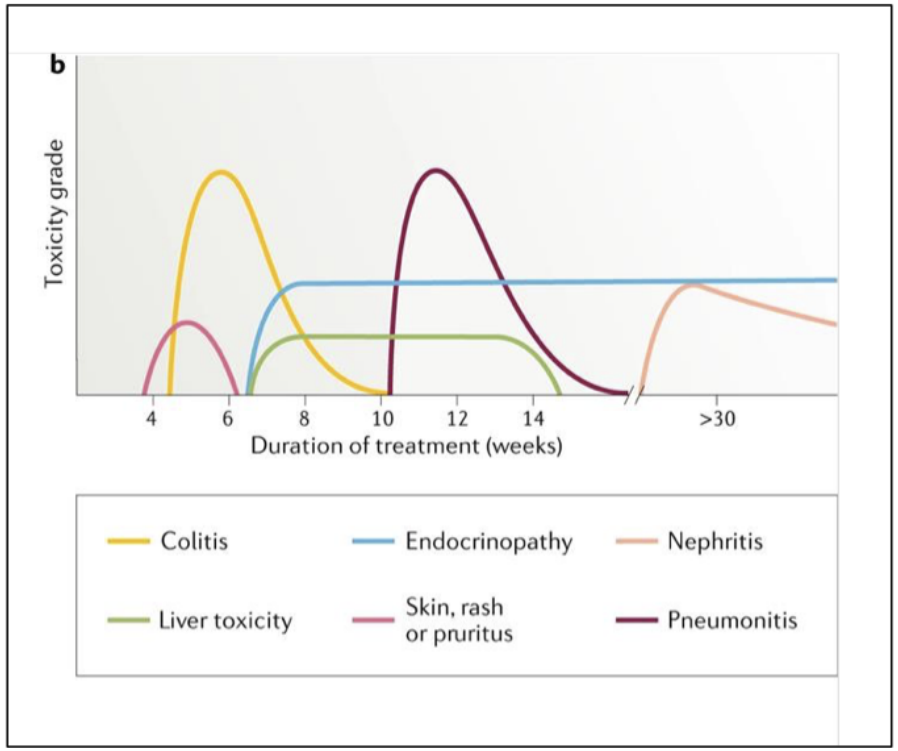
Adapted from slide made by Dr. Vaibhav Kumar and information from product labeling and/or BLA submissions

Safety – Immune Related Adverse Events (anti-PD-1)

Incidence of immune related adverse reactions (IMARs)

	All Grade	≥ 3
Diarrhea	6 to 19%	1%
Colitis	1 to 4%	0.3 to 2%
Pulmonary	1.5 to 5%	0 to 2%
Rash	9 to 16%	0.2 to 3.5%
Neurological	NR to 0.3%	NR to 0.3%
Endocrinopathy	7.3 to 23.4%	0 to 2%
Hepatic	0.3 to 10.8%	0 to 1.5%
Renal	NR to 2%	0 to 0.5%

Time course of immune related adverse events



Source: (Adapted-Table and Copied-Figure) Martins et al., Nature Reviews, 2019

Case study

- Patient:
  - 85-year-old male
- PMH:
  - HFrecEF, HTN, HLD, IPMNs, ESRD secondary to bilateral native nephrectomies for urogenital cancer s/p DDKT 2021
- HPI:
  - 1 year history of worsening fatigue, abdominal pain, weight loss

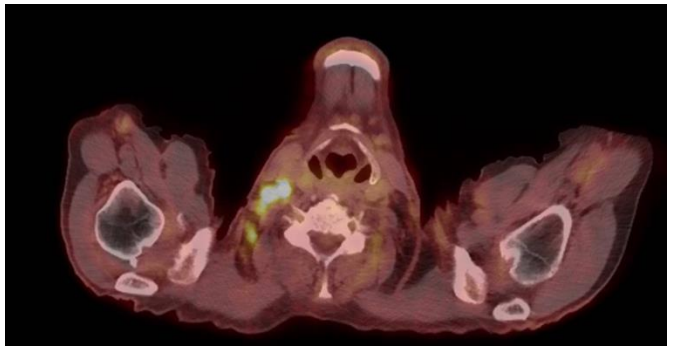
Case study

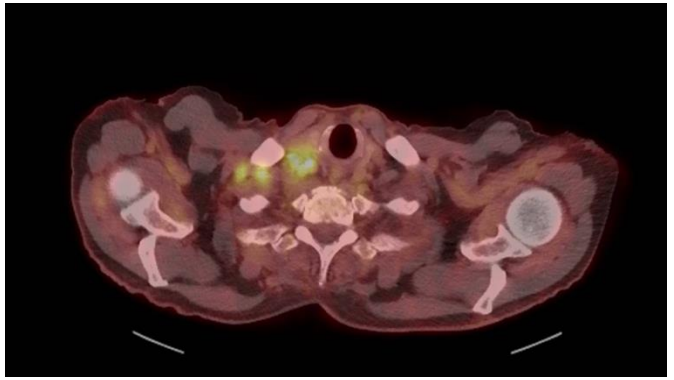
- Staging

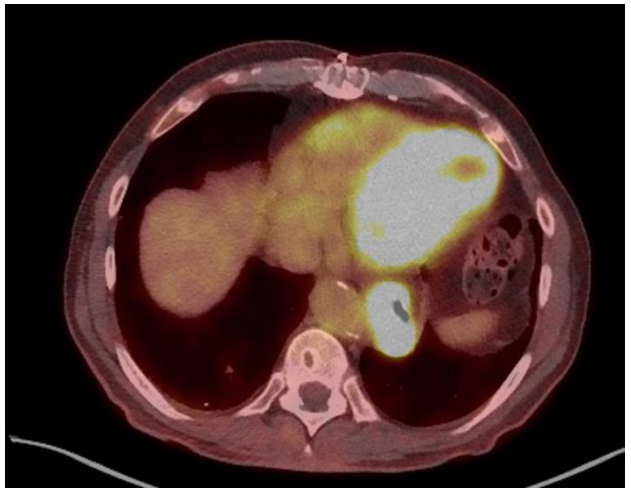
- EGD: large, ulcerated, partially circumferential (involving one-half of the lumen circumference) mass with oozing bleeding was found in the distal esophagus.

- Biopsy: invasive poorly differentiated adenocarcinoma with signet ring cell features, MMR deficient, HER2 IHC equivocal, arising in a background of intestinal metaplasia and high-grade dysplasia

- PET scan: right neck and supraclavicular adenopathy, SUV avid distal esophageal malignancy.

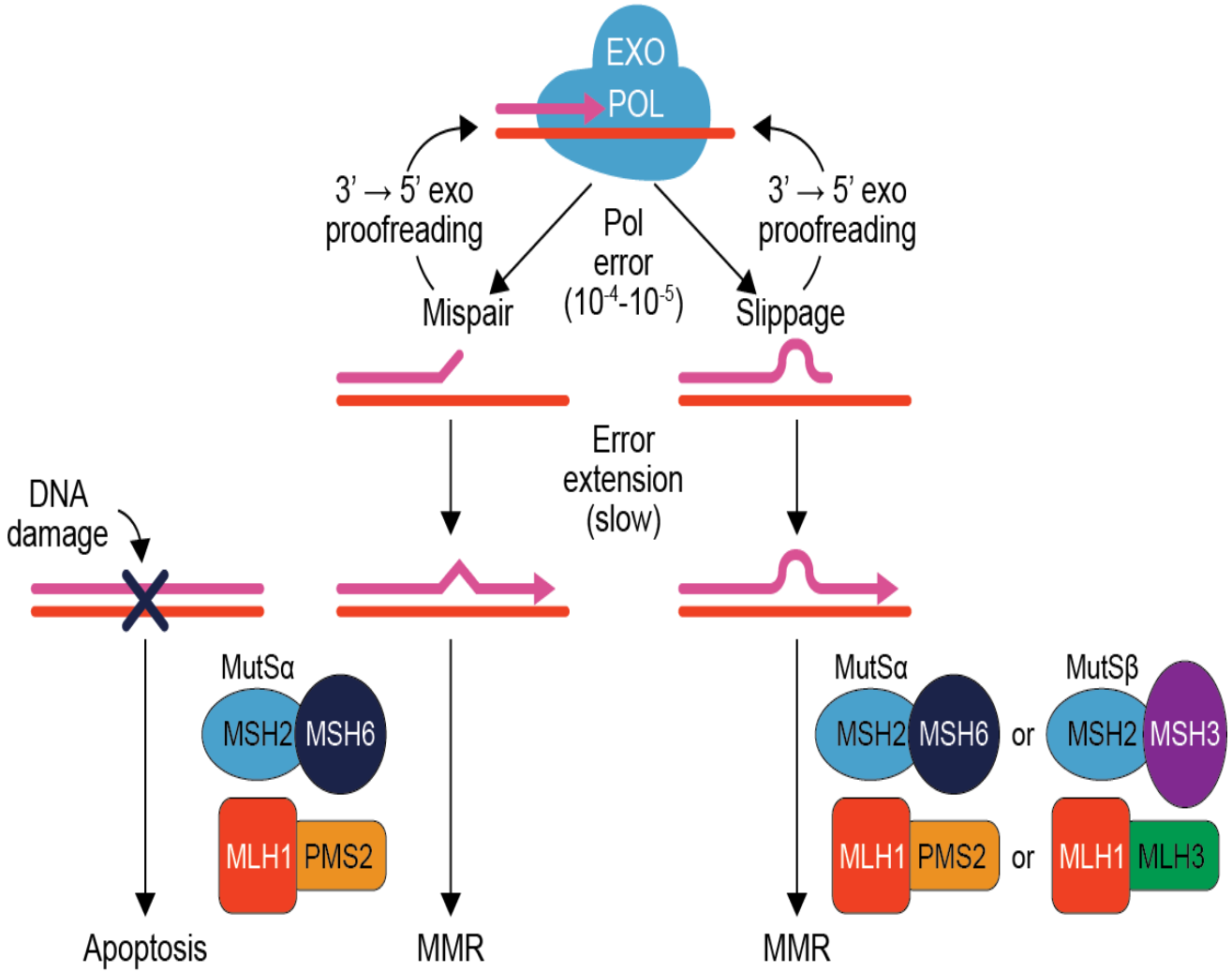




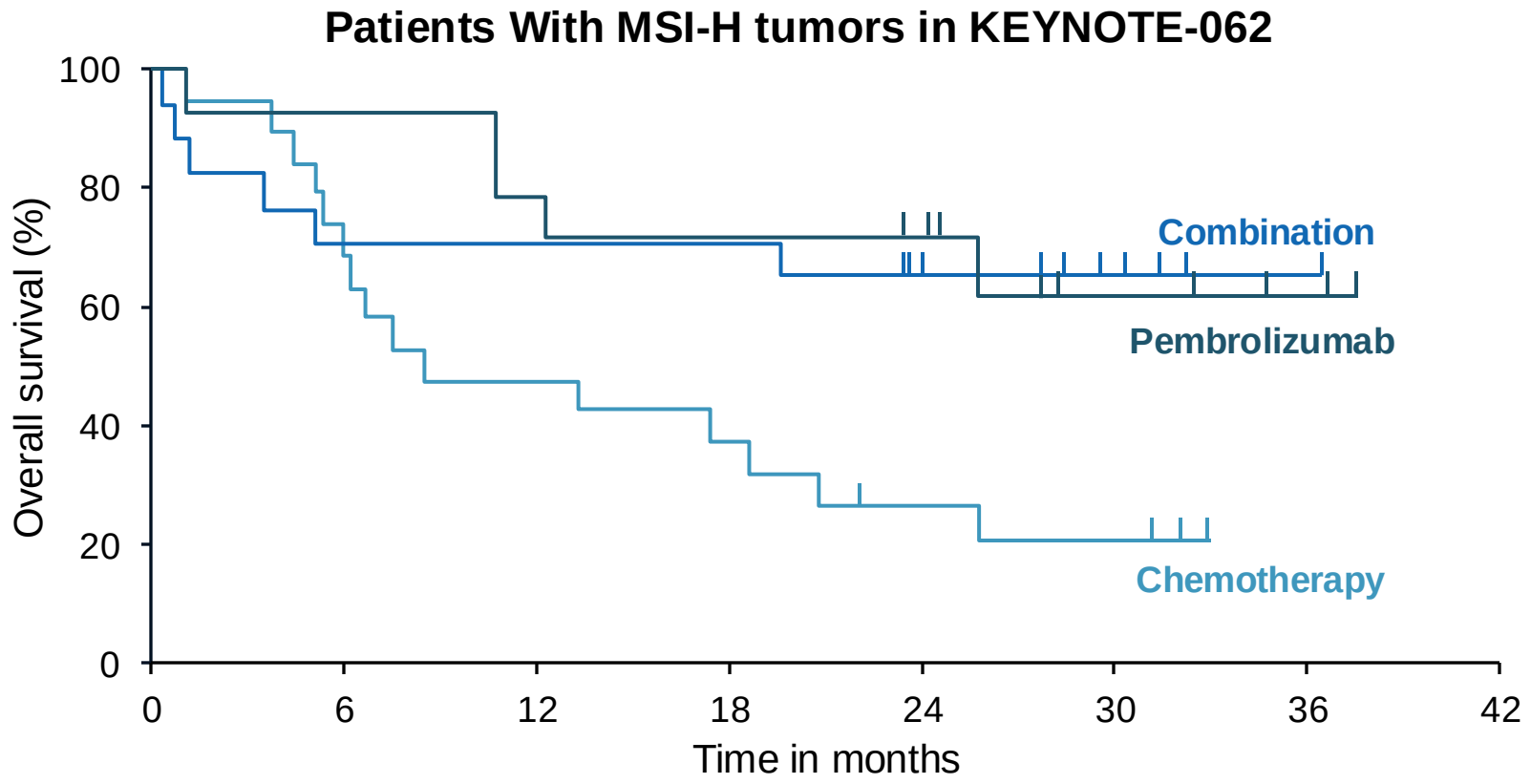


Microsatellite Unstable Disease

Mismatch Repair Leads to Very High Mutational Burden



KEYNOTE-062: First-Line Pembrolizumab ± Chemo



No. of subjects at risk

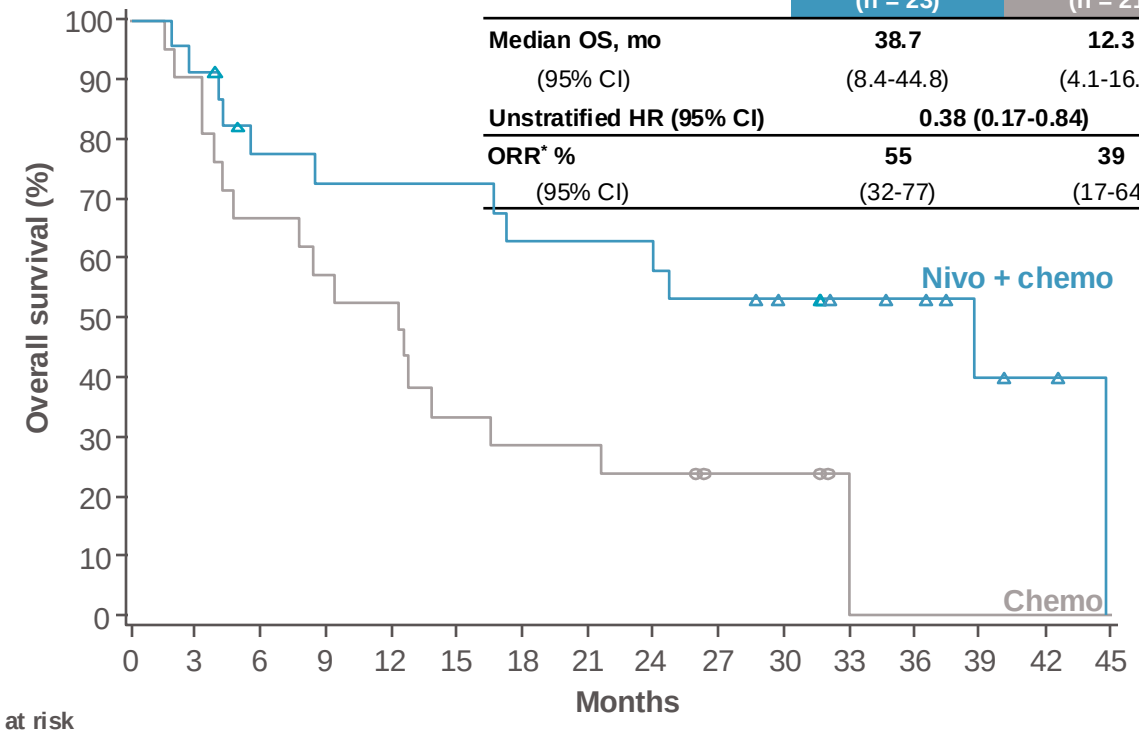
Pembrolizumab	14	13	11	10	9	4	2	0
Combination	17	12	12	12	9	4	1	0
Chemotherapy	19	13	9	7	4	3	0	0

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

Efficacy by MSI Status: Nivo + Chemo vs Chemo

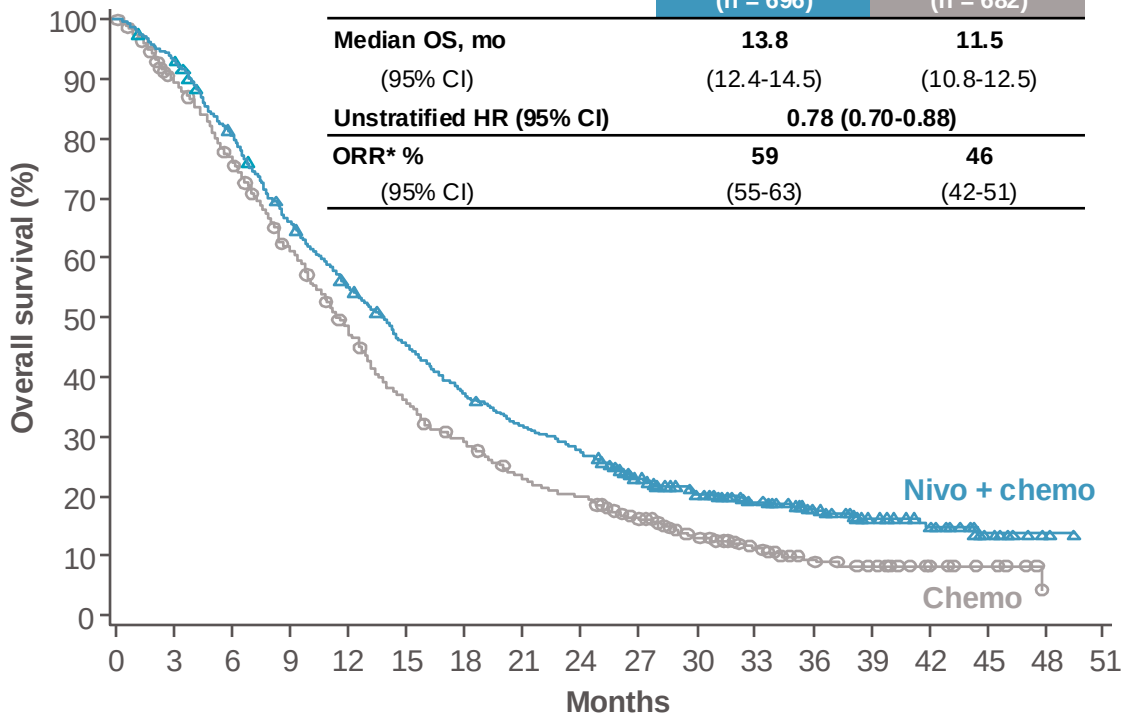
MSI-H

	Nivo + chemo (n = 23)	Chemo (n = 21)
Median OS, mo	**38.7**	**12.3**
(95% CI)	(8.4-44.8)	(4.1-16.5)
Unstratified HR (95% CI)	**0.38 (0.17-0.84)**	
ORR* %	**55**	**39**
(95% CI)	(32-77)	(17-64)



MSS

	Nivo + chemo (n = 696)	Chemo (n = 682)
Median OS, mo	**13.8**	**11.5**
(95% CI)	(12.4-14.5)	(10.8-12.5)
Unstratified HR (95% CI)	**0.78 (0.70-0.88)**	
ORR* %	**59**	**46**
(95% CI)	(55-63)	(42-51)



No. at risk

Nivo + chemo	23	21	16	15	15	15	13	13	12	11	9	7	6	3	2	0
Chemo	21	19	14	12	11	7	6	6	5	3	3	0	0	0	0	0

Nivo + chemo	696	646	554	452	375	308	251	214	184	137	103	75	50	29	22	9	2	0
Chemo	682	601	506	405	312	235	188	146	126	94	67	44	28	20	12	6	0	0

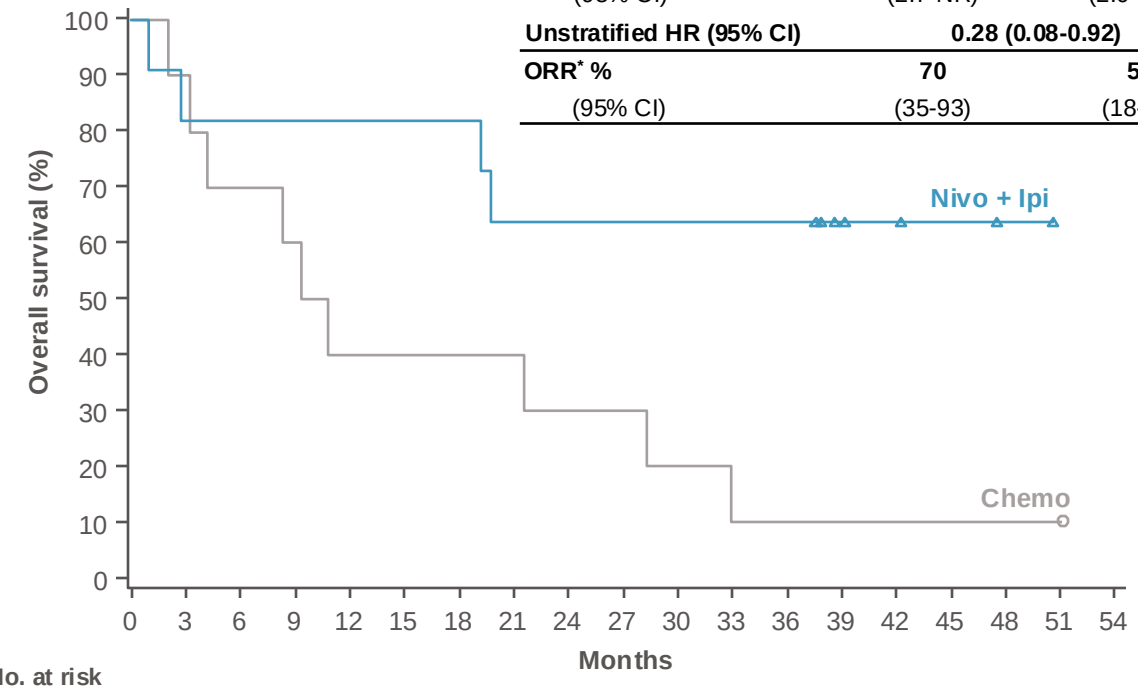
- Longer median OS and higher objective response rate (ORR) were observed in all randomized patients with MSI-H and MSS tumors with nivo + chemo vs chemo
  - Magnitude of benefit was greater in patients with MSI-H tumors, and patients with MSS tumors had results similar to the all-randomized population

Shitara K et al. *Nature*. 2022;603(7903):942-8.

Efficacy by MSI Status: Nivo + Ipi vs Chemo

MSI-H

	Nivo + Ipi (n = 11)	Chemo (n = 10)
Median OS, mo	**NR**	**10.0**
(95% CI)	(2.7-NR)	(2.0-28.2)
Unstratified HR (95% CI)	**0.28 (0.08-0.92)**	
ORR* %	**70**	**57**
(95% CI)	(35-93)	(18-90)

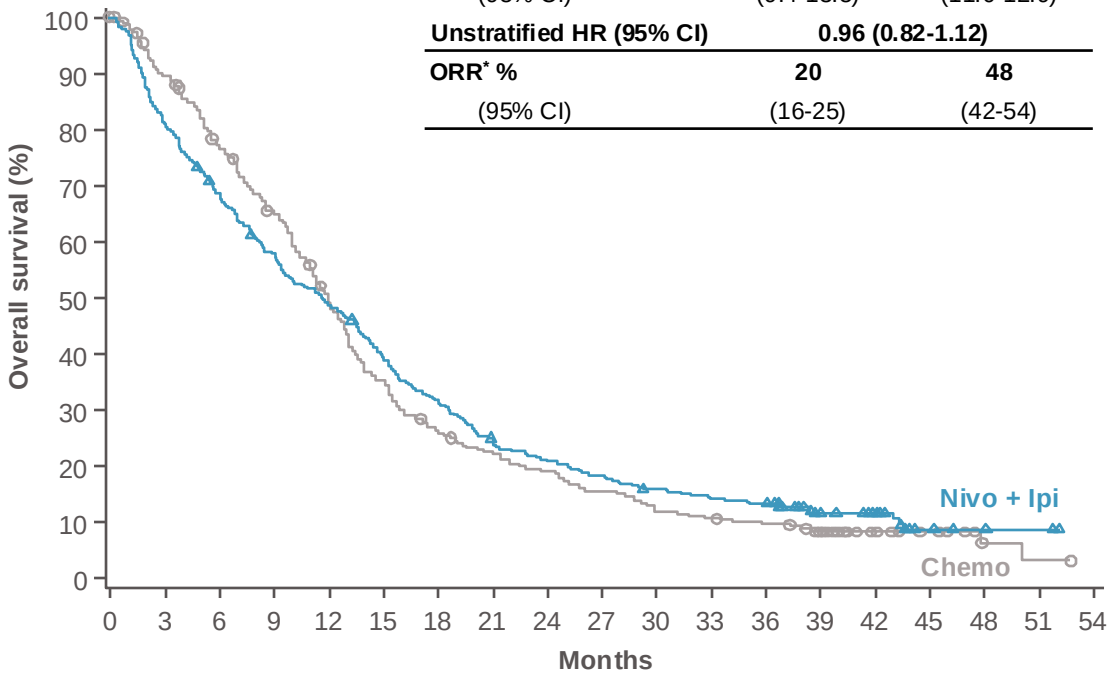


No. at risk

Nivo + Ipi	11	9	9	9	9	9	9	7	7	7	7	7	7	4	3	2	1	0	0
Chemo	10	9	7	6	4	4	4	4	3	3	2	1	1	1	1	1	1	1	0

MSS

	Nivo + Ipi (n = 355)	Chemo (n = 344)
Median OS, mo	**11.6**	**12.0**
(95% CI)	(9.4-13.5)	(11.0-12.9)
Unstratified HR (95% CI)	**0.96 (0.82-1.12)**	
ORR* %	**20**	**48**
(95% CI)	(16-25)	(42-54)



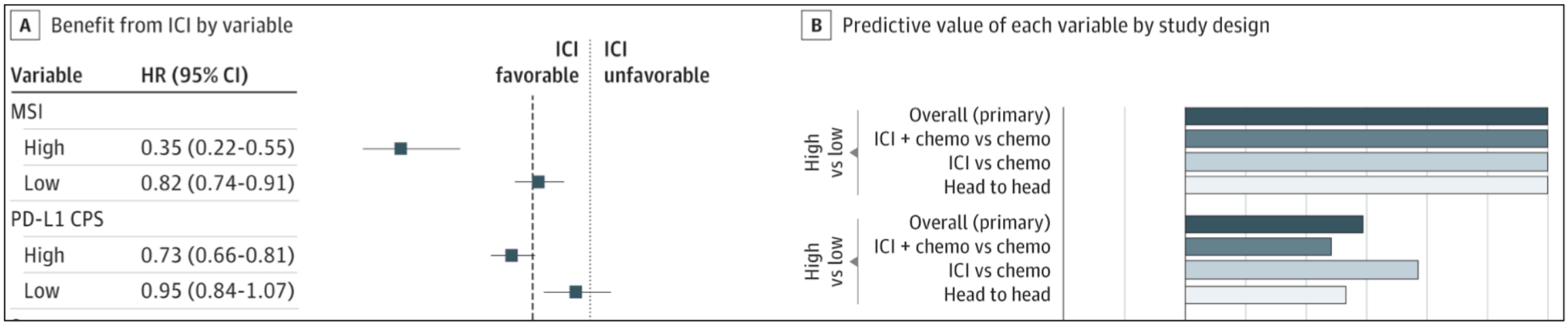
Nivo + Ipi	355	286	240	202	170	137	110	83	72	63	54	48	45	25	18	5	3	2	0
Chemo	344	303	257	216	162	116	85	72	61	49	39	34	30	22	14	8	2	1	0

- Longer median OS and higher ORR observed in all randomized patients with MSI-H tumors with nivo + ipi vs chemo, although sample size was small

Randomized patients who had target lesion measurements at baseline per BICR assessment. Patients with MSI-H: nivo + ipi, n = 10; chemo, n=7, patients with MSS: nivo + ipi, n=292; chemo, n=257.

Shitara K et al. *Nature*. 2022;603(7903):942-8.

PD-L1 in Gastric Cancer – External Meta-Analysis



Source: Copied (adapted) from Yoon et al, JAMA Onc, 2022

Abbreviations: MSI microsatellite instability; CPS combined positive score; ICI immune checkpoint inhibitor; HR hazard ratio

Metastatic gastric cancer

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy
- Oxaliplatin is preferred over cisplatin due to lower toxicity.

Preferred Regimens

- HER2 overexpression positive[c]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin and trastuzumab[f]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, trastuzumab[f] and pembrolizumab for PD-L1 CPS ≥1 (category 1)[g,h,17-18]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin and trastuzumab (category 1)[f,19]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, trastuzumab[f] and pembrolizumab for PD-L1 CPS ≥1 (category 1)[g,h,17-18]
- HER2 overexpression negative[c]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1)[g,h,20]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and pembrolizumab for PD-L1 CPS ≥1[g,h,21] (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS 1 to <10)
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and oxaliplatin[22-24]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, and pembrolizumab for PD-L1 CPS ≥1[g,h,21] (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS 1 to <10)
  - Fluoropyrimidine (fluorouracil[a] or capecitabine) and cisplatin[22,25-27]
- MSI-H/dMMR tumors (independent of PD-L1 status)[c]
  - Pembrolizumab[g,h,28-30]
  - Dostarlimab-gxly[g,h,31]
  - Nivolumab and ipilimumab[g,h,20]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab[g,h,20]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and pembrolizumab[g,h,29,30]

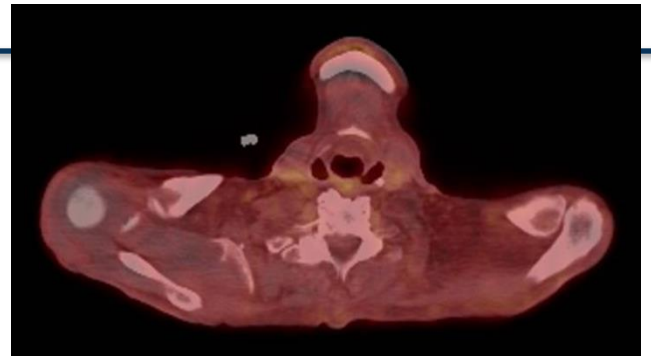
Other Recommended Regimens
- Fluorouracil[a,i] and irinotecan[j,32]
- Paclitaxel with or without carboplatin or cisplatin[j,33-37]
- Docetaxel with or without cisplatin[j,38-41]
- Fluoropyrimidine[j,26,42,43] (fluorouracil[a] or capecitabine)
- Docetaxel, cisplatin or oxaliplatin, and fluorouracil[a,j,44,45]

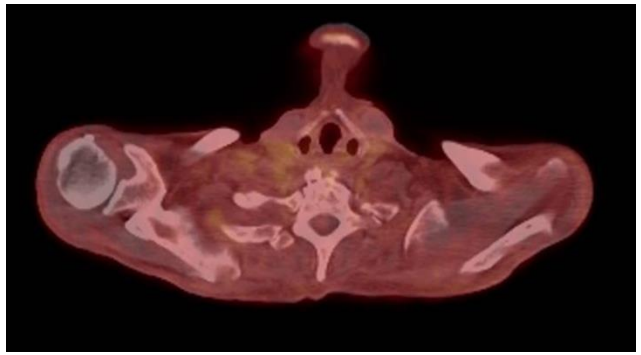
Useful in Certain Circumstances
- HER2 overexpression negative[c]
  - Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS <5) (category 2B)[g,h,20]

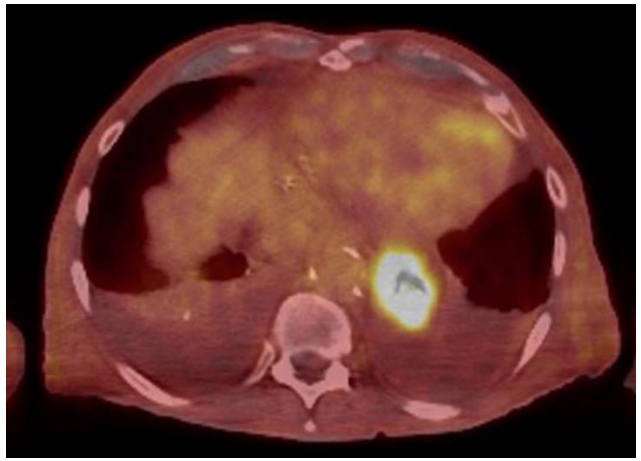
Gastric Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology

Case study

- Staging
- 11/02/2023 R cervical core LN biopsy: non-GC DLBCL; no EBER performed; Ki67 95%; Favor follicular lymphoma, grade 3B
- Patient was treated with Pola-RCHP x 4 cycles
- PET scan: slightly decreased avidity and extent of distal esophageal neoplasm. No FDG avid nodal or distant sites of disease.



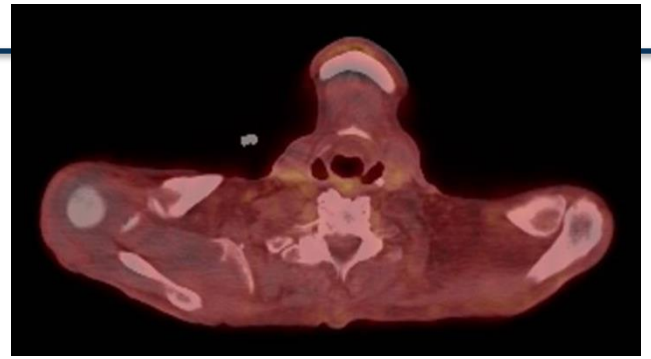


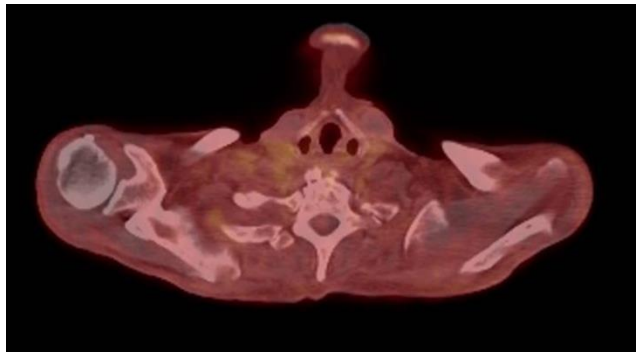


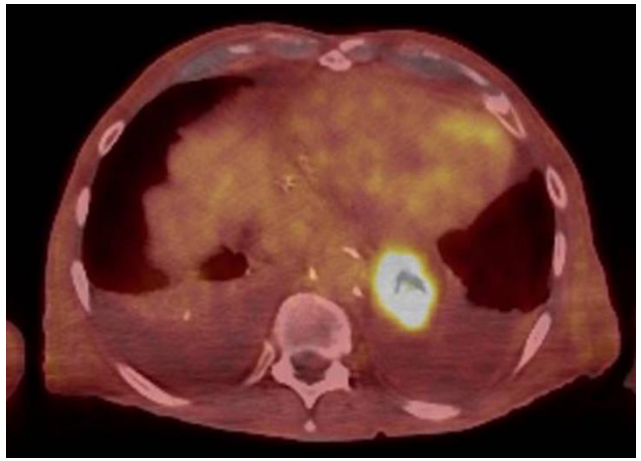
Case study

- Esophageal cancer treatment
  - Option 1: Chemotherapy with radiation
  - Option 2: Immunotherapy

- Things to consider – patient has a transplanted kidney. There is ~30-40% rate of graft failure.





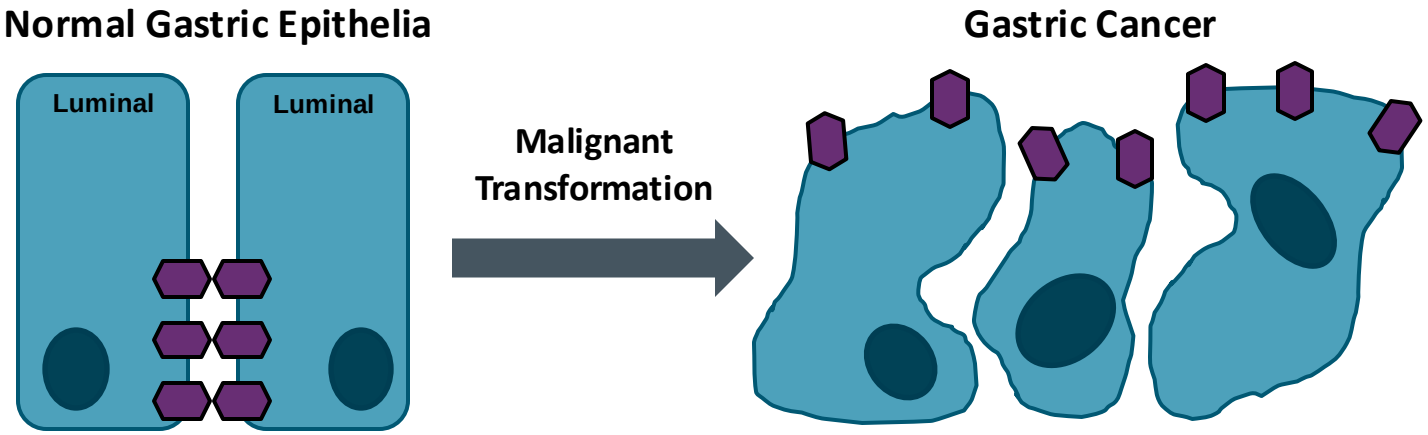


Other Targets

CLDN18.2

FGFR2

Claudin18.2: Leveraging Biology

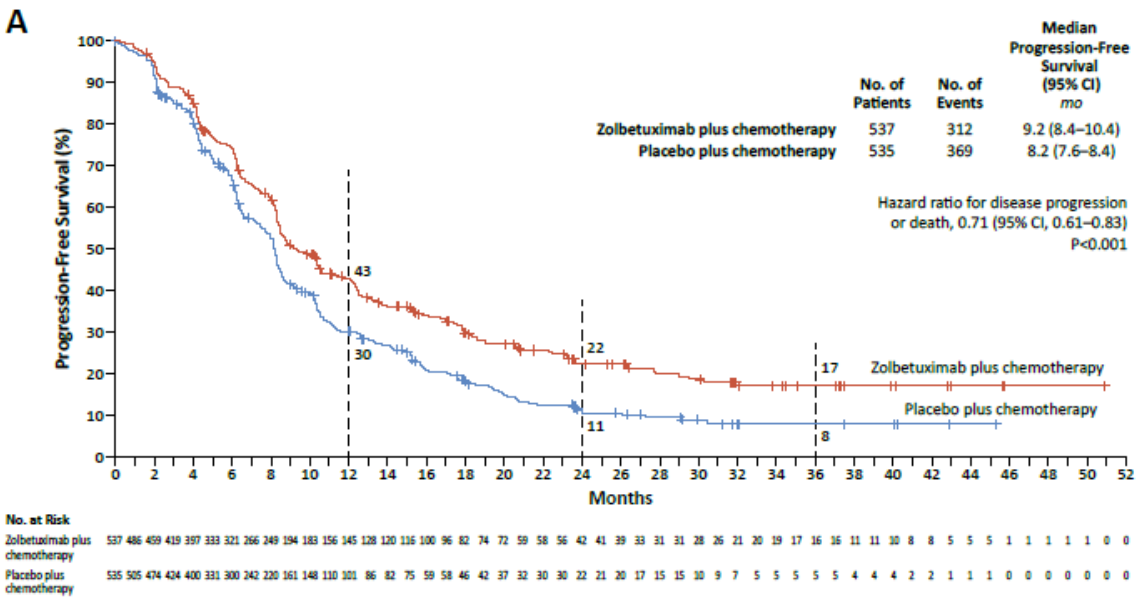


- Claudin18.2 is a major structural component of intercellular tight junctions
- Not routinely expressed in any normal tissue outside gastric mucosa (cancer-restricted antigen)
- Broadly expressed in several tumor types including gastric, GEJ, biliary, and pancreatic

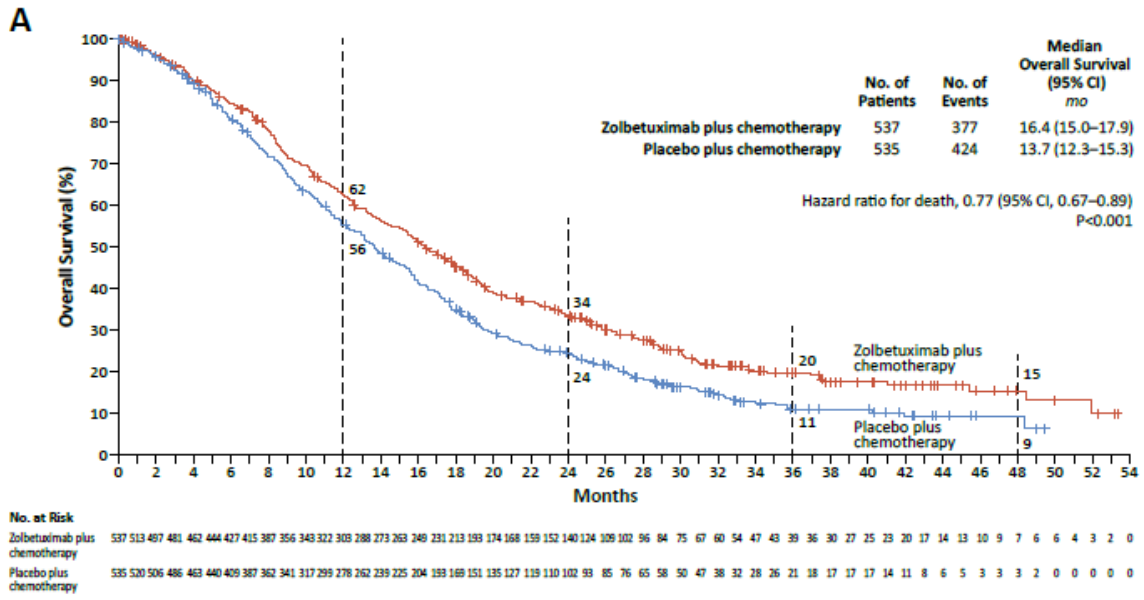
Baek. Anticancer Res. 2019;39:6973.

SPOTLIGHT and GLOW – Combined Final Analysis

Progression Free Survival



Overall Survival



Total Population – 1072 (n=537 Zolbe + chemo)
PFS HR 0.71 (0.61-0.83), p < 0.001
OS HR 0.77 (0.67-0.89), p < 0.01

Measurable disease (n=820),
Complete Response - 5.2%. v. 3.1%
Partial Response - 52.2%. v. 52.2%
Overall Response Rate - 57.4%. Vs. 55.3%

Key Toxicity

≥ Grade 3 toxicity higher than control
Nausea - 12.6%. vs. 4.7%
Vomiting 14.3%. vs. 4.9%
Decreased appetite - 6.4% vs. 2.5%

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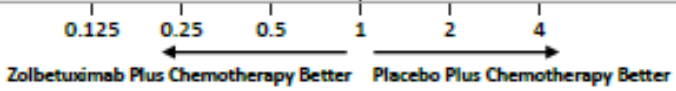
SPOTLIGHT and GLOW – Combined Final Analysis

B

Subgroup	Zolbetuximab Plus Chemotherapy	Placebo Plus Chemotherapy	Hazard Ratio (95% CI)
	no. events/no. patients		
All patients	377/537	424/535	0.77 (0.67–0.89)
Age			
≤65 yr	241/357	284/361	0.73 (0.62–0.87)
>65 yr	136/180	140/174	0.85 (0.67–1.07)
Sex			
Male	243/335	272/331	0.78 (0.66–0.93)
Female	134/202	152/204	0.76 (0.60–0.96)
Region			
Asia	166/245	190/247	0.71 (0.58–0.88)
Non-Asia	211/292	234/288	0.83 (0.69–1.00)
Number of metastatic sites			
0–2	274/408	312/407	0.76 (0.65–0.90)
≥3	103/129	112/128	0.78 (0.59–1.02)
Prior gastrectomy			
No	276/378	303/378	0.83 (0.71–0.98)
Yes	101/159	121/157	0.65 (0.50–0.85)
Lauren classification			
Diffuse	120/169	164/217	0.82 (0.65–1.04)
Intestinal	75/106	90/107	0.65 (0.47–0.88)
Mixed/other	96/135	85/103	0.88 (0.66–1.18)
Primary site			
Stomach	301/438	331/419	0.72 (0.62–0.84)
Gastroesophageal junction	76/99	93/116	1.02 (0.76–1.39)
Race			
White	175/234	183/224	0.89 (0.72–1.09)
Asian	171/254	196/255	0.69 (0.56–0.85)



Key Points

- Broad activity
- ? GEJ resistance?
- ? White people?

Validated Target

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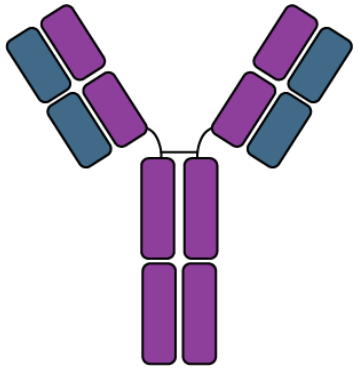
CLDN18.2 is a valid target:
Emerging CLDN18.2 Targeted Treatments

Monoclonal antibody

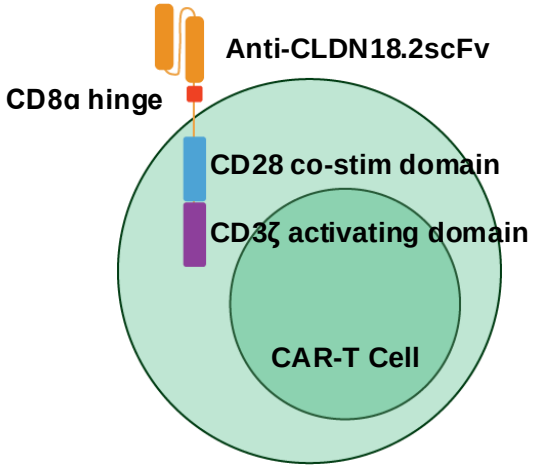
- **Humanized mAb**
- **Engineered mAb**



Fc mutations to enhance ADCC

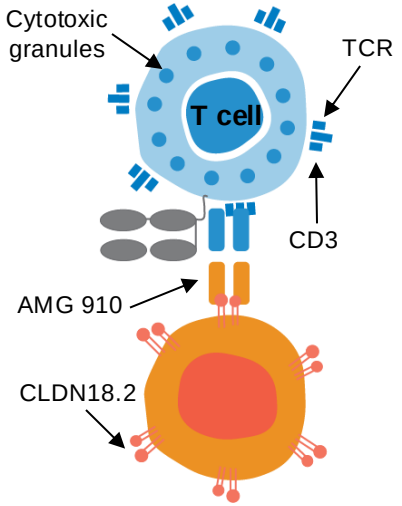
- IMAB306/zolbetuximab TST-001
- ABI011, MIL93, ZL1211

CAR-T



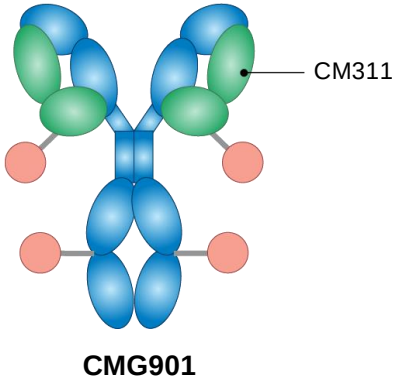
- CT-041, LCAR-C18S
- LY011

BITE Bispecific



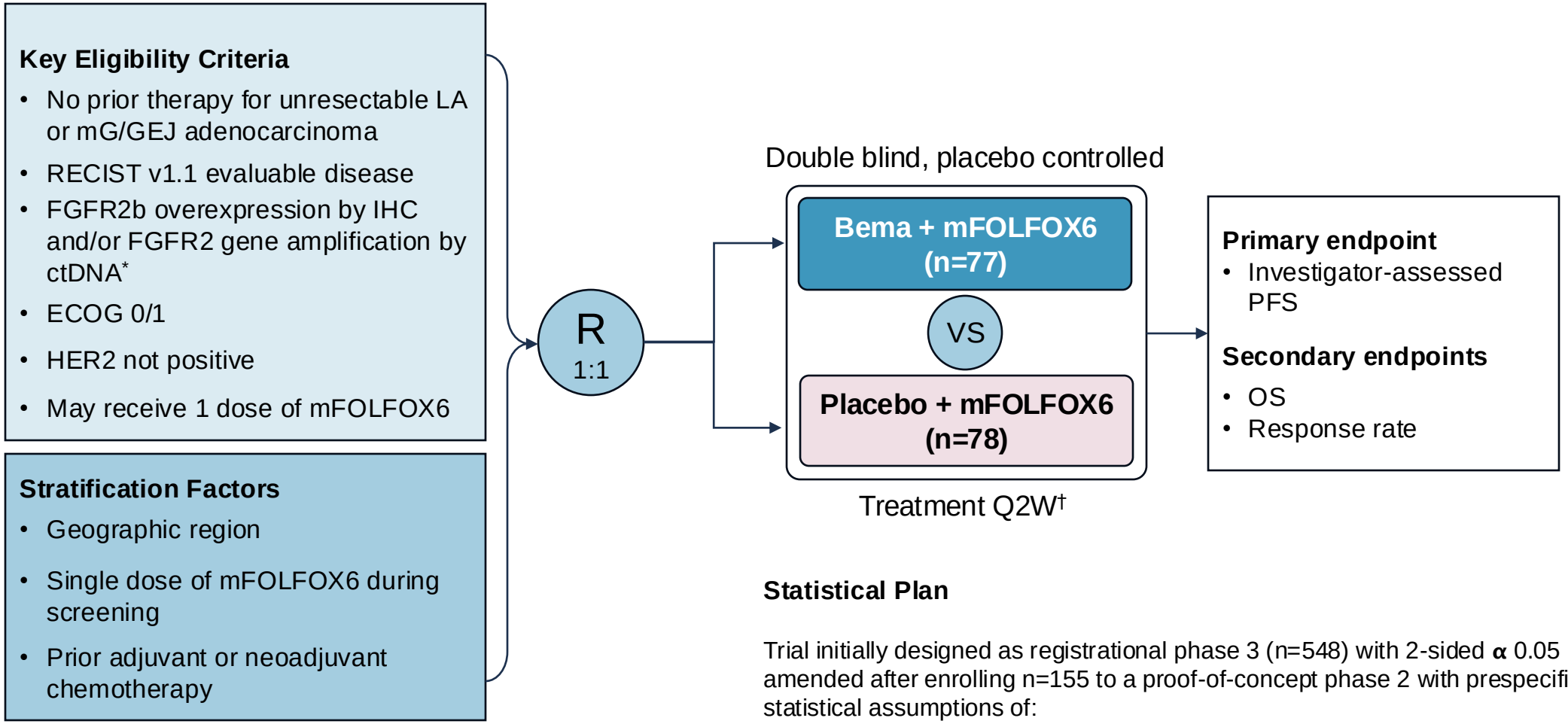
- AMG910/ASP2138 (CD3), Q-1802 (PD-L1)
- TJCD4B (4-1BB)
- PT886 (CD47)

ADCs



- CMG901, EO-3021
- TPX4589
- RC118
- LM302
- SOT102
- SKB315
- JS107
- IBI343

FIGHT Trial Design



*Central testing: IHC stain (Ventana): cut-off any 2+/3+; circulating tumor DNA (PGDx): cut-off 1.5X.
†15 mg/kg Q2W with a single 7.5-mg/kg dose on Cycle 1 Day 8.

Statistical Plan

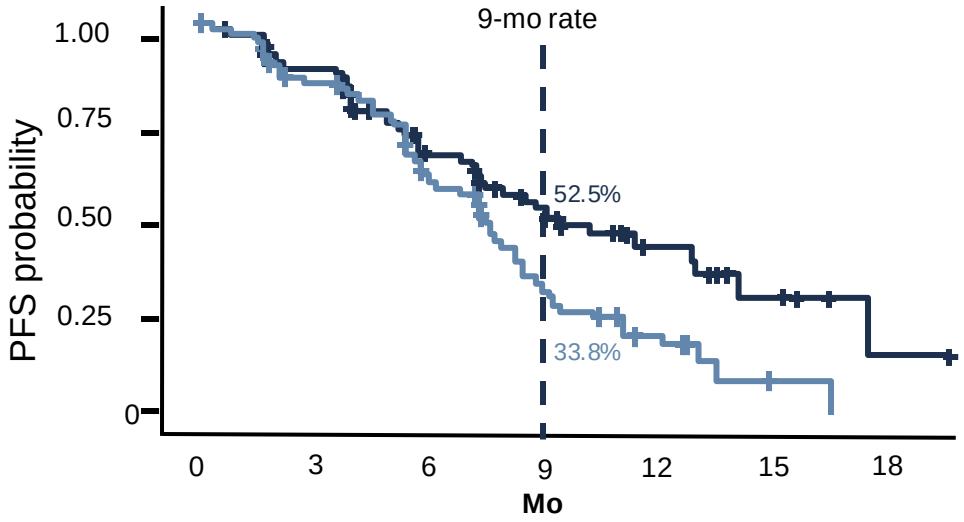
Trial initially designed as registrational phase 3 (n=548) with 2-sided **α** 0.05 amended after enrolling n=155 to a proof-of-concept phase 2 with prespecified statistical assumptions of:

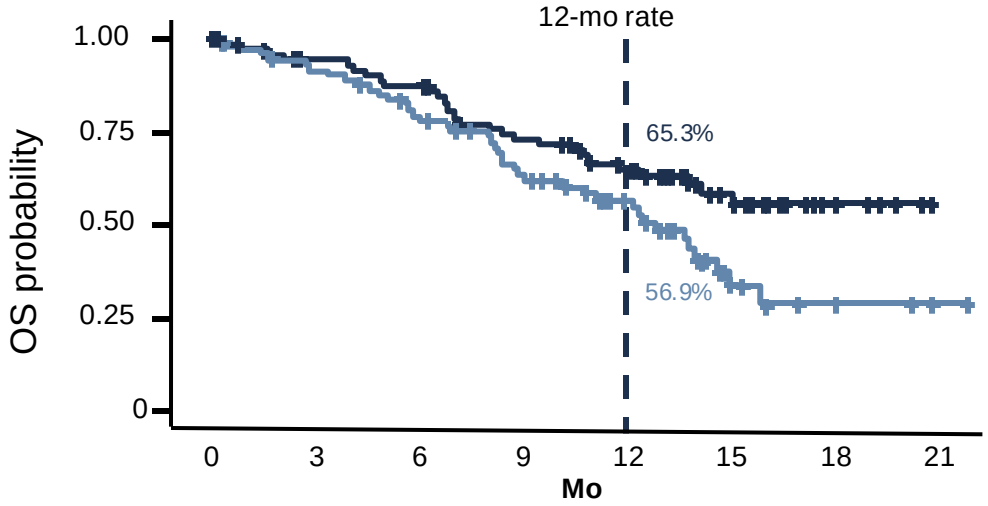
- Hierarchical sequential testing: PFS, then OS/ORR
- ≥84 events to demonstrate benefit at a HR ≤0.76 for PFS at 2-sided **α** of 0.2

Wainberg ZA. ASCO GI 2021. Abstract LBA160. Wainberg ZA et al. *Lancet Oncol*. 2022;23(11):1430-40.

FIGHT: First-Line Bemarituzumab + mFOLFOX6 vs Placebo + mFOLFOX6 in Advanced Gastric/GEJ Cancer

- Randomized phase 2 trial of bemarituzumab (anti-FGFR2b antibody) or placebo + (both + mFOLFOX6) for patients with no prior therapy and unresectable LA or mG/GEJ adenocarcinoma with *FGFR2b* overexpression/amplification (N=155)





	Bema + mFOLFOX6 (n=77)	Placebo + mFOLFOX6 (n=78)	
Median PFS, mo	9.5	7.4	HR 0.68; *P*=0.0727
Median OS, mo	Not reached	12.9	HR 0.58; *P*=0.0268

Wainberg ZA. ASCO GI 2021. Abstr LBA160. Wainberg ZA et al. *Lancet Oncol*. 2022;23(11):1430-40.

FORTITUDE Phase 3 Studies

Fortitude-101

FOLFOX +/- bemarituximab

Fortitude-102

FOLFOX + Nivolumab +/- bemarituximab

Both studies have completed accrual, with revised statistics with higher FGFR2 threshold

Case study

- After counseling, patient did undergo pembrolizumab x2 doses (200 mg).

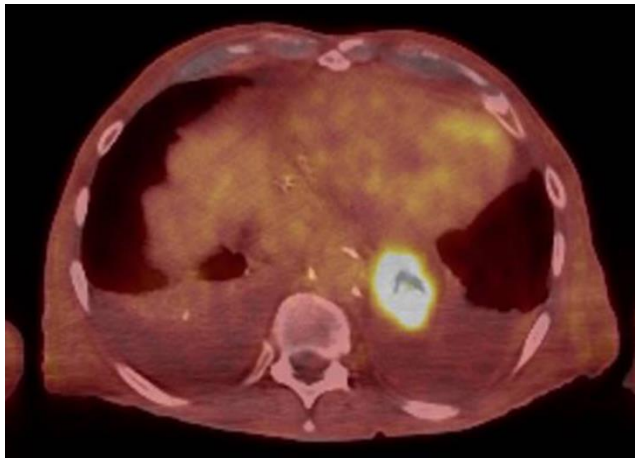
- PET: Decreased masslike avidity within the distal esophageal with residual linear avidity within the distal portion of the esophagus, distal to stent extending over a distance of approximately 6 cm, SUV 13.7, previously 9.6 cm SUV 21.1 possibly reflecting residual tumor +/- inflammatory process

- Pt was admitted with acute renal failure. Was given steroids.

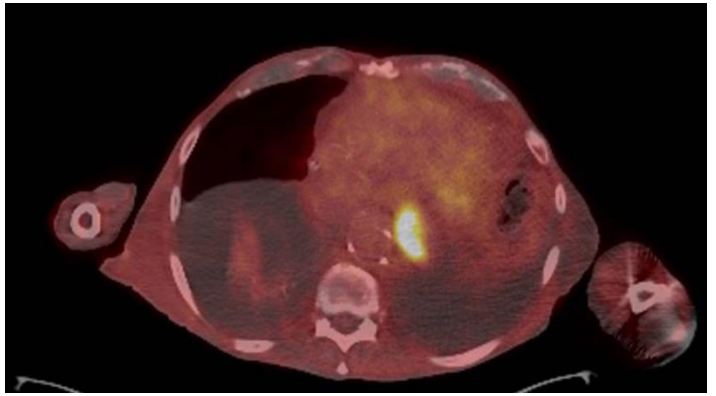
- Pt's creatinine is up to 6, he is making urine. Not requiring dialysis.

- No plan for further chemotherapy

PRE-treatment



Post-treatment



Conclusions

- Critical to obtain Biomarkers to optimally treat advanced Gastric/ GEJ adenocarcinoma
  - PD-L1
  - HER2
  - MMR
  - CLDN18.2
  - FGFR2
- Immunotherapy + chemotherapy for PD-L1 positive Gastric/GEJ adeno
- CLDN18.2 positive tumors – zolbetuximab
- HER2 – chemotherapy + pembrolizumab + trastuzumab

Thank You!

Manish A. Shah, MD
mas9313@med.cornell.edu
@mdmanishshah