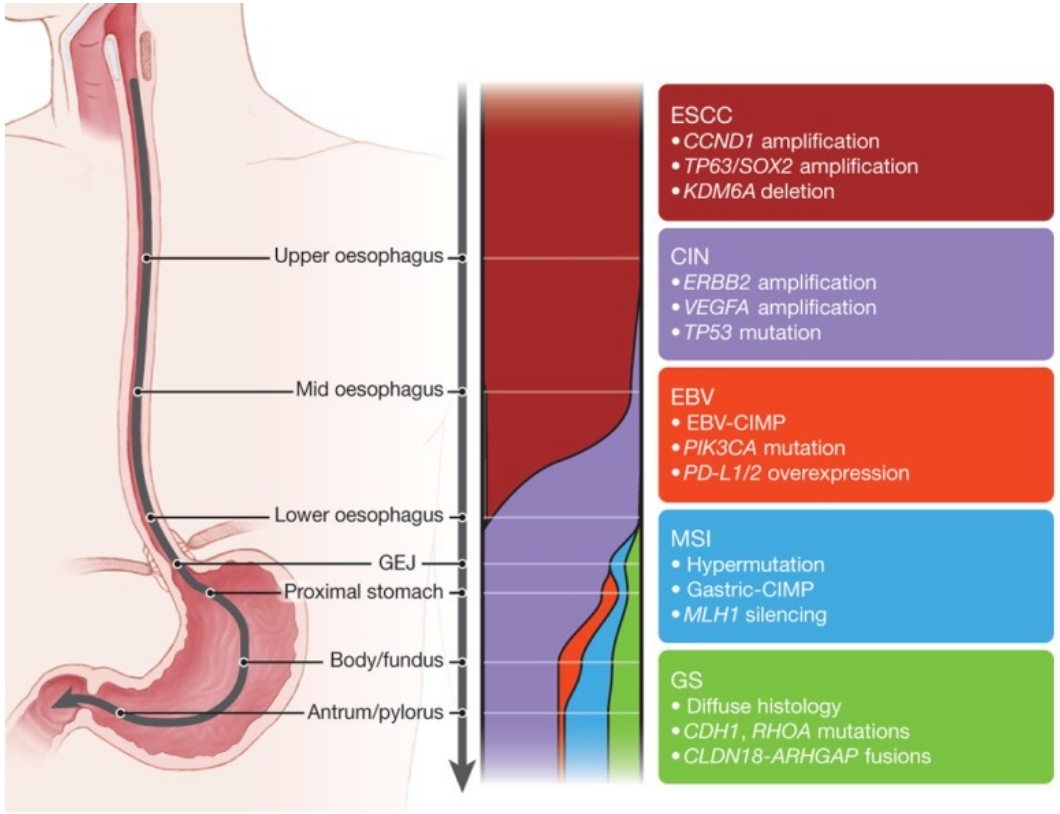
Esophagus and Gastric Cancer Update

Bassel El-Rayes, MD
Division Director Hematology Oncology
Deputy Cancer Center Director
O'Neal Comprehensive Cancer Center
University of Alabama at Birmingham

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

Resectable Disease

2021 ASCO ANNUAL MEETING

Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiotherapy: expanded efficacy and safety analyses from CheckMate 577

Ronan J. Kelly,[1] Jaffer A. Ajani,[2] Jaroslaw Kuzdzal,[3] Thomas Zander,[4] Eric Van Cutsem,[5] Guillaume Piessen,[6] Guillermo Mendez,[7] Josephine Feliciano,[8] Satoru Motoyama,[9] Astrid Lièvre,[10] Hope Uronis,[11] Elena Elimova,[12] Cecile Grootscholten,[13] Karen Geboes,[14] Jenny Zhang,[15] Samira Soleymani,[15] Ming Lei,[15] Prianka Singh,[15] James M. Cleary,[16] Markus Moehler[17]

- [1]The Charles A. Sammons Cancer Center at Baylor University Medical Center, Dallas, TX; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Jagiellonian University, John Paul II Hospital, Cracow, Poland; [4]University Hospital of Cologne, Cologne, Germany; [5]University Hospitals Gasthuisberg, Leuven and KULeuven, Leuven, Belgium; [6]University of Lille, Claude Huriez University Hospital, Lille, France; [7]Fundacion Favaloro, Buenos Aires, Argentina; [8]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD; [9]Akita University Hospital, Akita, Japan; [10]CHU Pontchaillou, Rennes 1 University, Rennes, France; [11]Duke Cancer Institute, Durham, NC; [12]Princess Margaret Cancer Centre, Toronto, ON, Canada; [13]Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; [14]UZ Gent, Gent, Belgium; [15]Bristol Myers Squibb, Princeton, NJ; [16]Dana Farber Cancer Institute, Boston, MA; [17]Johannes-Gutenberg University Clinic, Mainz, Germany

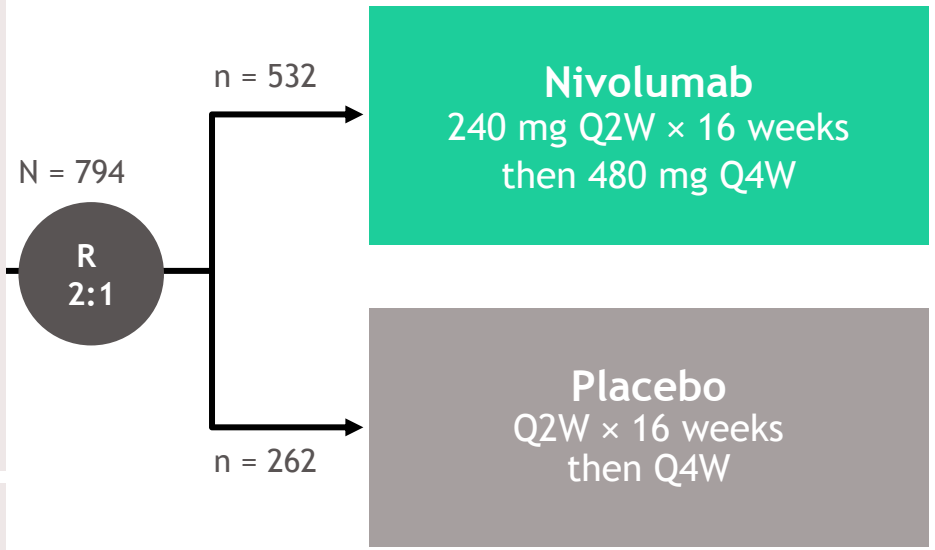
Abstract number 4003

CheckMate 577 study design

- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria
- Stage II/III EC/GEJC
- <u>Adenocarcinoma or squamous cell carcinoma</u>
- <u>Neoadjuvant CRT + surgical resection</u> (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0–1

Stratification factors
- Histology (squamous versus adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 versus ypN0)
- Tumor-cell PD-L1 expression (≥ 1% versus < 1%[c])



Primary endpoint:
- DFS[e]

Secondary endpoints:
- OS[f]
- OS rate at 1, 2, and 3 years

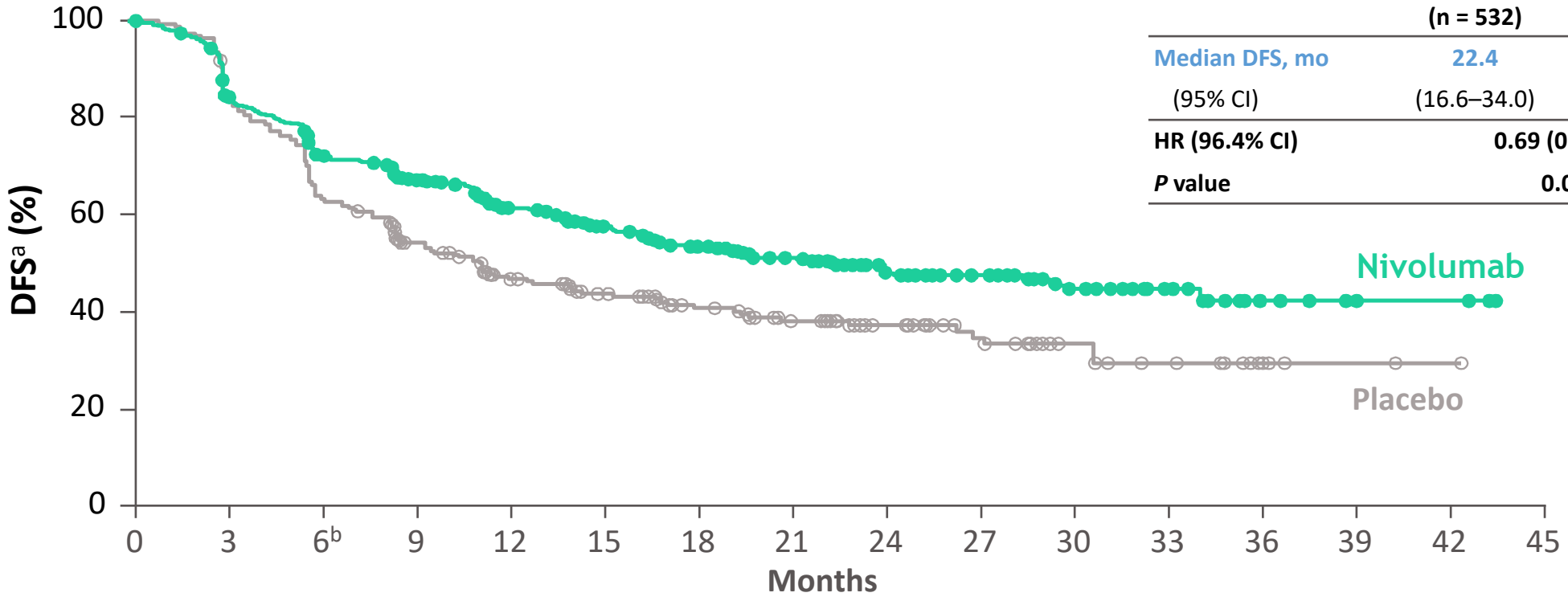
Exploratory endpoints included:
- Safety
- DMFS[g]
- PFS2[h]
- QoL

- Median follow-up was 24.4 months (range, 6.2–44.9)[i]
- Geographical regions: Europe (38%), United States and Canada (32%), Asia (13%), rest of the world (16%)

[a]ClinicalTrials.gov. NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a prespecified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]DMFS is defined as the time between randomization and the first distant recurrence or death, whichever occurs first; [h]PFS2 is defined as the time from randomization to progression after the first subsequent systemic therapy, initiation of second subsequent systemic therapy, or death, whichever is earlier; [i]Time from randomization date to clinical data cutoff (May 12, 2020).
Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203.

Disease-free survival (DFS)

	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6–34.0)	(8.3–14.3)
HR (96.4% CI)	**0.69 (0.56–0.86)**	
***P* value**	**0.0003[c]**	



No. at risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

[a]Per investigator assessment; [b]6-month DFS rates were 72% (95% CI, 68-76) in the nivolumab arm and 63% (95% CI, 57-69) in the placebo arm; [c]The boundary for statistical significance at the prespecified interim analysis required the *P* value to be less than 0.036.
Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203.

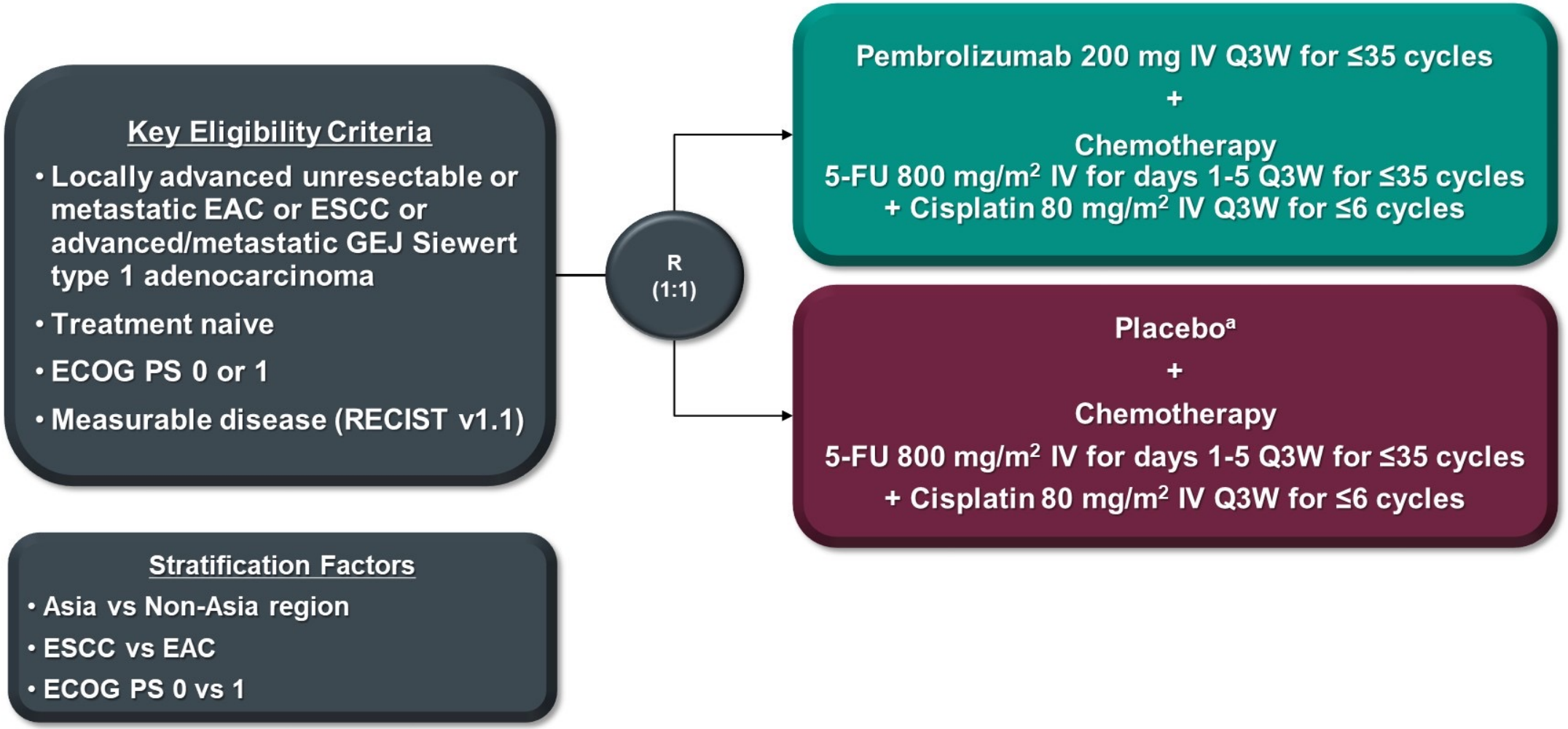
Metastatic Esophageal Cancer

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

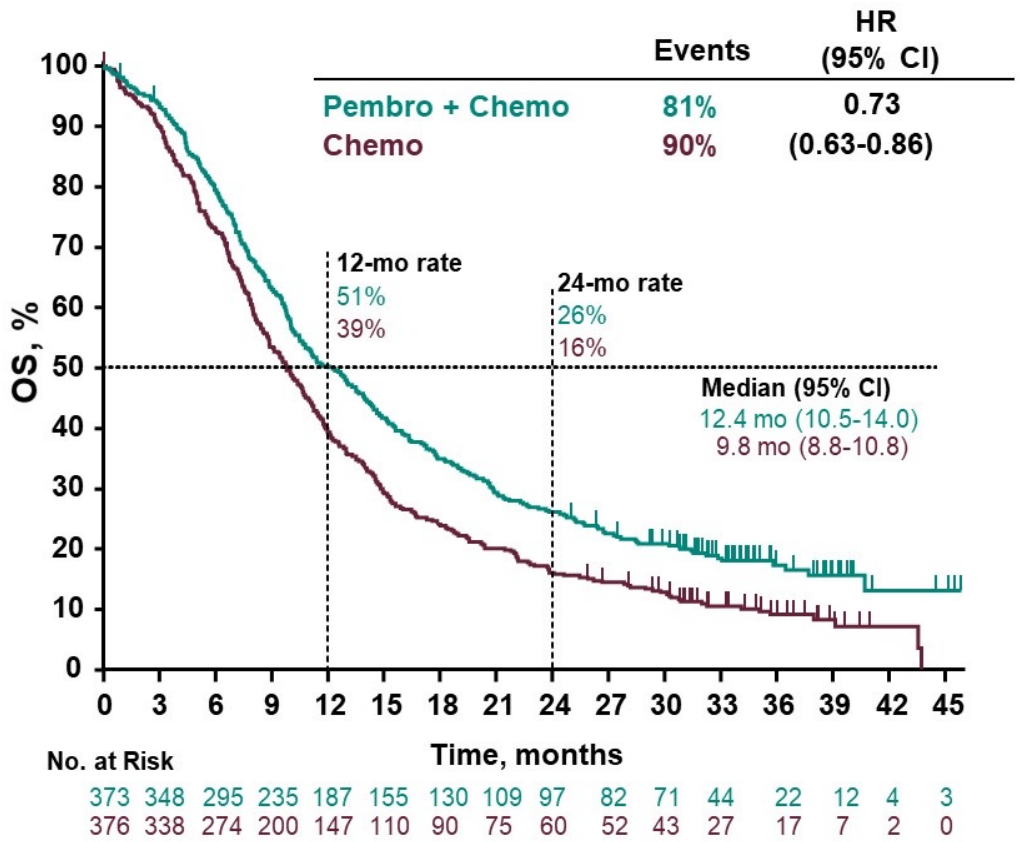
KEYNOTE-590 Study Design (NCT03189719)



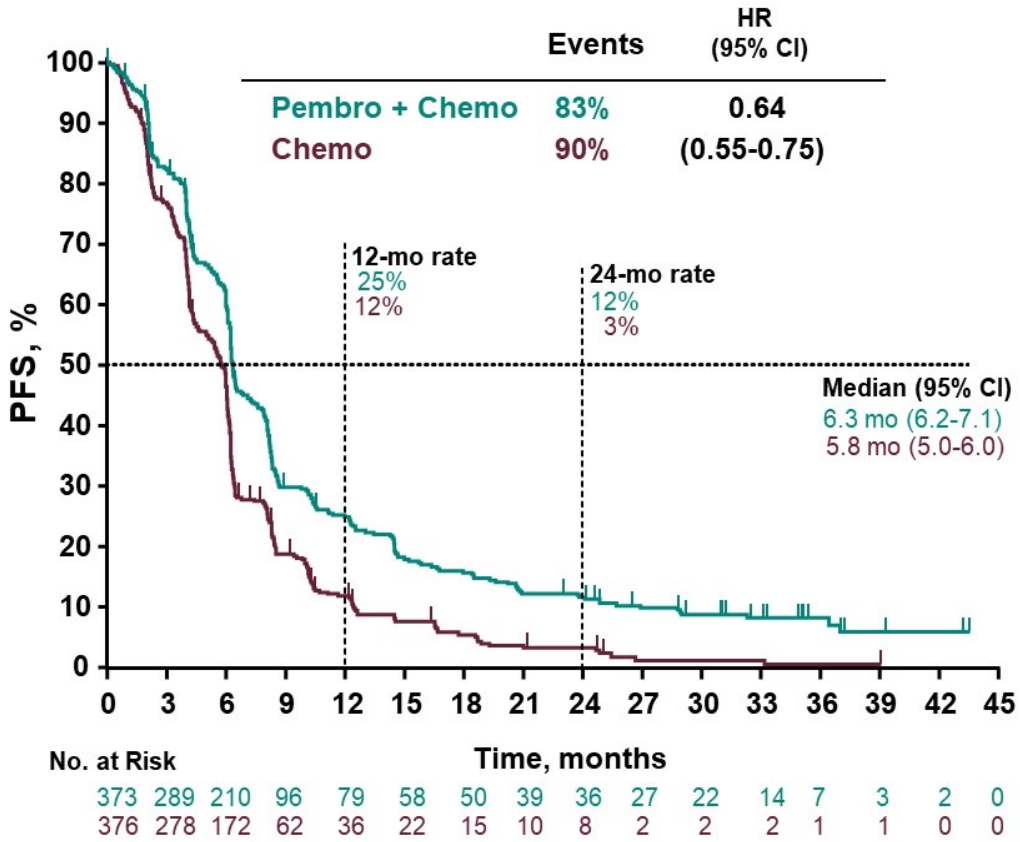
[a]Saline IV Q3W for ≤35 cycles. All treatments were continued for the specified number of cycles or until disease progression, intolerable toxicity, withdrawal of consent, or physician decision; EAC, esophageal adenocarcinoma; GEJ, gastroesophageal junction, ESCC, esophageal squamous cell carcinoma;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

Survival: All Patients

OS

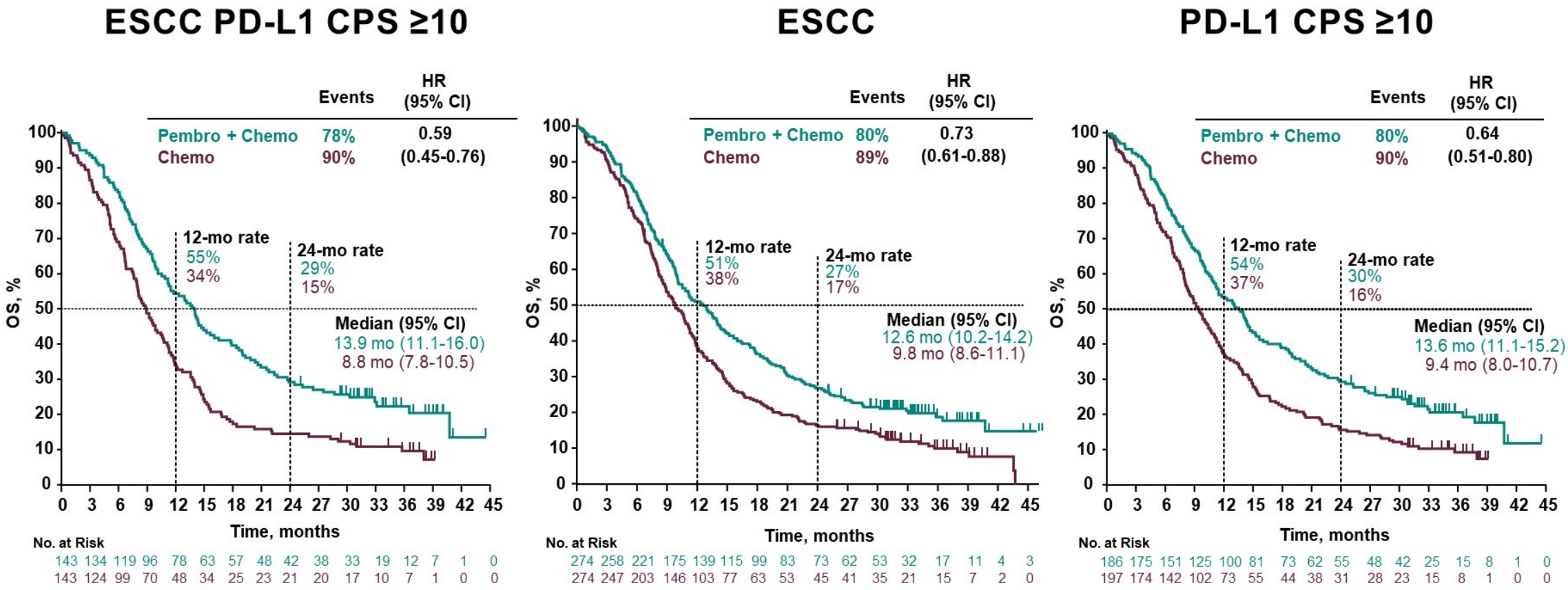


PFS



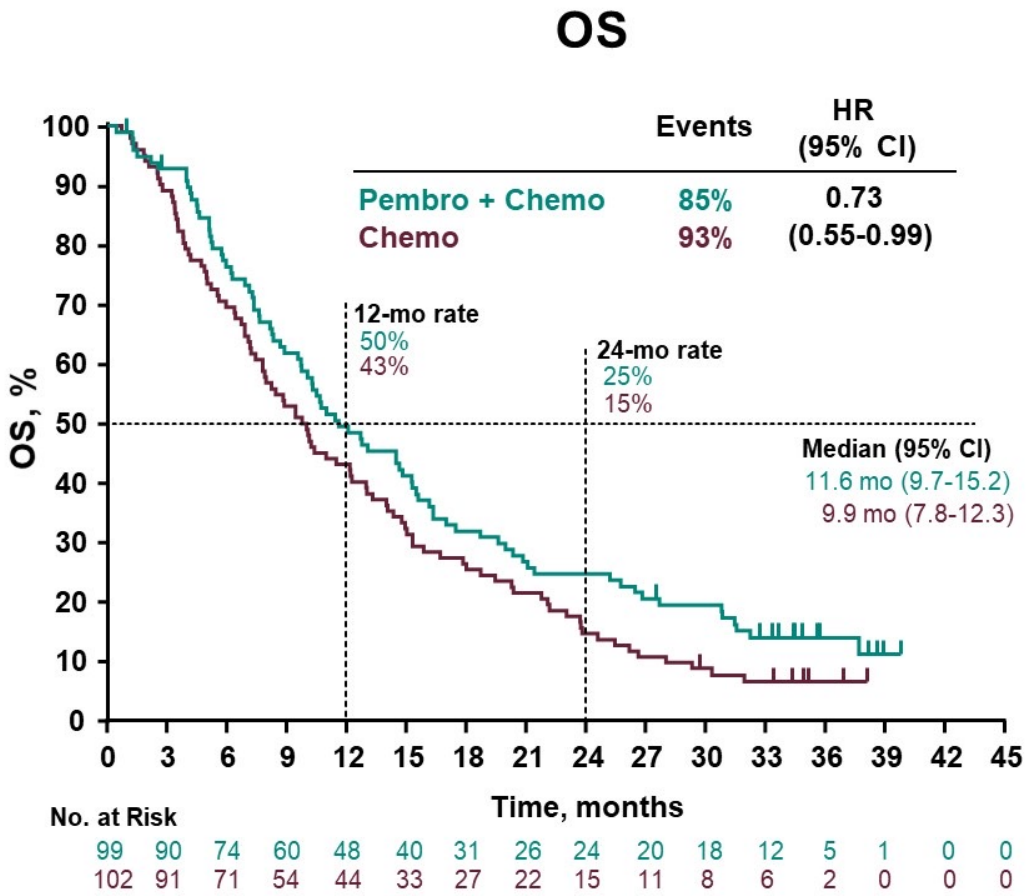
Data cut-off: July 9, 2021.

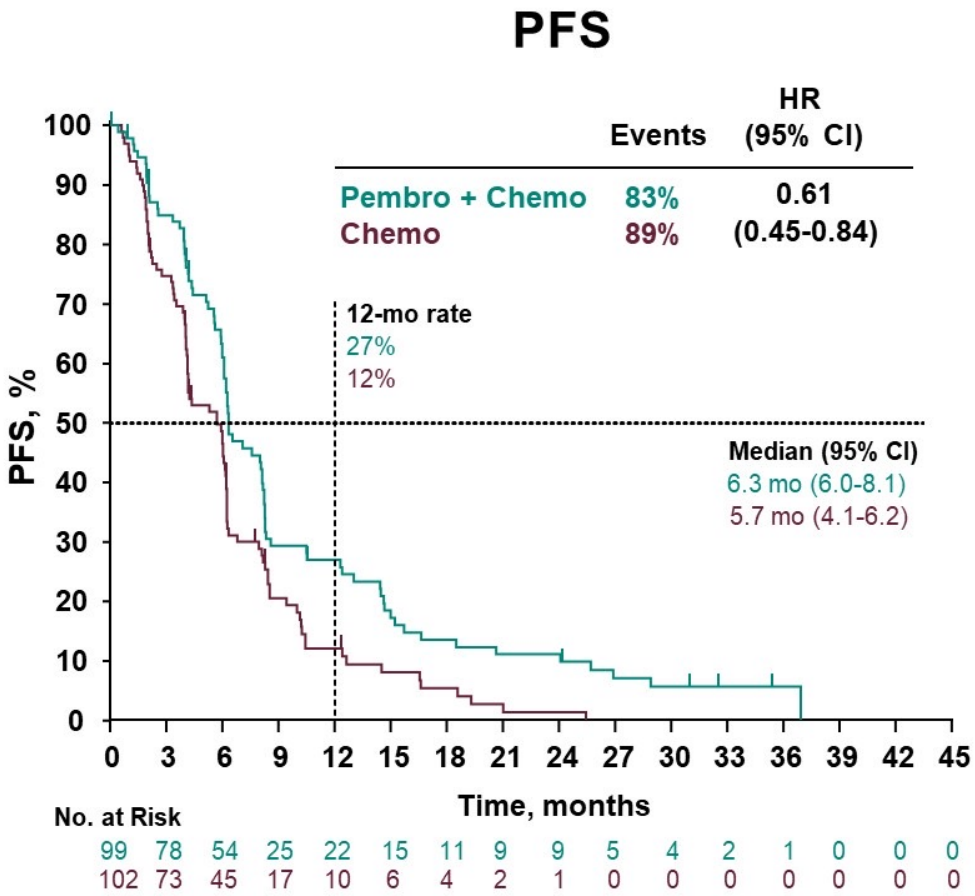
OS: Pre-specified Subgroups



Data cut-off: July 9, 2021.

Survival: Adenocarcinoma





Data cut-off: July 9, 2021.

Antitumor Response Summary

Best response, n (%)	Pembro + Chemo N = 373	Chemo N = 376
ORR, n (%)	**168 (45.0)**	**110 (29.3)**
Complete response	25 (6.7)	9 (2.4)
Partial response	143 (38.3)	101 (26.9)
Stable disease	126 (33.8)	174 (46.3)
Disease control rate	294 (78.8)	284 (75.5)
Progressive disease	43 (11.5)	59 (15.7)
Not evaluable/no assessment	36 (9.6)	33 (8.7)
Median DOR (range), mo	8.3 (1.2+ to 41.7+)	6.0 (1.5+ to 34.9+)
≥ 24 months response duration, %	**20.4**	**6.2**

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]

- [1]Royal Marsden Hospital, London & Surrey, UK; [2]Osaka University Graduate School of Medicine, Osaka, Japan; [3]The University of Texas MD Anderson Cancer Center, Houston, TX; [4]Affiliated Hospital Cancer Center, Academy of Military Medical Sciences, Beijing, China; [5]Klinika Onkologii i Radioterapii, Narodowy Instytut Onkologii, Warszawa, Poland; [6]Akita University Hospital, Akita, Japan; [7]Kanagawa Cancer Center, Kanagawa, Japan; [8]Kindai University Faculty of Medicine, Osakasayama, Japan; [9]National Taiwan University Hospital, Taipei, Taiwan; [10]Institut du Cancer de Montpellier, Montpellier, France; [11]Centre Oscar Lambret, Lille, France; [12]Fondazione IRCCS Instituto Nazionale dei Tumori, Milan, Italy; [13]Institute of Cancer of São Paulo, University of São Paulo, São Paulo, Brazil; [14]Odense University Hospital, Odense, Denmark; [15]Bristol Myers Squibb, Princeton, NJ; [16]National Cancer Center Hospital, Tokyo, Japan; [17]Keio University School of Medicine, Tokyo, Japan

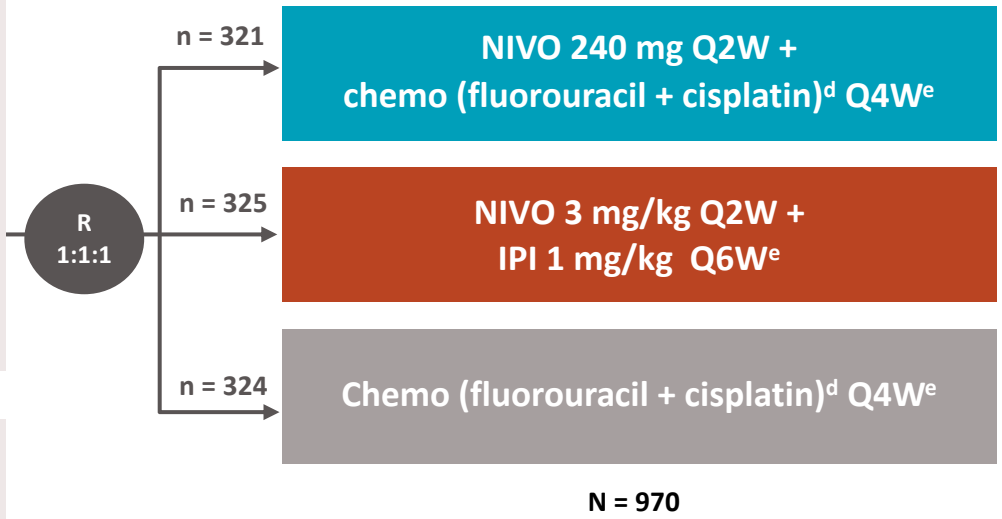
Abstract Number LBA4001

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%)

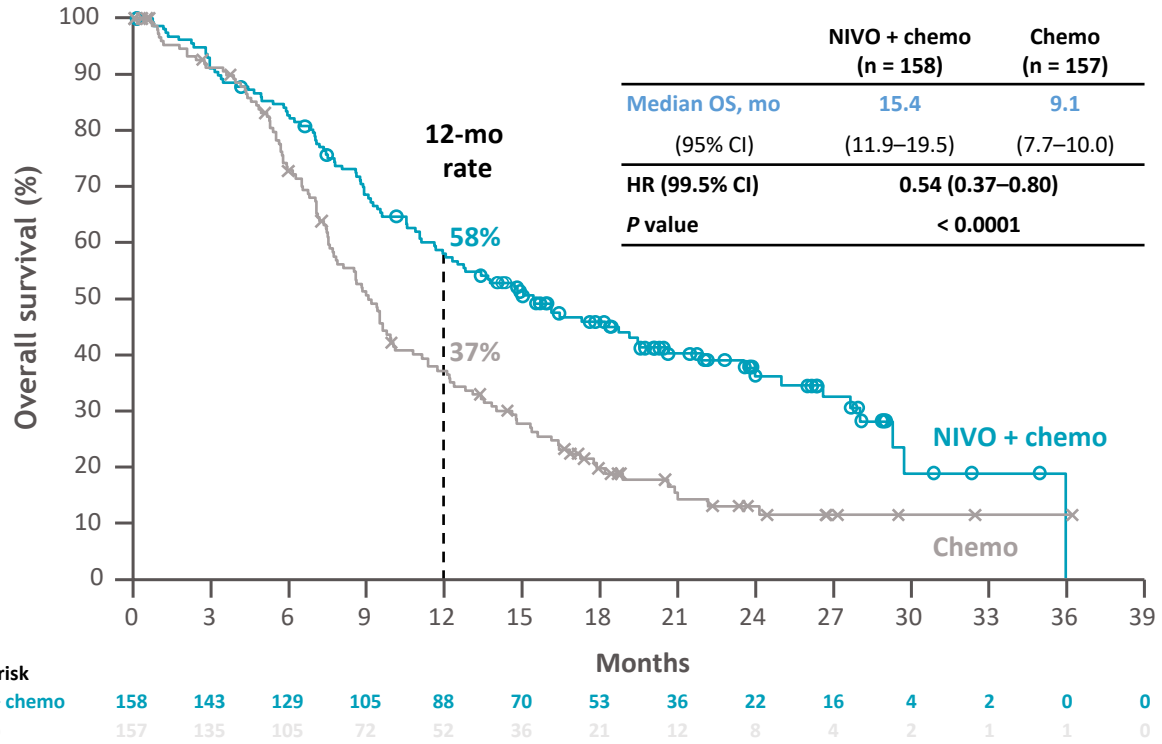
Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

- 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

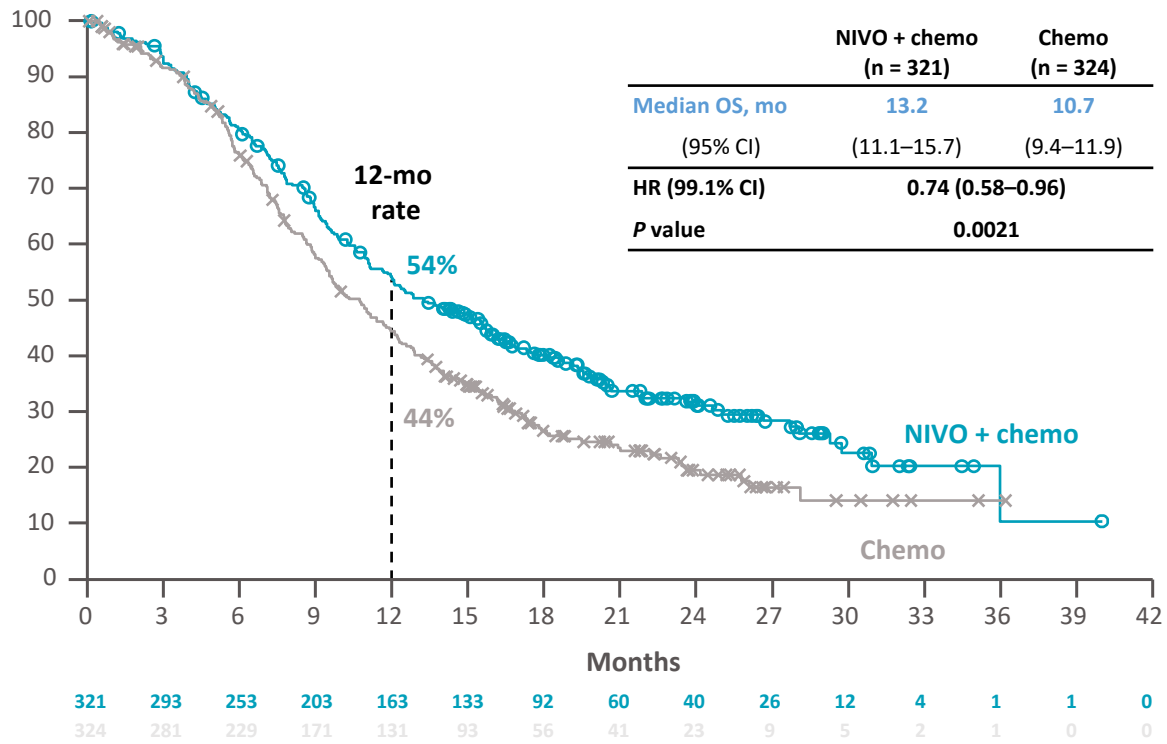
Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



	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	

No. at risk														
NIVO + chemo	158	143	129	105	88	70	53	36	22	16	4	2	0	0
Chemo	157	135	105	72	52	36	21	12	8	4	2	1	1	0

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	

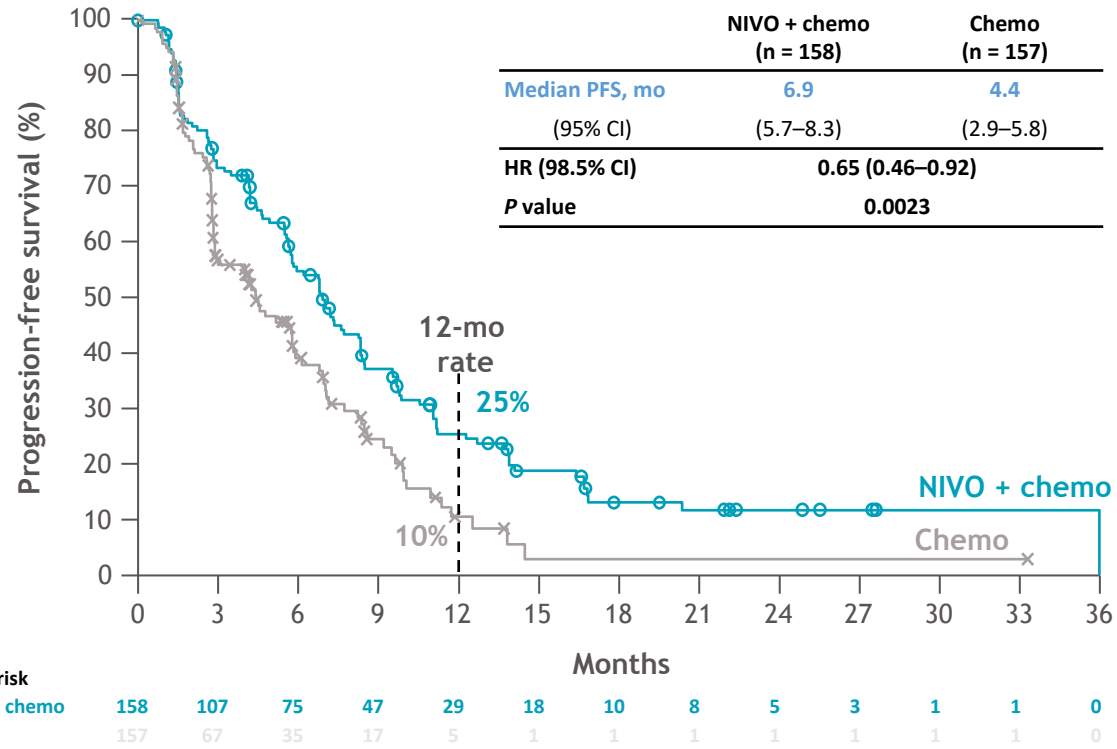
No. at risk														
NIVO + chemo	321	293	253	203	163	133	92	60	40	26	12	4	1	1	0
Chemo	324	281	229	171	131	93	56	41	23	9	5	2	1	0	0

- 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

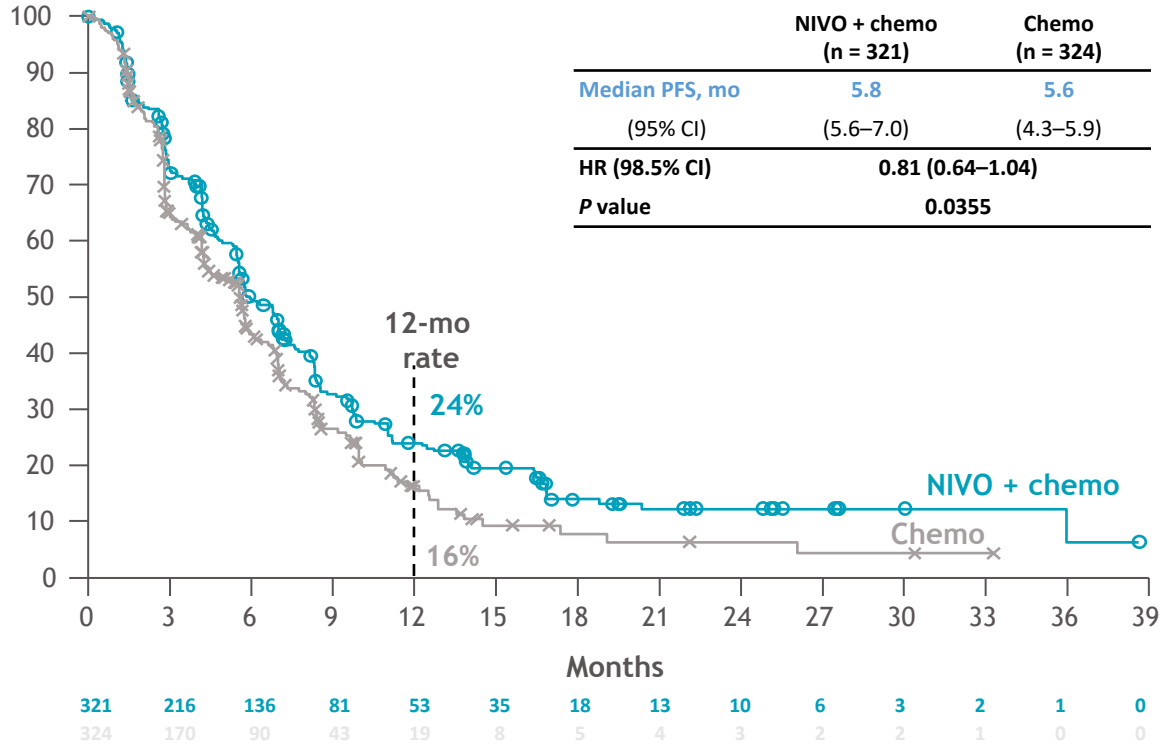
Primary endpoint (tumor cell PD-L1 ≥ 1%; per BICR)[a]



	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	

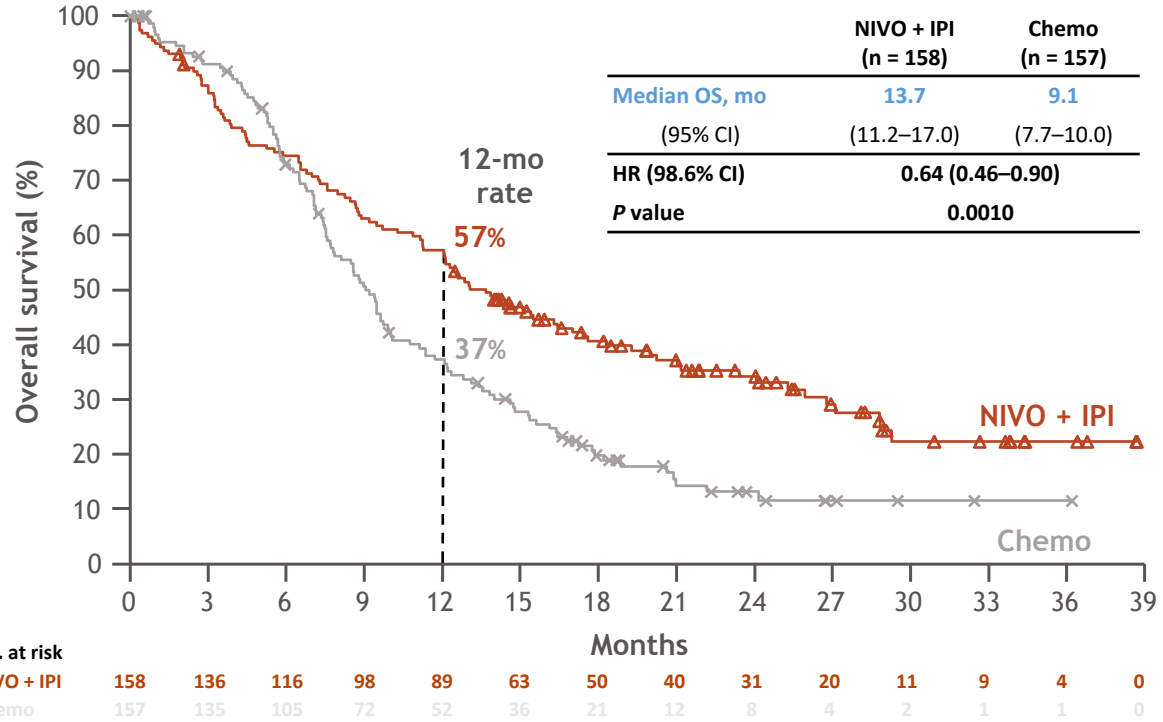
No. at risk													
NIVO + chemo	321	216	136	81	53	35	18	13	10	6	3	2	1	0
Chemo	324	170	90	43	19	8	5	4	3	2	2	1	0	0

- 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

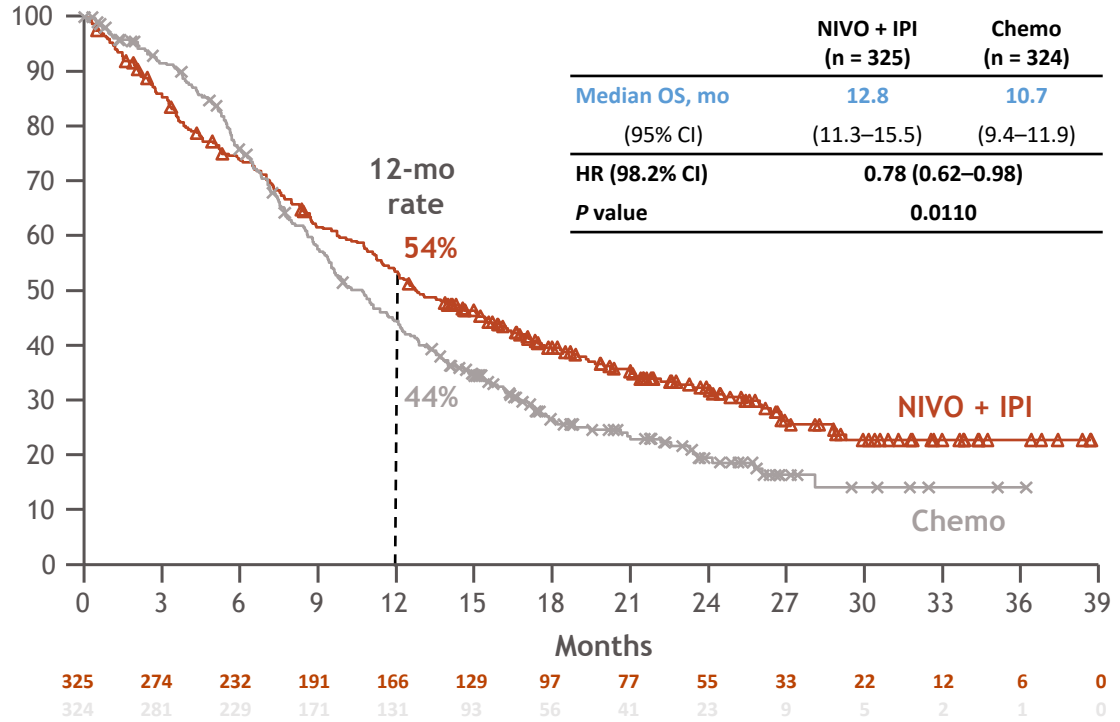
Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



	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	

No. at risk														
NIVO + IPI	158	136	116	98	89	63	50	40	31	20	11	9	4	0
Chemo	157	135	105	72	52	36	21	12	8	4	2	1	1	0

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	

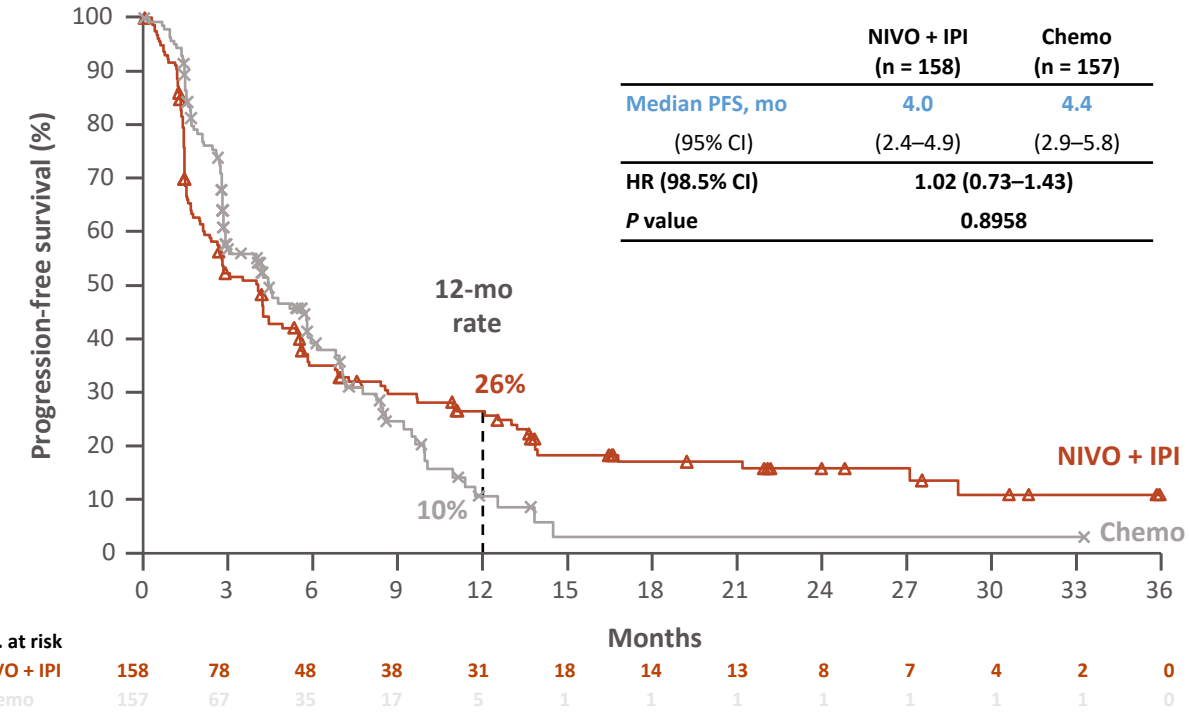
NIVO + IPI	325	274	232	191	166	129	97	77	55	33	22	12	6	0
Chemo	324	281	229	171	131	93	56	41	23	9	5	2	1	0

- 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.

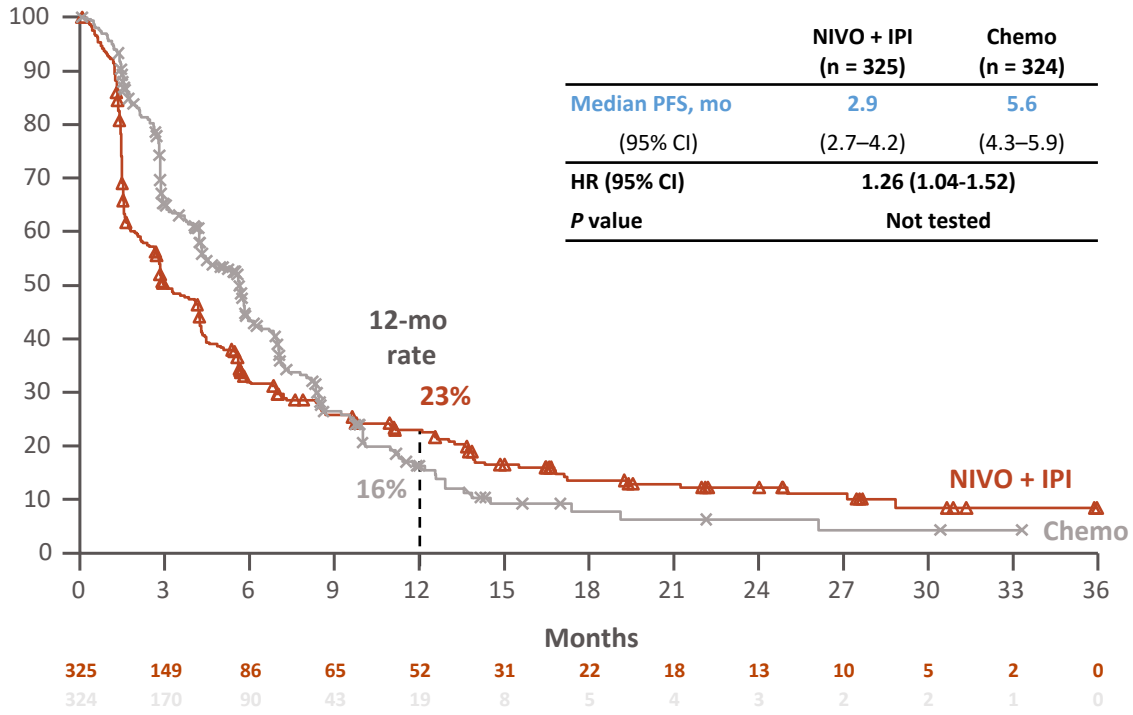
Progression-free survival: NIVO + IPI vs chemo

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]



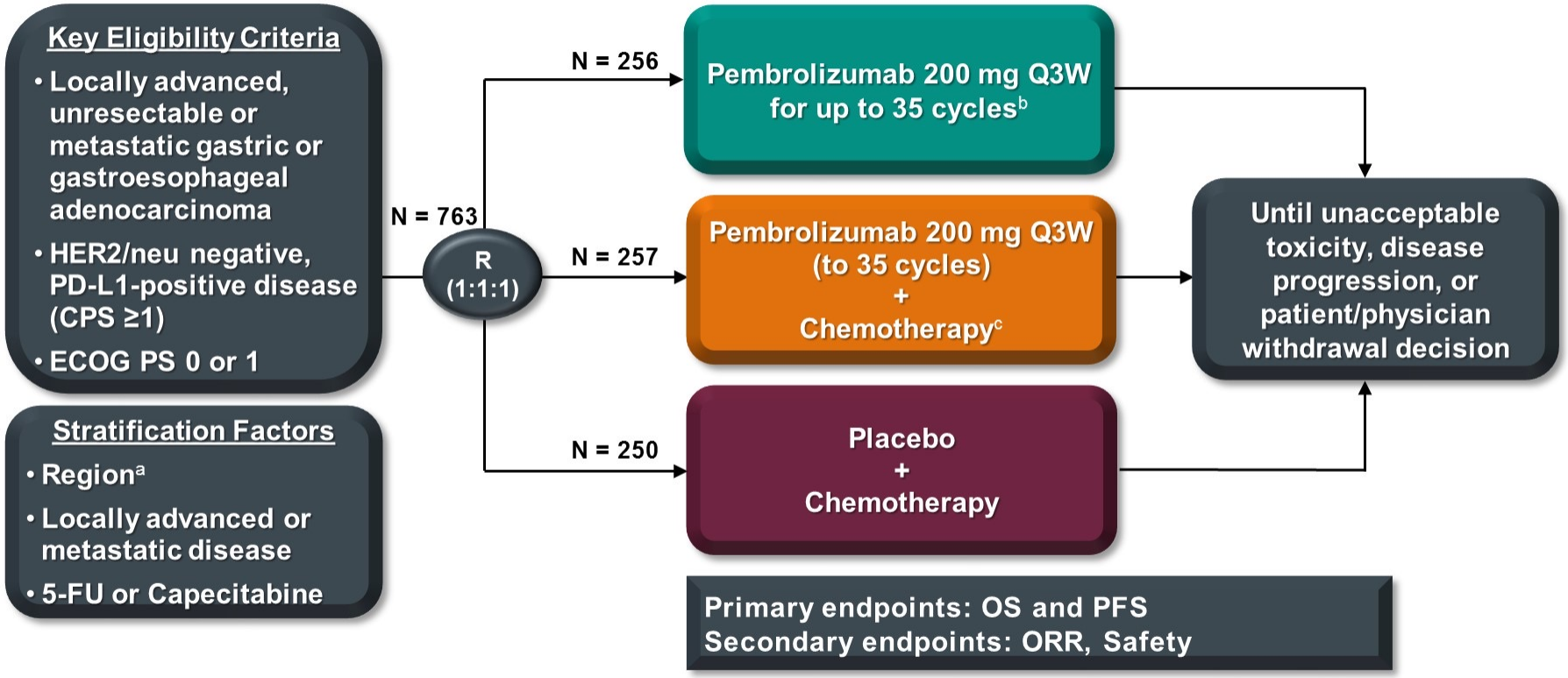
	NIVO + IPI (n = 325)	Chemo (n = 324)
Median PFS, mo	2.9	5.6
(95% CI)	(2.7–4.2)	(4.3–5.9)
HR (95% CI)	**1.26 (1.04-1.52)**	
***P* value**	**Not tested**	

- 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.

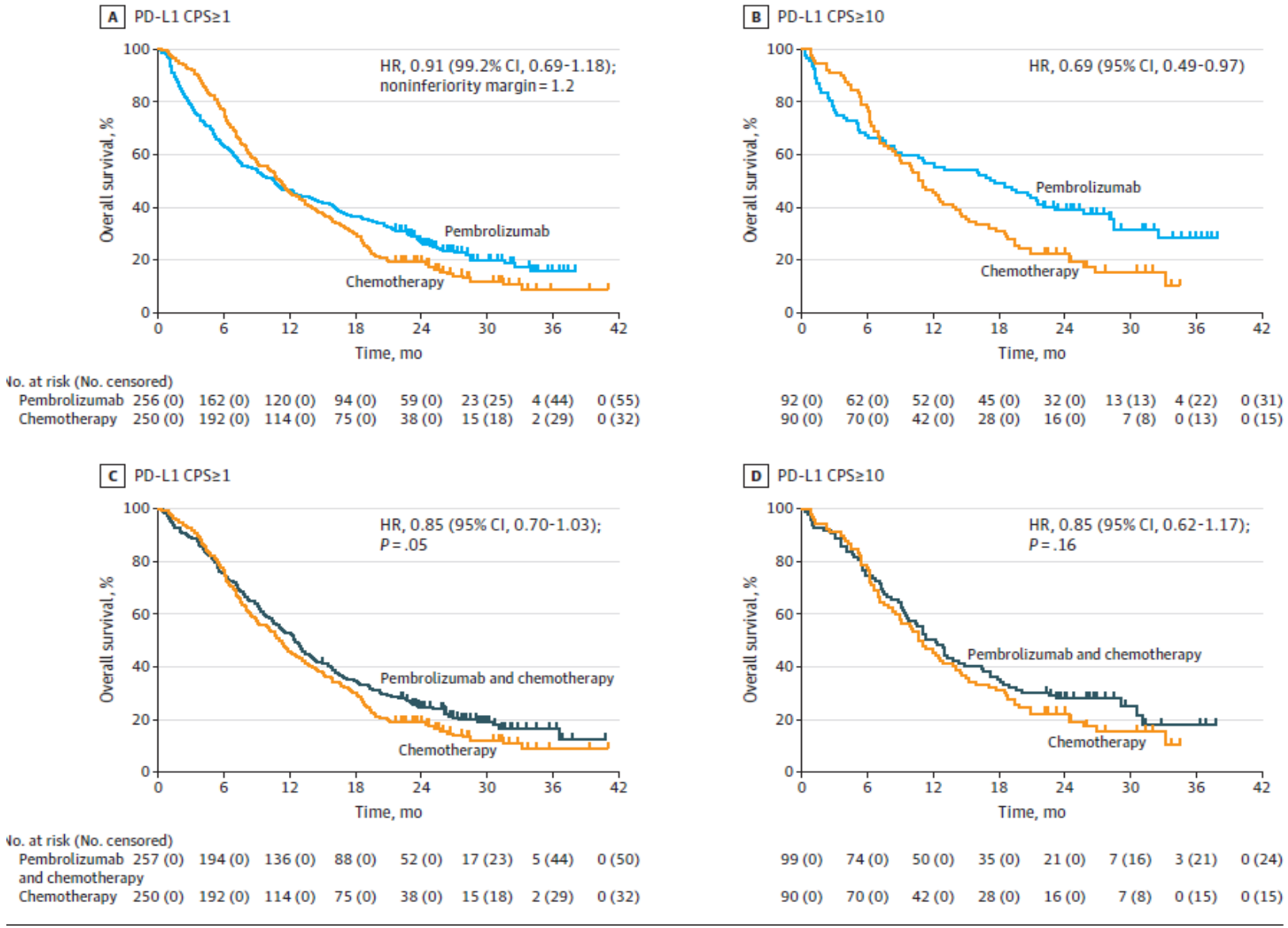
Metastatic Gastric/ GEJ Cancer

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

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]

[1]National Cancer Center Hospital East, Kashiwa, Japan; [2]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [3]Johannes-Gutenberg University Clinic, Mainz, Germany; [4]Clinica San Carlos de Apoquindo, Pontificia Universidad Católica, Santiago, Chile; [5]Fundacion Arturo Lopez Perez, Santiago, Chile; [6]Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China; [7]Cancer Institute Hospital of JFCR, Tokyo, Japan; [8]Klinika Onkologii i Radioterapii, Narodowy Instytut Onkologii, Warszawa, Poland; [9]II Klinika Chirurgii Ogólnej, Gastroenterologicznej i Nowotworów Układu Pokarmowego, Medical University of Lublin, Lublin, Poland; [10]Fundacao Pio Xii Hosp Cancer De Barretos, Barretos, Brazil; [11]Zhongshan Hospital Fudan University, Shanghai, China; [12]Oncology Center - Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [13]Princess Margaret Cancer Centre, Toronto, ON, Canada; [14]Bristol Myers Squibb, Princeton, NJ, USA; [15]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract number 240

CheckMate 649 Study Design

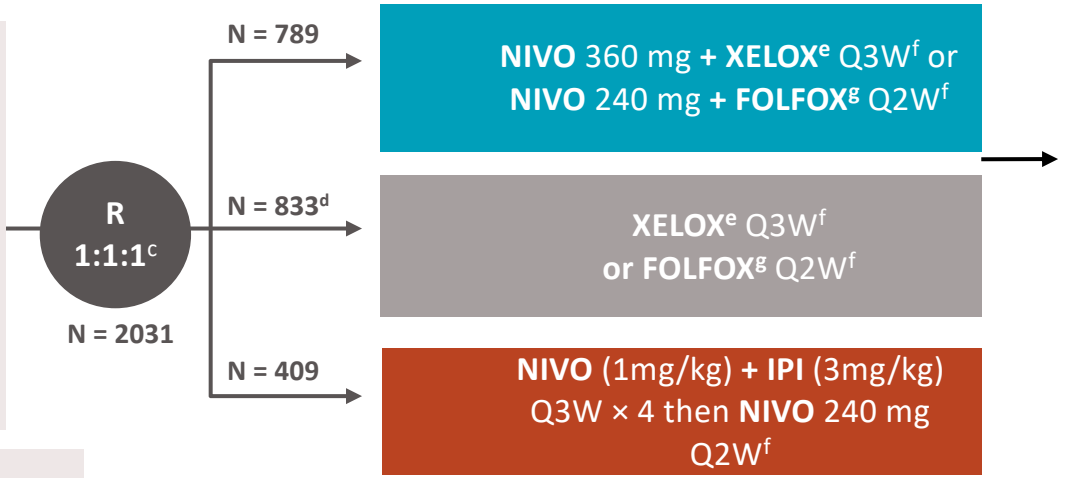
- CheckMate 649 is a randomized, open-label, phase 3 study[a]

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

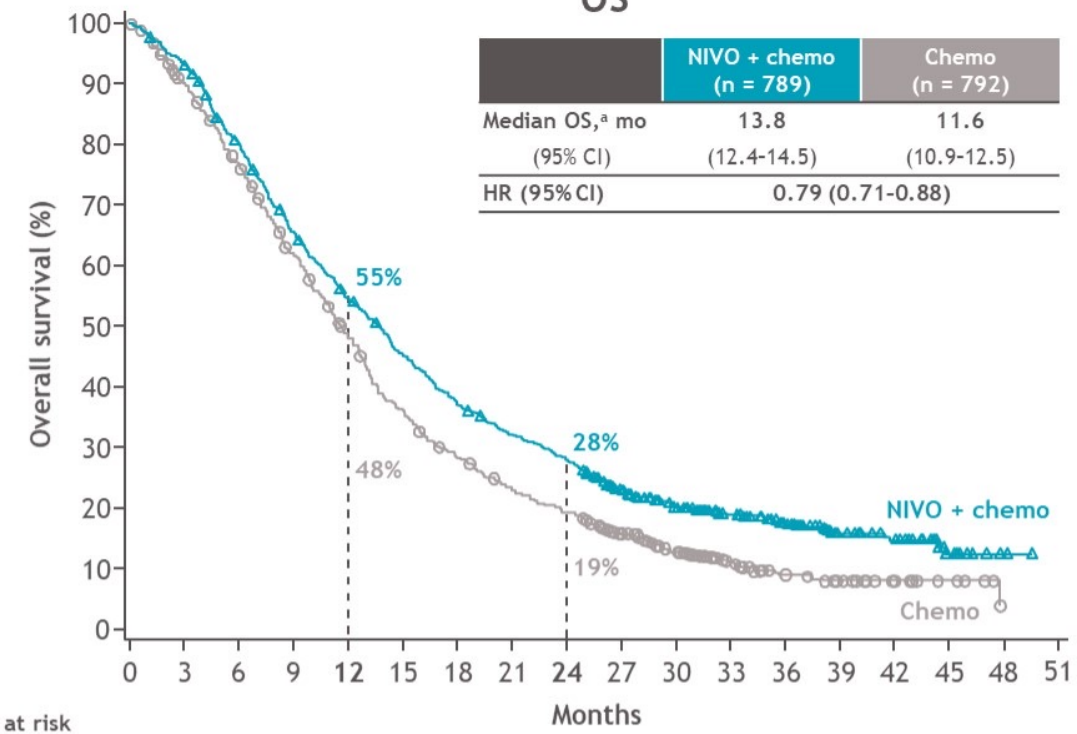
1. Janjigian YY et al. *Lancet*. 2021;398:27-40. 2. Janjigian YY et al. Presented at ESMO 2021.

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)	

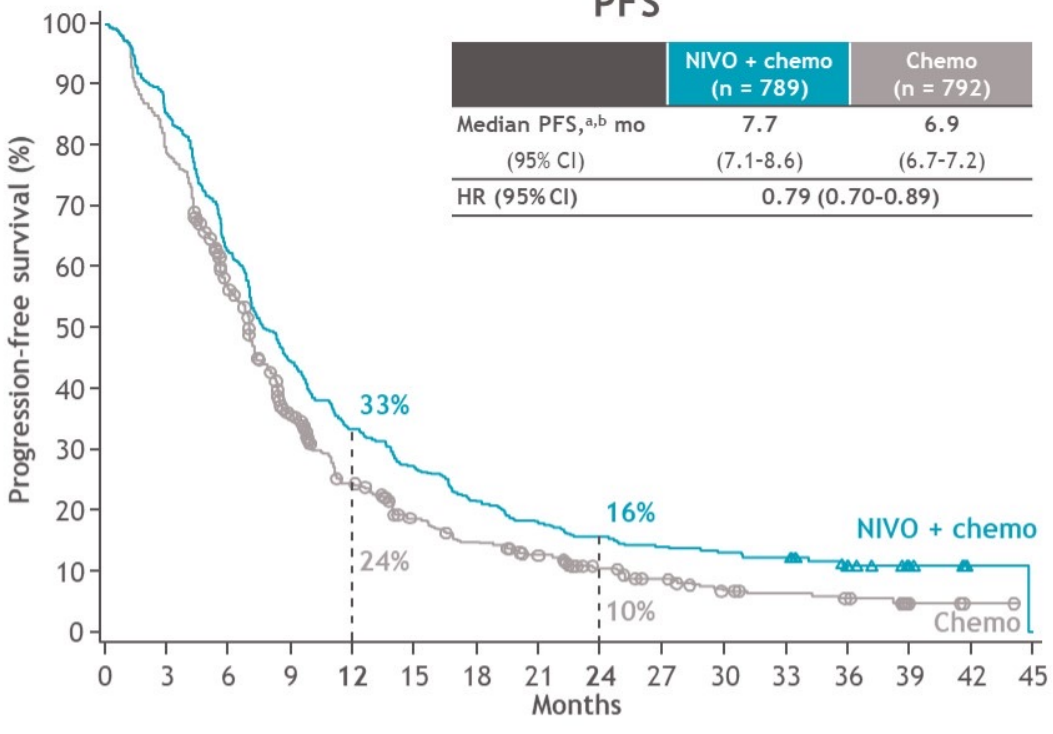


No. at risk

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)	



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

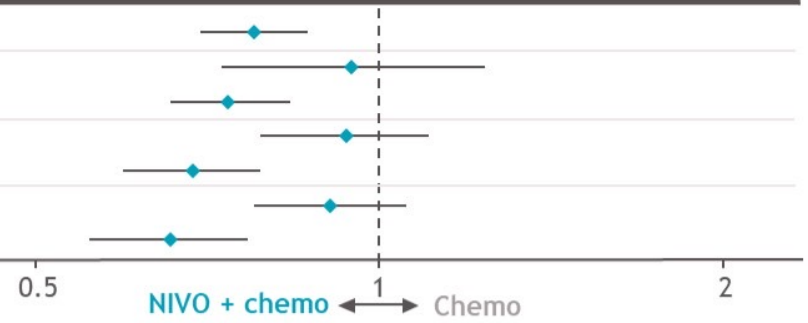
- Clinically meaningful improvement in OS and PFS with NIVO + chemo vs chemo was maintained with longer follow-up

[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.

Efficacy subgroup analysis by PD-L1 CPS

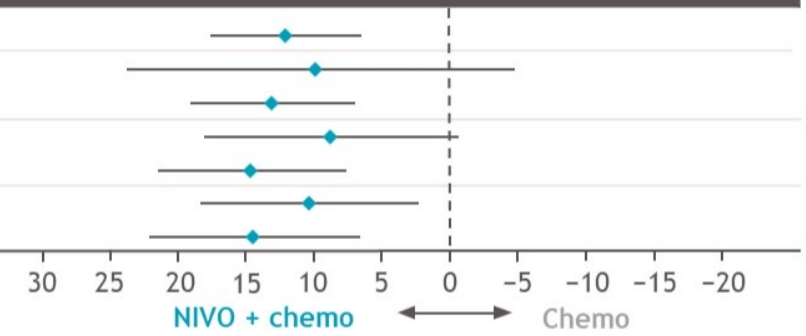
Overall survival

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	



Objective response rate

PD-L1 CPS[c]	Number of patients	Objective response rate, %		Unweighted ORR difference,[d] %	Unweighted ORR difference,[d] % (95% CI)
		NIVO + chemo	Chemo		
Overall (N = 1210)		58	46	12	
< 1	179	51	41	10	
≥ 1	1017	59	46	13	
< 5	428	55	46	9	
≥ 5	768	60	45	15	
< 10	579	58	47	10	
≥ 10	617	59	44	15	



- OS benefit with NIVO + chemo was enriched at higher PD-L1 CPS cutoffs
- ORR was higher across all PD-L1 CPS subgroups vs chemo

[a]PD-L1 CPS expression indeterminate/not evaluable/not reported, n = 19; [b]Unstratified HR for death (OS); [c]Randomized patients who had target lesion measurements at baseline, per BICR. PD-L1 CPS expression indeterminate/not evaluable/not reported, n = 14; [d]Percentages may not reflect an exact difference due to rounding.

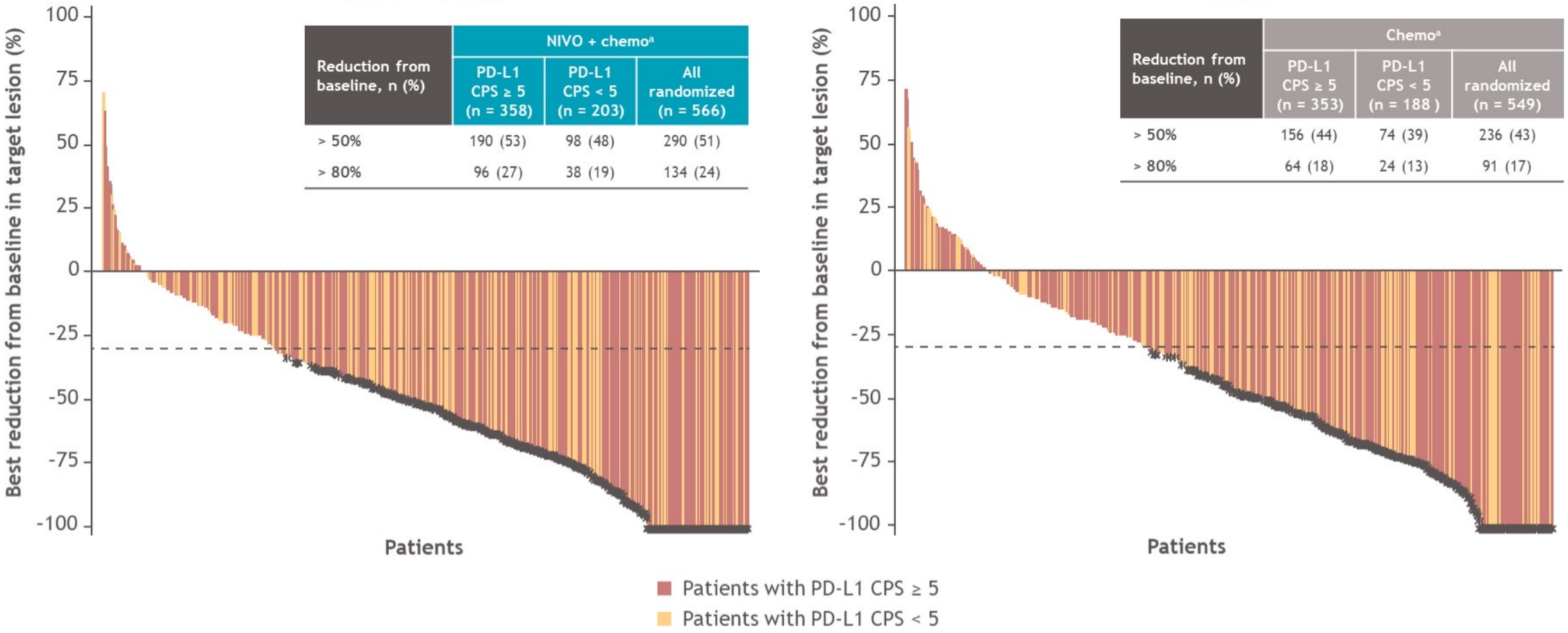
Best percentage reduction in tumor burden

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)

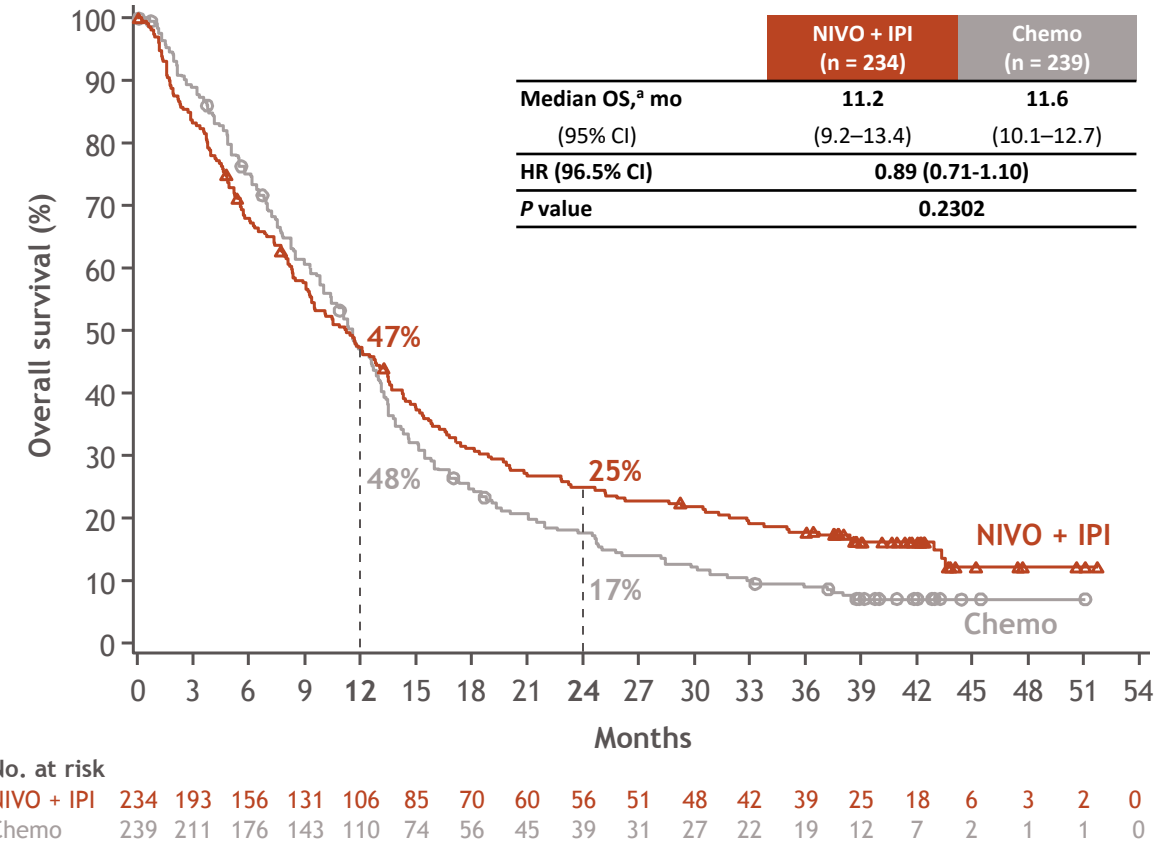


- More deep responses were observed with NIVO + chemo vs chemo regardless of PD-L1 CPS ≥ 5 or < 5

[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.

Overall survival: NIVO + IPI vs chemo

PD-L1 CPS ≥ 5

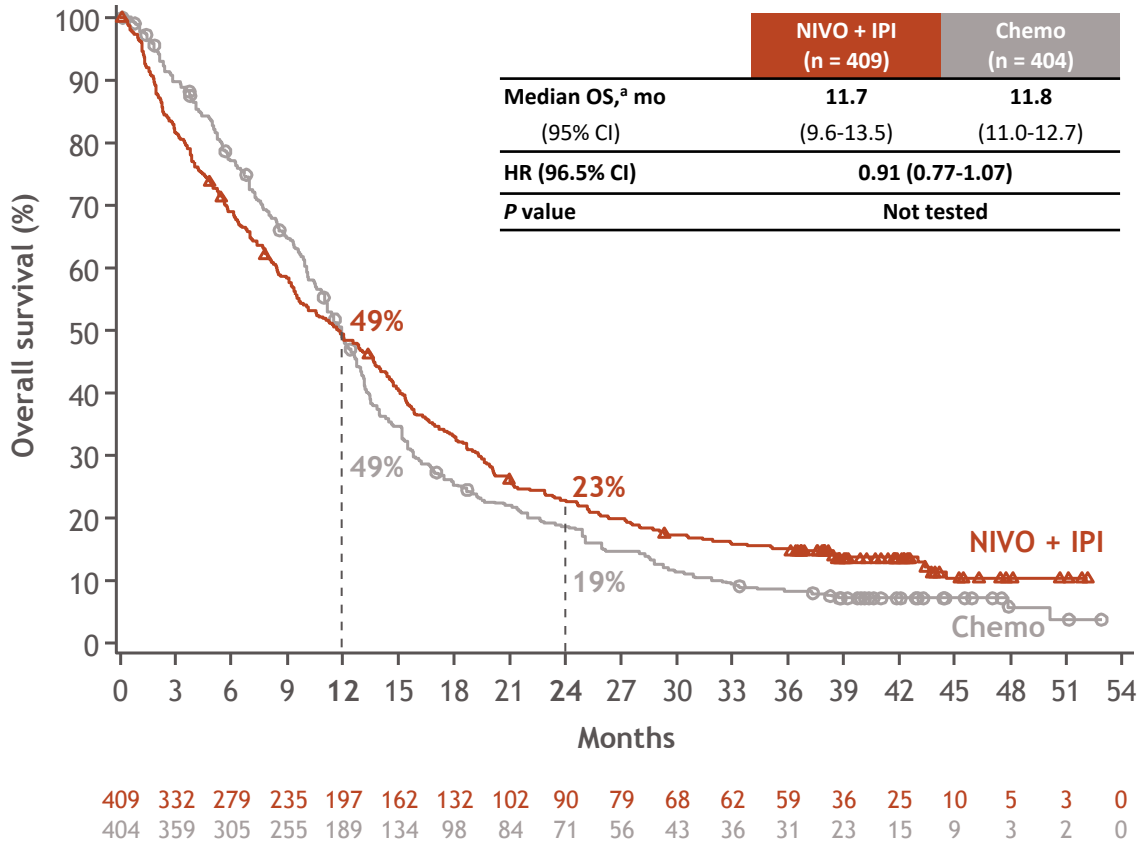


	NIVO + IPI (n = 234)	Chemo (n = 239)
Median OS,[a] mo	11.2	11.6
(95% CI)	(9.2–13.4)	(10.1–12.7)
HR (96.5% CI)	0.89 (0.71-1.10)	
P value	0.2302	

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



	NIVO + IPI (n = 409)	Chemo (n = 404)
Median OS,[a] mo	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	

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

- The hierarchically tested secondary endpoint of OS with NIVO + IPI vs chemo in patients with PD-L1 CPS ≥ 5 was not met; OS in all randomized patients was not statistically tested

- [a]Minimum follow-up, 35.7 months.

Metastatic Gastric/ GEJ Cancer MSI-H

MSI high

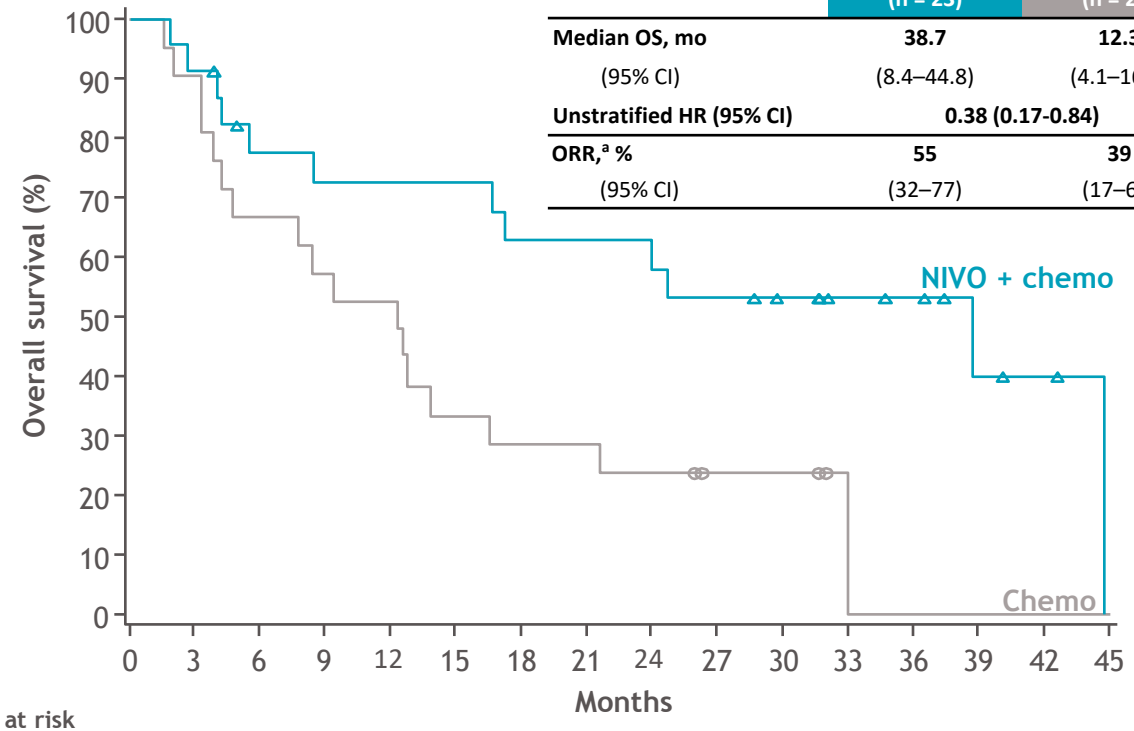
Characteristic	Patients, No. (%)					
	KEYNOTE-059[a]	KEYNOTE-061[b]		KEYNOTE-062[c]		
	Pembrolizumab	Pembrolizumab	Chemotherapy	Pembrolizumab	Pembrolizumab plus chemotherapy	Chemotherapy
Total patients, No.	7	15	12	14	17	19
PD-L1 CPS						
≥1	5 (71.4)	13 (86.7)	11 (91.7)	14 (100)	17 (100)	19 (100)
≥10	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)

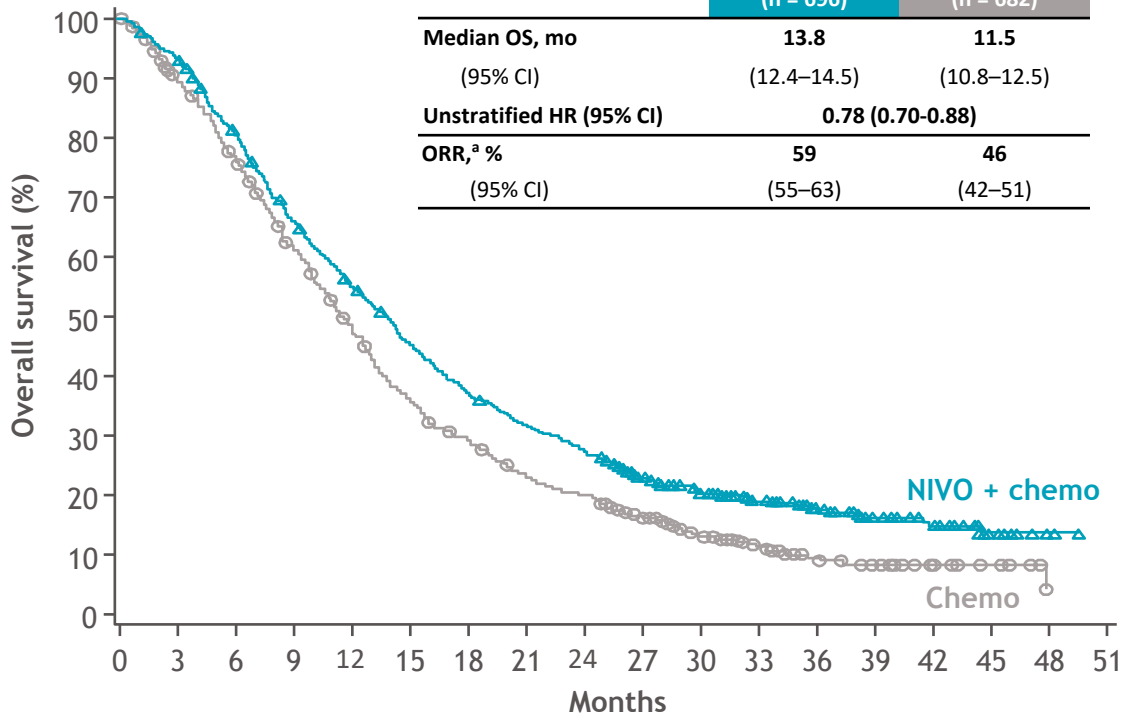


No. at risk

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

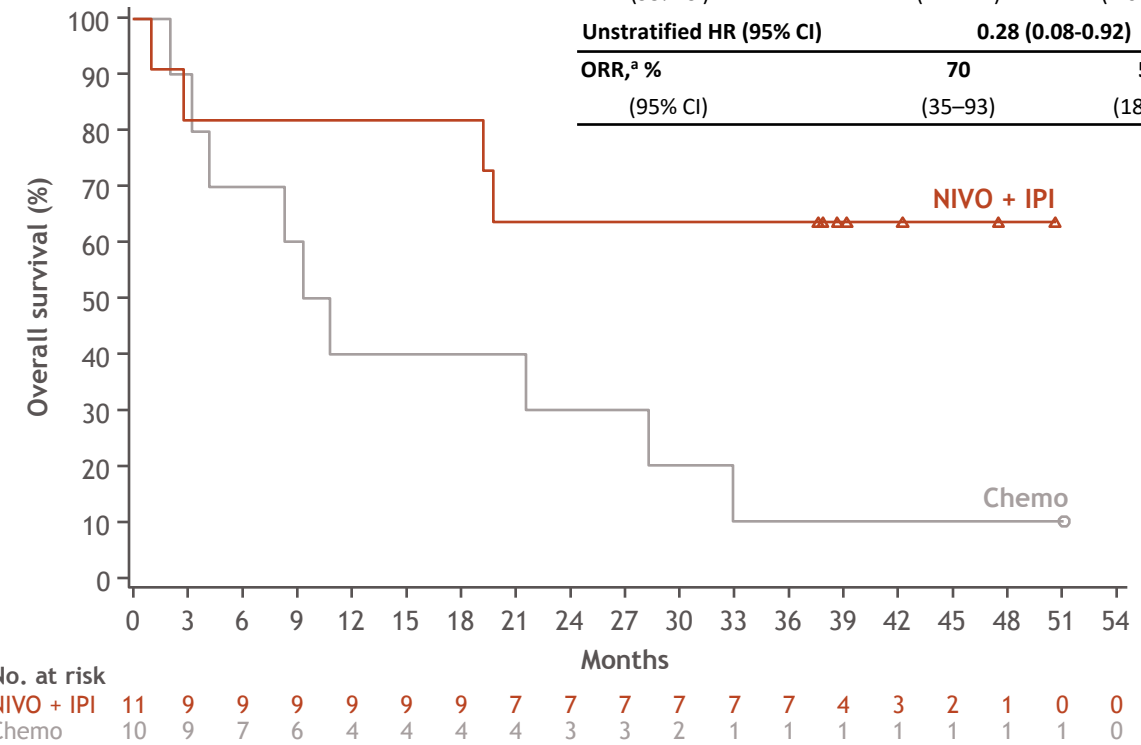
- Longer median OS and higher ORR were observed in all randomized patients with MSI-H and MSS tumors with NIVO + chemo vs chemo
  - The magnitude of benefit was greater in patients with MSI-H tumors, and patients with MSS tumors had results similar to the all randomized population

- [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

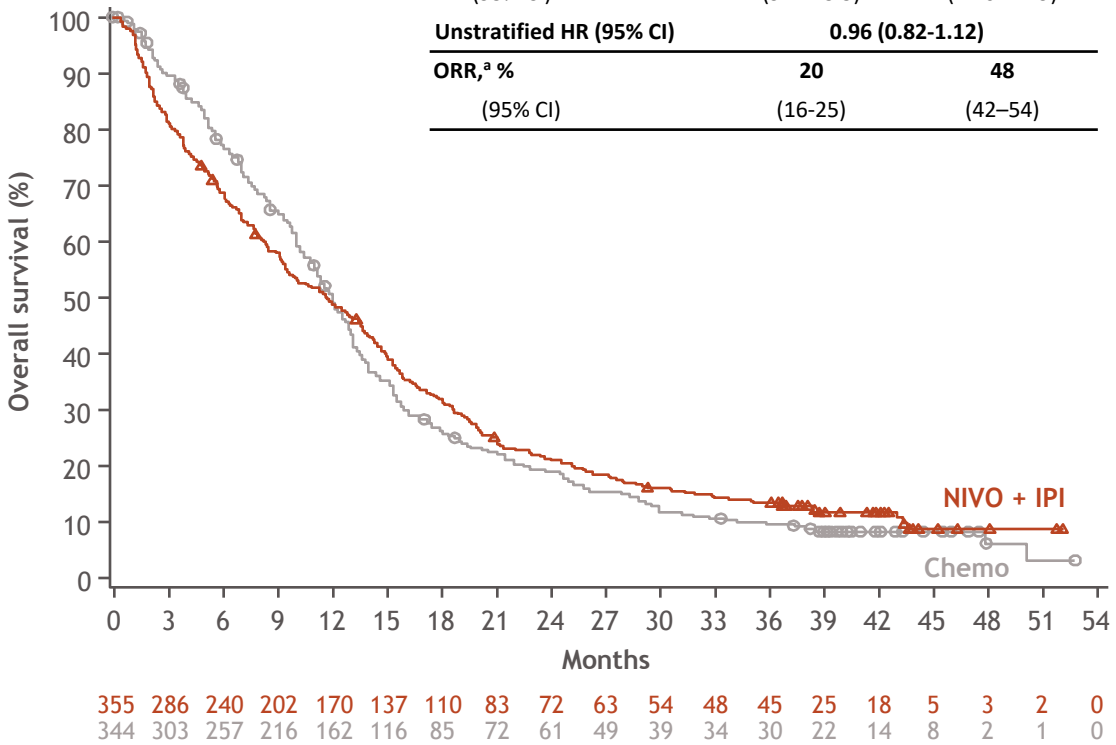
MSI-H

	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)

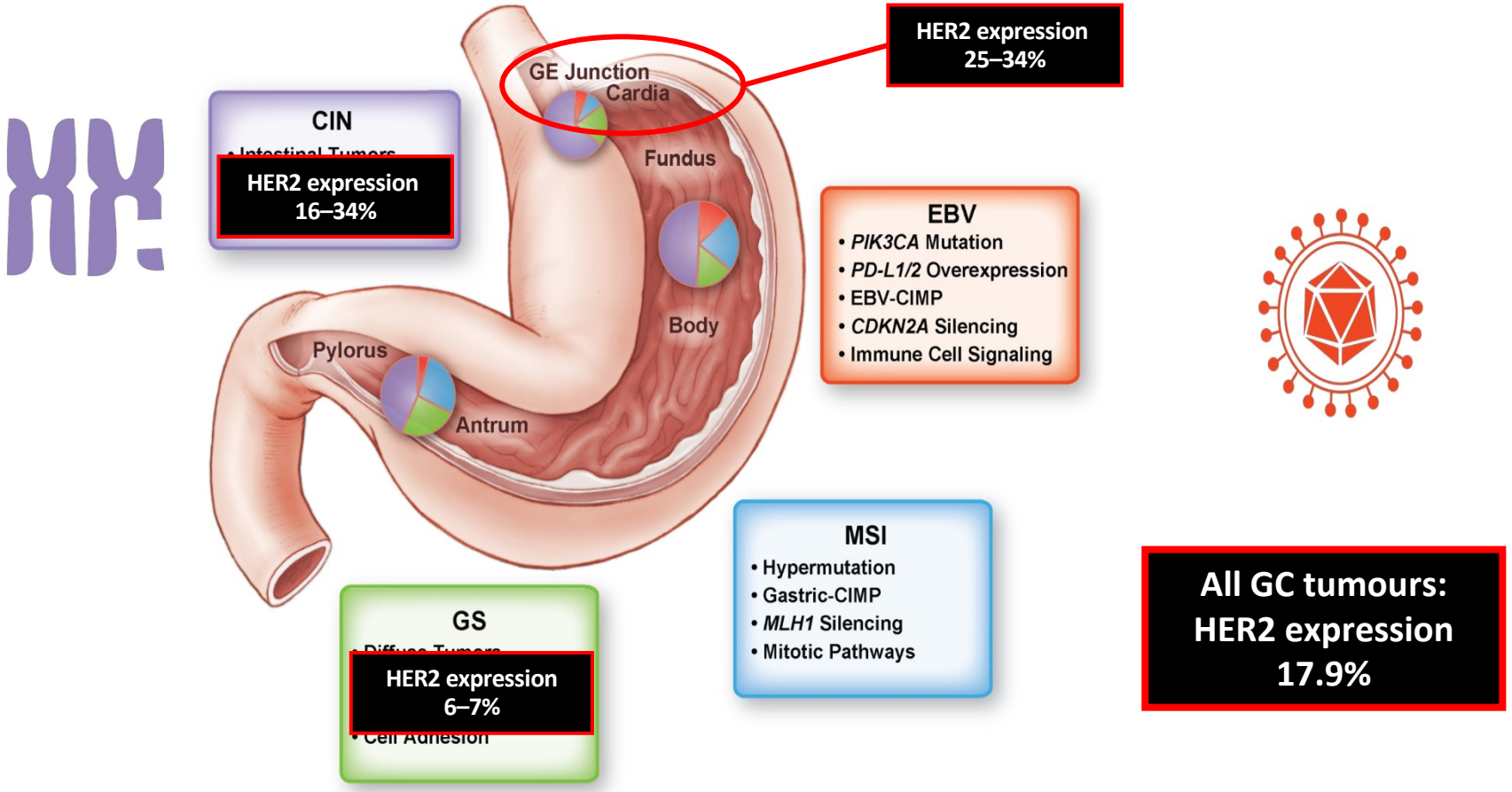


- Longer median OS and higher ORR observed in all randomized patients with MSI-H tumors with NIVO + IPI vs chemo, although sample size was small

- [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]

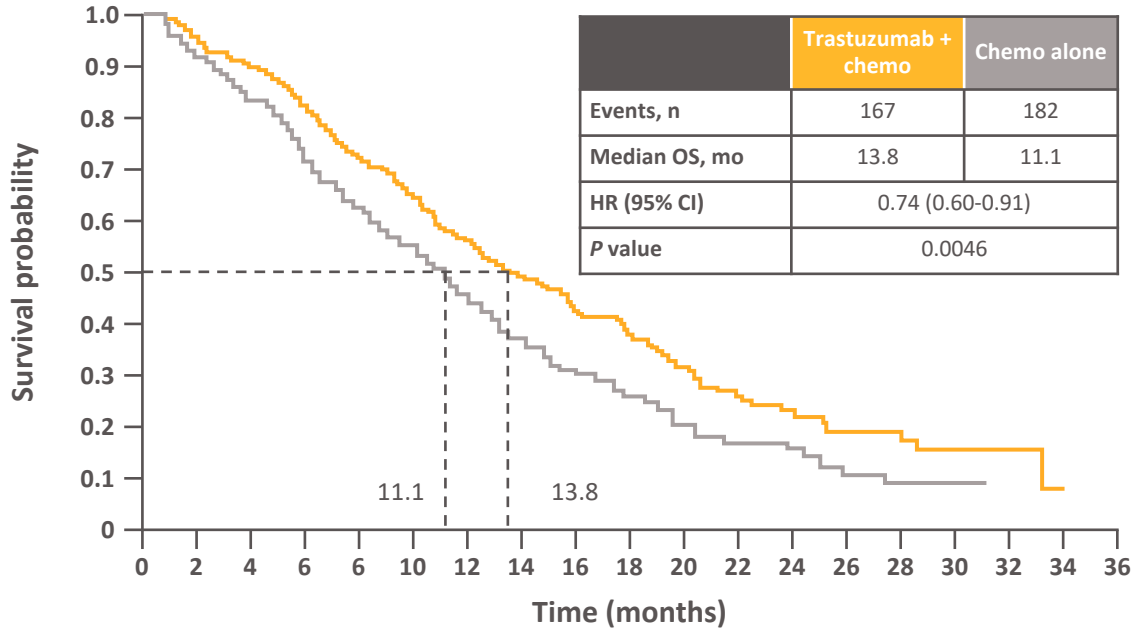


1. Bang et al. Lancet 2010; 2. Gravalos et al. Ann Oncol 2008; 3. Yano et al. ASCO 2004; 4. Gravolos et al. ASCO GI 2007; 5. Lordick et al. ECCO 2007; 6. Abrahao-Machado et al. World J Gastroenterol 2016.

Slide provided courtesy of Manish A. Shah, MD

ToGA Overall Survival: 1st-Line Gastric Cancer

Primary analysis population

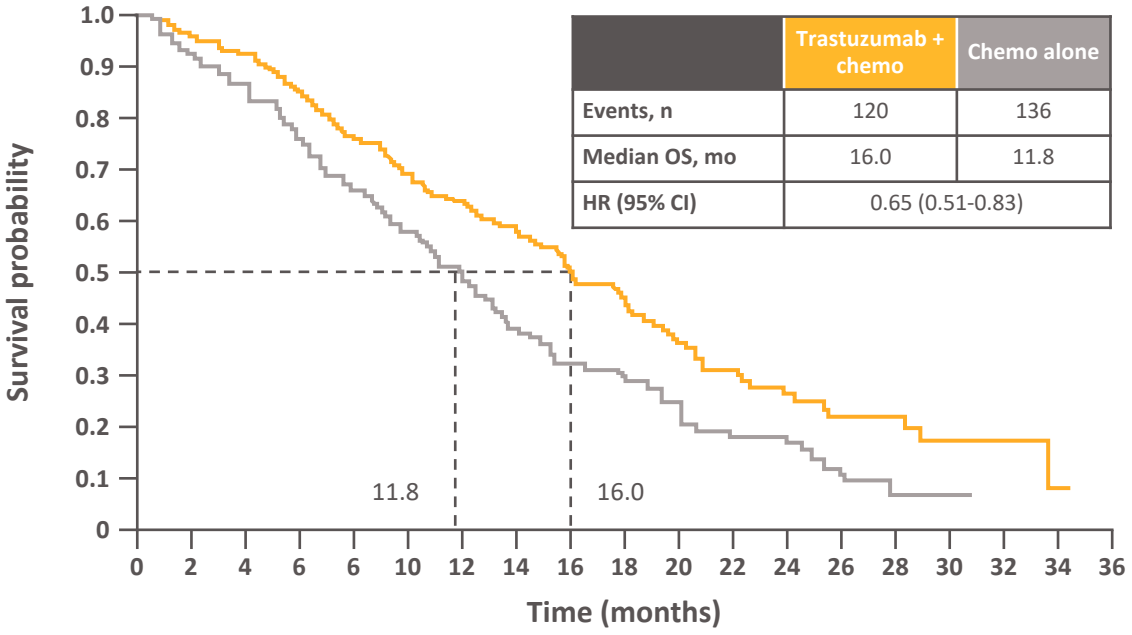


	Trastuzumab + chemo	Chemo alone
Events, n	167	182
Median OS, mo	13.8	11.1
HR (95% CI)	0.74 (0.60-0.91)	
P value	0.0046	

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.

Adapted from Bang 2010.

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)

R 1:1

PEMBRO 200 mg IV Q3W
+ Trastuzumab
+ FP or CAPOX[b] × ≤35

Placebo IV Q3W
+ Trastuzumab
+ FP or CAPOX[b] × ≤35

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

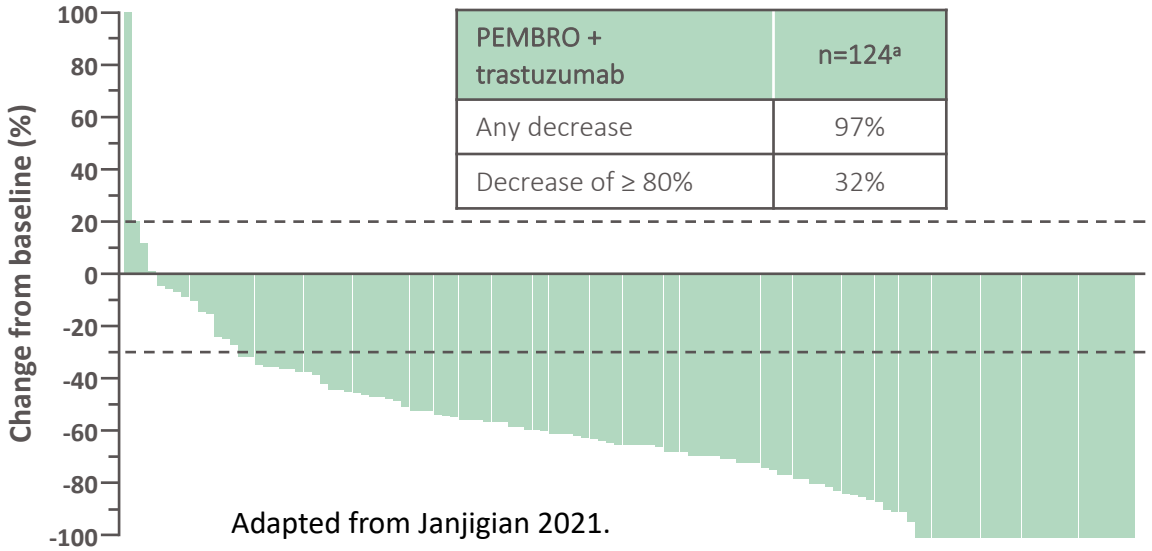
Key secondary endpoints:
- **ORR** and **DOR**[c]
- **Safety**

[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.

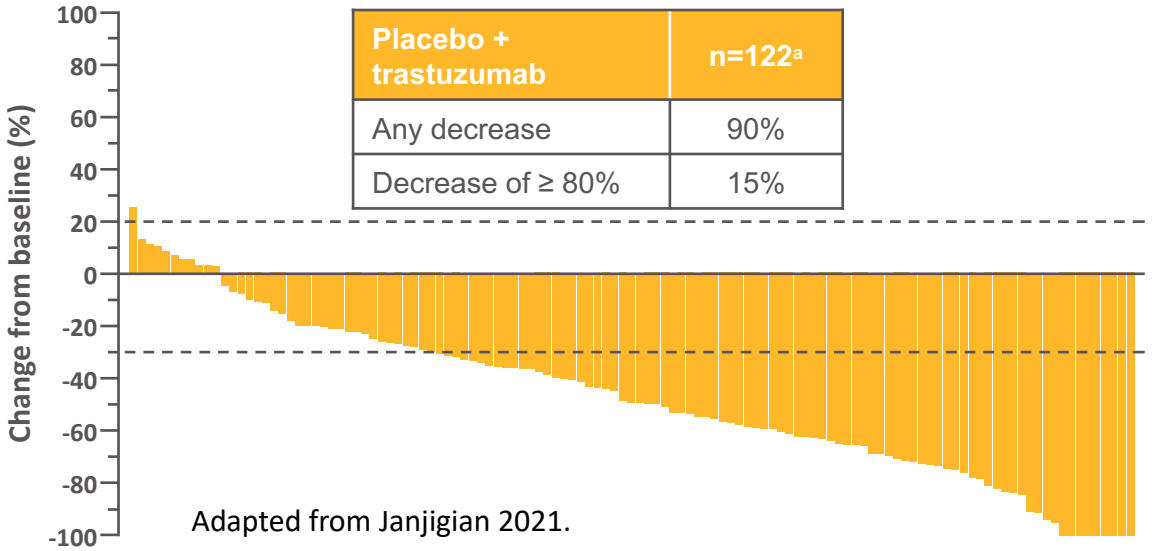
Pembrolizumab/Trastuzumab/Chemotherapy

FDA approved May 2021



PEMBRO + trastuzumab	n=124[a]
Any decrease	97%
Decrease of ≥ 80%	32%

Adapted from Janjigian 2021.



Placebo + trastuzumab	n=122[a]
Any decrease	90%
Decrease of ≥ 80%	15%

Adapted from Janjigian 2021.

ORR and DCR, % (95% CI)	PEMBRO + trastuzumab (n=133)	Placebo + trastuzumab (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 + trastuzumab (n=133)	Placebo + trastuzumab (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%)

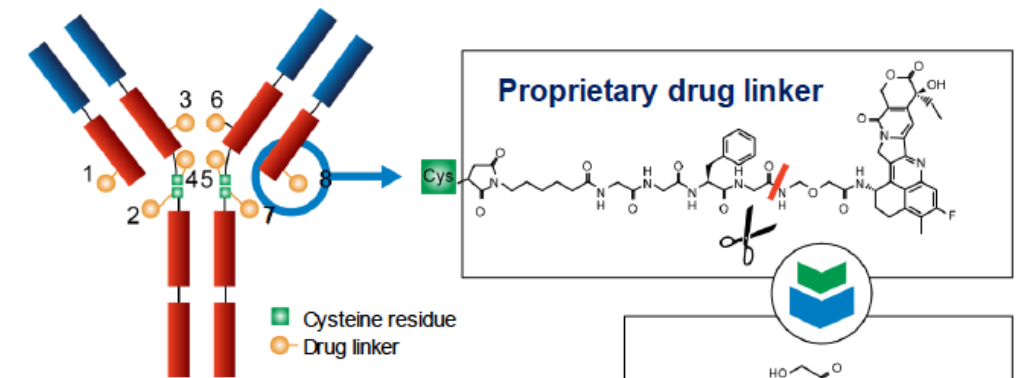
Duration of Response	PEMBRO + trastuzumab (n=133)	Placebo + trastuzumab (n=131)
Median[c]	10.6 mo	9.5 mo
Range	1.1+ to 16.5+	1.4+ to 15.4+
≥ 6-mo duration[c]	70.3%	61.4%
≥ 9-mo duration[c]	58.4%	51.1%

- Grade 3-5 AE rates did not differ between treatment arms (57%)

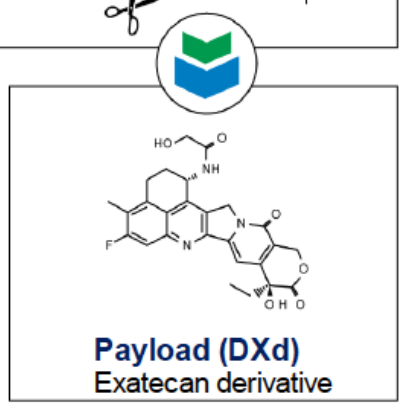
[a]Participants with RECIST-measurable disease at baseline and ≥1 evaluable post-baseline measurement. [b]Calculated using the Miettinen and Nurminen method stratified by the randomization stratification factors. [c]Kaplan-Meier estimation. The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

Janjigian YY et al. *J Clin Oncol*. 2021;39(15_suppl):4013. Presented at ASCO 2021.

Trastuzumab Deruxtecan Structure and Mechanism of Action[1]



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

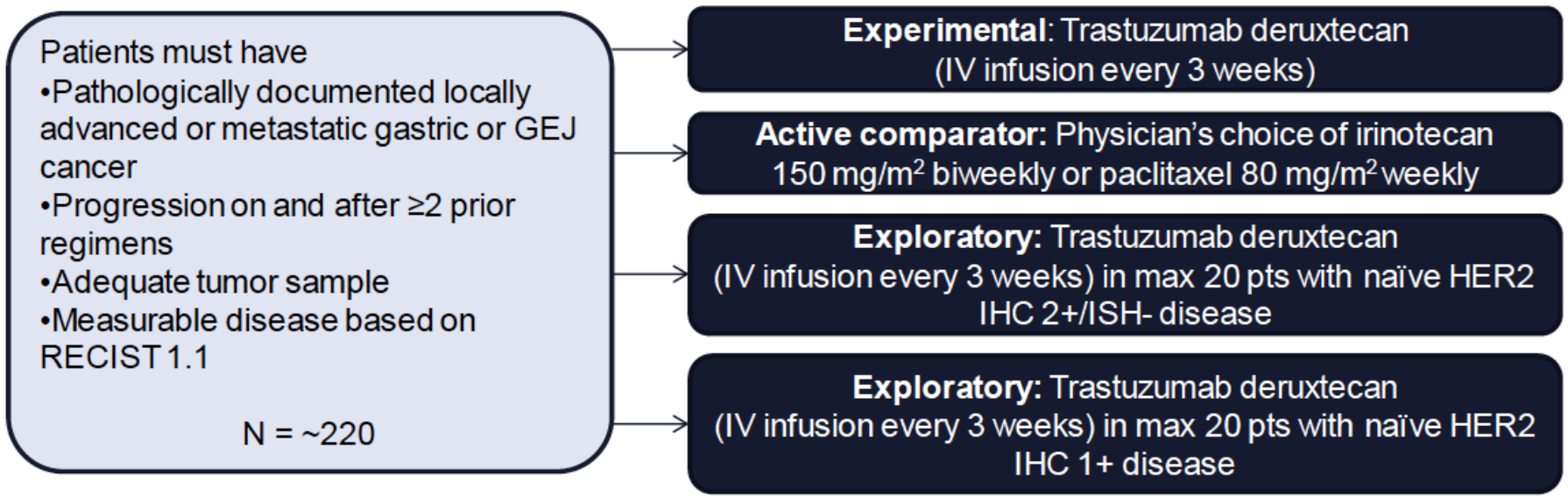


- Payload with a different MOA
- High potency of payload
- Payload with short systemic half-life
- Bystander effect
- Stable linker-payload
- Tumor-selective cleavable linker
- High drug-to-antibody ratio

- 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.

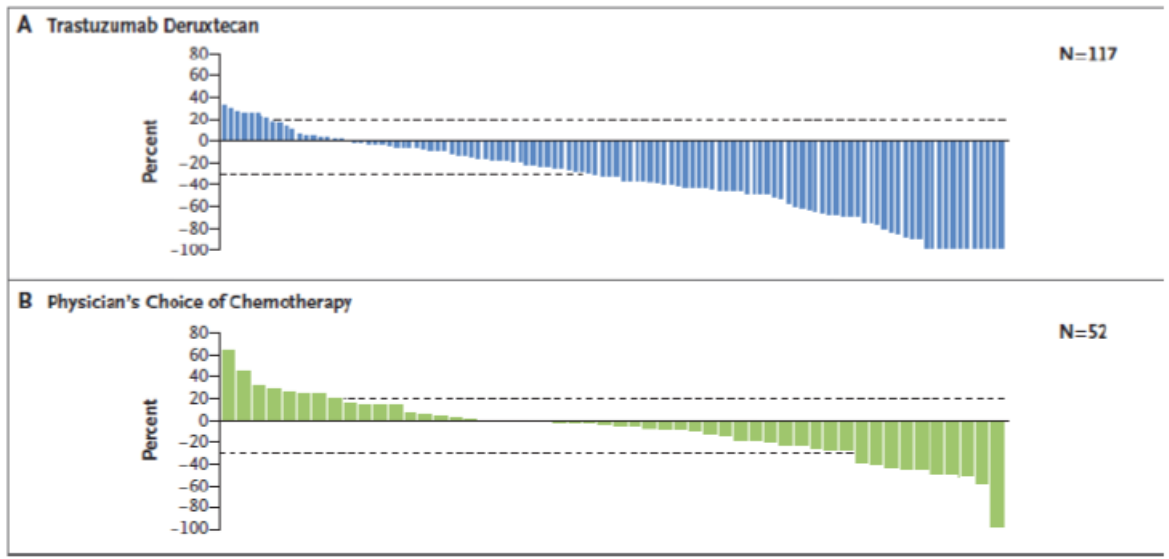
DESTINY-Gastric01: Phase 2 Trial of Trastuzumab Deruxtecan in Advanced HER2+ Gastric Cancer[1]

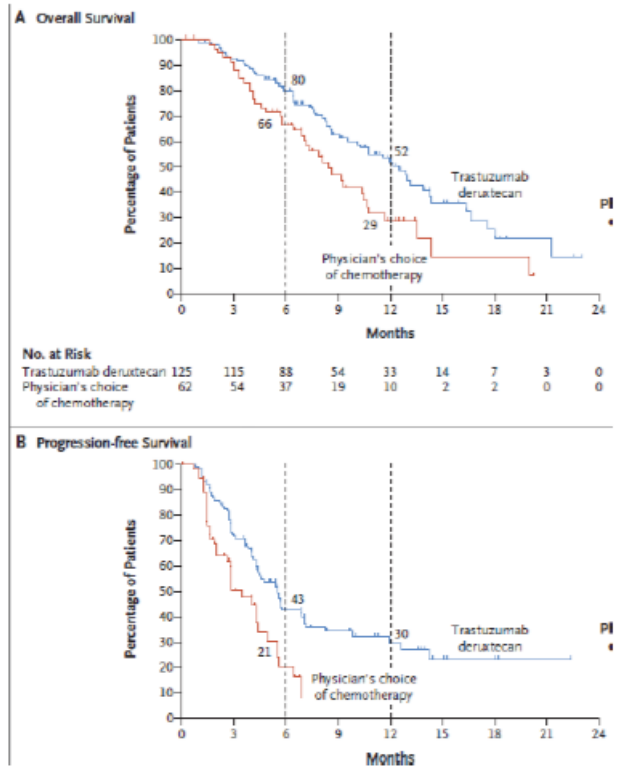


Outcomes

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

Summary - Resectable

- Adjuvant nivolumab demonstrated clinically meaningful efficacy in patients with resected EC/GEJC following neoadjuvant CRT compared to placebo
  - 31% reduction in the risk of recurrence or death and a doubling in median DFS
  - DFS benefit across multiple subgroups
  - Less frequent distant and locoregional recurrences
  - Improvement in DMFS and PFS2
- These results provide further support for adjuvant nivolumab as a new standard of care for patients with resected EC/GEJC who received neoadjuvant CRT with residual pathologic disease
- Gastric cancer options include perioperative therapy (FLOT) or adjuvant chemoradiotherapy

Summary – Advanced Stage

- Her2 , MSI and CPS (PDL1) need to be checked at a minimum
- 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 MSS Her2 negative 1L advanced gastroesophageal or gastric cancer should be treated with oxaliplatin + fluoropyrimidine and Nivolumab (if CPS ≥ 5) or Pembrolizumab (if CPS ≥ 10)
  - If CPS<5 options include doublet chemotherapy +/- Nivolumab
  - Subsequent lines therapy include ramucirumab/ paclitaxel and trifluridine/ tipiracil
- Patients with MSI H in 1-L advanced gastroesophageal or gastric cancer can be treated with pembrolizumab +/- chemo, nivolumab + chemo or NIVO + IPI
- NIVO + 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