Management of Metastatic Gastric/ GEJ Adenocarcinoma: First Line Therapy

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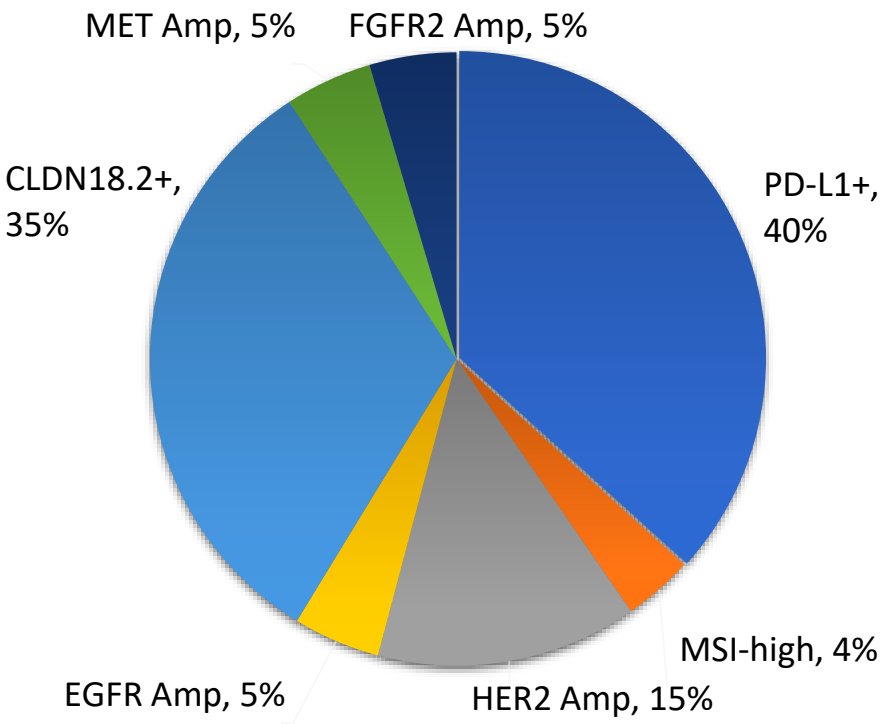
Key Biomarkers in Gastroesophageal Cancer



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;74(6):301-316.

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- **Pembrolizumab** approval for ≥3L treatment in the United States withdrawn (announced in July 2021)[4]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. Pembrolizumab prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125514s143lbl.pdf; 3. Högner A and 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[1]	KEYNOTE-859[2]	Rationale-05[3]
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)

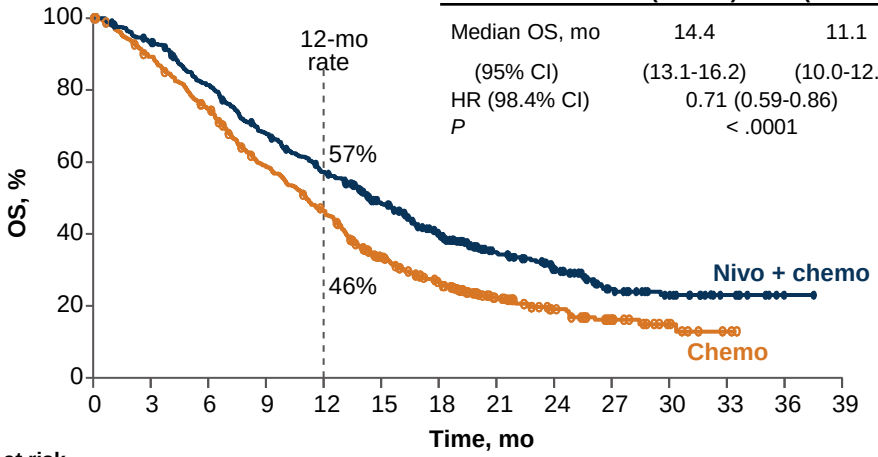
[a] Results from prespecified interim analysis of the first 264 patients.

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**

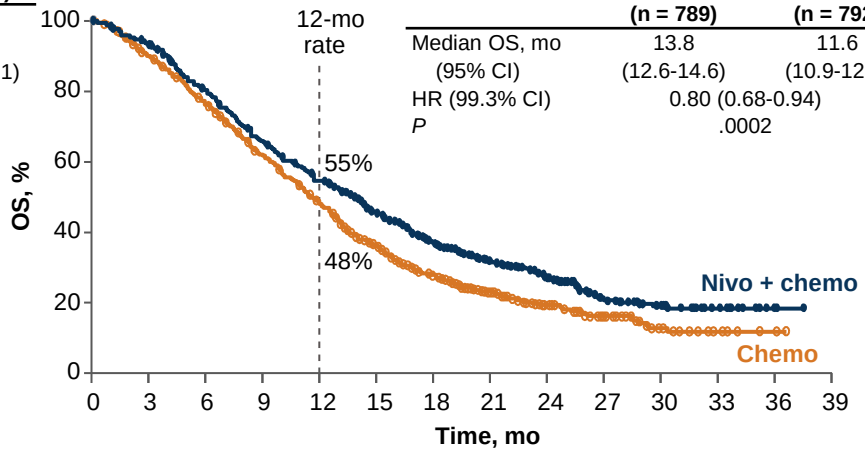
PD-L1 CPS ≥5



	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. 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

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

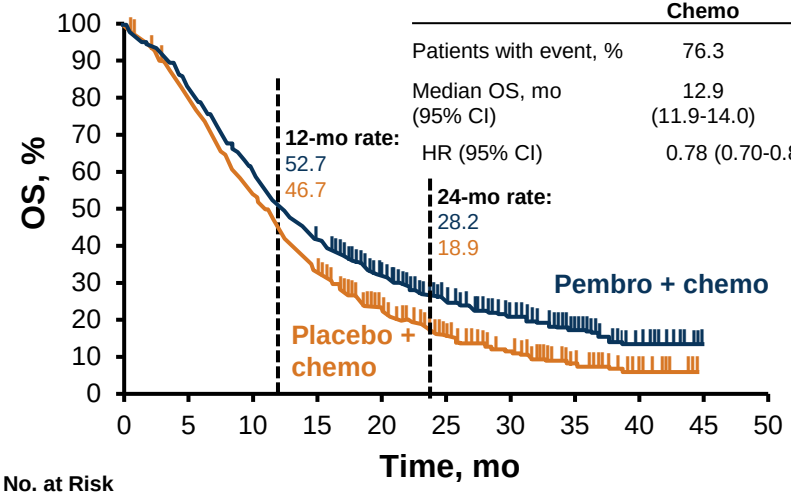
- Geographic region (EU/Israel/North America/Australia vs Asia vs rest of the world)
- PD-LI CPS (<1 vs >1)
- Choice of chemotherapy (FP vs CAPOX)

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

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

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

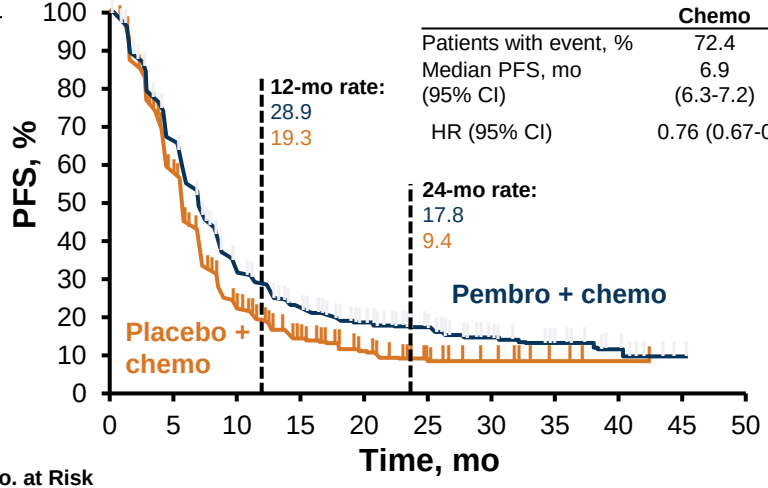
ITT Population OS



	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



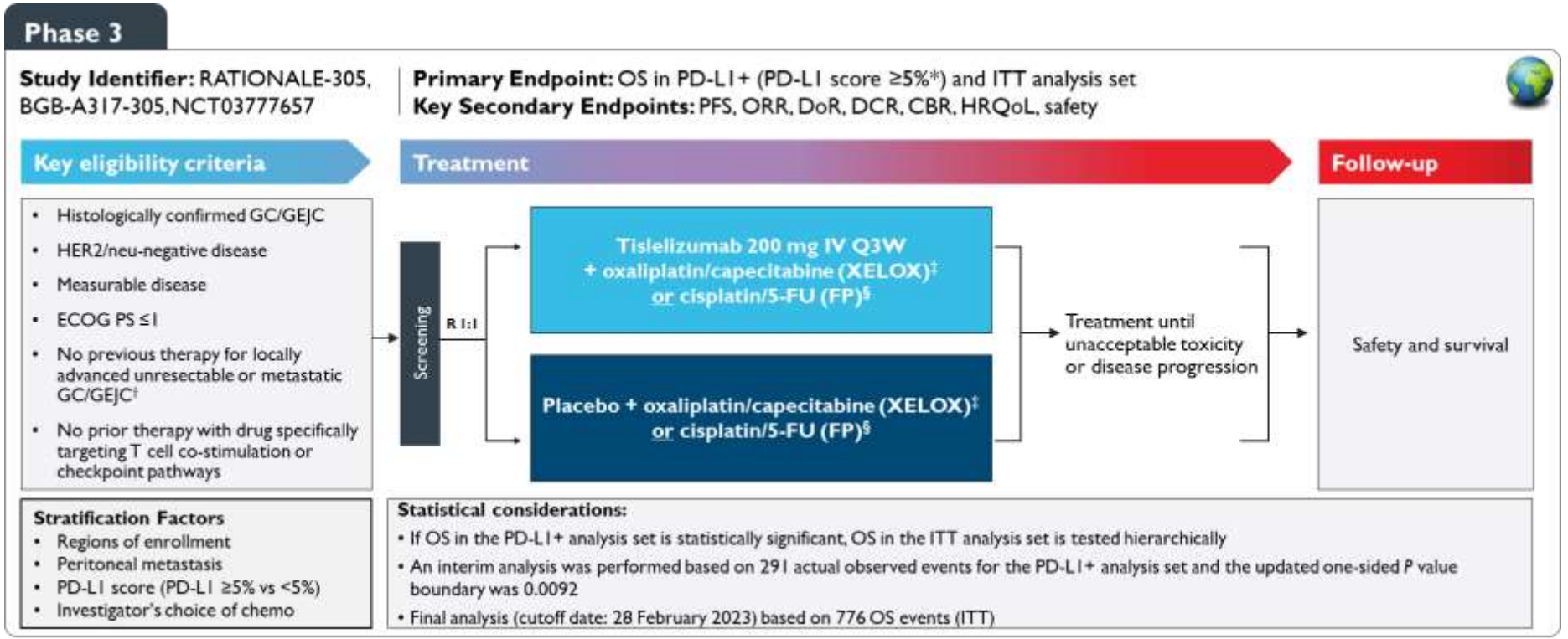
	Pembro + Chemo	Placebo + Chemo
Patients with event, %	72.4	77.1
Median PFS, mo (95% CI)	6.9 (6.3-7.2)	5.6 (5.5-5.7)
HR (95% CI)	0.76 (0.67-0.85); *P* < .0001	

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)

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

Rationale 305

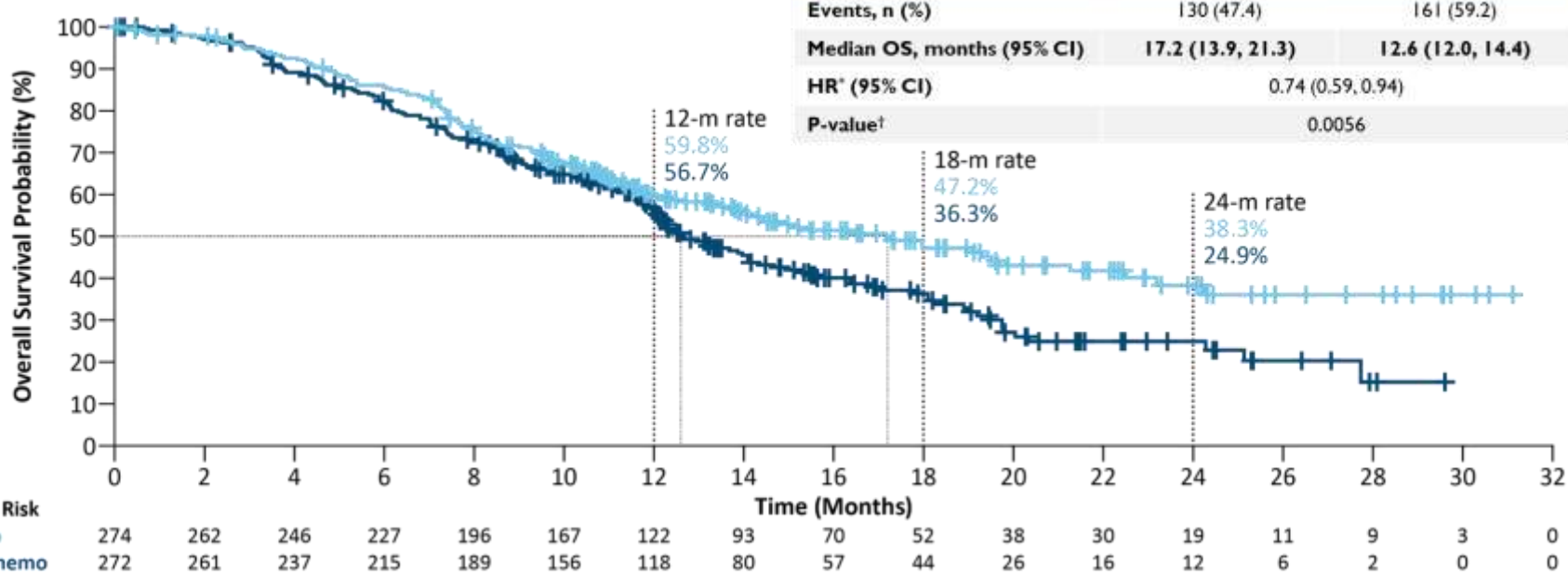


Moehler M et al. ASCO GI 2023. Abstract 286.

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	



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.

Moehler M et al. ASCO GI 2023. Abstract 286.

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 a slide by Dr Vaibhav Kumar

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	

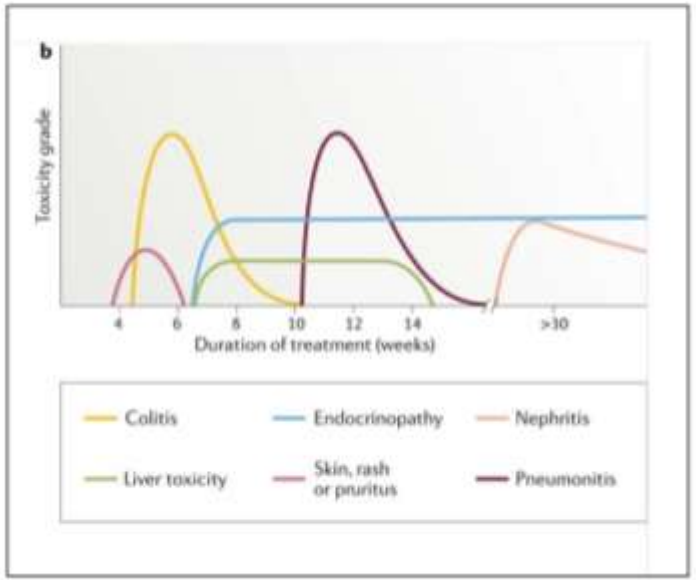
Adapted from a slide by Dr Vaibhav Kumar and information from product labeling and/or BLA submissions

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

Incidence of immune related adverse reactions (IMARs)

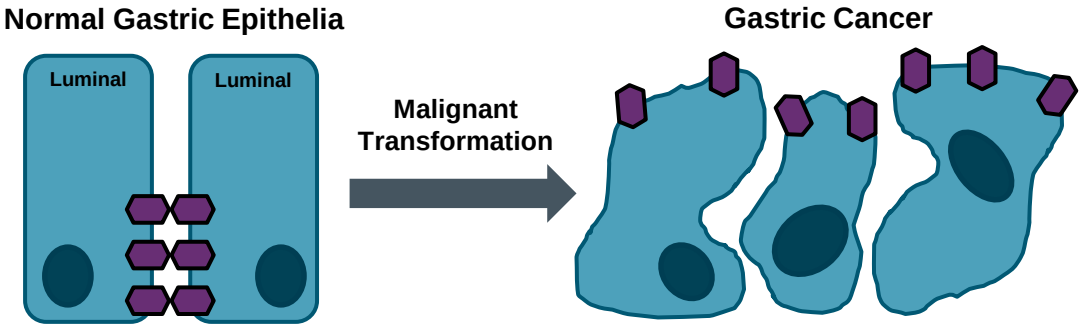
	All Grade	≥ 3
Diarrhea	6 to 19%	1%
Colitis	1 to 4%	0.3 to 2%
Pulmonary	1.5 to 5%	0 to 2%
Rash	9 to 16%	0.2 to 3.5%
Neurological	NR to 0.3%	NR to 0.3%
Endocrinopathy	7.3 to 23.4%	0 to 2%
Hepatic	0.3 to 10.8%	0 to 1.5%
Renal	NR to 2%	0 to 0.5%

Time course of immune related adverse events



Martins F et al. *Nat Rev Clin Oncol.* 2019;16(9):563-580.

Claudin18.2: Leveraging Biology

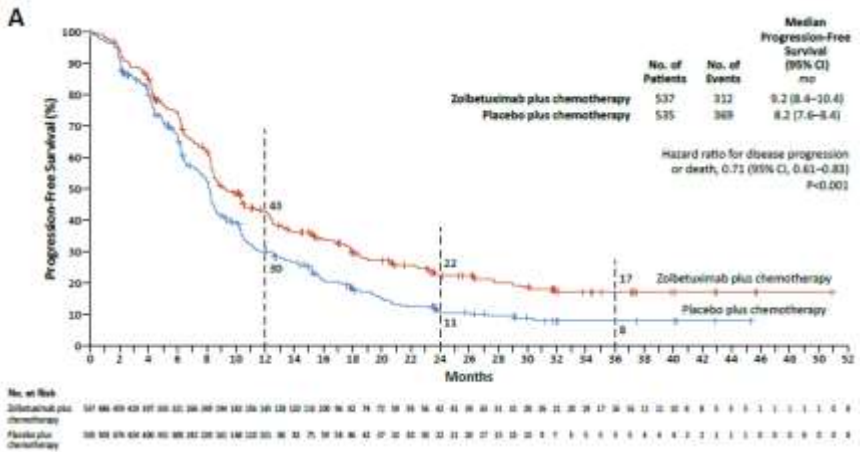


- Claudin18.2 is a major structural component of intercellular tight junctions
- Not routinely expressed in any normal tissue outside gastric mucosa (cancer-restricted antigen)
- Broadly expressed in several tumor types including gastric, GEJ, biliary, and pancreatic

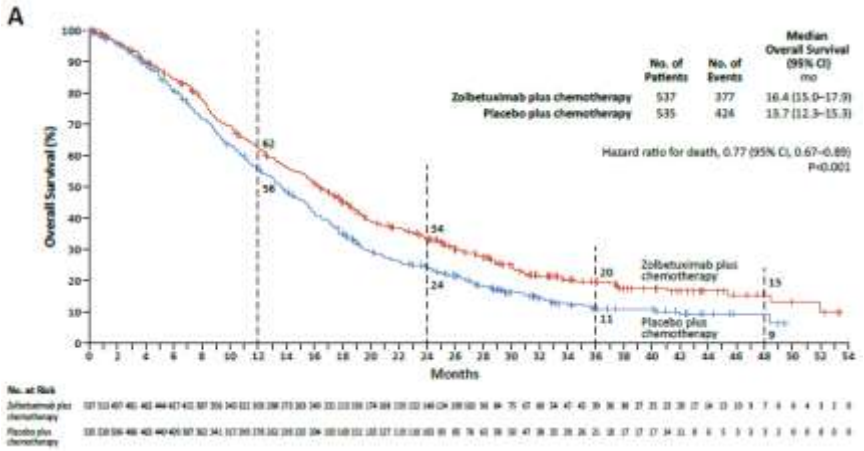
Baek JH et al. *Anticancer Res.* 2019;39(12):6973-6979.

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

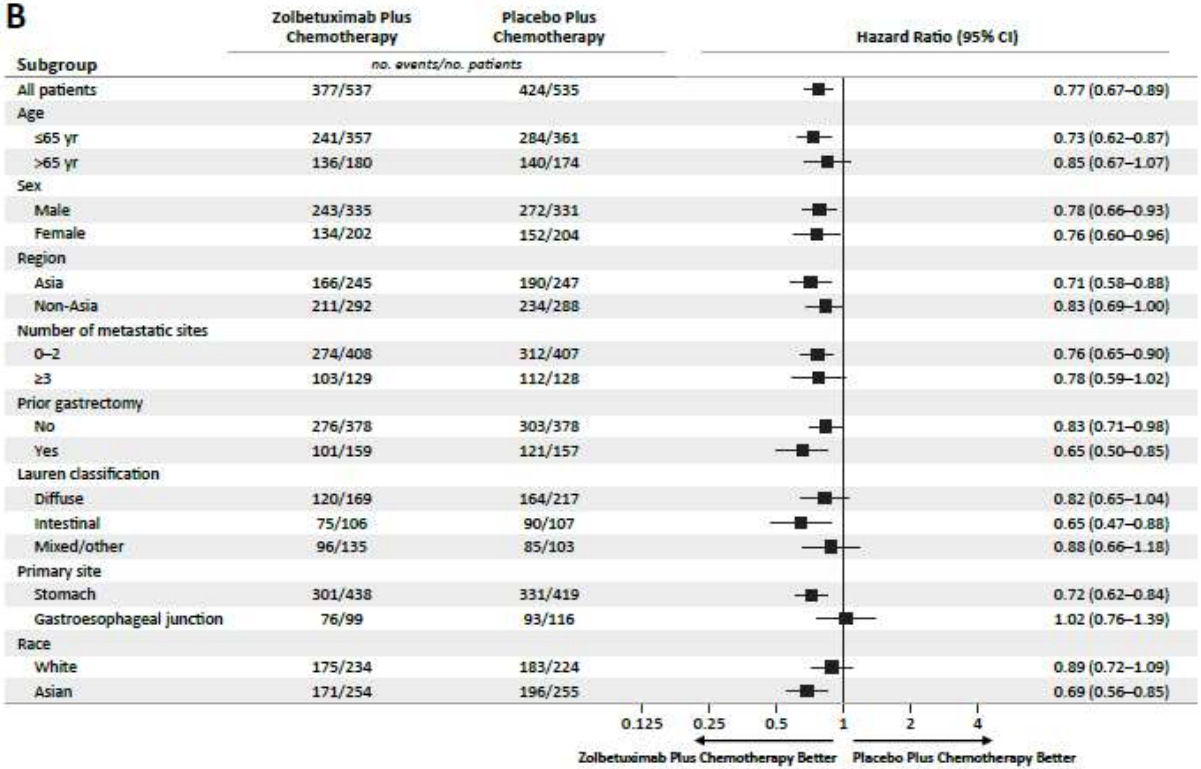
Measurable disease (n=820),
Complete Response - 5.2%. v. 3.1%
Partial Response - 52.2%. v. 52.2%
Overall Response Rate - 57.4%. Vs. 55.3%

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%

Shitara K, Shah MA et al. *N Engl J Med.* 2024;391(12):1159-1162.

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?

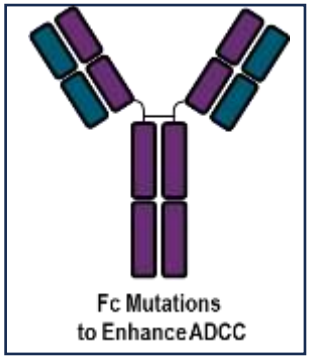
Validated Target

Shitara K, Shah MA et al. *N Engl J Med.* 2024;391(12):1159-1162.

CLDN 18.2 Targeted Therapies[a]

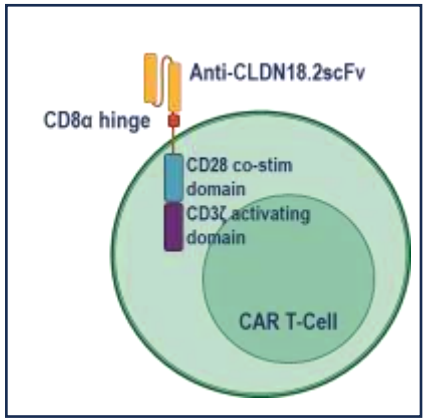
Monoclonal antibody

- Humanized mAb
- Engineered mAb



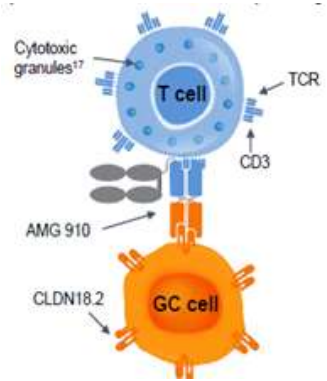
Zolbetuximab (FDA approved)
TST-001
ABI011, MIL93, ZL1211 etc.

CAR-T



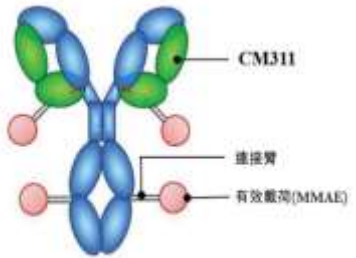
CT-041
LCAR-C18S
LY011

Bispecific



AMG910/ASP2138 (CD3)
TJ-CD4B (4-1BB)
PT886 (CD47)
Q-1802 (PD-L1)
IBI 389

ADCs



CMG901, EO-3021
TORL-2800
TPX4589
RC118
LM302
SOT102
SKB315
JS107
IBI343

[a]Agents on this slide are investigational unless indicated.

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!

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