IMMUNOTHERAPY IN HEAD AND NECK CANCER

SIMON ABI AAD, MD

FLORIDA PRECISION ONCOLOGY

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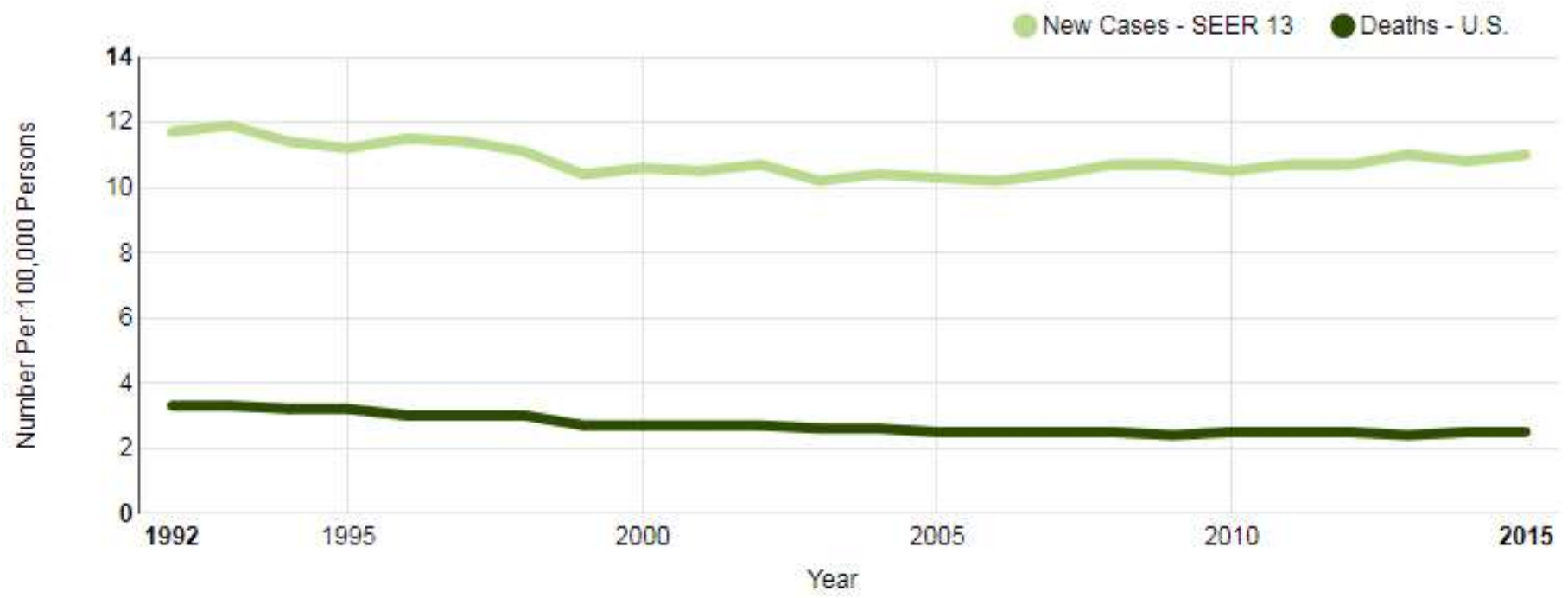
The Medical Educator Consortium

Some Statistics



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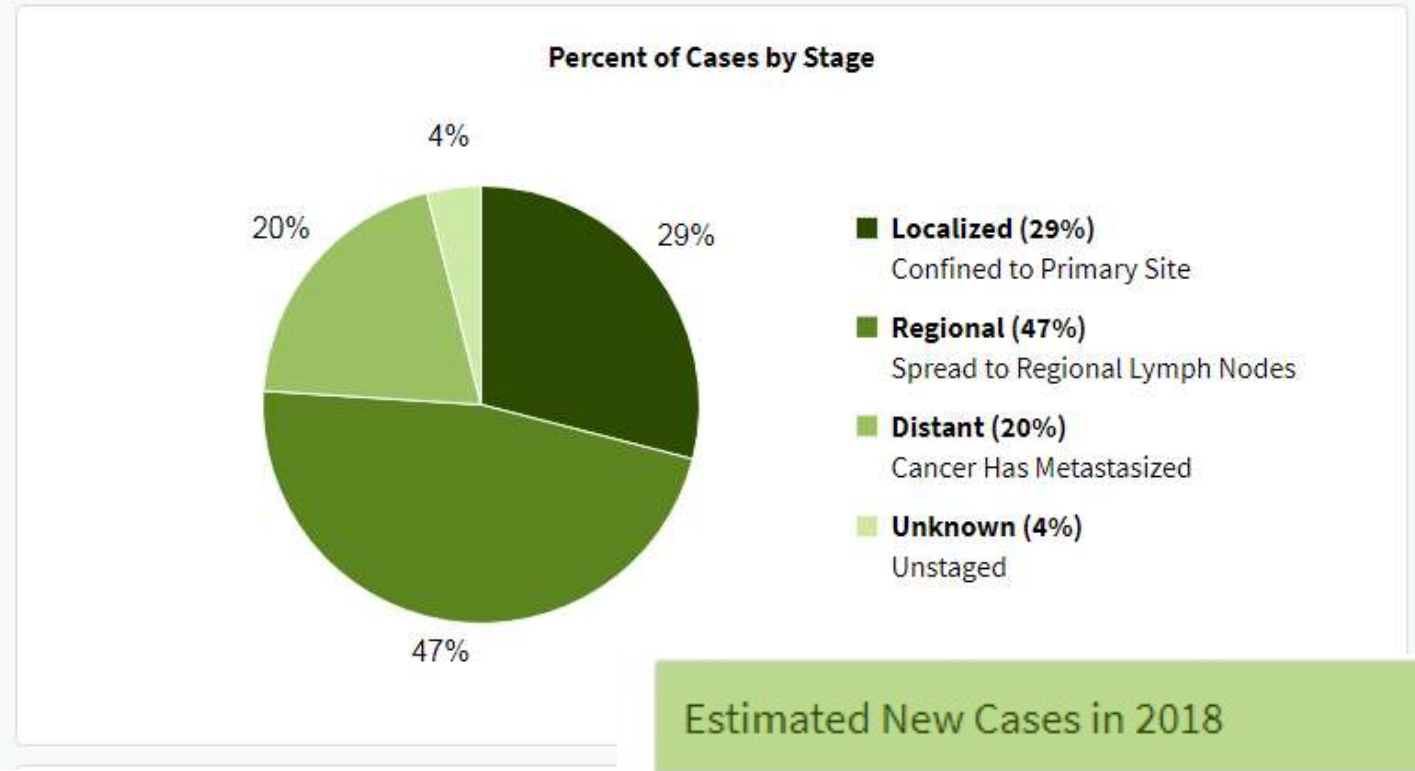
SEER 2018

Some Statistics

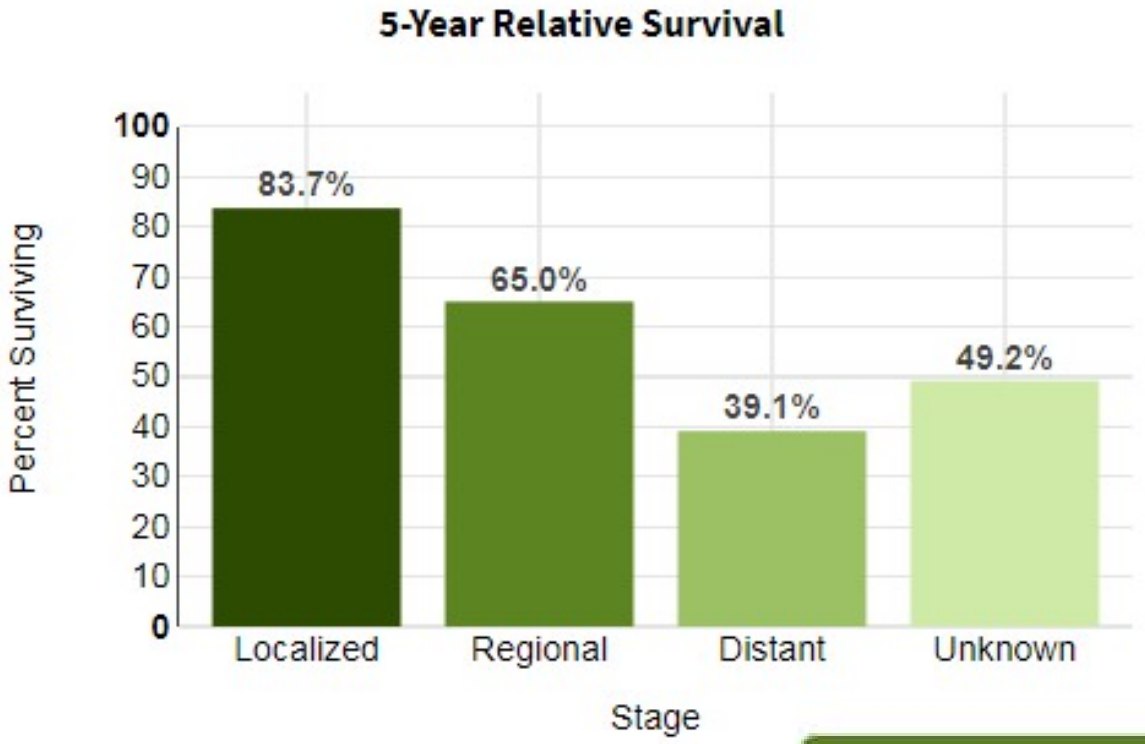


Estimated New Cases in 2018	51,540
% of All New Cancer Cases	3.0%

Estimated Deaths in 2018	10,030
% of All Cancer Deaths	1.6%

SEER 2018

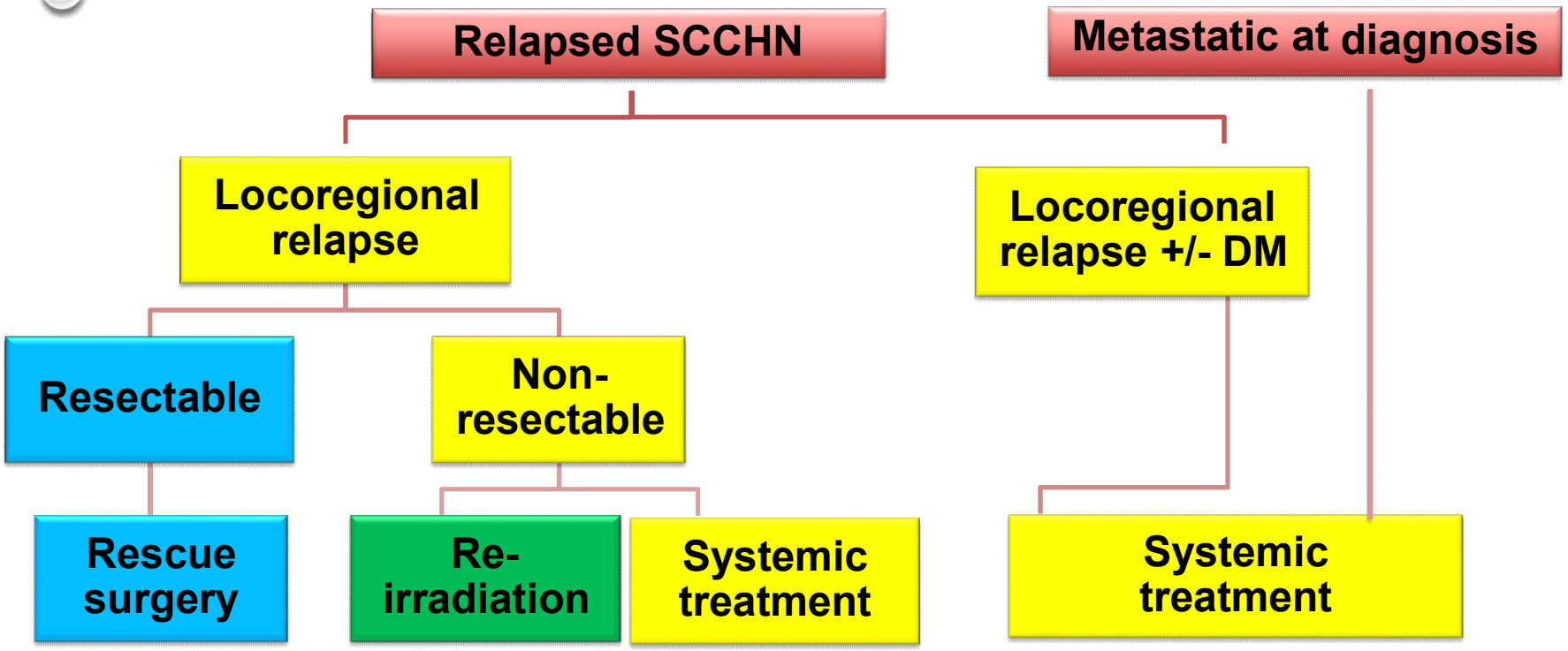
Some Statistics



Percent Surviving 5 Years
64.8%
2008-2014

SEER 2018

Treatment Options for R/M SCCHN



DM, distant mtastases; R/M, recurrent and/or metastatic

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Factors Associated With Poor Outcome

Patient Related
Poor performance status
Comorbidities
Poor cognitive status
Persistent use of carcinogens (smoking, alcohol)
Disease Related
Tumor sites (primary and recurrences)
Advanced state
Great volume disease
History of aggressive disease
Paraneoplastic hypercalcemia
Treatment Related
Previous treatments
Time to tumor progression
Poor or null response to previous treatment

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SCCHN R/M Not Suitable for Rescue Surgery or Re-Irradiation

- **Platinum-sensitive patients:**
  - **Recurrence after a combined treatment that included platinum with a PFS of more than 6 months**
  - **Platinum-naïve patients with R/M disease**
- **Platinum-refractory patients:**
  - **Recurrence after a combined treatment that included platinum with a PFS of less than 6 months**
  - **Patients with progressive disease during a platinum-containing treatment for R/M disease**

PFS, progression-free survival

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Cisplatin-Refractory R/M SCCHN

- Survival is very poor (≤6 months)
- Conventional anticancer treatments have not been effective in increasing survival
- Immunotherapy arises as a new treatment option in this setting

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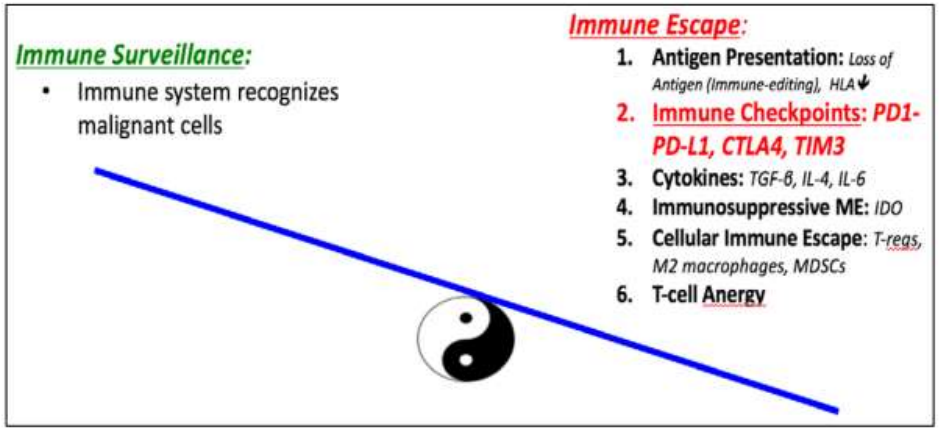
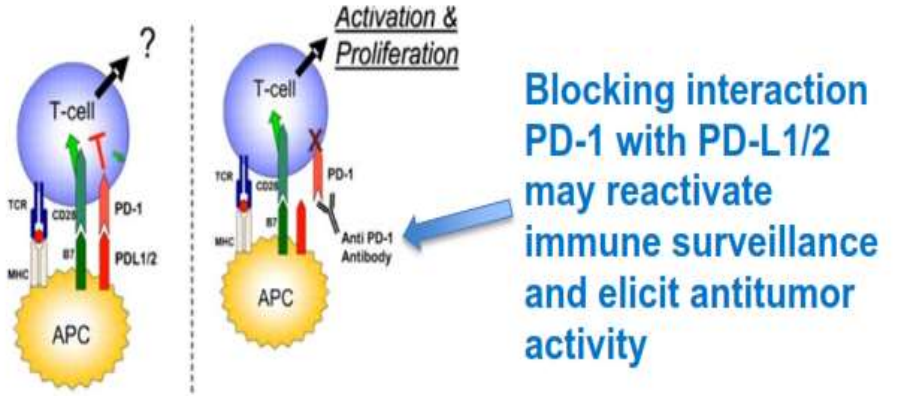
SCCHN May Benefit From Immune System–Targeted Treatments

- **High mutational burden due to tobacco usage, and expression of HPV-associated oncogenes, may contribute to immunogenicity in SCCHN tumors**
- **In HNSCC, tumors create a highly immunosuppressive microenvironment and can evade immune detection by exploiting inhibitory immune checkpoints such as PD-1/PD-L1**

Our goal is to:
Break Tolerance!





Blocking interaction PD-1 with PD-L1/2 may reactivate immune surveillance and elicit antitumor activity

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Keck MK, et al. *Clin Cancer Res*. 2015;21(4):870-881. Ferris RL. *J Clin Oncol*. 2015;33(29):3293-3304.

Targeting the PD1/PDL1 Pathway in HNSCC

	IO agent	N	Design	Population
Anti-PD-1	**Nivolumab (Checkmate 141)[1]**	**240**	**Phase III**	**Unselected for PD-L1, platinum refractory based therapy)**
	Pembrolizumab (Keynote-012)[2,3]	192	Single arm (Phase Ib)	PD-L1 positive (initial cohort)[1] and unselected for PD-L1 (expansion cohort)[3]
	Pembrolizumab (Keynote-055)[4]	171	Single arm (Phase II)	Unselected for PD-L1, after progression on platinum and cetuximab therapy
	Pembrolizumab (Keynote-040)[5]	**247**	**Phase III**	**Unselected for PD-L1, PD after platinum-containing months of multimodal therapy using platinum regimen for R/M HNSCC or progression within 3-6**
Anti-PD-L1	Durvalumab (study 1108)[6]	62	Single arm	Unselected for PD-L1 (received median 3 prior systemic Tx)
	Durvalumab (HAWK)[7]	112	Phase II Single arm	PD-L1 high (TC ≥25%), failure after 1 platinum-based chemotherapy in R/M setting
	Atezolizumab[8]	32	Phase Ia	Unselected for PD-L1, 53% received ≥2L

1. Ferris RL, et al. *N Engl J Med.* 2016;375(19):1856-1867. 2. Seiwert TY, et al. *Lancet Oncol.* 2016;17(7):956-965. 3. Chow LQ, et al. *J Clin Oncol.* 2016;34(32):3838-3845. 4. Bauml J, et al. *J Clin Oncol.* 2017;35(14):1542-1549. 5. Cohen EE, et al. *Ann Oncol.* 2017;28(suppl_5): Abstract LBA45_PR. 6. Segal NH, et al. *Ann Oncol.* 2016;27(Suppl 6): Abstract 949O. 7. Zandberg D, *et al. Ann Oncol.* 2017;28(Suppl 5):Abstract 1042O. 8. Bahleda R, et al. *Ann Oncol.* 2017;28(Suppl 5):1044O.

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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

Robert L. Ferris,[1] George Blumenschein Jr,[2] Jerome Fayette,[3] Joel Guigay,[4] A. Dimitrios Colevas,[5] Lisa Licitra,[6] Kevin J. Harrington,[7] Stefan Kasper,[8] Everett E. Vokes,[9] Caroline Even,[10] Francis Worden,[11] Nabil F. Saba,[12] Lara Carmen Iglesias Docampo,[13] Robert Haddad,[14] Tamara Rordorf,[15] Naomi Kiyota,[16] Makoto Tahara,[17] Mark Lynch,[18] Vijayvel Jayaprakash,[18] Li Li,[18] Maura L. Gillison[2]

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BACKGROUND

- Long-term prognosis for patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) post–platinum therapy has historically been poor, with a median overall survival (OS) of <6 months[1]
- Nivolumab demonstrated significant OS benefit and better tolerability vs investigator's choice (IC) in CheckMate 141, a randomized phase 3 trial:
  - Trial stopped early at the interim (primary) analysis due to statistically significant OS benefit
    - **Median OS: 7.5 vs 5.1 mo**; HR = 0.70 (97.73% CI: 0.51, 0.96); *P* = 0.01[2]
  - At minimum follow-up of 1-year, prolonged OS benefit was noted
    - **Median OS: 7.7 vs 5.1 mo**; HR = 0.71 (95% CI: 0.55, 0.90)[3]
  - Nivolumab was better tolerated, with stabilized quality of life, compared with IC (methotrexate, docetaxel, cetuximab)[2-4]
- At AACR 2018 (**2-year follow-up**) data in patients with R/M SCCHN post–platinum therapy from CheckMate 141

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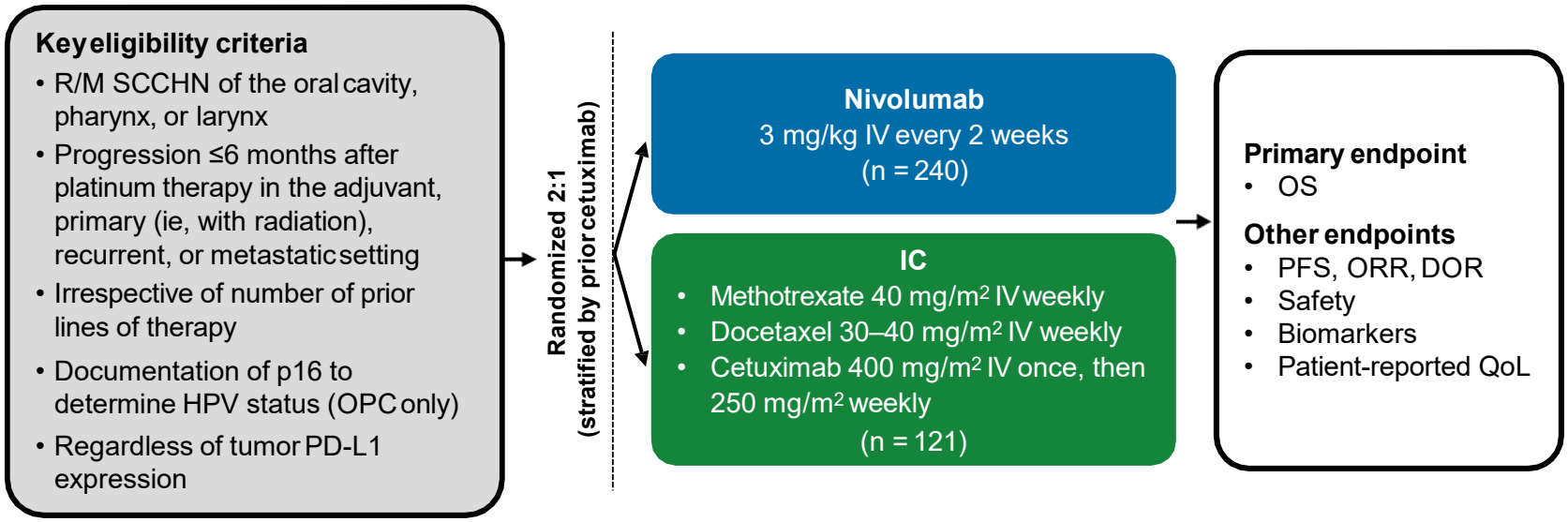
1. Saloura V, et al. *Cancer Chemother Pharmacol* 2014;73:1227–1239. 2. Ferris RL, et al. *N Engl J Med* 2016;375:1856–1867. 3. Gillison ML, et al. *The Oncologist* 2018; In Press. 4. Harrington KJ, et al. *Lancet Oncol* 2017;18:1104–1115.

CHECKMATE 141 STUDY DESIGN

- Randomized, open-label, phase 3 trial (NCT02105636)



- Data cutoff: September 2017 (minimum follow-up of 24.2 months)

DOR = duration of response; HPV = human papillomavirus; IV = intravenous; OPC = oropharyngeal cancer; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death ligand 1; PFS = progression-free survival; QoL = quality of life

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BASELINE CHARACTERISTICS

- Baseline characteristics were generally balanced between treatment arms, as previously reported

Patients, n (%)	Nivolumab (n = 240)	IC (n = 121)
Tumor PD-L1 expression[a]		
≥1% (PD-L1 expressors)	96 (40.0)	63 (52.1)
<1% (PD-L1 non-expressors)	76 (31.7)	40 (33.1)
Not quantifiable[b]	68 (28.3)	18 (14.9)
HPV status[c]		
Positive	64 (26.7)	29 (24.0)
Negative	56 (23.3)	37 (30.6)
Unknown/not reported	120 (50.0)	55 (45.5)

[a]PD-L1 status was determined using the Dako PD-L1 IHC 28-8 pharmDx test
[b]Tumor not present, sample not provided, or sample could not be processed
[c]HPV status was assessed using p16 immunohistochemical testing; required only for patients with OPC

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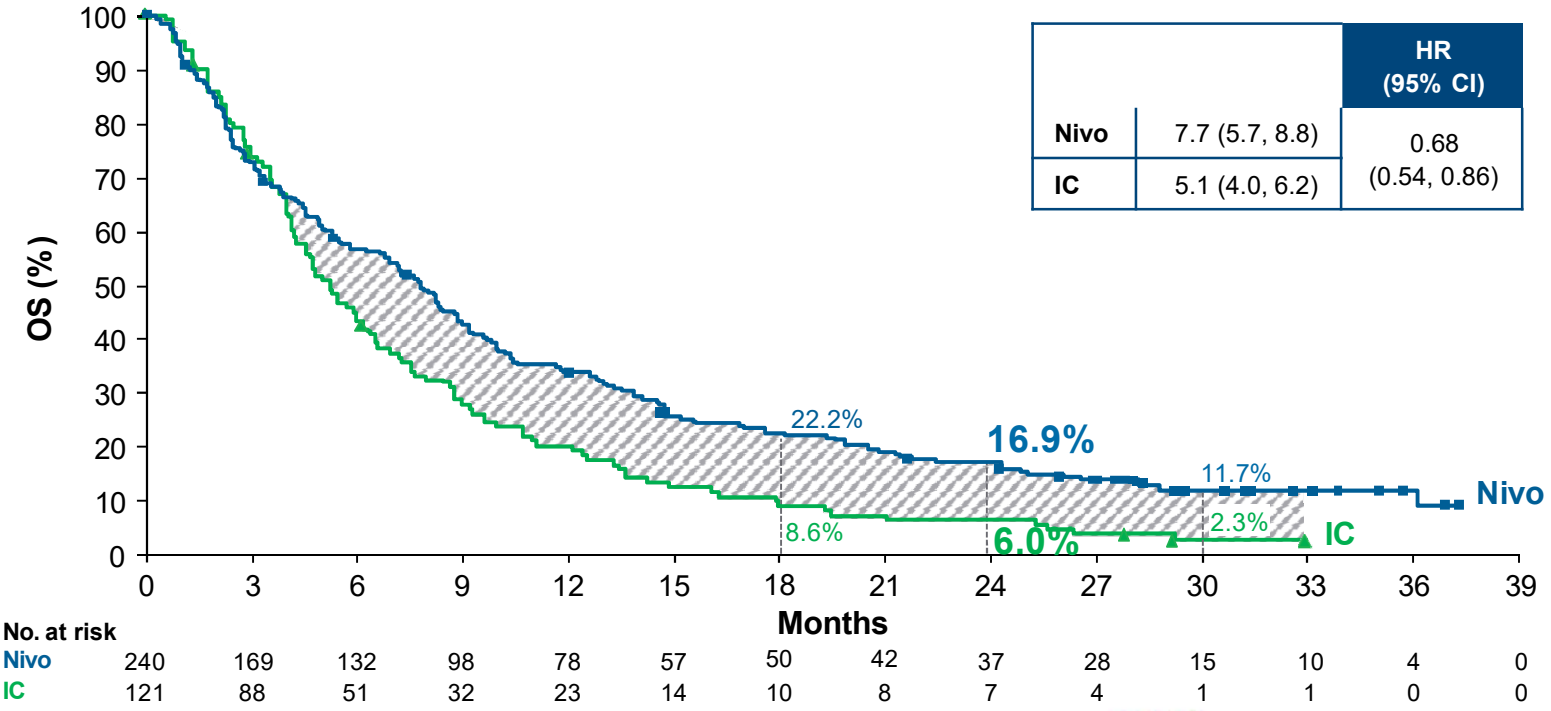
SUSTAINED OS BENEFIT IN THE OVERALL (ITT) POPULATION

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



		HR (95% CI)
Nivo	7.7 (5.7, 8.8)	0.68 (0.54, 0.86)
IC	5.1 (4.0, 6.2)	

No. at risk

Nivo	240	169	132	98	78	57	50	42	37	28	15	10	4	0
IC	121	88	51	32	23	14	10	8	7	4	1	1	0	0

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

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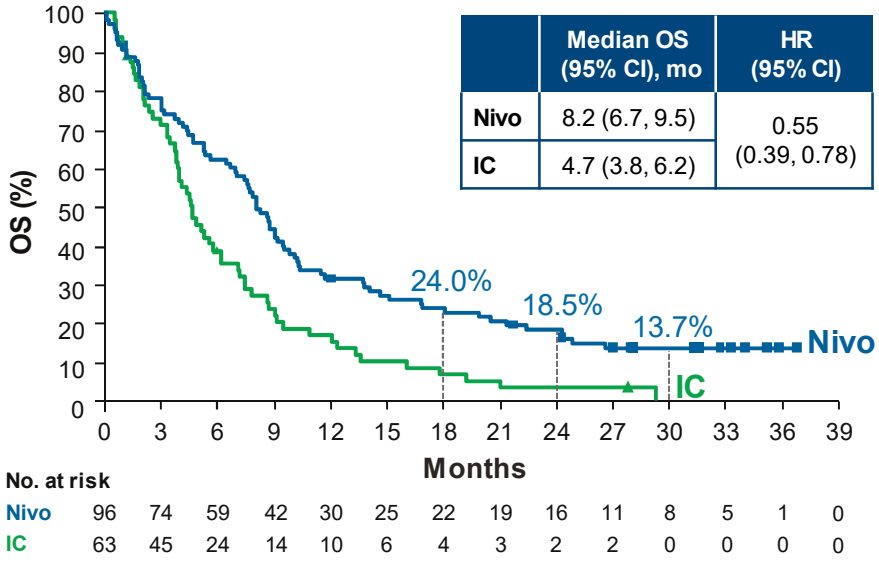
OS BENEFIT ACROSS PD-L1 EXPRESSORS AND NON-EXPRESSORS

- 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

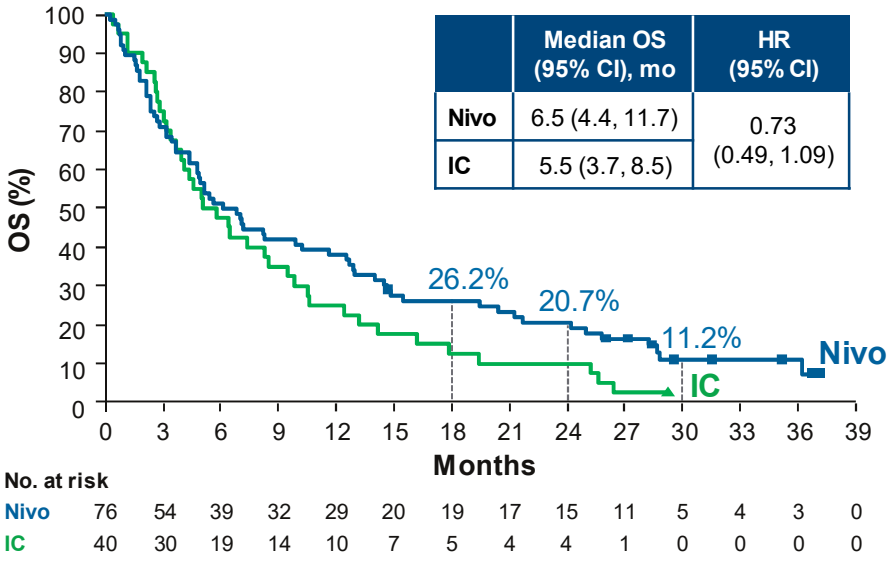
PD-L1 Expressors (≥1%)



	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

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OS IN PD-L1 NON-EXPRESSORS (<1%)

- In PD-L1 non-expressors, the HR for risk of death with nivolumab vs IC consistently trended lower with longer follow-up

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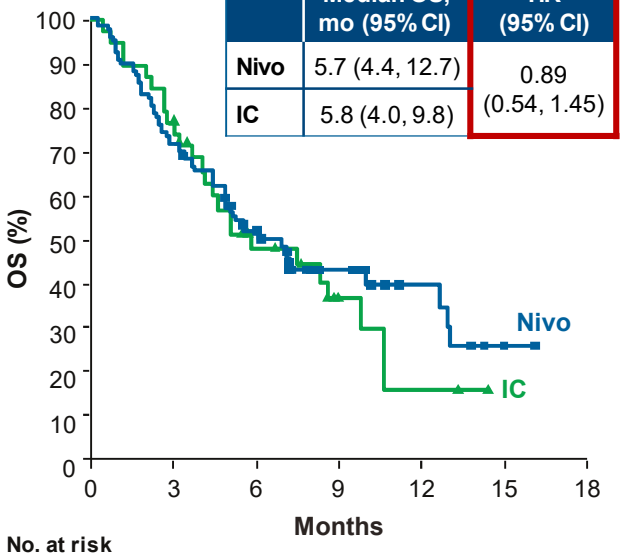
OS IN PD-L1 NON-EXPRESSORS (<1%)

- In PD-L1 non-expressors, the HR for risk of death with nivolumab vs IC consistently trended lower with longer follow-up

Primary Analysis[a]
(Dec 2015 data cutoff)

	Median OS, mo (95% CI)	HR (95% CI)
Nivo	5.7 (4.4, 12.7)	0.89 (0.54, 1.45)
IC	5.8 (4.0, 9.8)	



No. at risk

Nivo	73	52	33	17	8	3	0
IC	38	29	14	6	2	0	0

Symbols represent censored observations; [a]FromNEJM, Ferris RL et al., Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck, 375, 1856-67, Copyright © 2016 Massachusetts Medical Society. Reprinted w ith permission fromMassachusetts Medical Society.

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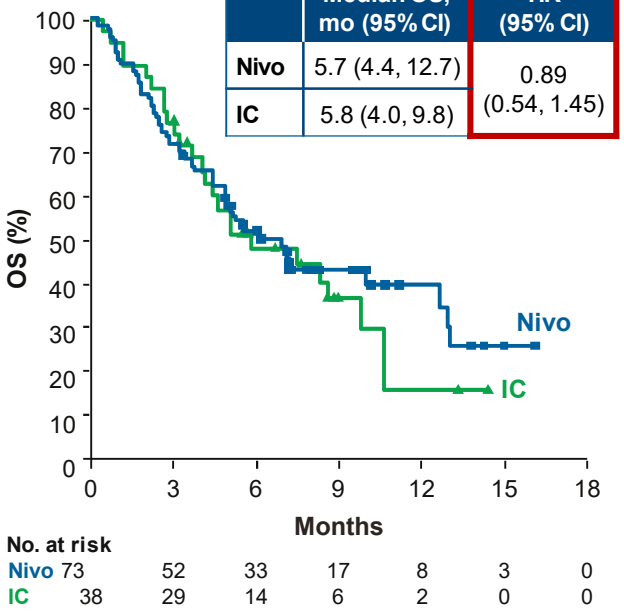
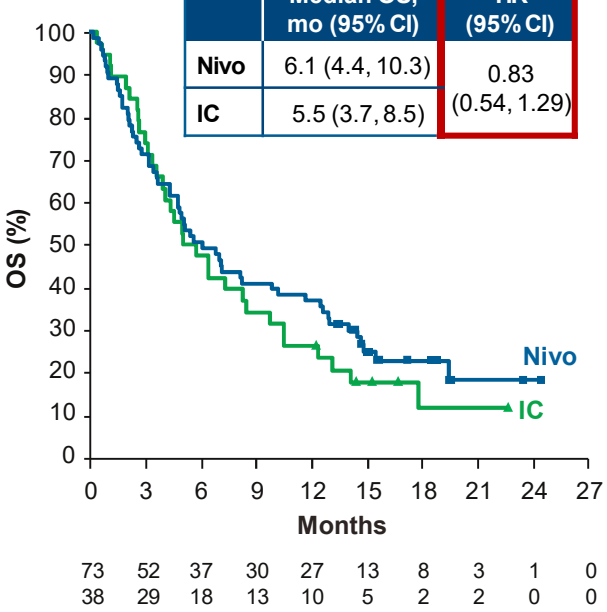


1-Year Follow-up (Sept 2016 data cutoff)

	Median OS, mo (95% CI)	HR (95% CI)
Nivo	6.1 (4.4, 10.3)	0.83 (0.54, 1.29)
IC	5.5 (3.7, 8.5)	



No. at risk							
Nivo	73	52	33	17	8	3	0
IC	38	29	14	6	2	0	0

73	52	37	30	27	13	8	3	1	0
38	29	18	13	10	5	2	2	0	0

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OS IN PD-L1 NON-EXPRESSORS (<1%)

- In PD-L1 non-expressors, the HR for risk of death with nivolumab vs IC consistently trended lower with longer follow-up

Primary Analysis[a] (Dec 2015 data cutoff)

	Median OS, mo (95% CI)	HR (95% CI)
Nivo	5.7 (4.4, 12.7)	0.89 (0.54, 1.45)
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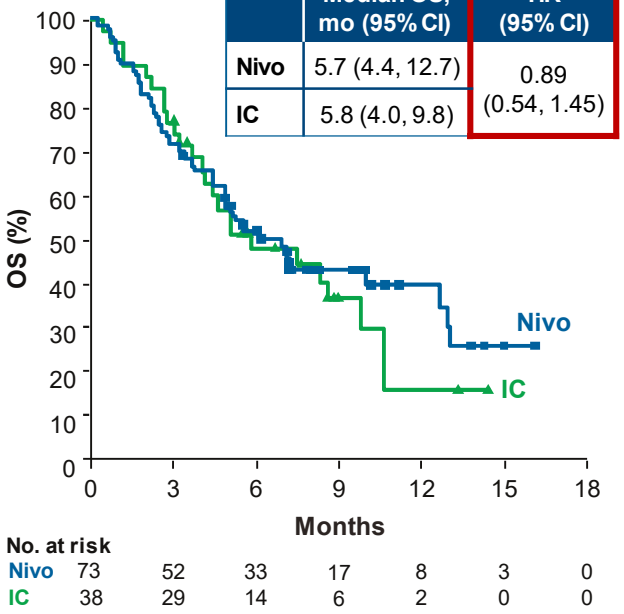

No. at risk

Nivo	73	52	33	17	8	3	0
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1-Year Follow-up (Sept 2016 data cutoff)

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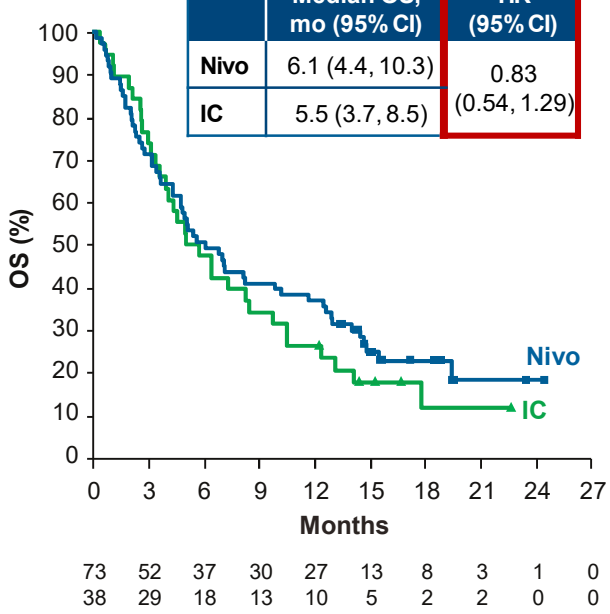
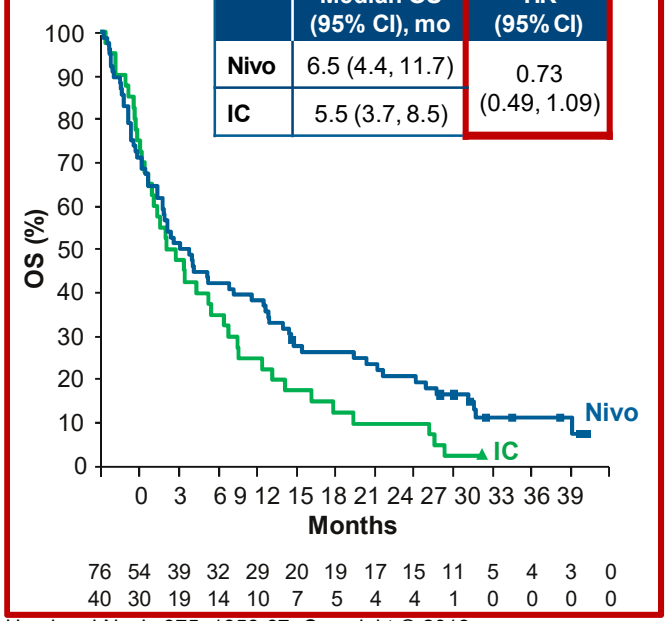
IC	5.5 (3.7, 8.5)	



Nivo	73	52	37	30	27	13	8	3	1	0
IC	38	29	18	13	10	5	2	2	0	0

2-Year Follow-up (Sept 2017 data cutoff)

	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)	



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

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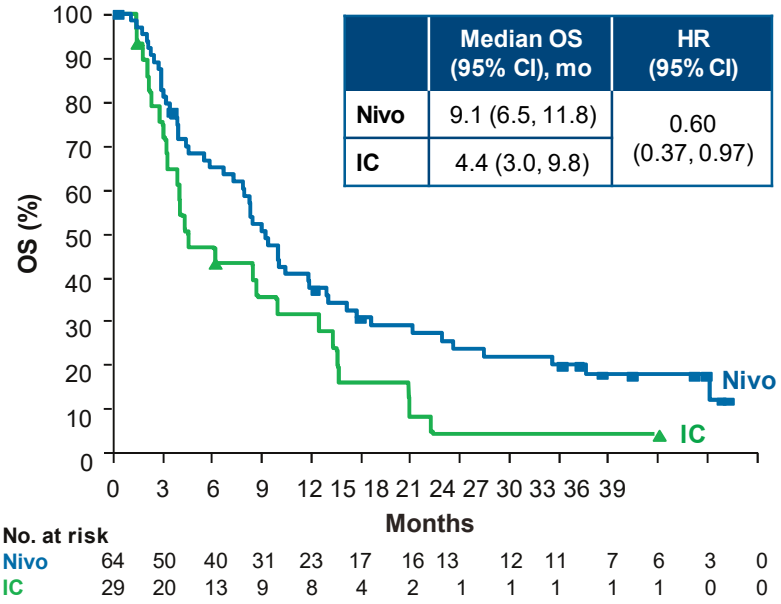
OS BY HPV STATUS

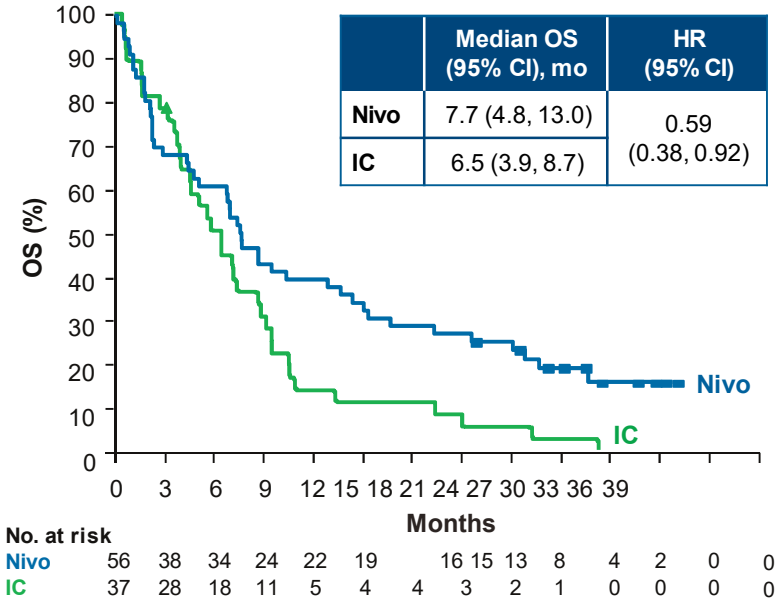
- Nivolumab demonstrated survival benefit in patients with HPV-positive and HPV-negative tumors, with comparable HRs for risk of death vs IC

HPV-Positive



	Median OS (95% CI), mo	HR (95% CI)
Nivo	9.1 (6.5, 11.8)	0.60 (0.37, 0.97)
IC	4.4 (3.0, 9.8)	

HPV-Negative



	Median OS (95% CI), mo	HR (95% CI)
Nivo	7.7 (4.8, 13.0)	0.59 (0.38, 0.92)
IC	6.5 (3.9, 8.7)	

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

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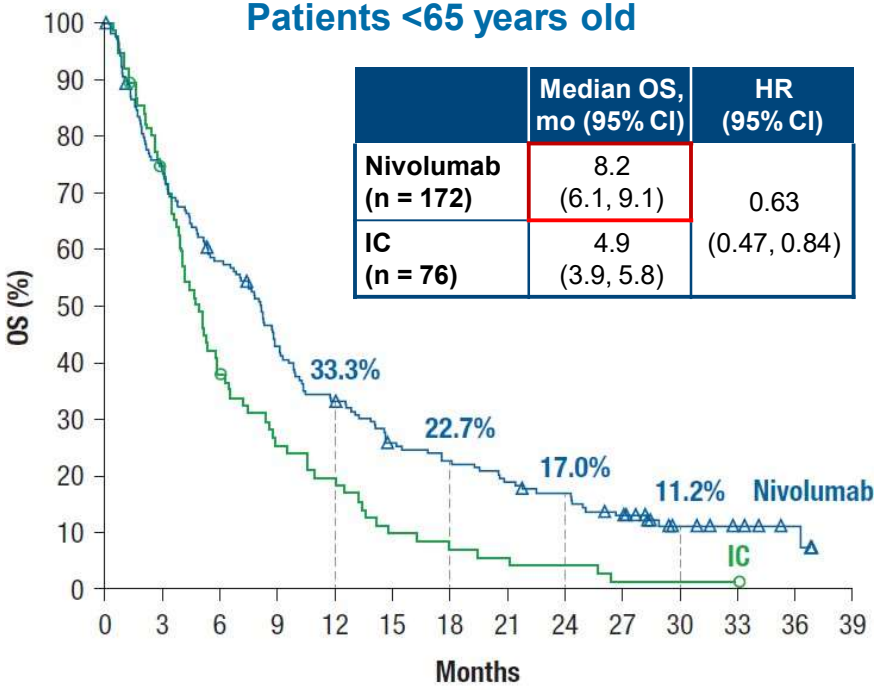
OVERALL SURVIVAL BY AGE

Patients <65 years old

	Median OS, mo (95% CI)	HR (95% CI)
Nivolumab (n = 172)	8.2 (6.1, 9.1)	0.63 (0.47, 0.84)
IC (n = 76)	4.9 (3.9, 5.8)	

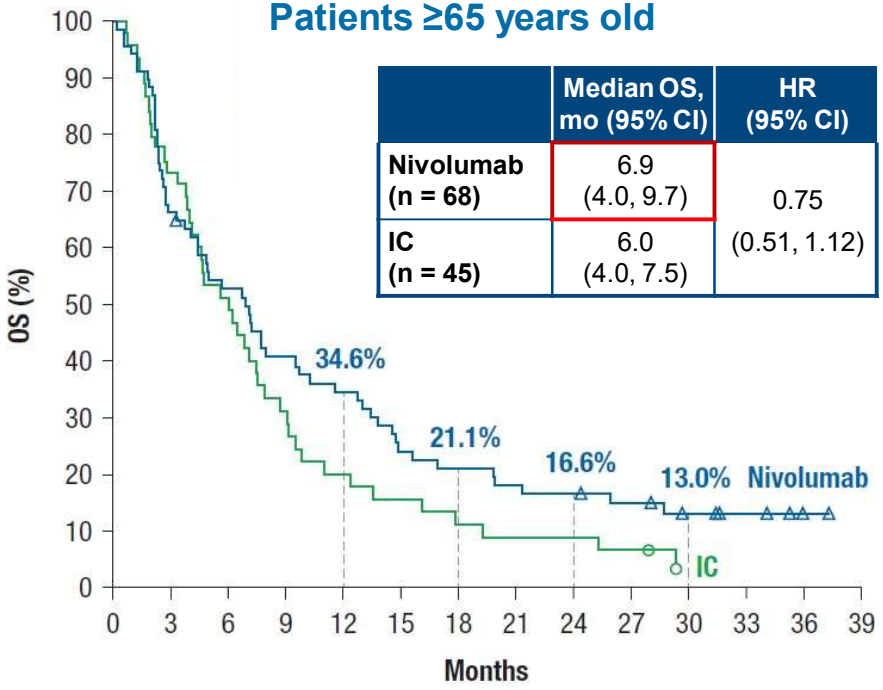


No. at risk

Nivo	172	124	97	71	55	41	36	30	26	19	9	6	3	0
IC	76	55	28	18	14	7	5	4	3	1	1	1	0	0

Patients ≥65 years old

	Median OS, mo (95% CI)	HR (95% CI)
Nivolumab (n = 68)	6.9 (4.0, 9.7)	0.75 (0.51, 1.12)
IC (n = 45)	6.0 (4.0, 7.5)	



	68	45	35	27	23	16	14	12	11	9	6	4	1	0
	45	33	23	14	9	7	5	4	4	3	0	0	0	0

Saba et al. ASCO 2018

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SUBSEQUENT THERAPIES AMONG PATIENTS WHO DISCONTINUED TREATMENT

- Nivolumab continued to improve in OS vs IC in spite of subsequent immunotherapy in 10.1% of patients in the IC arm

Patients, n (%)	Nivolumab (n = 228)	IC (n = 109)
Any therapy[a]	91 (39.9)	43 (39.4)
Radiotherapy	30 (13.2)	14 (12.8)
Surgery	2 (0.9)	3 (2.8)
Systemic therapy	82 (36.0)	36 (33.0)
Taxanes	35 (15.4)	11 (10.1)
Monoclonal antibodies (bevacizumab, cetuximab)	31 (13.6)	8 (7.3)
Other – approved agents	31 (13.6)	12 (11.0)
Folic acid analogue	22 (9.6)	7 (6.4)
Platinum-based chemotherapy	16 (7.0)	11 (10.1)
Other – experimental agents	15 (6.6)	3 (2.8)
Immunotherapy (nivolumab, pembrolizumab, durvalumab, urelumab)	12 (5.3)	11 (10.1)
PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab, durvalumab)	9 (3.9)	10 (9.2)
Unassigned	1 (0.4)	0

[a]Patients may have received more than 1 type of subsequent therapy, which was defined as non-study anticancer therapy started on or after first dosing date (or randomization date, if patient was not treated)

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TREATMENT-RELATED ADVERSE EVENTS

- The safety profile of nivolumab remained consistentwith previous analyses,[1,2] and manageable
  - Fewer grade 3–4 events in the nivolumab arm vs the IC arm
  - No new safety signals were reported
- The incidence of serious TRAEs was lower in the nivolumab arm (7.2%) vs the IC arm (15.3%)
- Rates of death due to drug toxicity remained unchanged from the primary analysis[1]

	Nivolumab (n = 236)		IC (n = 111)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE, n (%)	146 (61.9)	36 (15.3)	88 (79.3)	41 (36.9)
TRAEs in ≥15% of patients, n (%)				
Fatigue	37 (15.7)	5 (2.1)	20 (18.0)	3 (2.7)
Nausea	22 (9.3)	0	23 (20.7)	1 (0.9)
Anemia	12 (5.1)	3 (1.3)	19 (17.1)	6 (5.4)
Asthenia	10 (4.2)	1 (0.4)	17 (15.3)	2 (1.8)

1. Ferris RL, et al. *N Engl J Med* 2016;375:1856–1867. 2. Gillison ML, et al. *The Oncologist* 2018; In Press.
TRAE = treatment-related adverse event

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CONCLUSIONS

- Nivolumab improves OS vs IC in patients with R/M SCCHN post–platinum therapy, in the primary analysis of a randomized, phase 3 study (CheckMate 141)
  - Primary analysis: HR = 0.70 (97.73% CI: 0.51, 0.96); *P* = 0.01
  - 2-year follow-up: HR = 0.68 (95% CI: 0.54, 0.86)
- With long-term (2-year) follow-up, nivolumab demonstrated prolonged OS benefit compared with IC in the overall population with
  - Efficacy across PD-L1 expressors and non-expressors
  - Efficacy regardless of tumor HPV status
  - A favorable safety profile compared with IC maintained; no new safety signals observed
  - No observed differences in baseline characteristics or safety profile among long-term survivors in the nivolumab arm compared with the overall nivolumab population
- Nivolumab is an established therapeutic option in R/M SCCHN post–platinum therapy, with demonstrated long-term benefits in OS and safety compared with monotherapy options

UPDATED SURVIVAL RESULTS OF THE KEYNOTE-040 STUDY OF PEMBROLIZUMAB VS SOC CHEMOTHERAPY FOR RECURRENT OR METASTATIC HNSCC

Denis Soulières et al. AACR 2018

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PEMBROLIZUMAB AND HNSCC

Study	Population	ORR	Median DOR	Median PFS
KEYNOTE-012[1]	PD-L1–positive R/M HNSCC (N = 61)	18%	12.2 months	2 months
KEYNOTE-012 expansion cohort[2]	R/M HNSCC of any PD-L1 expression (N = 132)	Total: 18% PD-L1^{+}: 22% PD-L1^{-}: 4%	Not reached	2 months
KEYNOTE-055[3]	Platinum and cetuximab-refractory HNSCC of any PD-L1 expression (N = 171)	Total: 16% PD-L1^{+}: 18% PD-L1^{-}: 12%	8 months	2.1 months

1. Seiwert TY et al. *Lancet Oncol* 2016;17:956-965. 2. Chow LQM et al. *J Clin Oncol* 2016;34:3838-3845. 3. Bauml J et al. *J Clin Oncol* 2017;35:1542-1549.

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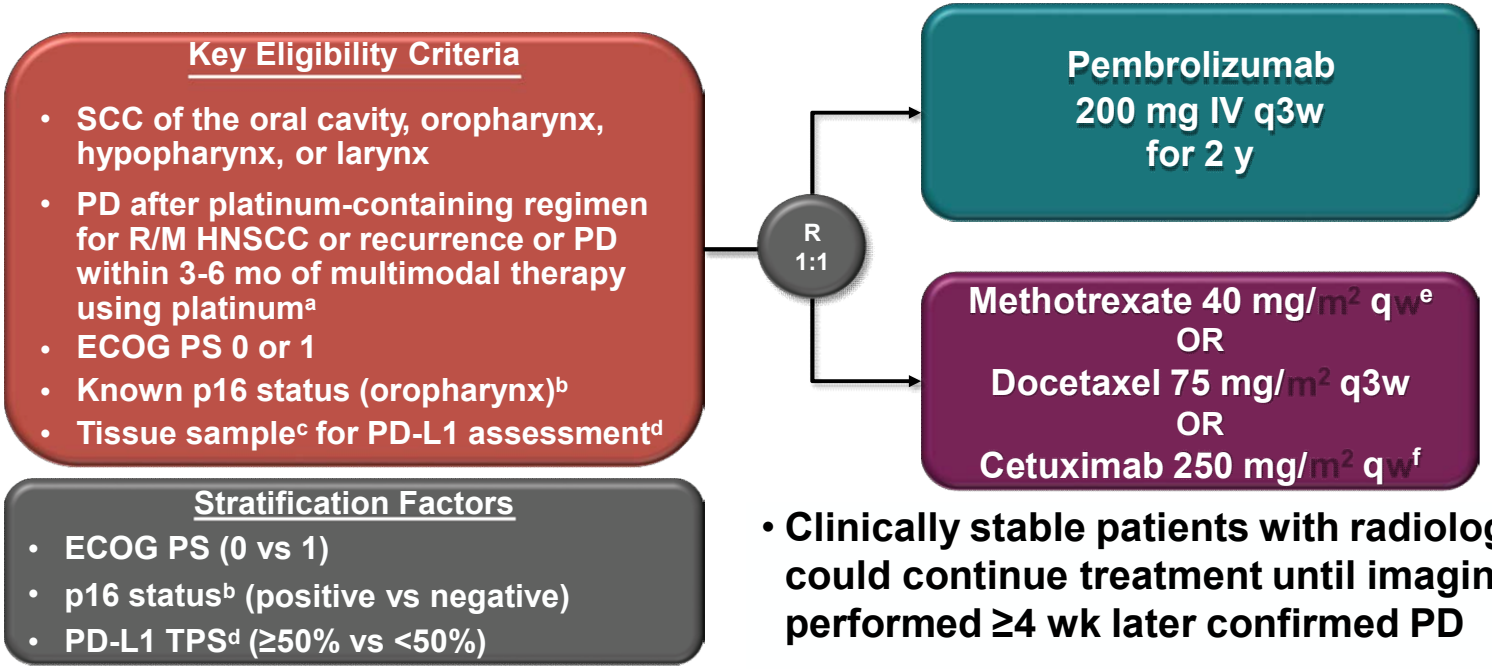
Phase III KEYNOTE-040 Study



- 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. 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.

Cohen E, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA45_PR.

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KEYNOTE – 040: PRIMARY AND UPDATED ANALYSES

- Primary analysis presented at ESMO 2017
  - Prespecified significance boundary: P = 0.0175
  - Data cutoff date: May 15, 2017
  - No. of Death: 377 (data outstanding for 11 patients)
  - OS: HR 0.81 (95% CI 0.66-0.99), P= 0.02024

- Updated analysis
  - Same data cutoff date: May 15, 2017 (i.e., update is without extending f/u duration)
  - Full acquisition of survival status, including the 11 pts previously outstanding
  - No. of death after acquisition of survival status: 388

FLORIDA PRECISION ONCOLOGY

Cohen E, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA45_PR.

KEYNOTE – 040: BASELINE CHARACTERISTICS

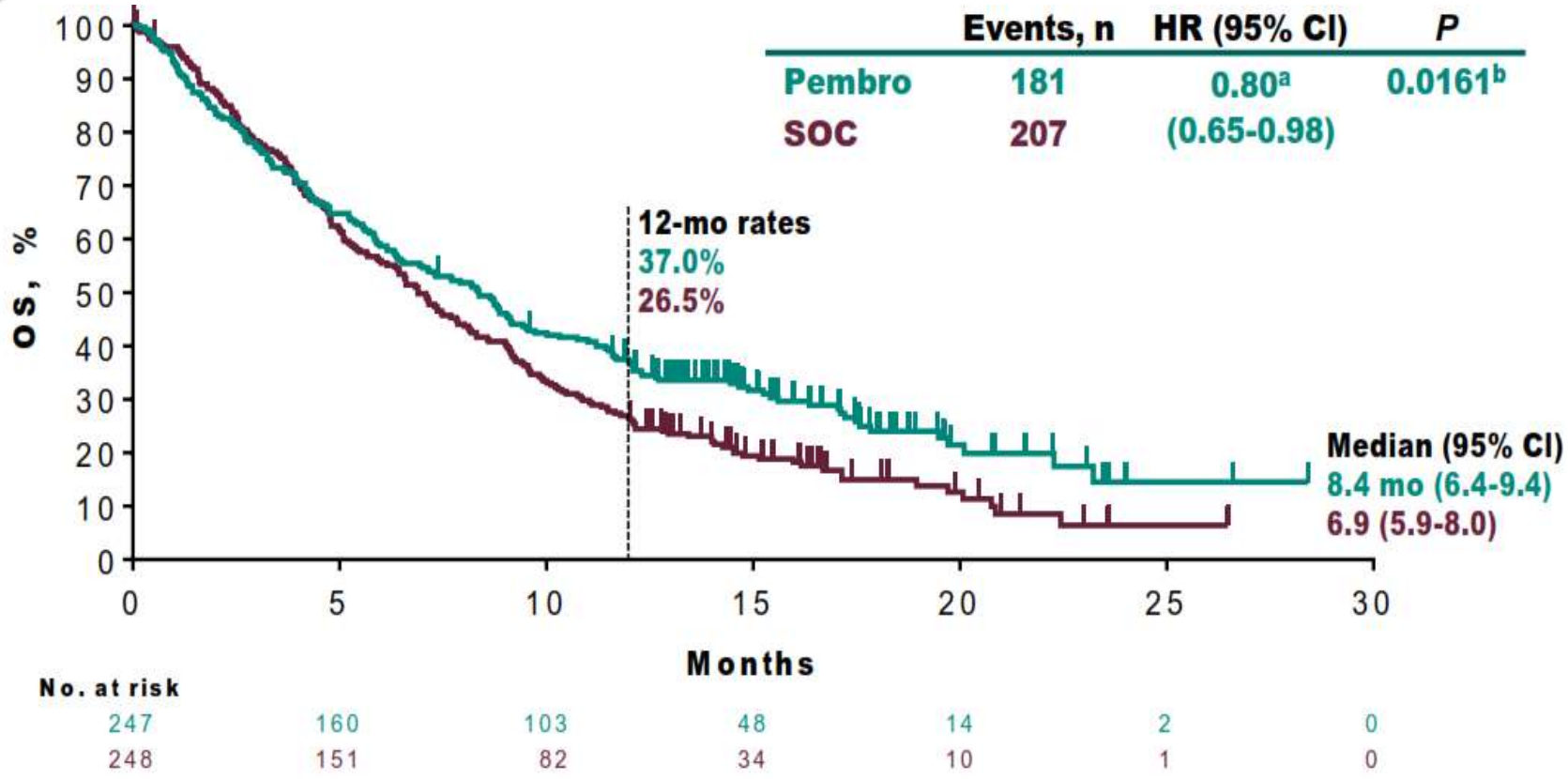
Characteristic, n (%)	Pembro N = 247	SOC N = 248
Age, median (range)	60 (19-85)	60 (34-78)
Male	207 (83.8)	205 (82.7)
ECOG PS 1	176 (71.3)	180 (72.6)
Current/former smoker	179 (72.5)	182 (73.4)
Region of enrollment		
Europe	147 (59.5)	158 (63.7)
North America	73 (29.6)	60 (24.2)
Rest of world	27 (10.9)	30 (12.1)

Characteristic, n (%)	Pembro N = 247	SOC N = 248
p16 positive (oropharynx)	61 (24.7)	58 (23.4)
PD-L1 TPS ≥50%	64 (25.9)	65 (26.2)
PD-L1 CPS ≥1	196 (79.4)	191 (77.0)
Prior therapy		
(Neo)adjuvant or definitive	34 (13.8)	40 (16.1)
First line	141 (57.1)	141 (56.9)
Second line	69 (27.9)	64 (25.8)
Third line	3 (1.2)	3 (1.2)

FLORIDA PRECISION ONCOLOGY

Cohen E, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA45_PR.

Updated Overall Survival in ITT Population



[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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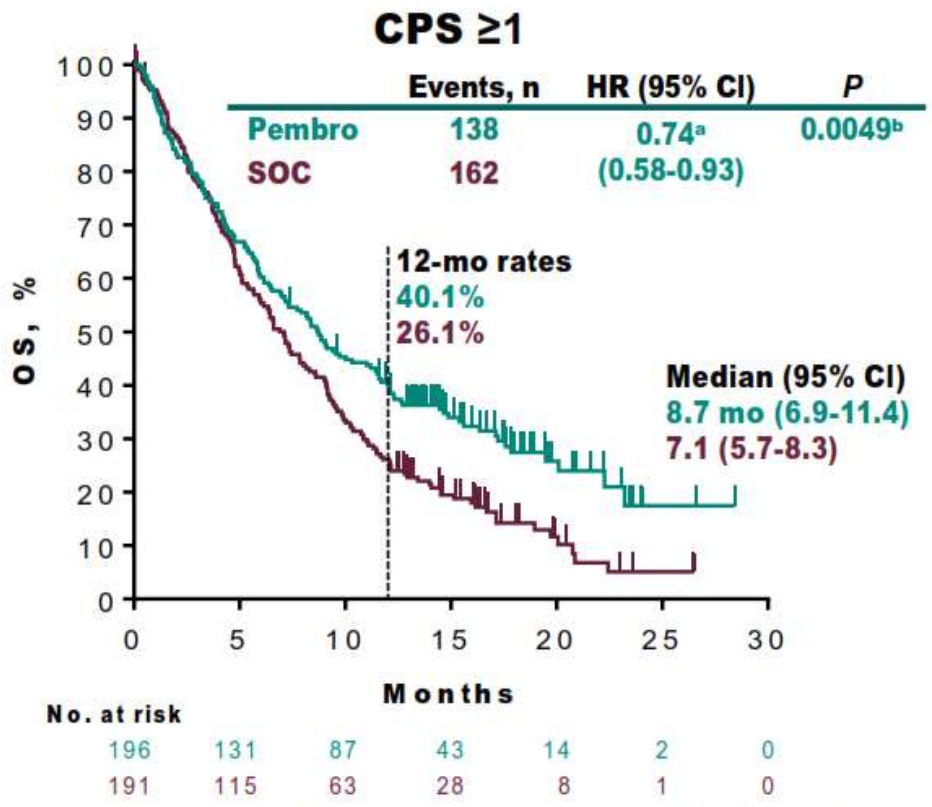
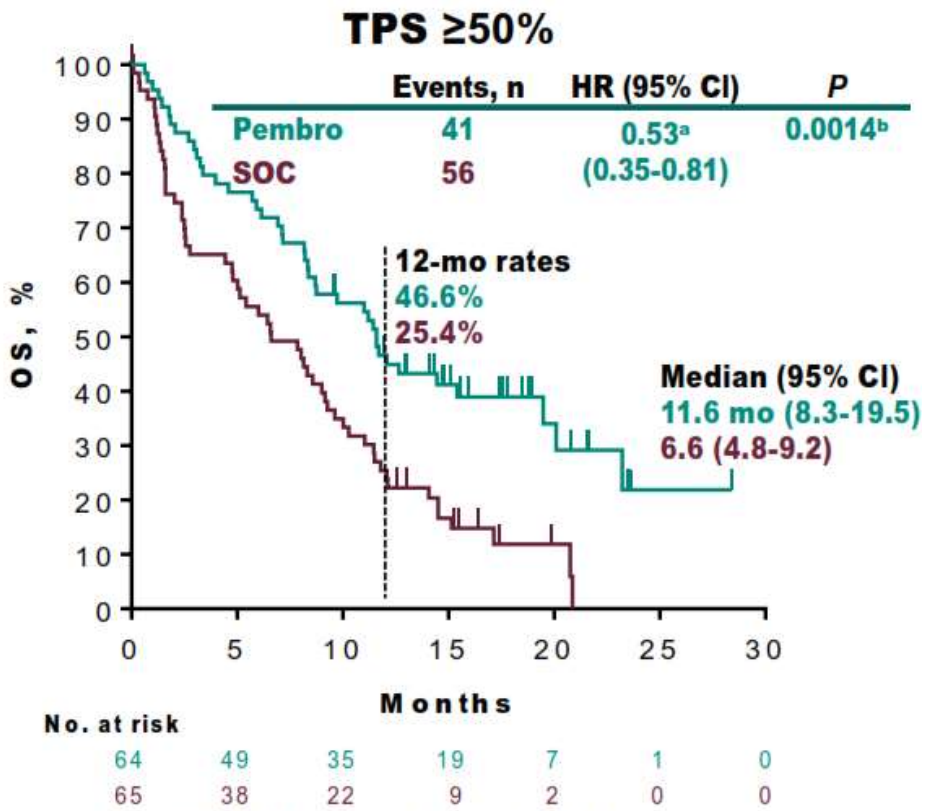
Updated Overall Survival by PD-L1 Expression





[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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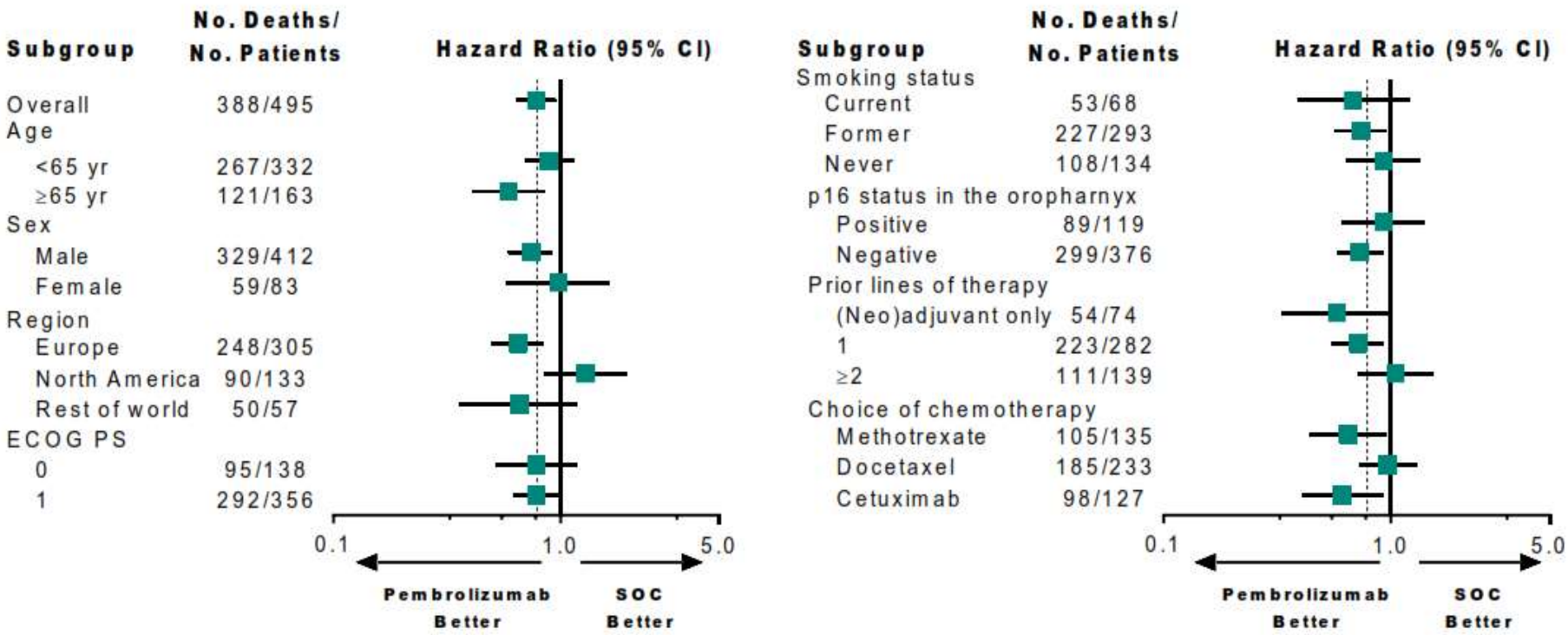
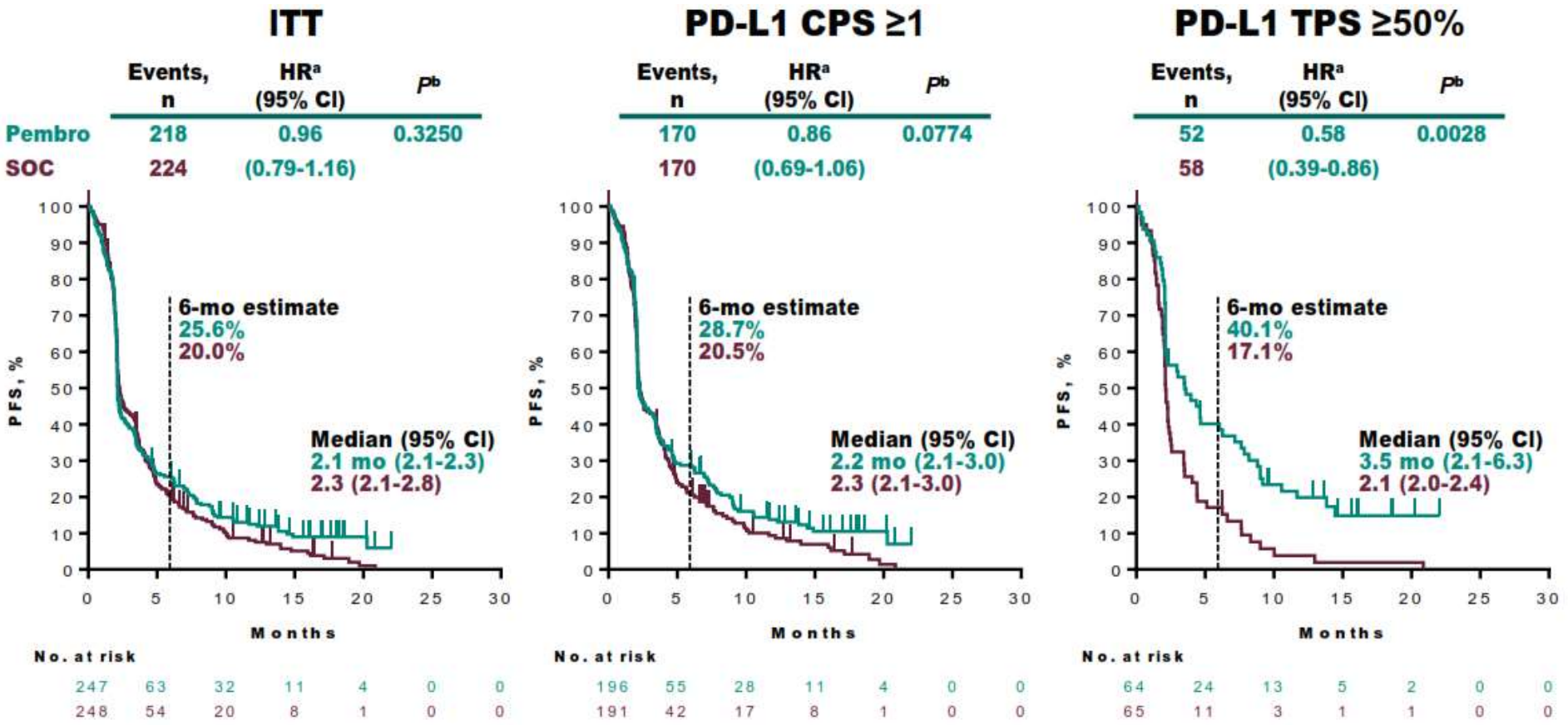
Updated Overall Survival by Subgroups



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

Denis Soulières et al. AACR 2018

UPDATED PROGRESSION-FREE SURVIVAL



[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.

Treatment-Related Aes with Incidence of > 10%

	Pembrolizumab (N = 246)		SOC (N = 234)	
Event, n (%)	Any Grade	Grade 3-5	Any Grade	Grade 3-5
Hypothyroidism	33 (13.4)	1 (0.4)	2 (0.9)	0
Fatigue	31 (12.6)	4 (1.6)	43 (18.4)	2 (0.9)
Diarrhea	20 (8.1)	4 (1.6)	24 (10.3)	1 (0.4)
Rash	19 (7.7)	1 (0.4)	34 (14.5)	1 (0.4)
Asthenia	18 (7.3)	1 (0.4)	28 (12.0)	4 (1.7)
Anemia	17 (6.9)	1 (0.4)	33 (14.1)	9 (3.8)
Nausea	12 (4.9)	0	29 (12.4)	1 (0.4)
Mucosal inflammation	9 (3.7)	1 (0.4)	30 (12.8)	5 (2.1)
Stomatitis	6 (2.4)	1 (0.4)	28 (12.0)	11 (4.7)
Neutrophil count decreased	3 (1.2)	1 ().4)	25 (10.7)	20 (8.5)
Alopecia	1 (0.4)	0	25 (10.7)	0

AEs did not change in updated analysis. Relationship to treatment was determined by the investigator.
Data cutoff date: May 15, 2017.

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SUMMARY

- After all survival data analyzed using the same data cutoff date and comparing with the primary analysis:
  - HR for OS decreased from 0.81 to 0.80
  - P-value for OS decreased from 0.02024 to 0.0161
  - Better treatment effect in patients with PDL1 expressing tumors
  - Apparent effect of immune checkpoint inhibitors in SOC arm after failure of SOC

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Summary of IO Efficacy Data in R/M HNSCC

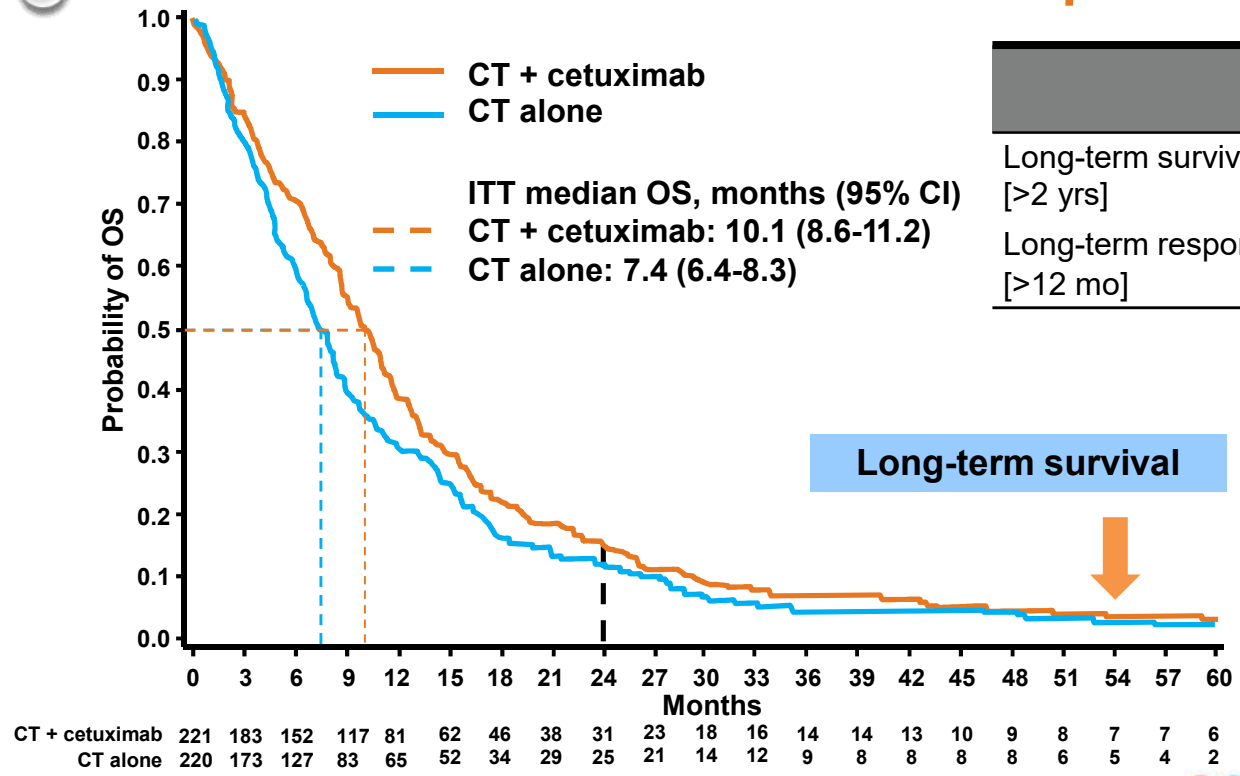
	CheckMate 141[1] all comers		KEYNOTE 040[2] all comers		Study 1108[3] all comers	HAWK[4] PD-L1 + only	NCT01375842[5] all comers
Treatment	Nivo N = 240	SOC N = 121	Pembro N = 247	SOC N = 248	Durva N = 62	Durva N = 111	Atezo N = 32
ORR, %	13.3	5.8	14.6	10.1	11	16.2	22
mPFS, mo	1.0	2.3	2.1	2.3		2.1	2.6
mOS, mo	7.7	5.1	8.4	7.1	8.9	7.1	6.0
12-mo OS rate, %	34%	19.7	37.3	27.2	42%	33.6	36

Nivo, nivolumab; pembro, pembrolizumab; durva, durvalumab; atezo, atezolizumab; SOC, standard of care

1. Ferris RL, et al. *N Engl J Med.* 2016;375(19):1856-1867. 2. Cohen EE, et al. *Ann Oncol.* 2017;28(Suppl 5): Abstract LBA45_PR. 3. Segal NH, et al. *Ann Oncol.* 2016;27(Suppl 6): Abstract 949O. 4. Zandberg D, *et al. Ann Oncol.* 2017;28(Suppl 5):Abstract 1042O. 5. Bahleda R, et al. *Ann Oncol.* 2017;28(Suppl 5):Abstract 1044O.

EXTREME Trial: Overall Survival

5-Year Follow-Up



	CT* n = 220	Cetuximab + CT* n = 222
Long-term survivors [>2 yrs]	25 (11%)	31 (14%)
Long-term responders [>12 mo]	3 (1%)	12 (5%)

Vermorken JB, et al. *N Engl J Med.* 2008;359(11):1116–1127. Vermorken JB, et al. *J Clin Oncol.* 2014;32(Suppl): Abstract 6021.

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EXTREME: Grade 3/4 Adverse Events

value n (%)	Platinum/5FU + Cetuximab [n = 219]	Platinum/ 5FU [n = 215]	*P*
Any event	179 (82)	164 (76)	.19
Neutropenia	49 (22)	50 (23)	.91
Anemia	29 (13)	41 (19)	.12
Thrombocytopenia	24 (11)	24 (11)	1.00
Skin reactions	20 (9)	1 (<1)	<.001
Hypokalemia	16 (7)	10 (5)	.31
Cardiac events	16 (7)	9 (4)	.22
Vomiting	12 (5)	6 (3)	.23
Asthenia Anorexia	11 (5)	12 (6)	.83
Hypomagnesemia	11 (5)	3 (1)	.05
Febrile neutropenia	11 (5)	3 (1)	.05
Dyspnea	10 (5)	10 (5)	1.00
	9 (4)	17 (8)	.11

Vermorken JB, et al. New Engl J Med 2008;359:1116–27

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)

Barbara Burtness,[1] Kevin Harrington,[2] Richard Greil,[3] Denis Soulières,[4] Makoto Tahara,[5] Gilberto de Castro,[6] Amanda Psyrri,[7] Neus Basté Rotllan,[8] Prakash Neupane,[9] Åse Bratland,[10] Thorsten Fuereder,[11] Brett GM Hughes,[12] Ricard Mesia,[13] Nuttapong Ngamphaiboon,[14] Tamara Rordorf,[15] Wan Zamaniah Wan Ishak,[16] Ananya Roy,[17] Jonathan Cheng,[17] Fan Jin,[17] Danny Rischin[18]

[1]Yale School of Medicine and Yale Cancer Center, New Haven, CT, USA; [2]The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust National Institute of Health Research Biomedical Research Centre, London, UK; [3]Paracelsus Medical University, Salzburg Cancer Research Institute, and Cancer Cluster Salzburg, Salzburg, Austria; [4]Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada; [5]National Cancer Center Hospital East, Kashiwa, Japan; [6]Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil; [7]National Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece; [8]Vall d'Hebron University Hospital, Barcelona, Spain (currently at Institut Gustave Roussy, Paris, France); [9]University of Kansas Medical Center, Kansas City, KS, USA; [10]Oslo University Hospital, Oslo, Norway; [11]Medical University of Vienna, Vienna, Austria; [12]Royal Brisbane and Women's Hospital and University of Queensland, Brisbane, QLD, Australia; [13]Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain; [14]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [15]University Hospital, Zurich, Switzerland; [16]University Malaya, Kuala Lumpur, Malaysia; [17]Merck & Co., Inc., Kenilworth, NJ, USA; [18]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

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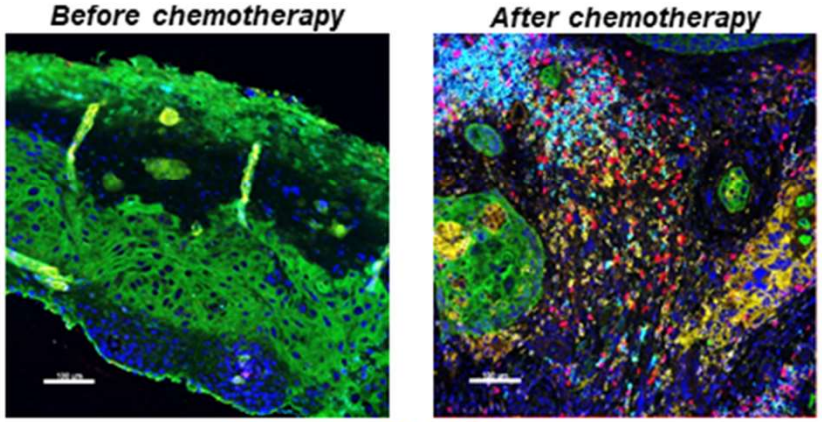
Immunotherapy and HNSCC

- PD-1 inhibitors pembrolizumab and nivolumab are approved for second-line R/M HNSCC treatment[1,2]
- Higher PD-L1 expression is associated with improved response to pembrolizumab[1]
- Chemotherapy is a rational combination partner for anti-PD-1 therapy[3]
  - Disrupts tumor architecture and may overcome immune exclusion
  - Results in antigen shedding
  - Induces rapid disease control

Chemotherapy induces tumor infiltration by lymphocytes

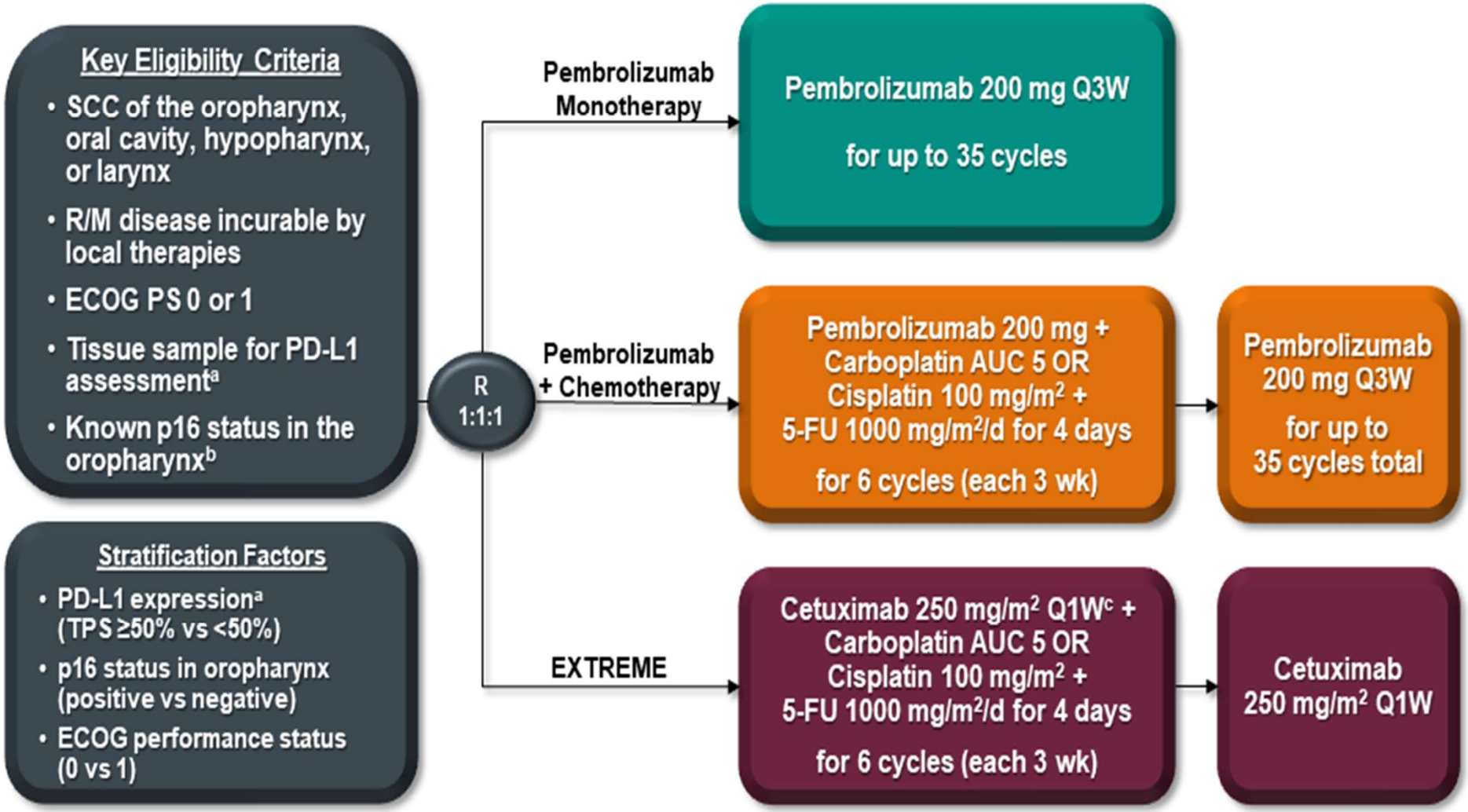


Images courtesy of D Rimm and WG Yarbrough, Yale School of Medicine and Yale Cancer Center.

1. Cohen EA et al. *Ann Oncol* 2017;28(suppl 5): abstr LBA45_PR.
2. Ferris RL et al. *N Engl J Med* 2016;375:1856-67.
3. Economopoulou P et al. *Ann Oncol* 2016;27:1675-85.

FLORIDA PRECISION ONCOLOGY

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.

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

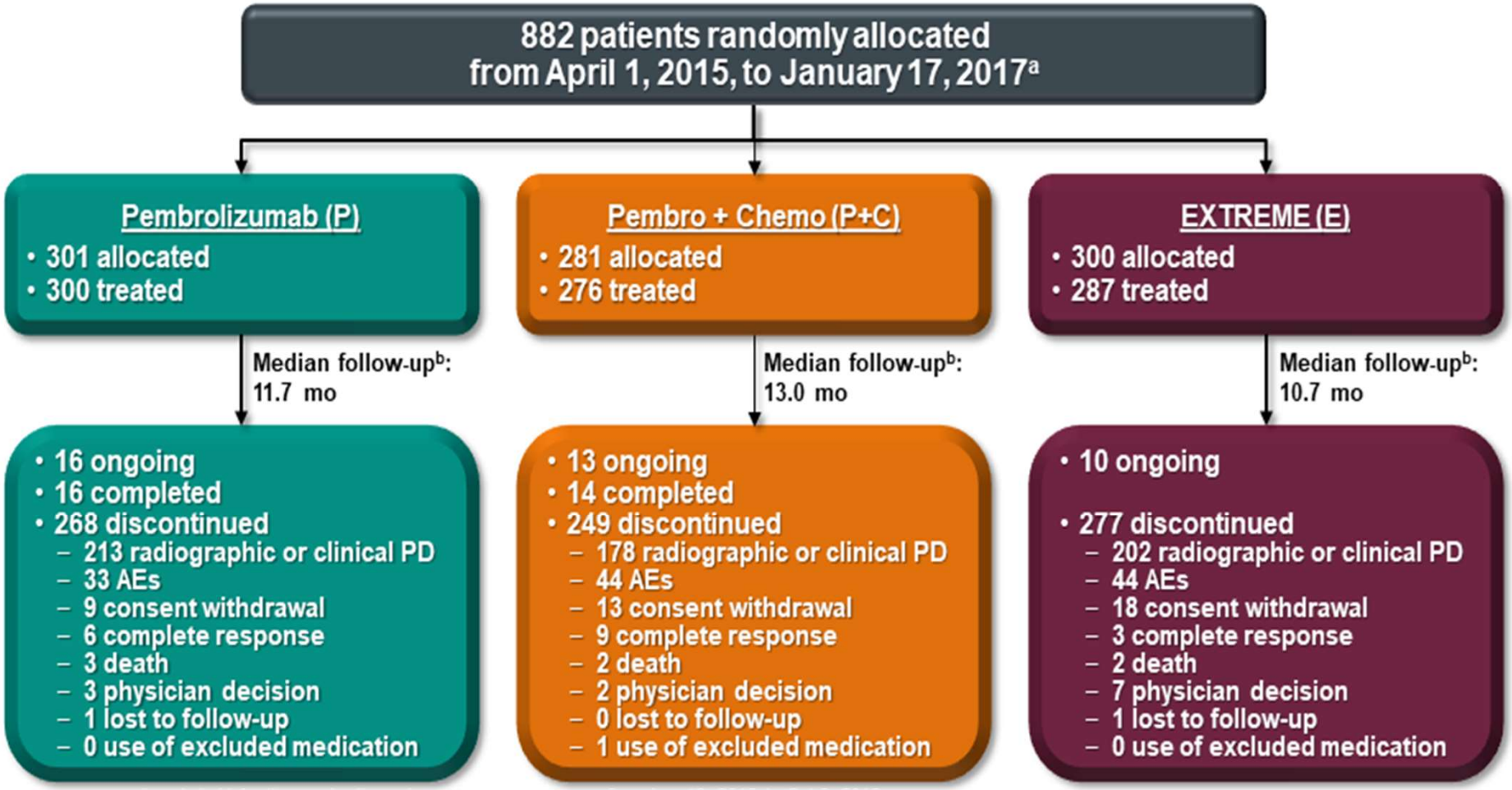
- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - PFS[b] rates at 6 and 12 mo
  - ORR[b]
  - Change from baseline and time to deterioration in quality of life (EORTC QLQ-C30 and H&N-35)[c]
- Total population
  - Safety and tolerability

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.

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.

ONCOLOGY

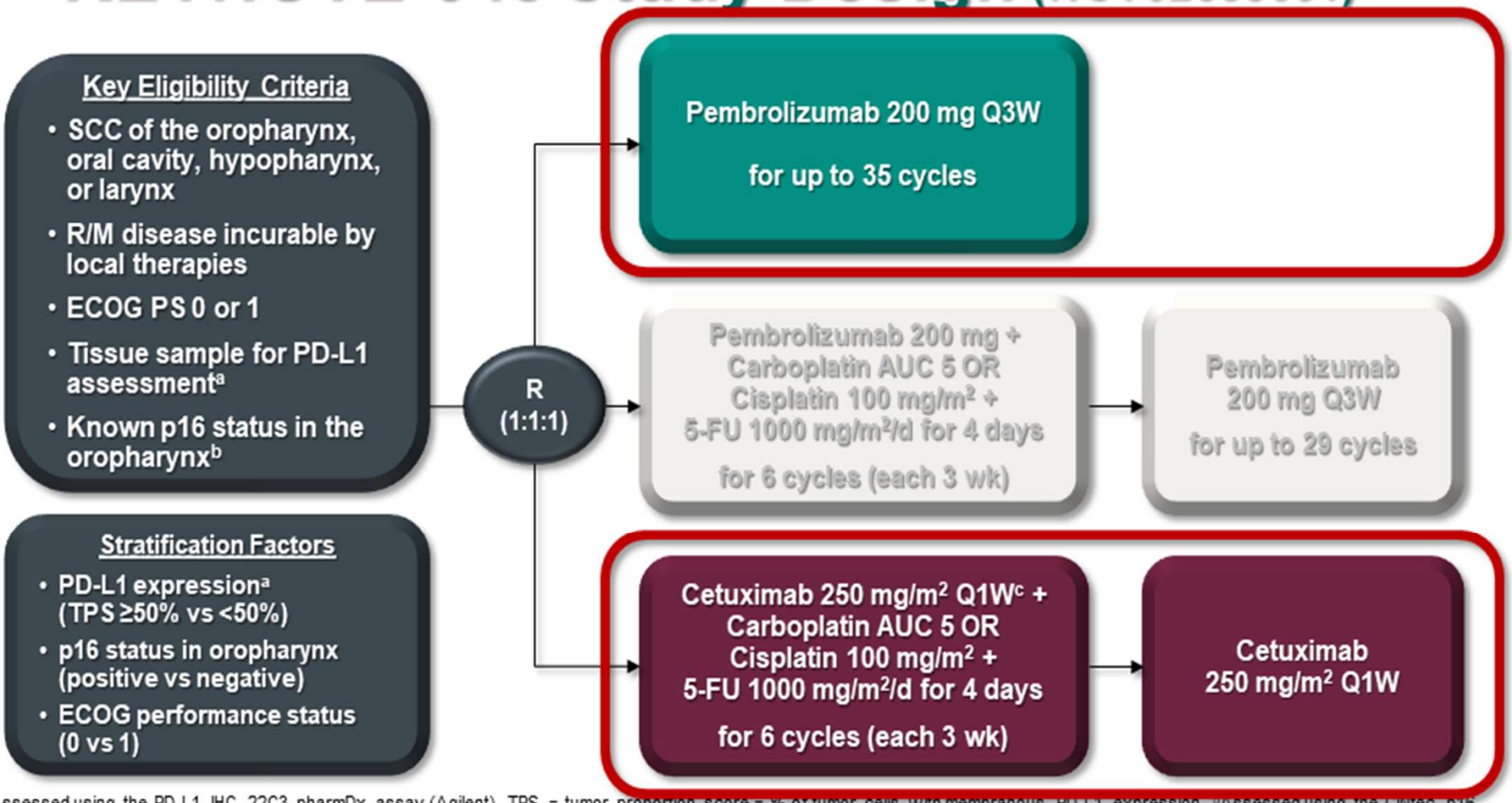
Baseline Characteristics, ITT Population

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.

FLORIDA PRECISION ONCOLOGY

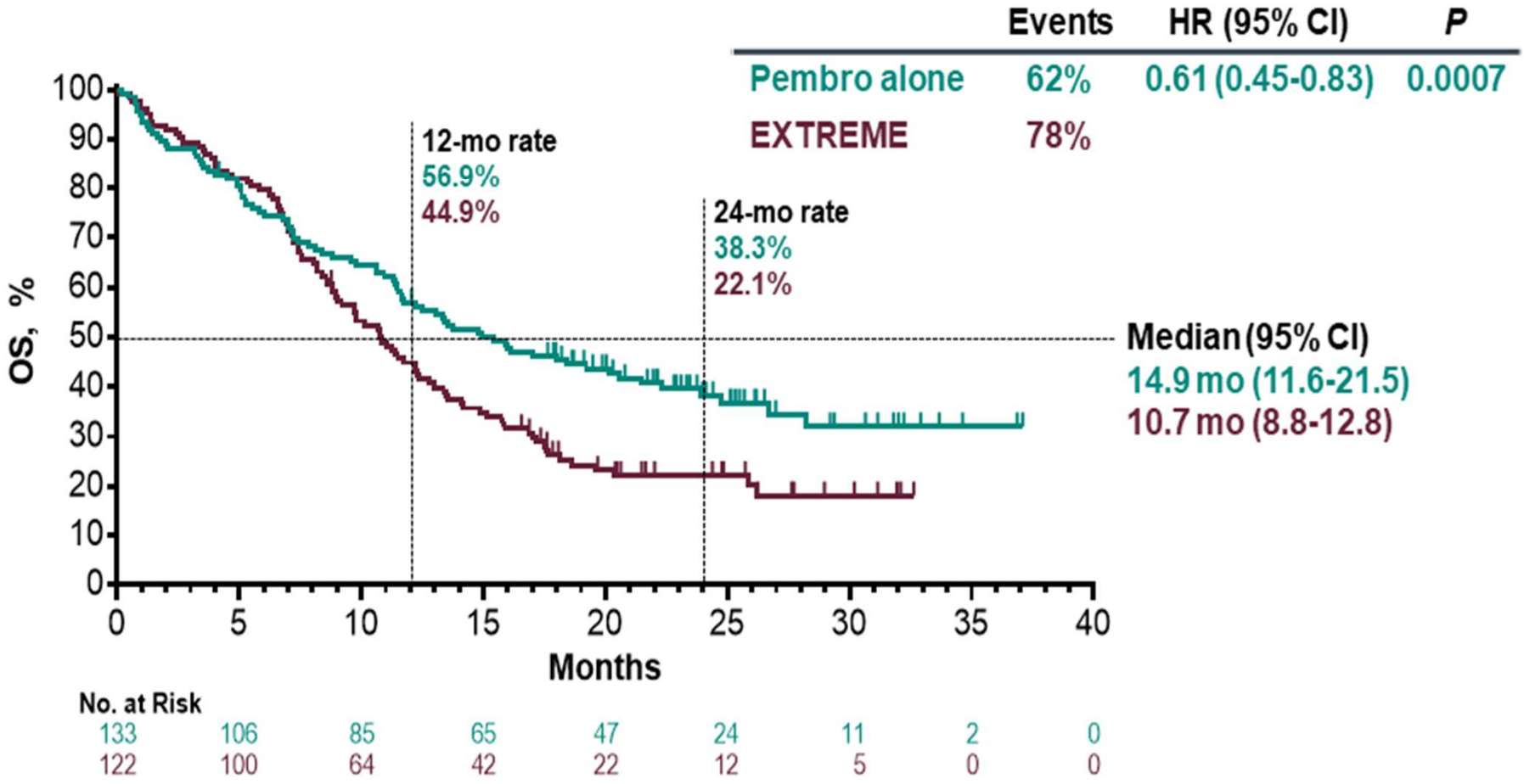
KEYNOTE-048 Study Design (NCT02358031)



[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.

FLORIDA PRECISION ONCOLOGY

Overall Survival: P vs E, CPS ≥20 Population

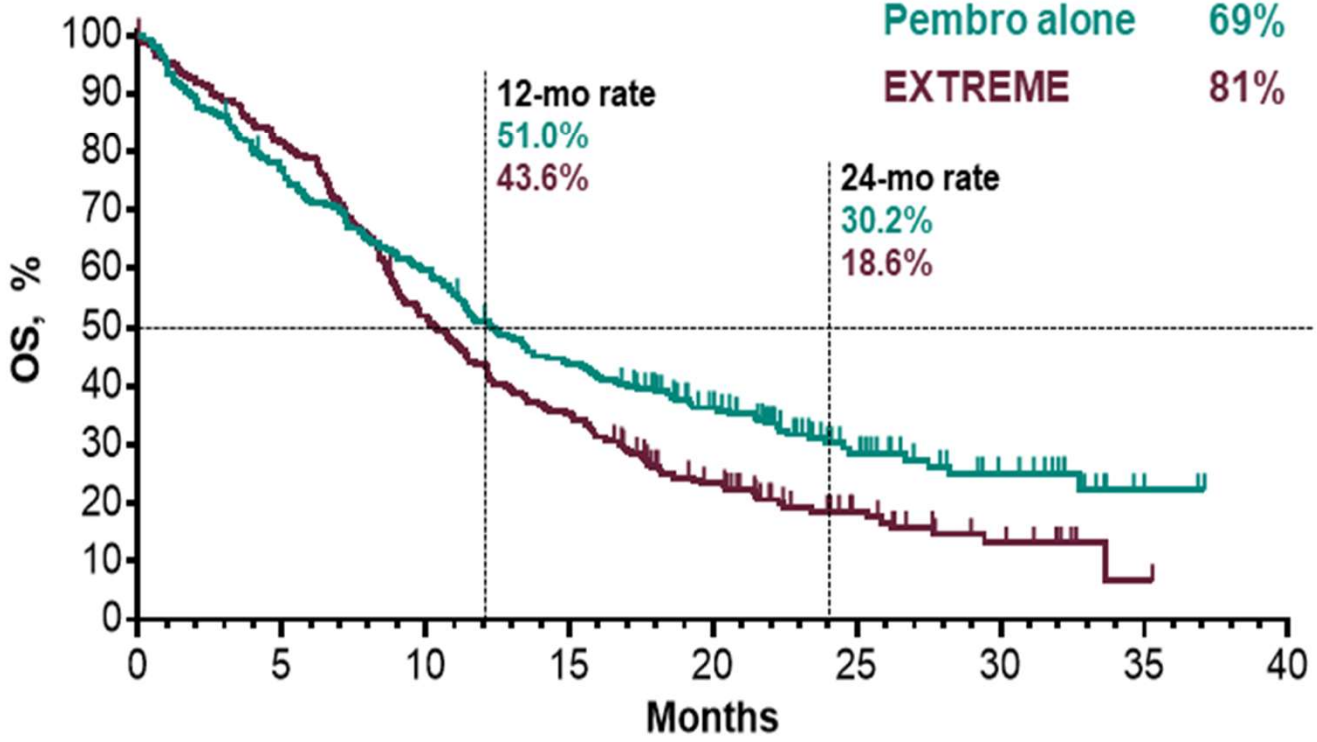


Data cutoff date: Jun 13, 2018.

FLORIDA REGIONAL ONCOLOGY

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%		



No. at Risk

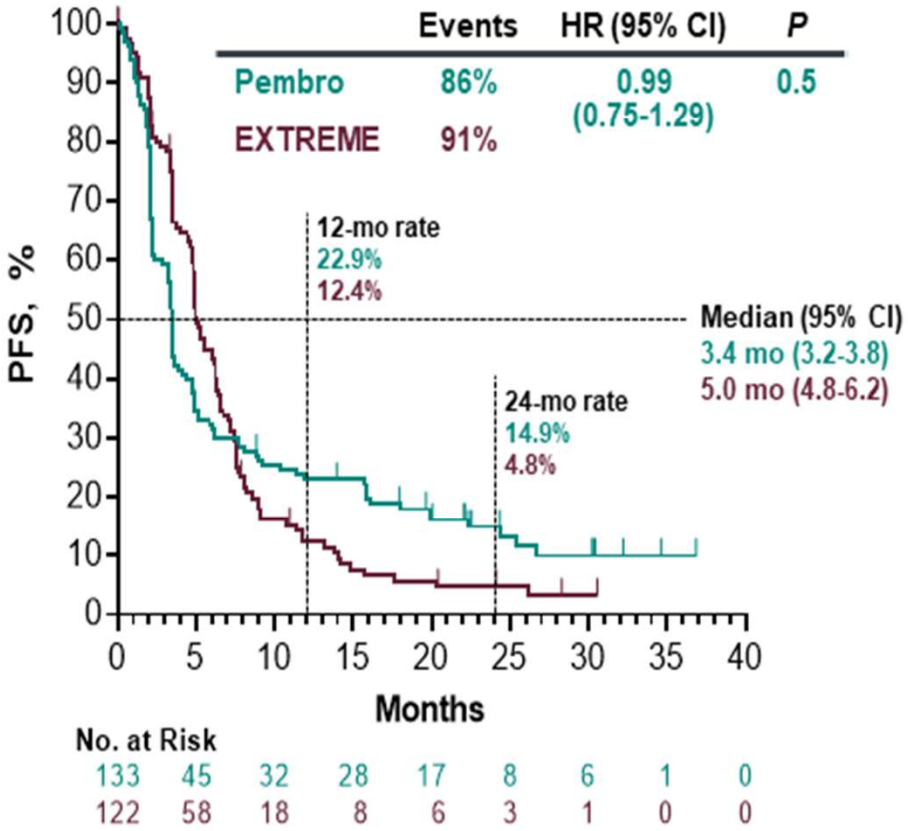
257	196	152	110	74	34	17	2	0
255	207	131	89	47	21	9	1	0

Data cutoff date: Jun 13, 2018.

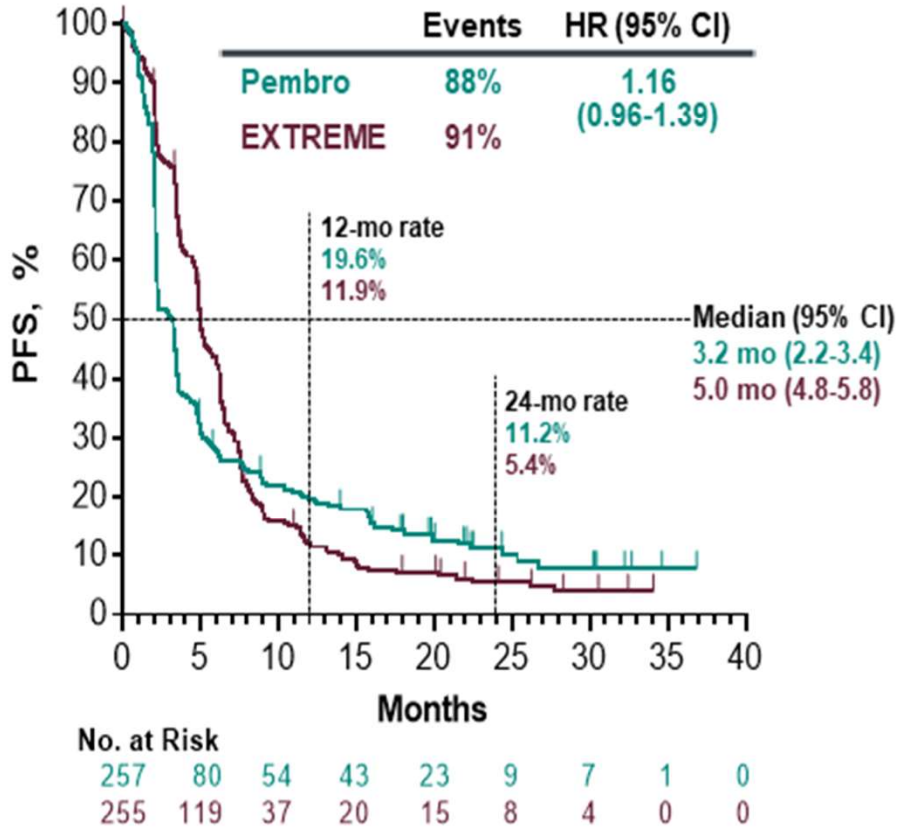
ONCOLOGY

Progression-Free Survival: P vs E

CPS ≥20



CPS ≥1



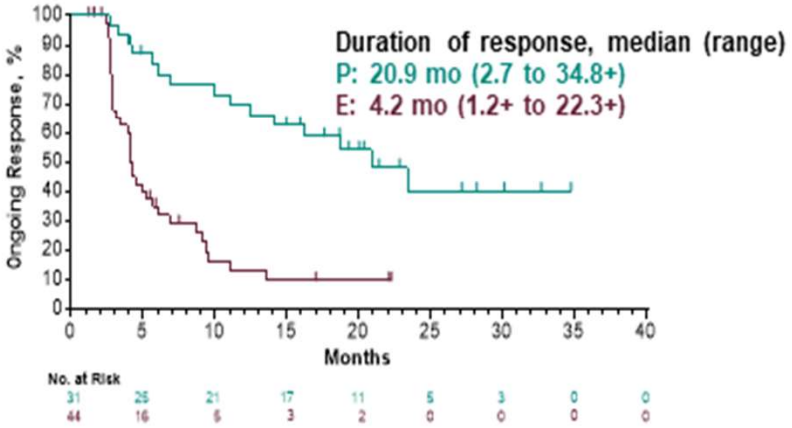
Progression-free survival assessed per RECIST v1.1 by blinded, independent central radiologic review.
Data cutoff date: Jun 13, 2018.

ONCOLOGY

Response Summary, P vs E

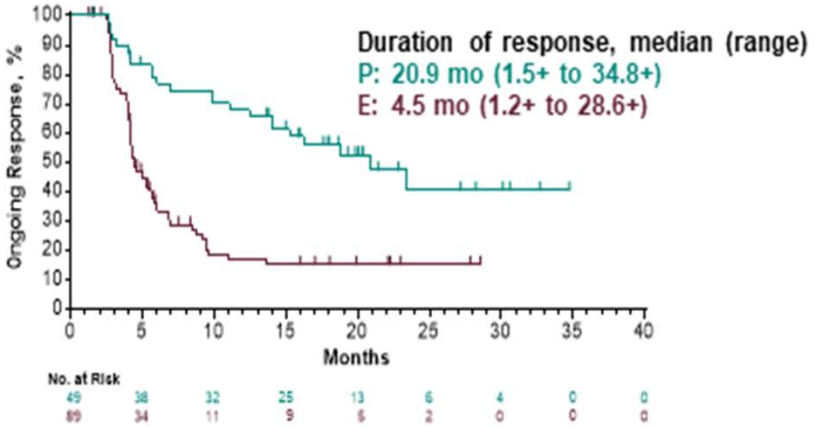
CPS ≥20

Confirmed Response, n (%)	Pembro N = 133	EXTREME N = 122
ORR	**31 (23.3)**	**44 (36.1)**
CR	10 (7.5)	4 (3.3)
PR	21 (15.8)	40 (32.8)
SD	40 (30.1)	42 (34.4)
PD	42 (31.6)	13 (10.7)
Non-CR/non-PD[a]	8 (6.0)	6 (4.9)
Not evaluable or assessed[b]	12 (9.0)	17 (13.9)



CPS ≥1

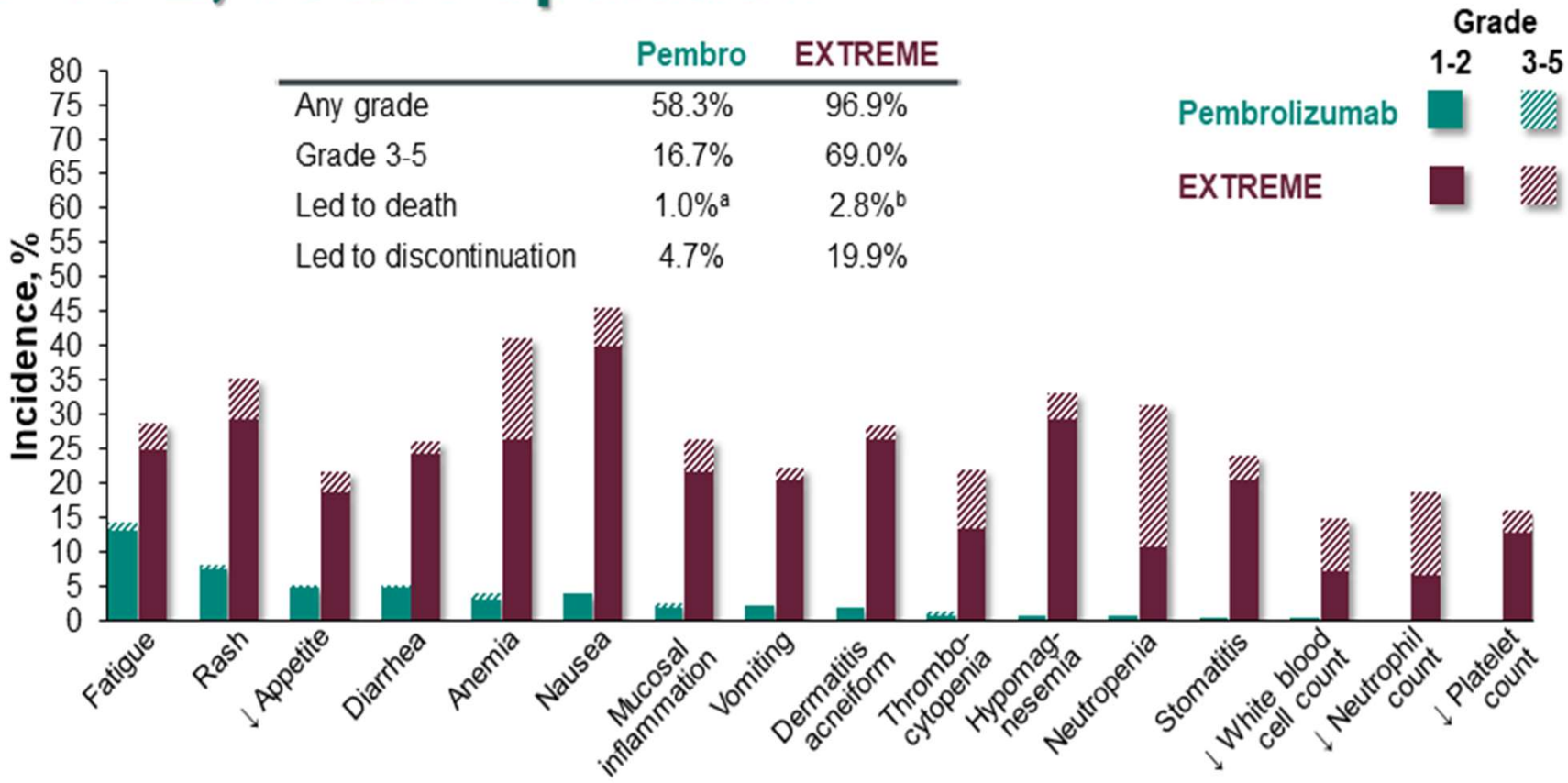
Confirmed Response, n (%)	Pembro N = 257	EXTREME N = 255
ORR	**49 (19.1)**	**89 (34.9)**
CR	14 (5.4)	7 (2.7)
PR	35 (13.6)	82 (32.2)
SD	72 (28.0)	83 (32.5)
PD	100 (38.9)	34 (13.3)
Non-CR/non-PD[a]	11 (4.3)	11 (4.3)
Not evaluable or assessed[b]	25 (9.7)	38 (14.9)



[a]Patients without measurable disease per central review at baseline who did not have CR or PD. [b]Patients who did not have a post-baseline imaging assessment evaluable for response or who did not have post-baseline imaging. Response assessed per RECIST v1.1 by blinded, independent central radiologic review. Data cutoff date: Jun 13, 2018.

Treatment-Related AEs With Incidence ≥15%, P vs E, Total Population

	Pembro	EXTREME
Any grade	58.3%	96.9%
Grade 3-5	16.7%	69.0%
Led to death	1.0%[a]	2.8%[b]
Led to discontinuation	4.7%	19.9%



Median (range) treatment duration was 3.5 mo (0.03-24.2) for pembrolizumab and 4.9 mo (0.03-35.3) for EXTREME.

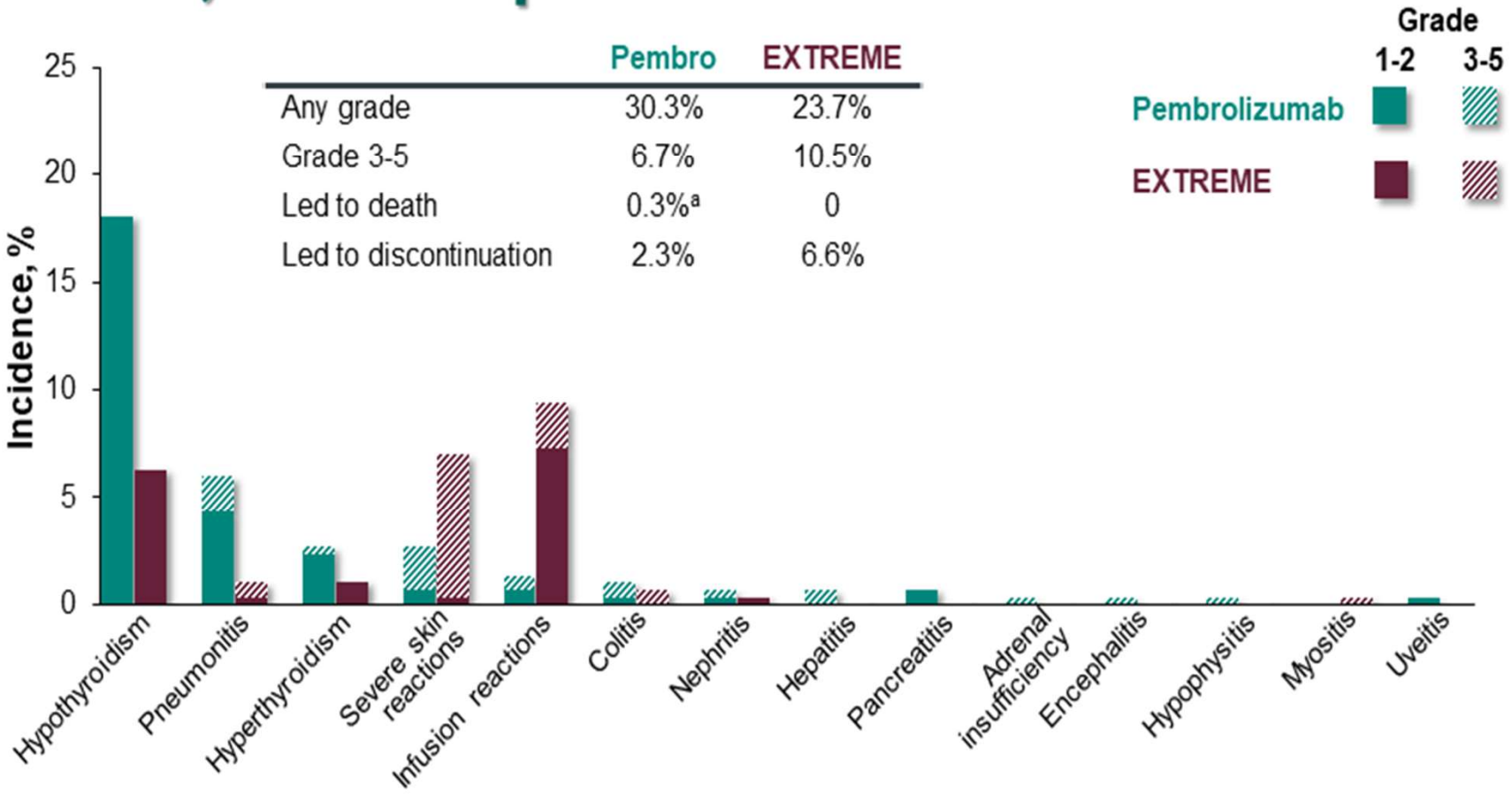
[a]Autoinflammatory disease, disseminated intravascular coagulation, and pneumonitis (n=1 each).

[b]Pneumonia (n=3), sepsis (n=2), and hypoxia, osteomyelitis, and pulmonary artery thrombosis (n=1 each). Data cutoff date: Jun 13, 2018.

ONCOLOGY

Immune-Mediated AEs and Infusion Reactions, P vs E, Total Population

	Pembro	EXTREME
Any grade	30.3%	23.7%
Grade 3-5	6.7%	10.5%
Led to death	0.3%[a]	0
Led to discontinuation	2.3%	6.6%



[a]Pneumonitis (n=1).
Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: Jun 13, 2018.

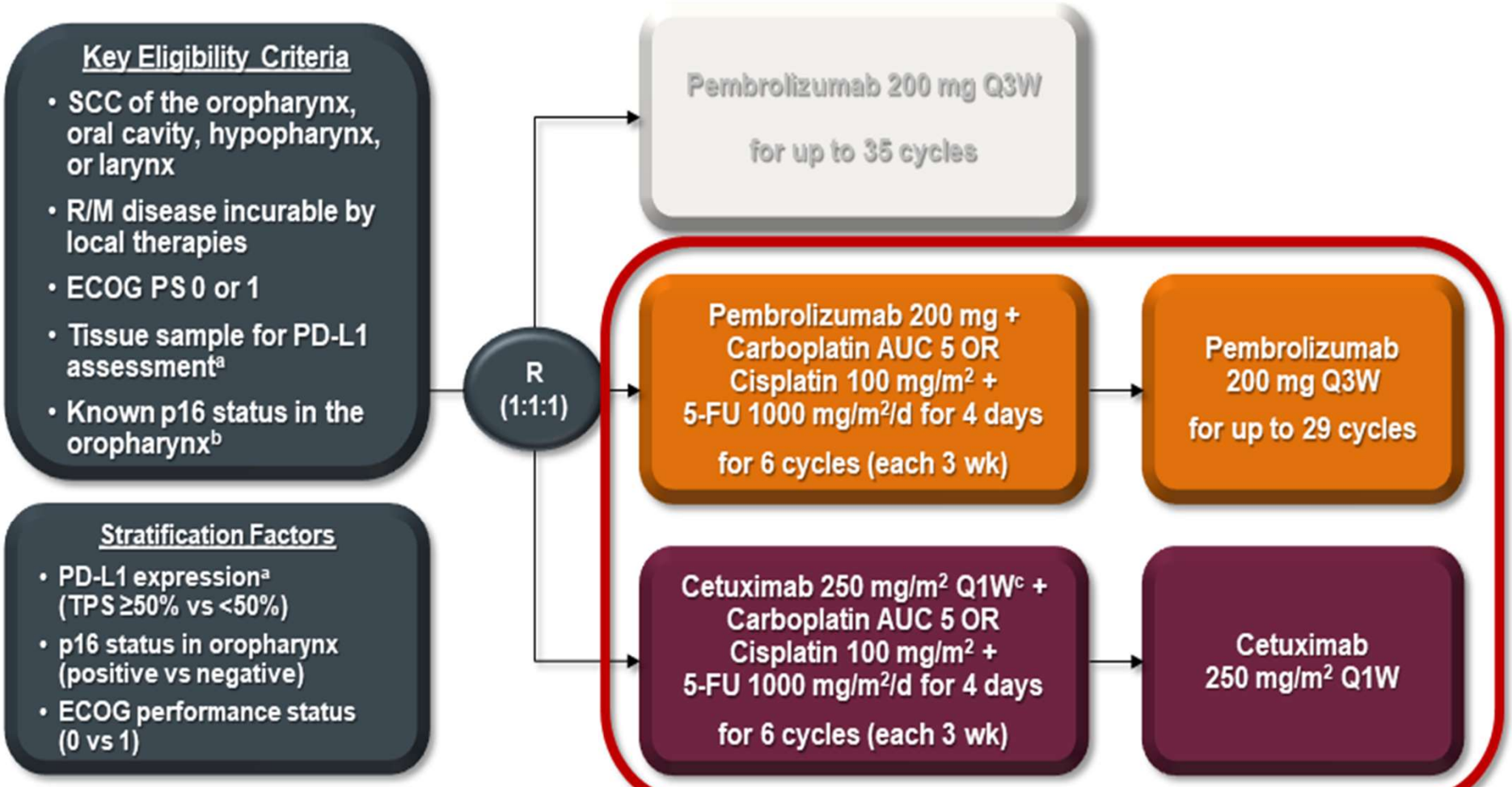
ONCOLOGY

Summary and Conclusions: Pembrolizumab Monotherapy vs EXTREME

- Pembrolizumab significantly improved OS vs EXTREME in the PD-L1 CPS ≥20 (HR 0.61, *P* = 0.0007) and CPS ≥1 (HR 0.78, *P* = 0.0086) populations
  - No PFS benefit for pembrolizumab
  - Although pembrolizumab had a lower ORR, responses were substantially more durable
- Pembrolizumab had a favorable safety profile vs EXTREME
  - Lower incidence of any-grade, grade 3-4, and grade 5 treatment-related AEs
  - Lower incidence of treatment-related AEs leading to discontinuation
  - Safety profiles as expected for pembrolizumab and EXTREME
- Data support pembrolizumab monotherapy as a new first-line standard-of-care for R/M HNSCC that expresses PD-L1

ONCOLOGY

KEYNOTE-048 Study Design (NCT02358031)

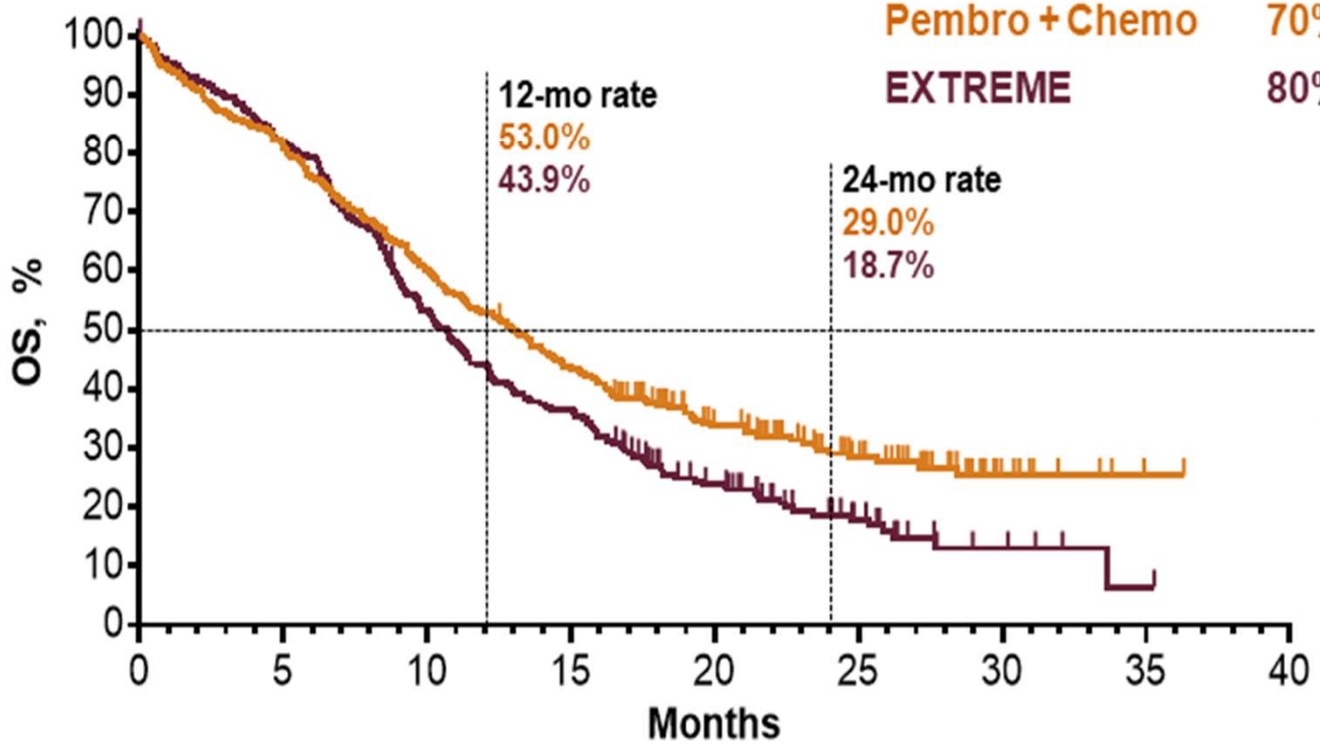


[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion [illegible] PD-L1 expression [illegible] p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

ONCOLOGY

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%		



Median (95% CI)
13.0 mo (10.9-14.7)
10.7 mo (9.3-11.7)

No. at Risk

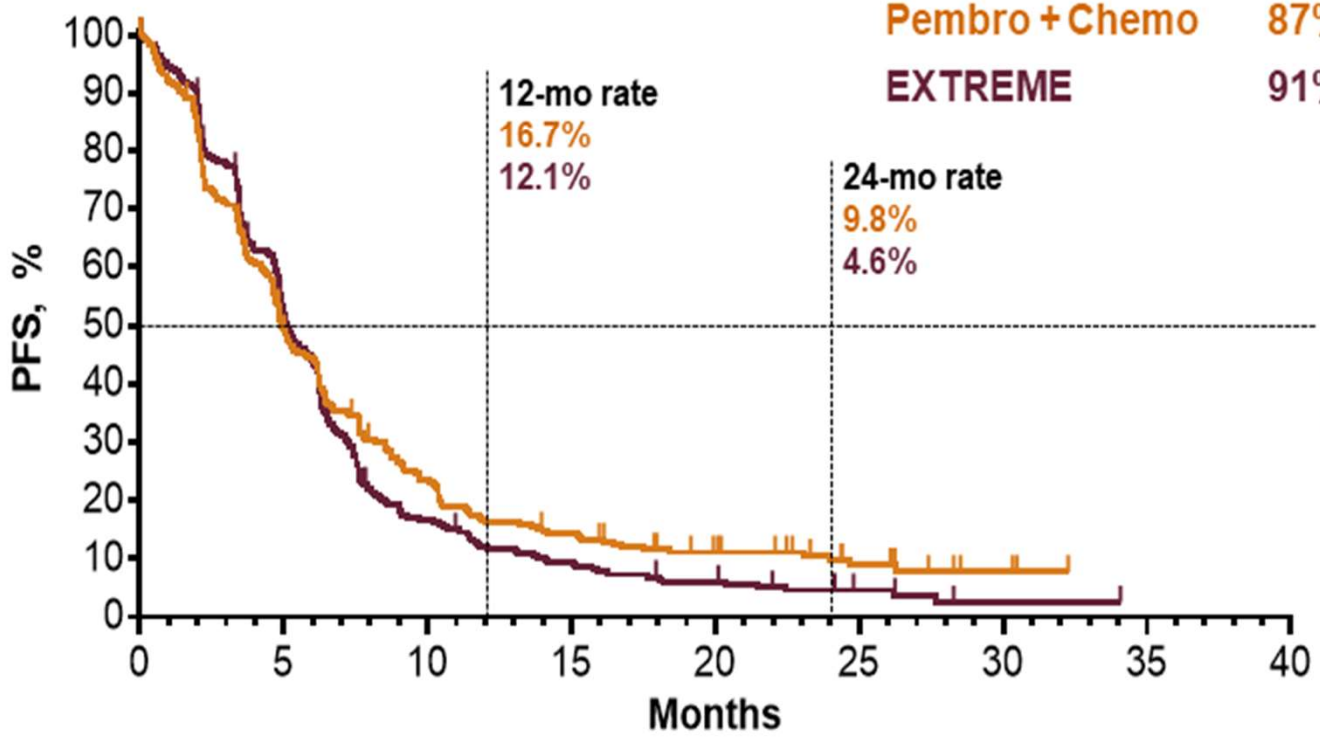
281	227	169	122	75	40	10	1	0
278	227	147	100	51	20	5	1	0

Data cutoff date: Jun 13, 2018.

ONCOLOGY

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%		



No. at Risk

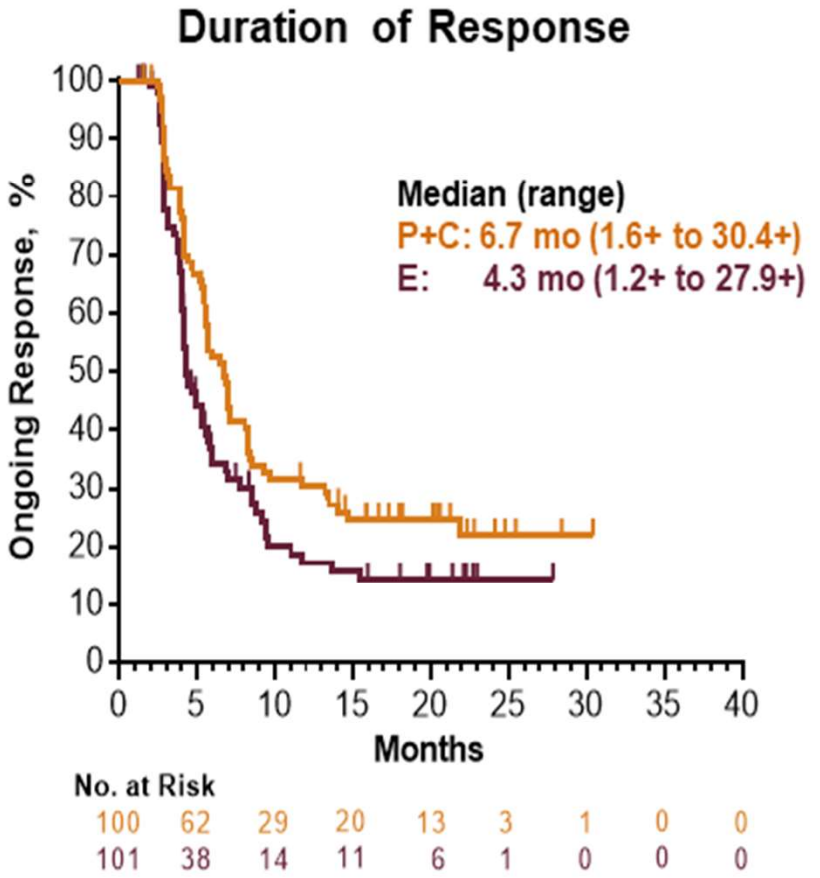
281	134	62	37	22	11	3	0	0
278	136	42	23	14	6	1	0	0

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

ONCOLOGY

Response Summary, P+C vs E, Total Population

Confirmed Response, n (%)	Pembro + Chemo N = 281	EXTREME N = 278
ORR	**100 (35.6)**	**101 (36.3)**
CR	17 (6.0)	8 (2.9)
PR	83 (29.5)	93 (33.5)
SD	78 (27.8)	94 (33.8)
PD	48 (17.1)	34 (12.2)
Non-CR/non-PD[a]	13 (4.6)	9 (3.2)
Not evaluable or assessed[b]	42 (14.9)	40 (14.4)

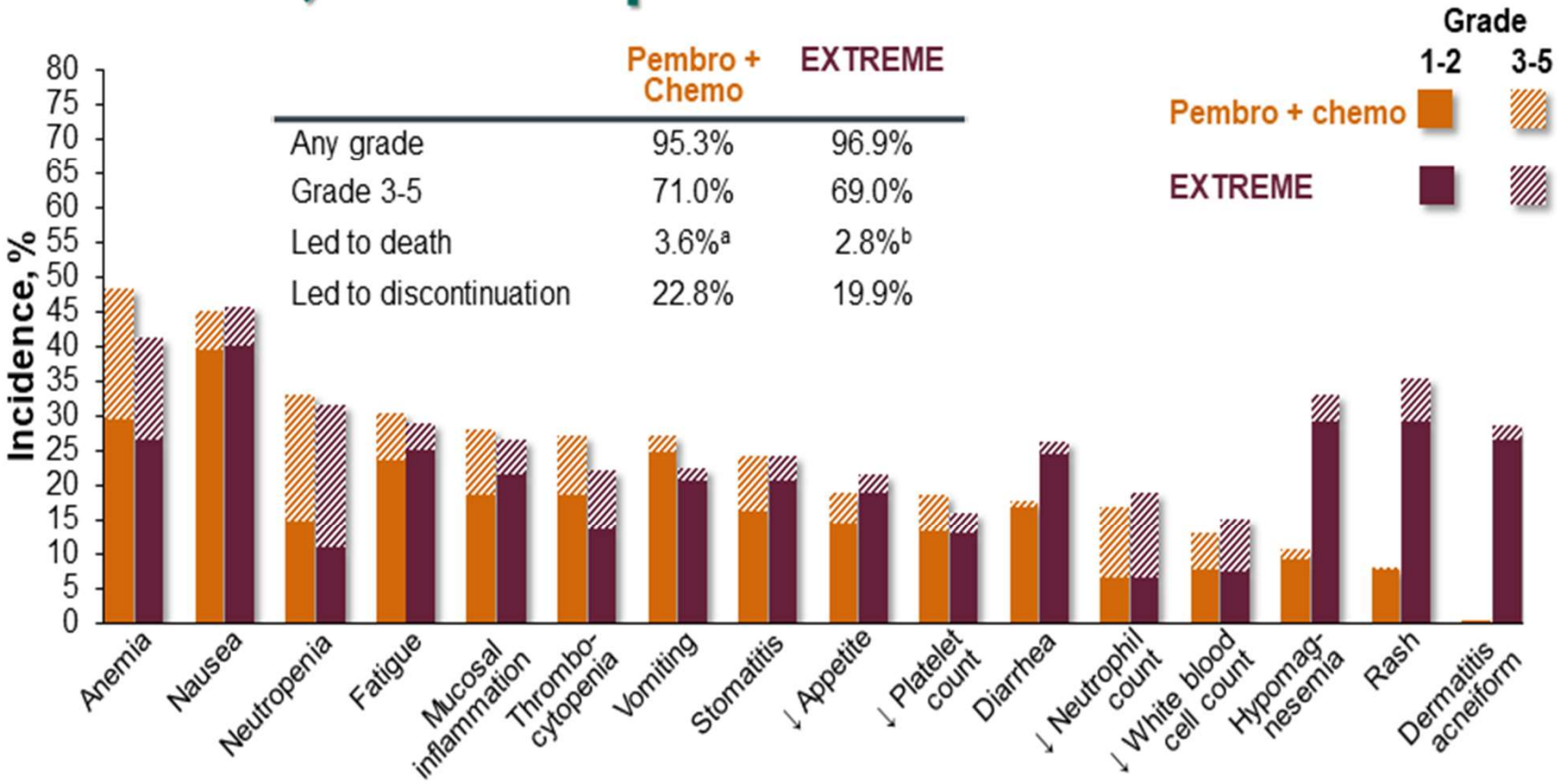


[a]Patients without measurable disease per central review at baseline who did not have CR or PD. [b]Patients who did not have a post-baseline imaging assessment evaluable for response or who did not have post-baseline imaging. Response assessed per RECIST v1.1 by blinded, independent central radiologic review. Data cutoff date: Jun 13, 2018.

ONCOLOGY

Treatment-Related AEs With Incidence ≥15%, P+C vs E, Total Population

	Pembro + Chemo	EXTREME
Any grade	95.3%	96.9%
Grade 3-5	71.0%	69.0%
Led to death	3.6%[a]	2.8%[b]
Led to discontinuation	22.8%	19.9%

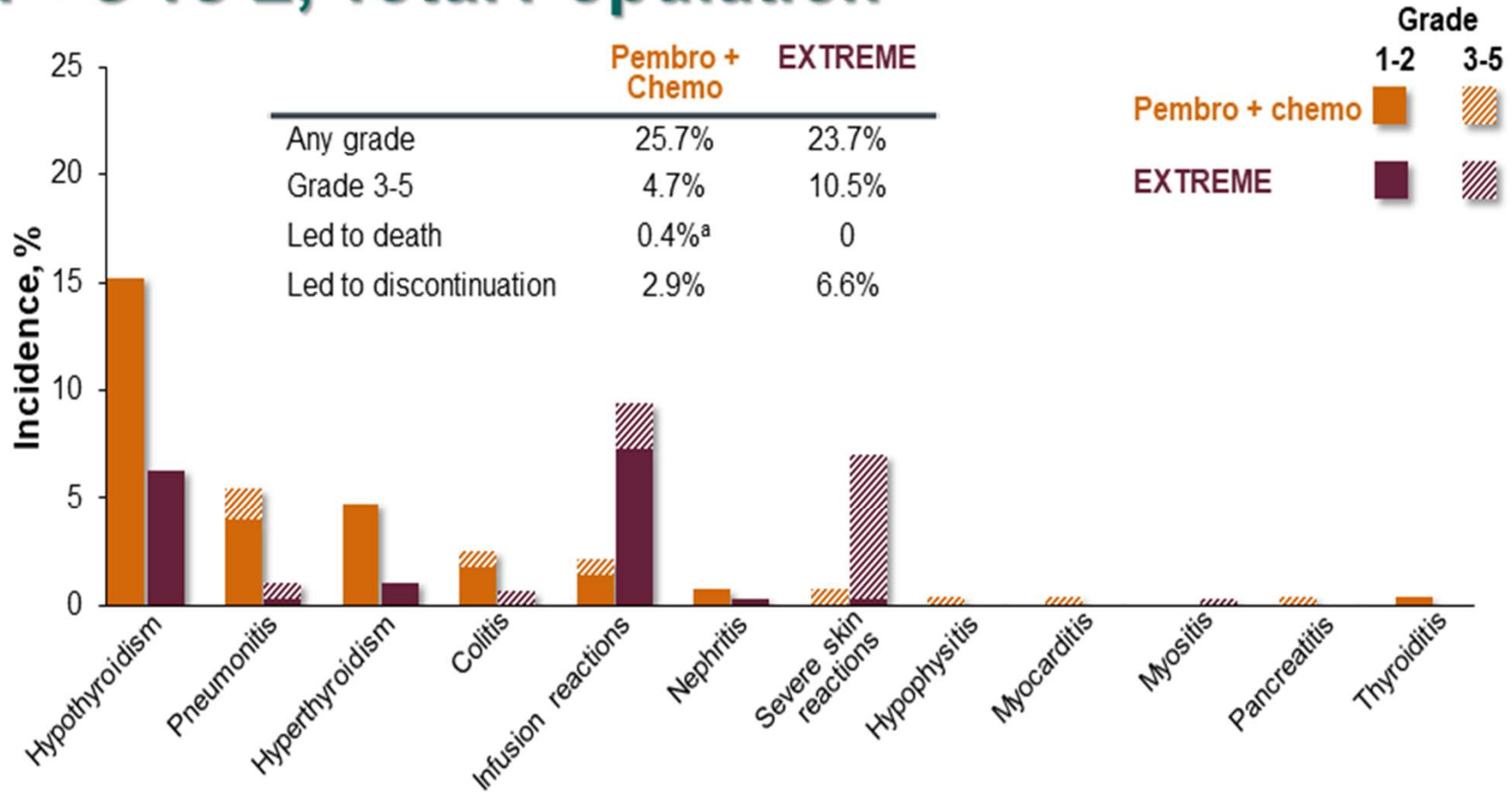


Median (range) treatment duration was 5.8 mo (0.1-24.2) for pembrolizumab + chemotherapy and 4.9 mo (0.03-35.3) for EXTREME.
[a]Septic shock (n=5) and cerebral ischemia, hemorrhage, interstitial lung disease, sepsis, and tumor hemorrhage (n=1 each).
[b]Pneumonia (n=3), sepsis (n=2), and hypoxia, osteomyelitis, and pulmonary artery thrombosis (n=1 each). Data cutoff date: Jun 13, 2018.

ONCOLOGY

Immune-Mediated AEs and Infusion Reactions, P+C vs E, Total Population

	Pembro + Chemo	EXTREME
Any grade	25.7%	23.7%
Grade 3-5	4.7%	10.5%
Led to death	0.4%[a]	0
Led to discontinuation	2.9%	6.6%



[a]Pneumonitis (n=1).
Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: Jun 13, 2018.

ONCOLOGY

Summary and Conclusions: Pembrolizumab + Chemotherapy vs EXTREME

- Pembrolizumab plus chemotherapy with a platinum and 5-FU significantly improved OS vs EXTREME in the total population (HR 0.77, *P* = 0.0034)
  - No PFS or ORR benefit for pembrolizumab plus chemotherapy
  - Responses to pembrolizumab plus chemotherapy were more durable
- Pembrolizumab plus chemotherapy had a comparable safety profile vs EXTREME
  - Similar incidence of any-grade, grade 3-4, and grade 5 treatment-related AEs
  - No unexpected toxicity in the pembrolizumab + chemotherapy arm
- Data support pembrolizumab plus platinum-based chemotherapy as a new first-line standard-of-care for R/M HNSCC

ONCOLOGY

Overall Survival Hypotheses to be Tested at the Final Analysis

- Superiority of pembrolizumab alone in the total population
  - At current analysis, pembrolizumab was noninferior to EXTREME in the total population (noninferiority boundary, 1.2)
- Superiority of pembrolizumab plus chemotherapy in the CPS ≥20 population
- Superiority of pembrolizumab plus chemotherapy in the CPS ≥1 population
  - Only if superiority in the CPS ≥20 population demonstrated

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Ongoing Phase III Studies With Immune Checkpoint Inhibitors in First-Line R/M HNSCC vs Standard of Care

Trial Name (NCT #)	Immunotherapy Agent(s) in Study	Phase	Population	Treatment Arms
CheckMate 651 (NCT02741570)	**Nivolumab, Ipilimumab**	**III**	**Previously untreated R/M HNSCC, ≥6 months since last dose of platinum**	**Nivolumab + Ipilimumab vs EXTREME**
KESTREL (NCT02551159) completed accrual	**Durvalumab Tremelimumab**	**III**		**Durvalumab vs Durvalumab + tremelimumab vs EXTREME**

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Key Take-Home Messages

- **Pembrolizumab +/- Chemo is the new standard first- line treatment for R/M HNSCC, recommended by international guidelines**
- **Nivolumab and pembrolizumab are the standard-of-care options for patients with R/M HNSCC after platinum-based therapy**

  In asymptomatic patients with no rapid progression, immune checkpoint can be continued until further radiographic assessment in 8 weeks
- **PD-L1 can not be used as a biomarker in SCCHN**
- **PD-1/PD-L1 inhibitors are in general well tolerated, but irAEs can develop; early recognition and management are important**

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QUESTIONS?