

Key Findings Informing the Treatment of Localized and Advanced Esophageal Cancer

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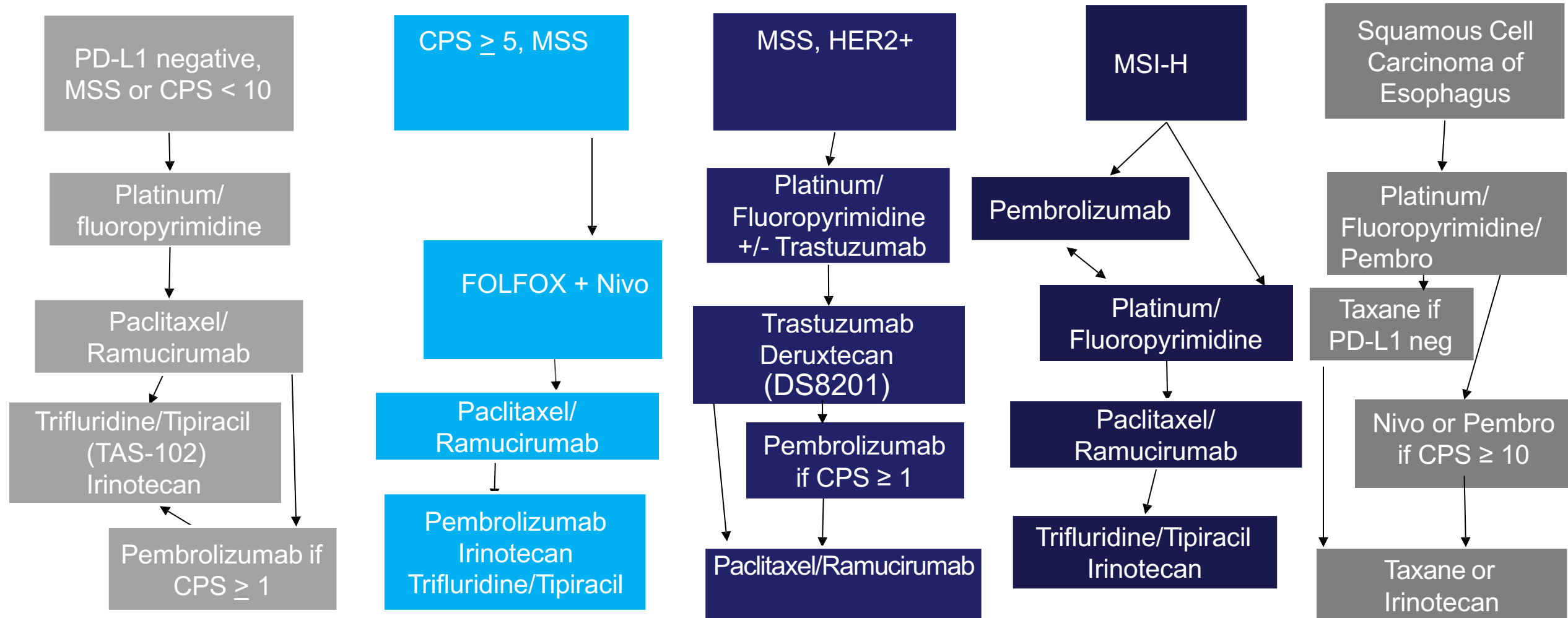
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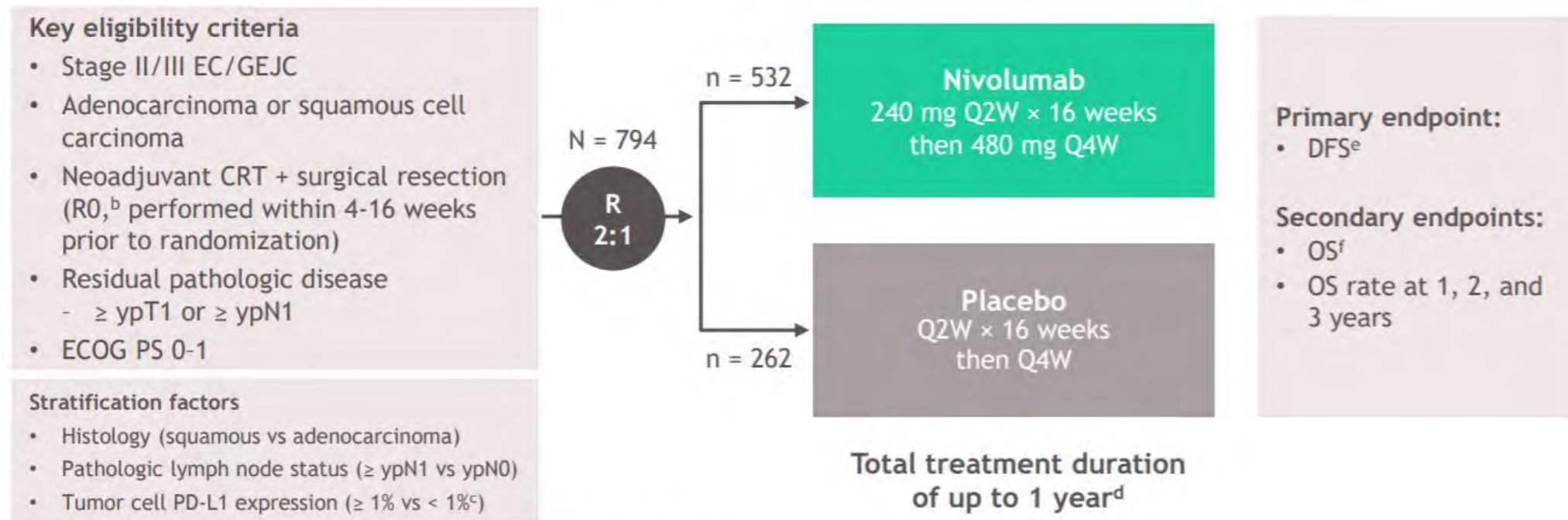
How to Treat Gastroesophageal Cancer in 2020?

Metastatic Gastroesophageal Cancer



CheckMate 577 study design

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



- 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%)

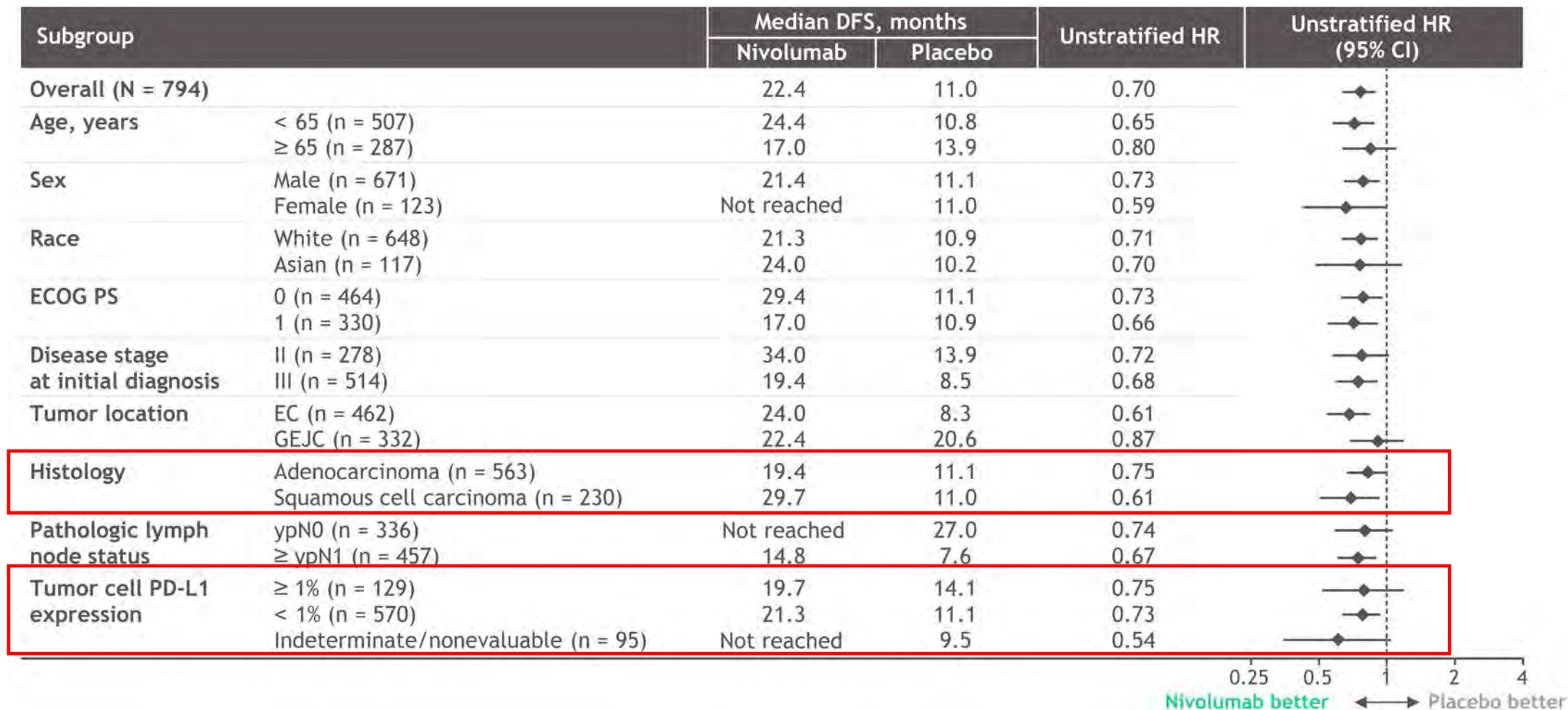
^aClinicalTrials.gov number, NCT02743494; ^bPatients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; ^c< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; ^dUntil disease recurrence, unacceptable toxicity, or withdrawal of consent; ^eAssessed 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; ^fThe study will continue as planned to allow for future analysis of OS; ^gTime from randomization date to clinical data cutoff (May 12, 2020).

CheckMate 577 – 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 \geq ypN1, %	57	58
Tumor cell PD-L1 expression, ^b %		
\geq 1%	17	15
< 1%	70	75
Indeterminate/nonevaluable	13	10

^aOther races not shown; ^bTumor cell PD-L1 expression determined from surgical specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako).

CheckMate 577 – Subgroup Analyses

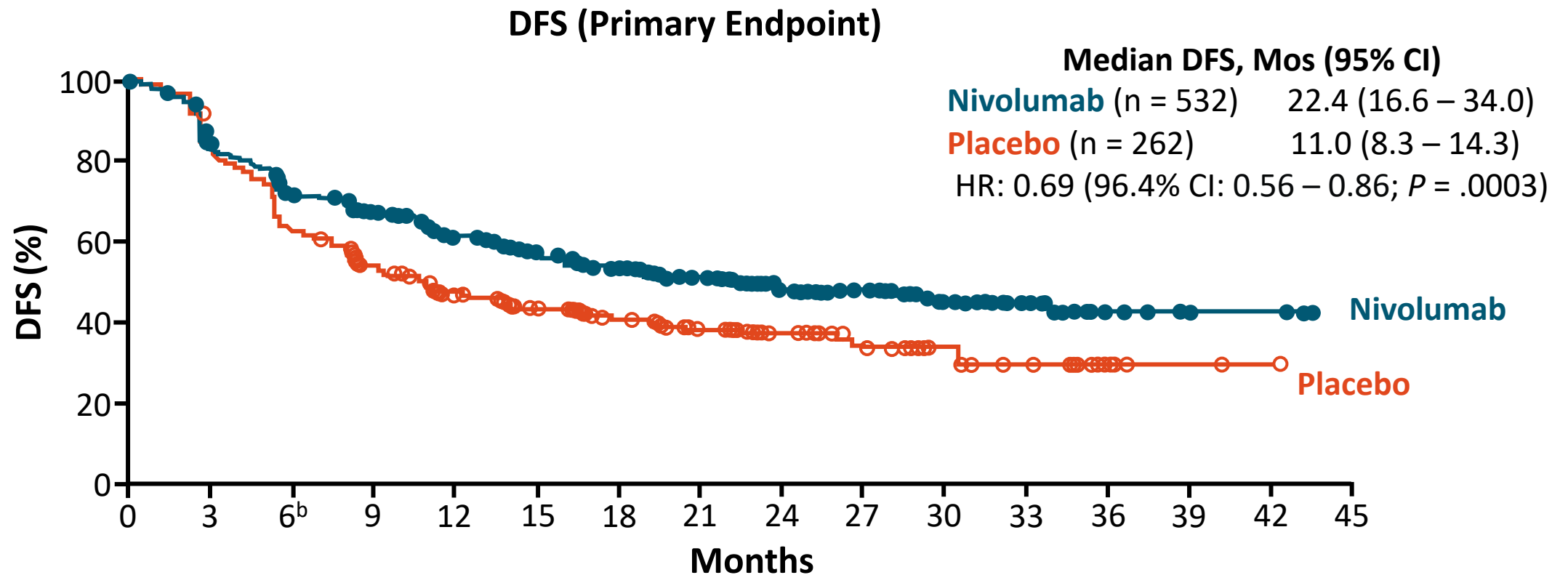


CheckMate 577 – Toxicities

Patients, n (%)	Nivolumab ^a n = 532		Placebo ^a n = 260	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AEs ^b	510 (96)	183 (34)	243 (93)	84 (32)
Serious AEs	158 (30)	107 (20)	78 (30)	53 (20)
AEs leading to discontinuation	68 (13)	38 (7)	20 (8)	16 (6)
Any TRAEs ^{b,c}	376 (71)	71 (13)	119 (46)	15 (6)
Serious TRAEs ^c	40 (8)	29 (5)	7 (3)	3 (1)
TRAEs leading to discontinuation ^c	48 (9)	26 (5)	8 (3)	7 (3)
TRAEs in ≥10% of treated patients in either arm ^b				
Fatigue	90 (17)	6 (1)	29 (11)	1 (< 1)
Diarrhea	88 (17)	2 (< 1)	39 (15)	2 (< 1)
Pruritus	53 (10)	2 (< 1)	9 (3)	0
Rash	52 (10)	4 (< 1)	10 (4)	1 (< 1)
Endocrine	93 (17)	5 (< 1)	6 (2)	0
Gastrointestinal	91 (17)	4 (< 1)	40 (15)	3 (1)
Hepatic	49 (9)	6 (1)	18 (7)	4 (2)
Pulmonary	23 (4)	6 (1)	4 (2)	1 (< 1)
Renal	7 (1)	1 (< 1)	2 (< 1)	0
Skin	130 (24)	7 (1)	28 (11)	1 (< 1)

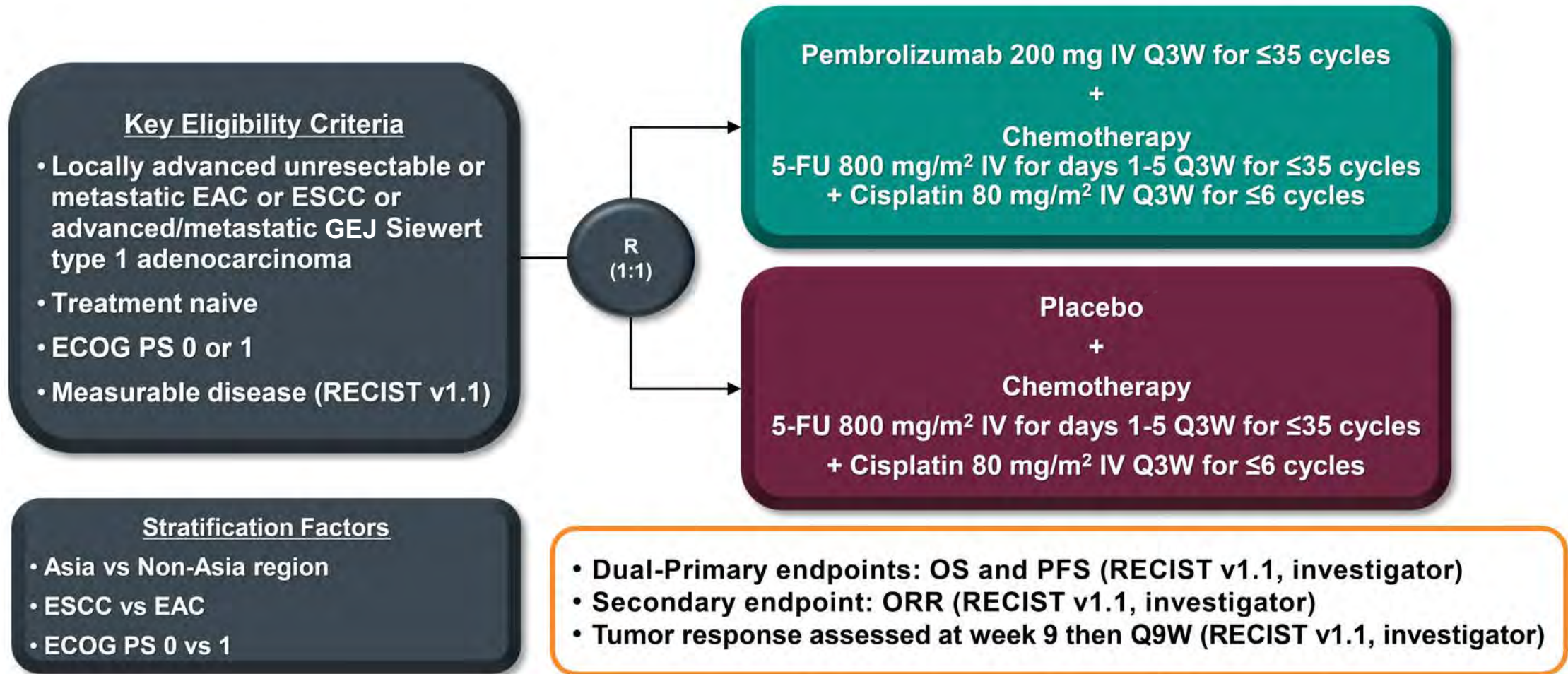
CheckMate 577: Adjuvant Nivolumab Following Neoadjuvant CRT/Resection in Esophageal/GEJ Cancer

- Randomized phase III trial of **adjuvant nivolumab** vs **placebo** following neoadjuvant CRT + surgical resection* for pts with stage II/III **esophageal/GEJ adenocarcinoma/SCC** (N = 794)



*Residual pathologic disease \geq ypT1 or \geq ypN1.

First-Line Metastatic Esophageal Cancer – KEYNOTE-590



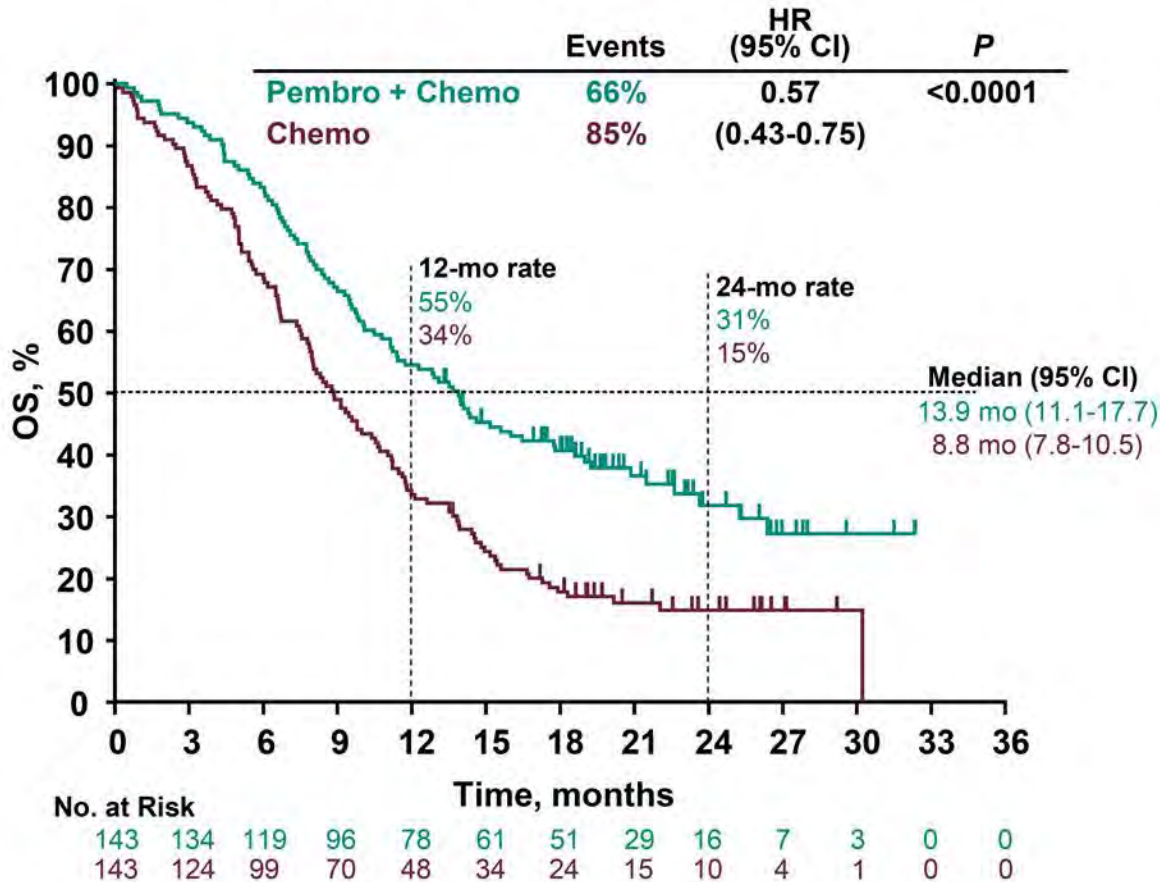
KEYNOTE-590 – Baseline Characteristics

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)
GEJ	41 (11.0)	50 (13.3)
PD-L1 CPS ≥10 ^a	186 (49.9)	197 (52.4)

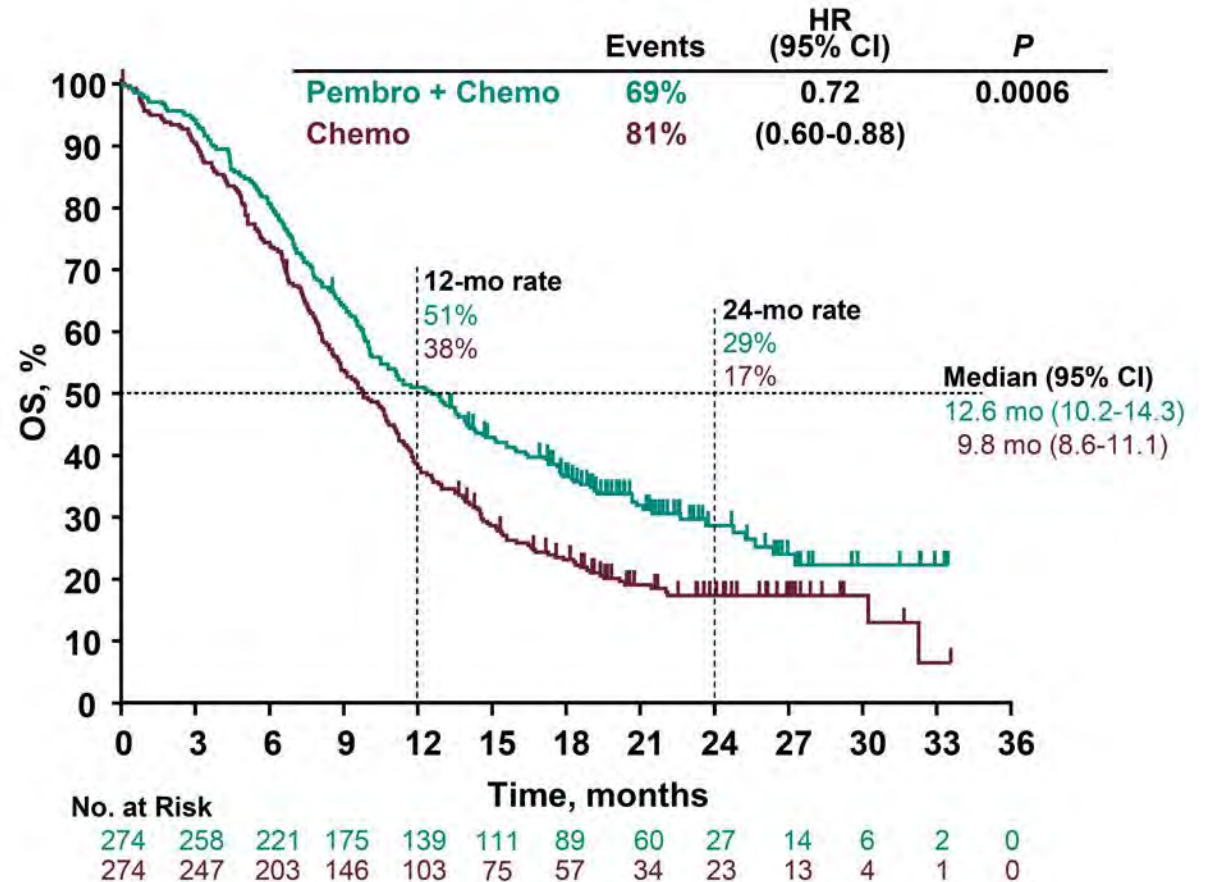
^aPD-L1 status was not evaluable or missing in 12 patients in the pembro + chemo group and 7 patients in the chemo group.
Data cut-off: July 2, 2020.

KEYNOTE-590 – Overall Survival in SCC Patients

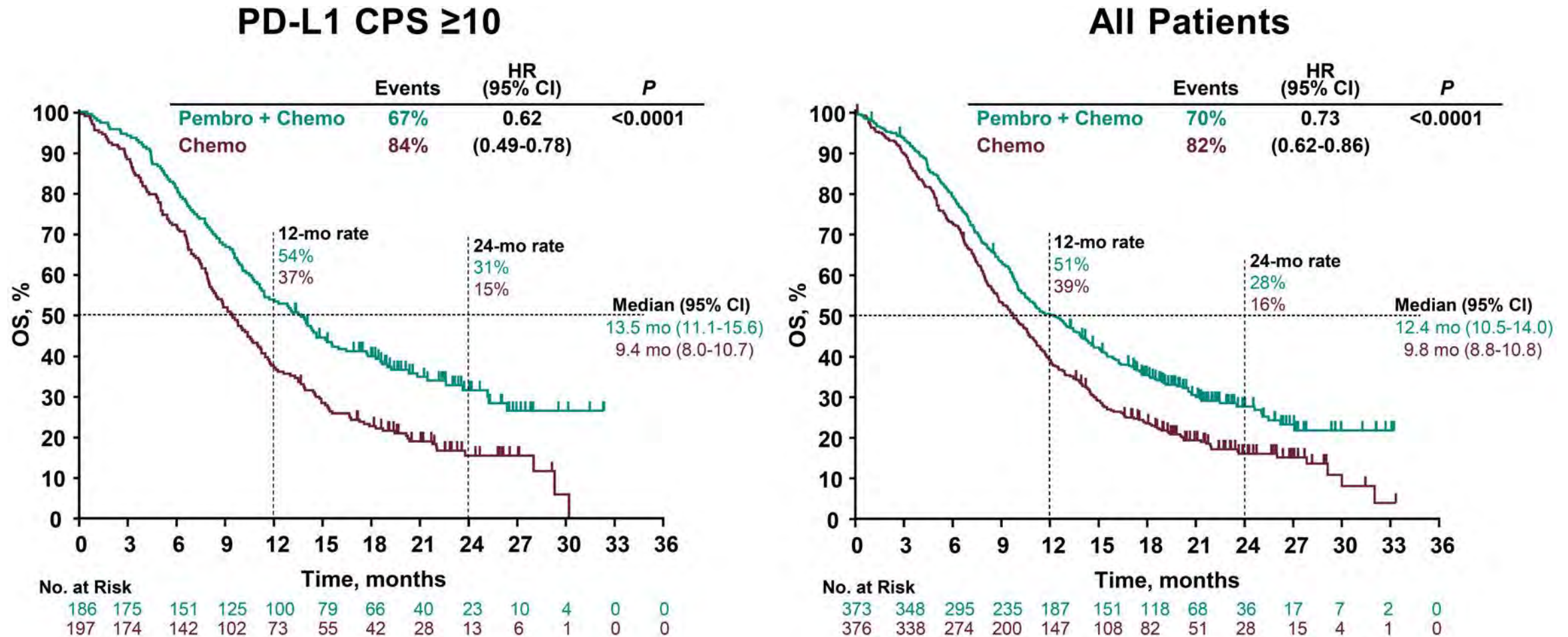
ESCC PD-L1 CPS ≥10



ESCC



KEYNOTE-590 – Overall Survival in All Patients

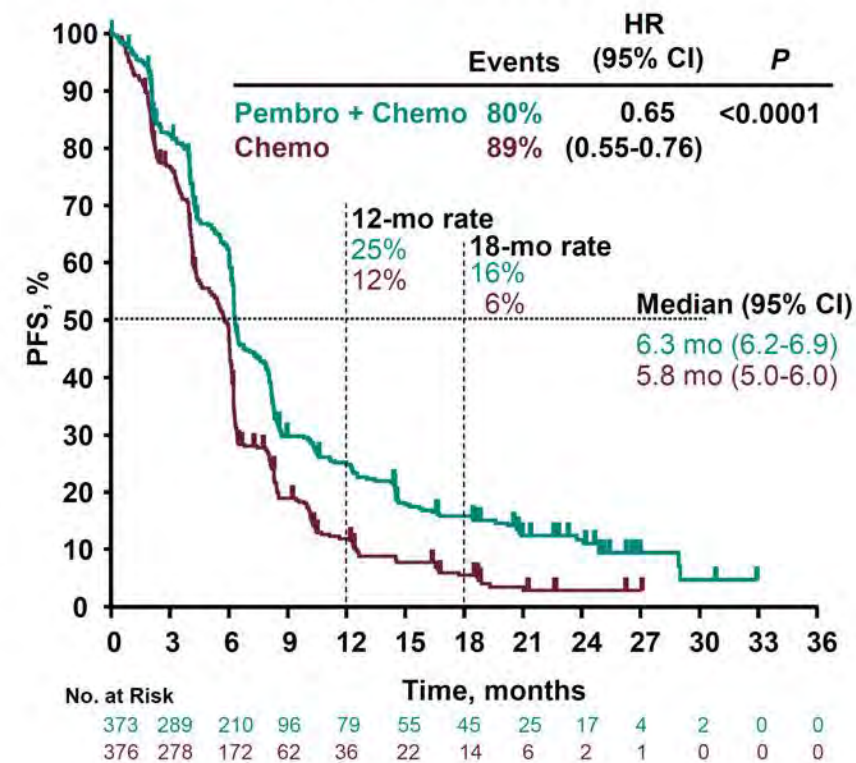
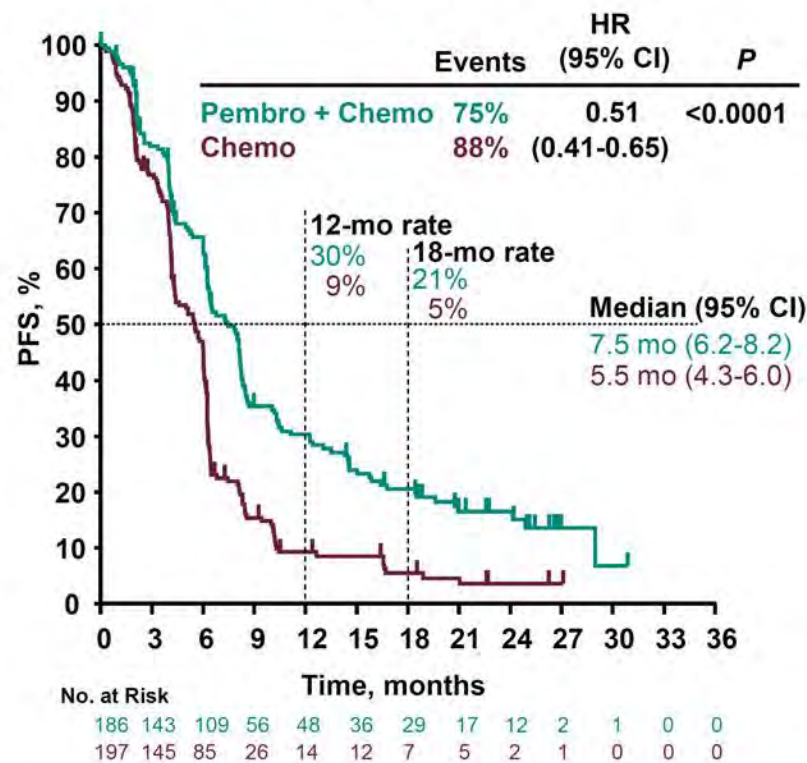
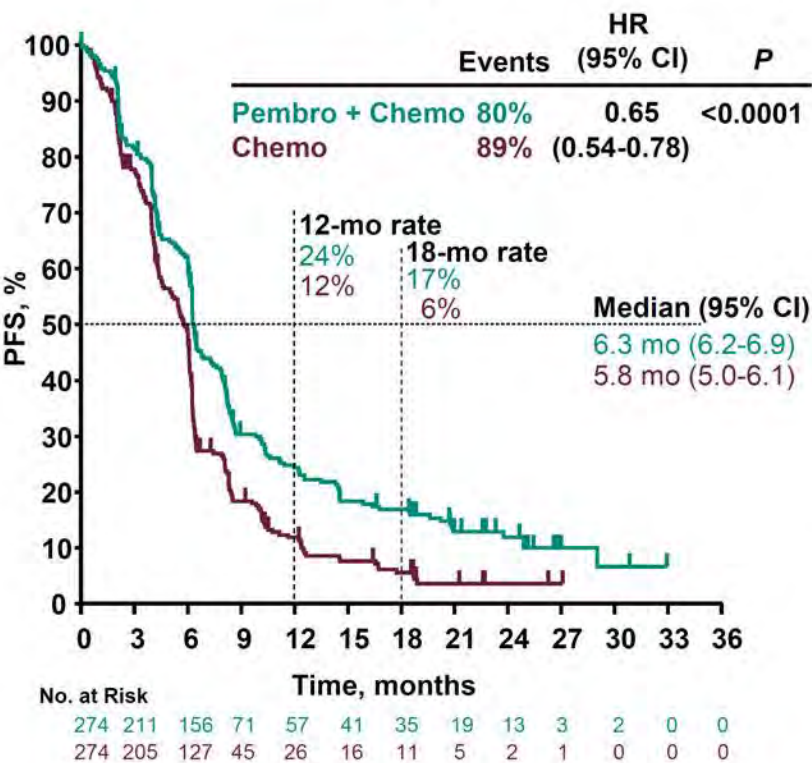


KEYNOTE-590 – Progression-Free Survival

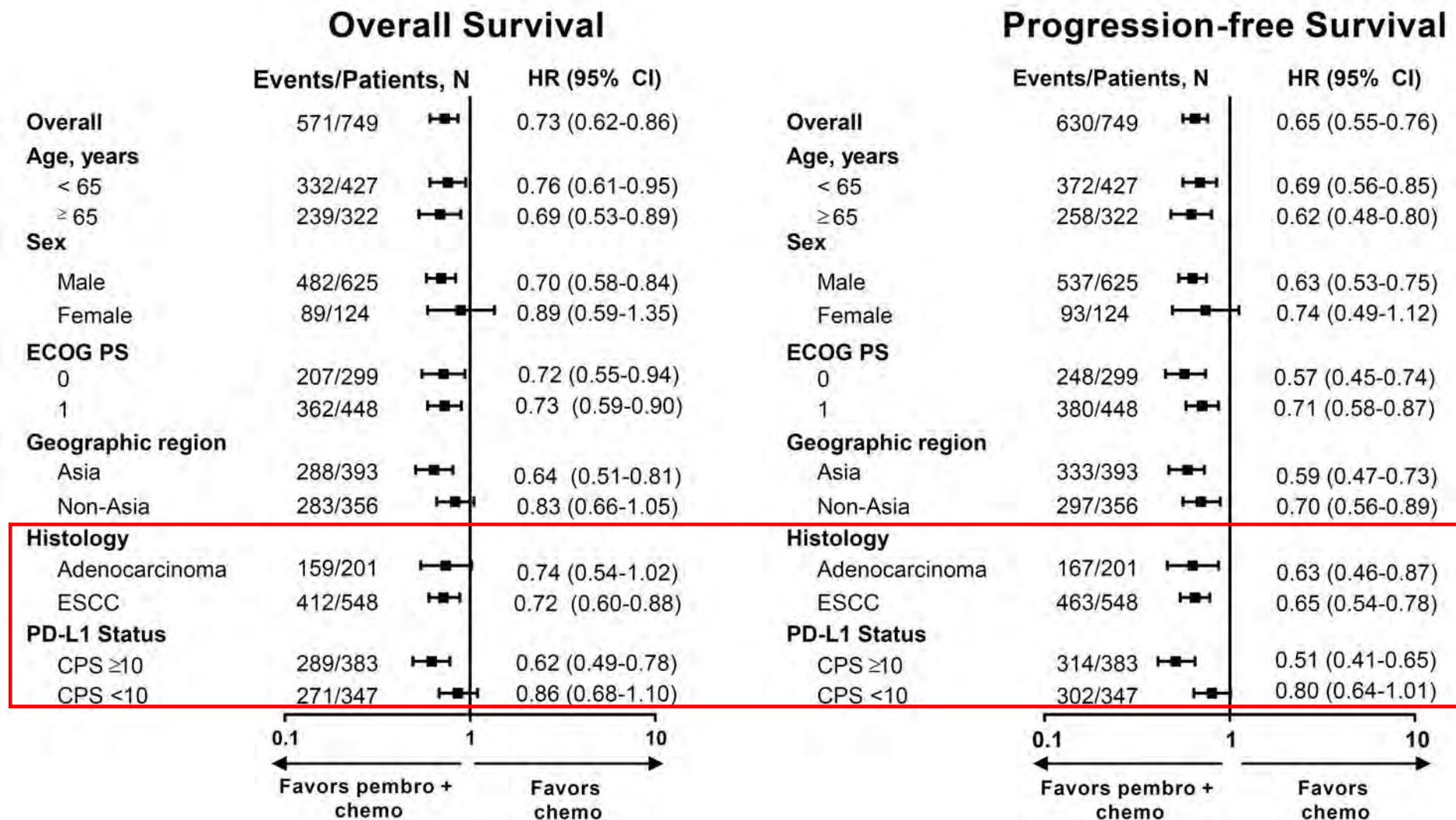
ESCC

PD-L1 CPS ≥10

All Patients

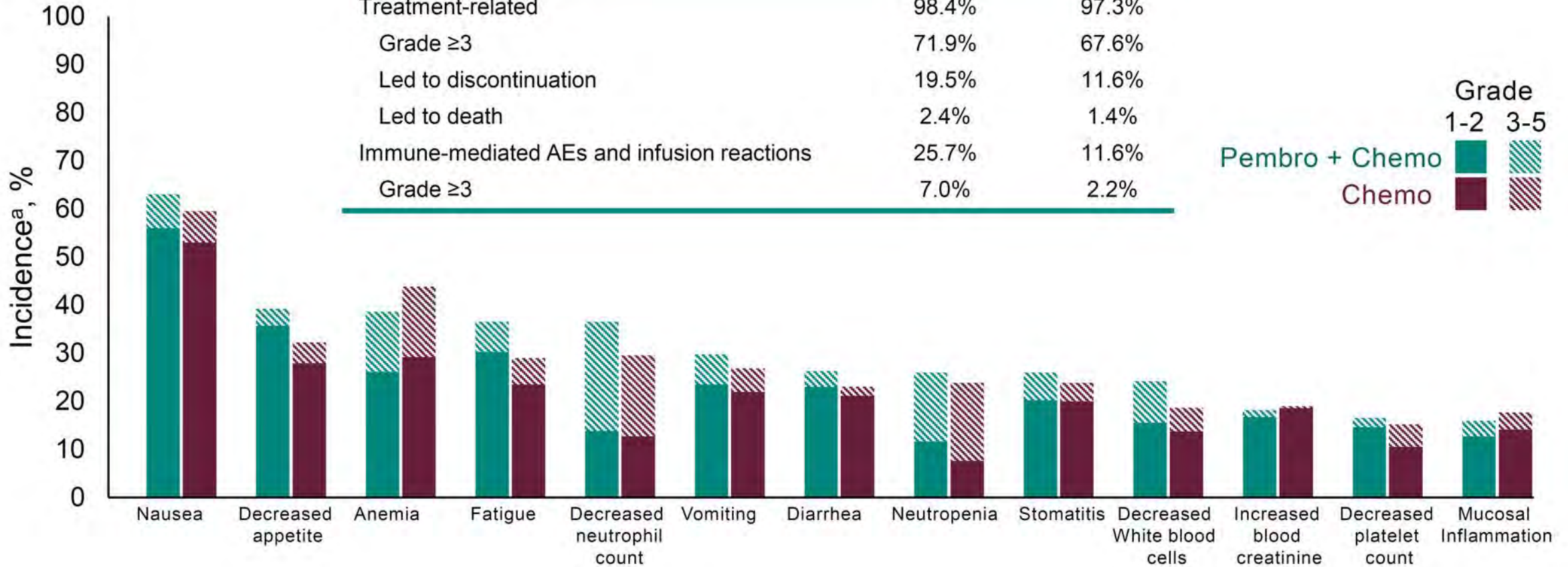


KEYNOTE-590 – Subgroup Analyses



KEYNOTE-590 – Adverse Events

AEs	Pembro + Chemo N = 370	Chemo N = 370
Any	100%	99.5%
Treatment-related	98.4%	97.3%
Grade ≥3	71.9%	67.6%
Led to discontinuation	19.5%	11.6%
Led to death	2.4%	1.4%
Immune-mediated AEs and infusion reactions	25.7%	11.6%
Grade ≥3	7.0%	2.2%



Phase 3 KEYNOTE-181 Study (NCT02564263)

Key Eligibility Criteria

- Advanced/metastatic adenocarcinoma or squamous-cell carcinoma of the esophagus or Siewert type 1 adenocarcinoma of the GEJ
- Measurable disease per RECIST v1.1
- Progression on or after first-line therapy
- ECOG PS 0-1

R (1:1)
N = 628

N = 314

Pembrolizumab
200 mg IV Q3W for up to 35 cycles

N = 314

Investigator's choice of 1 of the following:

- Paclitaxel 80-100 mg/m² on days 1, 8, 15 Q4W
- Docetaxel 75 mg/m² Q3W
- Irinotecan 180 mg/m² Q2W

Stratification by

- Histology: squamous-cell carcinoma /adenocarcinoma
- Region: Asia/Rest-of-world

Primary end points

OS in patients

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

Secondary end points

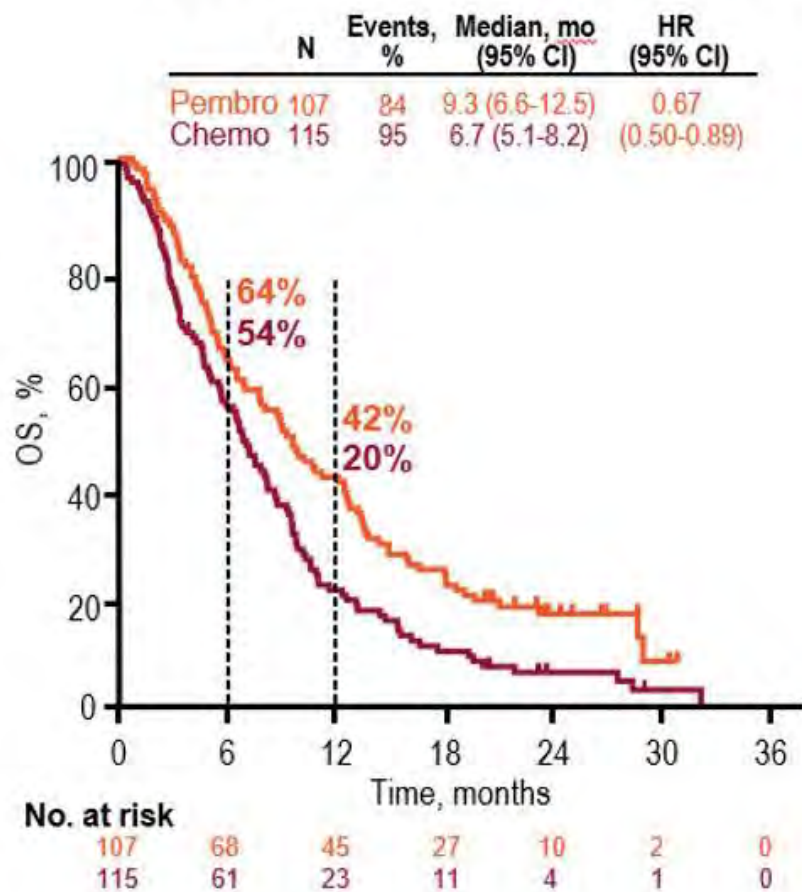
- PFS
- ORR
- Safety

Exploratory end points

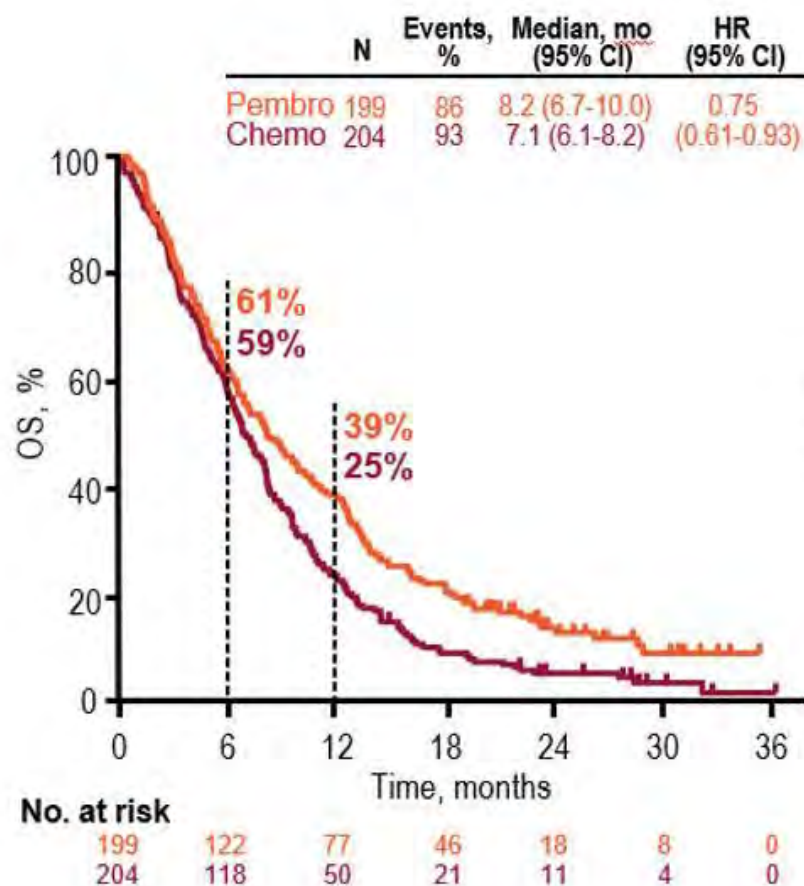
- HRQoL in patients whose tumor had a PD-L1 CPS ≥ 10

KEYNOTE-181: Overall Survival in the Global Population

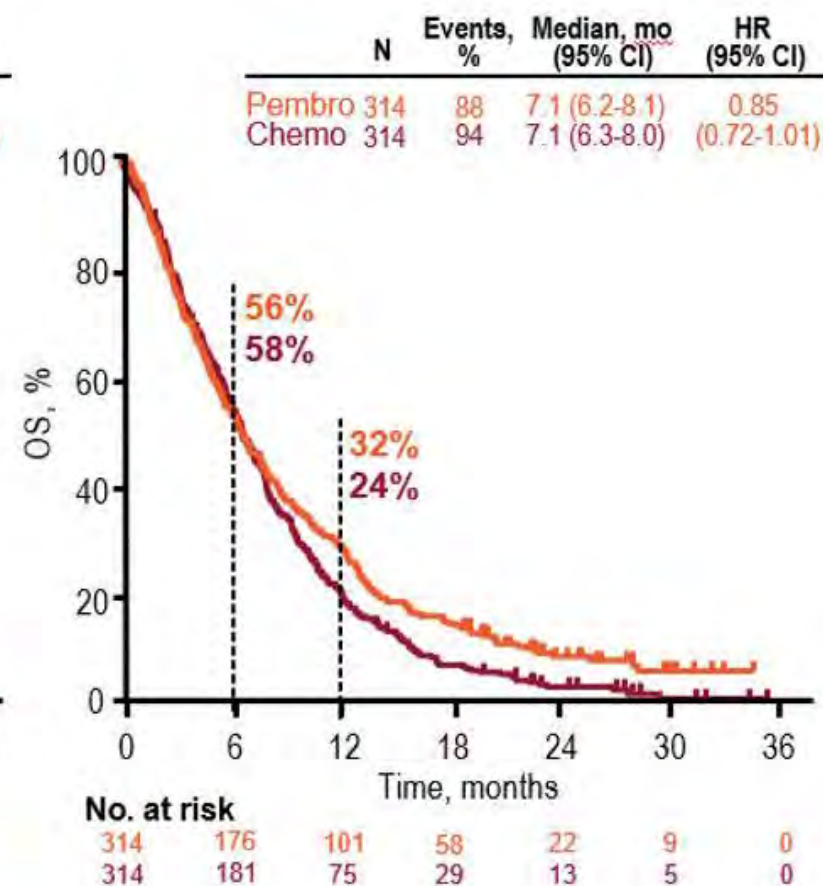
PD-L1 CPS ≥ 10 (n = 222)



SCC (n = 403)

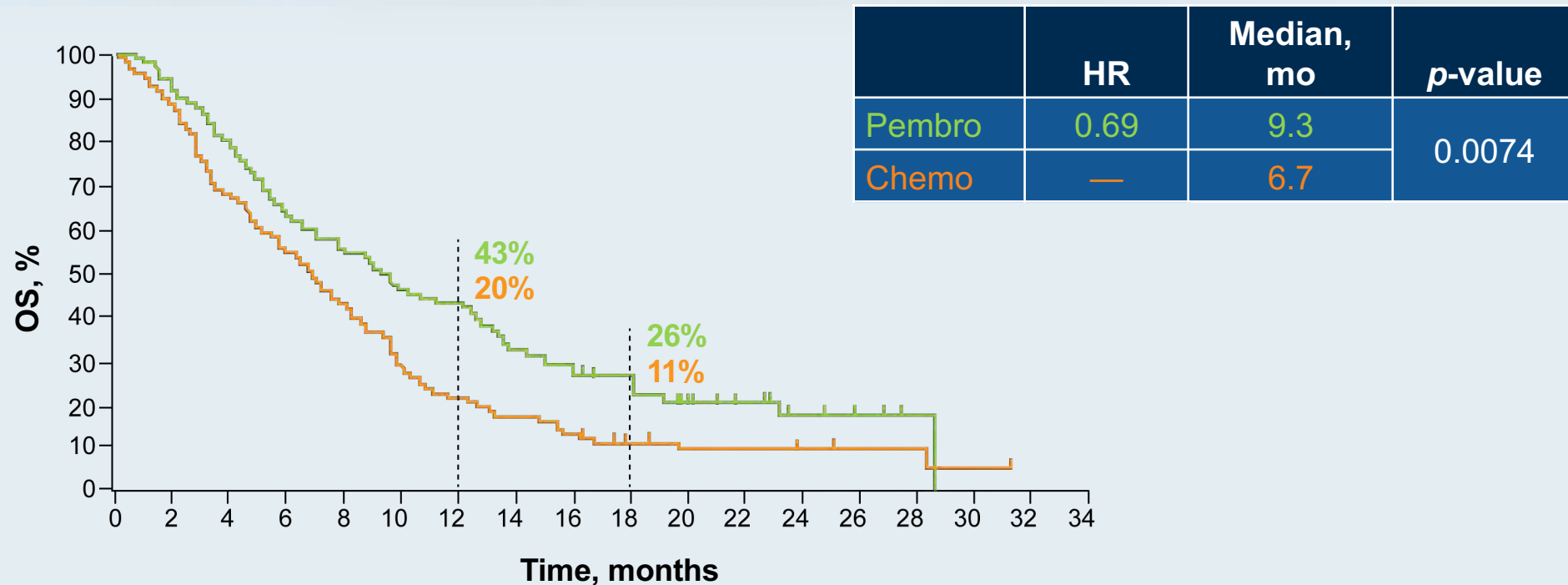


ITT (N = 628)



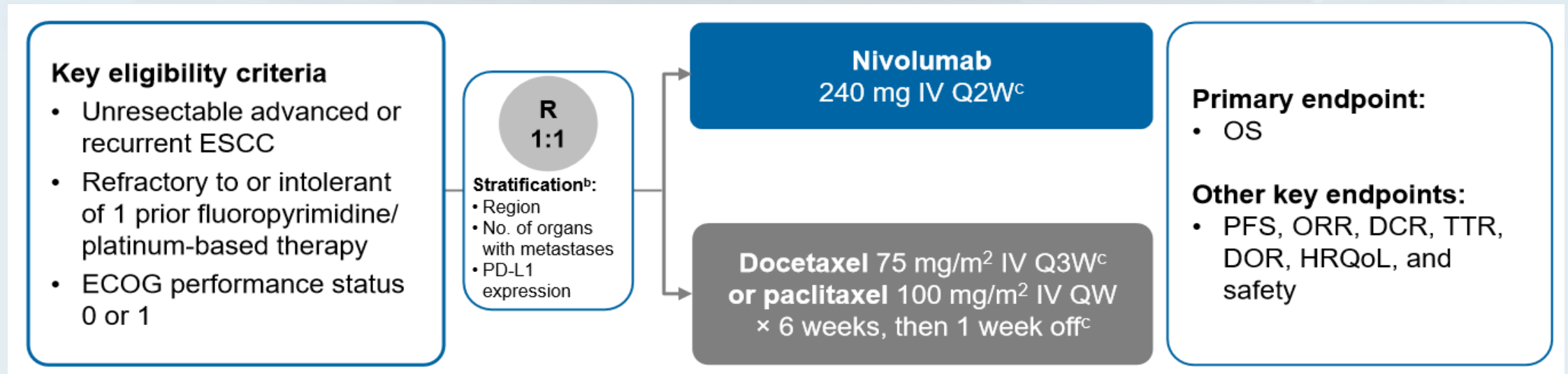
Data cutoff: February 13, 2019; these data represent an additional 4 months of follow up data from the October 15, 2018 cutoff.

KEYNOTE-181: Overall Survival (PD-L1 CPS ≥ 10) for Patients with Squamous Cell Carcinoma



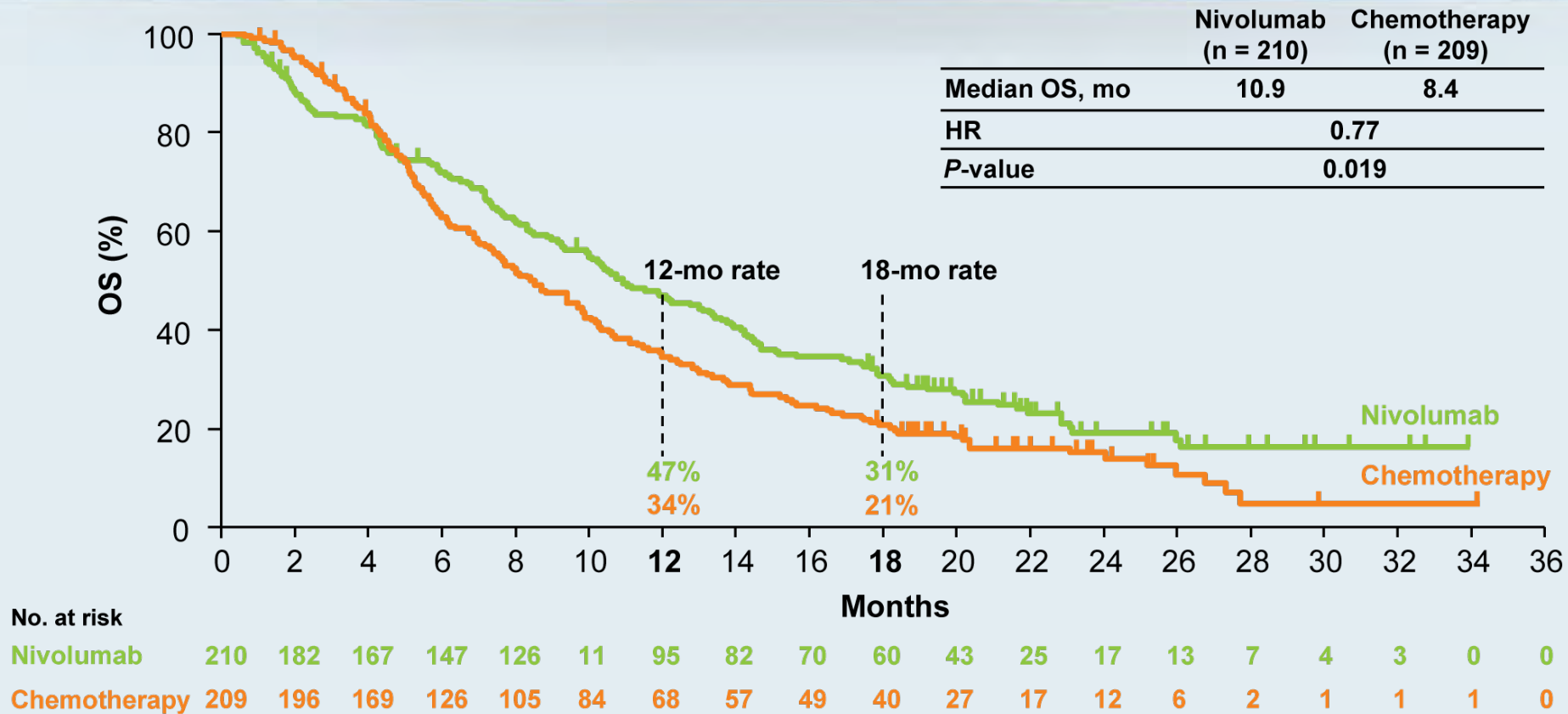
- ORR higher with pembrolizumab than with chemotherapy for patients with CPS ≥ 10 (21.5% vs 6.1%)
- Lower frequency of Grade 3-5 treatment-related adverse events with pembrolizumab than with chemotherapy (18.2% vs 40.9%); no new safety signals observed

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



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

ATTRACTION-3: Overall Survival



- Nivolumab demonstrated a statistically significant and clinically meaningful improvement in OS versus chemotherapy:
 - 23% reduction in the risk of death and a 2.5-month improvement in median OS
- Nivolumab showed an improved safety profile compared with chemotherapy:
 - More than 3 times lower incidence (18% vs 63%) of Grade 3-4 TRAEs

Case 1: Patient With Locally Advanced Esophageal Cancer

- 67-yr-old man with history of stage III (T3N1) distal esophageal adenocarcinoma
 - CC: Dysphagia on eating solid food, 25 lb weight loss, never had EGD before
- EGD: Tumor described as being in distal esophagus (above GEJ), HER2 + By IHC, negative by FISH
- CT scans: Thickening of GEJ, non-specific pulmonary nodules, no metastatic disease
- Case discussed at clinic. Options presented to patient included neoadjuvant chemo/XRT vs definitive chemoradiation
- Patient decided he wanted surgery

Case 1 Continued: Patient With Locally Advanced Esophageal Cancer

- Treated with neo-adjuvant carbo/paclitaxel/radiation (CROSS regimen) x 6 weeks, tolerated moderately with some esophagitis, weakness, and cytopenias
- Referral to Discussion about esophagectomy, decided to do it
 - Pathology: T2N1 (2/26)
- Patient was asymptomatic and observed for 6 months
- CT abd/pelvis: multiple enlarged LNs with biopsy proven left RP nodal recurrence (poorly differentiated adeno, CPS 5) started FOLFOX with initial improvement on imaging
- 6 months later, disease progression with new liver lesions
- Started on Pembro, better tolerated on chemo. SD on imaging

Case 2: Patient With Metastatic Esophageal Cancer

- 60 yr-old man with a 40 pack year history of smoking now with esophageal squamous cell carcinoma
 - CC: Odynophagia, Dysphagia on eating solid and liquids, 30 lb weight loss, never had EGD before
- EGD: Tumor described as being in mid-esophagus nearly completely obstructing, pathology showed SCC, PD-L1 CPS 10
- CT scans: Thickening of esophagus, 5-6 bilateral pulmonary nodules, largest was 2 cm, FDG avid on PET scan
- Patient underwent stent placement but no improvement, feeding tube placed
- Started on chemo with 5-FU/cisplatin + pembro

Case 2 continued: Patient With Metastatic Esophageal Cancer

- Chemo associated with fatigue, nausea/vomiting
- Some improvement in swallowing, but fatigue worsens, thyroid function testing indicates elevated TSH (> 10 mIU/L) and low free T4, suggesting primary hypothyroidism CT scans showed some improvement, swallowing mildly improved
- Referral to radiation, started palliative radiation with weekly carbo/paclitaxel
- After 4 months, CT scans show SD, platinum stopped and continued on 5-FU/Pembro
- CT abd/pelvis: several new areas in lungs
- Started on irinotecan as a single agent with SD

My Conclusions

- Adjuvant anti-PD-1 therapy has emerged as a standard treatment in poor pathologic responders to neoadjuvant chemoradiation; further biomarker analyses (PD-L1 CPS) needed
- Addition of anti-PD-1 therapy to first-line chemotherapy has entered into the treatment paradigm for unresectable/metastatic gastroesophageal cancer
- Patient selection still appears to be key:
 - ESCC, with greater likelihood of benefit in PD-L1 CPS ≥ 10
 - PD-L1 CPS ≥ 5 for adenocarcinomas of the stomach and GEJ (and likely esophagus)
- Tumor PD-L1 CPS (combined positive score) ascertainment may be different between the 28-8 and 22C3 assays (need more data)