How I treat metastatic esophageal and gastric cancer in 2023

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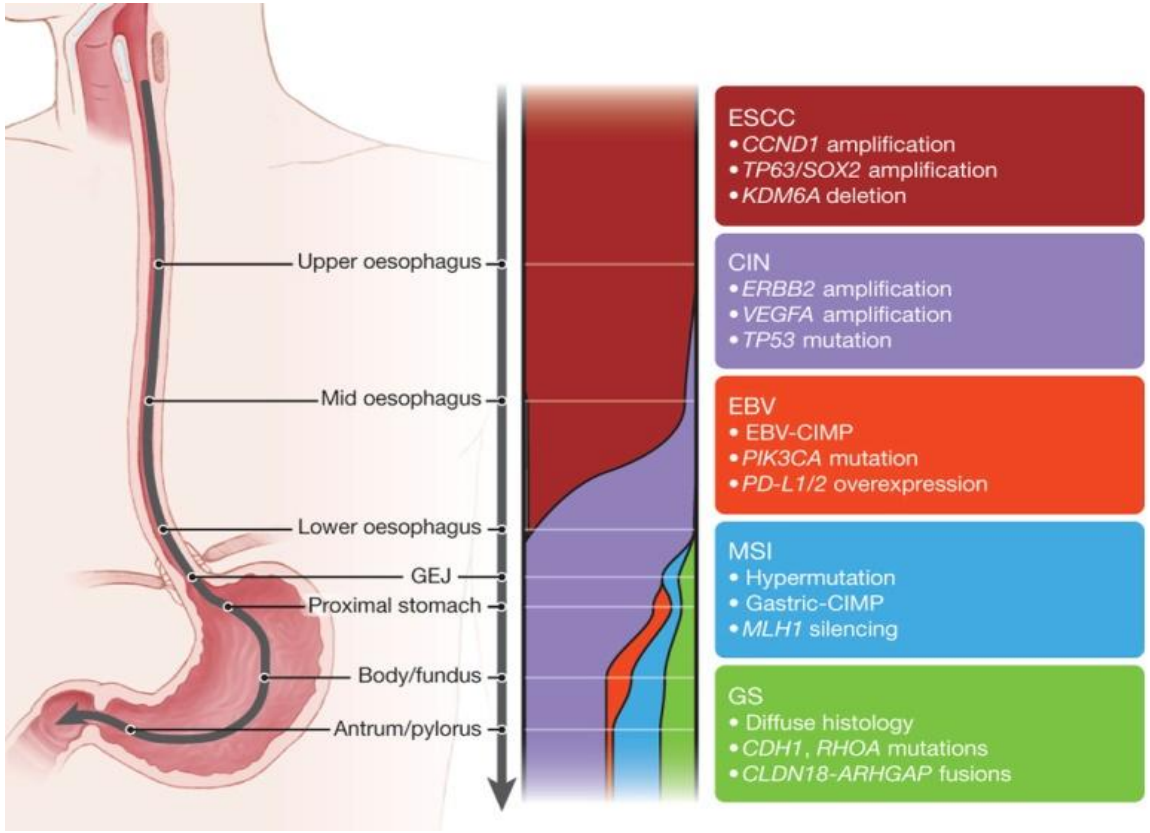
At Least 3 Distinct Diseases



- Gastric and gastroesophageal adenocarcinoma remains third cause of deaths globally.
- Median OS around 1 year for most part in western world
- Recent understanding of molecular and genetic variations

J Kim *et al. Nature* 1–9 (2017) doi:10.1038/nature20805
Fuchs et al. Lancet. 2019

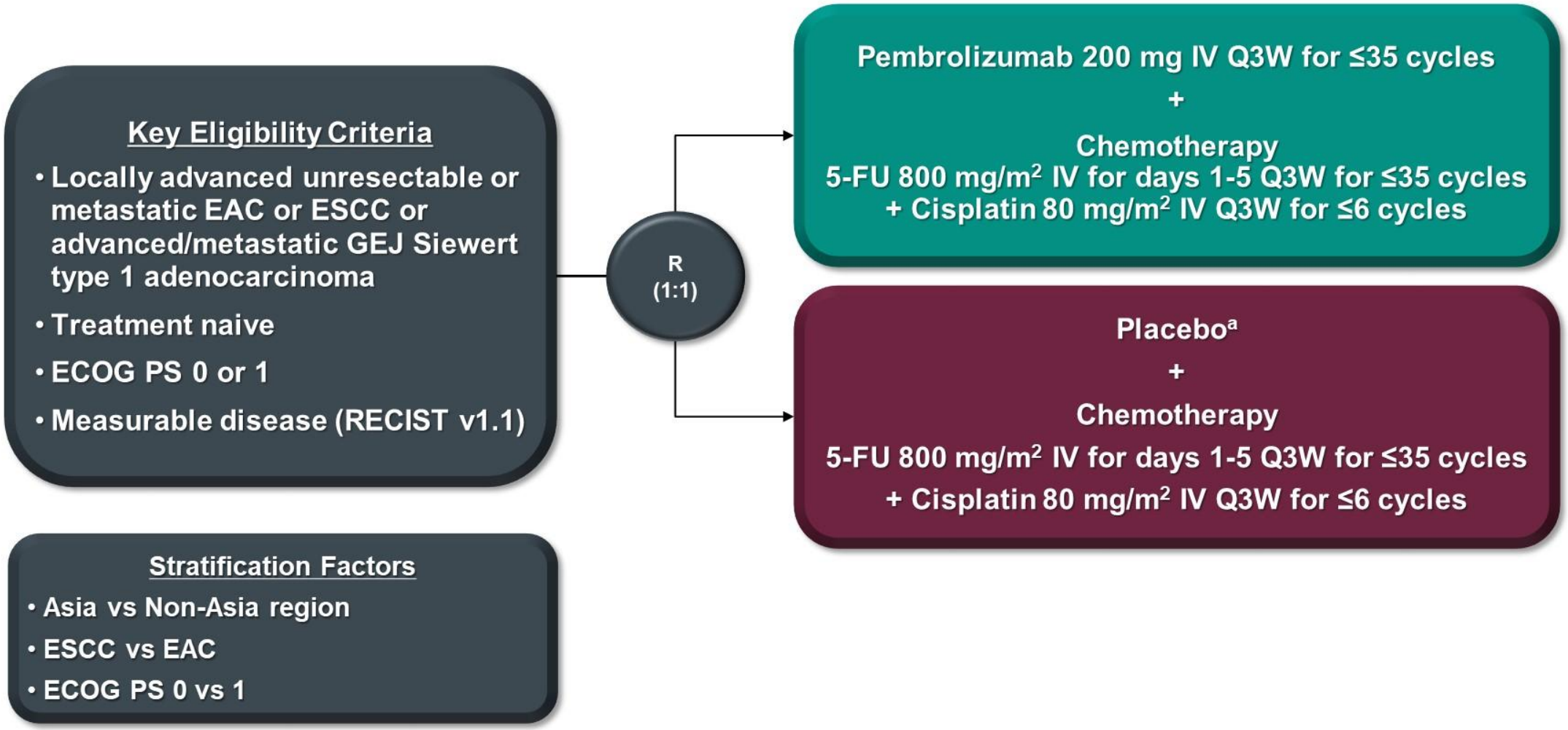
Metastatic Esophageal Cancer

First-line Pembrolizumab Plus Chemotherapy Versus Chemotherapy in Advanced Esophageal Cancer: Longer-term Efficacy, Safety, and Quality-of-life Results From the Phase 3 KEYNOTE-590 Study

Jean-Philippe Metges,[1] Ken Kato,[2] Jong-Mu Sun,[3] Manish A. Shah,[4] Peter Enzinger,[5] Antoine Adenis,[6] Toshihiko Doi,[7] Takashi Kojima,[7] Zhigang Li,[8] Sung-Bae Kim,[9] Byoung Chul Cho,[10] Wasat Mansoor,[11] Shau-Hsuan Li,[12] Patrapim Sunpaweravong,[13] Maria Alsina Maqueda,[14] Gary L. Buchschacher, Jr,[15] Wu Jimin,[16] Sukrut Shah,[16] Pooja Bhagia,[16] Lin Shen[17]

[1]CHU Brest – Institut de Cancerologie et d'Hematologie ARPEGO Network, Brest, France; [2]National Cancer Center Hospital, Tokyo, Japan; [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [4]Weill Cornell Medical College, New York, NY, USA; [5]Dana Farber Cancer Institute, Boston, MA, USA; [6]IRCM, Inserm, Université Montpellier, ICM, Montpellier, France; [7]National Cancer Center Hospital East, Kashiwa, Japan; [8]Shanghai Chest Hospital Esophageal Disease Center, Shanghai, China; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [10]Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea; [11]Christie Hospital NHS Trust, Manchester, United Kingdom; [12]Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan; [13]Prince of Songkla University Hospital, Songkhla, Thailand; [14]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [15]Kaiser Permanente Southern California, Los Angeles Medical Center, Los Angeles, CA, USA; [16]Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA; [17]Peking University Cancer Hospital & Institute; Beijing, China

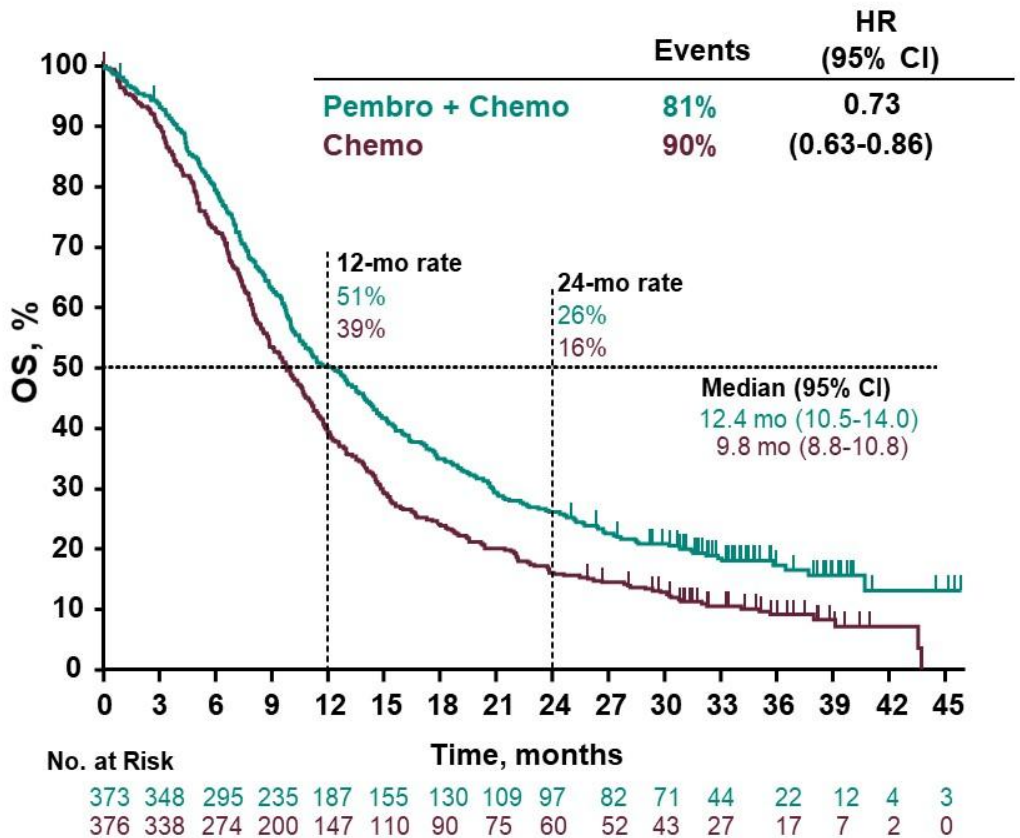
KEYNOTE-590 Study Design (NCT03189719)



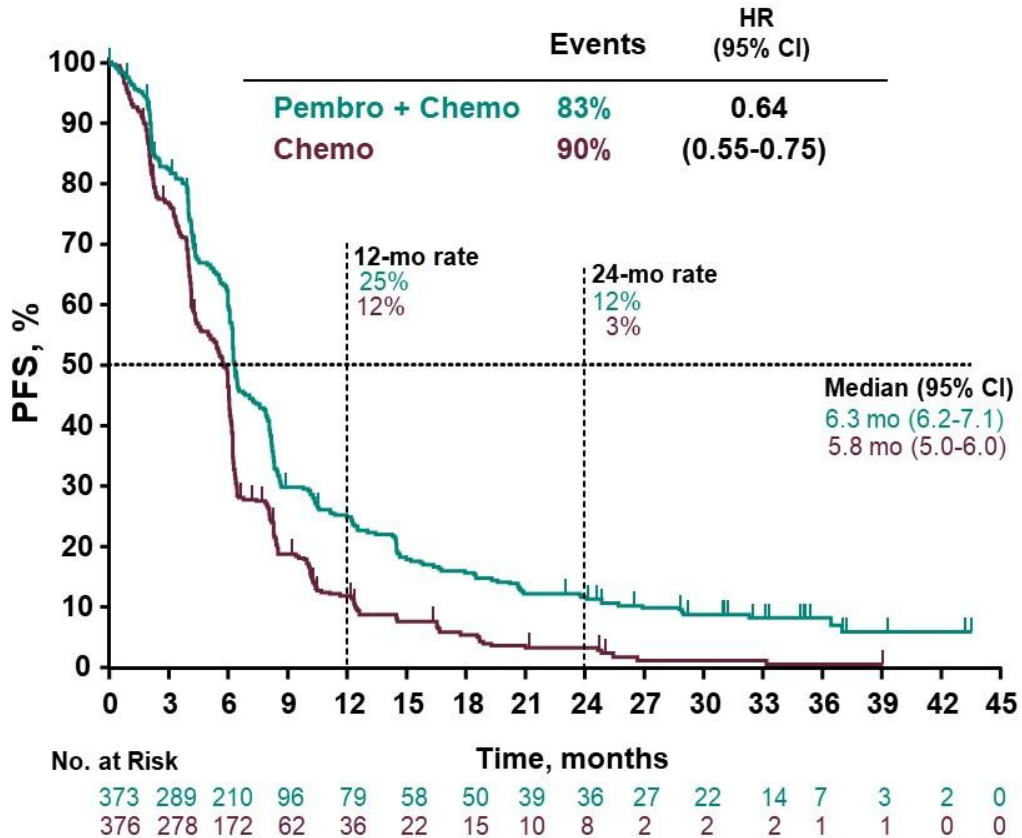
[a]Saline IV Q3W for ≤35 cycles. All treatments were continued for the specified number of cycles or until disease progression, intolerable toxicity, withdrawal of consent, or physician decision; EAC, esophageal adenocarcinoma; GEJ, gastroesophageal junction, ESCC, esophageal squamous cell carcinoma; Data cutoff: July 9, 2021.

Survival: All Patients

OS



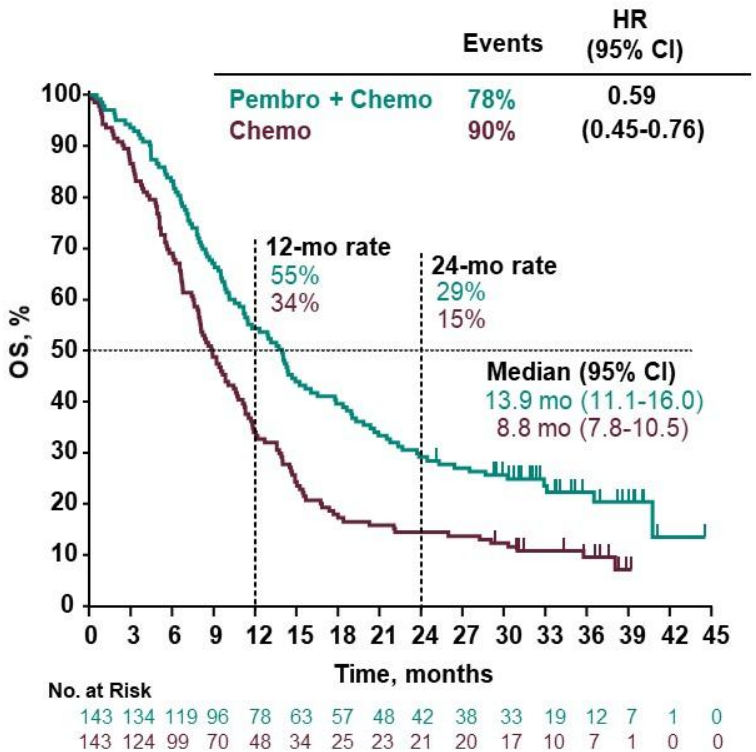
PFS



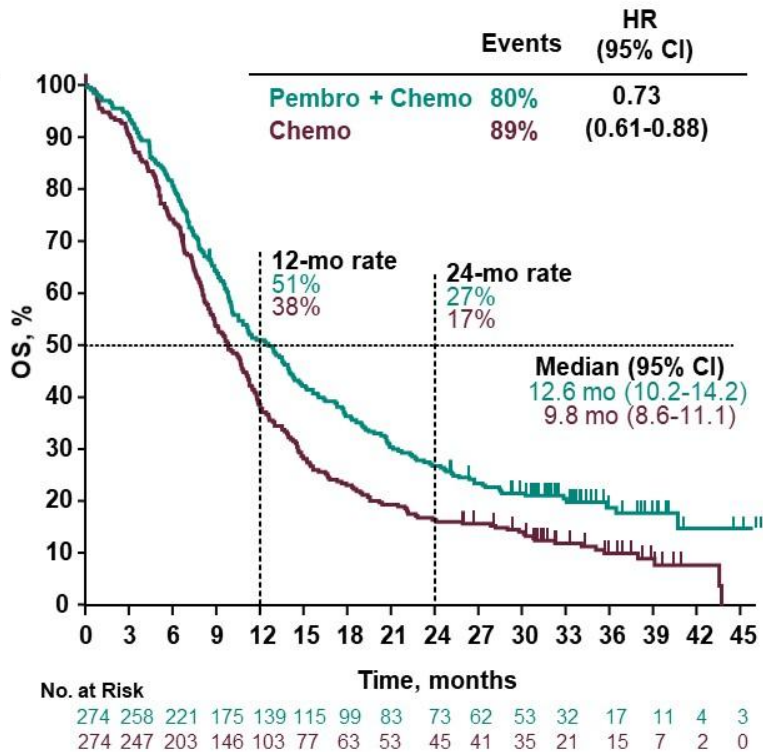
Data cut-off: July 9, 2021.

OS: Pre-specified Subgroups

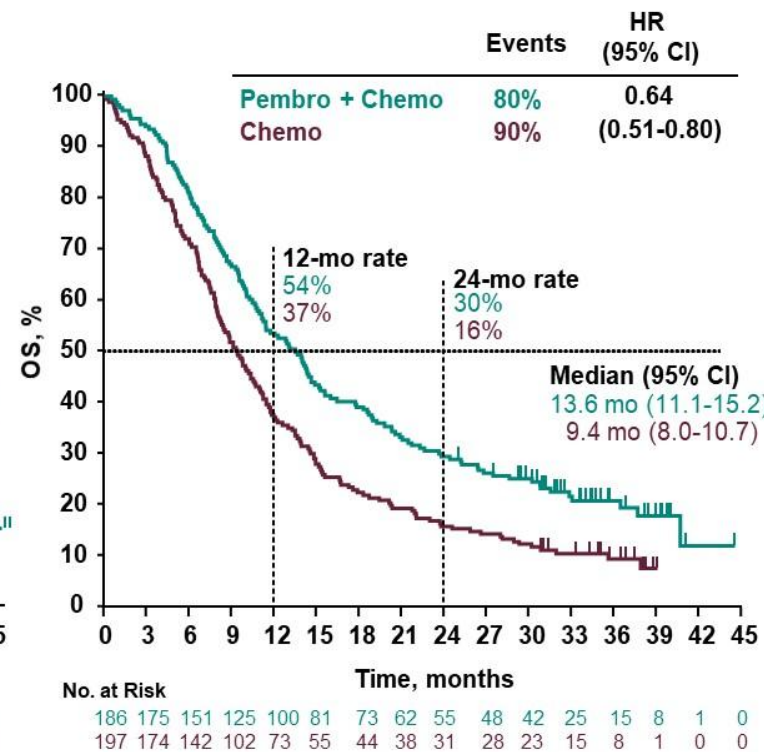
ESCC PD-L1 CPS ≥10



ESCC

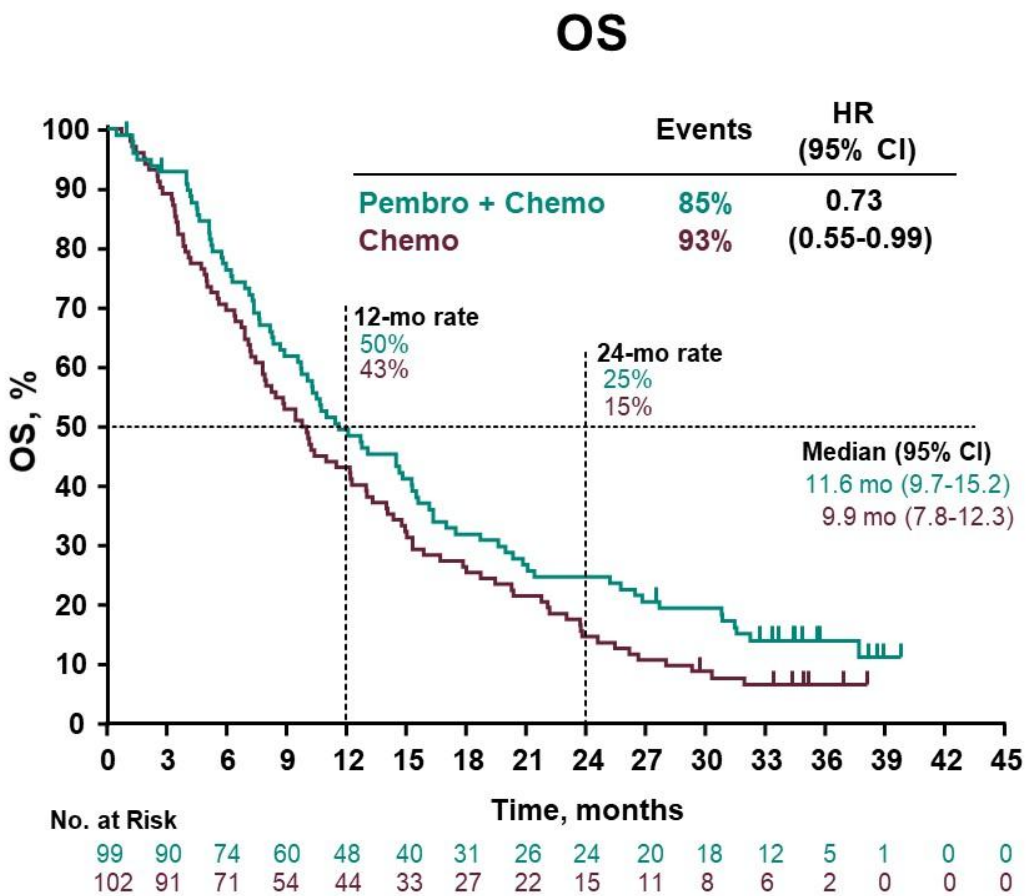


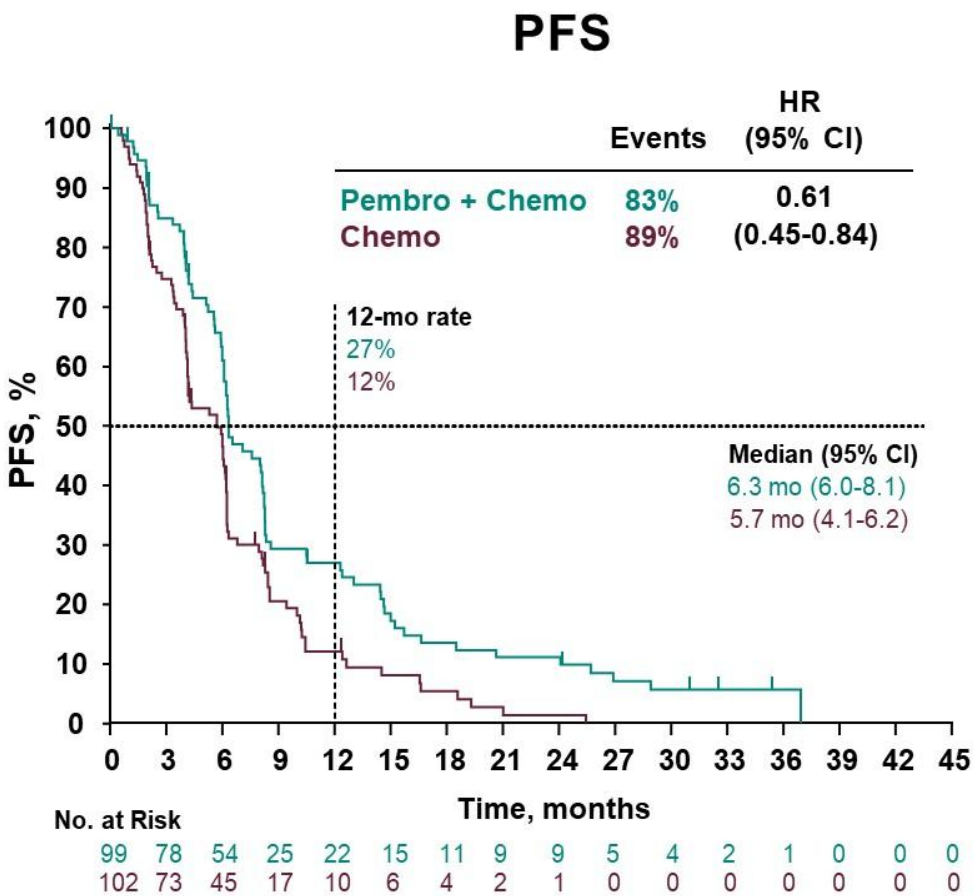
PD-L1 CPS ≥10



Data cut-off: July 9, 2021.

Survival: Adenocarcinoma





Data cut-off: July 9, 2021.

2021 ASCO ANNUAL MEETING

Nivolumab plus ipilimumab or nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced esophageal **squamous cell carcinoma**: first results of the CheckMate 648 study

Ian Chau,[1] Yuichiro Doki,[2] Jaffer A. Ajani,[3] Jianming Xu,[4] Lucjan Wyrwicz,[5] Satoru Motoyama,[6] Takashi Ogata,[7] Hisato Kawakami,[8] Chih-Hung Hsu,[9] Antoine Adenis,[10] Farid el Hajbi,[11] Maria Di Bartolomeo,[12] Maria Ignez Braghiroli,[13] Eva Holtved,[14] Ioannis Xynos,[15] Xuan Liu,[15] Ming Lei,[15] Kaoru Kondo,[15] Ken Kato,[16] Yuko Kitagawa[17]

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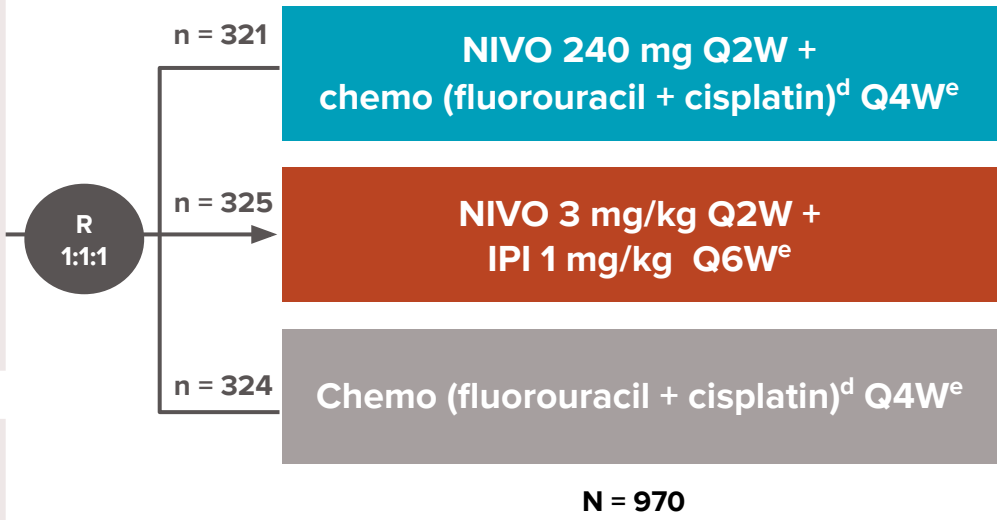
Abstract Number LBA4001

CheckMate 648 study design

- CheckMate 648 is a global, randomized, open-label phase 3 study[a]

Key eligibility criteria
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤ 1 vs ≥ 2)



Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

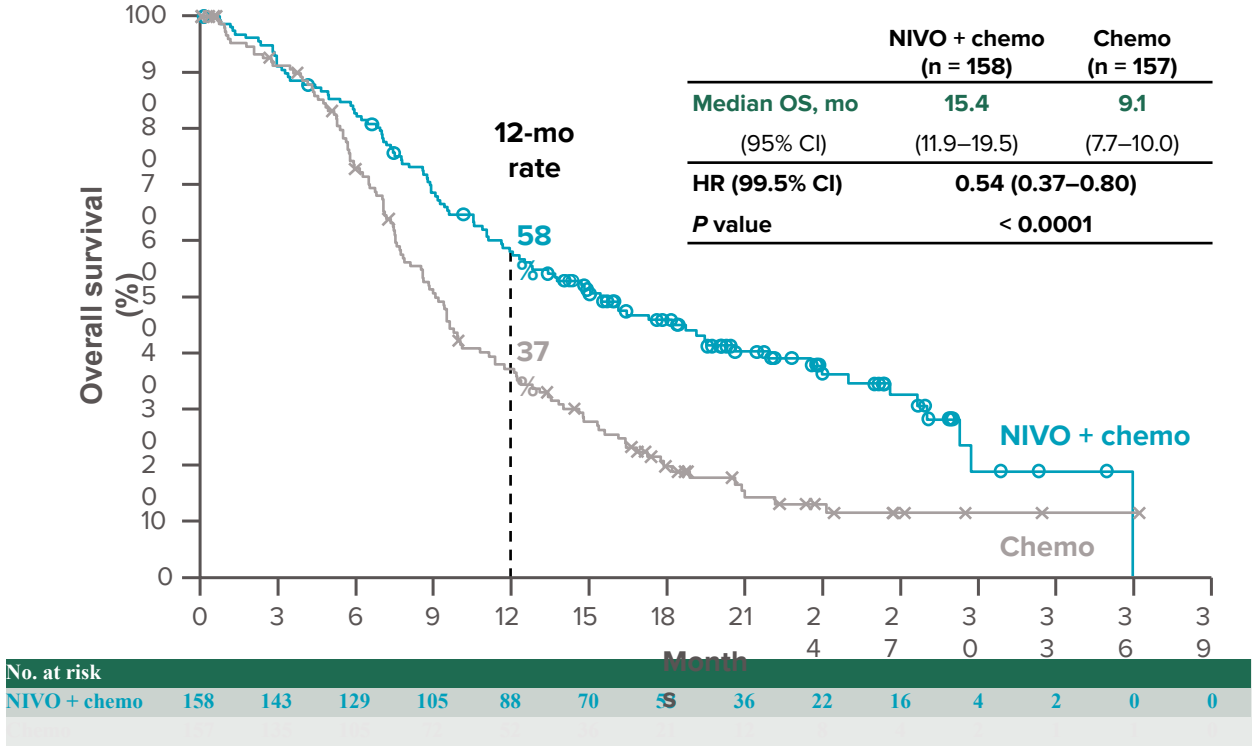
Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

- At data cutoff (January 18, 2021), the minimum follow-up was 12.9 months[g]

[a]ClinicalTrials.gov. NCT03143153; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]East Asia includes patients from Japan, Korea, and Taiwan; [d]Fluorouracil 800 mg/m^2 IV daily (days 1-5) and cisplatin 80 mg/m^2 IV (day 1); [e]Until documented disease progression (unless consented to treatment beyond progression for NIVO + IPI or NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given alone or in combination with IPI for a maximum of 2 years; [f]Per blinded independent central review (BICR); [g]Time from last patient randomized to clinical data cutoff.

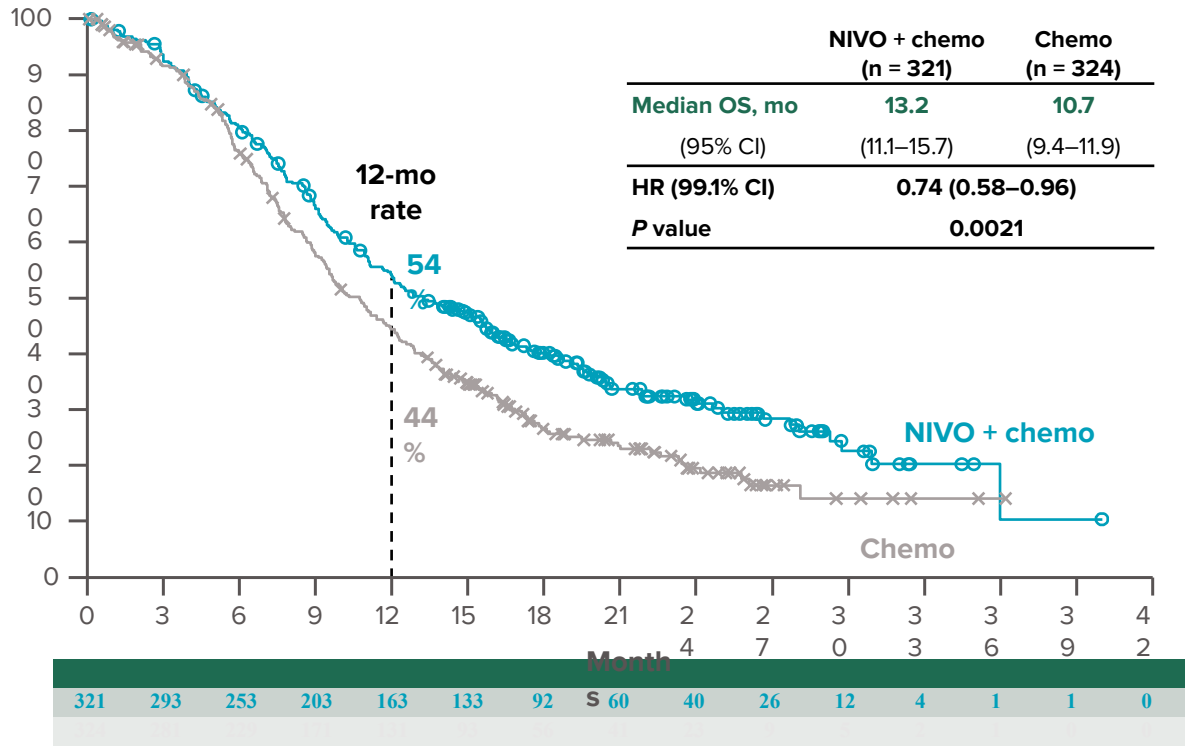
Overall survival: NIVO + chemo vs chemo

Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



	NIVO + chemo (n = 158)	Chemo (n = 157)
Median OS, mo	15.4	9.1
(95% CI)	(11.9–19.5)	(7.7–10.0)
HR (99.5% CI)	0.54 (0.37–0.80)	
P value	< 0.0001	

All randomized[a]



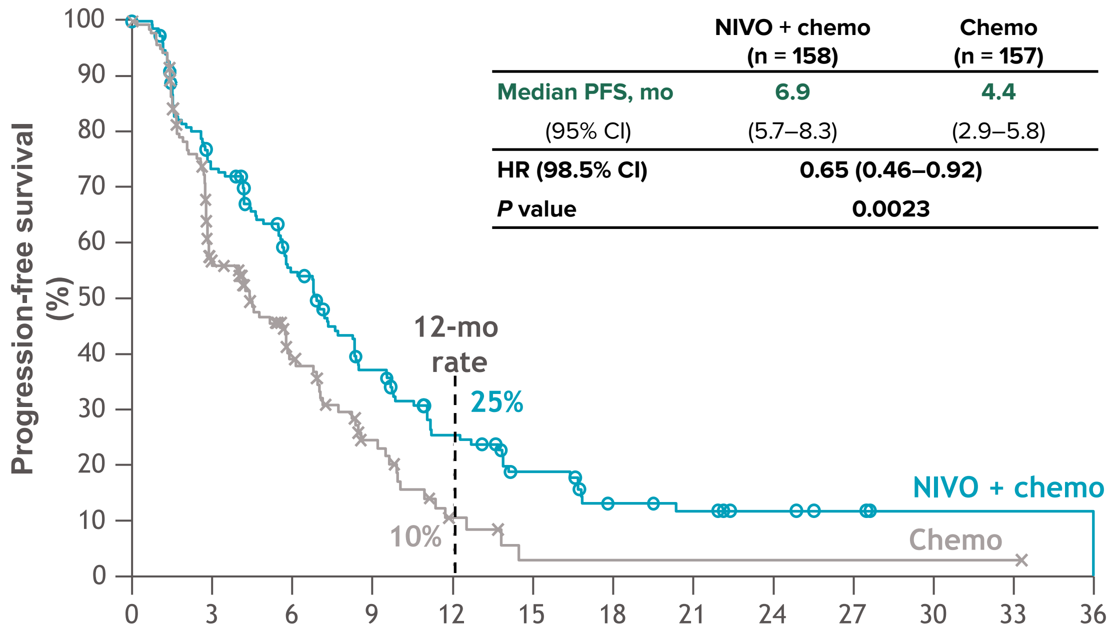
	NIVO + chemo (n = 321)	Chemo (n = 324)
Median OS, mo	13.2	10.7
(95% CI)	(11.1–15.7)	(9.4–11.9)
HR (99.1% CI)	0.74 (0.58–0.96)	
P value	0.0021	

- Superior OS with NIVO + chemo vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 46% reduction in the risk of death and a 6.3-month improvement in median OS
  - All randomized: 26% reduction in the risk of death and a 2.5-month improvement in median OS

[a]Minimum follow-up 12.9 months.

PFS: NIVO + chemo vs chemo

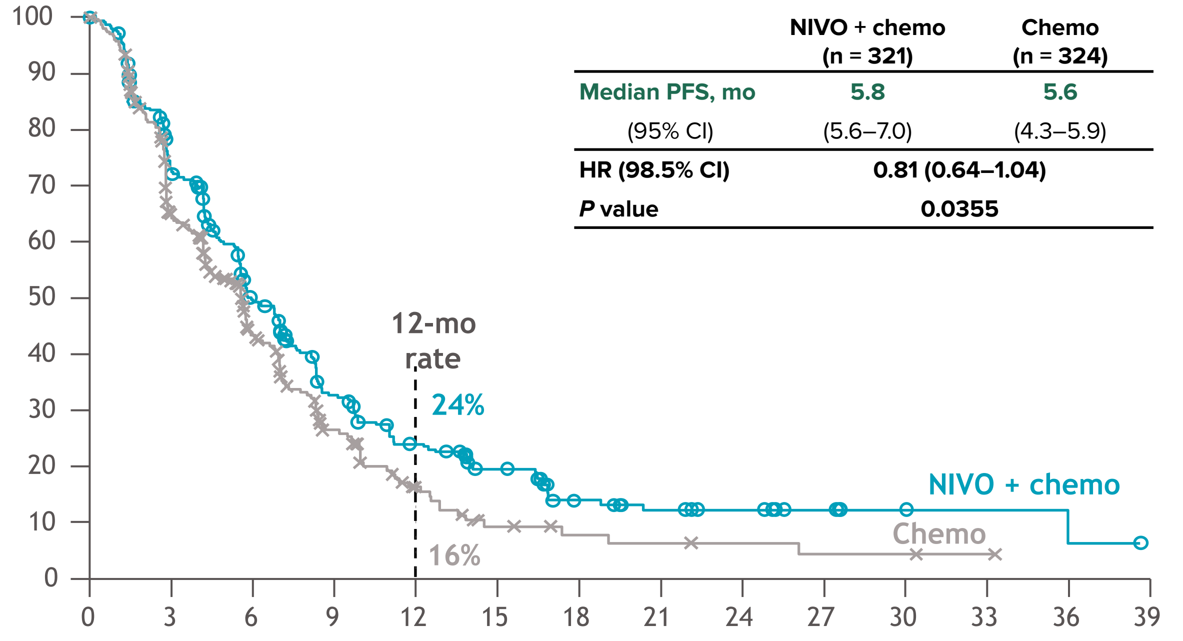
Primary endpoint (tumor cell PD-L1 ≥ 1%; per BICR)[a]



	NIVO + chemo (n = 158)	Chemo (n = 157)
Median PFS, mo	6.9	4.4
(95% CI)	(5.7–8.3)	(2.9–5.8)
HR (98.5% CI)	0.65 (0.46–0.92)	
P value	0.0023	

No. at risk													
NIVO + chemo	158	107	75	47	29	18	10	8	5	3	1	1	0
Chemo	157	67	35	17	5	1	1	1	1	1	1	1	0

All randomized (per BICR)[a]



	NIVO + chemo (n = 321)	Chemo (n = 324)
Median PFS, mo	5.8	5.6
(95% CI)	(5.6–7.0)	(4.3–5.9)
HR (98.5% CI)	0.81 (0.64–1.04)	
P value	0.0355	

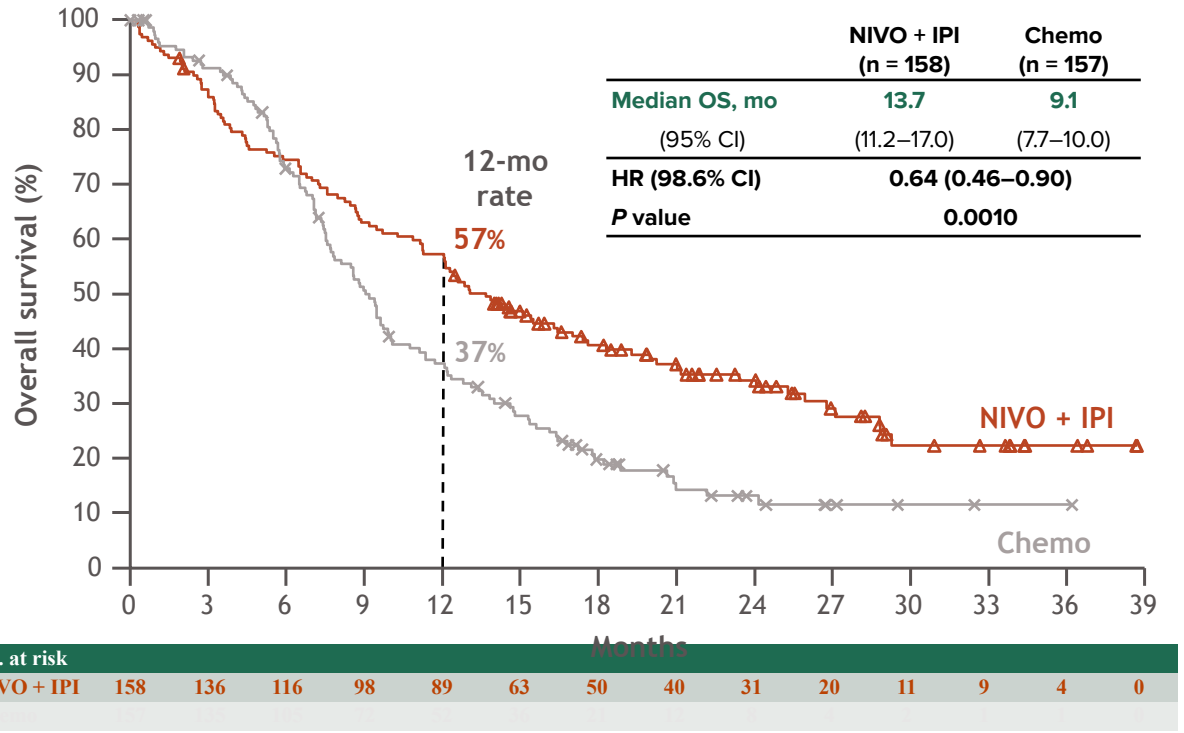
321	216	136	81	53	35	18	13	10	6	3	2	1	0
324	170	90	43	19	8	5	4	3	2	2	1	0	0

- Primary endpoint of PFS per BICR met in patients with tumor cell PD-L1 ≥ 1%
- Prespecified significance boundary for PFS per BICR not met in all randomized patients
- Improved PFS per INV[b] with HR of 0.53 (95% CI, 0.41–0.69) in tumor cell PD-L1 ≥ 1% and 0.69 (95% CI, 0.58–0.83) in all randomized populations

[a]Minimum follow-up 12.9 months; [b]Exploratory analysis.

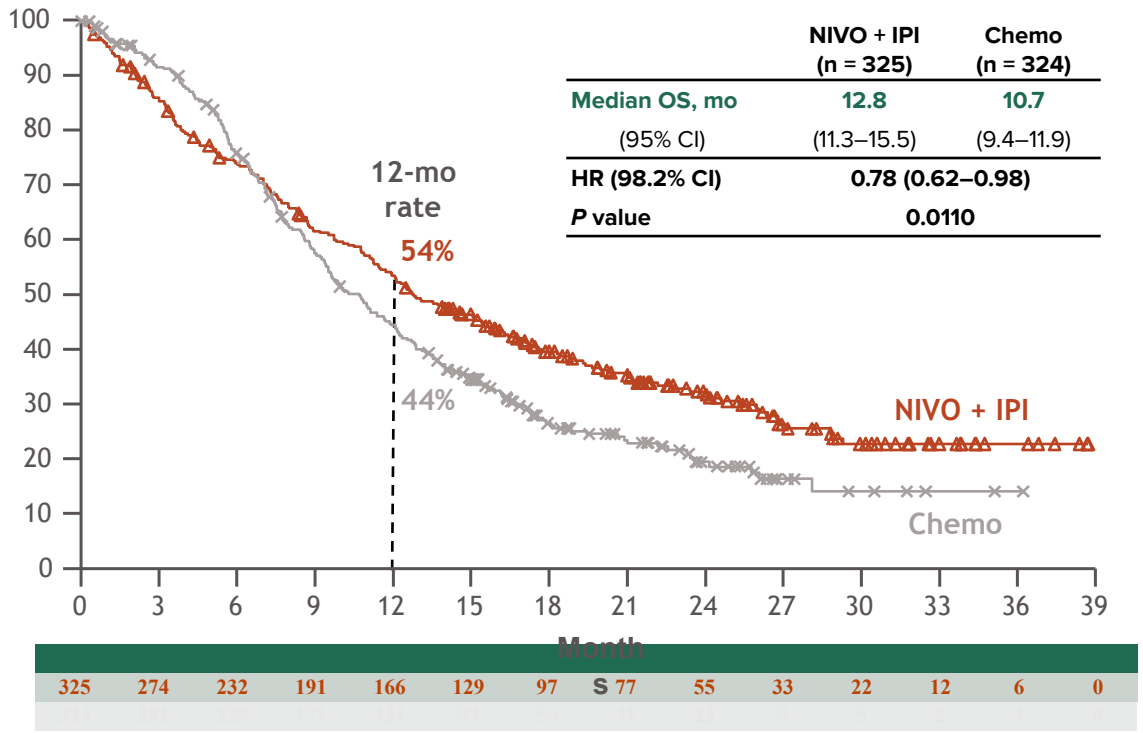
Overall survival: NIVO + IPI vs chemo

Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



	NIVO + IPI (n = 158)	Chemo (n = 157)
Median OS, mo	13.7	9.1
(95% CI)	(11.2–17.0)	(7.7–10.0)
HR (98.6% CI)	0.64 (0.46–0.90)	
P value	0.0010	

All randomized[a]



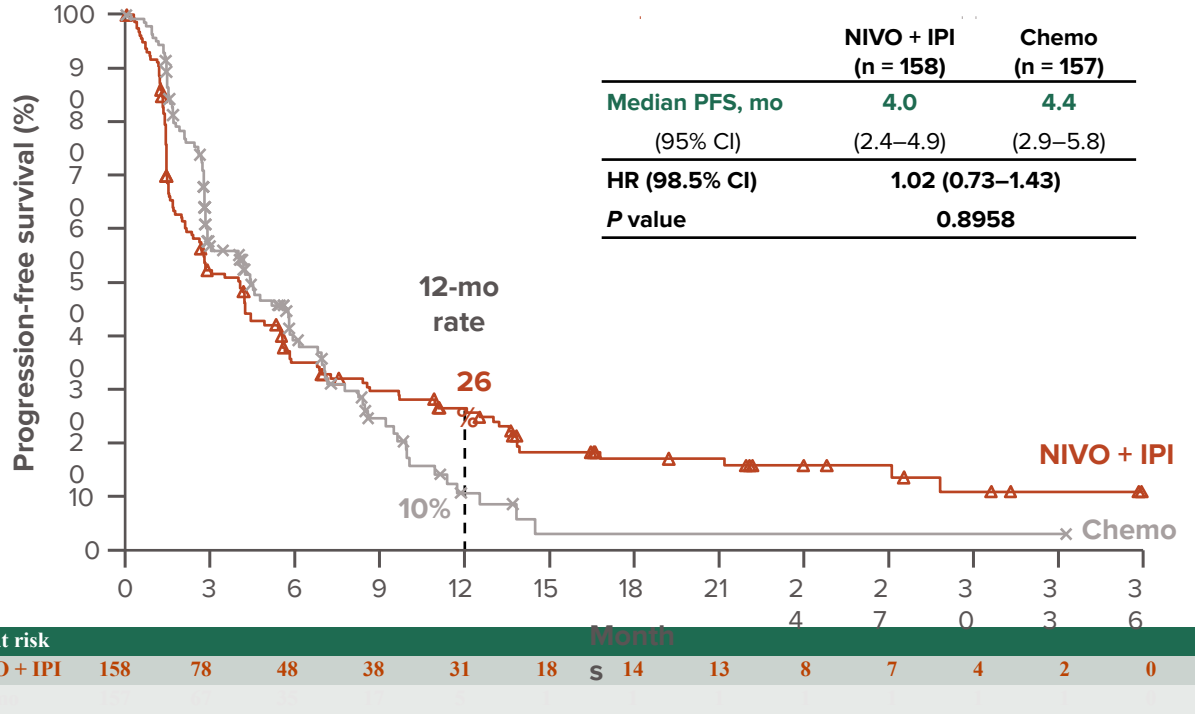
	NIVO + IPI (n = 325)	Chemo (n = 324)
Median OS, mo	12.8	10.7
(95% CI)	(11.3–15.5)	(9.4–11.9)
HR (98.2% CI)	0.78 (0.62–0.98)	
P value	0.0110	

- Superior OS with NIVO + IPI vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 36% reduction in the risk of death and a 4.6-month improvement in median OS
  - All randomized: 22% reduction in the risk of death and a 2.1-month improvement in median OS

[a]Minimum follow-up 12.9 months.

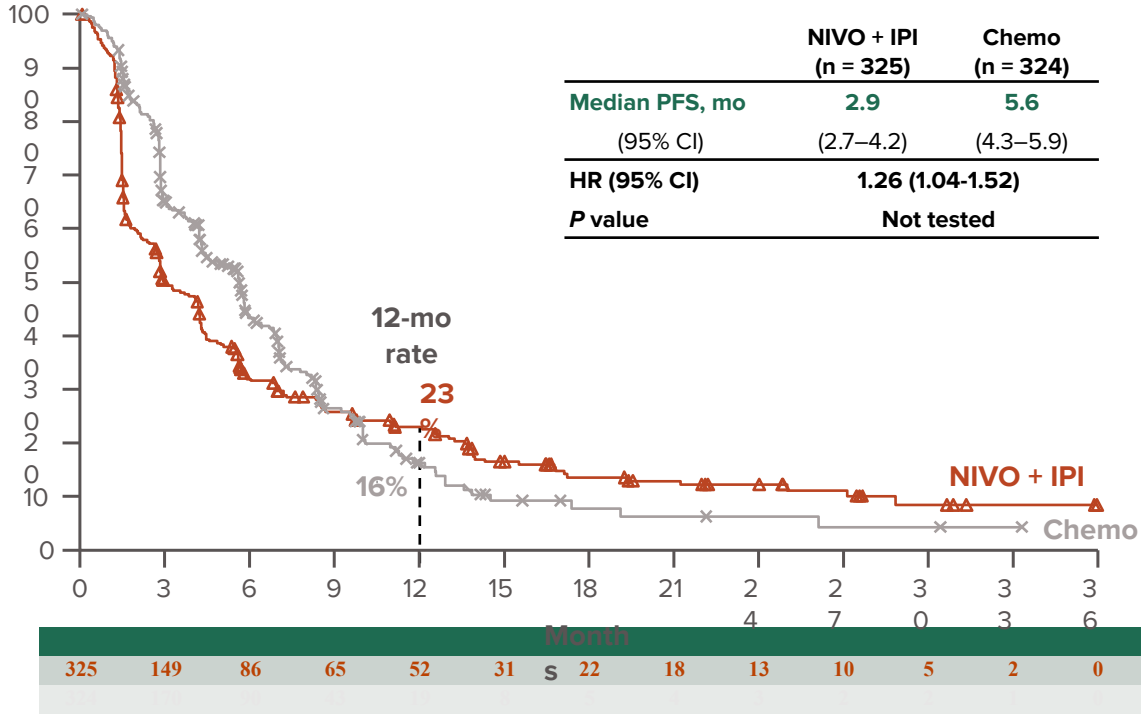
Progression-free survival: NIVO + IPI vs chemo

Primary endpoint (tumor cell PD-L1 ≥ 1%; per BICR)[a]



	NIVO + IPI (n = 158)	Chemo (n = 157)
Median PFS, mo	4.0	4.4
(95% CI)	(2.4–4.9)	(2.9–5.8)
HR (98.5% CI)	1.02 (0.73–1.43)	
P value	0.8958	

All randomized (per BICR)[a]



	NIVO + IPI (n = 325)	Chemo (n = 324)
Median PFS, mo	2.9	5.6
(95% CI)	(2.7–4.2)	(4.3–5.9)
HR (95% CI)	1.26 (1.04-1.52)	
P value	Not tested	

- Primary endpoint of PFS per BICR not met in patients with tumor cell PD-L1 ≥ 1%
- PFS per BICR not hierarchically tested in all randomized patients
- Directionally improved PFS per INV[b] with HR of 0.83 (95% CI, 0.64–1.07) in tumor cell PD-L1 ≥ 1% and 1.01 (95% CI, 0.85-1.21) in all randomized populations

[a]Minimum follow-up 12.9 months; [b]Exploratory analysis.

First-line: RATIONALE 306

Key eligibility criteria

- Unresectable locally advanced or metastatic ESCC
- No prior systemic treatment for advanced disease
- ECOG PS 0 or 1
- Measurable or evaluable disease per RECIST v1.1

R 1:1 DB

N=649

Tislelizumab 200 mg IV Q3W + investigator-chosen chemotherapy

Treatment until disease progression, intolerable toxicity, or withdrawal for other reasons

Matching placebo IV Q3W + investigator-chosen chemotherapy

Investigator-chosen chemotherapy:

- **Option A**: **Platinum + fluoropyrimidine**
  Cisplatin or oxaliplatin* + fluoropyrimidine†
- **Option B**: **Platinum + paclitaxel**
  Cisplatin or oxaliplatin* + paclitaxel‡

Stratification factors

- Geographic region (Asia [excluding Japan] vs Japan vs Rest of World)
- Prior definitive therapy (yes vs no)
- Investigator-chosen chemotherapy (platinum/fluoropyrimidine vs platinum/paclitaxel)

Endpoints

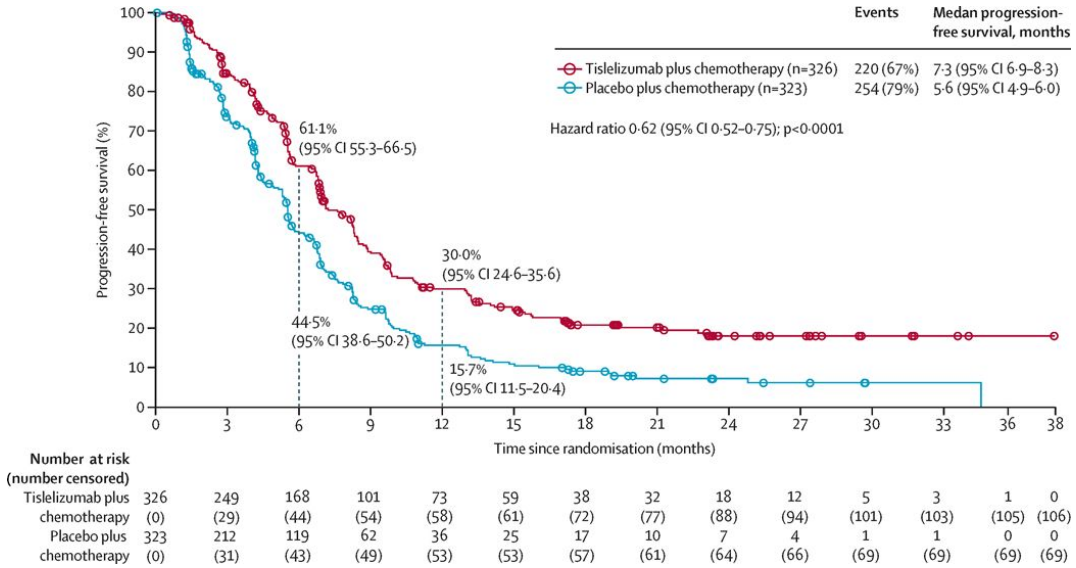
- **Primary endpoint:** OS in all randomized patients (ITT population)
- **Secondary endpoints**: PFS, ORR and DoR by investigator, OS in the PD-L1 score ≥ 10% subgroup§, HRQoL, and safety

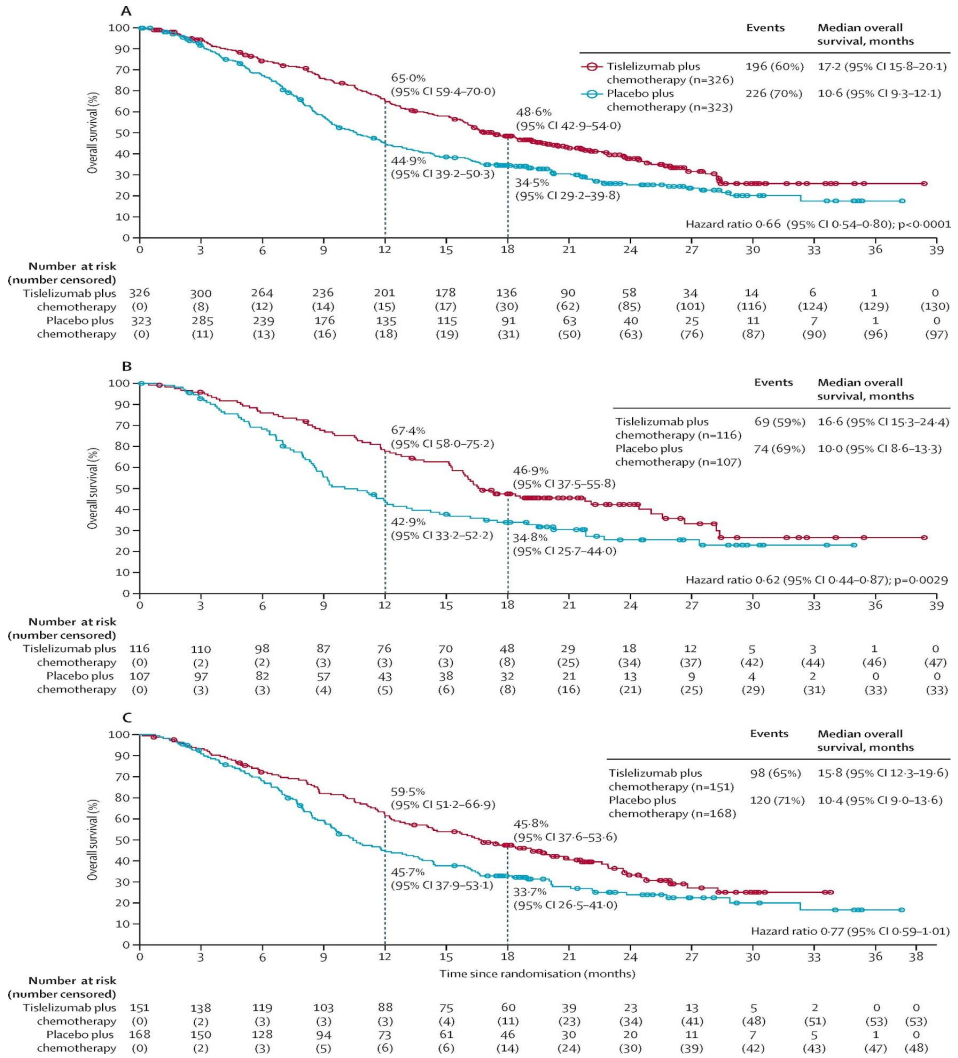
Yoon et al. ESMO GI 2022
Xu et.al. The Lancet Oncology 2023

		Tislelizumab + chemotherapy (n=326)	Placebo + chemotherapy (n=323)
Baseline characteristics			
Disease status at baseline, n (%)	Metastatic	279 (85.6)	282 (87.3)
	Locally advanced	47 (14.4)	41 (12.7)
Prior definitive therapy, n (%)	Definitive surgery§	107 (32.8)	107 (33.1)
	Definitive RT§	40 (12.3)	40 (12.4)
Centrally-assessed PD-L1 status¶, n (%)	PD-L1 score ≥ 10%	123 (37.7)	113 (35.0)
	PD-L1 score < 10%	165 (50.6)	176 (54.5)
	Unknown‖	38 (11.7)	34 (10.5)
Treatment			
Median duration of tislelizumab / placebo treatment, month (range)		6.4 (0.1–38.3)	4.9 (0.6–34.9)
Investigator-chosen chemotherapy options, n (%)	Platinum + fluoropyrimidine	147 (45.1)	146 (45.2)
	Platinum + paclitaxel	179 (54.9)	177 (54.8)
Post-treatment systemic therapies, n (%)	Systemic therapy	157 (48.2)	177 (54.8)
	Immunotherapy	46 (14.1)	72 (22.3)

Yoon et al. ESMO GI 2022

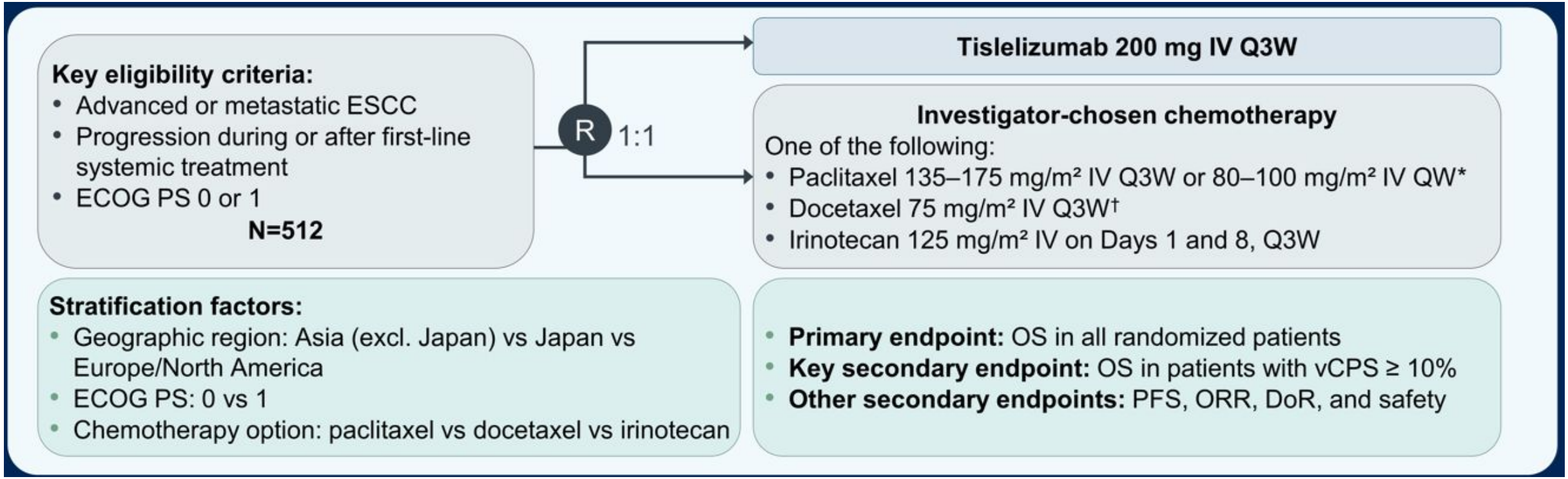
PFS and Overall Survival (PDL1-TAP Score)





The Lancet Oncology 2023 24483-495DOI: (10.1016/S1470-2045(23)00108-0)

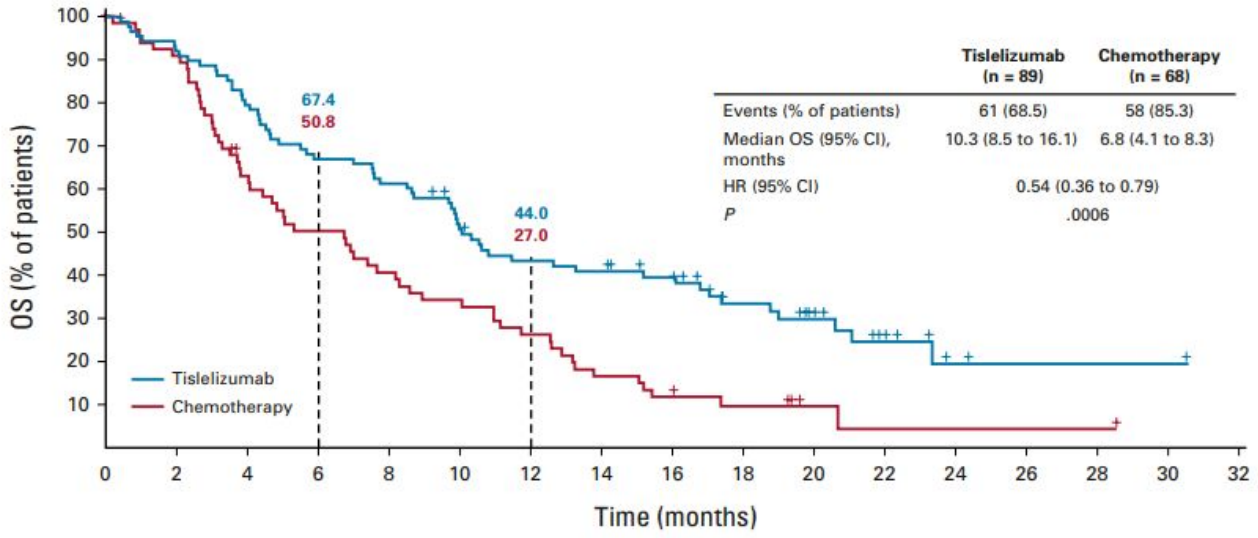
Second-Line: RATIONALE 302



Shen et al. JCO. 2022

PDL1 TAP≥10%

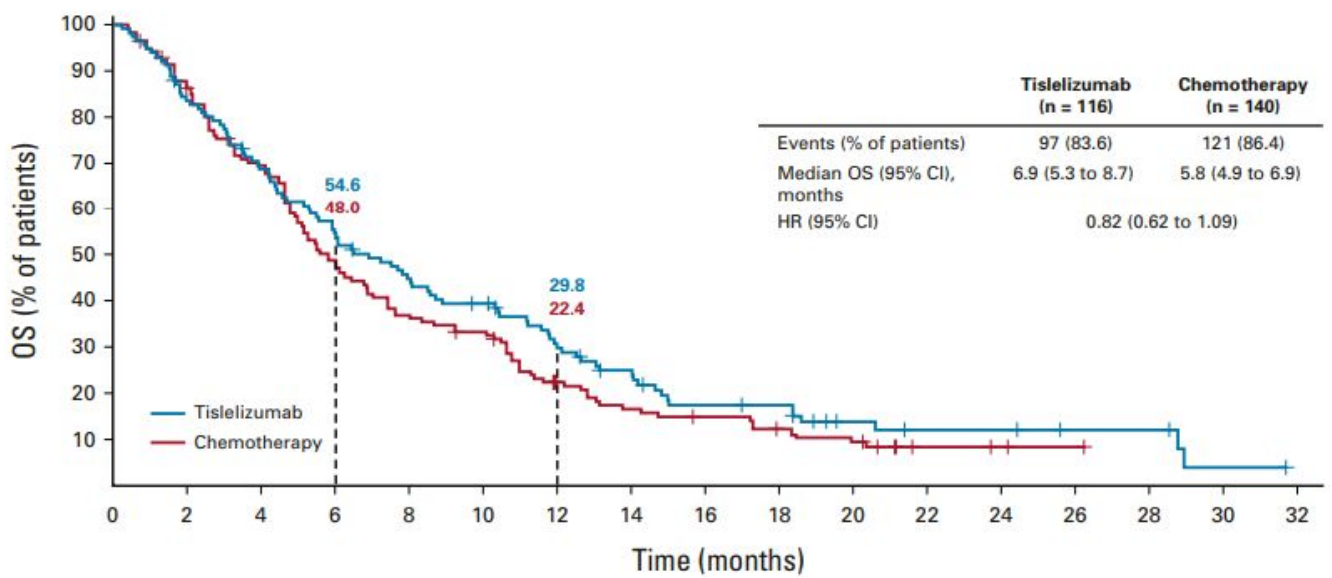
B



	Tislelizumab (n = 89)	Chemotherapy (n = 68)
Events (% of patients)	61 (68.5)	58 (85.3)
Median OS (95% CI), months	10.3 (8.5 to 16.1)	6.8 (4.1 to 8.3)
HR (95% CI)	0.54 (0.36 to 0.79)	
P	.0006	

PDL1 TAP<10%

C

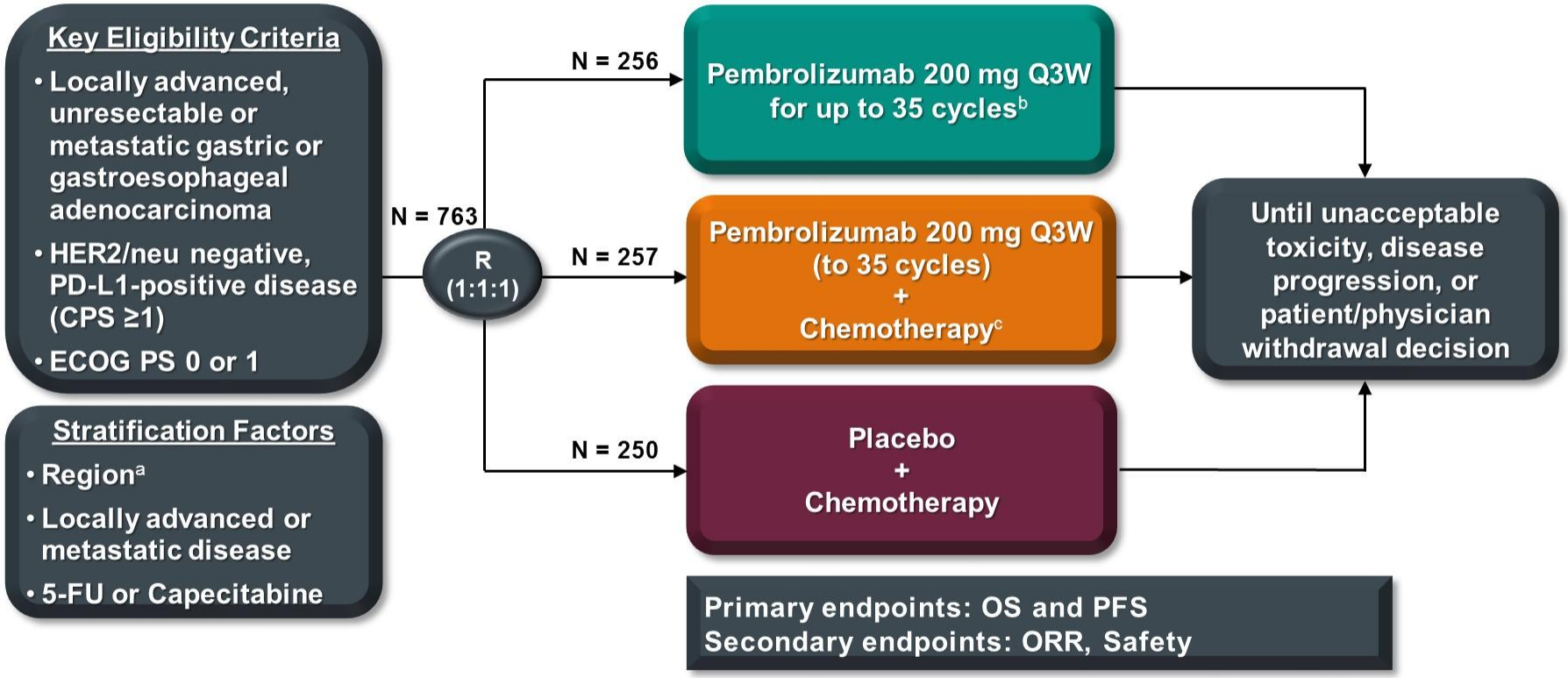


	Tislelizumab (n = 116)	Chemotherapy (n = 140)
Events (% of patients)	97 (83.6)	121 (86.4)
Median OS (95% CI), months	6.9 (5.3 to 8.7)	5.8 (4.9 to 6.9)
HR (95% CI)	0.82 (0.62 to 1.09)	

Shen et al. JCO. 2022

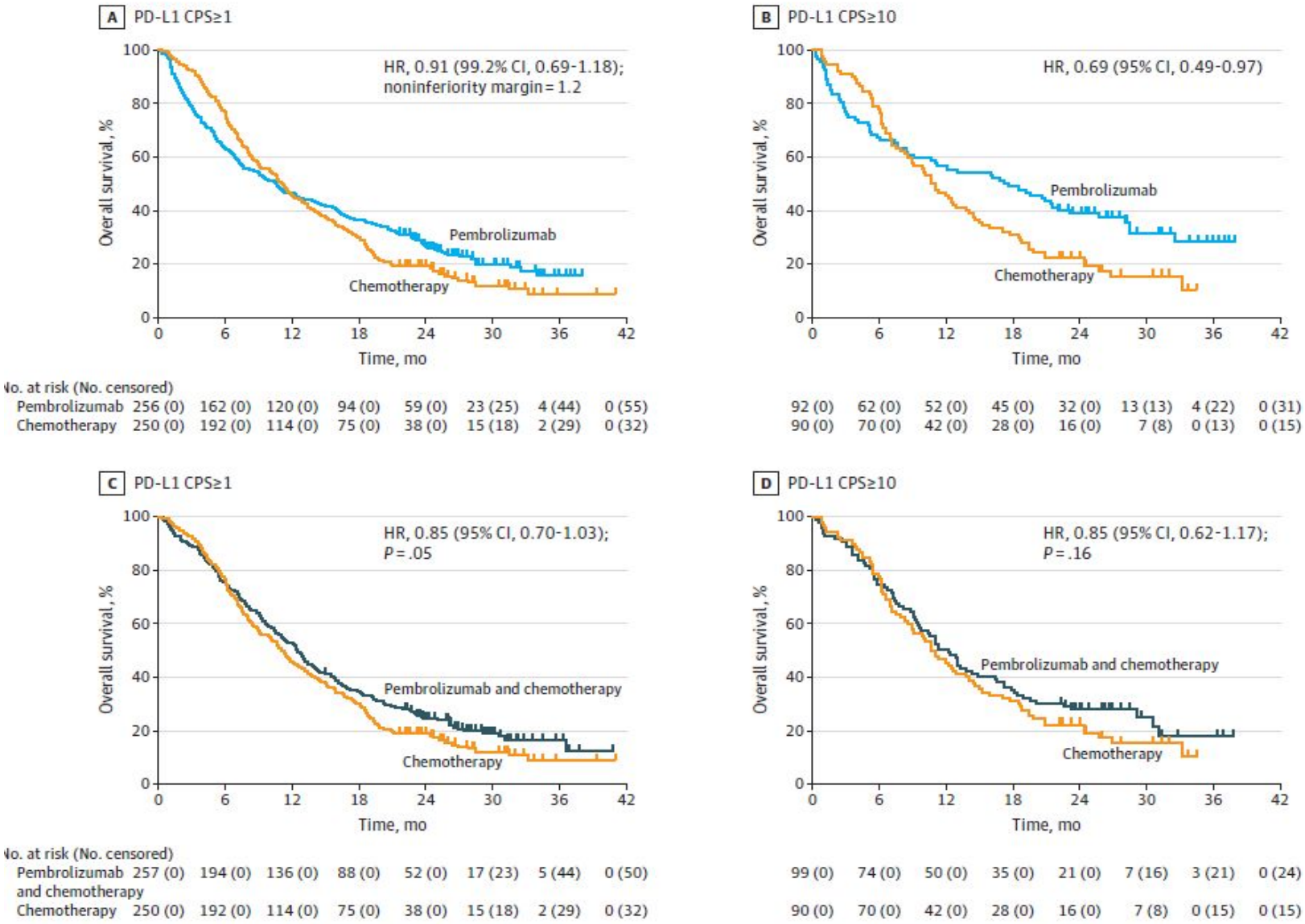
Metastatic Gastric/ GEJ Cancer

KEYNOTE-062 Study Design (NCT02494583)



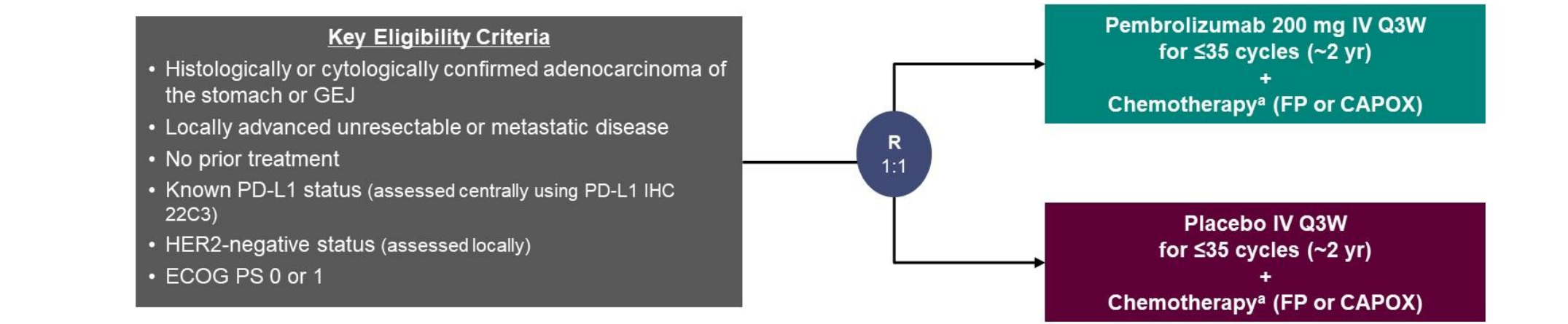
[a]EU/North America/Australia, Asia (South Korea, Hong Kong, Taiwan, Japan), Rest of World (including South America).
[b]Administration of pembrolizumab monotherapy was not blinded.
[c]Chemotherapy: Cisplatin 80 mg/m^2 Q3W + 5-FU 800 mg/m^2/d for 5 days Q3W or capecitabine BID d1-14 Q3W (Cisplatin may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

KN-62



Shitara et al. 2020. JAMA Onc

KEYNOTE-859 Study Design
Randomized, Double-Blind, Phase 3 Trial



Stratification Factors
- Geographic region (Europe/Israel/North America/ Australia vs Asia vs rest of world)
- PD-L1 CPS (<1 vs ≥1)
- Choice of chemotherapy[a] (FP vs CAPOX)

- **Primary End Point:** OS
- **Secondary End Points:** PFS,[b] ORR,[b] DOR,[b] and safety

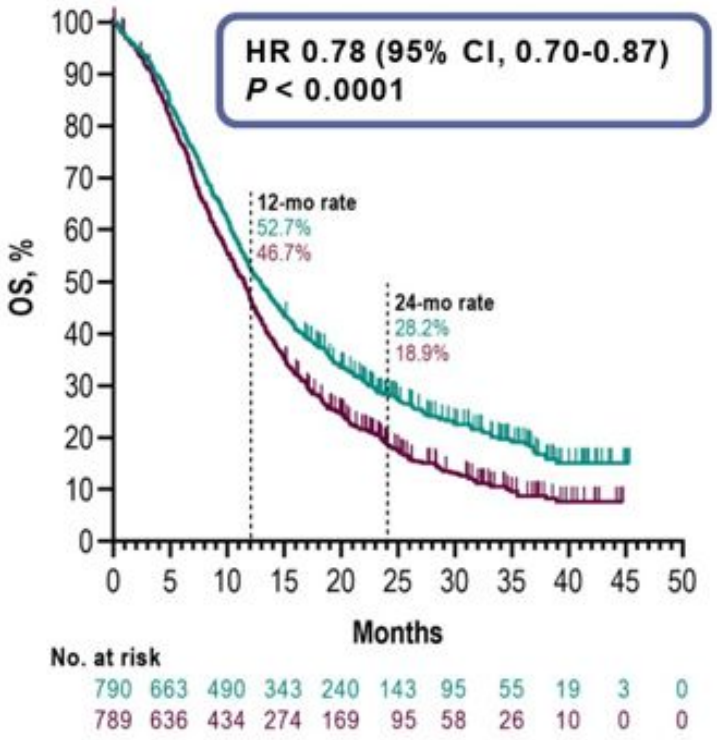
- **Alpha-controlled analyses:** OS, PFS, an ORR in the overall, PD-L1 CPS ≥1, and PD-L1 CPS ≥10 populations

[a] FP: 5-fluorouracil 800 mg/m^2/day IV continuous on days 1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 orally twice daily on days 1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W. Cisplatin and oxaliplatin have been limited to 6 cycles as per local country guidelines.
[b] Assessed per RECIST v1.1 by blinded, independent central review.
ClinicalTrials.gov number, NCT03675737.

Rha et al. ASCO 2023

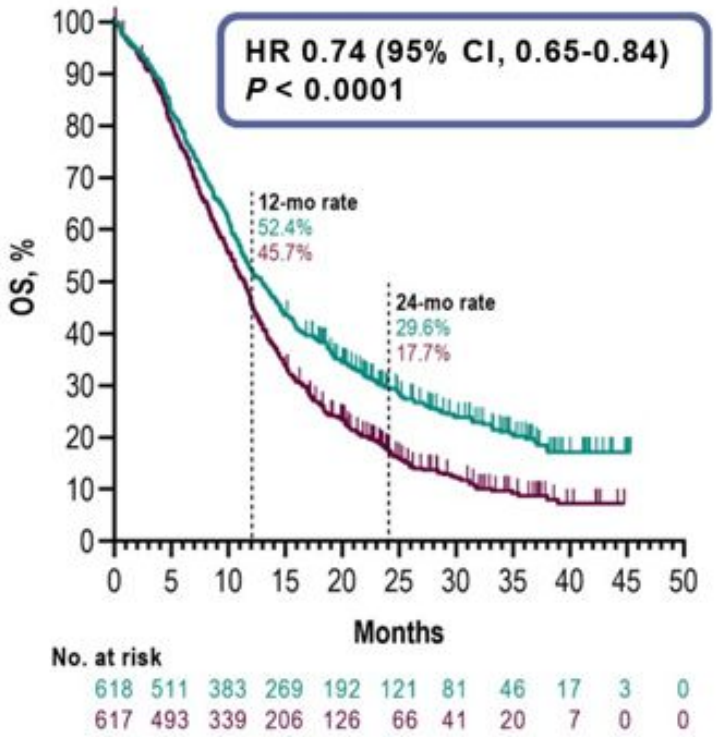
Overall[1]

	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	76.3%	12.9 (11.9-14.0)
Placebo + chemo	84.4%	11.5 (10.6-12.1)



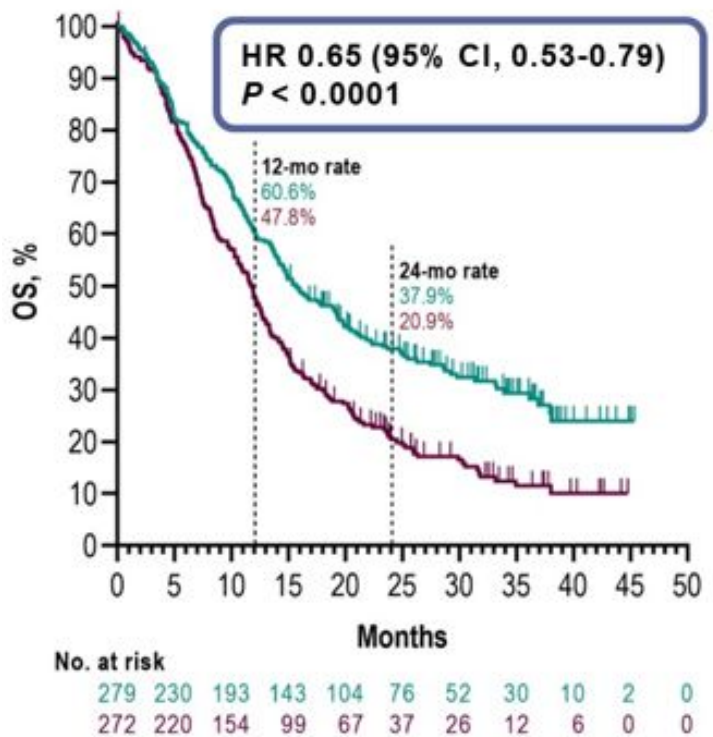
PD-L1 CPS ≥1

	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	75.1%	13.0 (11.6-14.2)
Placebo + chemo	85.3%	11.4 (10.5-12.0)



PD-L1 CPS ≥10

	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	67.4%	15.7 (13.8-19.3)
Placebo + chemo	83.1%	11.8 (10.3-12.7)



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Overall Survival in Subgroups

PD-L1 CPS ≥1

	No. Events/ No. Participants	Hazard ratio (95% CI)
Overall	990/1235	0.74 (0.652-0.838)
Age		
<65 years	612/741	0.73 (0.621-0.855)
≥65 years	378/494	0.73 (0.595-0.892)
Sex		
Female	309/365	0.69 (0.551-0.865)
Male	681/870	0.74 (0.638-0.864)
Geographic region		
Asia	299/401	0.70 (0.556-0.877)
W Eur/Isr/N Am/Australia	272/332	0.76 (0.595-0.961)
Rest of world	419/502	0.76 (0.624-0.918)
ECOG performance status		
0	341/451	0.66 (0.535-0.823)
1	649/784	0.77 (0.657-0.894)
Primary tumor location		
GEJ	235/287	0.71 (0.547-0.927)
Stomach	754/947	0.73 (0.634-0.844)
Histologic subtype		
Diffuse	391/456	0.73 (0.601-0.897)
Intestinal	345/454	0.78 (0.635-0.969)
Indeterminate	252/323	0.64 (0.494-0.822)
Disease status		
Metastatic	951/1184	0.73 (0.643-0.831)
Liver metastases		
No	572/723	0.71 (0.600-0.835)
Yes	417/511	0.77 (0.631-0.929)
Prior gastrectomy/esophagectomy		
No	839/1014	0.77 (0.674-0.885)
Yes	145/214	0.59 (0.422-0.816)
PD-L1 CPS		
≥10	414/551	0.64 (0.523-0.772)
1-9	574/682	0.83 (0.705-0.979)
Chemo choice at randomization		
CAPOX	832/1056	0.72 (0.626-0.824)
FP	158/179	0.82 (0.601-1.125)

PD-L1 CPS ≥10

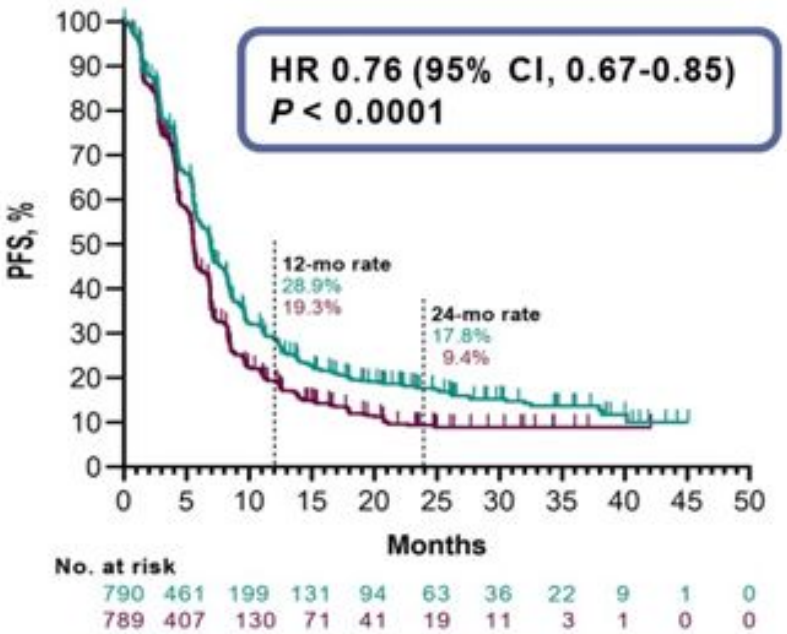
	No. Events/ No. Participants	Hazard ratio (95% CI)
Overall	414/551	0.65 (0.532-0.787)
Age		
<65 years	247/320	0.67 (0.522-0.864)
≥65 years	167/231	0.59 (0.437-0.806)
Sex		
Female	123/153	0.58 (0.405-0.830)
Male	291/398	0.65 (0.514-0.818)
Geographic region		
Asia	126/184	0.63 (0.441-0.889)
W Eur/Isr/N Am/Australia	107/142	0.83 (0.565-1.213)
Rest of world	181/225	0.58 (0.431-0.784)
ECOG performance status		
0	141/202	0.58 (0.416-0.816)
1	273/349	0.65 (0.515-0.830)
Primary tumor location		
GEJ	103/138	0.57 (0.384-0.852)
Stomach	311/413	0.65 (0.521-0.815)
Histologic subtype		
Diffuse	161/191	0.57 (0.415-0.779)
Intestinal	143/210	0.77 (0.556-1.073)
Indeterminate	109/149	0.49 (0.327-0.724)
Disease status		
Metastatic	398/526	0.64 (0.524-0.780)
Liver metastases		
No	245/322	0.60 (0.464-0.769)
Yes	169/229	0.69 (0.511-0.940)
Prior gastrectomy/esophagectomy		
No	360/462	0.65 (0.526-0.800)
Yes	53/88	0.62 (0.360-1.060)
Chemo choice at randomization		
CAPOX	351/477	0.63 (0.512-0.781)
FP	63/74	0.62 (0.378-1.029)

Data cutoff date: October 3, 2022.

Rha et al. ASCO 2023

Overall[1]

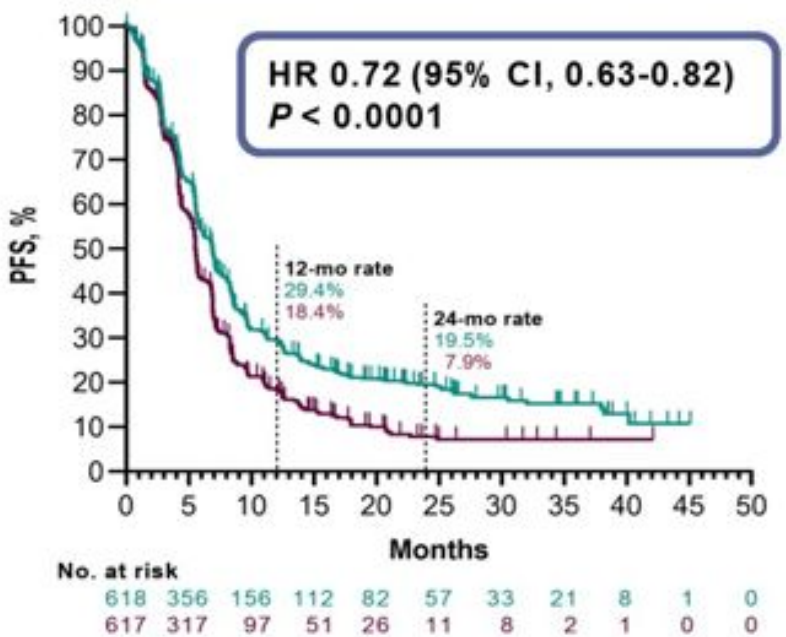
	Pts w/ Event	Median PFS (95% CI), mo
Pembro + chemo	72.4%	6.9 (6.3-7.2)
Placebo + chemo	77.1%	5.6 (5.5-5.7)



	Pembro + Chemo	Placebo + Chemo
ORR, % (95% CI)	51.3% (47.7-54.8)	42.0% (38.5-45.5)
Δ (95% CI)	9.3 (4.4-14.1); *P* = 0.00009	
mDOR (range)	8.0 mo (1.2+ - 41.5+)	5.7 mo (1.3+ - 34.7+)

PD-L1 CPS ≥1

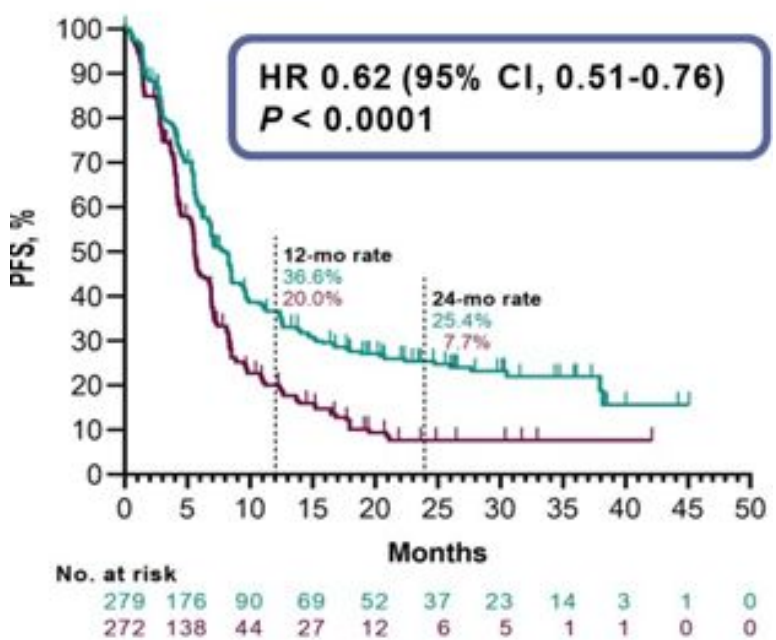
	Pts w/ Event	Median PFS (95% CI), mo
Pembro + chemo	71.7%	6.9 (6.0-7.2)
Placebo + chemo	78.3%	5.6 (5.4-5.7)



	Pembro + Chemo	Placebo + Chemo
ORR, % (95% CI)	52.1% (48.1-56.1)	42.6% (38.7-46.6)
Δ (95% CI)	9.5 (3.9-15.0); *P* = 0.00041	
mDOR (range)	8.3 mo (1.2+ - 41.5+)	5.6 mo (1.3+ - 34.2+)

PD-L1 CPS ≥10

	Pts w/ Event	Median PFS (95% CI), mo
Pembro + chemo	68.1%	8.1 (6.8-8.5)
Placebo + chemo	77.2%	5.6 (5.4-6.7)



	Pembro + Chemo	Placebo + Chemo
ORR, % (95% CI)	60.6% (54.6-66.3)	43.0% (37.1-49.1)
Δ (95% CI)	17.5 (9.3-23.5); *P* = 0.00002	
mDOR (range)	10.9 mo (1.2+ - 41.5+)	5.8 mo (1.4+ - 31.2+)

Rha et al. ASCO 2023

ASCO® Gastrointestinal Cancers Symposium

Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: expanded analyses from 24-month follow-up of CheckMate 649

Kohei Shitara,[1] Yelena Y. Janjigian,[2] Markus Moehler,[3] Marcelo Garrido,[4] Carlos Gallardo,[5] Lin Shen,[6] Kensei Yamaguchi,[7] Lucjan Wyrwicz,[8] Tomasz Skoczylas,[9] Arinilda Bragagnoli,[10] Tianshu Liu,[11] Mustapha Tehfe,[12] Elena Elimova,[13] Samira Soleymani,[14] Ming Lei,[14] Kaoru Kondo,[14] Mingshun Li,[14] Jaffer A. Ajani[15]

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Abstract number 240

CheckMate 649 Study Design

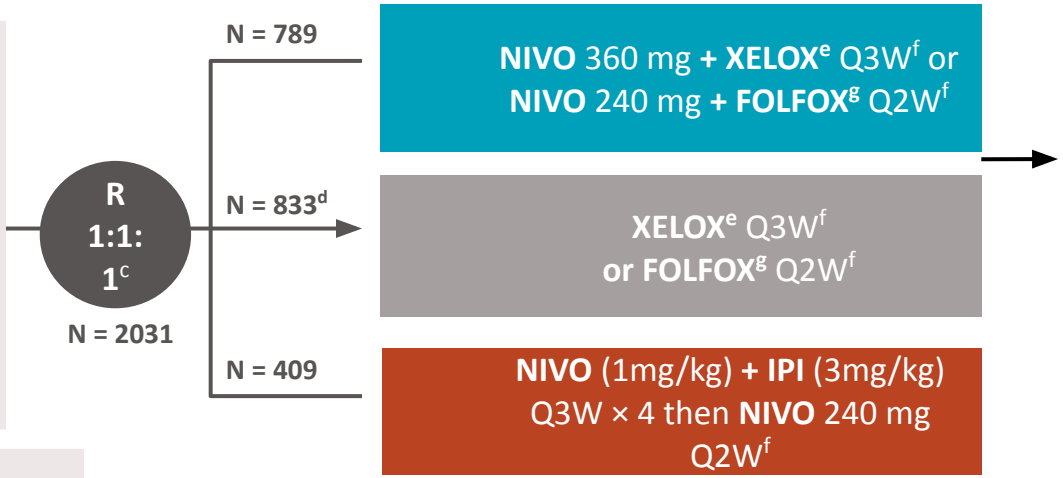
- CheckMate 649 is a randomized, open-label, phase 3 study[a]

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 US/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



Dual primary endpoints

NIVO + chemo vs chemo
- **OS** and **PFS**[h] (PD-L1 CPS ≥ 5)

Hierarchically tested secondary efficacy endpoints

NIVO + chemo vs chemo
- **OS** (PD-L1 CPS ≥ 1, all randomized)

NIVO + IPI vs chemo
- **OS** (PD-L1 CPS ≥ 5, all randomized)

PD-L1 CPS ≥ 5:

- **955/1581 (60%) patients in the NIVO + chemo vs chemo comparison**
- **473/813 (58%) patients in the NIVO+IPI vs chemo comparison**

- At data cutoff (May 27, 2021), the minimum follow-up[i] was 24.0 months in the NIVO + chemo arm and 35.7 months in the NIVO + IPI arm

[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 NIVO + IPI arm was closed. Upon DMC recommendation (31-May-2018), enrollment to the NIVO + IPI arm was stopped early due to an observed increase in rates of early death and toxicity. Patients already in the NIVO+IPI arm were allowed to remain on study based on the DMC recommendation. [d]Includes patients that were concurrently randomized to receive chemo versus NIVO + IPI (October 2016–June 2018) and NIVO + chemo (June 2018-Apr 2019). [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1–14). [f]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo or NIVO + IPI), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years.
[g]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). [h]BICR assessed. [i]Time from concurrent randomization of the last patient to data cutoff

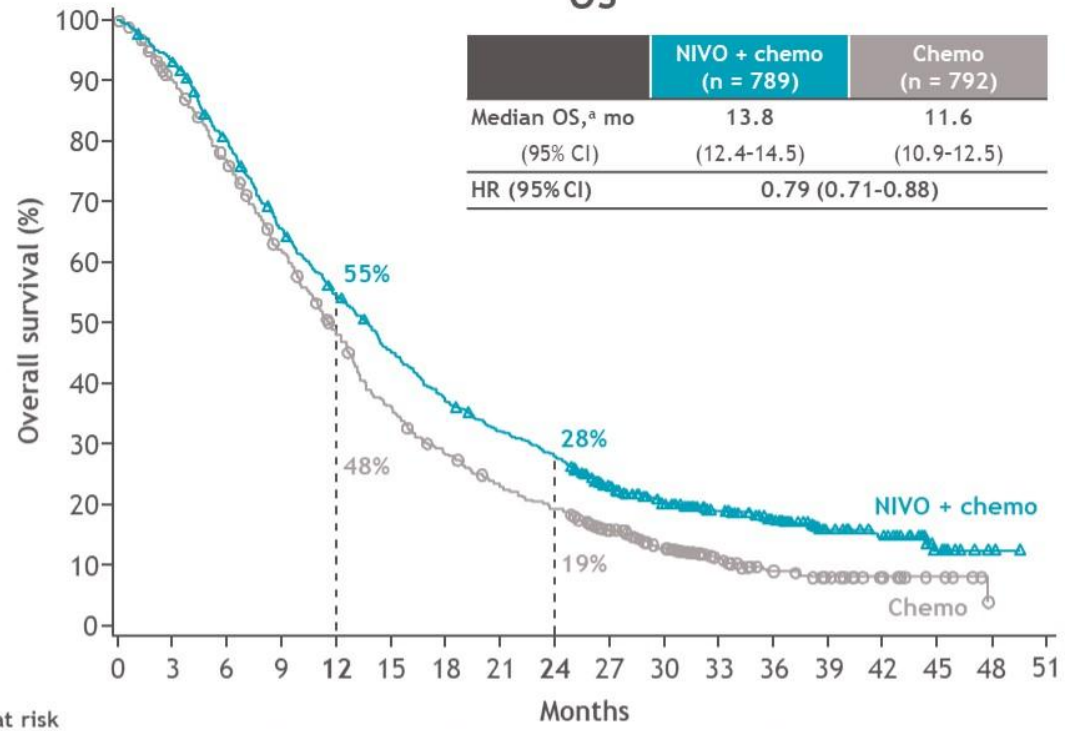
1. Janjigian YY et al. *Lancet*. 2021;398:27-40. 2. Janjigian YY et al. Presented at ESMO 2021.

Overall survival and progression-free survival

All randomized patients

OS

	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS,[a] mo	13.8	11.6
(95% CI)	(12.4-14.5)	(10.9-12.5)
HR (95% CI)	0.79 (0.71-0.88)	

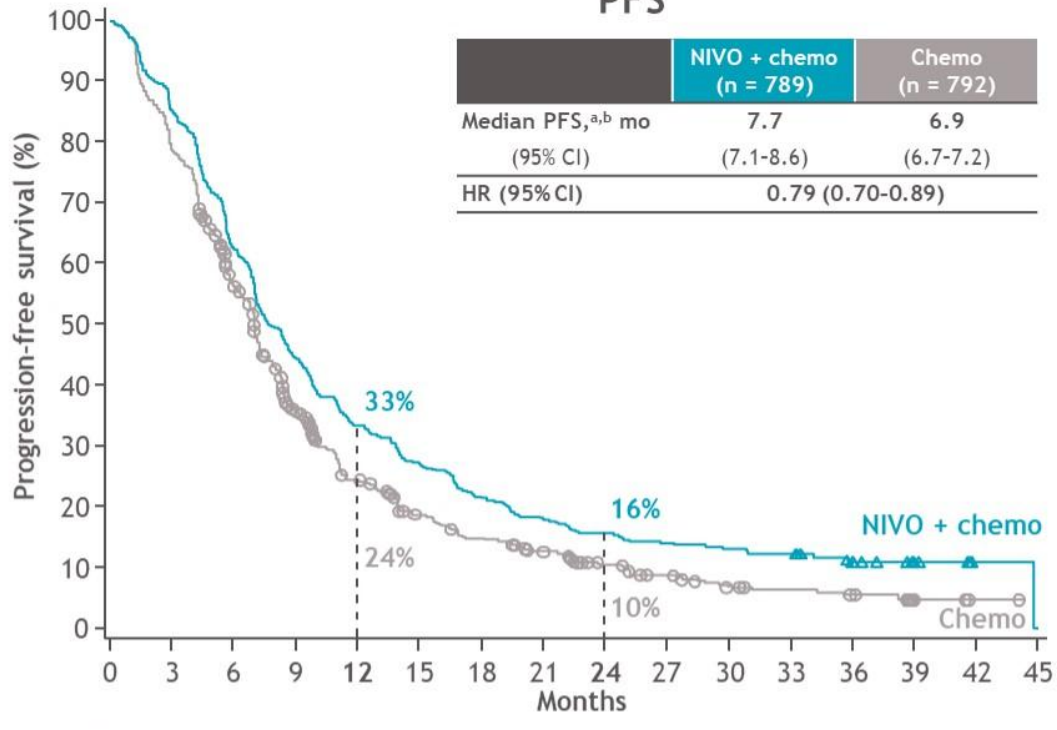


No. at risk

NIVO + chemo	789	733	624	508	422	349	287	246	212	156	115	84	57	33	25	9	2	0
Chemo	792	701	591	475	364	273	215	170	144	103	72	46	28	20	12	6	0	0

PFS

	NIVO + chemo (n = 789)	Chemo (n = 792)
Median PFS,[a,b] mo	7.7	6.9
(95% CI)	(7.1-8.6)	(6.7-7.2)
HR (95% CI)	0.79 (0.70-0.89)	



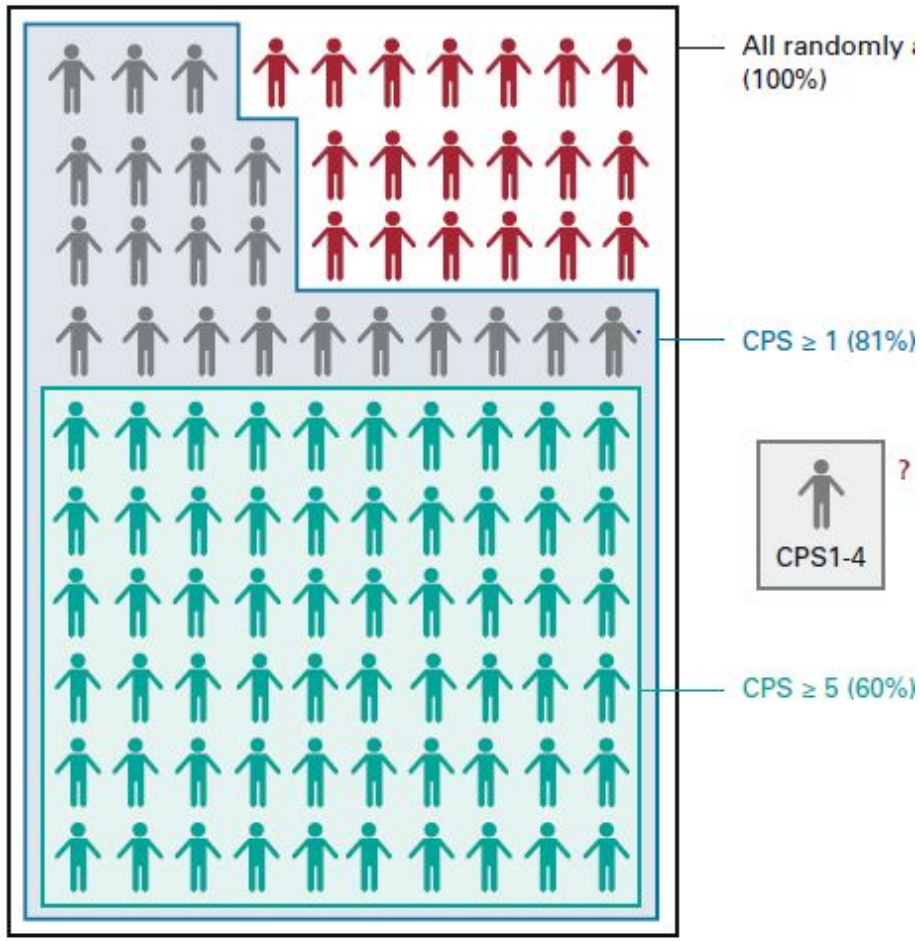
	789	640	431	295	209	166	126	96	74	53	37	25	11	6	1	0		
	792	552	359	213	135	96	75	59	40	29	18	15	10	3	1	0		

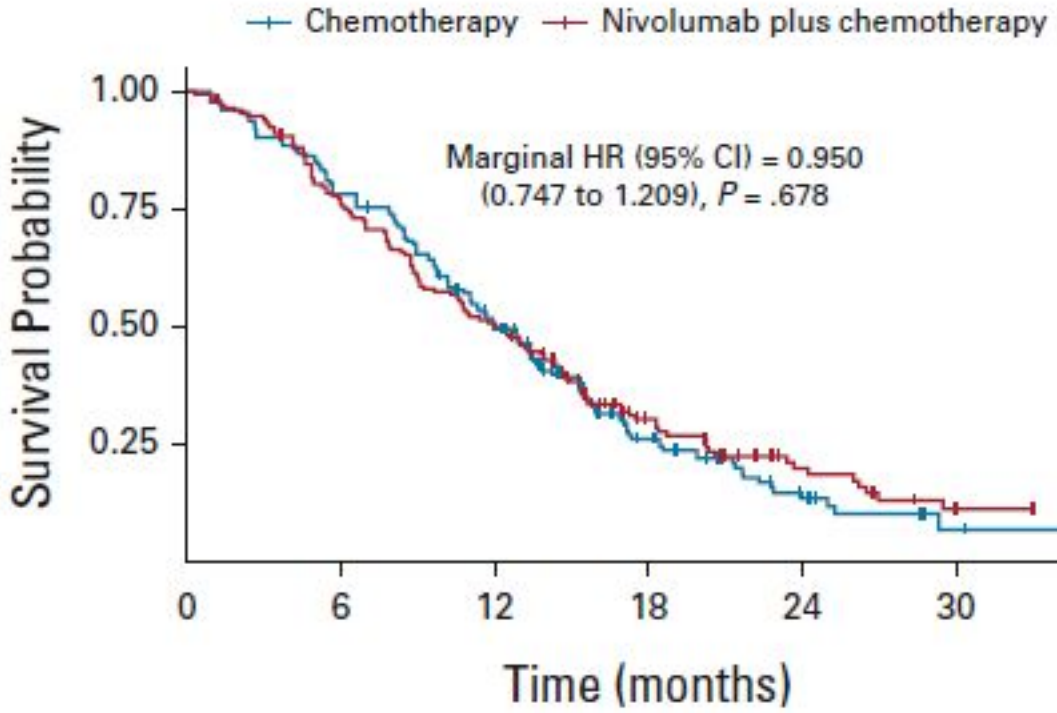
- Clinically meaningful improvement in OS and PFS with NIVO + chemo vs chemo was maintained with longer follow-up

[a]Minimum follow-up, 24.0 months. [b]Per BICR assessment. Janjigian YY et al. Oral presentation at ESMO; September 16-21, 2021; Virtual. Abstract LBA7.

CheckMate-649

Nivolumab plus chemotherapy *v* chemotherapy
for first-line treatment of advanced gastroesophageal adenocarcinoma





Overall survival

PD-L1 CPS[a]	Number of patients	Median, months		Unstratified HR[b]	Unstratified HR (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 1581)		13.8	11.6	0.78	
< 1	265	13.1	12.5	0.95	
≥ 1	1297	13.8	11.3	0.74	
< 5	607	12.4	12.3	0.94	
≥ 5	955	14.4	11.1	0.69	
< 10	795	12.4	12.5	0.91	
≥ 10	767	15.0	10.9	0.66	

OS benefit was enriched with higher PD-L1 CPS cutoff suggesting lack of benefit in PD-L1 <5

Janjigian et al. Lancet 2020.
Zhao et al. JCO 2021

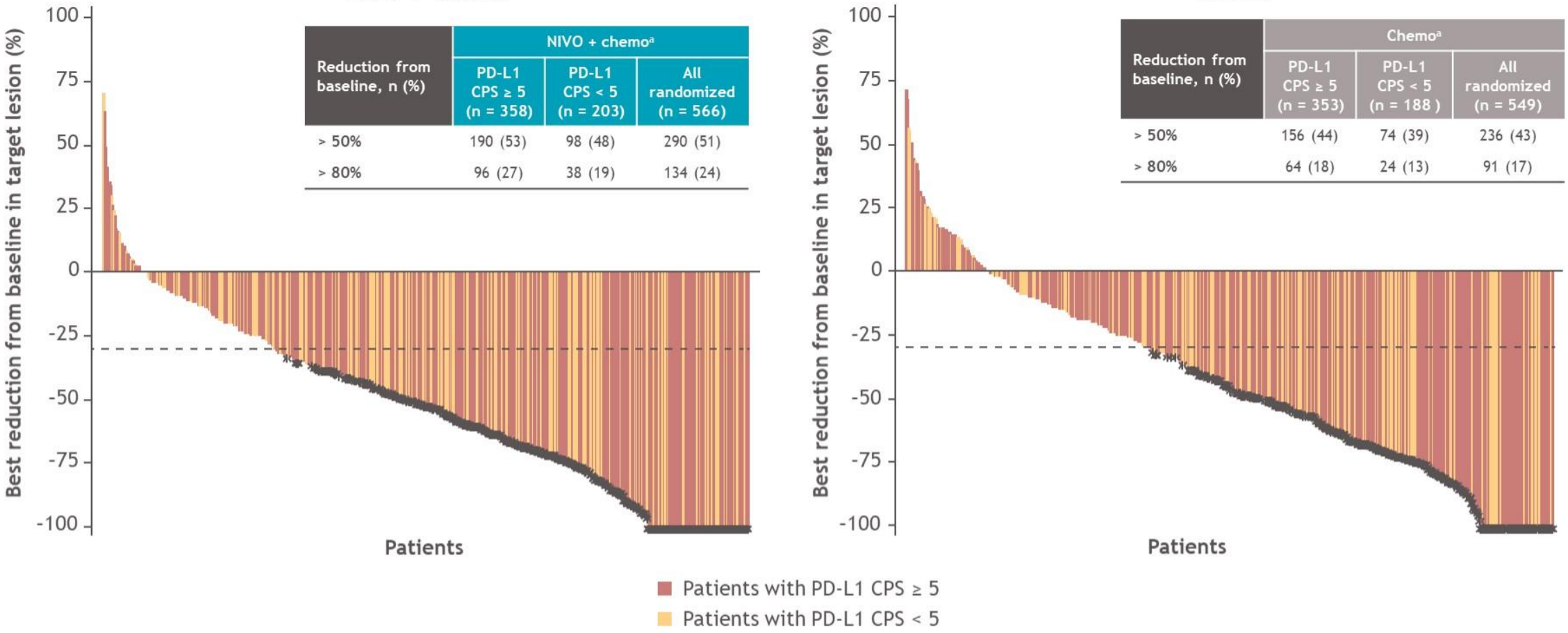
Best percentage reduction in tumor burden

NIVO + chemo

Reduction from baseline, n (%)	NIVO + chemo[a]		
	PD-L1 CPS ≥ 5 (n = 358)	PD-L1 CPS < 5 (n = 203)	All randomized (n = 566)
> 50%	190 (53)	98 (48)	290 (51)
> 80%	96 (27)	38 (19)	134 (24)

Chemo

Reduction from baseline, n (%)	Chemo[a]		
	PD-L1 CPS ≥ 5 (n = 353)	PD-L1 CPS < 5 (n = 188)	All randomized (n = 549)
> 50%	156 (44)	74 (39)	236 (43)
> 80%	64 (18)	24 (13)	91 (17)

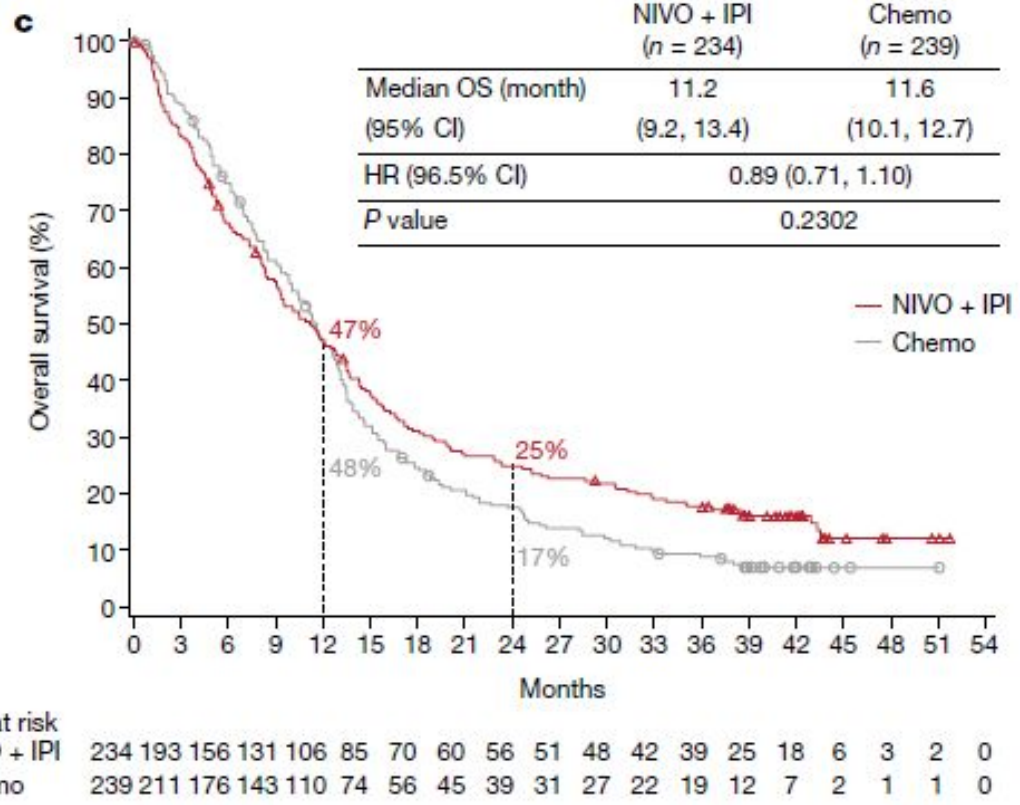


- More deep responses were observed with NIVO + chemo vs chemo regardless of PD-L1 CPS ≥ 5 or < 5

[a]All randomized patients who had measurable disease at baseline per BICR and at least 1 on-treatment tumor assessment. Best reduction is maximum reduction in sum of diameters of target lesions. Horizontal reference line indicates the 30% reduction consistent with a response per RECIST v1.1. Asterisk symbol represents responders.

Nivo+IPI not superior to chemo

CPS PDL≥5%

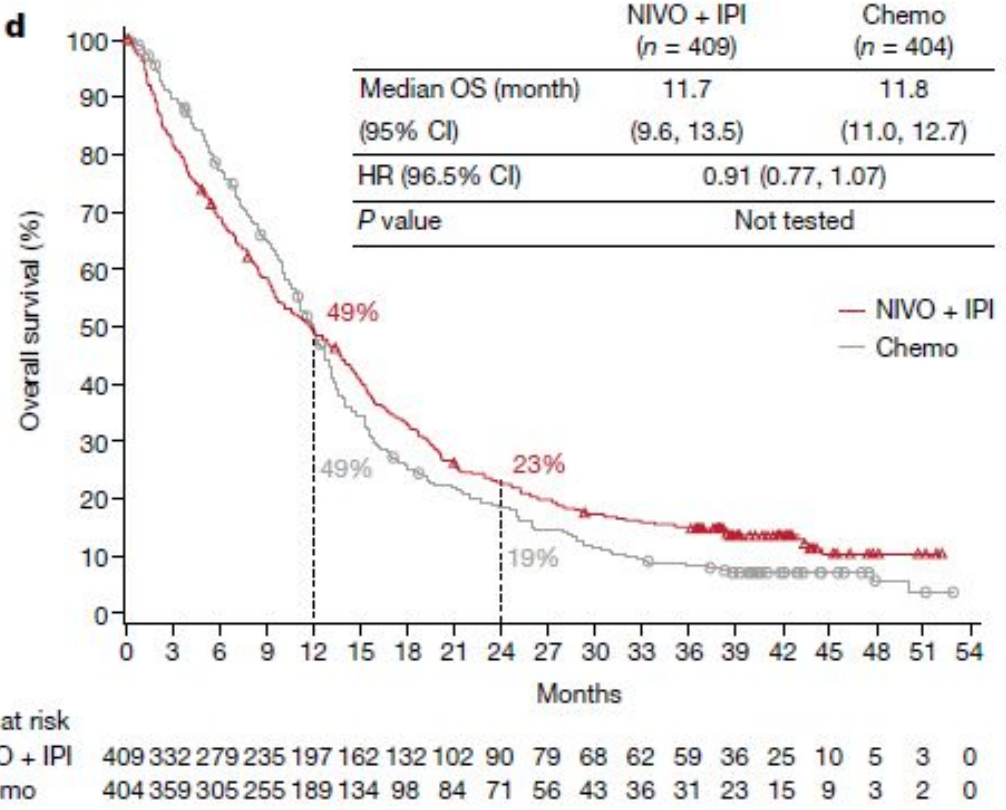


	NIVO + IPI (*n* = 234)	Chemo (*n* = 239)
Median OS (month)	11.2	11.6
(95% CI)	(9.2, 13.4)	(10.1, 12.7)
HR (96.5% CI)	0.89 (0.71, 1.10)	
P value	0.2302	

No. at risk

NIVO + IPI	234	193	156	131	106	85	70	60	56	51	48	42	39	25	18	6	3	2	0
Chemo	239	211	176	143	110	74	56	45	39	31	27	22	19	12	7	2	1	1	0

All Randomized Patients



	NIVO + IPI (*n* = 409)	Chemo (*n* = 404)
Median OS (month)	11.7	11.8
(95% CI)	(9.6, 13.5)	(11.0, 12.7)
HR (96.5% CI)	0.91 (0.77, 1.07)	
P value	Not tested	

No. at risk

NIVO + IPI	409	332	279	235	197	162	132	102	90	79	68	62	59	36	25	10	5	3	0
Chemo	404	359	305	255	189	134	98	84	71	56	43	36	31	23	15	9	3	2	0

Shitara et al. Nature 2022.

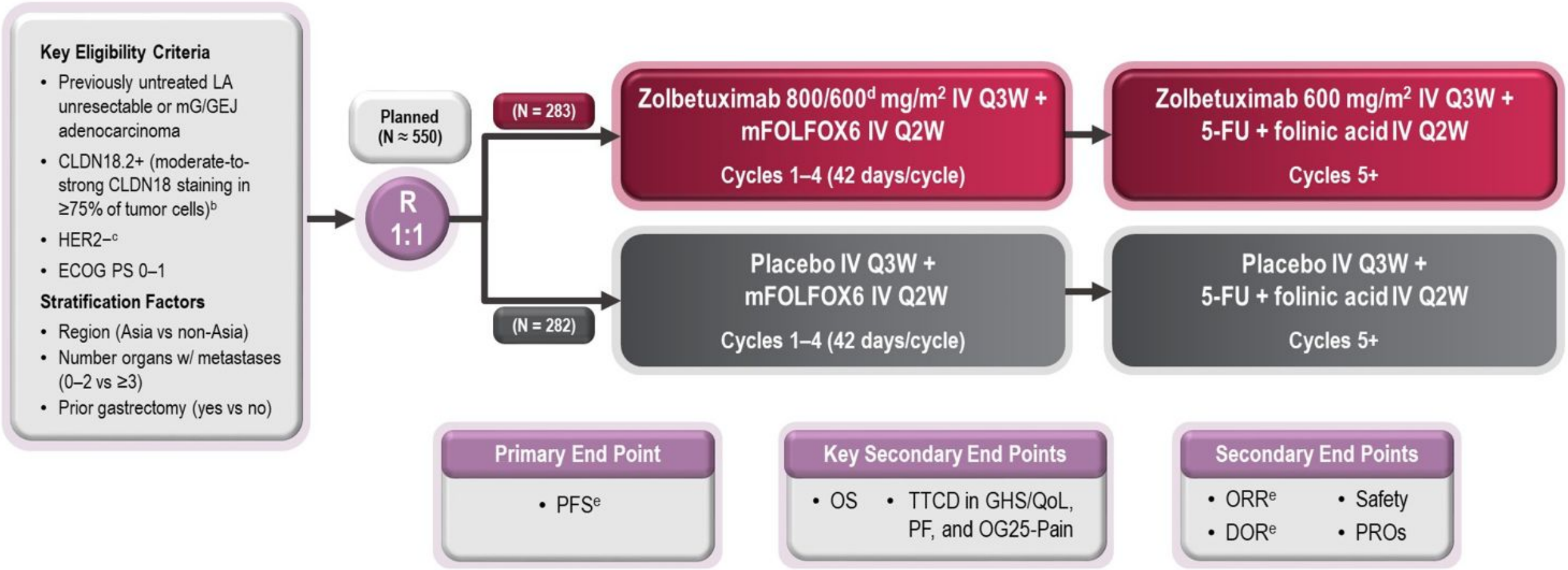
New Biomarker: Claudin 18.2

- CLDN 18.2 is a tight junction protein expressed in normal and malignant gastric mucosa cells.
- During malignant transformation, CLDN18.2 may become exposed on the surface of the adenocarcinoma cells.
- CLDN 18.2 positivity is 30-44%
  - Region
    - 36% in Asia Pacific
    - 35% North America
    - 44% Europe and Middle East
  - Tumor Type
    - 48.3% diffuse type
    - 38.8% intestinal type
  - PDL1 status in CLDN+ tumors
    - CPS≥5 17.4%
- Zolbetuximab is a chimeric IgG1 monoclonal antibody that targets CLDN18.2 and induces ADCC/CDC

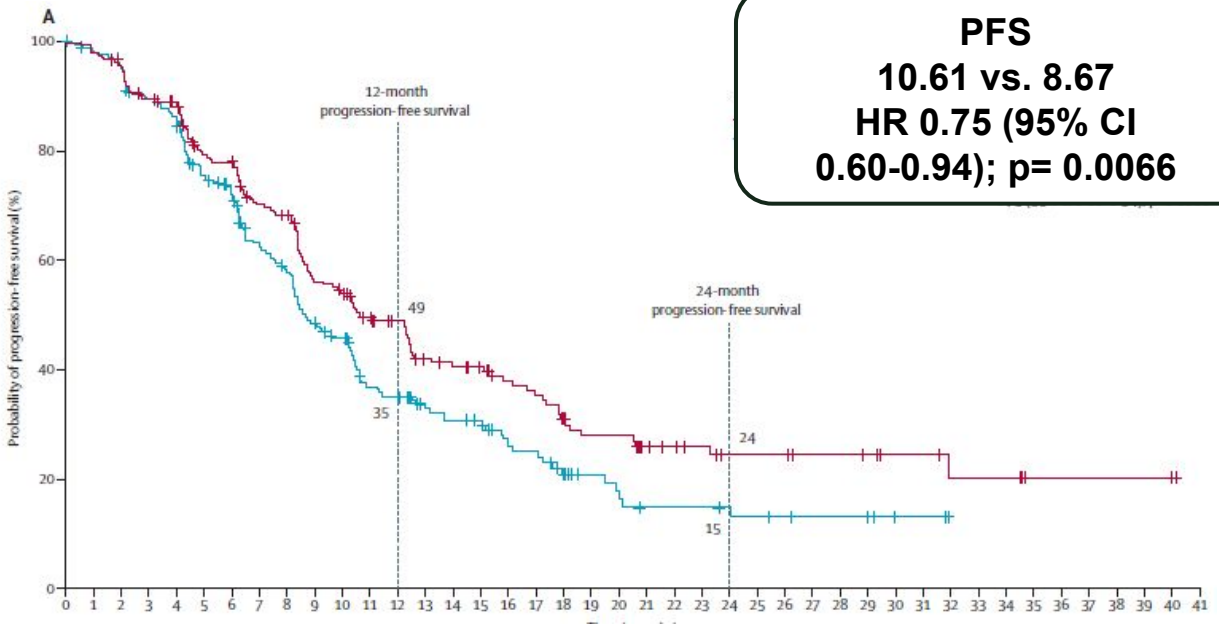
Kubota et al. 2023 ESMO Open
Shitara et al. Lancet 2023

Study Design: SPOTLIGHT

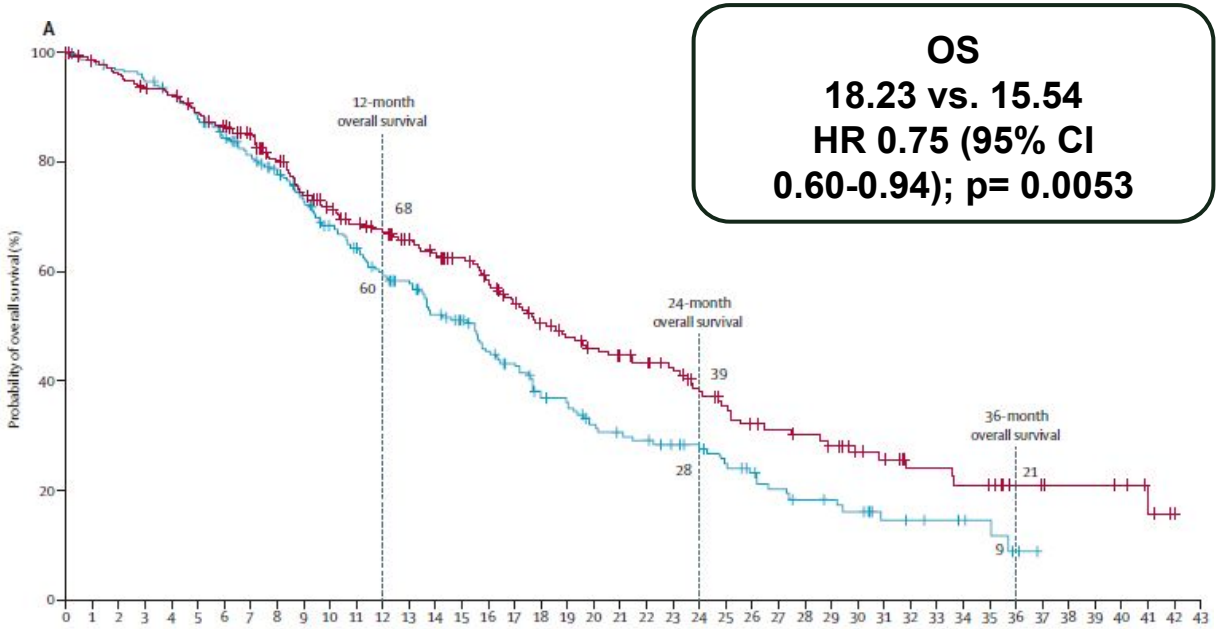
Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial



Shitara et al. Lancet 2023



PFS
10.61 vs. 8.67
HR 0.75 (95% CI 0.60-0.94); p= 0.0066



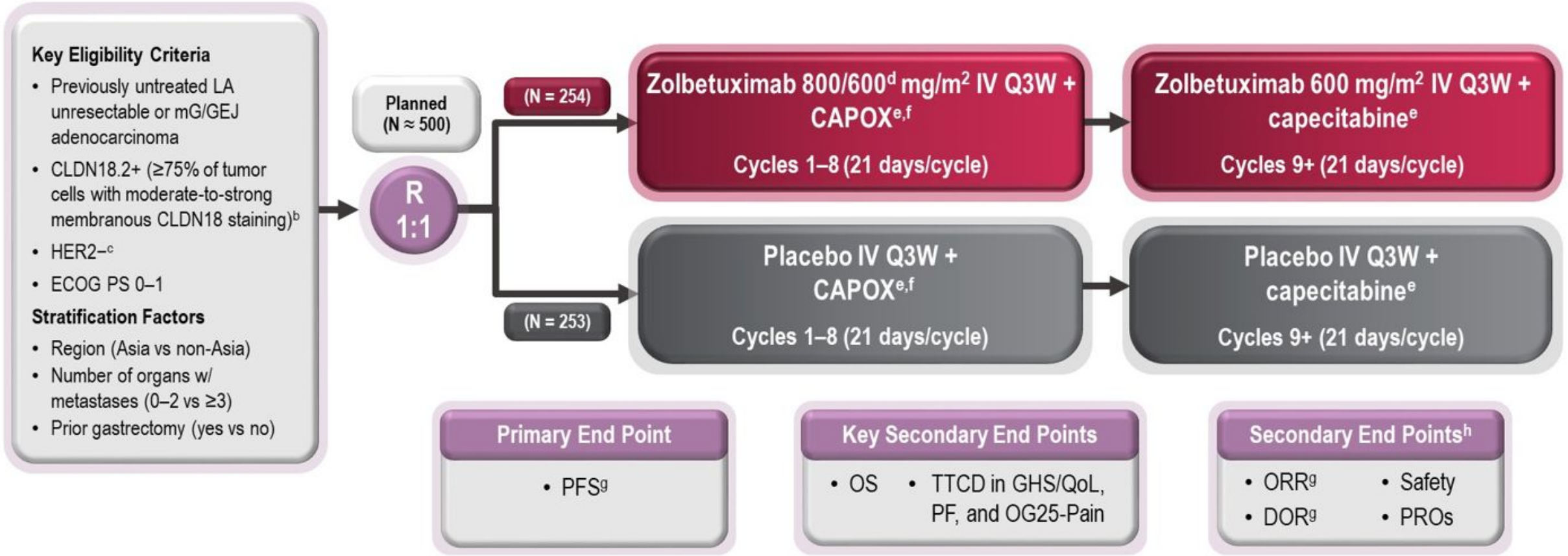
OS
18.23 vs. 15.54
HR 0.75 (95% CI 0.60-0.94); p= 0.0053

- Zolbetuximab did NOT improve ORR of 48%
- Nausea and vomiting most common side effects (82%; grade 3/4 16%)

Shitara et al. Lancet 2023

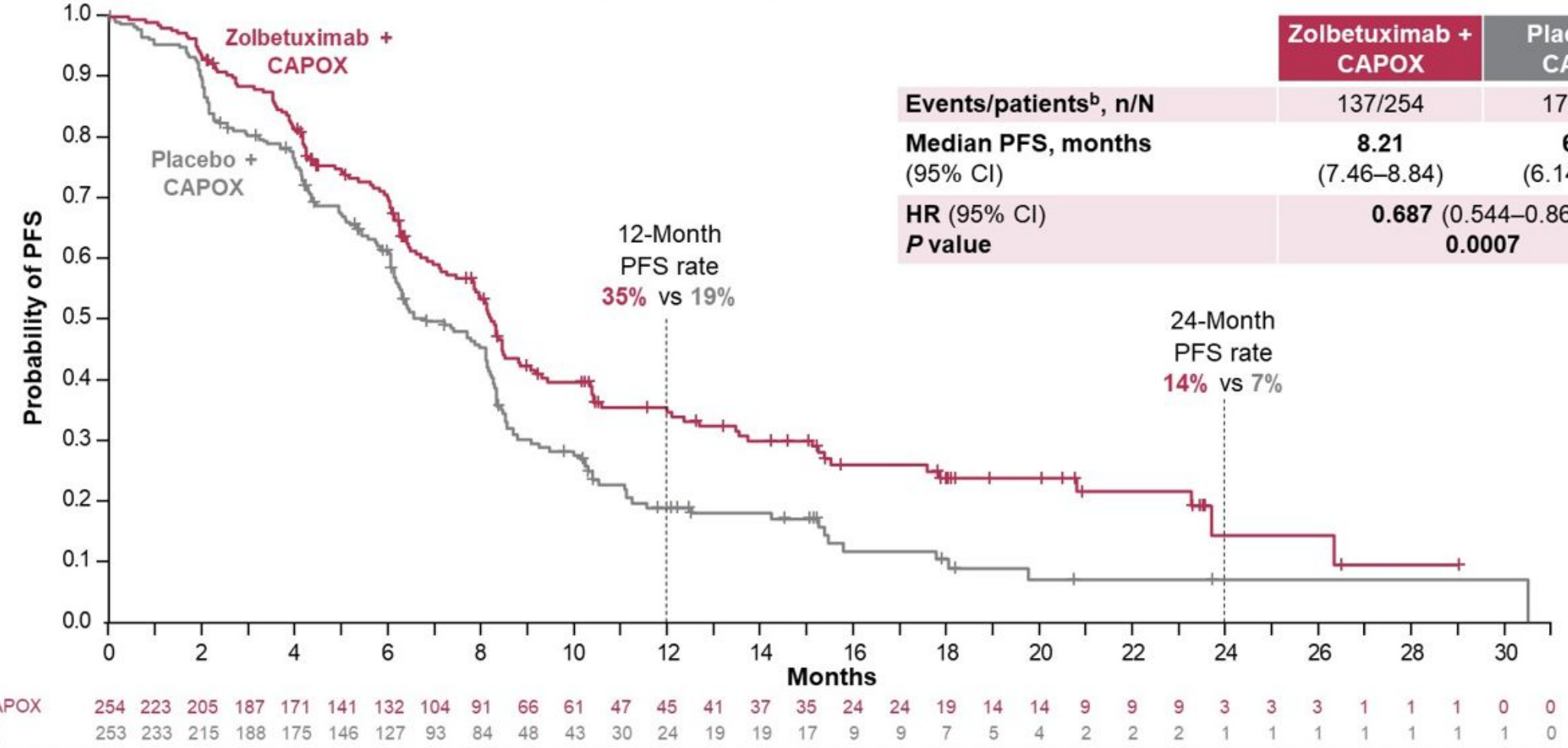
Study Design: GLOW

Global[a], randomized, double-blinded, placebo-controlled, phase 3 trial



Shah et al. ASCO plenary series March 2023

Primary End Point: PFS by Independent Review Committee[a]



	Zolbetuximab + CAPOX	Placebo + CAPOX
Events/patients[b], n/N	137/254	172/253
Median PFS, months (95% CI)	**8.21** (7.46–8.84)	**6.80** (6.14–8.08)
HR (95% CI)	**0.687** (0.544–0.866)	
***P* value**	**0.0007**	

PFS was significantly longer with zolbetuximab + CAPOX vs placebo + CAPOX

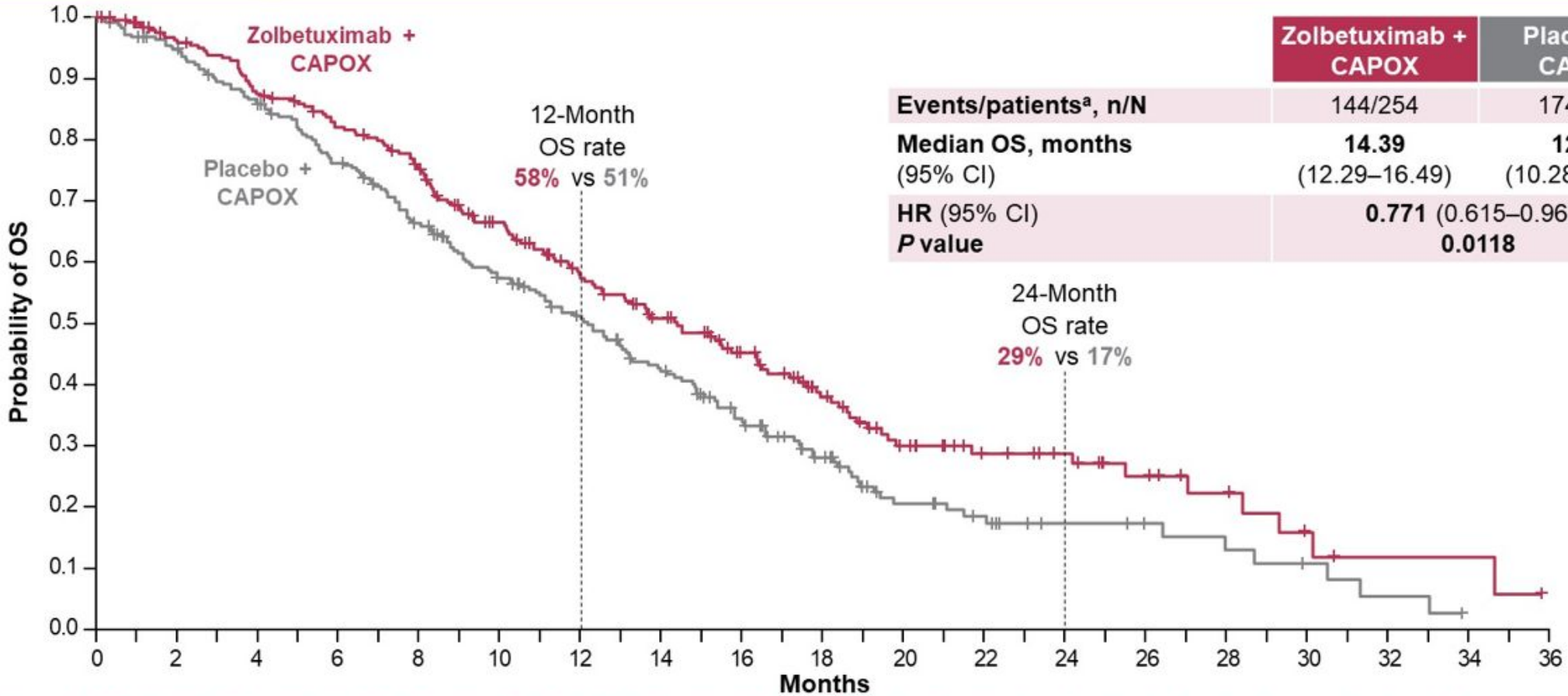
The benefit was maintained across most prespecified subgroups

Data cutoff: October 7, 2022; Median follow-up = 12.62 months (zolbetuximab + CAPOX) vs 12.09 months (placebo + CAPOX).

[a]Per RECIST version 1.1; [b]117/254 (46.1%) patients assigned to zolbetuximab + CAPOX and 81/253 (32.0%) of patients assigned to placebo + CAPOX were censored.

Shah et al. ASCO plenary series March 2023

Key Secondary End Point: OS



	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**	

No. at Risk

Zolbetuximab + CAPOX	254	243	233	226	211	203	193	187	171	150	138	125	108	100	87	80	68	61	47	38	31	27	22	21	18	13	12	9	8	6	4	2	2	2	2	1	0
Placebo + CAPOX	253	243	235	220	210	197	181	168	152	136	125	115	104	92	82	70	59	49	40	27	22	20	16	12	10	10	8	7	6	5	4	3	2	2	0	0	0

OS was significantly longer in patients treated with zolbetuximab + CAPOX vs placebo + CAPOX
The benefit was maintained across most prespecified subgroups
Subsequent anticancer therapies (47% zolbetuximab arm; 55% placebo arm) were balanced between arms

Data cutoff: October 7, 2022; Median follow-up = 17.71 months (zolbetuximab + CAPOX) vs 18.43 months (placebo + CAPOX).

[a]110/254 (43.3%) patients assigned to zolbetuximab + CAPOX and 79/253 (31.2%) of patients assigned to placebo + CAPOX were censored.

Shah et al. ASCO plenary series March 2023

Zolbetuximab

- Improves PFS 2 months and OS 2.5-3 months
- Not much added ORR
- Nausea and vomiting are main side effects
- Studies are looking at combination with nivolumab

Metastatic Gastric/ GEJ Cancer MSI-H

MSI high

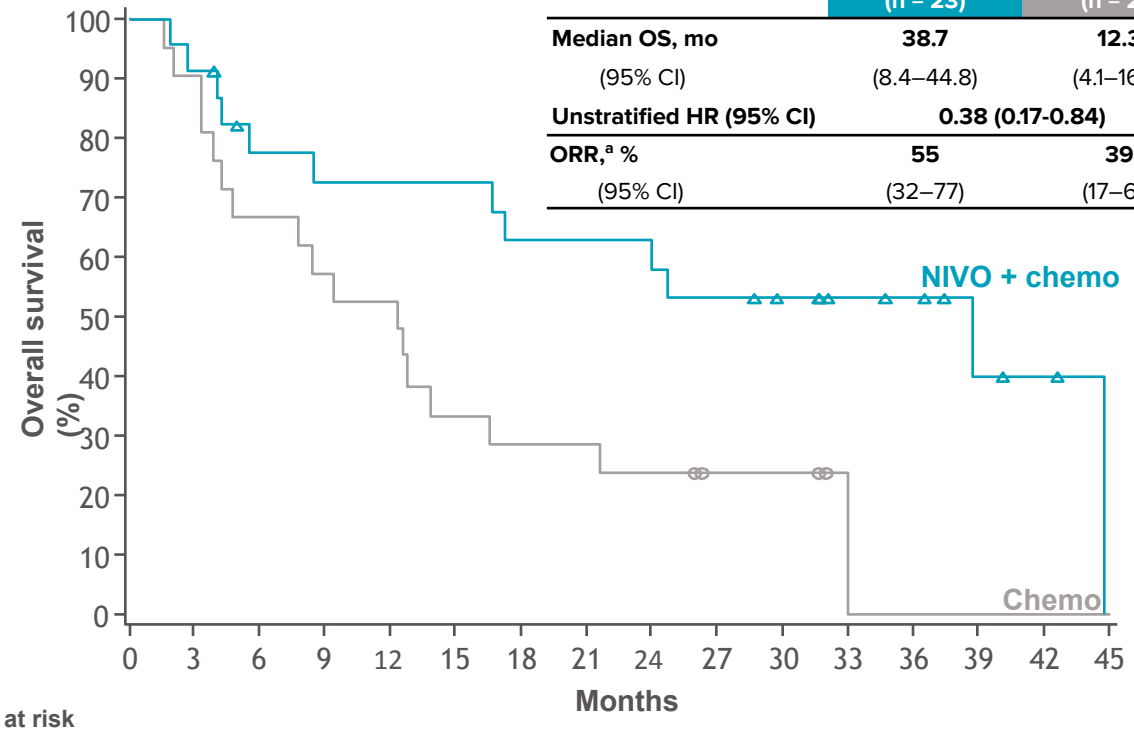
Characteristic	Patients, No. (%)					
	KEYNOTE-059[a]	KEYNOTE-061[b]		KEYNOTE-062[c]		
	Pembrolizumab	Pembrolizumab	Chemotherapy	Pembrolizumab	Pembrolizumab plus chemotherapy	Chemotherapy
Total patients, No.	7	15	12	14	17	19
PD-L1 CPS						
≥1	5 (71.4)	13 (86.7)	11 (91.7)	14 (100)	17 (100)	19 (100)
≥10	2 (28.6)	8 (53.3)	5 (41.7)	11 (78.6)	11 (64.7)	10 (52.6)
Objective response rate, % (95% CI)	57.1 (18.4-90.1)	46.7 (21.3-73.4)	16.7 (2.1-48.4)	57.1 (28.9-82.3)	64.7 (38.3-85.8)	36.8 (16.3-61.6)
Best overall response rate, %						
Complete	28.6	6.7	8.3	7.1	35.3	10.5
Partial	28.6	40.0	8.3	50.0	29.4	26.3
Stable disease	14.3	40.0	58.3	21.4	17.6	42.1
Progressive disease	0	6.7	0	14.3	0	10.5
Duration of response, median (range), mo	NR (20.0[d]-26.8[d])	NR (5.5-26.0[d])	NR (2.2[d]-12.2[d])	21.2 (1.4[d]-33.6[d])	NR (1.6[d]-34.5[d])	7.0 (2.0-30.4[d])
Survival, median (95% CI), mo						
Progression-free	NR (1.1-NR)	17.8 (2.7-NR)	3.5 (2.0-9.8)	11.2 (1.5-NR)	NR (3.6-NR)	6.6 (4.4-8.3)
Overall	NR (1.1-NR)	NR (5.6-NR)	8.1 (2.0-16.7)	NR (10.7-NR)	NR (3.6-NR)	8.5 (5.3-20.8)
Estimated overall survival rate, % (95% CI)						
12 mo	71 (NA)	73 (44-89)	25 (6-50)	79 (47-92)	71 (43-87)	47 (24-67)
24 mo	57 (NA)	59 (31-79)	NA	71 (41-88)	65 (38-82)	26 (10-57)

Chao et al. JAMA Onc. April 2021

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,[a] %	**55**	**39**
(95% CI)	(32–77)	(17–64)

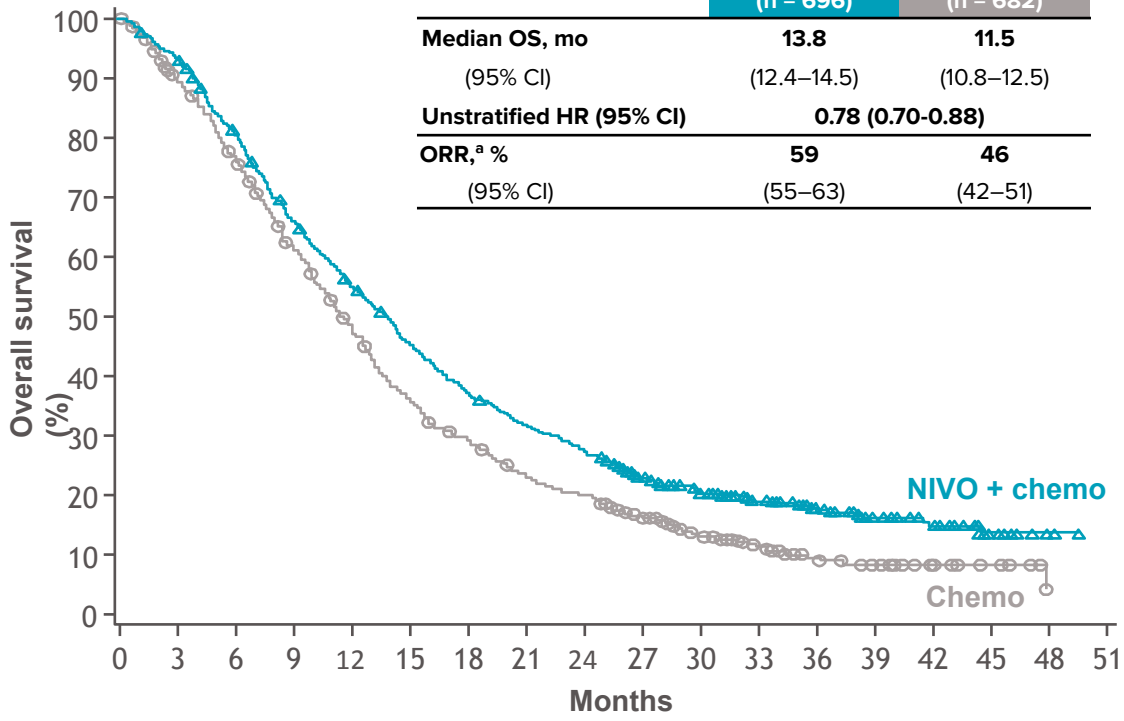


No. at risk

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

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,[a] %	**59**	**46**
(95% CI)	(55–63)	(42–51)



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

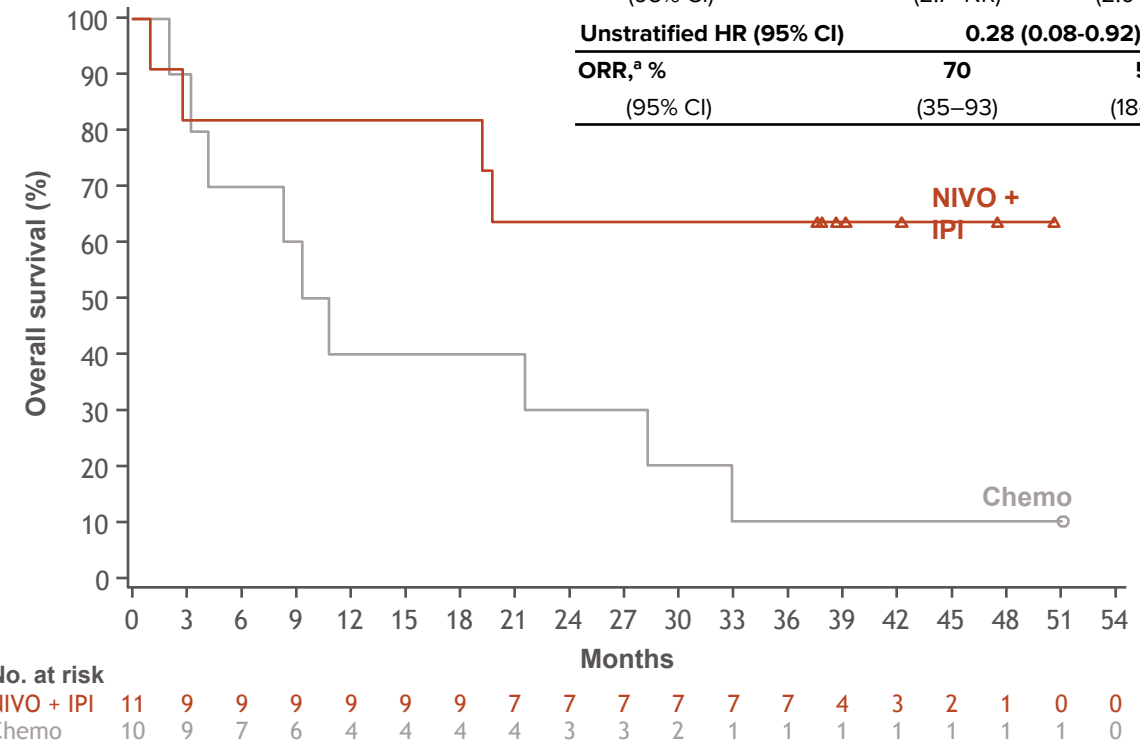
- Longer median OS and higher ORR were observed in all randomized patients with MSI-H and MSS tumors with NIVO + chemo vs chemo
  - The magnitude of benefit was greater in patients with MSI-H tumors, and patients with MSS tumors had results similar to the all randomized population

- [a]Randomized patients who had target lesion measurements at baseline per BICR assessment. MSI-H: NIVO + chemo, n = 20; chemo, n = 18, patients with MSS: NIVO + chemo, n = 535; chemo, n = 533.

Efficacy by MSI status: NIVO + IPI vs chemo

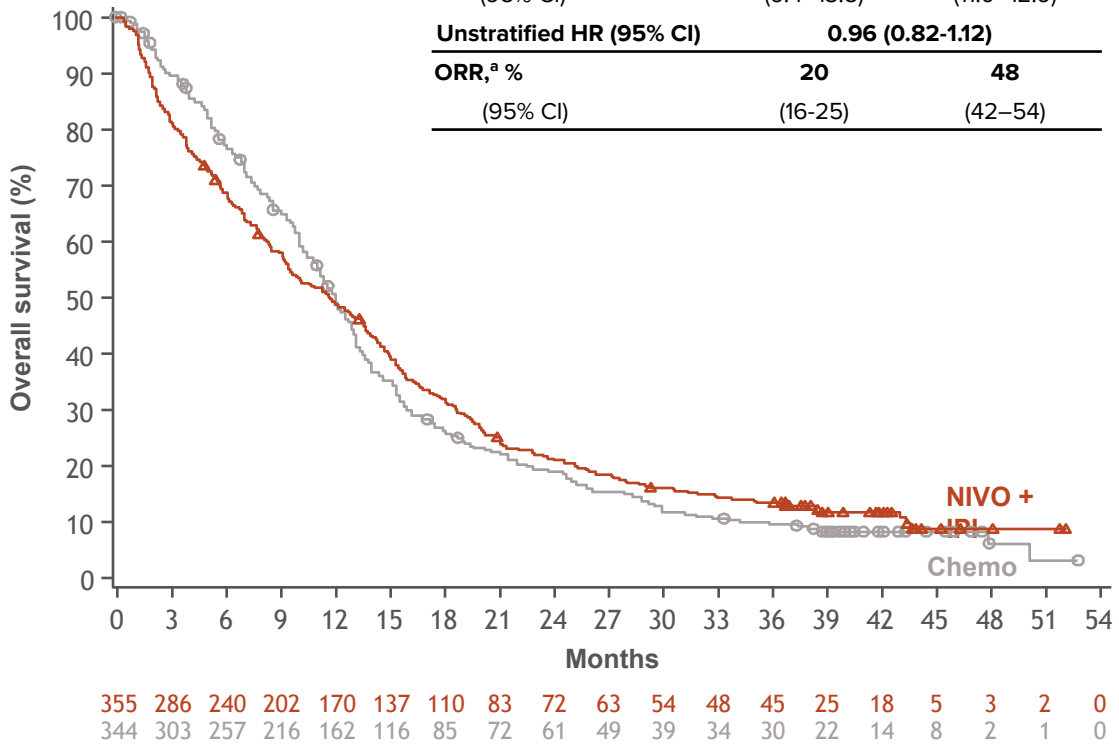
MSI-H

	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,[a] %	**70**	**57**
(95% CI)	(35–93)	(18–90)



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,[a] %	**20**	**48**
(95% CI)	(16-25)	(42–54)

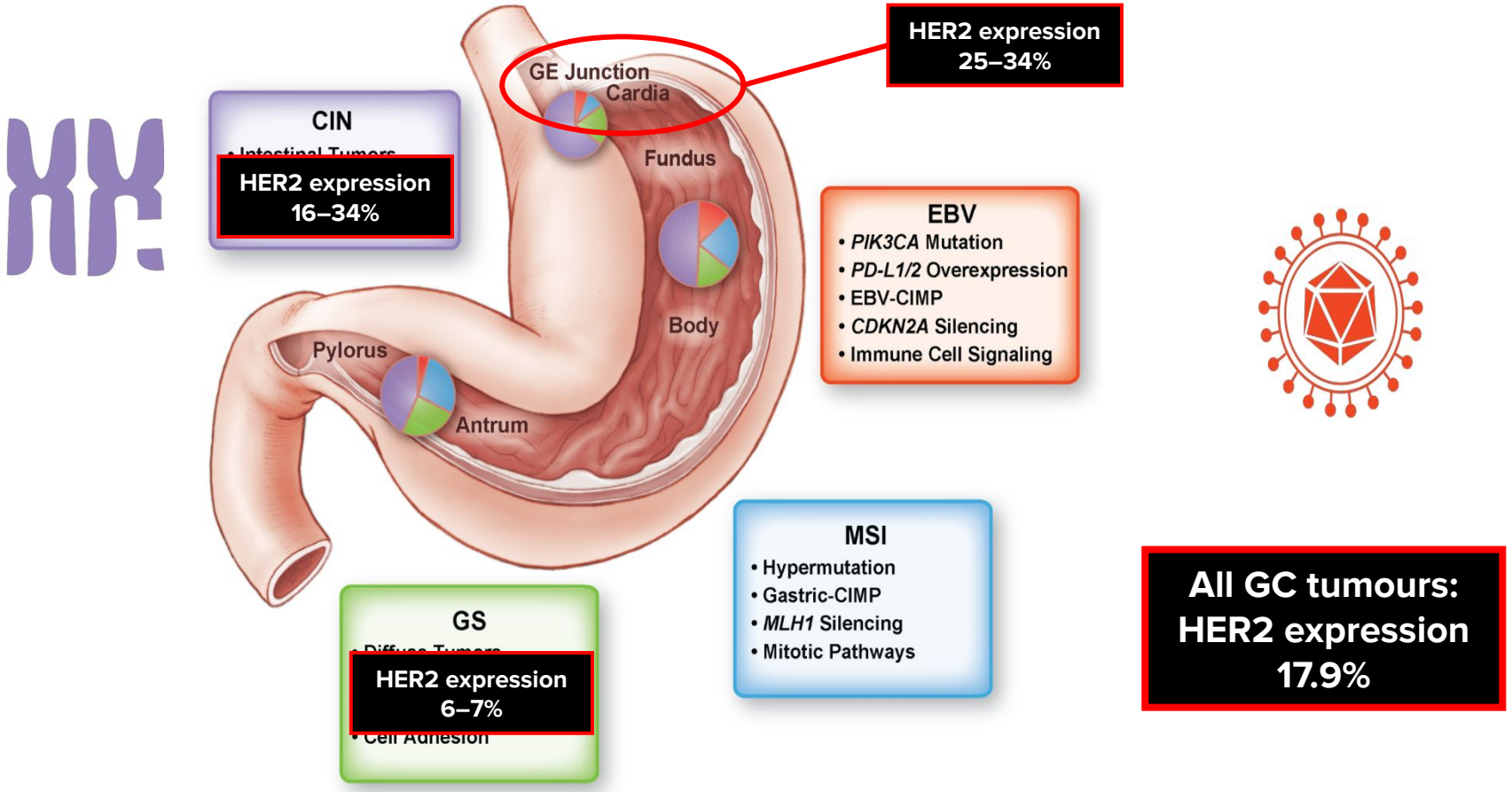


- Longer median OS and higher ORR observed in all randomized patients with MSI-H tumors with NIVO + IPI vs chemo, although sample size was small

- [a]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.

Metastatic Gastric/ GEJ Cancer Her2 Positive

Incidence of HER2 Expression by IHC or FISH[1-6]

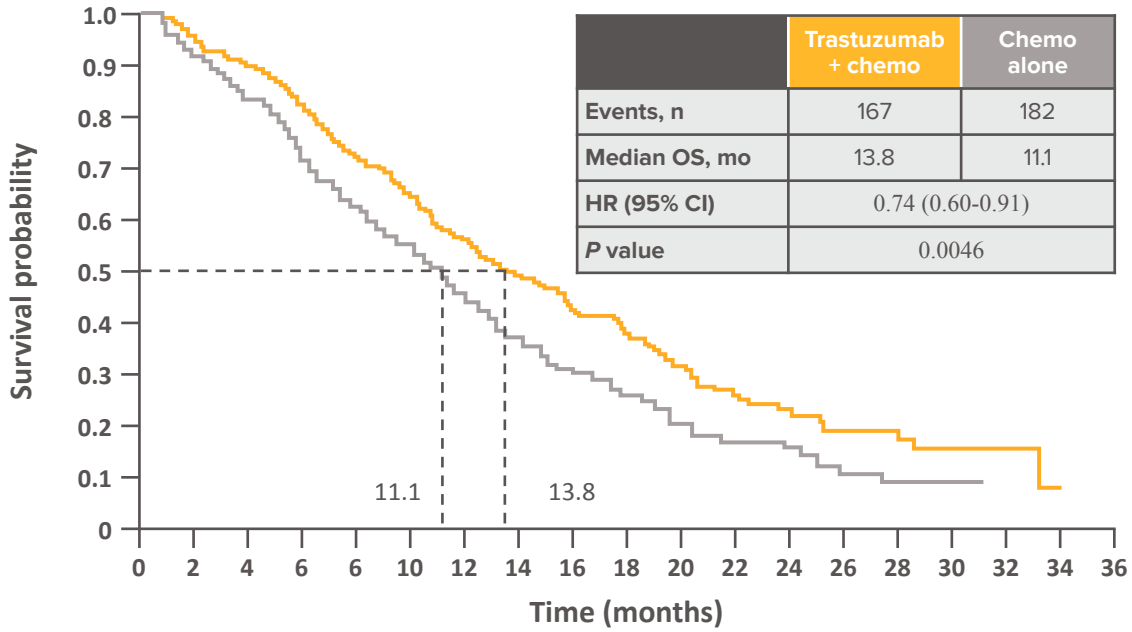


1. Bang et al. Lancet 2010; 2. Gravalos et al. Ann Oncol 2008; 3. Yano et al. ASCO 2004; 4. Gravolos et al. ASCO GI 2007; 5. Lordick et al. ECCO 2007; 6. Abrahão-Machado et al. World J Gastroenterol 2016.

Slide provided courtesy of Manish A. Shah, MD

ToGA Overall Survival: 1st-Line Gastric Cancer

Primary analysis population

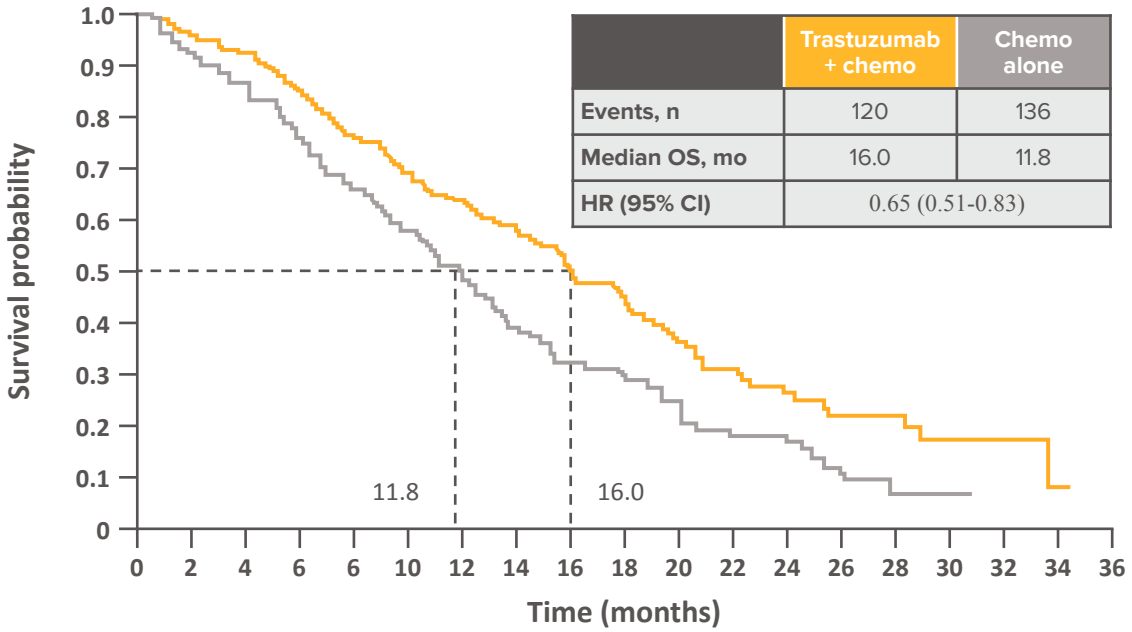


	Trastuzumab + chemo	Chemo alone
Events, n	167	182
Median OS, mo	13.8	11.1
HR (95% CI)	0.74 (0.60-0.91)	
P value	0.0046	

No. at risk

Trastuzumab + chemo	294	277	246	209	173	147	113	90	71	56	43	30	21	13	12	6	4	1	0
Chemo alone	290	266	223	185	143	117	90	64	47	32	24	16	14	7	6	5	0	0	0

HER2 IHC 2+/FISH+ or IHC 3+ population



	Trastuzumab + chemo	Chemo alone
Events, n	120	136
Median OS, mo	16.0	11.8
HR (95% CI)	0.65 (0.51-0.83)	

Trastuzumab + chemo	228	218	196	170	142	122	100	84	65	51	39	28	20	12	11	5	4	1	0
Chemo alone	218	198	170	141	112	96	75	53	39	28	20	13	11	4	3	3	0	0	0

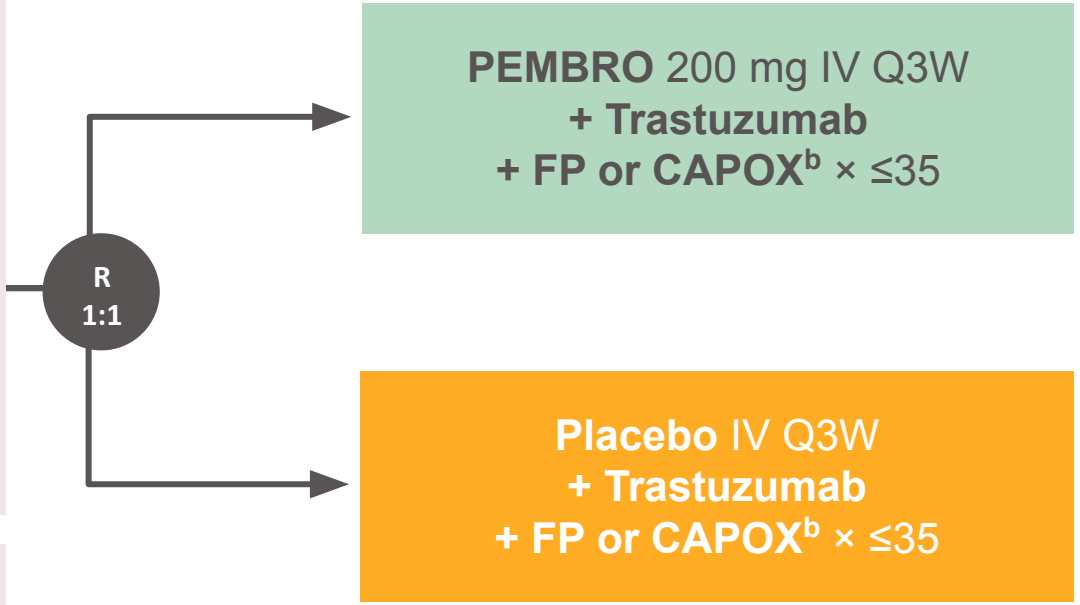
- Grade 3-4 AE rates did not differ between treatment arms (68%)
- Treatment-related deaths occurred in 3% (10) of patients in the trastuzumab + chemo arm vs 1% (3) of patients in the chemo alone arm

Bang Y et al. *Lancet*. 2010;376:687-697.

KEYNOTE-811: Study Design
HER2 Positive Gastric Cancer

Key eligibility criteria
- Unresectable or metastatic gastric or GEJ adenocarcinoma
- No prior systemic therapy in advanced setting
- HER2-positive tumor by central review (IHC 3+ or IHC 2+ in combination with ISH+ (or FISH+)
- ECOG PS 0–1

Stratification factors
- Geographic region (Australia/Europe/Israel/North America vs Asia vs ROW)
- PD-L1 CPS (≥1 vs <1)
- Chemotherapy choice (FP vs CAPOX)



Dual primary endpoints:
- **OS** and **PFS**[c]

Key secondary endpoints:
- **ORR** and **DOR**[c]
- **Safety**

[a]ClinicalTrials.gov number, NCT03615326. [b]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W. [c]Per RECIST v1.1 by BICR.

1. ClinicalTrials.gov. NCT03615326. Accessed July 2021. 2. Janjigian YY et al. *J Clin Oncol*. 2021;39(15_suppl):4013. Presented at ASCO 2021. 3. Chung HC et al. *Future Oncol*. 2021;17(5):491-501.

KEYNOTE-811: Outcome

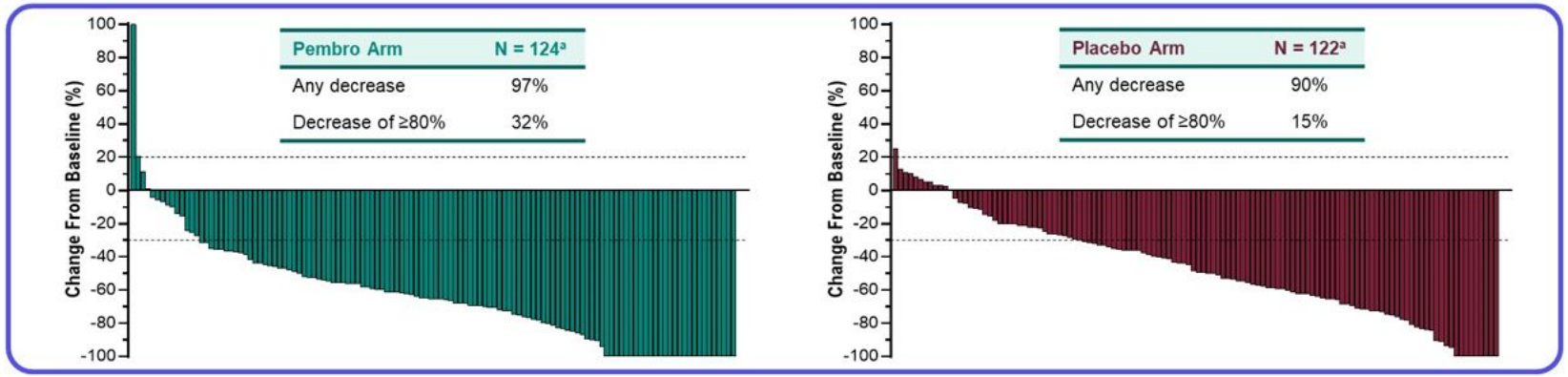
HER2 Positive Gastric Cancer

Patient Population

	Pembro Arm (N = 133)	Placebo Arm (N = 131)
Age, median (range)	62 y (19-84)	61 y (32-83)
Male sex	84%	79%
Region of enrollment		
Aus/EU/Isr/NAm	31%	34%
Asia	30%	30%
ROW	39%	37%
ECOG PS 1	51%	55%
Primary location of stomach	72%	68%
Histologic subtype		
Diffuse	21%	20%
Intestinal	61%	48%
Indeterminate	18%	32%
PD-L1 CPS ≥1	88%	85%
HER2 status		
IHC 2+, ISH positive	18%	21%
IHC 3+	82%	79%
Choice of chemotherapy		
CAPOX	86%	88%
FP	14%	12%

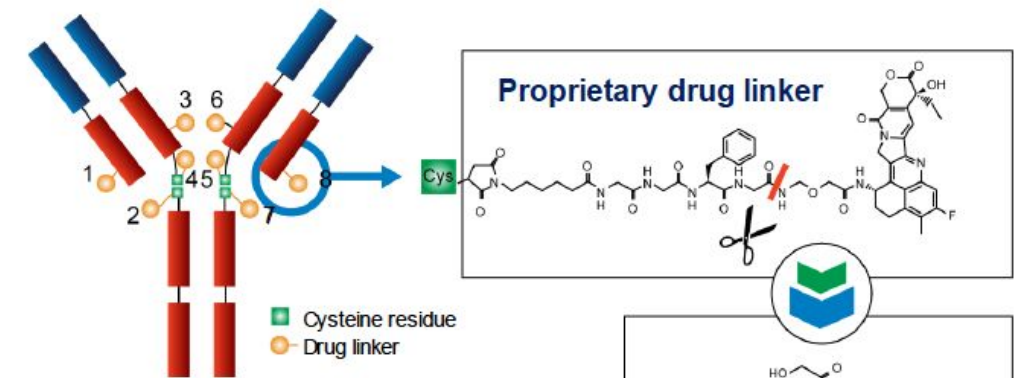
ORR and DCR, % (95% CI)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
ORR	**74.4% (66.2-81.6)**	**51.9% (43.0-60.7)**
ORR difference[b]	**22.7% (11.2-33.7) *P* = 0.00006**	
DCR	96.2% (91.4-98.8)	89.3% (82.7-94.0)

Best Response, n (%)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
CR	**15 (11%)**	**4 (3%)**
PR	**84 (63%)**	**64 (49%)**
SD	29 (22%)	49 (37%)
PD	5 (4%)	7 (5%)
Not evaluable	0	2 (2%)
Not assessed	0	5 (4%)

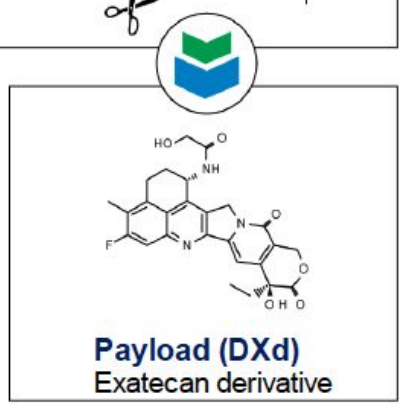


Janjigian et al. Presented at ASCO 2021
Janjigian et al. Nature 2021

Trastuzumab Deruxtecan Structure and Mechanism of Action[1]



Conjugation chemistry
The linker is connected to cysteine residue of the antibody

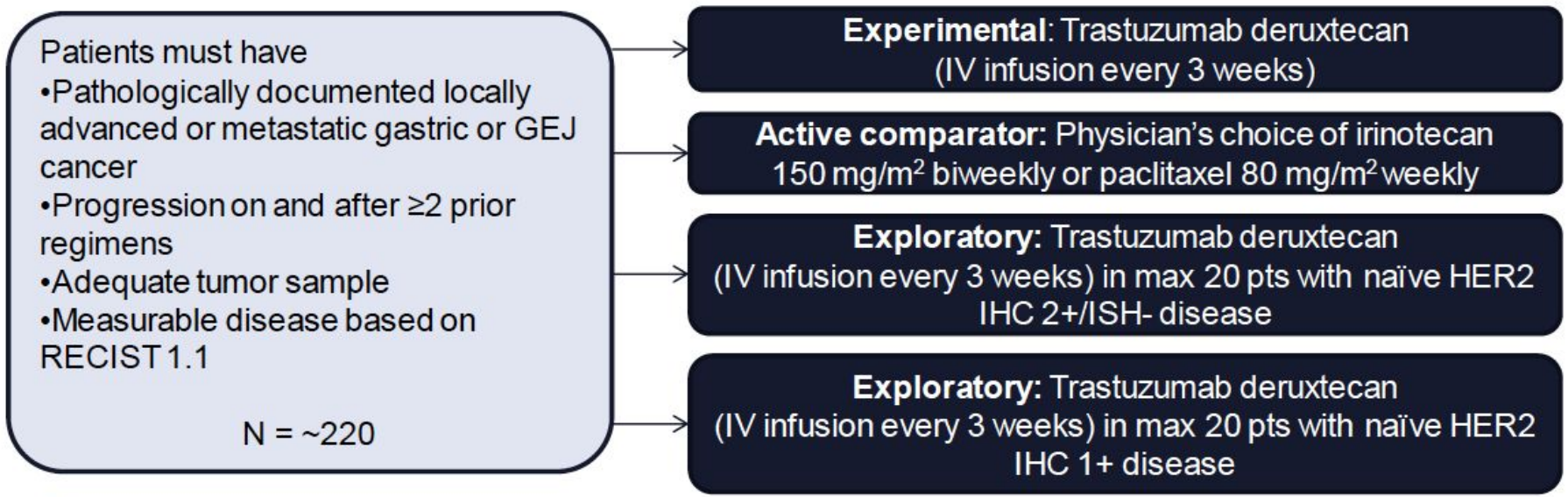


- Payload with a different MOA
- High potency of payload
- Payload with short systemic half-life
- Bystander effect
- Stable linker-payload
- Tumor-selective cleavable linker
- High drug-to-antibody ratio

- Trastuzumab deruxtecan (DS-8201a) designed with goal of improving critical attributes of an ADC

1. Iwata H et al. *J Clin Oncol*. 2018;36(15 suppl):2501-2501.

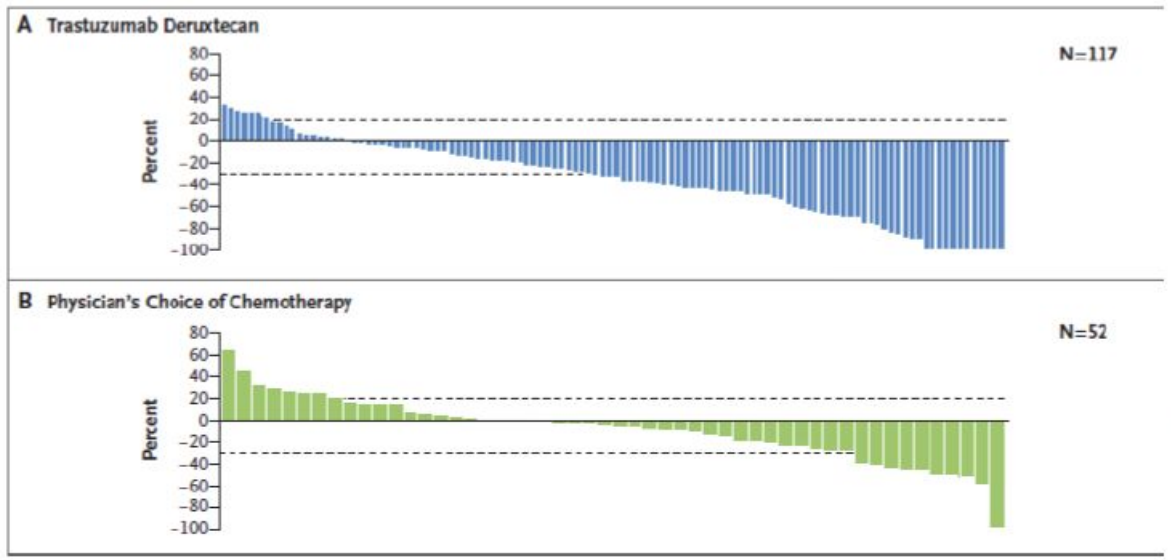
DESTINY-Gastric01: Phase 2 Trial of Trastuzumab Deruxtecan in Advanced HER2+ Gastric Cancer[1]

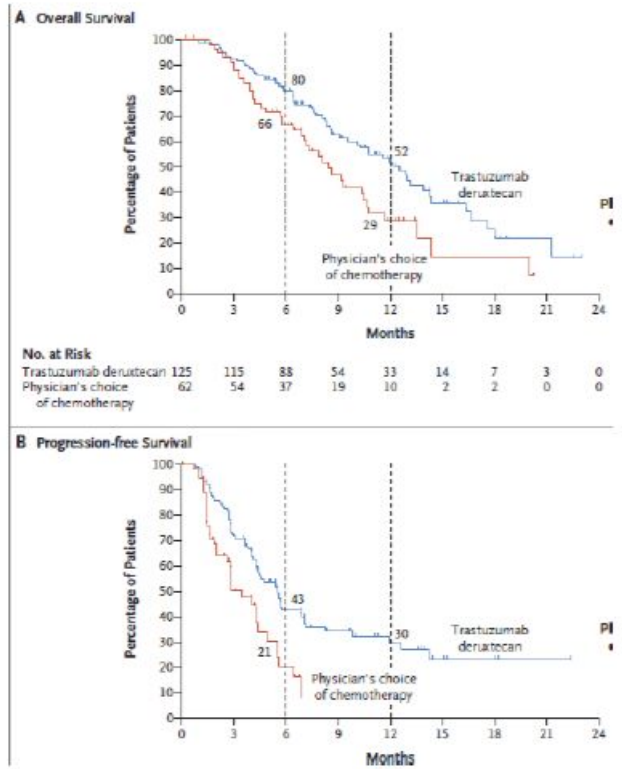


Outcomes

Primary: % of participants in the experimental and active comparator groups with objective response
Secondary: % of participants in the experimental and active comparator groups with PFS, OS, DOR, DCR, TTF, ORR, Cmax, AUClast, and AUC0-21

DESTINY Gastric01





Shitara NEJM 2020

T-DXd after Trastuzumab Progression: Adverse Events

DESTINY-Gastric02 – 2nd line in West

n (%)	Patients (N = 79) Any Grade	Grade ≥3
Patients with ≥1 TRAEs	74 (93.7)	21 (26.6)
TRAEs with ≥15% incidence in all patients		
Nausea	46 (58.2)	3 (3.8)
Fatigue	29 (36.7)	3 (3.8)
Vomiting	26 (32.9)	1 (1.3)
Diarrhea	22 (27.8)	1 (1.3)
Decreased appetite	18 (22.8)	1 (1.3)
Alopecia	17 (21.5)	0
Anemia	15 (19.0)	6 (7.6)
Decreased platelet count	13 (16.5)	1 (1.3)
Decreased neutrophil count	12 (15.2)	6 (7.6)

DESTINY-Gastric01 ≥3rd line in East

Table 3. Adverse Events Occurring in at Least 20% of the Patients Treated with Trastuzumab Deruxtecan.*

Preferred Term	Trastuzumab Deruxtecan (N=125)			Physician's Choice of Chemotherapy (N=62)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Nausea	79 (63)	6 (5)	0	29 (47)	1 (2)	0
Neutrophil count decreased†	79 (63)	48 (38)	16 (13)	22 (35)	10 (16)	5 (8)
Decreased appetite	75 (60)	21 (17)	0	28 (45)	8 (13)	0
Anemia‡	72 (58)	47 (38)	0	19 (31)	13 (21)	1 (2)
Platelet count decreased§	49 (39)	12 (10)	2 (2)	4 (6)	1 (2)	1 (2)
White-cell count decreased¶	47 (38)	26 (21)	0	22 (35)	5 (8)	2 (3)
Malaise	43 (34)	1 (1)	0	10 (16)	0	0
Diarrhea	40 (32)	3 (2)	0	20 (32)	1 (2)	0
Vomiting	33 (26)	0	0	5 (8)	0	0
Constipation	30 (24)	0	0	14 (23)	0	0
Pyrexia	30 (24)	0	0	10 (16)	0	0
Alopecia	28 (22)	0	0	9 (15)	0	0
Fatigue	27 (22)	9 (7)	0	15 (24)	2 (3)	0
Lymphocyte count decreased‖	27 (22)	8 (6)	6 (5)	2 (3)	0	1 (2)

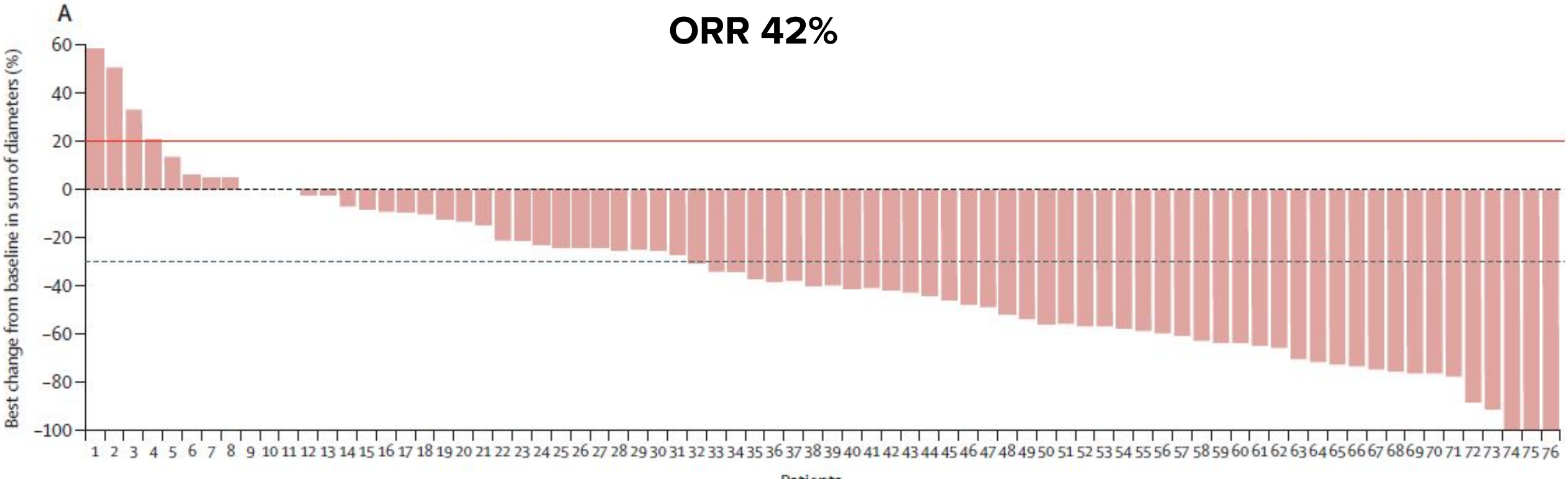
Shitara K et al. *NEJM*, 2020

DESTINY-Gastric02: Second Trastuzumab Deruxtecan

- Single arm; western countries
- Second-line

- Eight patients(10%) ILD/pneumonitis
  - Two (3%) grade 1
  - Four (5%) grade 2
  - 2 died (2%) grade 5

ORR 42%



Van Custem et al. Lancet Onc 2023

Summary

- Her2 , MSI and CPS (PDL1) need to be checked at a minimum
  - Soon Claudin 18.2
- Trastuzumab adds value in first line **Her 2 amplified** GC.
  - Trastuzumab Pembrolizumab Chemo is now standard in 1 L
  - Trastuzumab Deruxtecan is now standard post-Trastuzumab (watch for ILD)
- Patients with **MSI H** in 1-L advanced gastroesophageal or gastric cancer can be treated with pembrolizumab +/- chemo, nivolumab + chemo or NIVO + IPI
- Patients with **MSS Her2 negative** 1L advanced gastroesophageal or gastric cancer should be treated with Chemotherapy/Nivolumab (if CPS ≥ 5) or Chemotherapy/Pembrolizumab (if CPS ≥ 1)
  - If **CPS<5** doublet chemotherapy
  - **CPS>10** option of using Pembrolizumab
  - Subsequent lines therapy include ramucirumab/ paclitaxel and trifluridine/ tipiracil
- NIVO + chemo, Tisle+chemo, and NIVO + IPI each represent a new potential 1L standard of care for patients with **advanced ESCC**
- Pembrolizumab + chemo represents a new potential 1L standard of care for patients with advanced esophageal cancer
- Tisle represents a potential treatment option in second line ESCC (PDL-1 TAP>10)

O'NEAL COMPREHENSIVE CANCER CENTER

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM