CZECH HEAD AND NECK CANCER
COOPERATIVE GROUP

Imunoterapie v léčbě nádorů hlavy a krku

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Prague Onco 2019, 25. ledna 2019

Systémová léčba inoperabilních a metastatických skvamózních karcinomů hlavy a krku

Paliativní systémová léčba – chemoterapie

Monochemoterapie (cDDP, CBDCA, MTX…)

Polychemoterapie (cDDP-FU)

Medián přežití bez CHT 4-6 měsíců

s CHT 6-8 měsíců

Chemotherapy in R/M SCCHN

Effectivity of chemotherapy regimens (1st line) in R/M SCCHN in randomized clinical trials

Regimen	ORR, %	Median survival, months
Cisplatin + 5-fluorouracil[1–4]	30–32	5.5–8.7
Cisplatin[1,3]	15–17	5.0–6.7
5-fluorouracil[1]	13	6.1
Carboplatin + 5-fluorouracil[2]	21	5.0
Methotrexate[2]	10	5.6
Cisplatin, methotrexate, bleomycin, vincristine[3]	34	7.0
Cisplatin + paclitaxel[4]	26	8.1

1. *Jacobs C et al J Clin Oncol 1992*
2. *Forastiere AA et al J Clin Oncol 1992*
3. *Clavel M et al. Ann Ocol 1994*
4. *Gibson MK et al J Clin Oncol 2005*

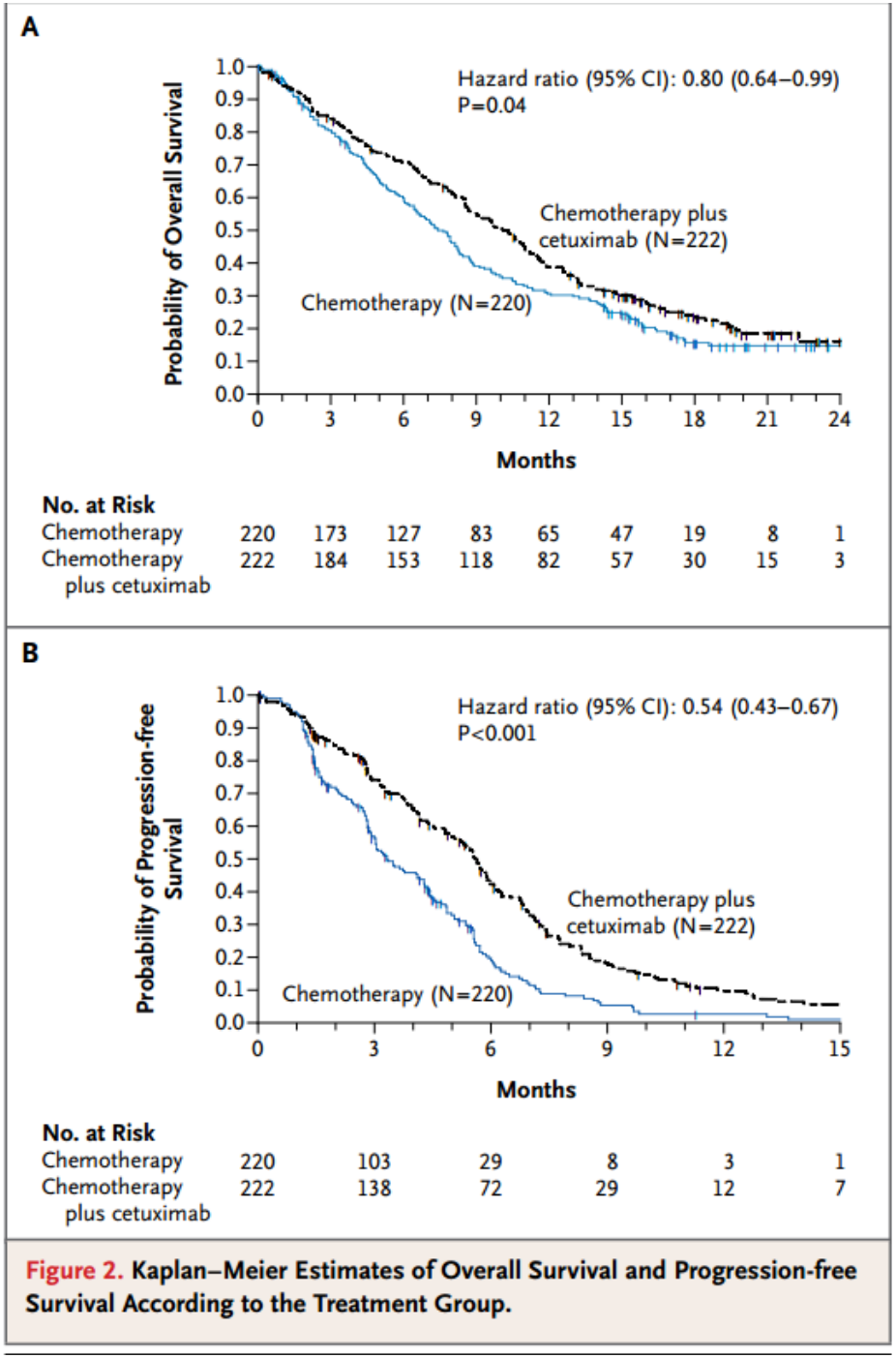


Figure 2. Kaplan–Meier Estimates of Overall Survival and Progression-free Survival According to the Treatment Group.

EXTREME trial

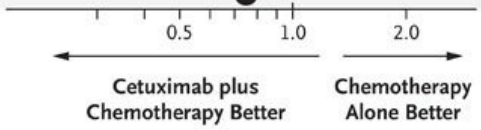
mOS:10.1 months in the cetuximab group and 7.4 months in the CT-alone group (HR, 0.80; 95% CI, 0.64-0.99; P=0.04)

mPFS:5.6 months in the cetuximab group and 3.3 months in the CT-alone group (HR, 0.54; 95% CI, 0.43-0.67; P<0.001)

Vermorken JB, et al. N Engl J Med 2008

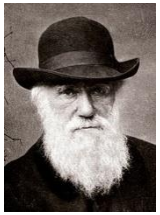
EXTREME trial

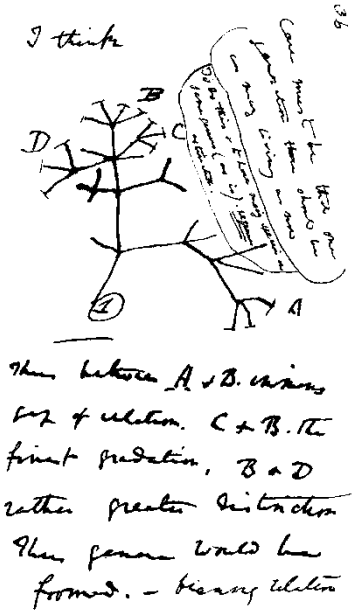
Subgroup	No. of Patients	Median Overall Survival (Cetuximab plus Chemotherapy vs. Chemotherapy) *mo*	Hazard Ratio (95% CI)
All patients	442	10.1 vs. 7.4	0.80 (0.64–0.99)
Age			
<65 yr	365	10.5 vs. 7.3	0.74 (0.59–0.94)
≥65 yr	77	9.1 vs. 7.8	1.07 (0.65–1.77)
Karnofksy performance score			
<80	52	6.3 vs. 4.4	1.14 (0.64–2.04)
≥80	390	10.6 vs. 7.9	0.75 (0.60–0.94)
Platinum regimen			
Cisplatin	284	10.6 vs. 7.3	0.69 (0.53–0.91)
Carboplatin	149	9.7 vs. 8.3	0.98 (0.69–1.41)
Previous treatment			
Neoadjuvant chemotherapy	57	10.7 vs. 6.3	0.82 (0.46–1.49)
Radiochemotherapy	129	8.6 vs. 7.5	0.90 (0.61–1.34)
Primary tumor site			
Oral cavity	88	11.0 vs. 4.4	0.42 (0.26–0.67)
Oropharynx	149	10.9 vs. 7.9	0.85 (0.58–1.23)
Larynx	111	8.6 vs. 8.4	0.99 (0.65–1.51)
Hypopharnyx	62	8.4 vs. 8.9	1.14 (0.64–2.04)
Tumor grade			
Well- or moderately differentiated	269	9.5 vs. 6.5	0.72 (0.55–0.94)
Poorly differentiated	92	10.8 vs. 9.4	1.00 (0.62–1.60)
Baseline quality-of-life score			
≤Median	129	7.4 vs. 5.9	0.86 (0.59–1.24)
>Median	98	13.9 vs. 9.2	0.70 (0.43–1.12)
Percentage of EGFR-detectable cells			
>0 to <40%	64	10.9 vs. 7.8	0.72 (0.40–1.28)
≥40%	341	10.1 vs. 7.1	0.75 (0.59–0.95)



Vermorken JB, et al. N Engl J Med 2008

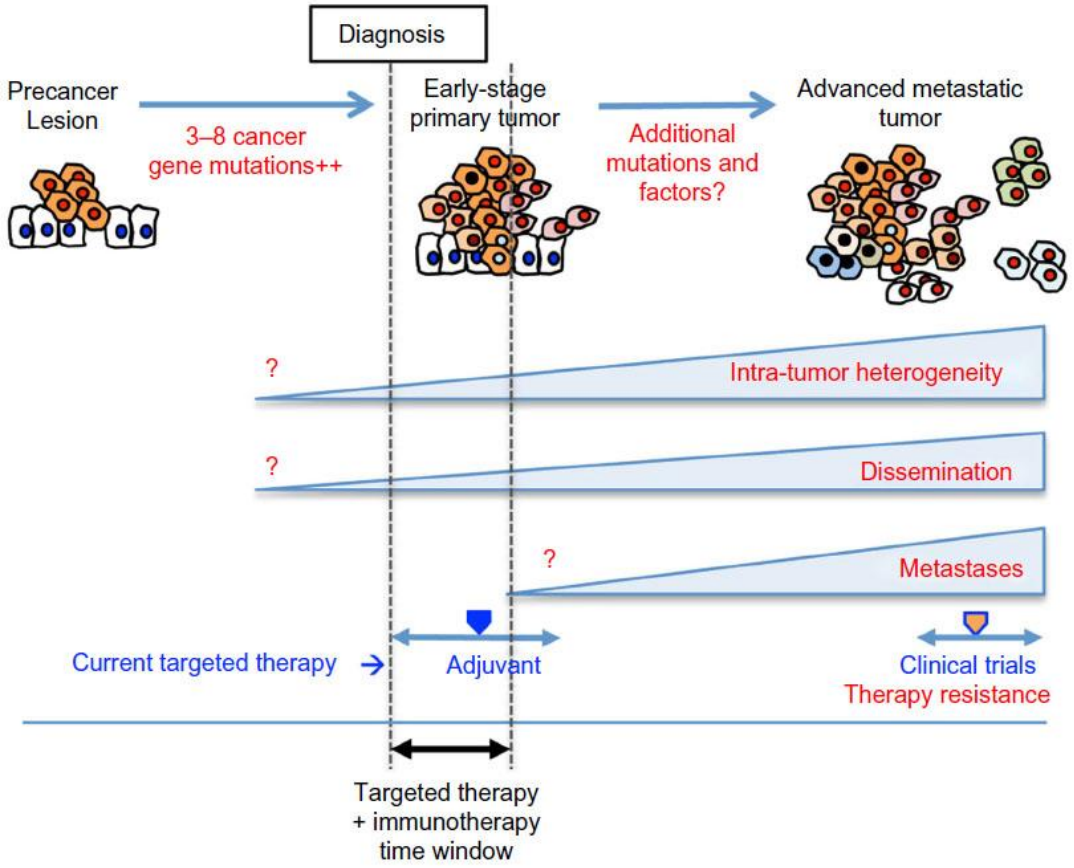
Tumor cell heterogeneity



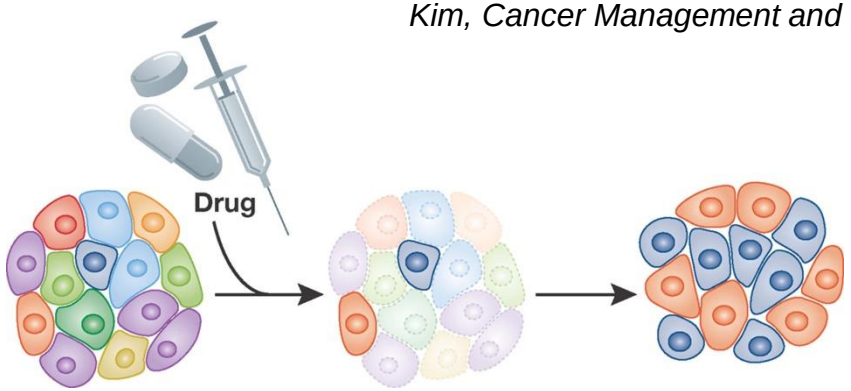


Charles Darwin (1809-1882)

1859: „*On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life*“

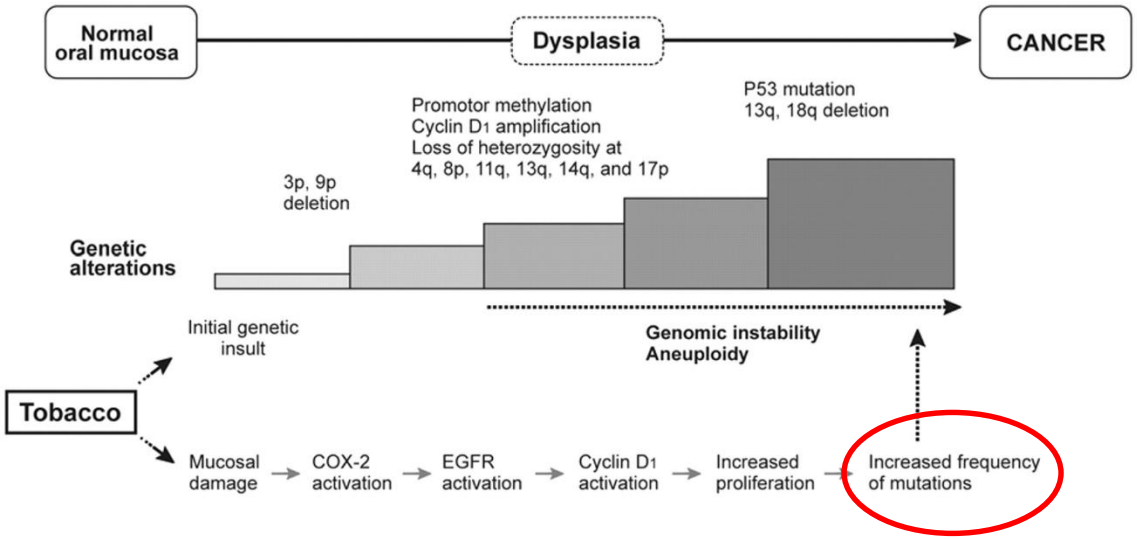


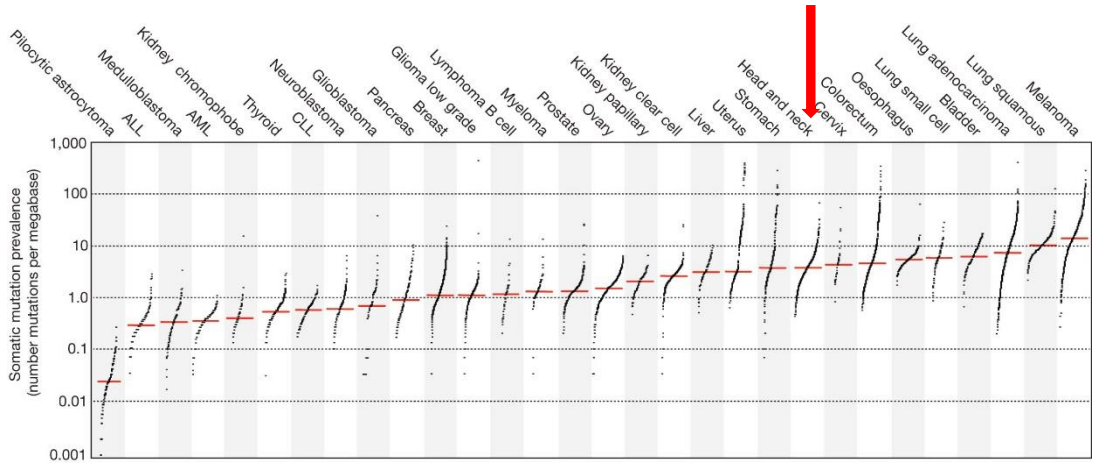
Kim, Cancer Management and Research. 2014



Saunders et al. MBO Molecular Medicine, 2012

The prevalence of somatic mutations in SCHNC.





LB Alexandrov et al. Nature 2013

Pembrolizumab ve 2. linii SCCHN

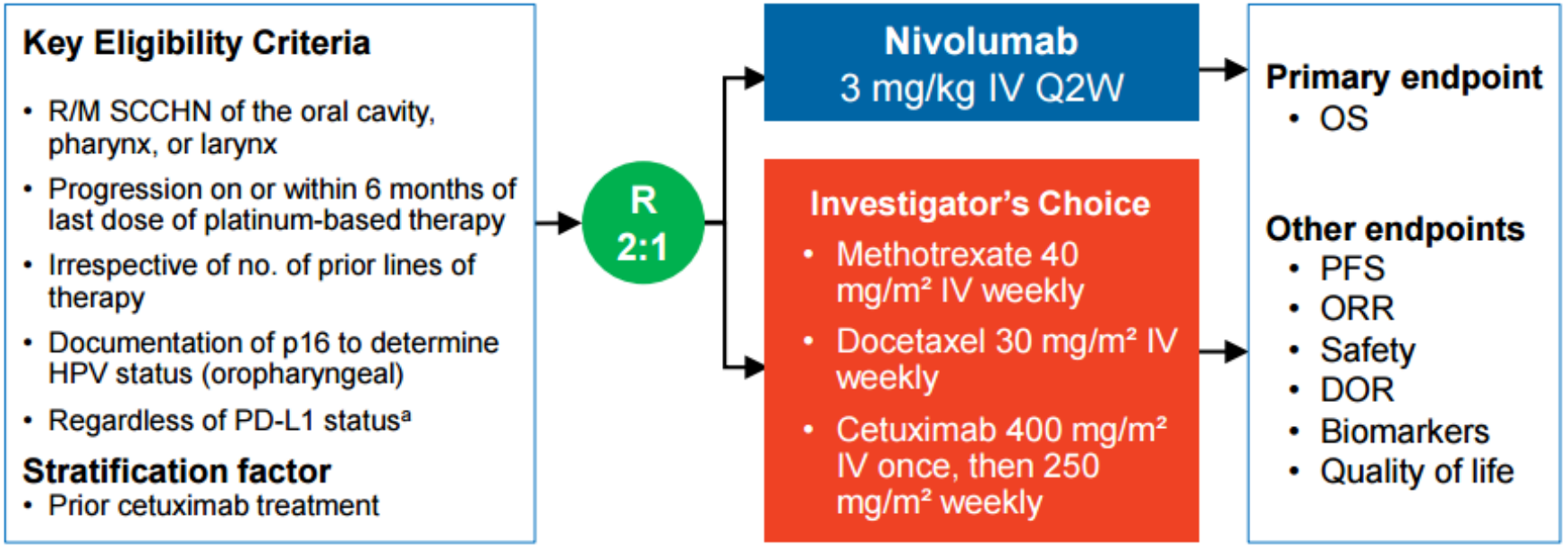
Keynote-012:

- 192 R/M HNSCC pts were enrolled
- 61% received ≥ 2 therapies for recurrent disease
- ORR (confirmed) was 17.7%
- ORR was 21.9% in HPV^+ pts and 15.9% in HPV^- pts.
- Median OS was 8.5 mo.
- The 6-mo PFS rate was 24.9%.

Mehra et al. ASCO 2016

Phase 3 CheckMate 141 Study Design
Nivolumab in R/M SCCHN After Platinum Therapy

- Randomized, global, phase 3 trial of the efficacy and safety of nivolumab vs investigator's choice in patients with R/M SCCHN



[a]Tissue required for testing.

DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized.
Clinicaltrials.gov NCT02105636.

Ferris et al. ASCO 2016

Demographics

Nivolumab in R/M SCCHN After Platinum Therapy

	Nivolumab (n = 240)	Investigator's Choice (n = 121)	Total (N = 361)
Median age, years	**59.0**	**61.0**	**60.0**
<65, n (%)	172 (71.7)	76 (62.8)	248 (68.7)
Smoking/tobacco use, n (%)			
Current/former	191 (79.6)	85 (70.2)	276 (76.5)
Never	39 (16.3)	31 (25.6)	70 (19.4)
ECOG performance status, n (%)			
0	49 (20.4)	23 (19.0)	72 (19.9)
1	189 (78.8)	94 (77.7)	283 (78.4)
≥2	1 (0.4)	3 (2.5)	4 (1.1)
Not reported	1 (0.4)	1 (0.8)	2 (0.6)
Number of prior lines of systemic cancer therapy, n (%)			
1	106 (44.2)	58 (47.9)	164 (45.4)
2	80 (33.3)	45 (37.2)	125 (34.6)
≥3	54 (22.5)	18 (14.9)	72 (19.9)
p16 status[a,b], n (%)			
Positive	63 (26.3)	29 (24.0)	92 (25.5)
Negative	50 (20.8)	36 (29.8)	86 (23.8)
Not tested	127 (52.9)	56 (46.3)	183 (50.7)

[a]Required from patients with oropharyngeal cancer only. [b]Determined via p16 immunohistochemistry.

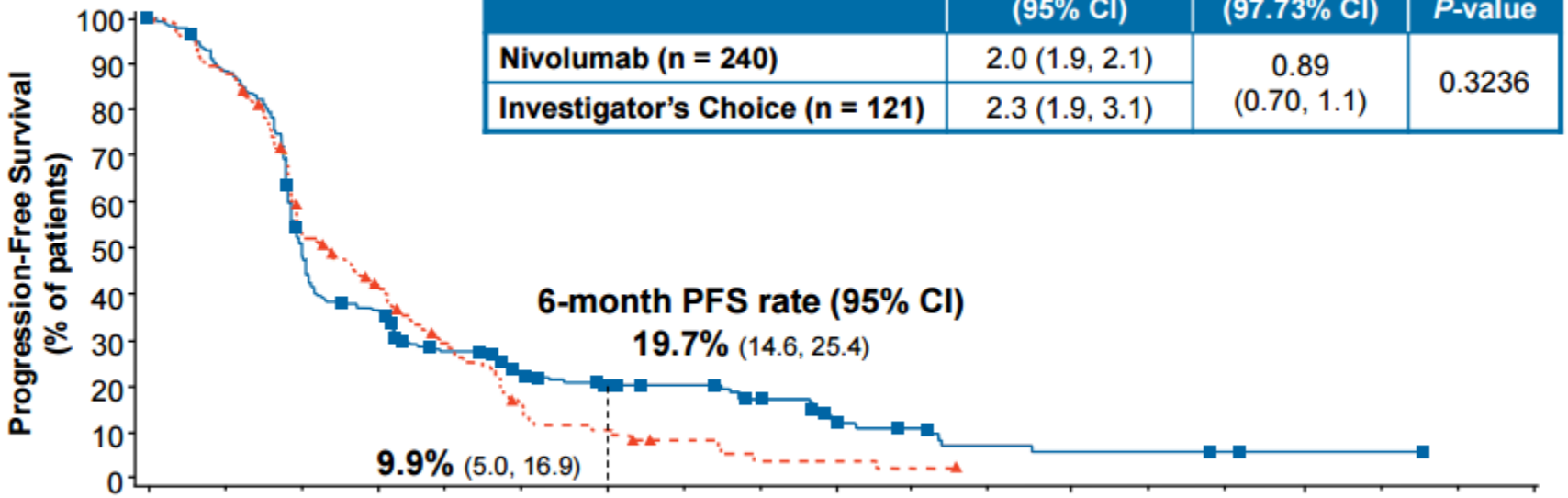
ECOG = Eastern Cooperative Oncology Group.

Ferris et al. ASCO 2016

Progression-Free Survival

Nivolumab in R/M SCCHN After Platinum Therapy

	Median OS, mo (95% CI)	HR (97.73% CI)	*P*-value
Nivolumab (n = 240)	2.0 (1.9, 2.1)	0.89 (0.70, 1.1)	0.3236
Investigator's Choice (n = 121)	2.3 (1.9, 3.1)		



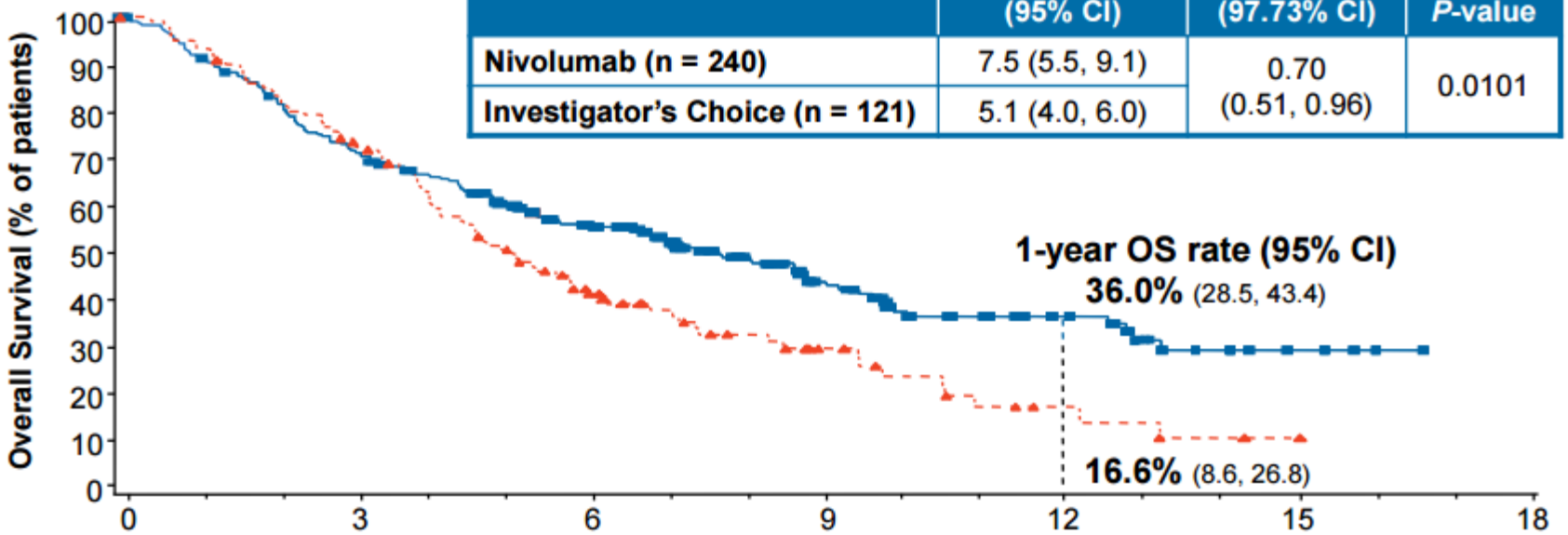
No. at Risk							
Nivolumab	240	79	32	12	4	1	0
Investigator's Choice	121	43	9	2	0	0	0

Ferris et al. ASCO 2016

Overall Survival

Nivolumab in R/M SCCHN After Platinum Therapy

	Median OS, mo (95% CI)	HR (97.73% CI)	*P*-value
Nivolumab (n = 240)	7.5 (5.5, 9.1)	0.70 (0.51, 0.96)	0.0101
Investigator's Choice (n = 121)	5.1 (4.0, 6.0)		

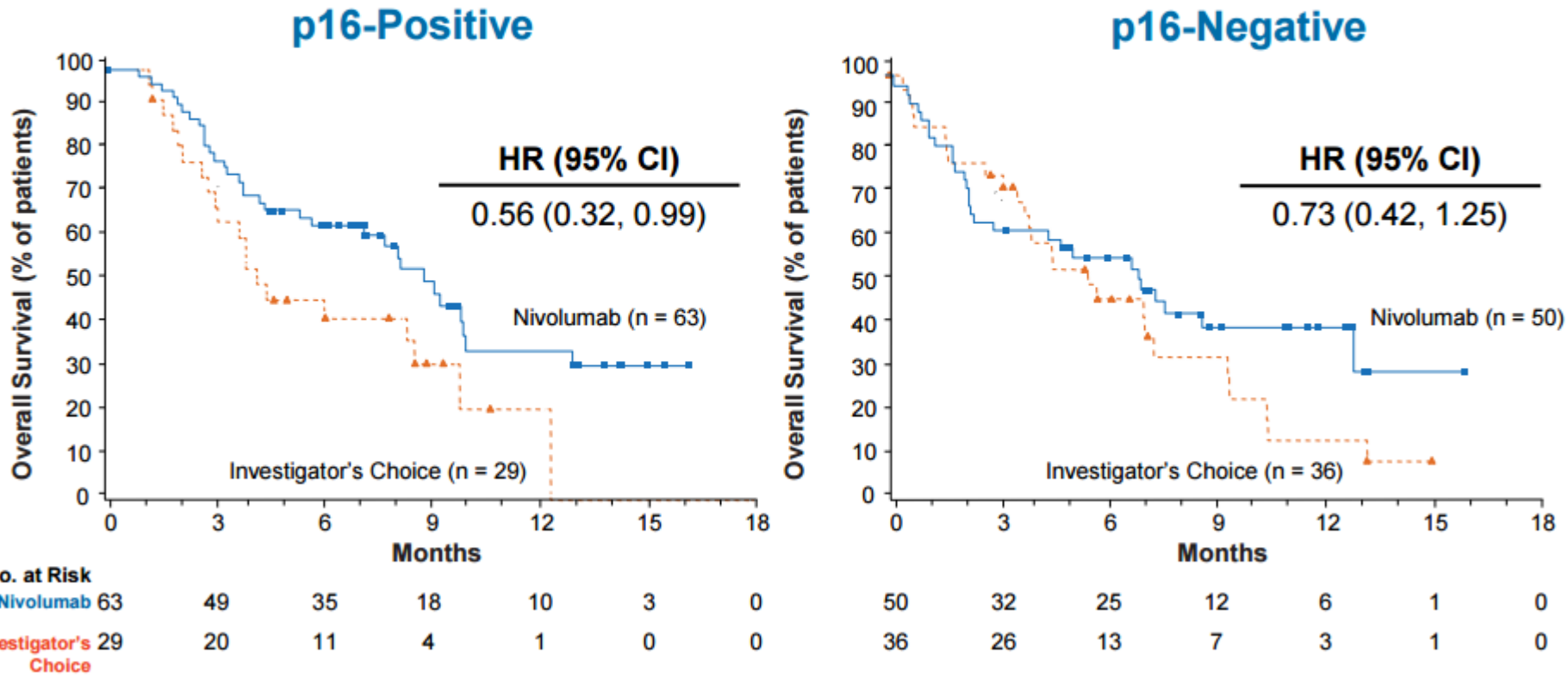


No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Investigator's Choice	121	87	42	17	5	1	0

Ferris et al. ASCO 2016

Overall Survival by p16 Status

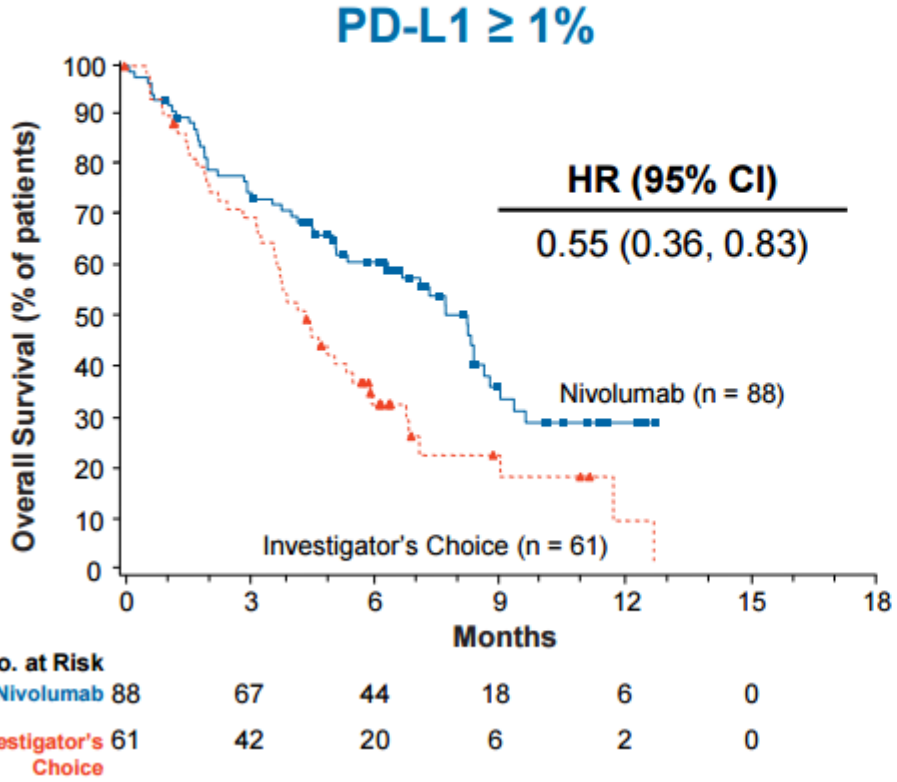
Nivolumab in R/M SCCHN After Platinum Therapy

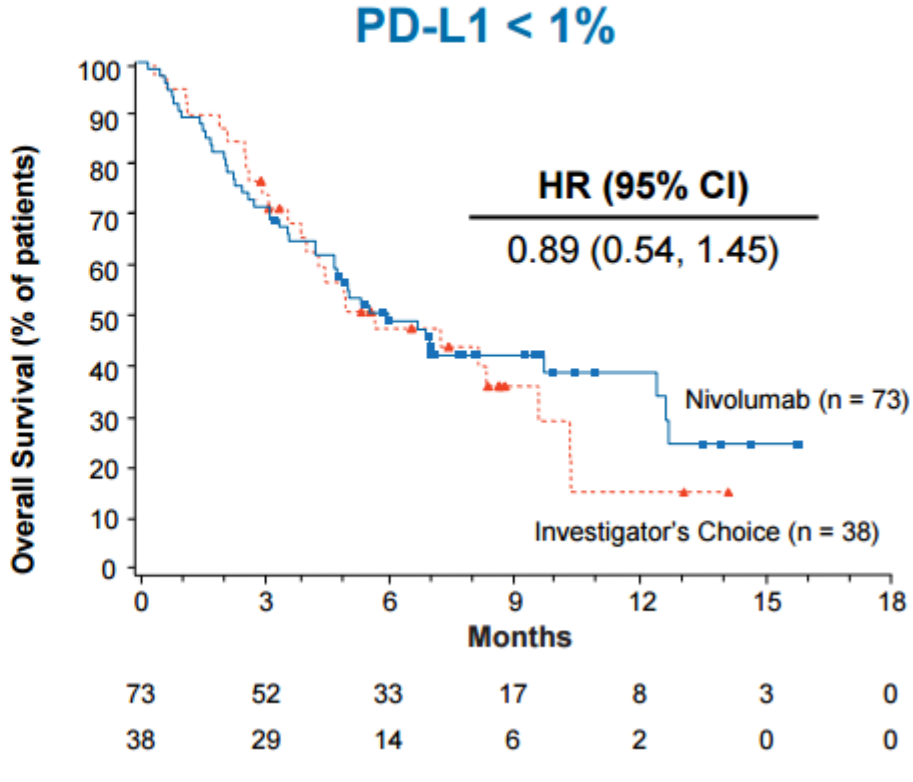


Ferris et al. ASCO 2016

Overall Survival by Tumor PD-L1 Expression at 1%

Nivolumab in R/M SCCHN After Platinum Therapy





Ferris et al. ASCO 2016

American Association for Cancer Research Meeting (AACR) 2018

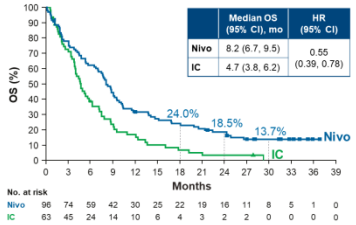
Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-yr outcomes in the overall population and PD-L1 subgroups of CheckMate 141

OS Benefit Across PD-L1 Expressors and Non-Expressors

- OS rates at 18, 24, and 30 months were similar in both groups
  - PD-L1 expressors: nivolumab continued to provide OS benefit, with 45% reduction in risk of death vs IC
  - PD-L1 non-expressors: nivolumab resulted in 27% reduction in risk of death vs IC

PD-L1 Expressors (≥1%)

	Median OS (95% CI), mo	HR (95% CI)
Nivo	8.2 (6.7, 9.5)	0.55 (0.39, 0.78)
IC	4.7 (3.8, 6.2)	

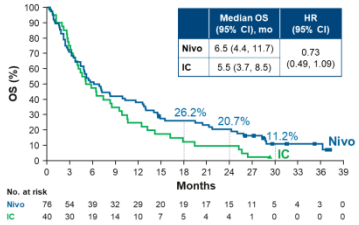


No. at risk

Nivo	96	74	59	42	30	25	22	19	16	11	8	5	1	0
IC	63	45	24	14	10	6	4	3	2	2	0	0	0	0

PD-L1 Non-Expressors (<1%)

	Median OS (95% CI), mo	HR (95% CI)
Nivo	6.5 (4.4, 11.7)	0.73 (0.49, 1.09)
IC	5.5 (3.7, 8.5)	



No. at risk

Nivo	76	54	39	32	29	20	19	17	15	11	5	4	3	0
IC	40	30	19	14	10	7	5	4	4	1	0	0	0	0

Symbols represent censored observations

Oral Oncology, July 2018

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Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression

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CD274 protein, human (PD-L1 Protein, Human)
Clinical Trial, Phase III
Survival Analysis
Survivors (Long-term Survivors)

ABSTRACT

Objectives: We report 2-year results from CheckMate 141 to establish the long-term efficacy and safety profile of nivolumab and outcomes by tumor PD-L1 expression in patients with recurrent or metastatic (R/M),platinum-refractory squamous cell carcinoma of the head and neck (SCCHN).

Methods: Patients with R/M SCCHN with tumor progression/recurrence within 6 months of platinum therapy were randomized 2:1 to nivolumab 3 mg/kg every 2 weeks or investigator's choice (IC). Primary endpoint: overall survival (OS). Data cutoff: September 2017.

Results: With 24.2 months' minimum follow-up, nivolumab (n = 240) continued to improve OS vs IC (n = 121), hazard ratio (HR) = 0.68 (95% CI 0.54–0.86). Nivolumab nearly tripled the estimated 24-month OS rate (16.9%) vs IC (6.0%), and demonstrated OS benefit across patients with tumor PD-L1 expression ≥ 1% (HR [95% CI] = 0.55 [0.39–0.78]) and < 1% (HR [95% CI] = 0.73 [0.49–1.09]), and regardless of tumor HPV status. Estimated OS rates at 18, 24, and 30 months with nivolumab were consistent irrespective of PD-L1 expression (< 1%/ ≥ 1%). In the nivolumab arm, there were no observed differences in baseline characteristics or safety profile between long-term survivors and the overall population. Grade 3–4 treatment-related adverse event rates were 15.3% and 36.9% for nivolumab and IC, respectively.

Conclusion: Nivolumab significantly improved OS at the primary analysis and demonstrated prolonged OS benefit vs IC and maintenance of a manageable and consistent safety profile with 2-year follow-up. OS benefit

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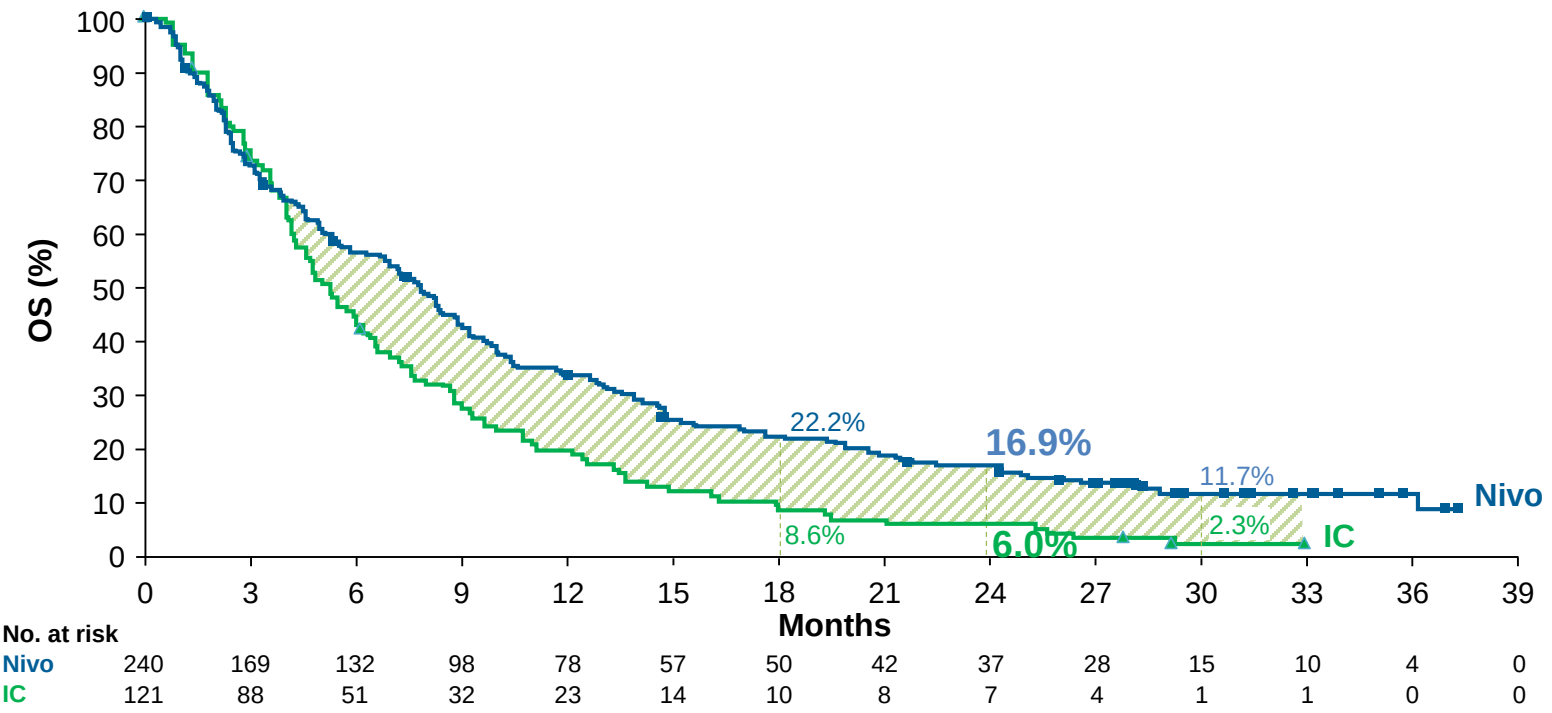
Sustained OS Benefit in the Overall (ITT) Population

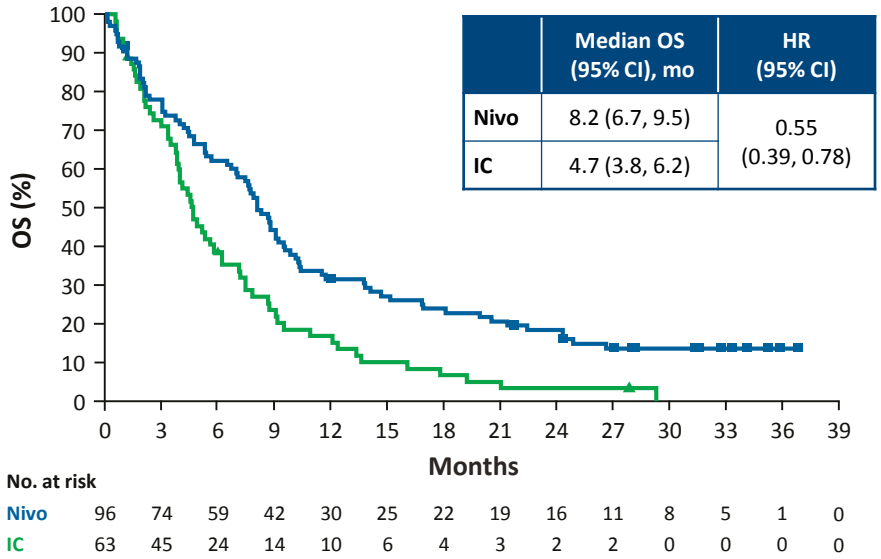
- Nivolumab reduced the risk of death by 32% vs IC
- The 24-month OS rate was nearly tripled with nivolumab compared with IC



Symbols represent censored observations. ITT = intent-to-treat; Nivo, nivolumab

Ferris et al., AACR 2018

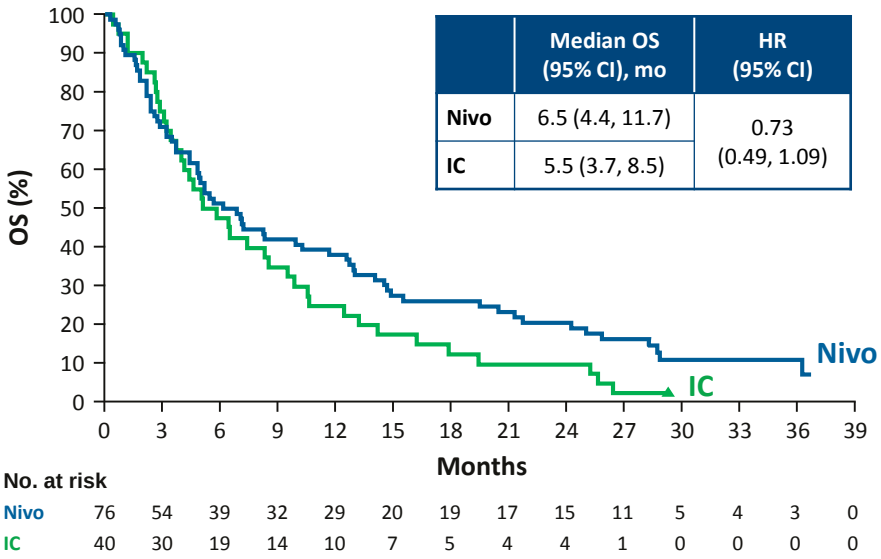
OS Benefit Across PD-L1 Expressors and Non-Expressors



	Median OS (95% CI), mo	HR (95% CI)
Nivo	8.2 (6.7, 9.5)	0.55 (0.39, 0.78)
IC	4.7 (3.8, 6.2)	

No. at risk

Nivo	96	74	59	42	30	25	22	19	16	11	8	5	1	0
IC	63	45	24	14	10	6	4	3	2	2	0	0	0	0



	Median OS (95% CI), mo	HR (95% CI)
Nivo	6.5 (4.4, 11.7)	0.73 (0.49, 1.09)
IC	5.5 (3.7, 8.5)	

No. at risk

Nivo	76	54	39	32	29	20	19	17	15	11	5	4	3	0
IC	40	30	19	14	10	7	5	4	4	1	0	0	0	0

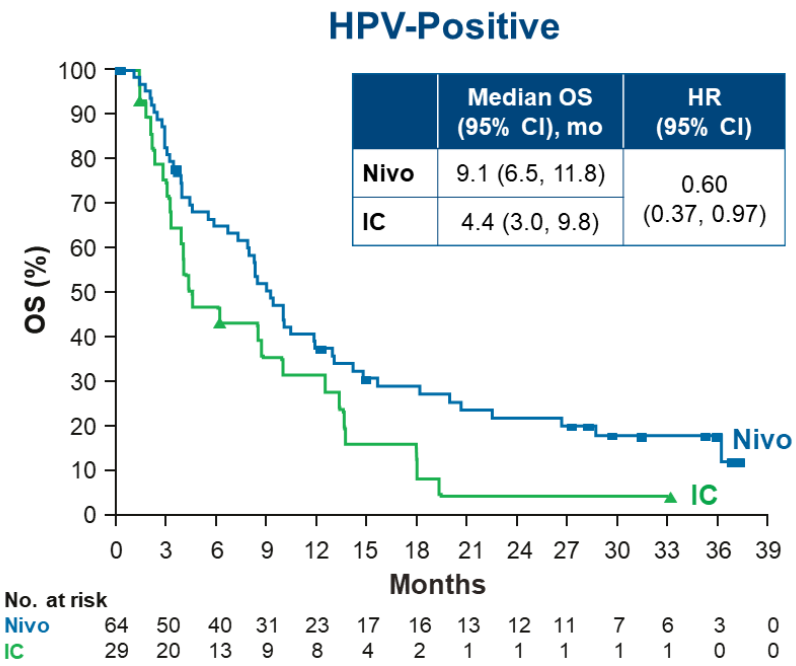
Symbols represent censored observations

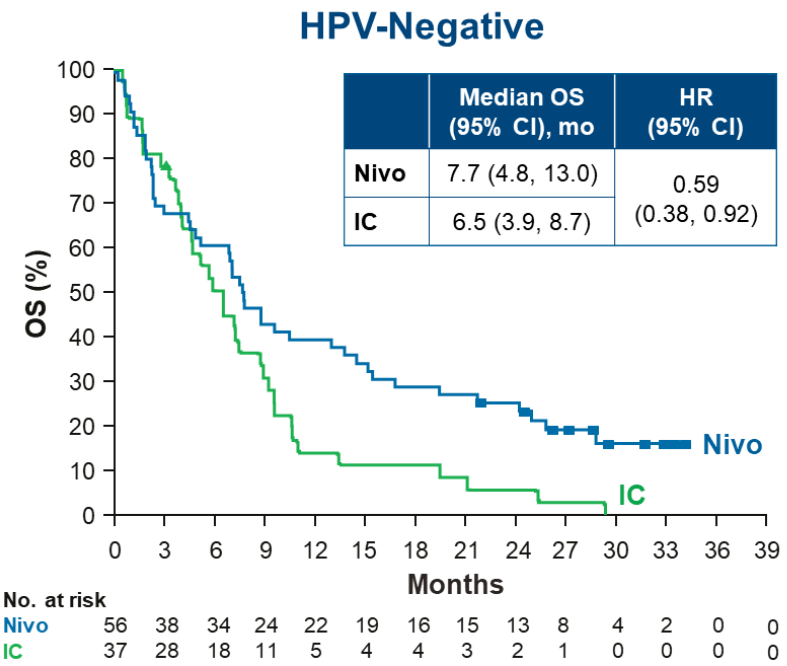
- OS rates at 18, 24, and 30 months were similar in both groups
  - PD-L1 expressors: nivolumab continued to provide OS benefit, with 45% reduction in risk of death vs IC
  - PD-L1 non-expressors: nivolumab resulted in 27% reduction in risk of death vs IC

Ferris et al., AACR 2018

OS by HPV Status[a]

- Nivolumab demonstrated survival benefit in patients with HPV-positive and HPV-negative tumors, with comparable HRs for risk of death vs IC





[a]HPV testing was required only for patients with OPC; symbols represent censored observations

Ferris et al., AACR 2018

Soulières KN040
AACR 2018

Updated Survival Results of the KEYNOTE-040 Study of Pembrolizumab vs Standard-of-Care Chemotherapy for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma

Denis Soulières, Ezra EW Cohen, Christophe Le Tourneau, José Dinis, Lisa Licitra, Myung-Ju Ahn, Ainara Soria, Jean-Pascal Machiels, Nicolas Mach, Ranee Mehra, Barbara Burtness, Pingye Zhang, Jonathan Cheng, Ramona Swaby, Kevin J Harrington

INVENTING FOR LIFE

Soulières KN040
AACR 2018

Phase 3 KEYNOTE-040 Study (NCT02252042)

Key Eligibility Criteria
- SCC of the oral cavity, oropharynx, hypopharynx, or larynx
- PD after platinum-containing regimen for R/M HNSCC or recurrence or PD within 3-6 mo of multimodal therapy using platinum[a]
- ECOG PS 0 or 1
- Known p16 status (oropharynx)[b]
- Tissue sample[c] for PD-L1 assessment[d]

Stratification Factors
- ECOG PS (0 vs 1)
- p16 status[b] (positive vs negative)
- PD-L1 TPS[d] (≥50% vs <50%)

R 1:1

Pembrolizumab 200 mg IV Q3W for 2 y

Methotrexate 40 mg/m² QW[e] OR Docetaxel 75 mg/m² Q3W OR Cetuximab 250 mg/m² QW[f]

- Clinically stable patients with radiologic PD could continue treatment until imaging performed ≥4 wk later confirmed PD
- Crossover not permitted

[a]Limit of 2 prior therapies for R/M HNSCC. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Newly collected preferred. [d]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [e]Could be increased to 60 mg/m² QW in the absence of toxicity. [f]Following a loading dose of 400 mg/m².

INVENTING FOR LIFE

Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study

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Summary

Background There are few effective treatment options for patients with recurrent or metastatic head-and-neck squamous cell carcinoma. Pembrolizumab showed antitumour activity and manageable toxicity in early-phase trials. We aimed to compare the efficacy and safety of pembrolizumab versus standard-of-care therapy for the treatment of head-and-neck squamous cell carcinoma.

Methods We did a randomised, open-label, phase 3 study at 97 medical centres in 20 countries. Patients with head-and-neck squamous cell carcinoma that progressed during or after platinum-containing treatment for recurrent or metastatic disease (or both), or whose disease recurred or progressed within 3–6 months of previous multimodal therapy containing platinum for locally advanced disease, were randomly assigned (1:1) in blocks of four per stratum with an interactive voice-response and integrated web-response system to receive pembrolizumab 200 mg every 3 weeks intravenously or investigator's choice of standard doses of methotrexate, docetaxel, or cetuximab intravenously (standard-of-care group). The primary endpoint was overall survival in the intention-to-treat population. Safety was analysed in the as-treated population. This trial is registered with ClinicalTrials.gov, number NCT02252042, and is no longer enrolling patients.

Findings Between Dec 24, 2014, and May 13, 2016, 247 patients were randomly allocated to pembrolizumab and 248 were randomly allocated to standard of care. As of May 15, 2017, 181 (73%) of 247 patients in the pembrolizumab group and 207 (83%) of 248 patients in the standard-of-care group had died. Median overall survival in the intention-to-treat population was 8·4 months (95% CI 6·4–9·4) with pembrolizumab and 6·9 months (5·9–8·0) with standard of care (hazard ratio 0·80, 0·65–0·98; nominal p=0·0161). Fewer patients treated with pembrolizumab than with standard of care had grade 3 or worse treatment-related adverse events (33 [13%] of 246 *vs* 85 [36%] of 234). The most common treatment-related adverse event was hypothyroidism with pembrolizumab (in 33 [13%] patients) and fatigue with standard of care (in 43 [18%]). Treatment-related death occurred in four patients treated with pembrolizumab (unspecified cause, large intestine perforation, malignant neoplasm progression, and Stevens-Johnson syndrome) and two patients treated with standard of care (malignant neoplasm progression and pneumonia).

Interpretation The clinically meaningful prolongation of overall survival and favourable safety profile of pembrolizumab in patients with recurrent or metastatic head and neck squamous cell carcinoma support the further evaluation of pembrolizumab as a monotherapy and as part of combination therapy in earlier stages of disease.

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Introduction

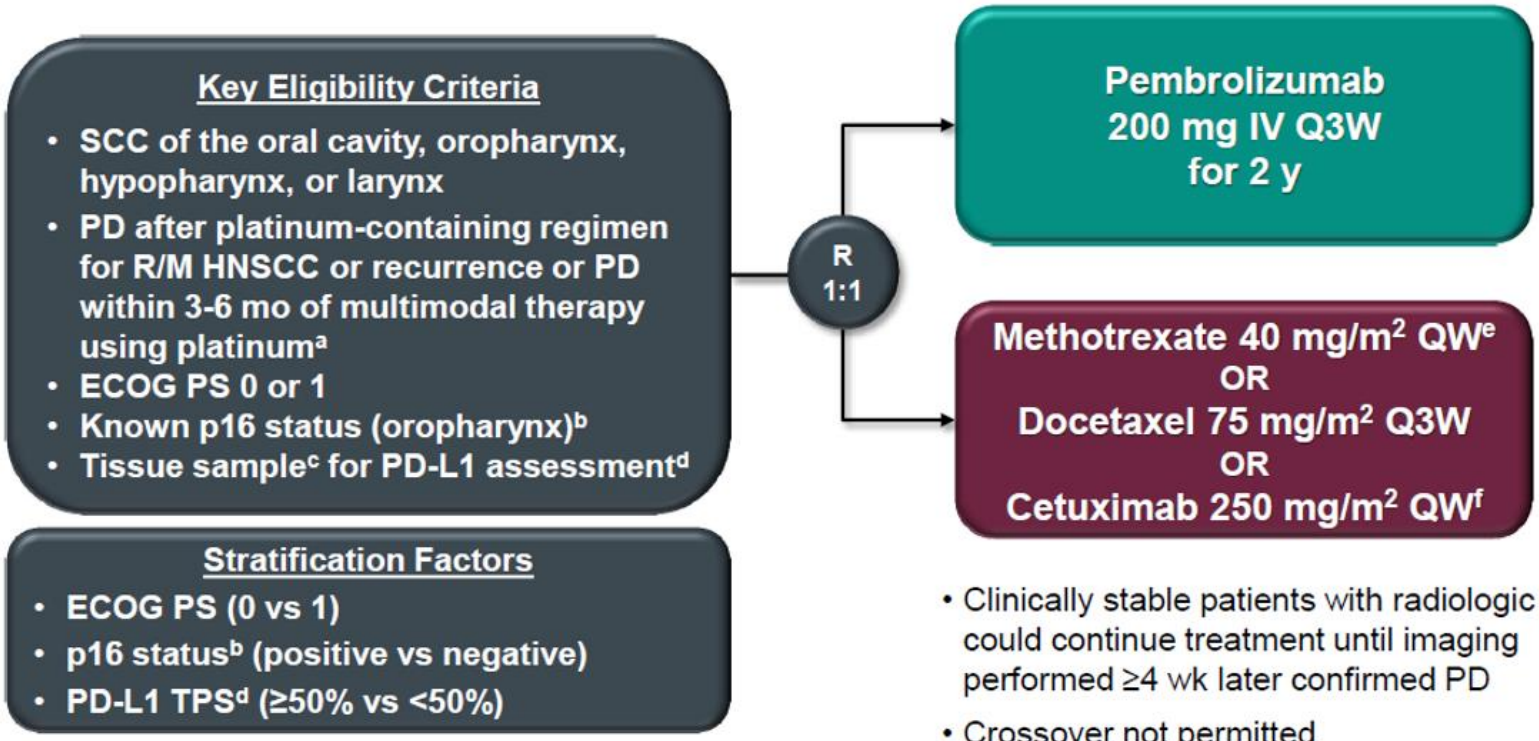
Despite multimodal therapy including platinum-based chemoradiotherapy, more than 50% of patients with locoregionally advanced squamous cell carcinoma of the head and neck have recurrence or develop metastases (or both) within 3 years of treatment.[1–3] Platinum-based combination chemotherapy regimens and cetuximab are commonly used in the first-line recurrent and metastatic settings.[1,2] The EXTREME regimen, which consists of platinum, fluorouracil, and cetuximab, is approved in many countries for first-line treatment of patients whose disease progressed more than 6 months after receiving a platinum-containing chemoradiotherapy regimen administered with curative intent.[4] Until 2017, treatment options for recurrent and metastatic disease following progression on a platinum-based regimen were limited to single-agent chemotherapy or cetuximab, which yield a median overall survival of 7 months or less.[1,5–7]

Inhibitors of the programmed death 1 (PD-1) pathway, which is implicated in tumour immune escape, have emerged as valid treatment options in patients

Soulieres et al., AACR 2018

Soulières KN040
AACR 2018

Phase 3 KEYNOTE-040 Study (NCT02252042)



- Clinically stable patients with radiologic PD could continue treatment until imaging performed ≥4 wk later confirmed PD
- Crossover not permitted

[a]Limit of 2 prior therapies for R/M HNSCC. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%.
[c]Newly collected preferred. [d]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [e]Could be increased to 60 mg/m² QW in the absence of toxicity. [f]Following a loading dose of 400 mg/m².

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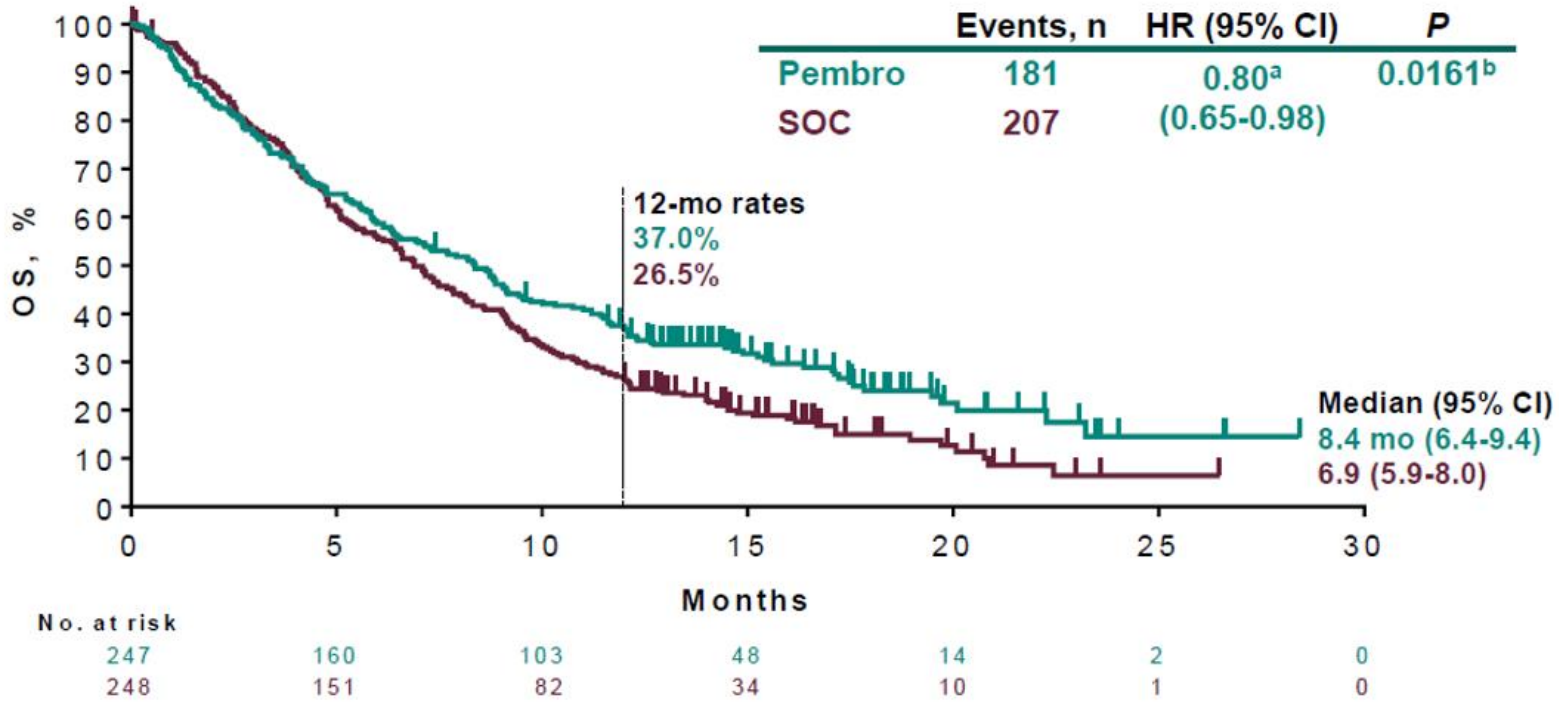
Soulieres et al., AACR 2018

Soulières KN040
AAACR 2018

Updated Overall Survival: ITT



[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. [b]Nominal one-sided *P* value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

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With increasing PD-L1 expression, there was a trend towards better outcomes

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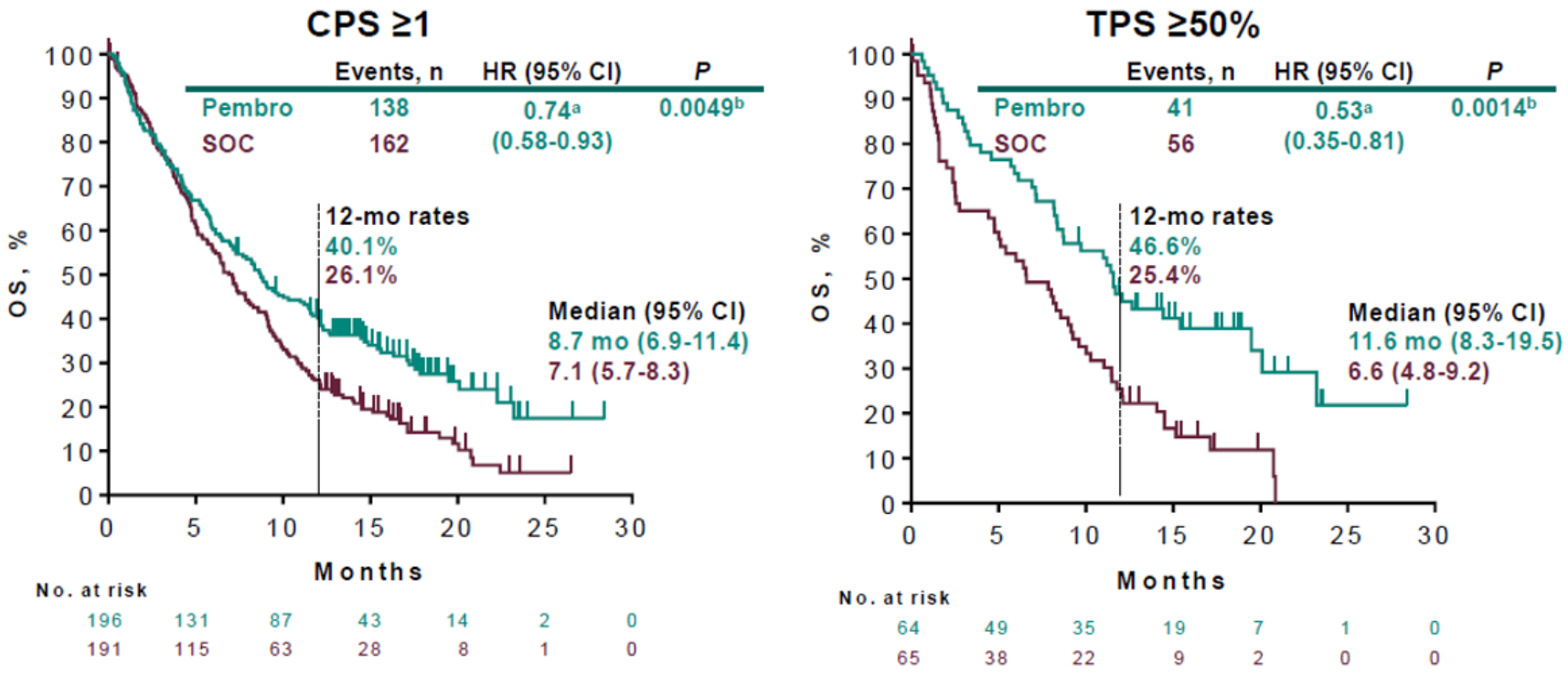
Updated Overall Survival by PD-L1 Expression



[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. [b]Nominal one-sided *P* value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

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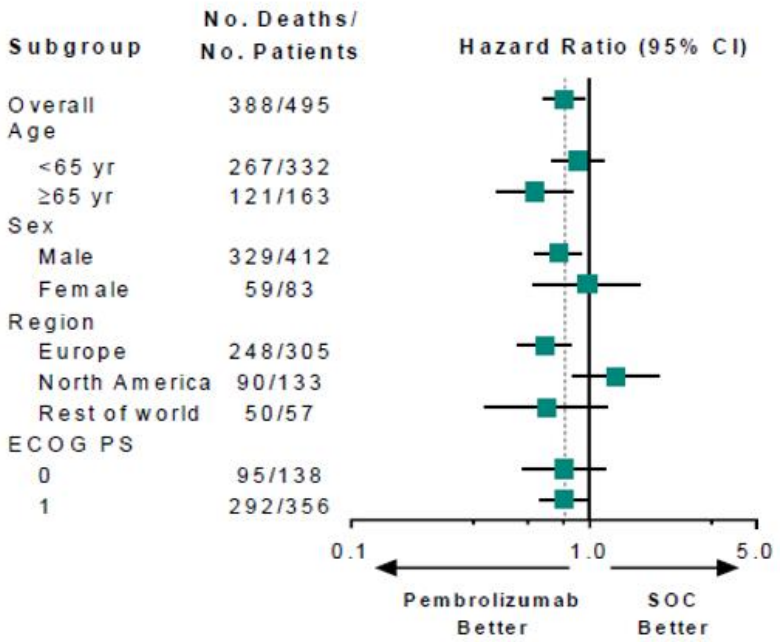
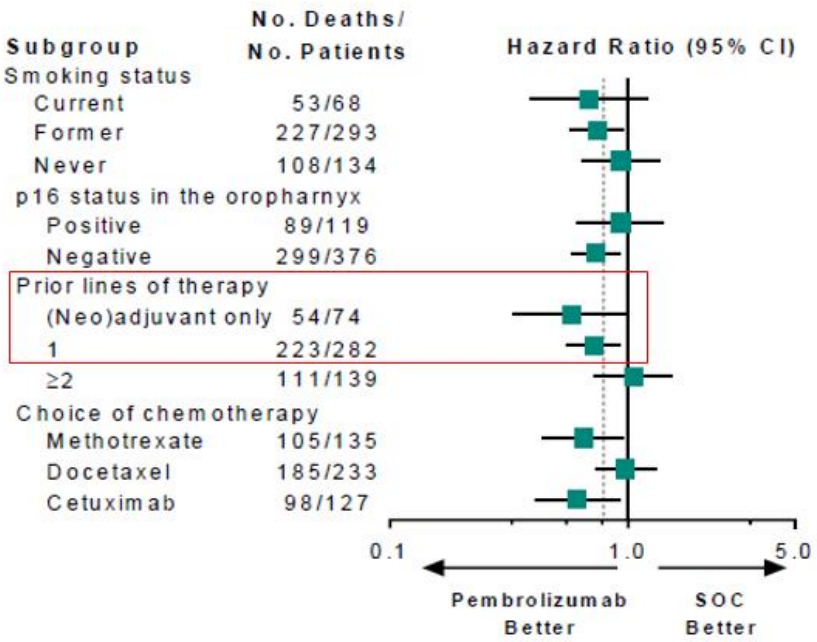
Updated Overall Survival: Subgroups





Unstratified Cox proportional hazards model with treatment as a covariate.
Data cutoff date: May 15, 2017.

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MUNICH 2018 ESMO congress

KEYNOTE-048: Phase 3 Study of First-Line Pembrolizumab for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC)

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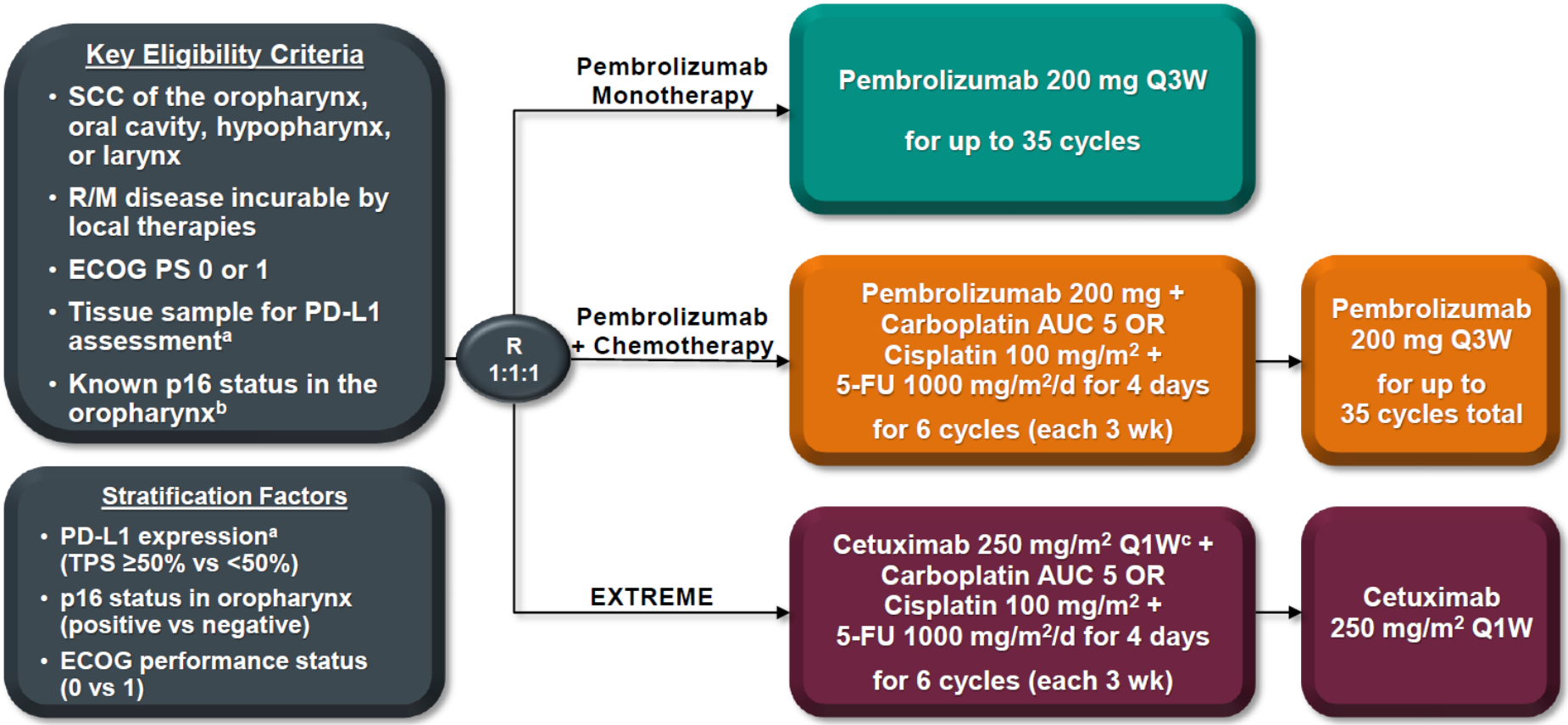
KEYNOTE-048 Study Design (NCT02358031)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

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Study End Points: Pembrolizumab vs EXTREME and Pembrolizumab + Chemotherapy vs EXTREME

Primary

- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - OS
  - PFS[b]

Secondary

- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - PFS[b] rates at 6 and 12 mo
  - ORR[b]
  - Change from baseline and time to deterioration in quality of life (EORTC QLQ-C30 and H&N-35)[c]
- Total population
  - Safety and tolerability

Key Exploratory

- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - Duration of response[b]

[a]Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay. CPS = combined positive score = number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100.
[b]Assessed per RECIST v1.1 by blinded, independent central review.
[c]To be presented at a later date.

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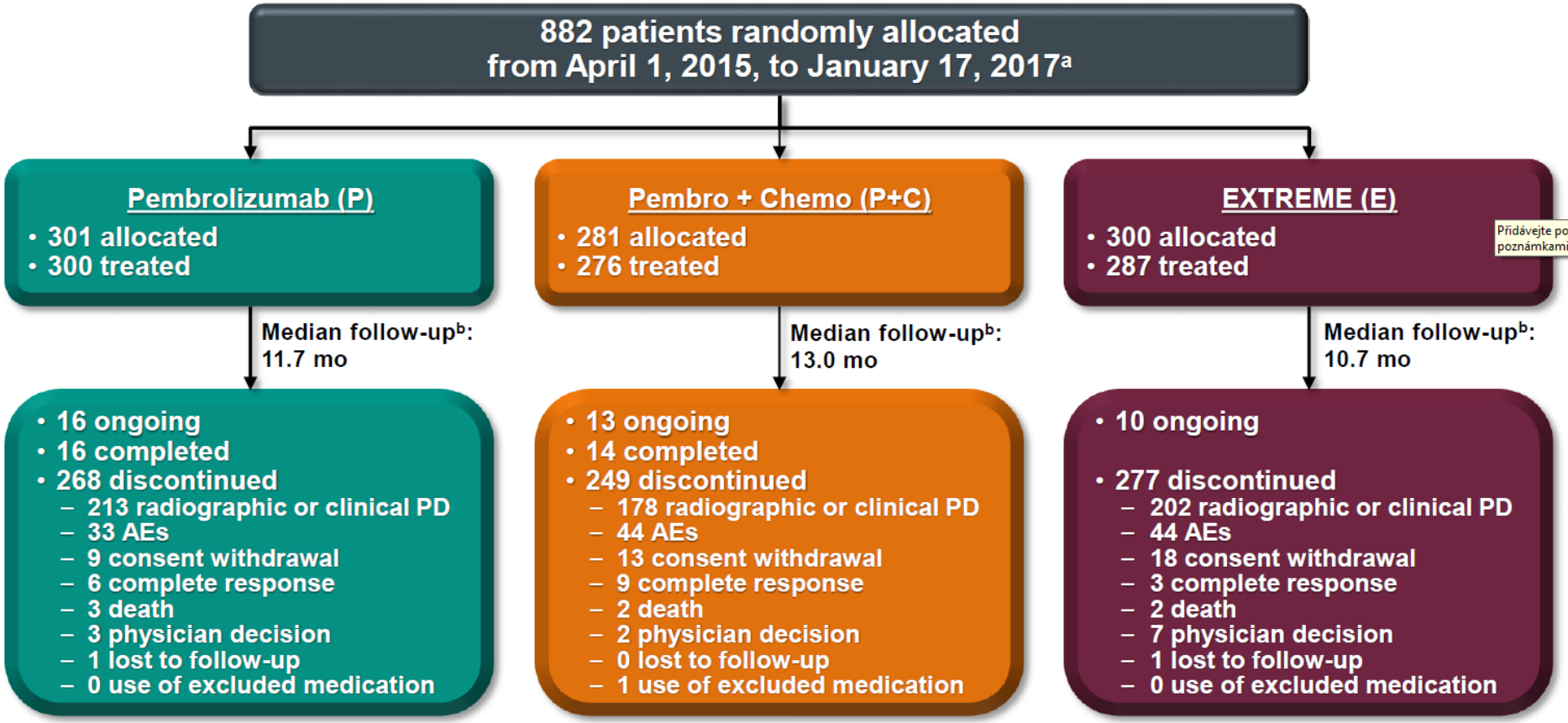
Disposition of All Randomized Patients



[a]There was an enrollment hold for the pembrolizumab + chemotherapy arm from Aug 13, 2015 to Oct 2, 2015.
[b]Defined as the time from randomization to the date of death or database cutoff date of Jun 13, 2018, if the patient was alive.

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Baseline Characteristics, ITT Population

Characteristic, n (%)	Pembro Alone vs EXTREME		Pembro + Chemo vs EXTREME	
	Pembro N = 301	EXTREME N = 300	Pembro + Chemo N = 281	EXTREME N = 278[a]
Age, median (range), yrs	62 (22-94)	61 (24-84)	61 (20-85)	61 (24-84)
Male	250 (83.1)	261 (87.0)	224 (79.7)	242 (87.1)
ECOG PS 1	183 (60.8)	183 (61.0)	171 (60.9)	170 (61.2)
Current/former smoker	239 (79.4)	234 (78.0)	224 (79.7)	215 (77.3)
p16 positive (oropharynx)	63 (20.9)	67 (22.3)	60 (21.4)	61 (21.9)
PD-L1 status				
TPS ≥50%	67 (22.3)	66 (22.0)	66 (23.5)	62 (22.3)
CPS ≥20	133 (44.2)	122 (40.7)	126 (44.8)	110 (39.6)
CPS ≥1	257 (85.4)	255 (85.0)	242 (86.1)	235 (84.5)
Disease status[b]				
Metastatic	216 (71.8)	203 (67.7)	201 (71.5)	187 (67.3)
Recurrent only[c]	82 (27.2)	94 (31.3)	76 (27.0)	88 (31.7)

[a]Patients randomized to EXTREME during the pembro + chemo enrollment hold were excluded from all pembro + chemo vs EXTREME efficacy comparisons.
[b]3 patients in the pembro arm, 3 patients in the EXTREME arm, and 4 patients in the pembro + chemo arm had neither metastatic nor recurrent disease.
[c]Includes locally recurrent disease and disease that spread to cervical lymph nodes. Data cutoff date: Jun 13, 2018.

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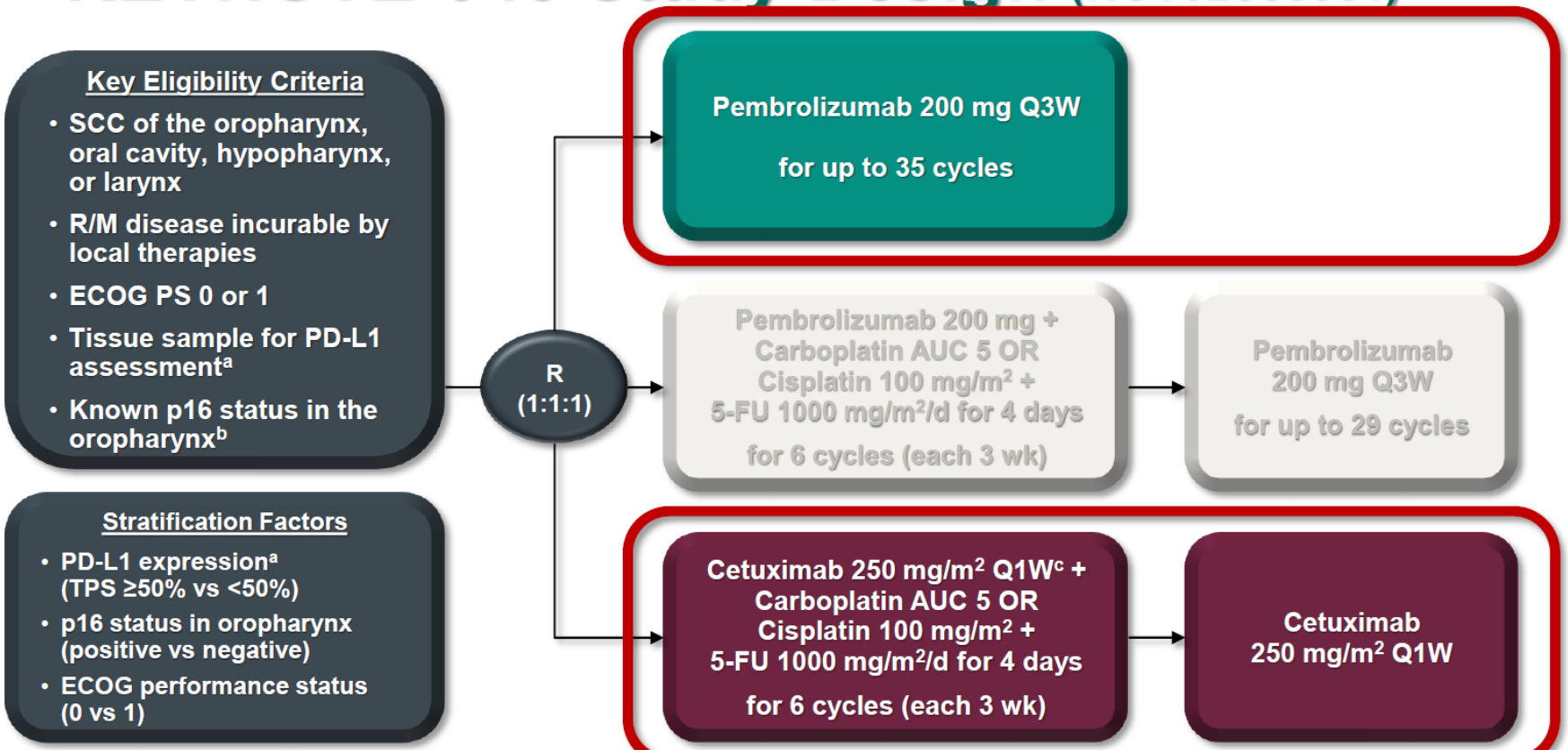
KEYNOTE-048 Study Design (NCT02358031)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

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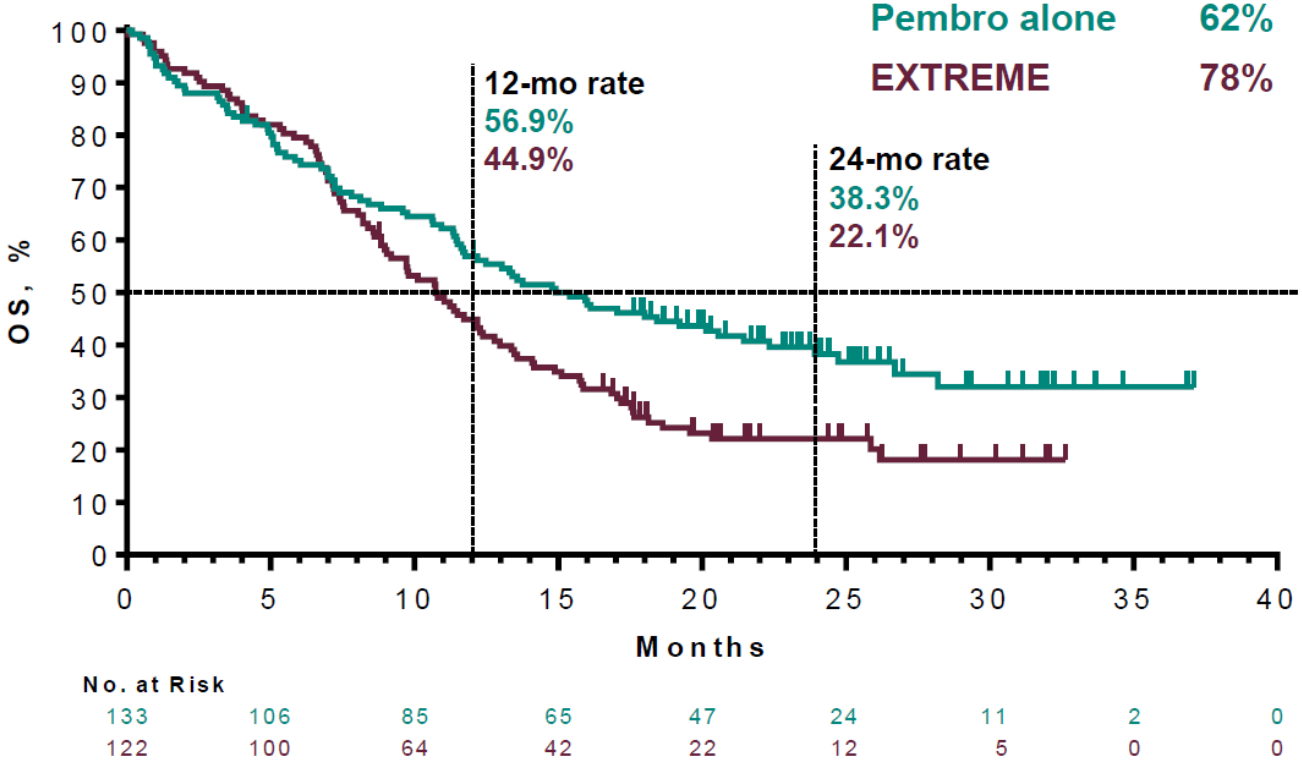
Overall Survival: P vs E, CPS ≥20 Population

	Events	HR (95% CI)	*P*
Pembro alone	62%	0.61 (0.45-0.83)	0.0007
EXTREME	78%		



Data cutoff date: Jun 13, 2018.

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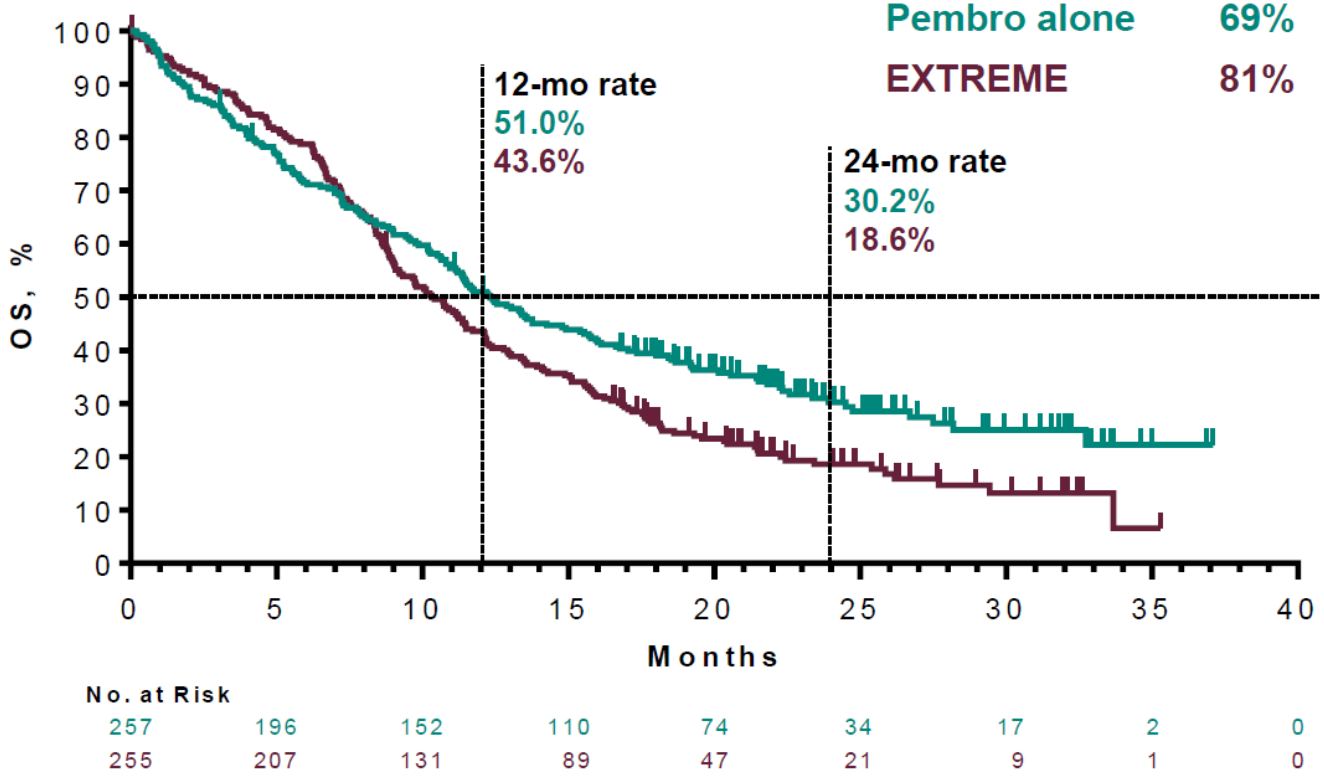
Overall Survival: P vs E, CPS ≥1 Population

	Events	HR (95% CI)	*P*
Pembro alone	69%	0.78 (0.64-0.96)	0.0086
EXTREME	81%		



Data cutoff date: Jun 13, 2018.

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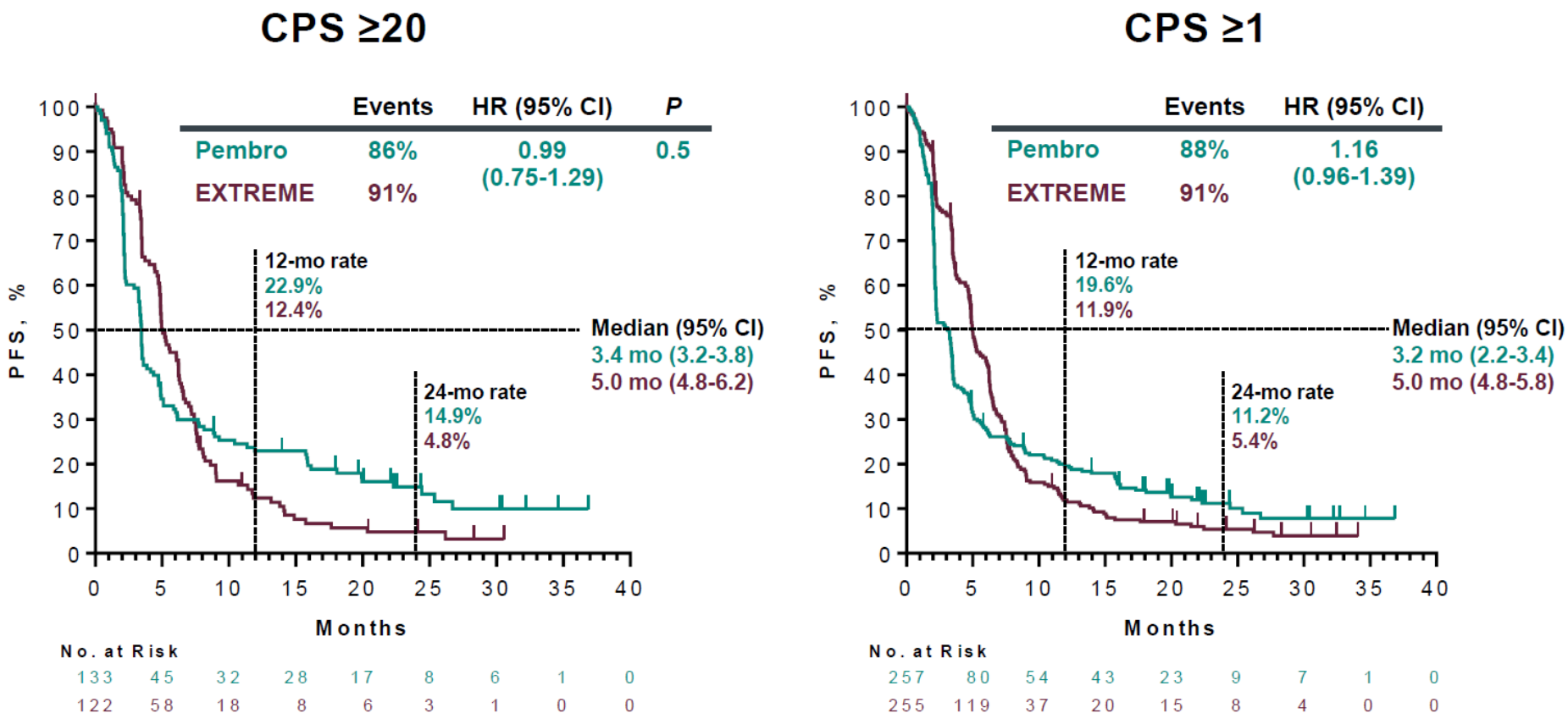
Progression-Free Survival: P vs E



Progression-free survival assessed per RECIST v1.1 by blinded, independent central radiologic review.
Data cutoff date: Jun 13, 2018.

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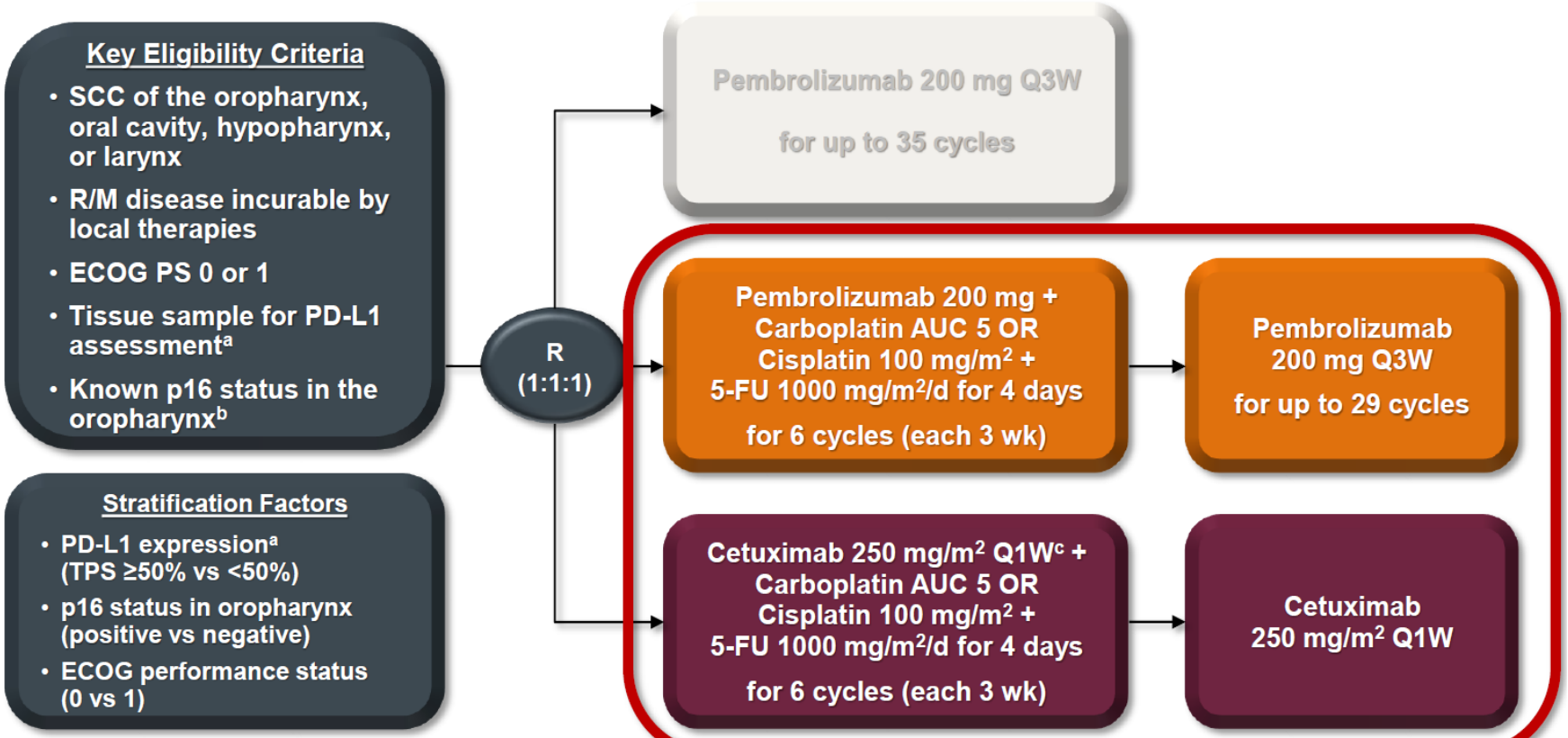
KEYNOTE-048 Study Design (NCT02358031)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion [illegible] of tumor cells with membranous PD-L1 expression. Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

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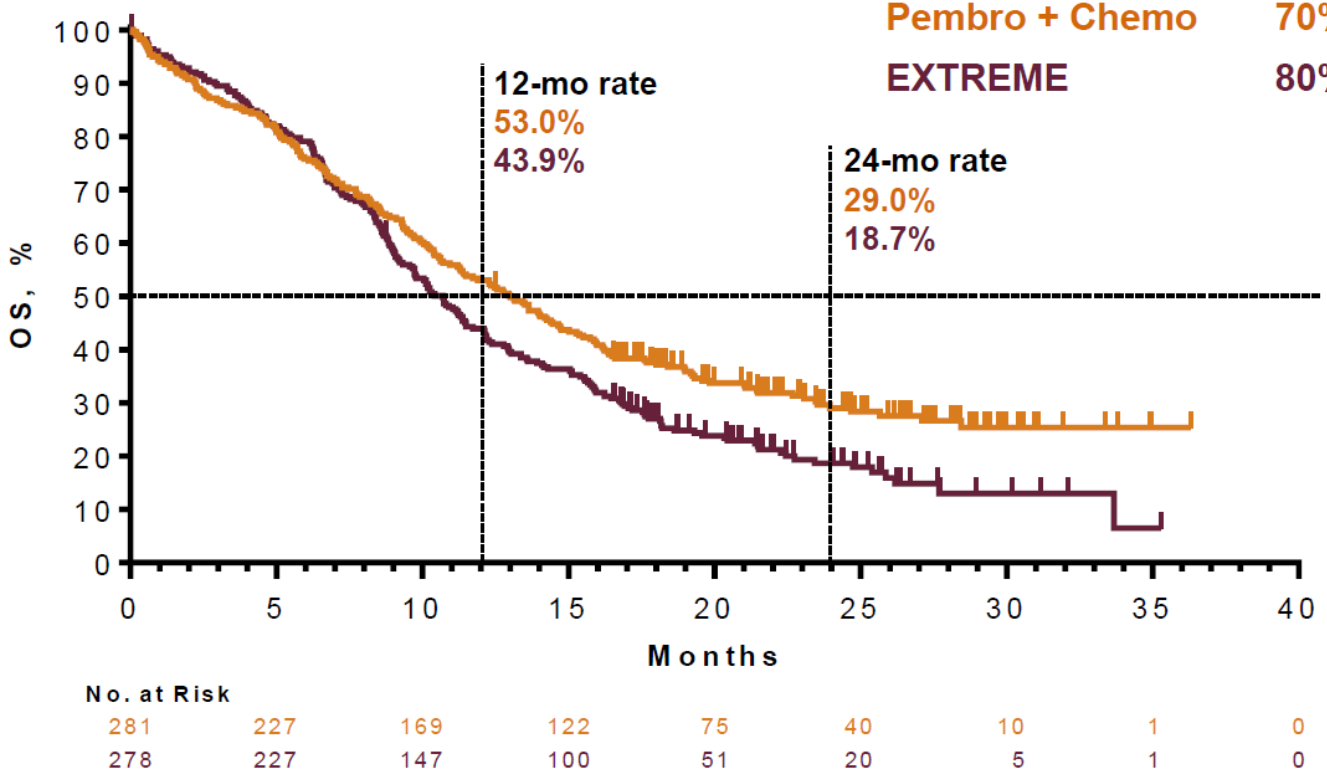
Overall Survival: P+C vs E, Total Population

	Events	HR (95% CI)	*P*
Pembro + Chemo	70%	0.77 (0.63-0.93)	0.0034
EXTREME	80%		



Data cutoff date: Jun 13, 2018.

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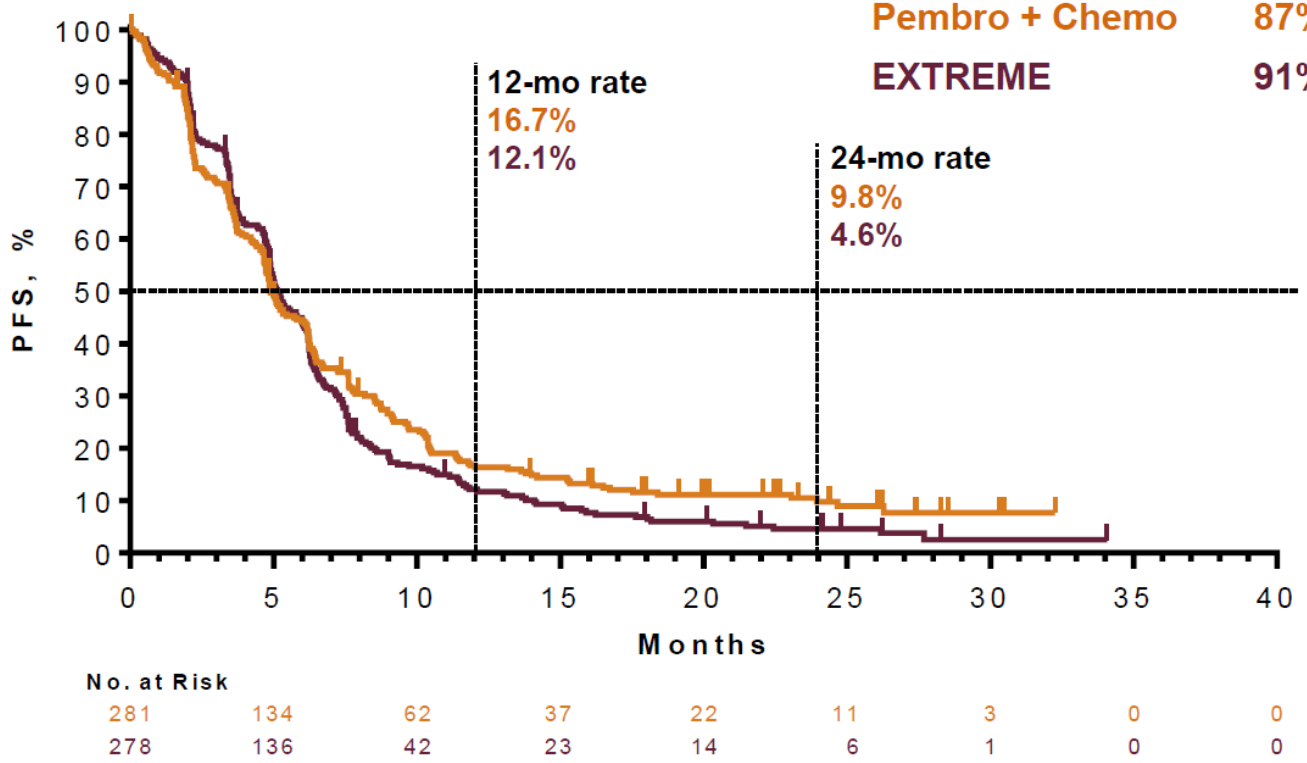
Progression-Free Survival: P+C vs E, Total Population



	Events	HR (95% CI)	*P*
Pembro + Chemo	87%	0.92 (0.77-1.10)	0.2
EXTREME	91%		

Median (95% CI)
4.9 mo (4.7-6.0)
5.1 mo (4.9-6.0)

Progression-free survival assessed per RECIST v1.1 by blinded, independent central radiologic review.
Data cutoff date: Jun 13, 2018.

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Další studie

Trial	Ramena	linie
EAGLE (Phase III)	durvalumab vs. durvalumab+tremelimumab vs. SoC	2. a další (po selhání Pt derivátu)
KESTREL (Phase III)	durvalumab vs. durvalumab+tremelimumab vs. SoC (EXTREME)	1. linie
CheckMate 651 (Phase III)	nivolumab + ipilimumab vs. SoC (EXTREME)	1. linie
CheckMate 714 (Phase III)	nivolumab + ipilimumab vs. Nivolumab + placebo	1. linie

Další studie

Trial	Ramena	linie
IMSTAR-HN (Phase III)	nivolumab or nivolumab+ipilimumab. vs. standard follow-up in surgical resectable cancer after adjuvant therapy	Kurativní přístup
NIVOPOSTOP	nivolumab + cDDP-RT vs. cDDP-RT postoperatively	Kurativní přístup
NCT03349710	nivolumab + cDDP-RT vs. placebo + cDDP-RT nebo nivolumab + cetuximab-RT vs. placebo + cetuximab-RT postoperatively	Kurativní přístup
MK-3475-412/KEYNOTE-412	pembrolizumab vs. placebo + cDDP-RT-RT	Kurativní přístup
MK-3475-689	pembrolizumab prior to surgery and in combination with RT post-surgery vs. SoC	Kurativní přístup
REACH	avelumab + RT-cetuximab vs. SoC: cisplatin-RT or RT-cetuximab	Kurativní přístup
JAVELIN HEAD AND NECK 100	avelumab + RT-cDDP vs. RT-cDDP	Kurativní přístup
NCT03452137	atezolizumab vs. placebo as adjuvant therapy after definitive local therapy	Kurativní přístup

Závěr:

- **Moderní imunoterapie získávat svou úlohu i u nádorů hlavy a krku**
- **Studie prokázaly efekt anti-PD-1 léčby ve druhé a dalších liniích rekurentních/metastatických nádorů hlavy a krku**
- **Čekáme na definitivní výsledky s anti-PD-1/anti-PD-L1 v první linii rekurentních/metastatických nádorů hlavy a krku**
- **Čekáme na výsledky studií anti-PD-1/anti-PD-L1 terapie v kombinaci s radioterapií a operačním výkonem v kurativních indikacích**
- **Predikce účinnosti imunoterapie…**

Děkuji za pozornost

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