Optimal Management of Metastatic Gastric/Gastroesophageal Cancer

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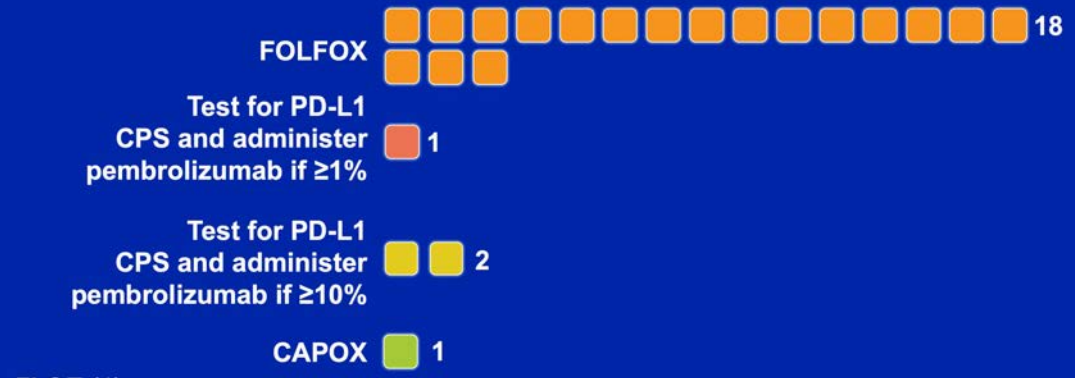
Regulatory and reimbursement issues aside, what would you currently recommend as first-line therapy for a patient with minimally symptomatic, low-volume, HER2-negative, MSS metastatic squamous cell cancer of the esophagus?

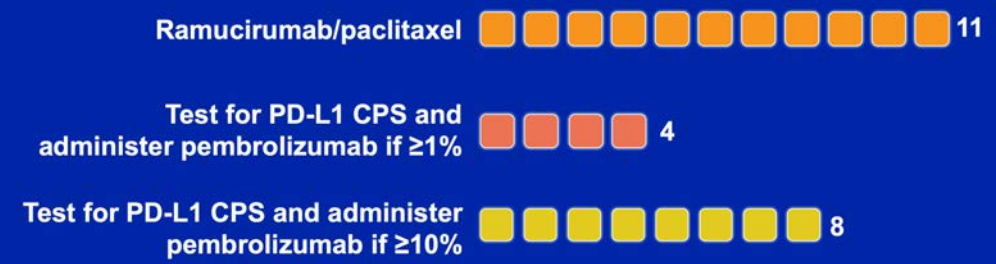
5-FU/platinum (1)

Regulatory and reimbursement issues aside, what would you currently recommend as first-line therapy for a patient with minimally symptomatic, low-volume, HER2-negative, MSS metastatic gastric adenocarcinoma?



FLOT (1)

Regulatory and reimbursement issues aside, what would you currently recommend as second-line therapy for a patient with metastatic HER2-negative, MSS gastric adenocarcinoma who has experienced disease progression on first-line FOLFOX?



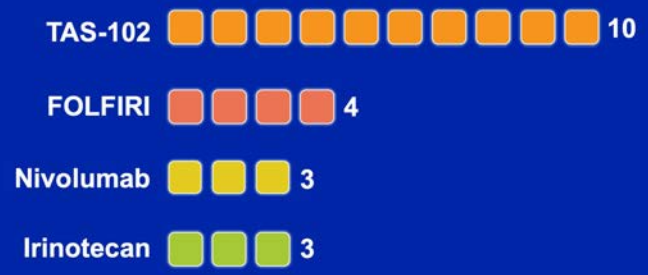
Gastroesophageal Cancer

HER2-negative disease

- Sequencing of systemic therapies, including ramucirumab
- Integration of PD-L1 testing
- Selection and use of anti-PD-1/PD-L1 antibodies

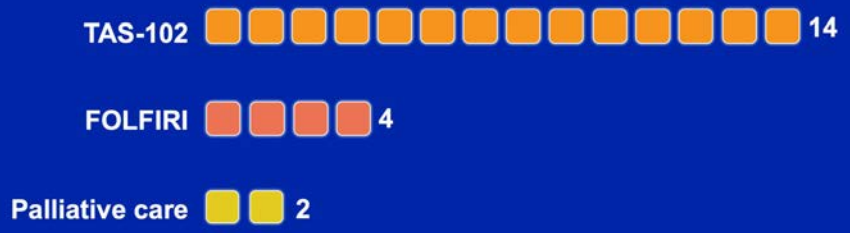
HER2-positive disease

What is your usual third-line treatment for a younger patient (PS 0) with metastatic HER2-negative, MSS gastric cancer (PD-L1 CPS <1) who has experienced disease progression on FOLFOX and paclitaxel/ramucirumab?



Palliative care (2)

What is your usual next treatment for a younger patient (PS 0) with metastatic HER2-negative, MSS gastric cancer who has experienced disease progression on FOLFOX, paclitaxel/ramucirumab and an anti-PD-1/PD-L1 antibody?



Irinotecan (1)

A 60-yo patient with metastatic HER2-positive, MSS gastric cancer responds to FOLFOX/trastuzumab but then experiences disease progression after 8 months. Which second-line treatment would you recommend?

Continue trastuzumab and switch to FOLFIRI (2), Irinotecan (1)

Gastroesophageal Cancer

HER2-negative disease

- Sequencing of systemic therapies, including ramucirumab
- Integration of PD-L1 testing
- Selection and use of anti-PD-1/PD-L1 antibodies

HER2-positive disease

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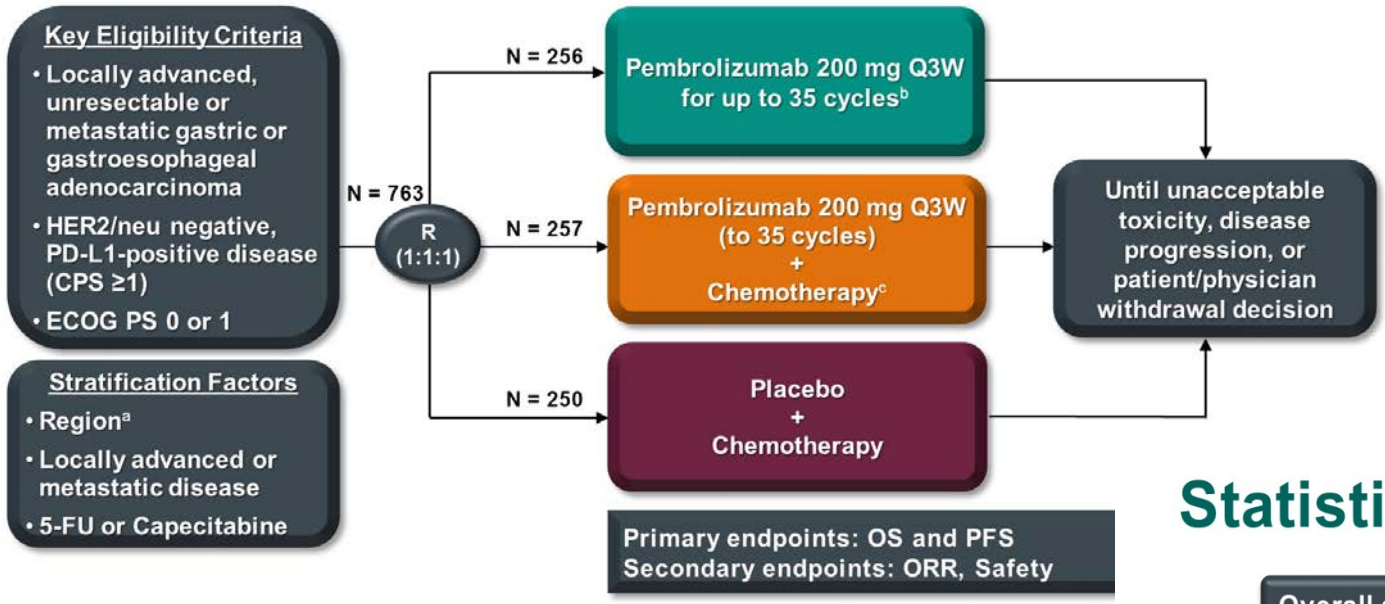
Disclosures: Crystal Denlinger

- **Advisory Committee:** Astellas, AstraZeneca Pharmaceuticals LP, Exelixis Inc
- **Consulting Agreements:** Bristol-Myers Squibb Company, Merck
- **Contracted Research:** Agios Pharmaceuticals Inc, Amgen Inc, Array BioPharma Inc, AstraZeneca Pharmaceuticals LP, BeiGene, Bristol-Myers Squibb Company, Exelixis Inc, Lilly, MacroGenics Inc, Sanofi Genzyme, ZymoGenetics Inc.

Pembrolizumab in 1st Line Gastric Adenocarcinoma

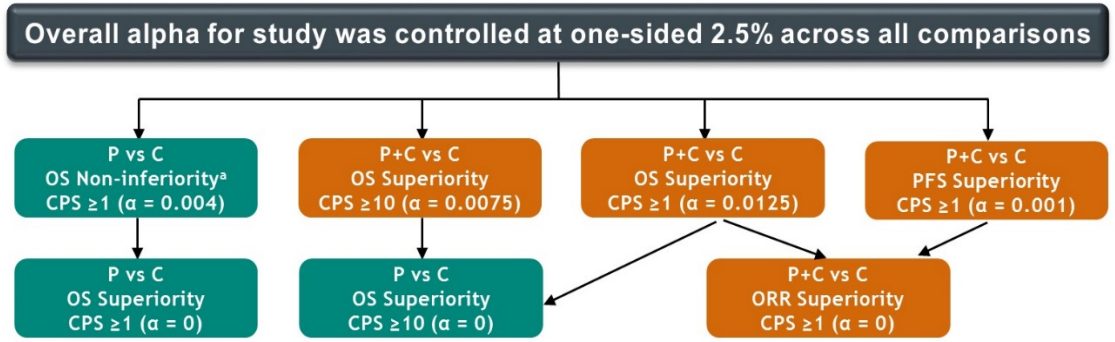
KEYNOTE-062 Study Design (NCT02494583)



[a]EU/North America/Australia, Asia (South Korea, Hong Kong, Taiwan, Japan), Rest of World (including South America).
[b]Administration of pembrolizumab monotherapy was not blinded.
[c]Chemotherapy: Cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2/d for 5 days Q3W or capecitabine BID d1-14 Q3W (Cisplatin may be capped at 6 cycles a

	Pembro	P + C	Chemo
CPS ≥ 10	92 (36%)	99 (39%)	90 (36%)
MSI-high	14 (5%)	17 (7%)	19 (8%)
MSI-H + CPS ≥ 10	11 (79%)	11 (65%)	10 (53%)

Statistical Considerations



- Hypotheses in top row tested first and in parallel
  - Remaining hypotheses tested only if preceding hypothesis was positive
  - Prespecified analysis plan allowed alpha passing from successful hypotheses
- Final analysis: planned to occur ≥22 months after last patient was randomized and ~415 OS events observed in P+C and C treatment groups in patients with PD-L1 CPS ≥1

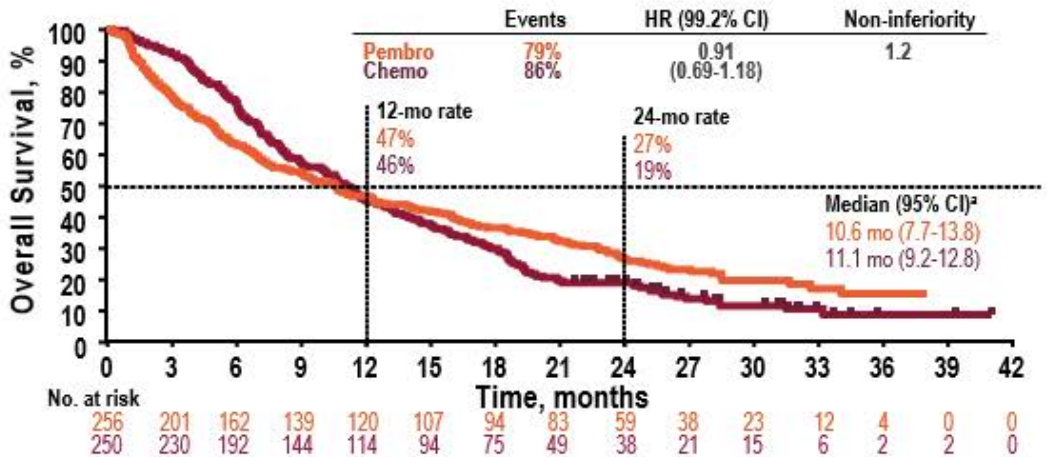
[a]Alpha passed from non-inferiority to superiority test; Median follow-up, 11.3 months (range, 0.2-41.2); Data cutoff: March 26, 2019.

Tabernero 2019 ASCO Annual Meeting, Chung 2019 ESMO Asia

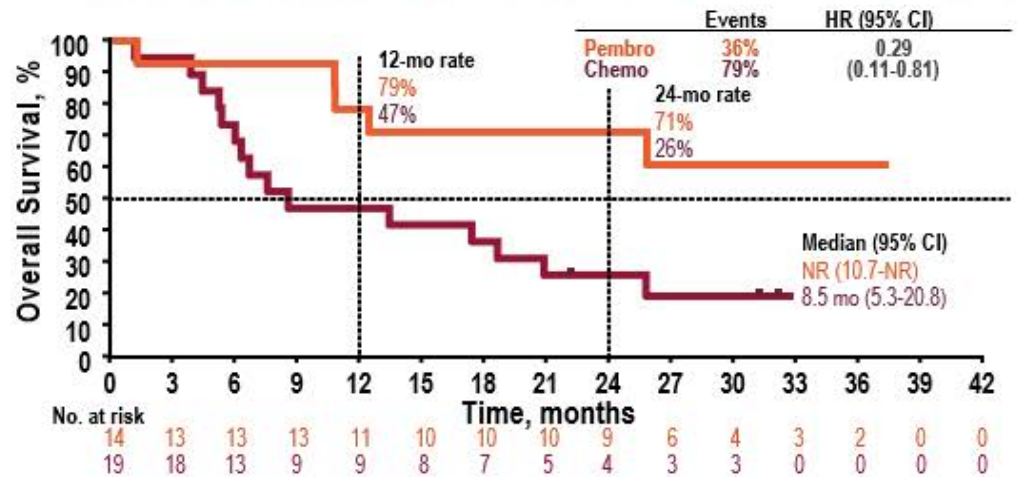
KEYNOTE 062: Overall Survival
Pembro Monotherapy

CPS ≥1

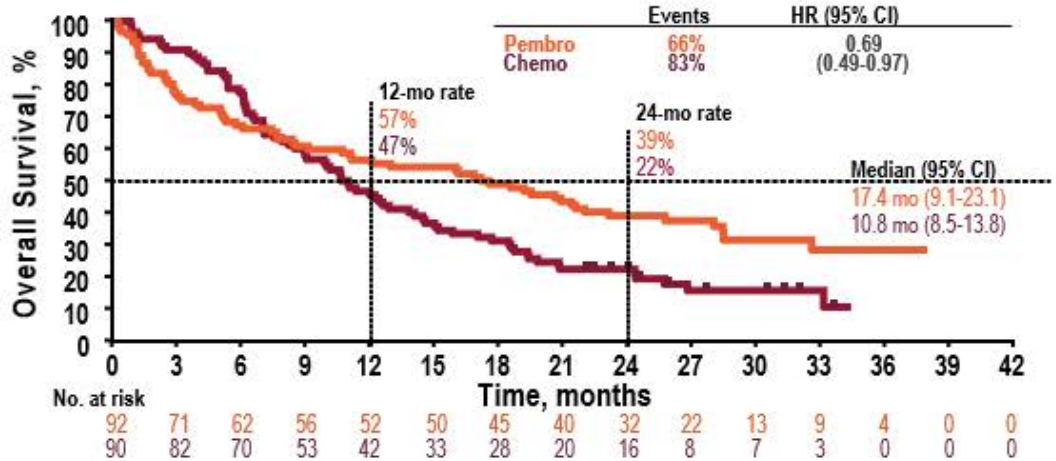
Overall

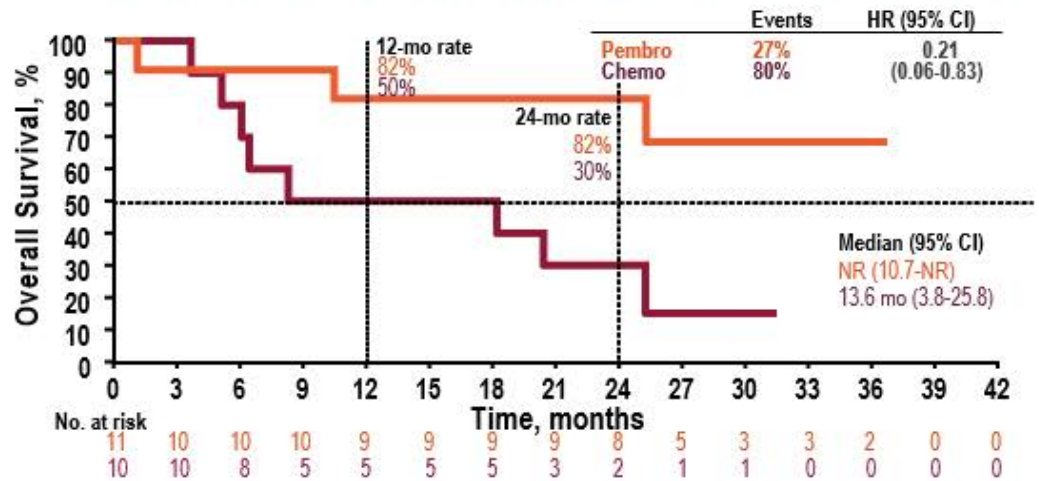


MSI-H Group



CPS ≥10





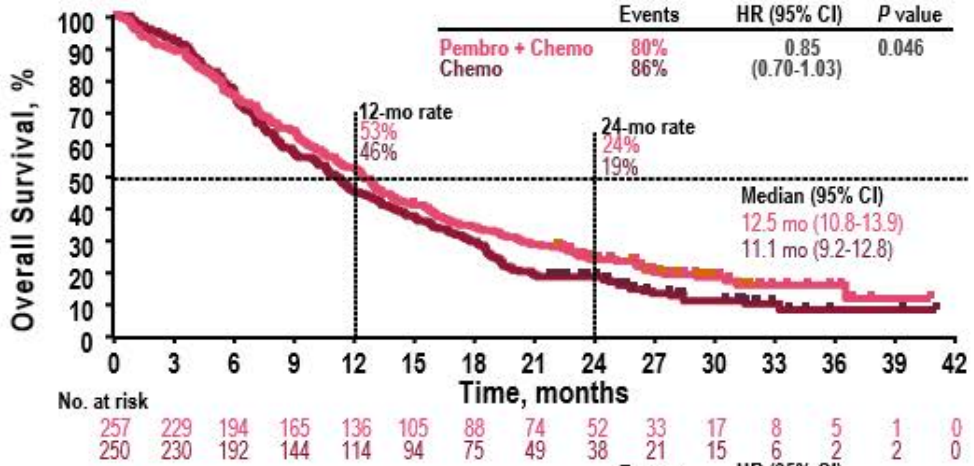
Data cutoff: March 26, 2019.

Chung 2019 ESMO Asia

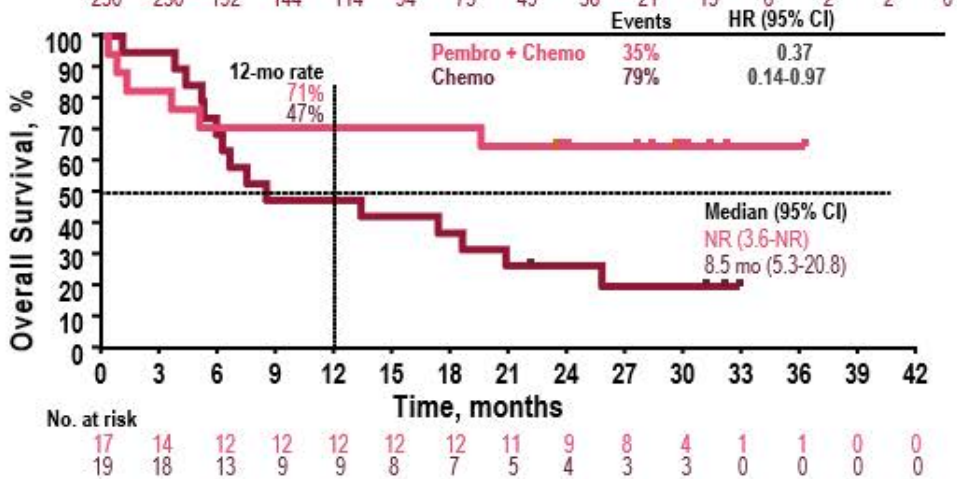
KEYNOTE 062: Overall Survival Pembro + Chemo

CPS ≥1

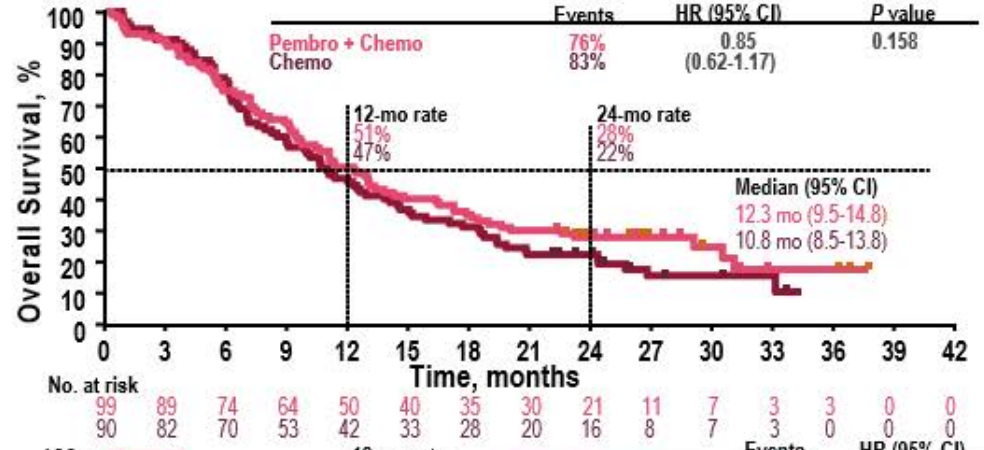
Overall

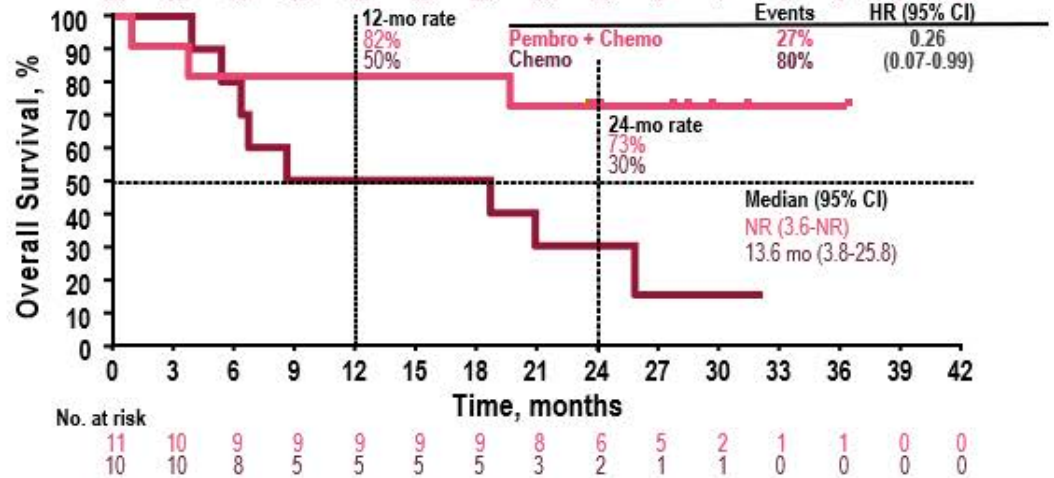


MSI-H Group



CPS ≥10

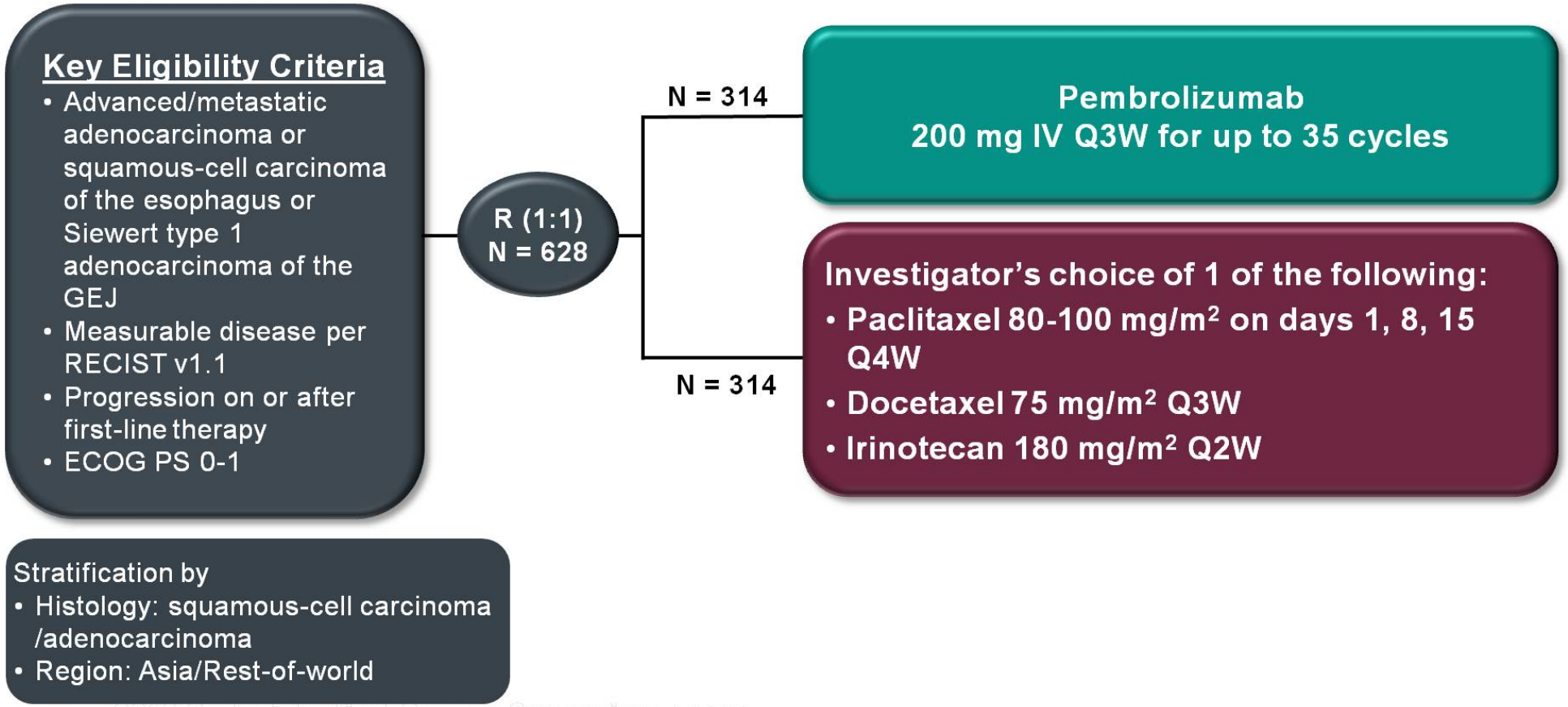




Data cutoff: March 26, 2019.

Chung 2019 ESMO Asia

Phase 3 KEYNOTE-181 Study (NCT02564263)



Primary end points

OS in patients
- In the ITT group
- With SCC
- Whose tumor had a PD-L1 CPS ≥10

Secondary end points

- PFS
- ORR
- Safety

Exploratory end points

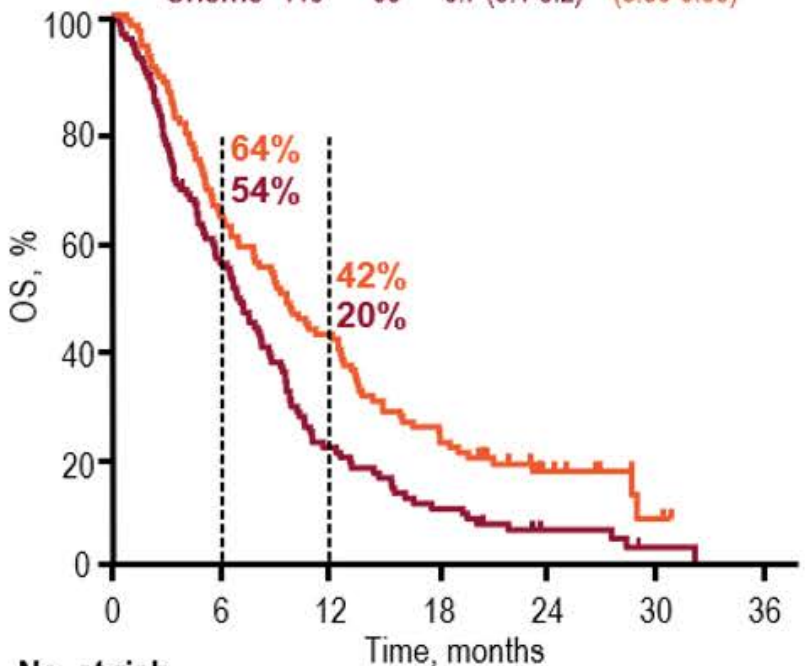
- HRQoL in patients whose tumor had a PD-L1 CPS ≥10

Presented By Takashi Kojima at 2019 Gastrointestinal Cancer Symposium and Sung-Bae Kim at 2019 ESMO Asia Congress

Overall Survival in the Global Population

PD-L1 CPS ≥10 (n = 222)

	N	Events, %	Median, mo (95% CI)	HR (95% CI)
Pembro	107	84	9.3 (6.6-12.5)	0.67
Chemo	115	95	6.7 (5.1-8.2)	(0.50-0.89)

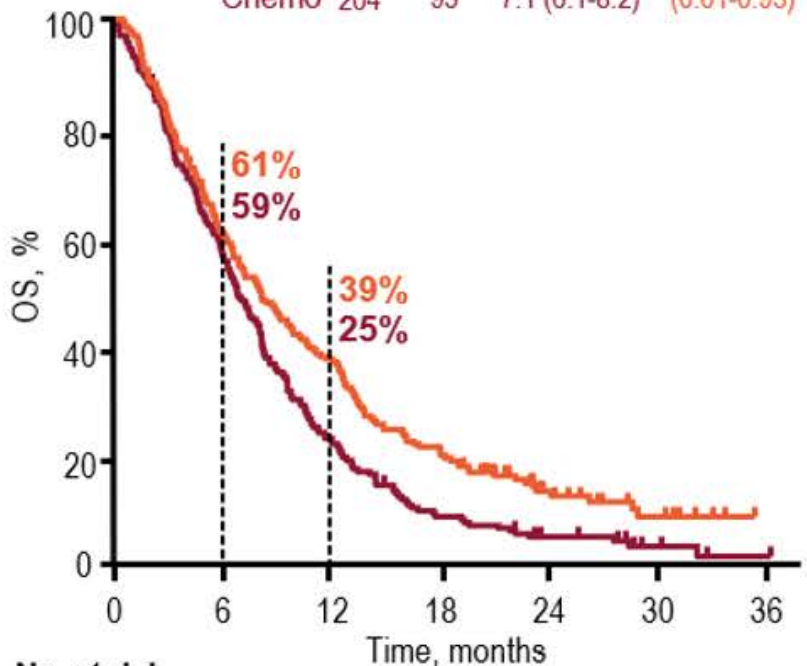


No. at risk

107	68	45	27	10	2	0
115	61	23	11	4	1	0

SCC (n = 403)

	N	Events, %	Median, mo (95% CI)	HR (95% CI)
Pembro	199	86	8.2 (6.7-10.0)	0.75
Chemo	204	93	7.1 (6.1-8.2)	(0.61-0.93)

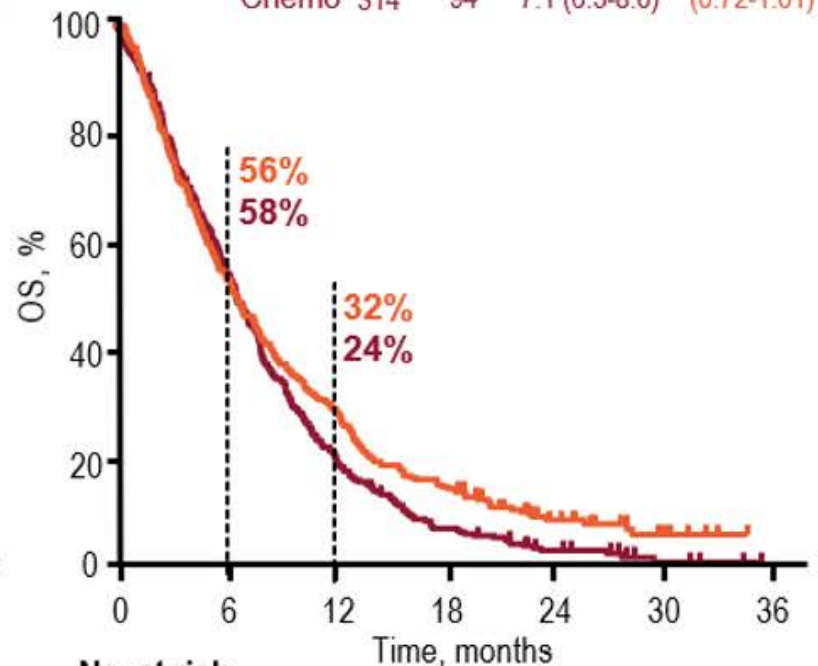


No. at risk

199	122	77	46	18	8	0
204	118	50	21	11	4	0

ITT (N = 628)

	N	Events, %	Median, mo (95% CI)	HR (95% CI)
Pembro	314	88	7.1 (6.2-8.1)	0.85
Chemo	314	94	7.1 (6.3-8.0)	(0.72-1.01)



No. at risk

314	176	101	58	22	9	0
314	181	75	29	13	5	0

Data cutoff: February 13, 2019; these data represent an additional 4 months of follow up data from the October 15, 2018 cutoff.

Bang et al, 2019 ESMO Asia

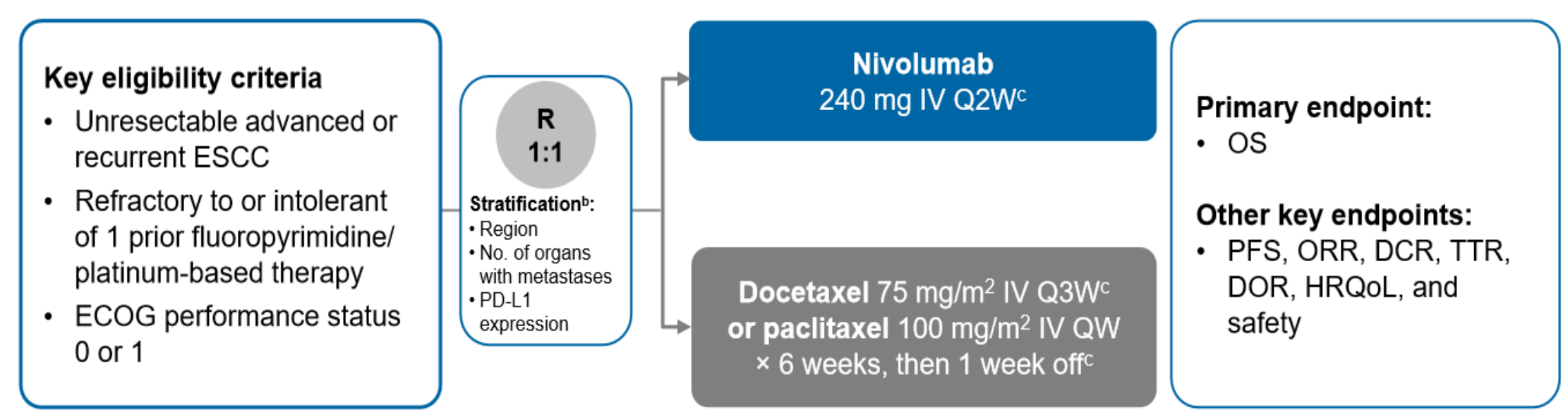
KEYNOTE-181: Pembrolizumab vs Chemotherapy in Esophageal Cancer

	CPS ≥ 10 (N=222)			Squamous Cell Carcinoma (N=401)			All Patients (N=628)		
	Pembro	Chemo	HR/ P value	Pembro	Chemo	HR/ P value	Pembro	Chemo	HR/ P value
PFS	2.6 mo	3.0 mo	HR 0.73 (0.54-0.97)	2.2 mo	3.1 mo	HR 0.92 (0.75-1.13)	2.1 mo	3.4 mo	HR 1.11 (0.94-1.31)
12 month PFS	21%	7%		15%	9%		12%	10%	
ORR	21.5%	6.1%	0.0006	16.7%	7.4%	0.0022	13.1%	6.7%	0.0037
DOR	9.3 mo	7.7 mo		8.5 mo	10.7 mo		8.5 mo	10.7 mo	

	PD-L1 CPS ≥ 10 SCC		PD-L1 CPS ≥ 10 ACC	
	Pembro (N=86)	Chemo (N=82)	Pembro (N=22)	Chemo (N=33)
Median OS	10.1 mo	6.7 mo	6.6 mo	6.9 mo
• HR (95% CI)	0.61 (0.44-0.85)		0.87 (0.49-1.55)	
• 12 mo OS (%)	47%	23%	24%	15%
Median PFS	3.2 mo	2.3 mo	2.1 mo	3.7 mo
• 12 mo PFS (%)	23%	7%	14%	7%
ORR (%)	22%	7%	18%	3%

Kojima 2019 ASCO GI, Shah 2019 ASCO GI, Bang et al, 2019 ESMO Asia

ATTRACTION-3: Nivolumab in Esophageal Squamous Cell Carcinoma (ESCC)

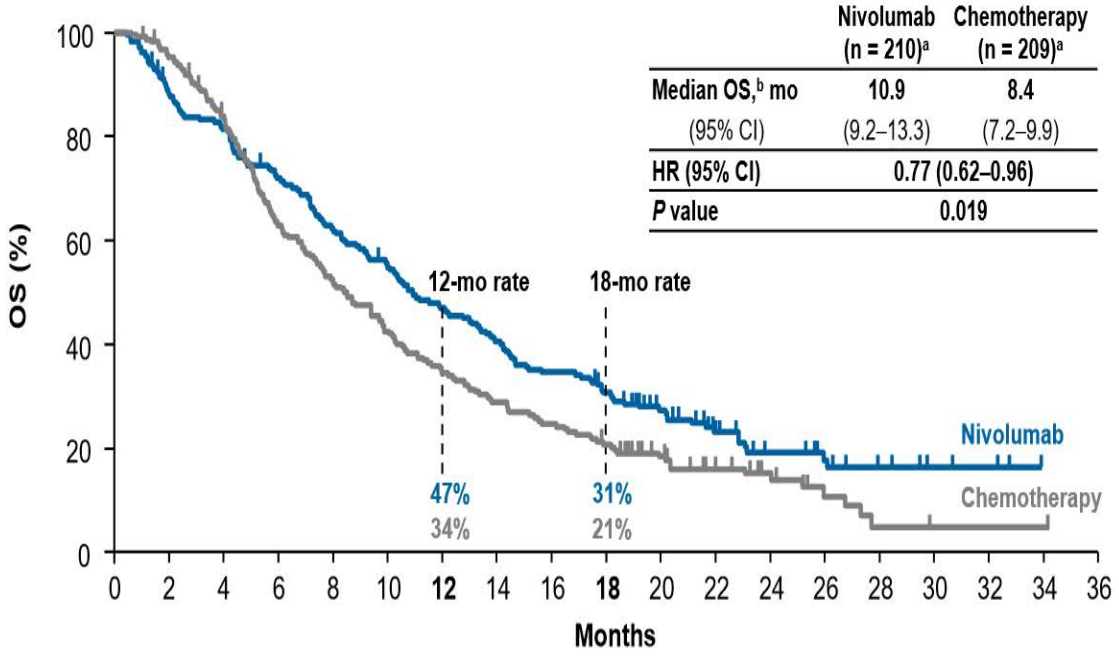


	Nivolumab	Chemotherapy	P value
Overall Response Rate	19%	22%	0.63
Disease Control Rate	37%	63%	
Median Time to Response	2.6 months	1.5 months	
Duration of Response	6.9 months	3.9 months	
Treatment-Related Adverse Events	66%	95%	
Dose delays due to Adverse Events	39%	50%	

Cho BC et al ESMO 2019 Annual Congress and Kato K et al Lancet Oncology 2019

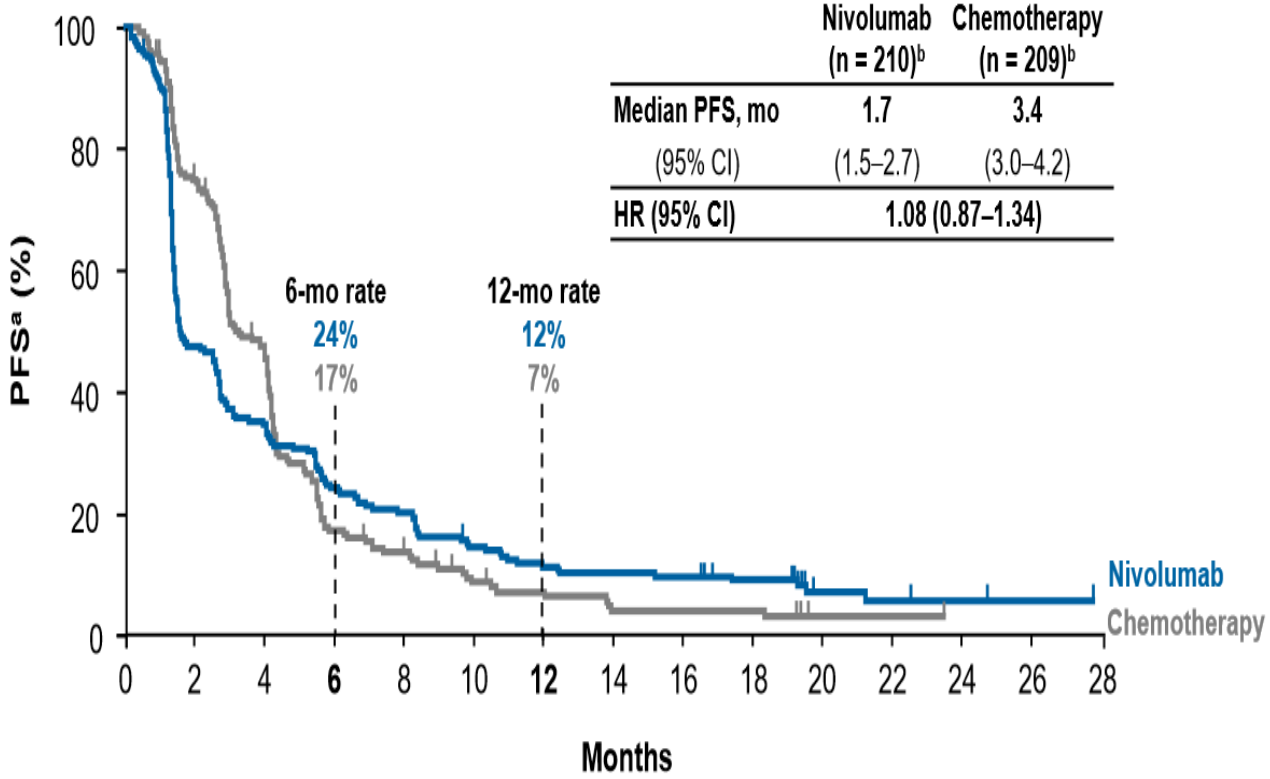
ATTRACTION-3: Nivolumab in ESCC

Overall Survival



	Nivolumab (n = 210)[a]	Chemotherapy (n = 209)[a]
Median OS,[b] mo	10.9	8.4
(95% CI)	(9.2–13.3)	(7.2–9.9)
HR (95% CI)	0.77 (0.62–0.96)	
P value	0.019	

Progression-Free Survival

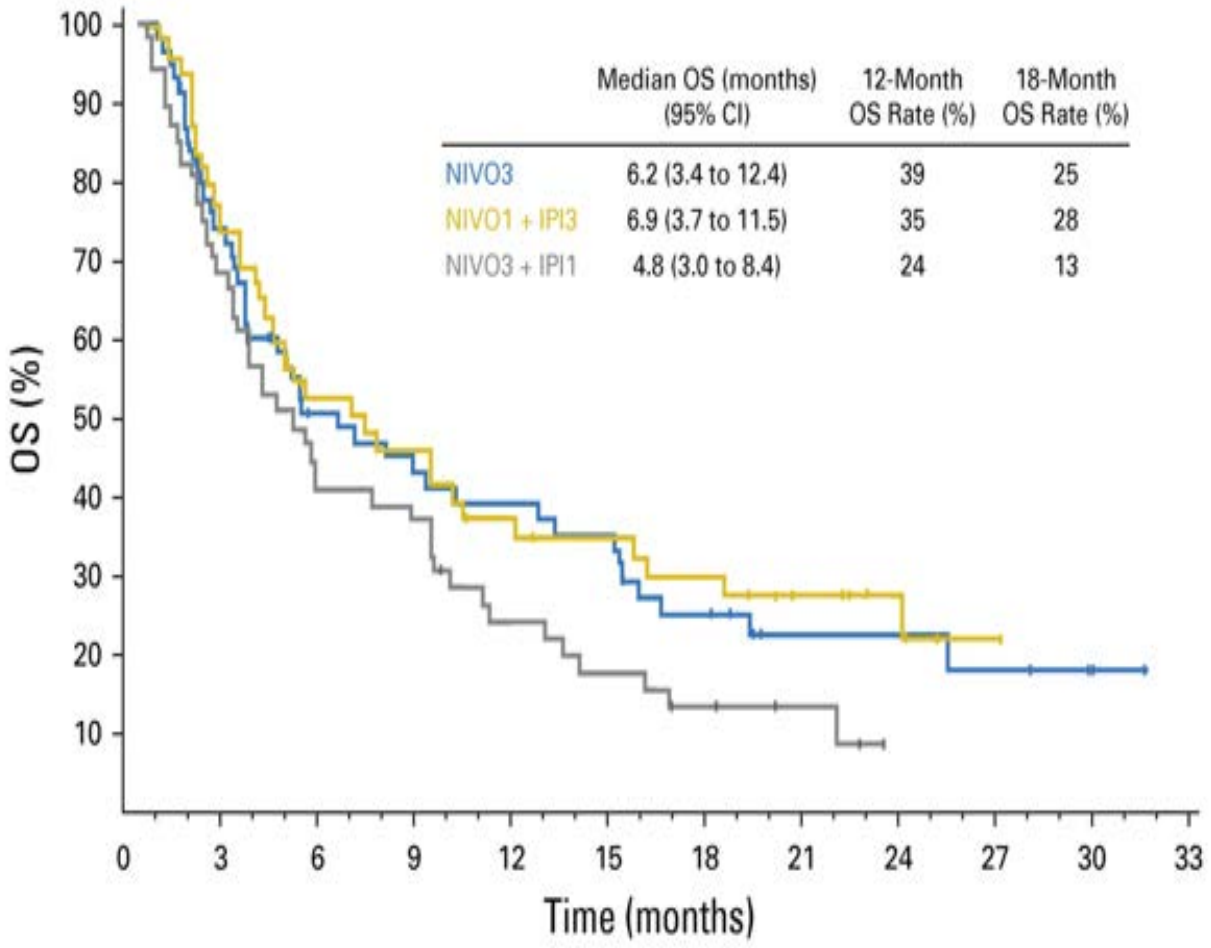


	Nivolumab (n = 210)[b]	Chemotherapy (n = 209)[b]
Median PFS, mo	1.7	3.4
(95% CI)	(1.5–2.7)	(3.0–4.2)
HR (95% CI)	1.08 (0.87–1.34)	

Kato et al Lancet Oncology 2019

Inhibiting the PD-1 and CTLA-4 Pathways

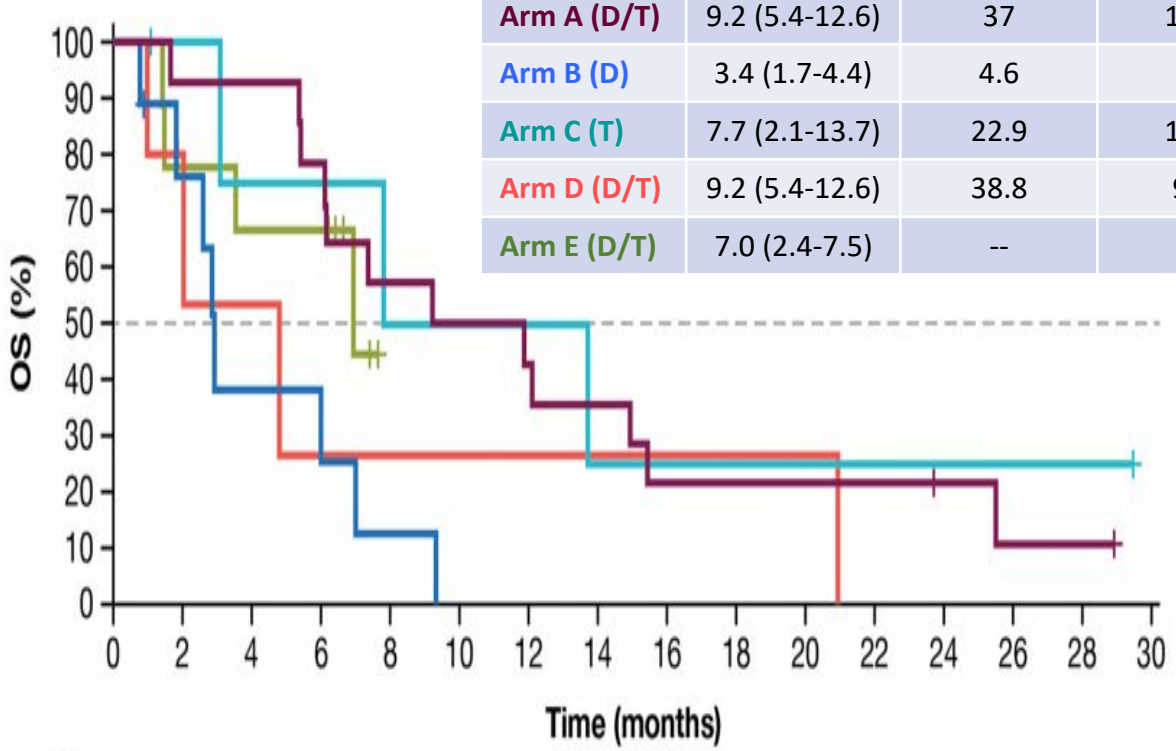
Nivolumab and Ipilimumab



Janjigian et al, Journal of Clinical Oncology 2018

Durvalumab and Tremelimumab

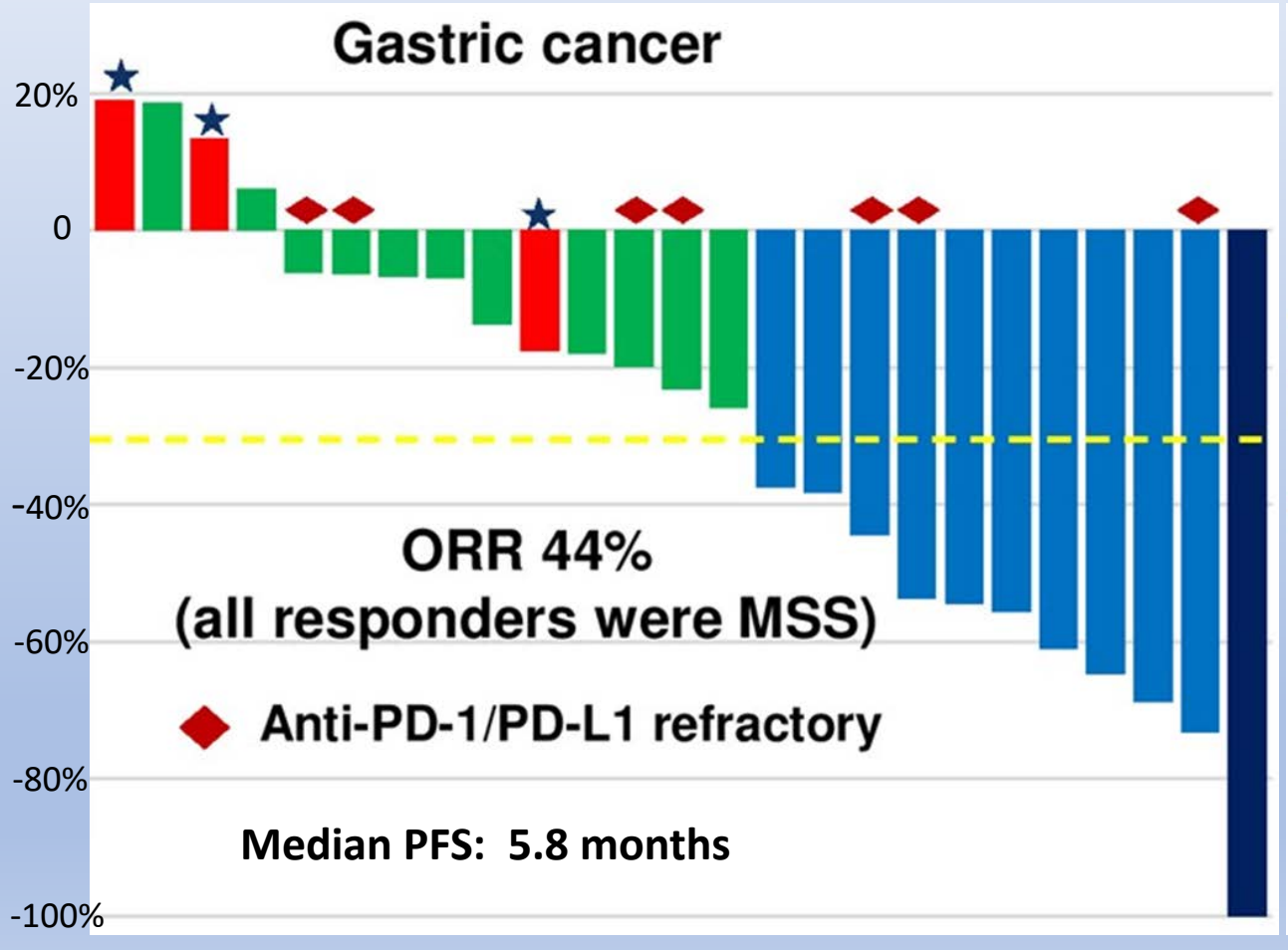
	Median OS (mo)	12-month OS Rate (%)	24 month OS rate (%)
Arm A (D/T)	9.2 (5.4-12.6)	37	18.5
Arm B (D)	3.4 (1.7-4.4)	4.6	0
Arm C (T)	7.7 (2.1-13.7)	22.9	11.5
Arm D (D/T)	9.2 (5.4-12.6)	38.8	9.7
Arm E (D/T)	7.0 (2.4-7.5)	--	--



Kelly et al, Clinical Cancer Research 2019

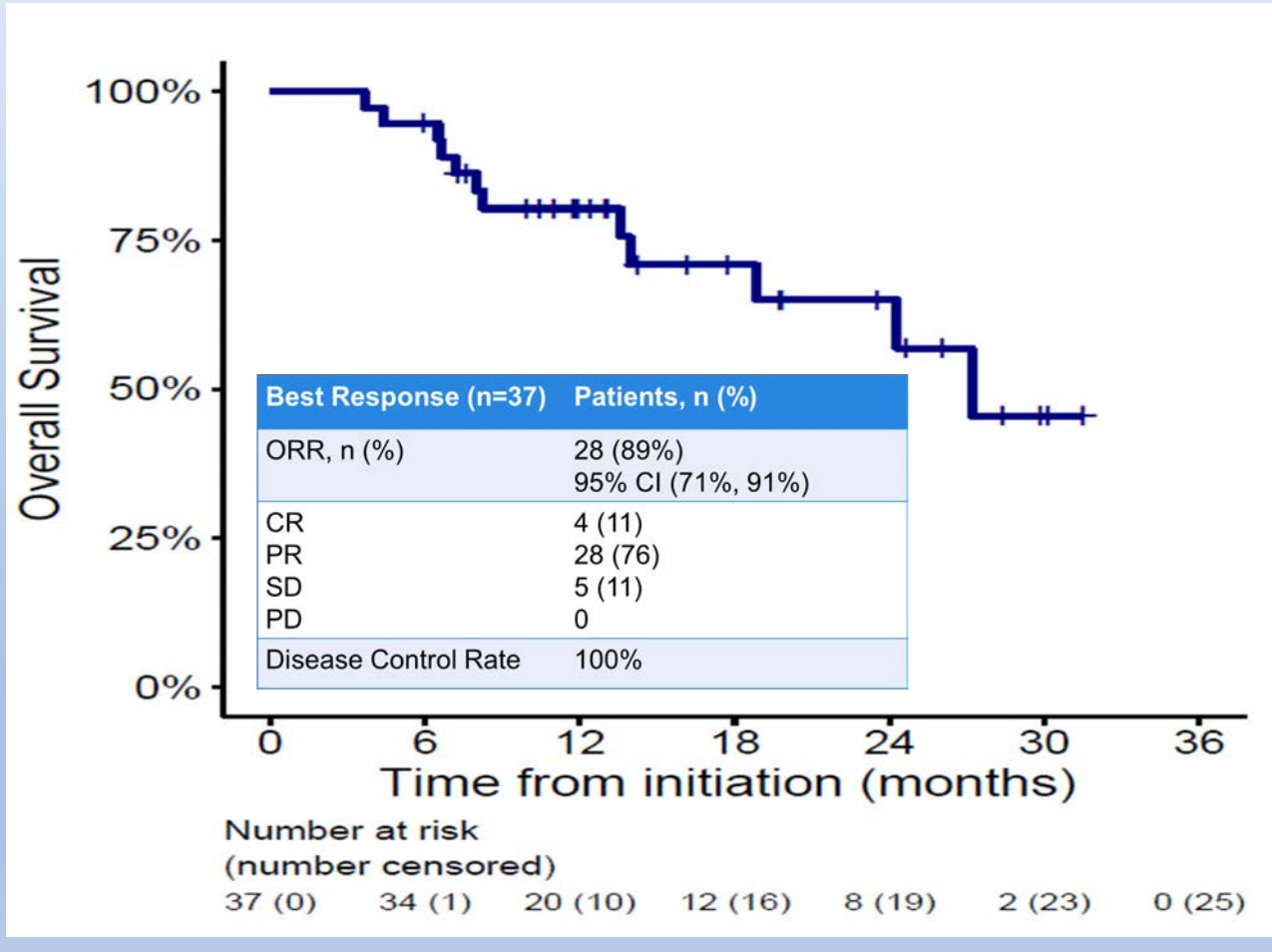
Targeted Combinations

REGONIVO: Regorafenib + Nivolumab



Fukuoka et al, 2019 ASCO Annual Meeting

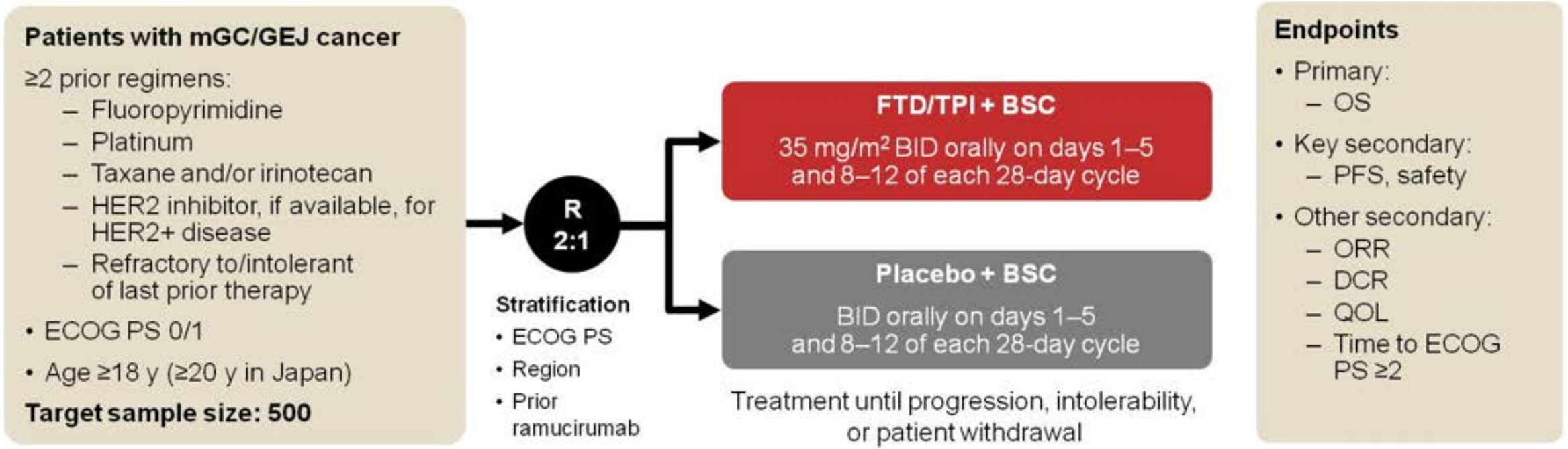
CapeOx + Trastuzumab + Pembrolizumab



Best Response (n=37)	Patients, n (%)
ORR, n (%)	28 (89%) 95% CI (71%, 91%)
CR PR SD PD	4 (11) 28 (76) 5 (11) 0
Disease Control Rate	100%

Figure courtesy of Yelena Janjigian, Janjigian et al, ESMO 2019

TAGS – Multicenter, Randomized, Double-blind, Phase 3 Study

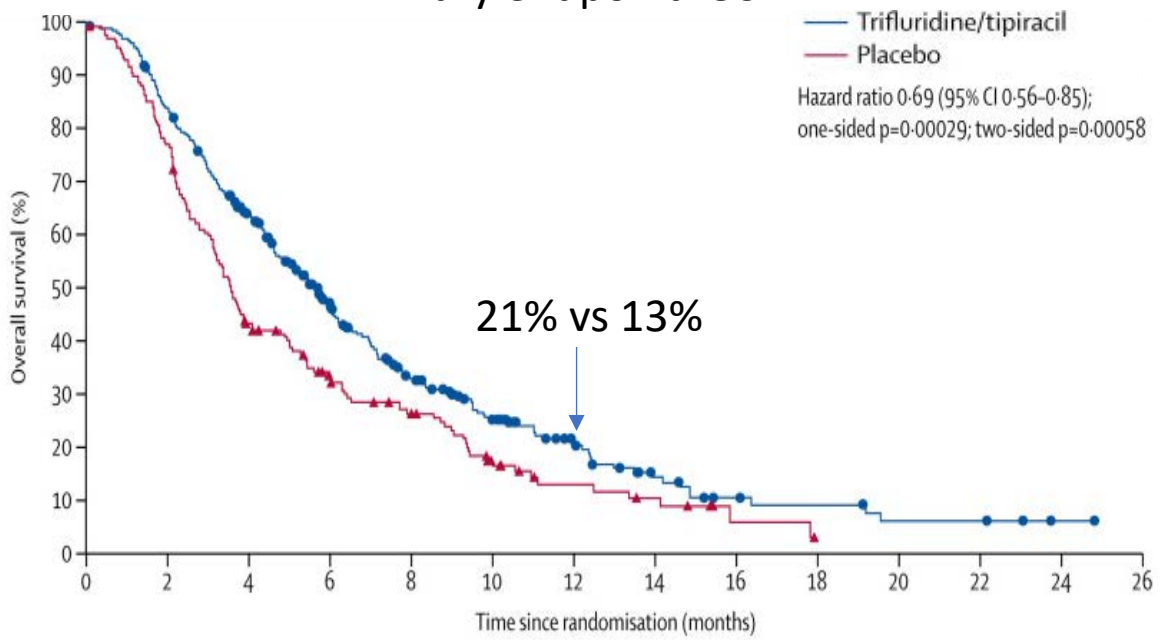


<u>Trifluridine/Tipiracil Profile</u>:
Adverse events: Cytopenias most common
Dose modifications due to adverse events: 58%
Dose discontinuation due to adverse events: 13%

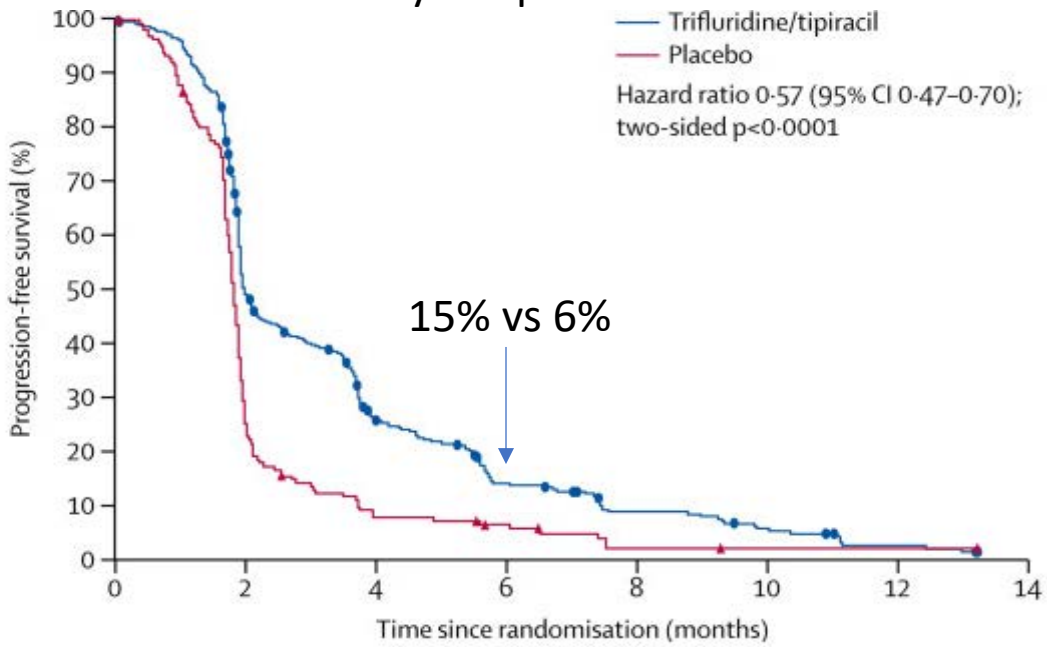
Shitara et al Lancet Oncology 2018, Ilson et al JAMA Oncology 2020

Trifluridine/Tipiracil in Gastric Cancer: TAGS

Primary endpoint: OS



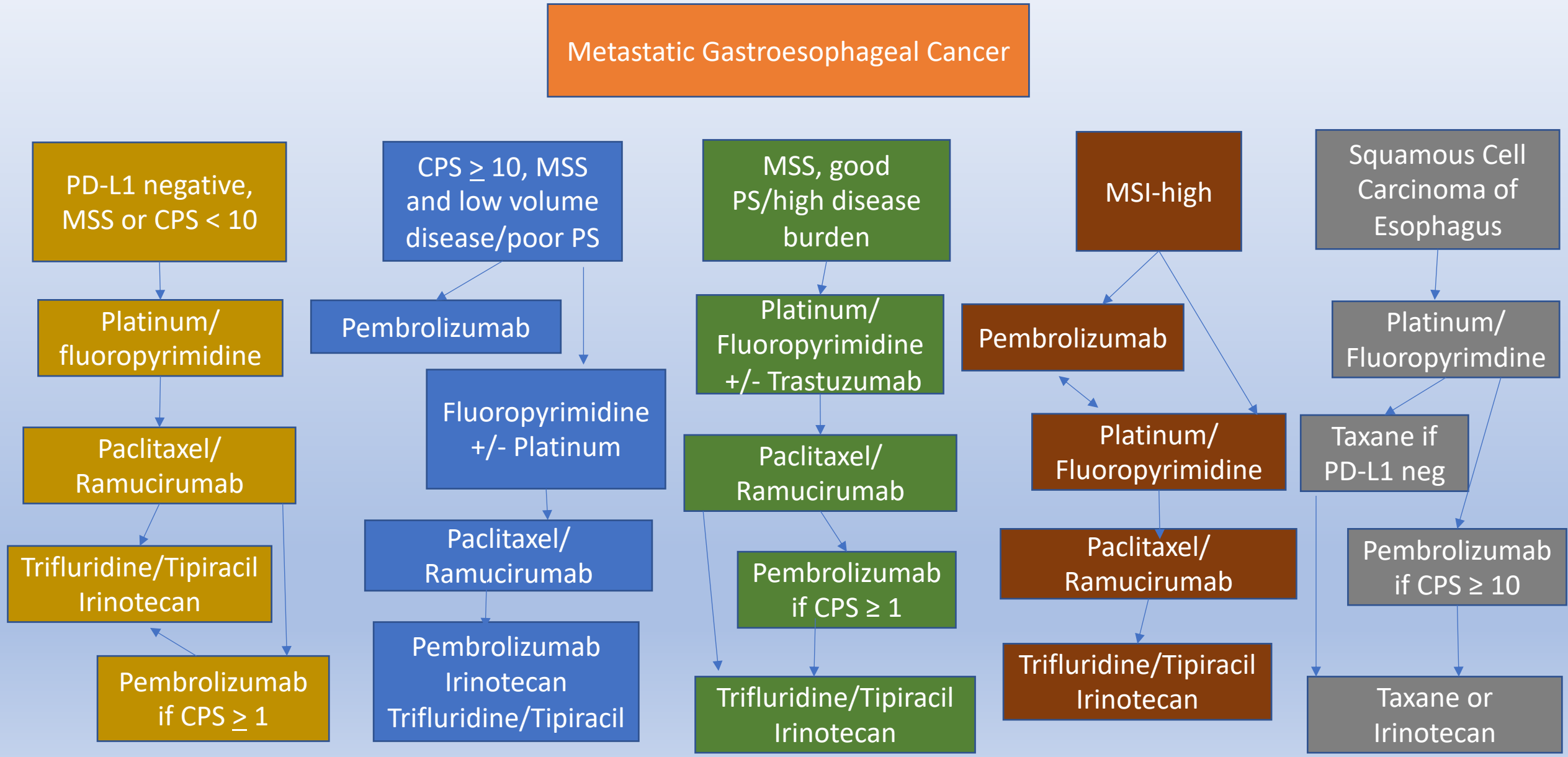
Secondary endpoint: PFS



	Trifluridine/Tipiracil	Placebo	P value
Overall Survival	5.7 months	3.6 months	P=0.00058
	HR 0.69 (95% CI 0.56-0.85)		
Progression-Free Survival	2.0 months	1.8 months	P< 0.0001
	HR 0.57 (95% CI 0.47-0.70)		
Overall Response Rate	4%	2%	P=0.28
Disease Control Rate	44%	14%	P<0.0001

Shitara et al Lancet Oncology 2018

How to Treat Gastroesophageal Cancer in 2020?

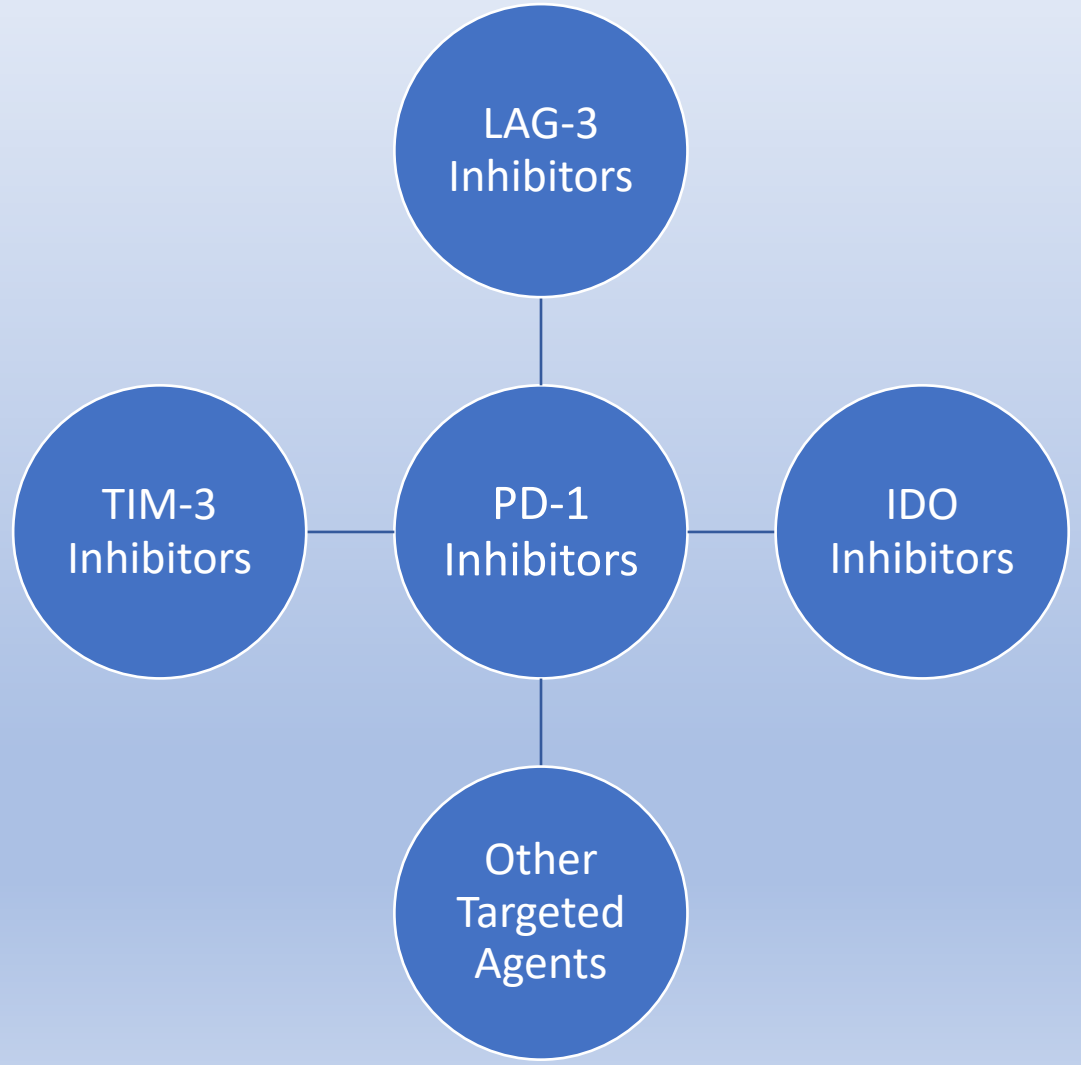


Future Directions: Large Phase 3 Trials

		Disease Site and Type	Arms	Status
HER2 Negative	CHECKMATE 649	Front-line metastatic	• FOLFOX or CapeOx • CapeOx + Nivolumab • Nivolumab + Ipilimumab—closed June 2018	Active, not recruiting
	JAVELIN Gastric 100	Front-line metastatic	• Avelumab maintenance after FOLFOX/CapeOx	Active, not recruiting
	KEYNOTE-859	Front-line metastatic	• FP or CapeOX + Pembrolizumab or Placeob	Recruiting
	RATIONALE-305	Front-line metastatic	• FP or CapeOx + Tislelizumab or placebo	Recruiting
HER2 positive	MAHOGANY	Front-line metastatic HER2+	• FOLFOX/CapeOx + Margetuximab • FOLFOX/CapeOx + Margetuximab + INCMGA00012 • Margetuximab + INCMGA00012 • FOLFOX/CapeOx + trastuzumab	Recruiting
	KEYNOTE-811	Front-line metastatic HER2+	• FP or CapeOx or SOX + pembrolizumab + trastuzumab • FP or CapeOx or SOX + trastuzumab + placebo	Recruiting
Perioperative	KEYNOTE-585	Perioperative	• FP or FLOT + pembrolizumab or placebo	Recruiting
SCC Esophageal		Front-line metastatic	• FP or Platinum/paclitaxel + tislelizumab or placebo	Recruiting
Esophageal/GEJ adenocarcinoma	CHECKMATE 648	Front-line metastatic	• FP • FP + Nivolumab • Nivolumab + Ipilimumab	Active, not recruiting
	ECOG EA2174	Neoadjuvant chemoradiotherapy + adjuvant	• Weekly Carboplatin/paclitaxel • Weekly Carboplatin/paclitaxel + nivolumab • Post-operative nivolumab • Post-operative nivolumab + ipilimumab	Recruiting
	CHECKMATE 577	Neoadjuvant chemoradiotherapy + adjuvant	• Postoperative nivolumab or placebo	Active, not recruiting

www.clinicaltrials.gov 1/17/2020

The Future Clinical Trials: Immunotherapy Combinations



www.clinicaltrials.gov 1/17/2020