Immunotherapy in upper GI cancers

14th Belgian Symposium on the Integration of Molecular Biology Advances into Oncology Clinical Practice and Post-MASCC, 27/11/2020

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Esophageal - gastric cancer anno 2020

- **<u>Current therapies that we are using:</u>**
  - Cisplatinum/carboplatinum – 5-FU de Gramont +/- trastuzumab
  - Modified FOLFOX
  - Paclitaxel + ramucirumab
  - Docetaxel
  - Ramucirumab monotherapy
  - Modified FOLFIRI
  - Trifluridine-tipiracil (= Lonsurf®) recently reimbursed in Belgium

  - **<u>Immunotherapy</u>: unclear position in first-line gastric cancer; in second- and third-line gastric-esophageal cancer, there is a benefit in the Asian population, MSI-high group, PD-L1 CPS-score ≥ 10 and TMB-high group…**

ESMO 2020 and esophageal - gastric cancer

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Nivolumab has shown already a significant survival benefit for heavily pretreated patients with advanced or recurrent (advanced) gastric/gastroesophageal junction (G/GEJ) cancer:

ATTRACTION-2

ESMO 2020 esophagus-stomach: immunotherapy

VIRTUAL 2020 ESMO congress

Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: first results of the CheckMate 649 study

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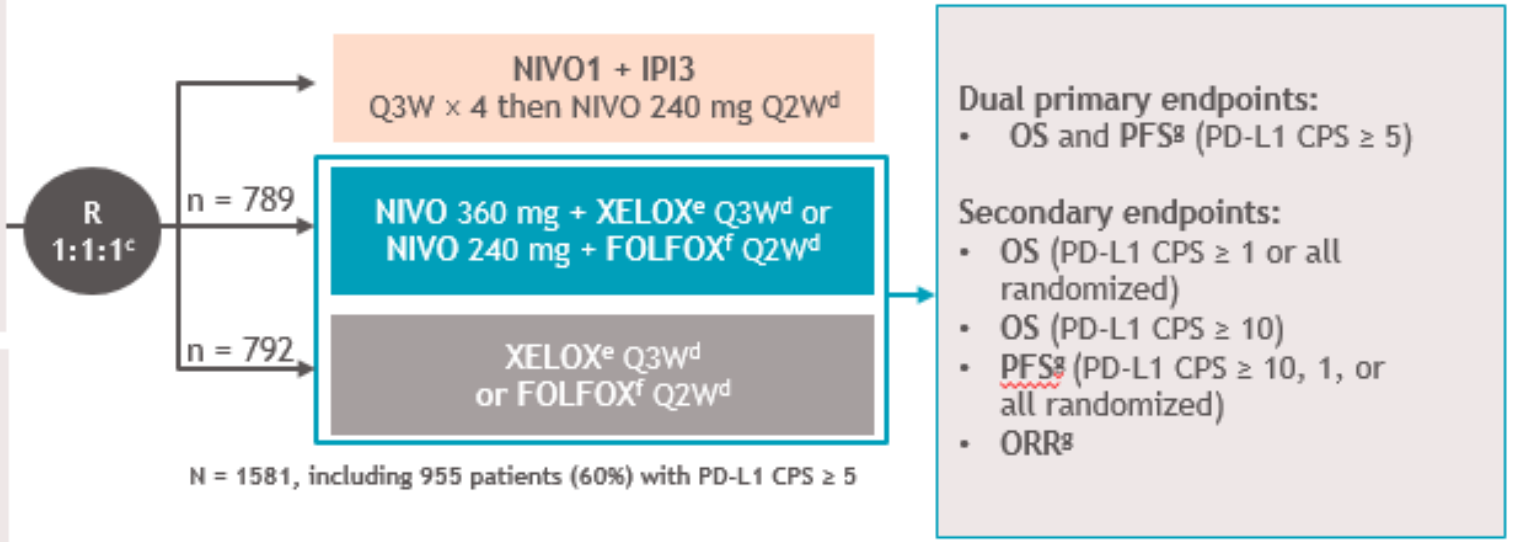
CheckMate 649 study design

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



- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]

[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 NIVO1+IPI3 group was closed; [d]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1-14); [f]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); [g]BICR assessed; [h]Time from concurrent randomization of the last patient to NIVO + chemo vs chemo to data cutoff.

Baseline characteristics

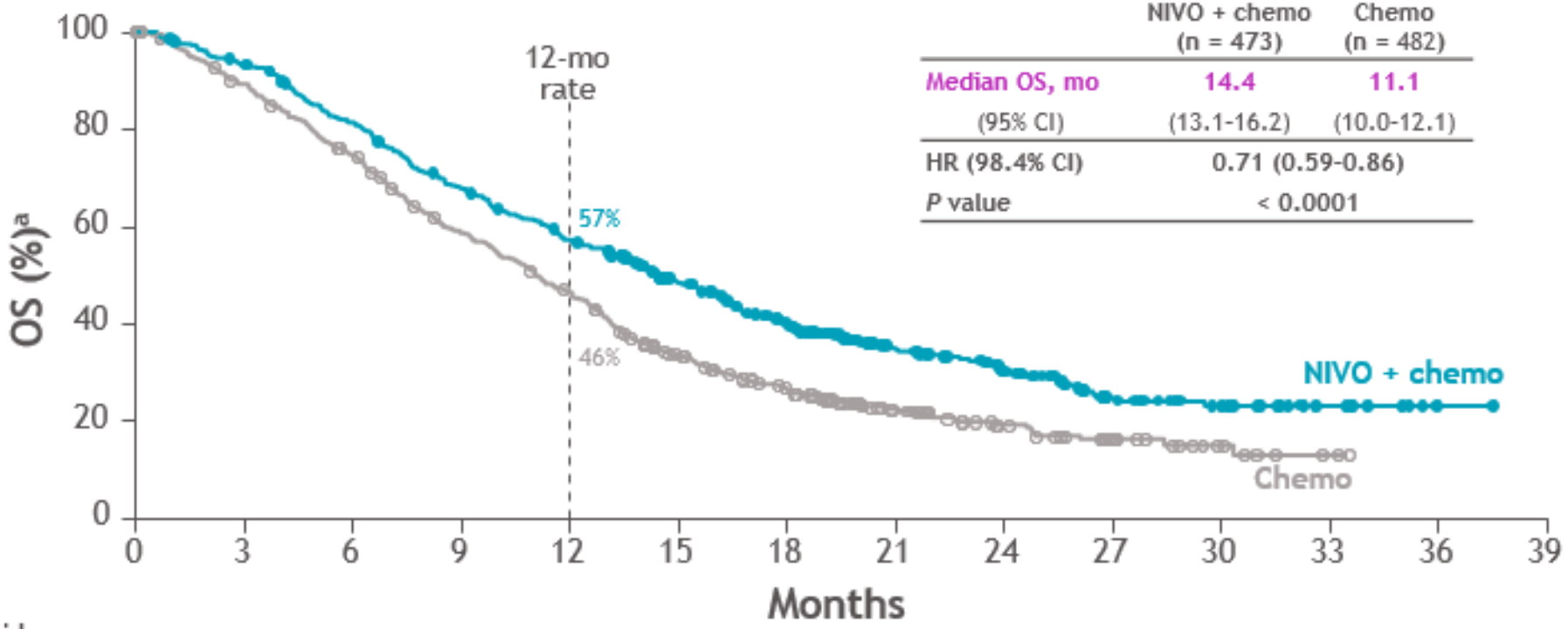
	PD-L1 CPS ≥ 5	
	NIVO + chemo (n = 473)	Chemo (n = 482)
Median age (range), years	63 (18-88)	62 (23-90)
Male, %	70	72
Non-Asian/Asian, %	75/25	76/24
ECOG PS 1, %	59	58
Primary tumor location, %		
GC	70	69
GEJC	18	18
EAC	12	13
Metastatic disease, %	96	96
Liver metastases, %	40	45
Signet ring cell carcinoma, %	15	14
MSI status,[a] %		
MSS	89	88
MSI-high	4	3
FOLFOX/XELOX received on study,[b] %	51/49	52/48

- The distribution of baseline characteristics was consistent with that of all randomized patients

[a]MSI status was not reported or invalid for 75 patients; [b]All treated patients with PD-L1 CPS ≥ 5: NIVO + chemo, n = 468 and chemo, n = 465.

Overall survival

Primary endpoint (PD-L1 CPS ≥ 5)



	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (98.4% CI)	0.71 (0.59-0.86)	
P value	< 0.0001	

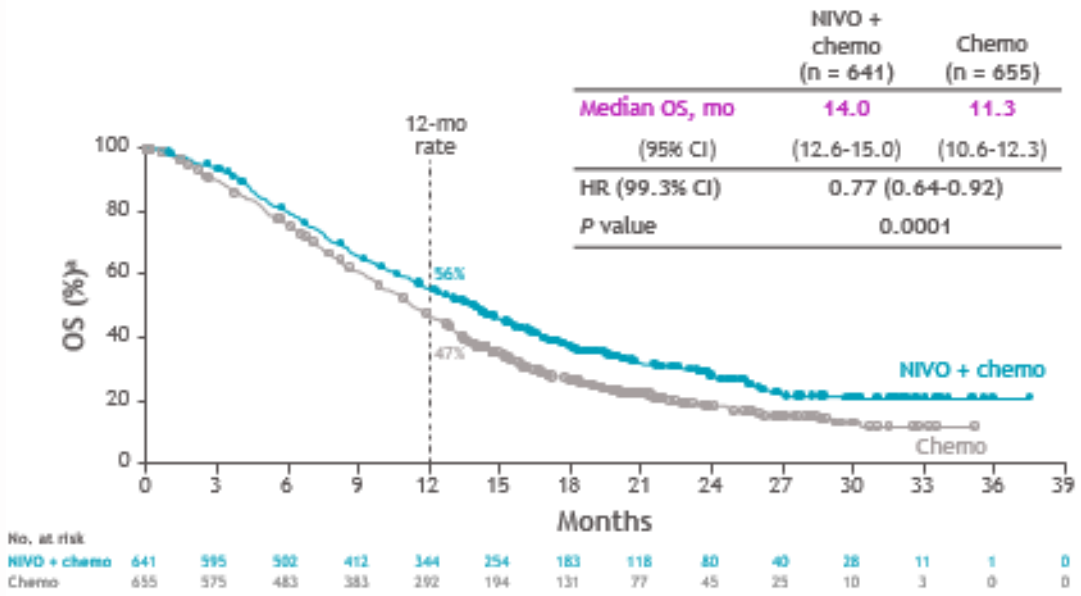
No. at risk														
NIVO + chemo	473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemo	482	421	350	271	211	138	98	56	34	19	8	2	0	0

- Superior OS, 29% reduction in the risk of death, and a 3.3-month improvement in median OS with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5

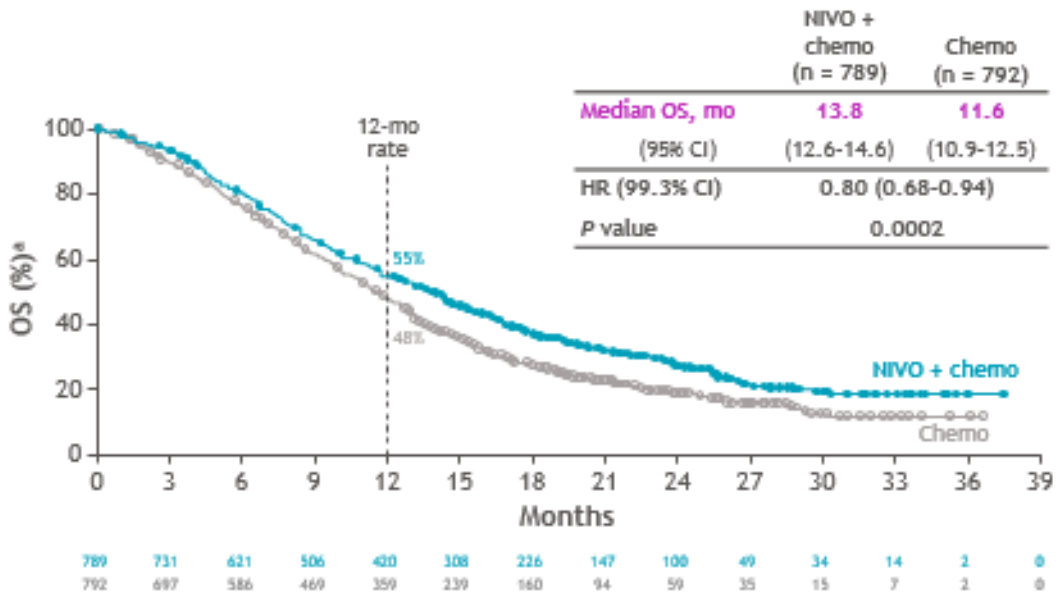
[a]Minimum follow-up 12.1 months.

Overall survival

PD-L1 CPS ≥ 1



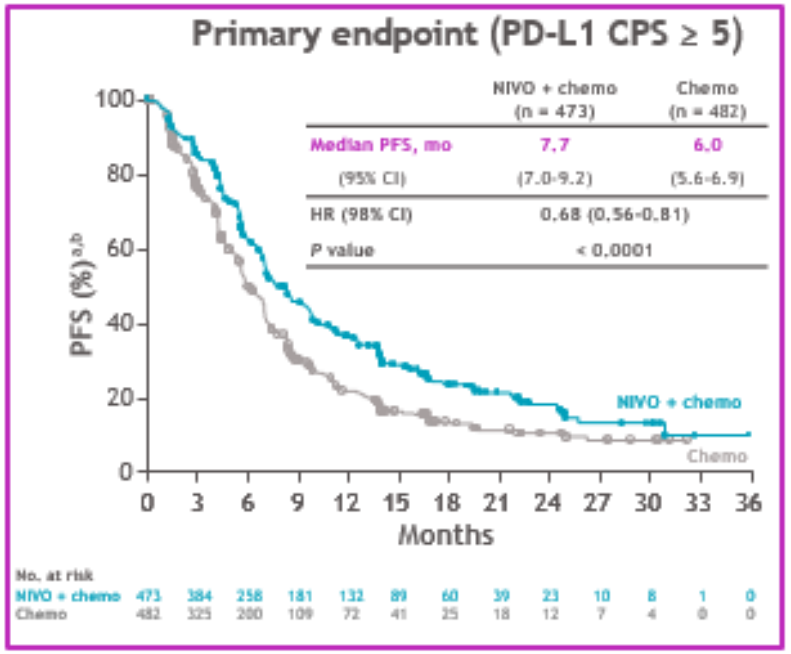
All randomized



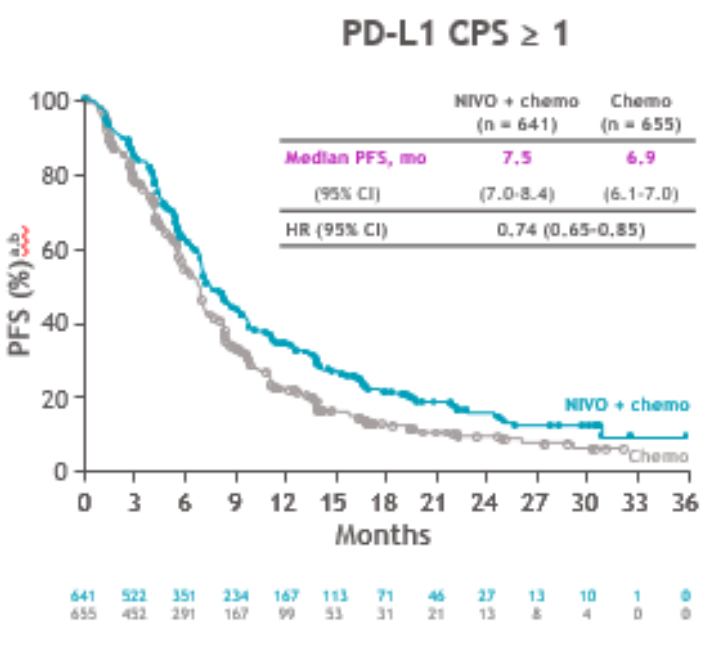
- Superior OS benefit in PD-L1 CPS ≥ 1 and all randomized patients with NIVO + chemo versus chemo

[a]Minimum follow-up 12.1 months.

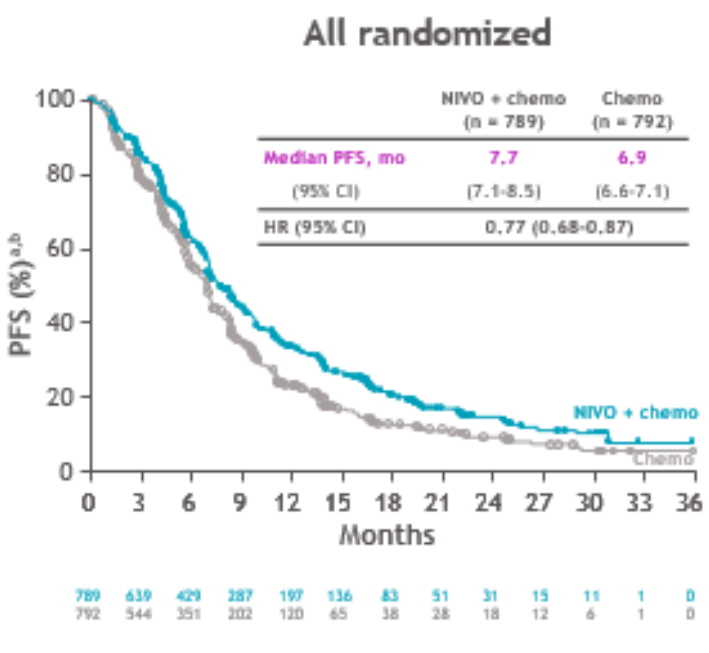
Progression-free survival



12-mo rate: NIVO + chemo, 36%; chemo, 22%



NIVO + chemo, 34%; chemo, 22%



NIVO + chemo, 33%; chemo, 23%

- Superior PFS, 32% reduction in the risk of progression or death with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5
- PFS benefit with NIVO + chemo versus chemo in PD-L1 CPS ≥ 1 and all randomized patients

[a]Per BICR assessment; [b]Minimum follow-up 12.1 months.

Summary

- NIVO is the first PD-1-inhibitor to demonstrate superior OS and PFS in combination with chemo versus chemo alone in previously untreated patients with advanced GC/GEJC/EAC
  - Statistically significant and clinically meaningful OS benefit in patients whose tumors expressed PD-L1 CPS ≥ 5 and ≥ 1 and in all randomized patients
  - Survival benefit across multiple pre-specified subgroups (assessed in primary population)
  - PFS benefit in PD-L1 CPS ≥ 5 (statistically significant), PD-L1 CPS ≥ 1, and all randomized patients
- No new safety signals were identified with NIVO + chemo
- **NIVO + chemo represents a new potential standard 1L treatment for patients with advanced GC/GEJC/EAC**

Biomarker analysis

CheckMate 649

- Secondary endpoints: PD-L1 CPS≥1 and all randomised patients

	n	Hazard Ratio	Δ	p value	
CPS ≥ 5	953	0.71 (0.59–0.86)	3.3	< 0.0001	
CPS ≥ 1	1296	0.77 (0.64–0.92)	2.7	0.001	> 70% CPS ≥ 5
All patient	1581	0.80 (0.68–0.94)	2.2	0.002	> 60% CPS ≥ 5

CPS ≥1 and "All patient" groups are **enriched** with immunogenic CPS ≥ 5 tumours
→ may not be representative of general GEA population[1]
→ may be more sensitive to nivolumab than regular CPS ≥1 and "All patient" groups outside trial

[1] Hegewisch-Becker S, et al. ASCO. July 3 2020.

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Nivolumab plus chemotherapy versus chemotherapy alone in patients with previously untreated advanced or recurrent gastric/ gastroesophageal junction (G/GEJ) cancer: ATTRACTION-4 (ONO-4538-37) study

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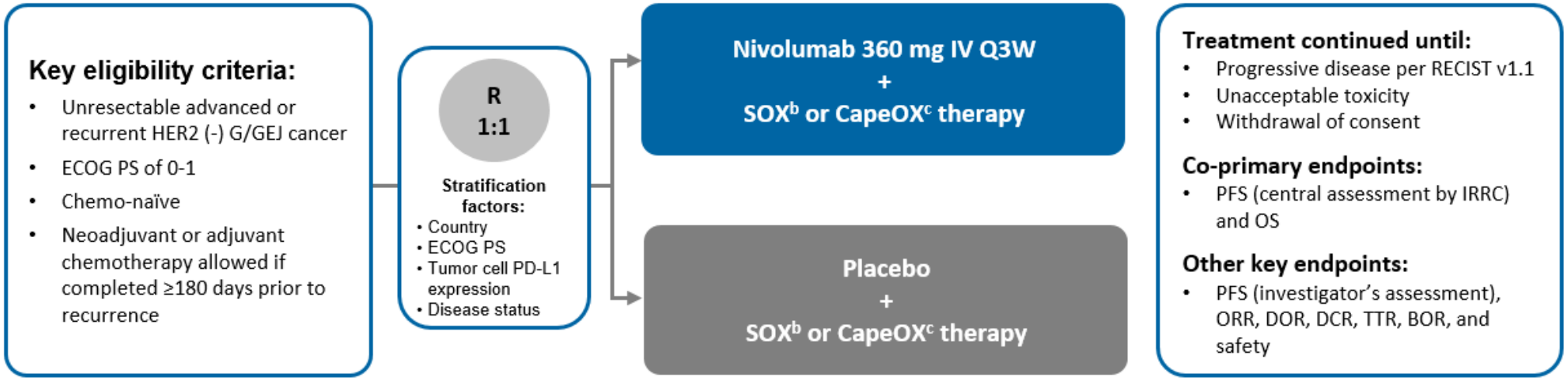
Phase 3 part of ATTRACTION-4: Study Design

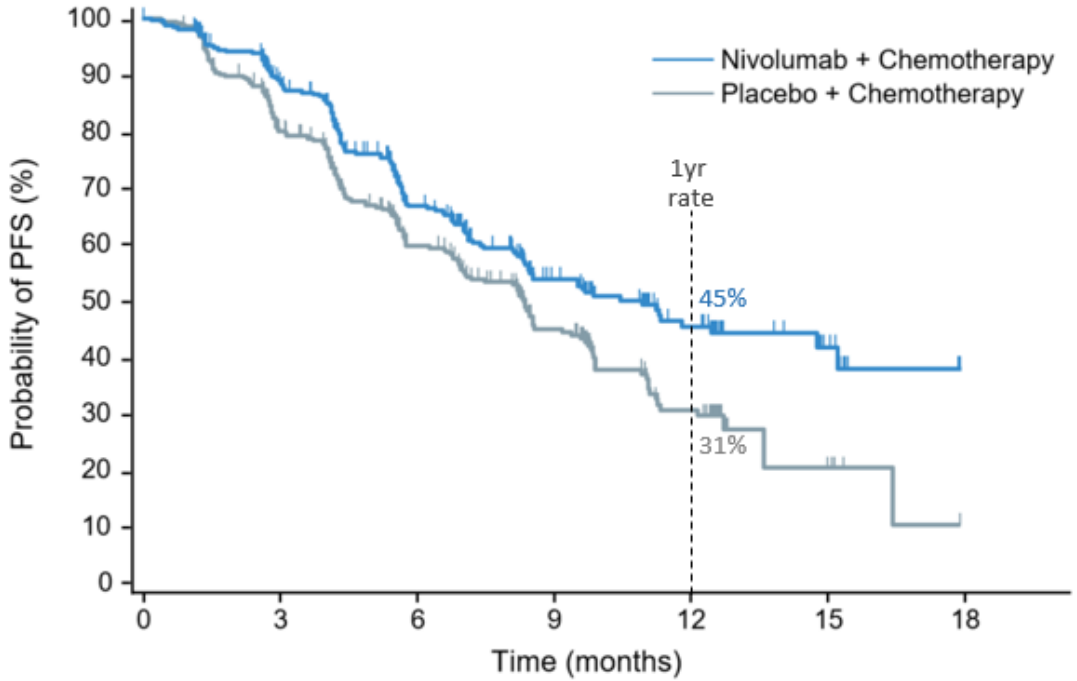
- Phase 3 part of ATTRACTION-4 is a double-blind, randomized controlled study conducted at 130 centers in Japan, Korea, and Taiwan[a]



- At data cutoff for interim analysis of PFS (31 Oct 2018), the median follow-up period was 11.6 months
- At data cutoff for final analysis of OS (31 Jan 2020), the median follow-up period was 26.6 months
- A total of 724 patients were randomized between Mar 2017 and May 2018

[a]ClinicalTrials.gov Identifier: NCT02746796,
[b]SOX : S-1 (tegafur-gimeracil-oteracil potassium) 40 mg/m^2 orally twice daily (days 1–14) and Oxaliplatin 130 mg/m^2 IV (day 1), q3w
[c]CapeOX : Capecitabine 1000 mg/m^2 orally twice daily (days 1–14) and Oxaliplatin 130 mg/m^2 IV (day 1), q3w

Progression-Free Survival (Interim Analysis)

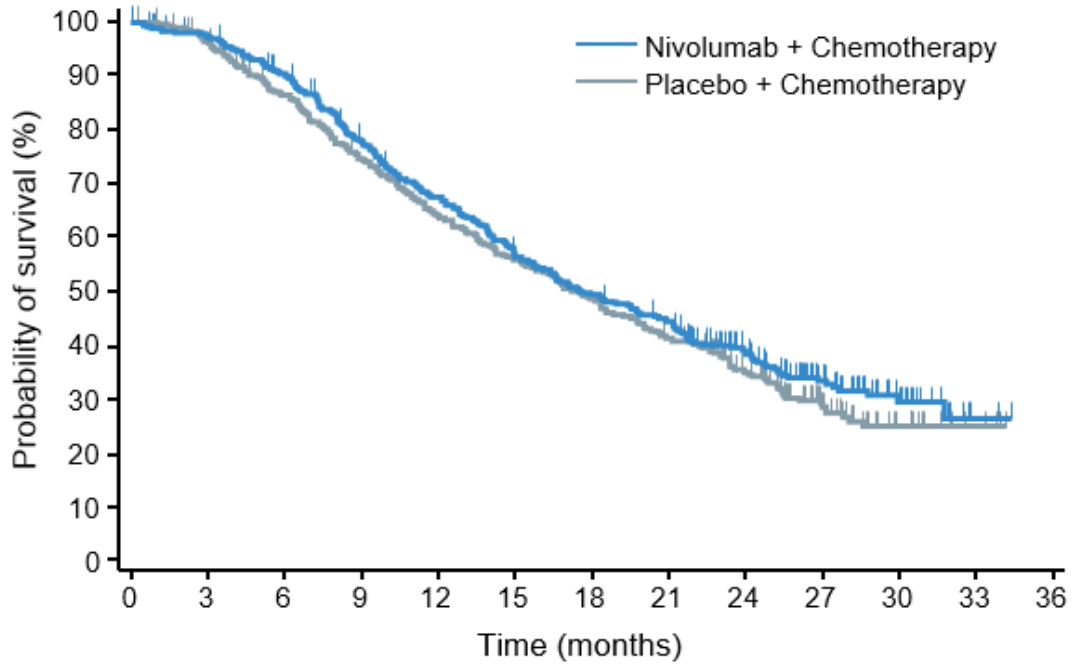


At Risk							
Nivolumab + Chemotherapy	362	274	168	94	46	13	0
Placebo + Chemotherapy	362	259	160	80	30	5	0

	Nivolumab + Chemotherapy N = 362	Placebo + Chemotherapy N = 362
Median PFS, months (95% CI)	10.45 (8.44-14.75)	8.34 (6.97-9.40)
Hazard ratio (98.51% CI)	0.68 (0.51-0.90)	
P value	0.0007	
1yr PFS rate (%)	45.4	30.6

Data cut off : 31 Oct 2018 at interim analysis

Overall Survival (Final Analysis)



At Risk													
Nivolumab + Chemotherapy	362	346	318	269	232	193	169	150	102	58	23	2	0
Placebo + Chemotherapy	362	342	301	259	219	192	167	141	97	48	16	5	0

	Nivolumab + Chemotherapy N = 362	Placebo + Chemotherapy N = 362
Median OS, months (95% CI)	17.45 (15.67-20.83)	17.15 (15.18-19.65)
Hazard ratio (95% CI)	0.90 (0.75-1.08)	
P value	0.257	

Data cut off : 31 Jan 2020 at final analysis

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Summary and Conclusion

- NIVO + Chemo demonstrated a statistically significant improvement in PFS, but not in OS
  - Higher overall response rates and more durable responses
- The pre-specified objective of the phase 3 part of ATTRACTION-4 was achieved, showing clinically meaningful efficacy
- NIVO + Chemo demonstrated a manageable safety profile
- NIVO + Chemo could be considered a new first-line treatment option in unresectable advanced or recurrent G/GEJ cancer

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Why OS difference between these two **nivolumab** gastric studies?

Possible explanation…

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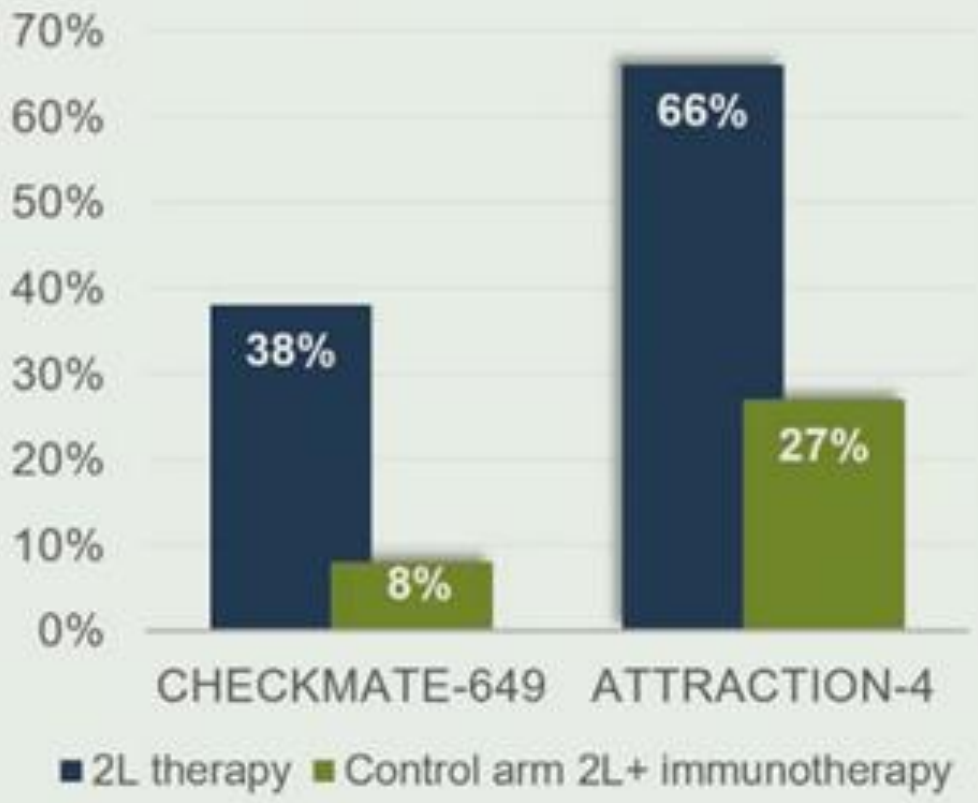
CheckMate 649 and ATTRACTION-4

Post-trial therapy and overall survival



Increased use of 2L treatment and 2L+ immune checkpoint inhibitors in ATTRACTION-4 may act as a confounder for overall survival.

In CheckMate 649 Asian cohort (n=228), median OS was 16.1 vs 11.5m (HR 0.64) in favour of nivolumab.

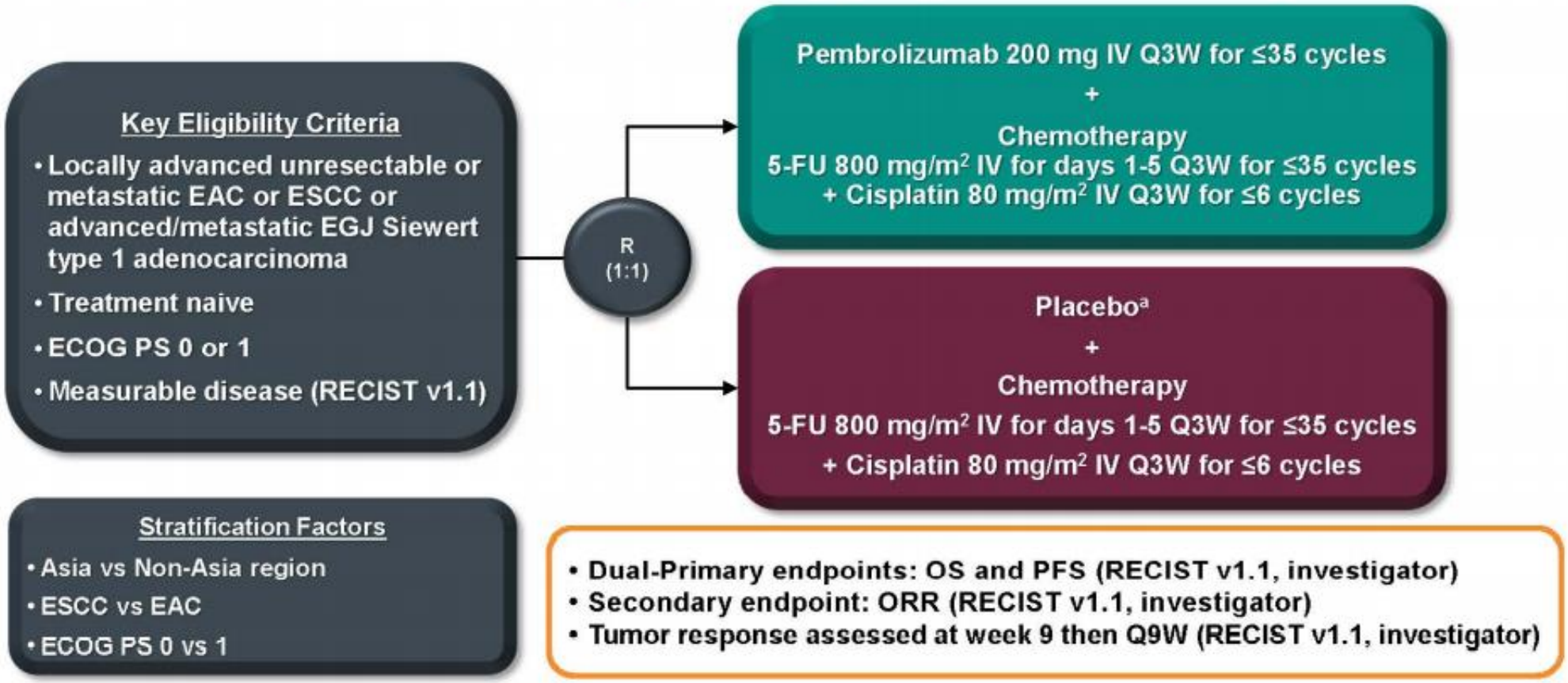
Sensitivity analysis of ATTRACTION-4 considering 2L+ immunotherapy use may be useful.

Pembrolizumab Plus Chemotherapy Versus Chemotherapy as First-Line Therapy in Patients With Advanced Esophageal Cancer: The Phase 3 KEYNOTE-590 Study

Ken Kato,[1] Jong-Mu Sun,[2] Manish A. Shah,[3] Peter Enzinger,[4] Antoine Adenis,[5] Toshihiko Doi,[6] Takashi Kojima,[6] Jean-Philippe Metges,[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] Eray Goekkurt,[15] Qi Liu,[16] Sukrut Shah,[16] Pooja Bhagia,[16] Lin Shen[17]

[1]National Cancer Center Hospital, Tokyo, Japan; [2]Samsung Medical Center, Sungkyunkwan University Seoul, Republic of Korea, [3]Weill Cornell Medical College, New York, NY, USA; [4]Dana Farber Cancer Institute, Boston, MA, USA; [5]IRCM, Inserm, Université Montpellier, ICM, Montpellier, France; [6]National Cancer Center Hospital East, Kashiwa, Japan; [7]CHU Brest – Institut de Cancerologie et d'Hematologie ARPEGO Network, Brest, France; [8]Shanghai Chest Hospital Esophageal Disease Center, Shanghai, China; [9]Asan Medical Center, 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]Hematology Oncology Practice Eppendorf, and University Cancer Center Hamburg, Hamburg, Germany; [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; EGJ, esophagogastric junction, ESCC, esophageal squamous cell carcinoma.

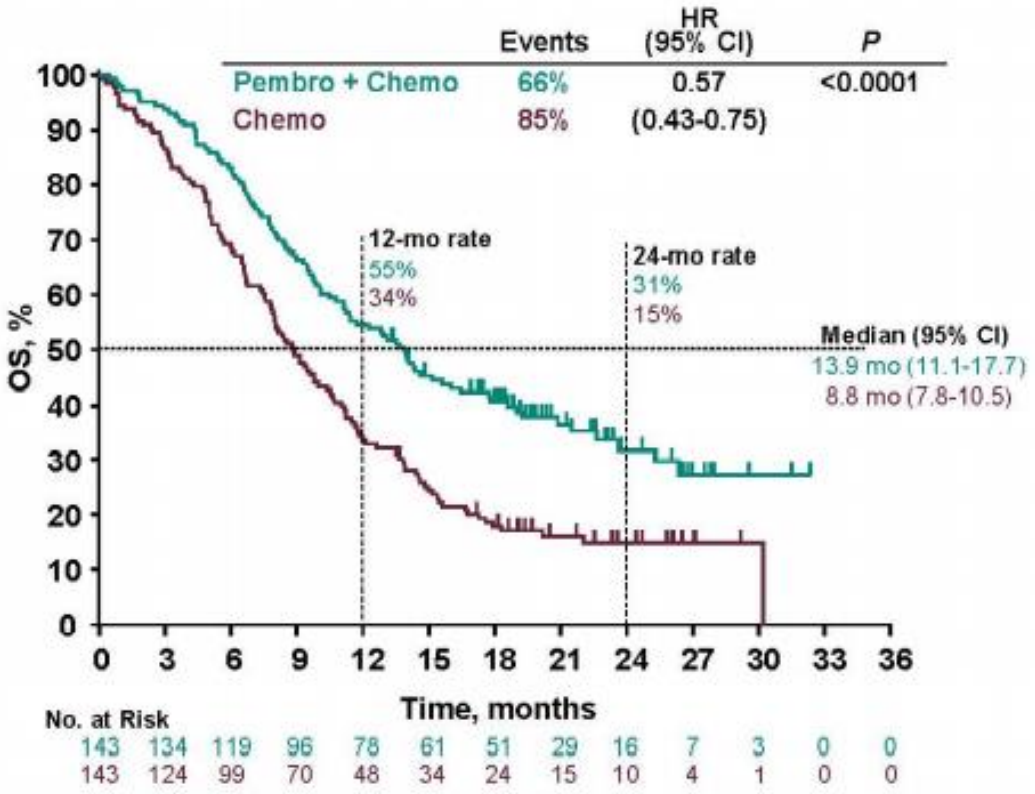
Baseline Characteristics (ITT)

Characteristic, n (%)	Pembro + Chemo N = 373	Chemo N = 376
Median age, years (range)	64.0 (28-94)	62.0 (27-89)
≥65 years	172 (46)	150 (40)
Male	306 (82.0)	319 (84.8)
Asia Region	196 (52.5)	197 (52.4)
ECOG PS 1	223 (59.8)	225 (59.8)
Metastatic disease	344 (92.2)	339 (90.2)
Unresectable/locally-advanced	29 (7.8)	37 (9.8)
Squamous-cell carcinoma	274 (73.5)	274 (72.9)
Adenocarcinoma	99 (26.5)	102 (27.1)
Esophageal	58 (15.5)	52 (13.8)
EGJ	41 (11.0)	50 (13.3)
PD-L1 CPS ≥10[a]	186 (49.9)	197 (52.4)

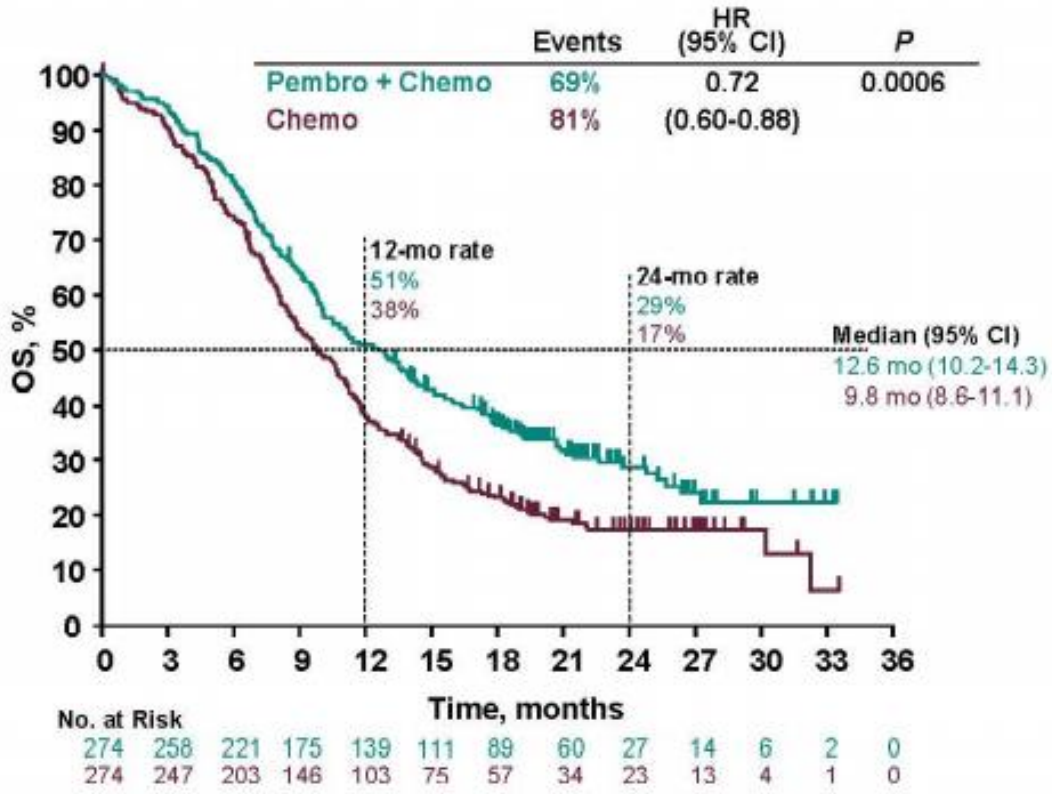
[a]PD-L1 status was not evaluable or missing in 12 patients in the pembro + chemo group and 7 patients in the chemo group.
Data cut-off: July 2, 2020.

Overall Survival

ESCC PD-L1 CPS ≥10



ESCC



Data cut-off: July 2, 2020.

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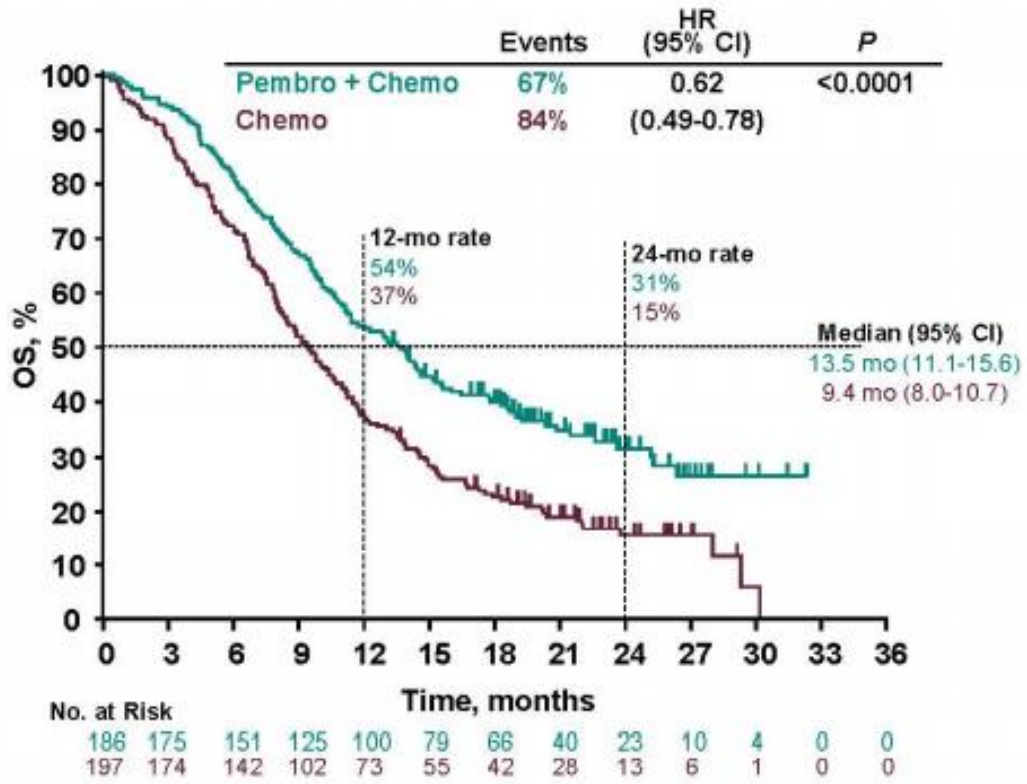
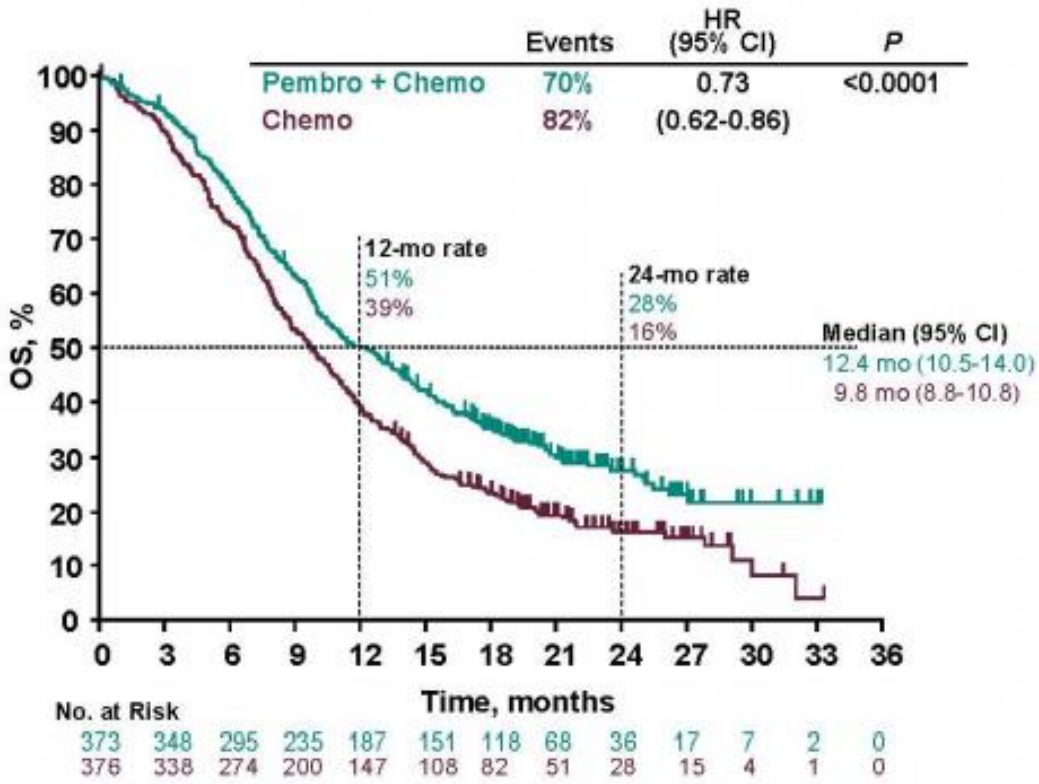
Overall Survival

PD-L1 CPS ≥10



All Patients



Data cut-off: July 2, 2020.

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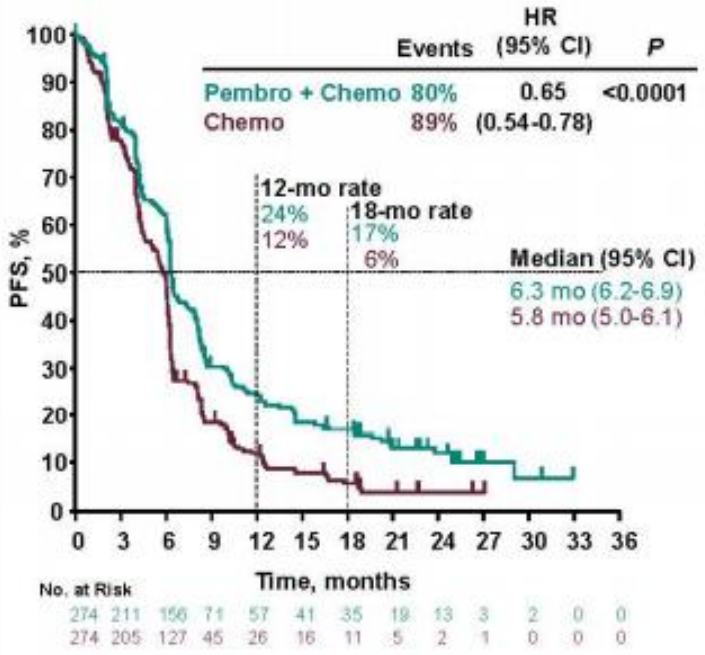
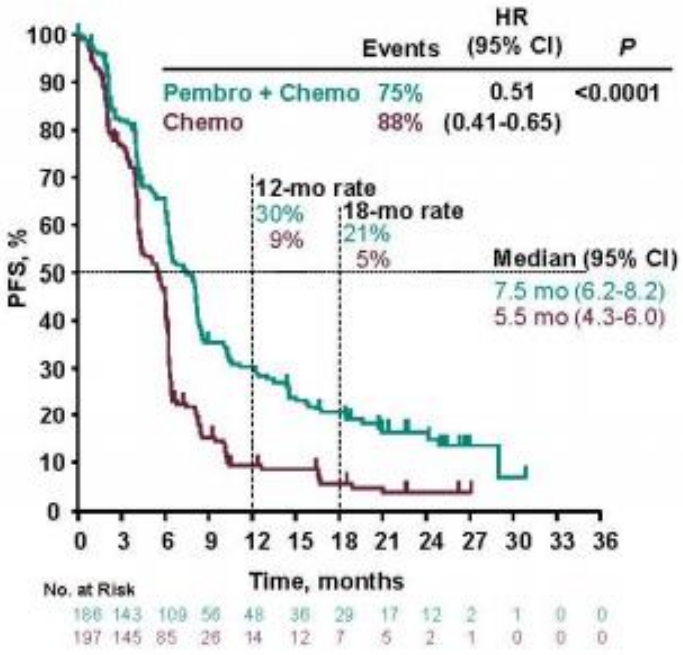
Progression-Free Survival
(RECIST v1.1, investigator)

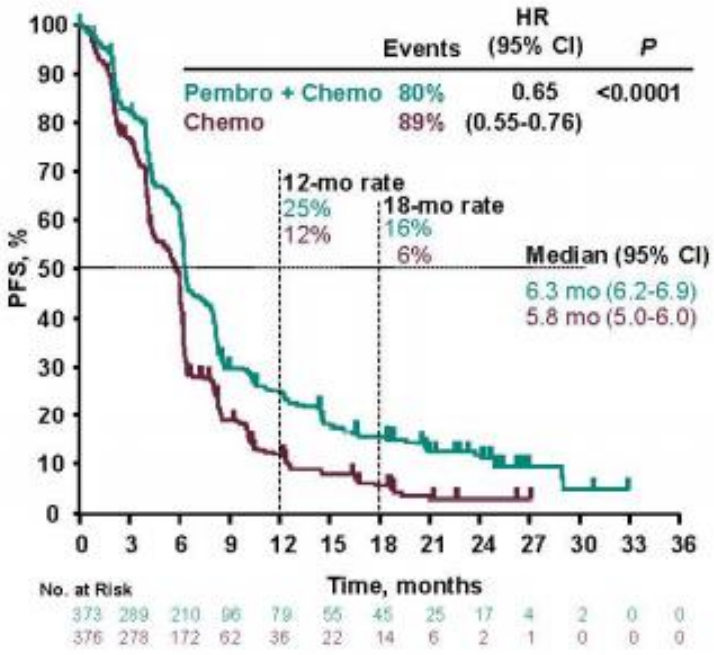
ESCC



PD-L1 CPS ≥10



All Patients



Data cut-off: July 2, 2020.

Summary and Conclusions

- First-line pembrolizumab plus chemotherapy vs chemotherapy plus placebo provided a statistically significant and clinically meaningful improvement in OS, PFS, and ORR in patients with locally advanced and metastatic esophageal cancer including EGJ adenocarcinoma
  - Superior OS: ESCC CPS ≥10 (HR 0.57, *P*<0.001), ESCC (HR 0.72, *P*=0.006), CPS ≥10 (HR 0.62, *P*<0.001), all patients (HR 0.73, *P*<0.001)
  - Superior PFS: ESCC (HR 0.65), CPS ≥10 (HR 0.51), all patients (HR 0.65), all *P*<0.001
  - Superior ORR: all patients (45.0% vs 29.3%, Δ15.8%, *P*<0.001)
- Comparable safety profile between the two treatment groups
  - No new safety signals detected
- Pembrolizumab plus chemotherapy should be a new standard-of-care as first-line therapy in patients with locally advanced and metastatic esophageal cancer including EGJ adenocarcinoma

Adjuvant therapy esophageal cancer: the same way like we do in melanoma?

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Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer following neoadjuvant chemoradiation therapy: first results of the CheckMate 577 study

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CheckMate 577 study design

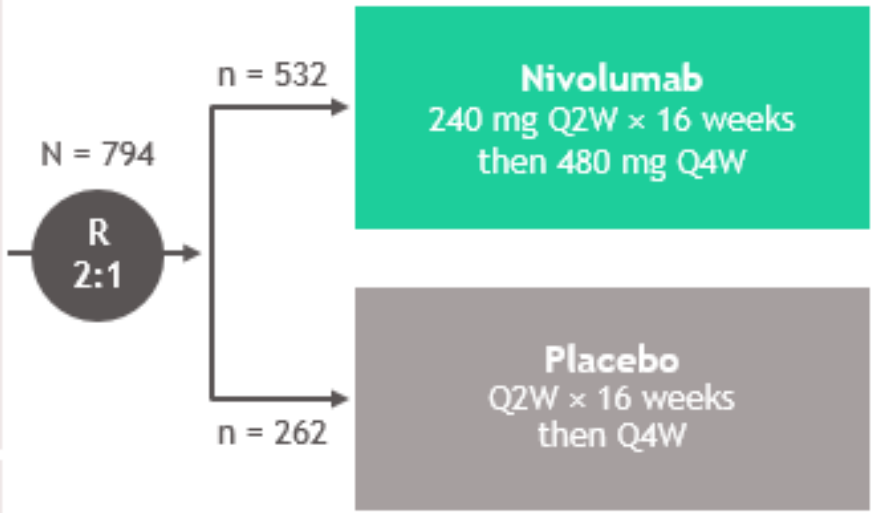
- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria

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

Stratification factors

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



Total treatment duration of up to 1 year[d]

Primary endpoint:

- DFS[e]

Secondary endpoints:

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

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

[a]ClinicalTrials.gov number, 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 pre-specified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]Time from randomization date to clinical data cutoff (May 12, 2020).

Baseline characteristics

	Nivolumab (n = 532)	Placebo (n = 262)
Median age (range), years	62.0 (26-82)	61.0 (26-86)
Male, %	84	85
Race,[a] %		
White	81	82
Asian	16	13
ECOG PS, %		
0	58	60
1	42	40
Disease stage at initial diagnosis, %		
II	34	38
III	66	62
Tumor location, %		
EC	60	59
GEJC	40	41
Histology, %		
Squamous cell carcinoma	29	29
Adenocarcinoma	71	71
Pathologic lymph node status ≥ ypN1, %	57	58
Tumor cell PD-L1 expression,[b] %		
≥ 1%	17	15
< 1%	70	75
Indeterminate/nonevaluable	13	10

[a]Other races not shown; [b]Tumor cell PD-L1 expression determined from surgical specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako).

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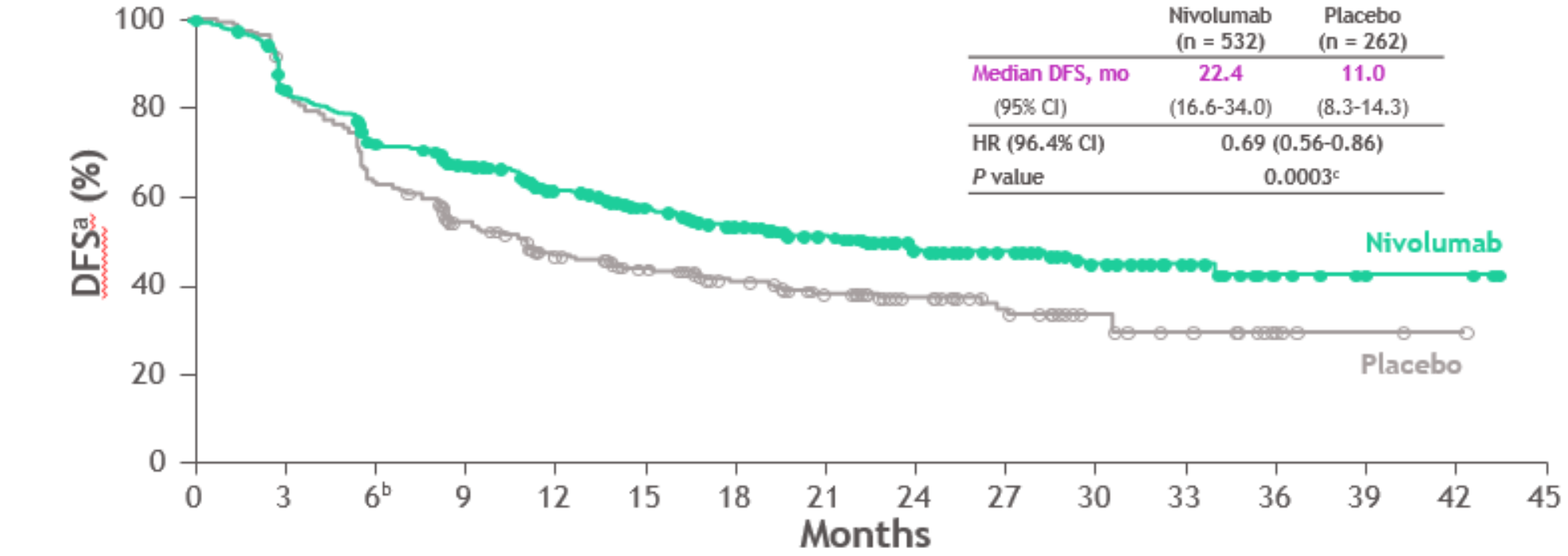
Disease-free survival



	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]	

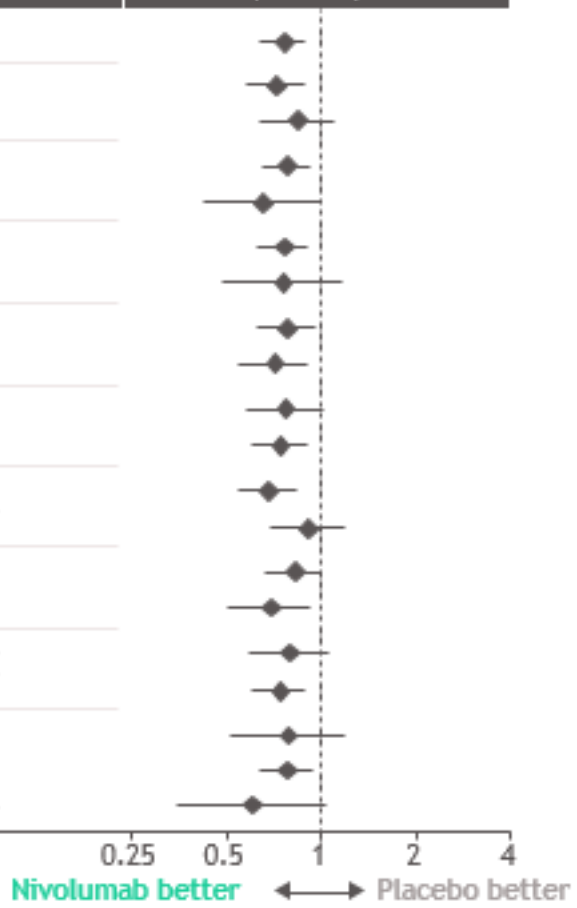
No. at risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

- 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 pre-specified interim analysis required the *P* value to be less than 0.036.

Disease-free survival by subgroups

Subgroup		Median DFS, months		Unstratified HR	Unstratified HR (95% CI)
		Nivolumab	Placebo		
Overall (N = 794)		22.4	11.0	0.70	
Age, years	< 65 (n = 507)	24.4	10.8	0.65	
	≥ 65 (n = 287)	17.0	13.9	0.80	
Sex	Male (n = 671)	21.4	11.1	0.73	
	Female (n = 123)	Not reached	11.0	0.59	
Race	White (n = 648)	21.3	10.9	0.71	
	Asian (n = 117)	24.0	10.2	0.70	
ECOG PS	0 (n = 464)	29.4	11.1	0.73	
	1 (n = 330)	17.0	10.9	0.66	
Disease stage at initial diagnosis	II (n = 278)	34.0	13.9	0.72	
	III (n = 514)	19.4	8.5	0.68	
Tumor location	EC (n = 462)	24.0	8.3	0.61	
	GEJC (n = 332)	22.4	20.6	0.87	
Histology	Adenocarcinoma (n = 563)	19.4	11.1	0.75	
	Squamous cell carcinoma (n = 230)	29.7	11.0	0.61	
Pathologic lymph node status	ypN0 (n = 336)	Not reached	27.0	0.74	
	≥ ypN1 (n = 457)	14.8	7.6	0.67	
Tumor cell PD-L1 expression	≥ 1% (n = 129)	19.7	14.1	0.75	
	< 1% (n = 570)	21.3	11.1	0.73	
	Indeterminate/nonevaluable (n = 95)	Not reached	9.5	0.54	



- DFS favored nivolumab versus placebo across these pre-specified subgroups

Summary

- Nivolumab is the first adjuvant therapy to provide a statistically significant and clinically meaningful improvement in DFS versus placebo in resected EC/GEJC following neoadjuvant CRT
  - 31% reduction in the risk of recurrence or death and a doubling in median DFS
  - DFS benefit across multiple pre-specified subgroups
- Nivolumab was well tolerated with an acceptable safety profile
  - Incidence of serious TRAEs and TRAEs leading to discontinuation were ≤ 9% with nivolumab and 3% with placebo
- These results represent the first advance in years for this group of patients, potentially establishing adjuvant nivolumab as a new standard of care

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Lenvatinib + pembrolizumab

after the endometrial cancer success story:

Lenvatinib plus pembrolizumab in patients with advanced gastric cancer in the first-line or second-line setting (EPOC1706): an open-label, single-arm, phase 2 trial

Kawazoe et al. Lancet Oncology 2020

- **Background:** pembrolizumab, an anti-PD-1 antibody, results in tumour response in around 15% of pts with advanced gastric cancer who have a PD-L1 CPS of at least 1. Lenvatinib, a multikinase inhibitor of VEGF receptors and other receptor tyrosine kinases, substantially decreased tumour-associated macrophages and increased infiltration of CD8 T-cells, resulting in enhanced anti-tumour activity of PD-1 inhibitors in an in-vivo model. We aimed to assess the combination of lenvatinib plus pembrolizumab in pts with advanced gastric cancer in a phase 2 study.
- **Methods:** this study was an open-label, single-arm, phase 2 trial undertaken at the National Cancer Center Hospital East (Chiba, Japan). Eligible pts were aged 20 years or older and had metastatic or recurrent adenocarcinoma of the stomach or gastro-oesophageal junction, an Eastern Cooperative Oncology Group performance status of 0 or 1, and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1), irrespective of the number of previous lines of treatment. Pts received 20 mg oral lenvatinib daily plus 200 mg intravenous pembrolizumab every 3 weeks until disease progression, development of intolerable toxicity, or withdrawal of consent. The **primary endpoint was objective response rate** according to RECIST, analysed in all pts who were eligible and received protocol treatment at least once. The safety analysis included all those who received protocol treatment at least once, regardless of eligibility.
- **Findings:** between Oct 15, 2018, and March 25, 2019, 29 pts were enrolled in the first-line or second-line settings. At data cutoff (March 20, 2020), the median follow-up was 12·6 months (IQR 10·5–14·3). 20 (**69%**, 95% CI 49–85) **of** 29 **pts had an objective response**. The most common grade 3 treatment-related adverse events were hypertension (in 11 [38%] pts), proteinuria (five [17%]) and platelet count decrease (two [7%]). No grade 4 treatment-related adverse events, serious treatment-related adverse events, or treatment-related deaths occurred.
- **Interpretation:** **lenvatinib plus pembrolizumab showed promising anti-tumour activity with an acceptable safety profile** in pts with advanced gastric cancer. On the basis of these results, a confirmatory trial will be planned in the future.

Efficacy outcomes

Tumor response, n (%)	All patients (n=29)	Tumor response	All patients (n=29)
Complete response	1 (3)	**ORR**, n (%, 95% CI)	20 (69, 49-85)**
Partial response	19 (66)	**Immune-related ORR**, n (%, 95% CI)	20 (69, 49-85)
Stable disease	9 (31)*	**Disease control**, n (%, 95% CI)	29 (100, 88-100)
Disease progression	0	**Median PFS**, months (95% CI)	7.1 (5.4-13.7)
		Median OS, months (95% CI)	NR (11.8-NR)

*Eight patients showed initial tumor shrinkage from baseline. **Includes one patient who was MMR-deficient. CI, confidence interval; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

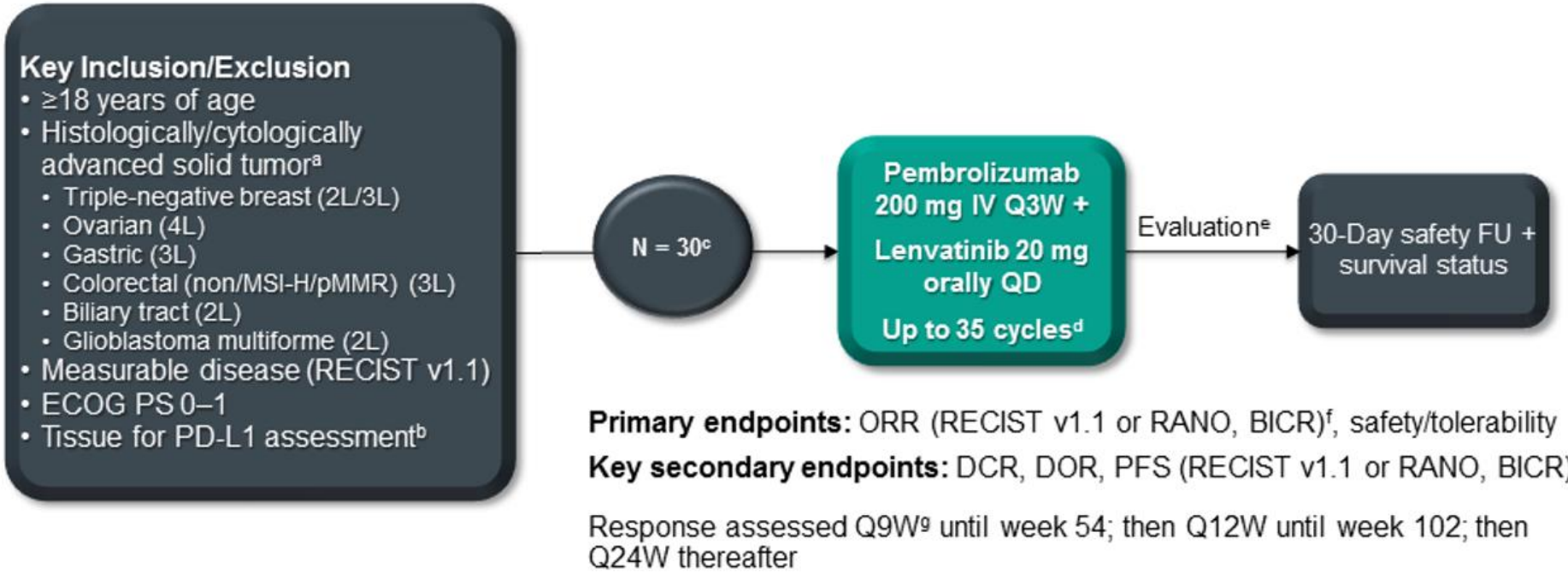
Efficacy in Selected Subgroups and Biomarker Analysis

Objective Response Rates by Patient Characteristics[2]

Patient Characteristic	n (%)	Objective response n (%)	Patient Characteristic	n (%)	Objective response n (%)
Liver metastases	13 (45)	7 (54)	**EBV positive**	1 (3)	1 (100)
Peritoneum metastases	9 (31)	4 (44)	**PD-L1 CPS ≥1**	19 (66)	16 (84)
First-line	14 (48)	10 (71)	**PD-L1 CPS <1**	10 (34)	4 (40)
Second-line	15 (52)	10 (67)	**PD-L1 CPS ≥10**	5 (17)	5 (100)
MMR-proficient	27 (93)	19 (70)	**TMB-high***	11 (52)	9 (82)
MMR-deficient	2 (7)	1 (50)	**TMB-low***	10 (48)	6 (60)

*Median (10.01) as the cut-off. CPS, combined positive score; EBV, Epstein-Barr virus; HER2, human epidermal growth factor receptor 2; MMR, mismatch repair; PD-L1, programmed death-ligand 1; TMB, tumor mutation burden.

LEAP-005 (NCT03797326)

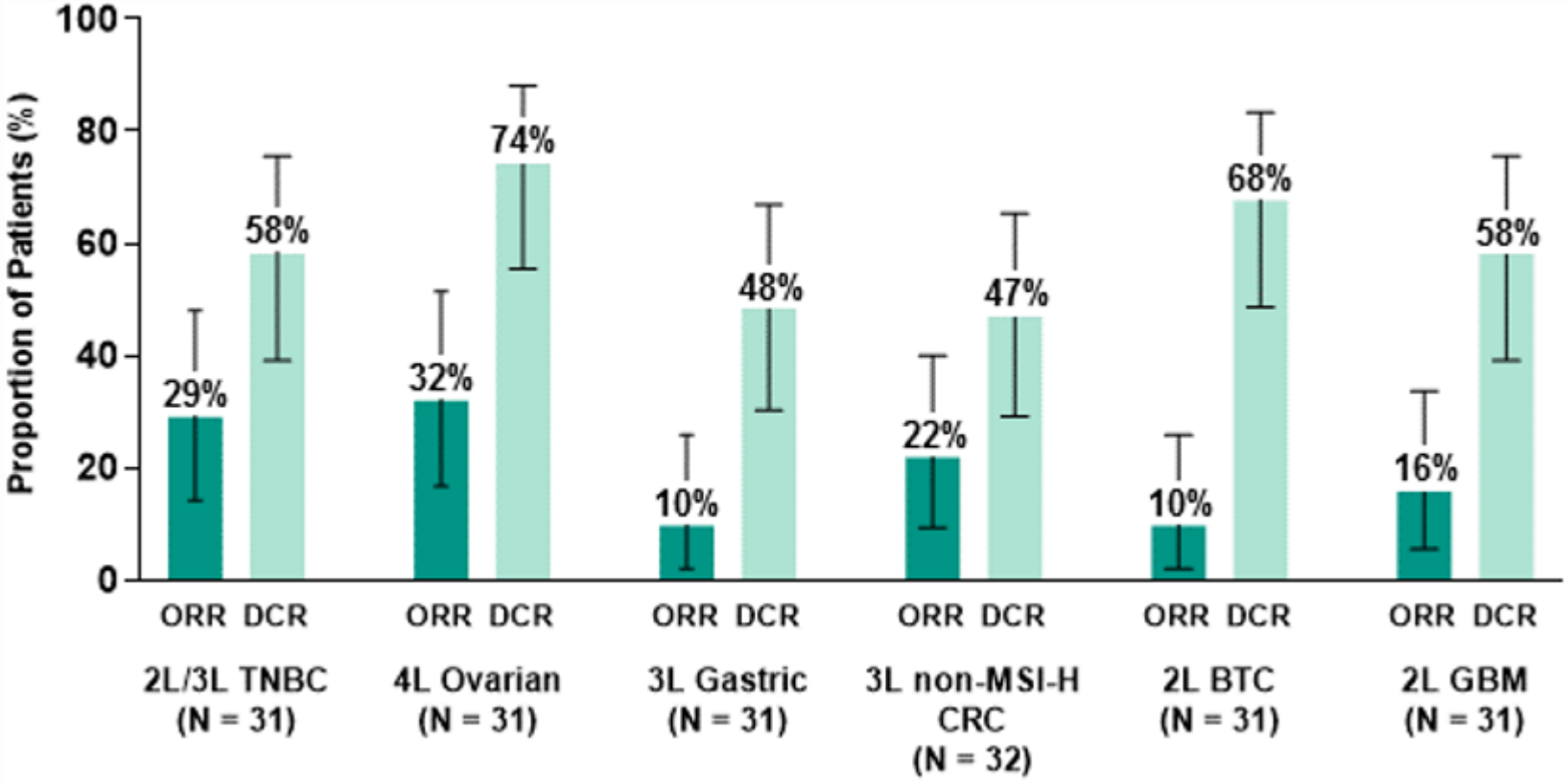


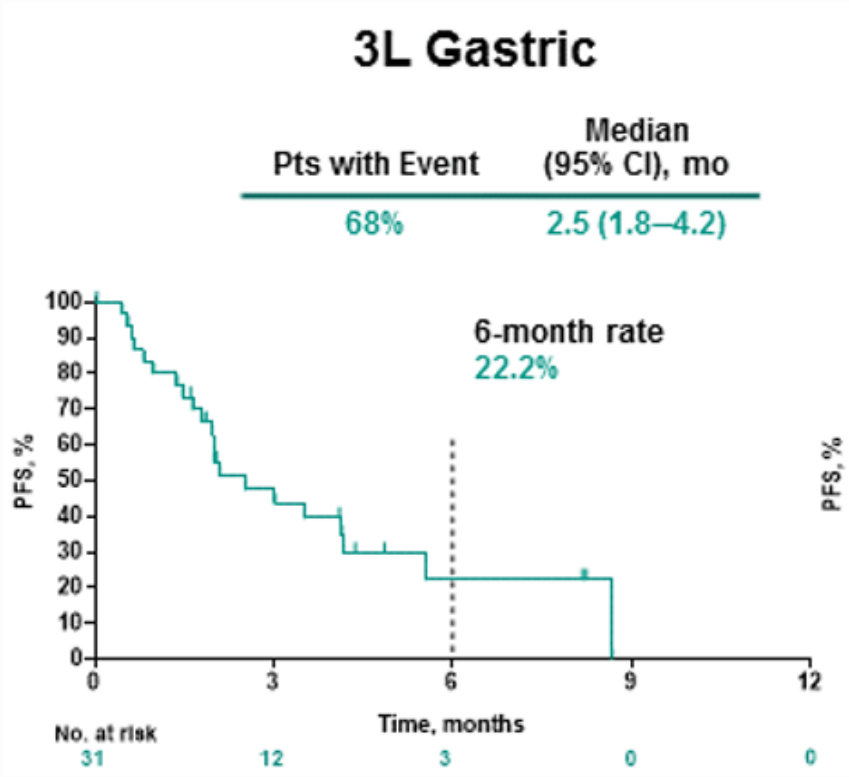
Primary endpoints: ORR (RECIST v1.1 or RANO, BICR)[f], safety/tolerability

Key secondary endpoints: DCR, DOR, PFS (RECIST v1.1 or RANO, BICR)[f]

Response assessed Q9W[g] until week 54; then Q12W until week 102; then Q24W thereafter

BICR blinded independent central review. [a]Numbers in parentheses indicate line of therapy. [b]PD-L1 status assessed centrally using PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA). [c]Initial planned enrollment per cohort. [d]With investigator and sponsor approval, patients with disease progression before completing 35 cycles could remain on treatment if they were experiencing clinical benefit without intolerable toxicity; patients experiencing clinical benefit could continue lenvatinib treatment beyond 35 cycles. [e]In interim analysis, if adequate ORR determined, cohort expansion to 100 patients. [f]Response assessed per RECIST v1.1, RANO (for glioblastoma), or iRECIST. [g]For glioblastoma cohort, response was assessed Q6W until week 18, then Q9W until week 54.





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Take from ESMO 2020 to home messages

- In metastatic gastric cancer/GEJ-tumours/esophageal adenocarcinoma: **nivolumab + chemotherapy** is on the way to the new standard therapy in 1st line, certainly when CPS-score ≥ 5...
- In metastatic esophageal cancer: **pembrolizumab + chemotherapy** is on the way to the new standard therapy in 1st line, certainly when CPS-score ≥ 10…
- Resected esophageal cancer/GEJ-tumours after chemoradiotherapy and not after FLOT chemotherapy: **adjuvant nivolumab** makes its prudent entry, is OS today important here or are we copycatting melanoma?
- **Lenvatinib+pembrolizumab** combination enters promisingly the field of metastatic gastric cancer: the earlier the better?

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