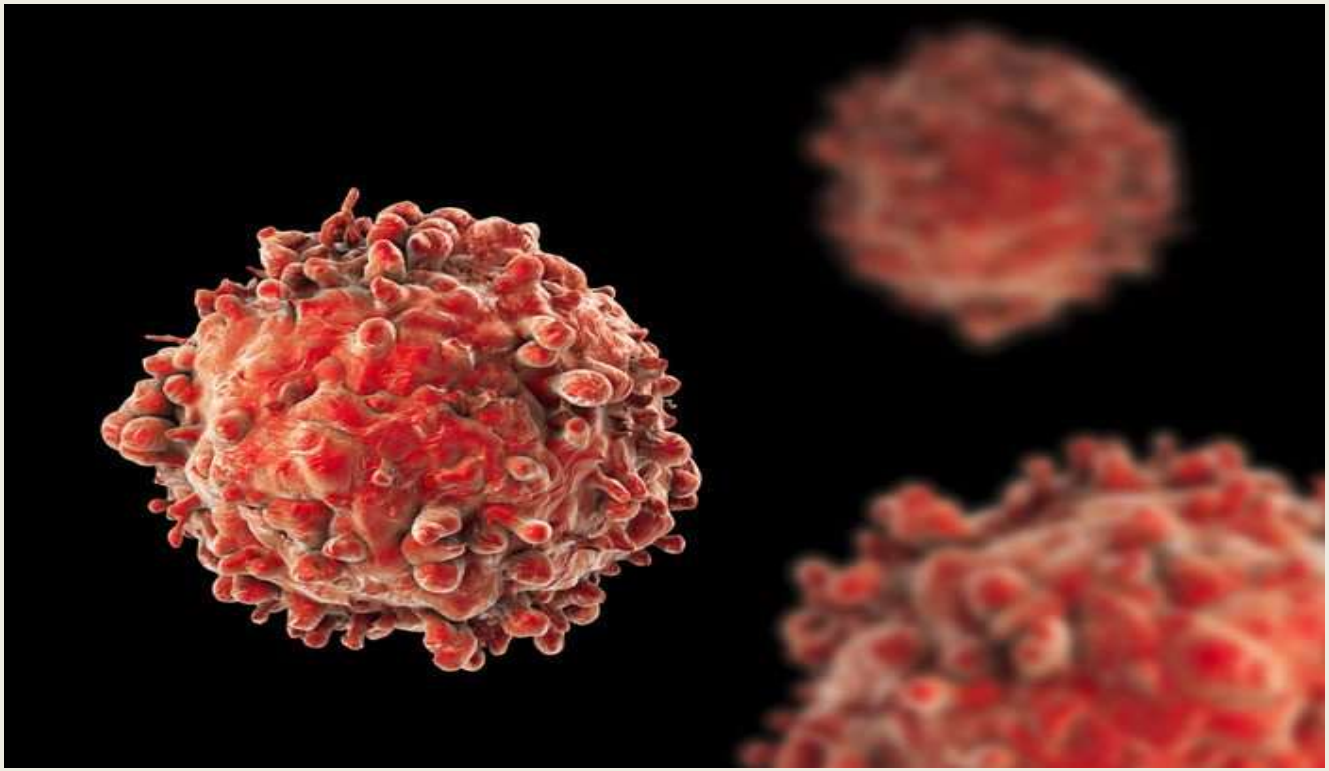
Immunotherapy in Head and Neck Cancer



Raja Mudad, M.D. FACP
Florida Precision Oncology
Aventura, FL

Head and Neck Cancer

Worldwide:	> 800,000 new cases/year
Worldwide:	~ 300,000 deaths/year
In the U.S:	53,000 new cases in 2019 (Oral cavity and pharynx)
	12,410 (Larynx)
In the U.S:	10,860 deaths in 2019 (Oral cavity and pharynx)
	3760 deaths in 2019 (Larynx)

Squamous cell carcinoma accounts for 90%

Current expected 5-year survival of ~65% (57% in 1975)

Most patients present with locally advanced disease with a high risk of recurrence

Bray et al., 2018

Head and Neck Cancer

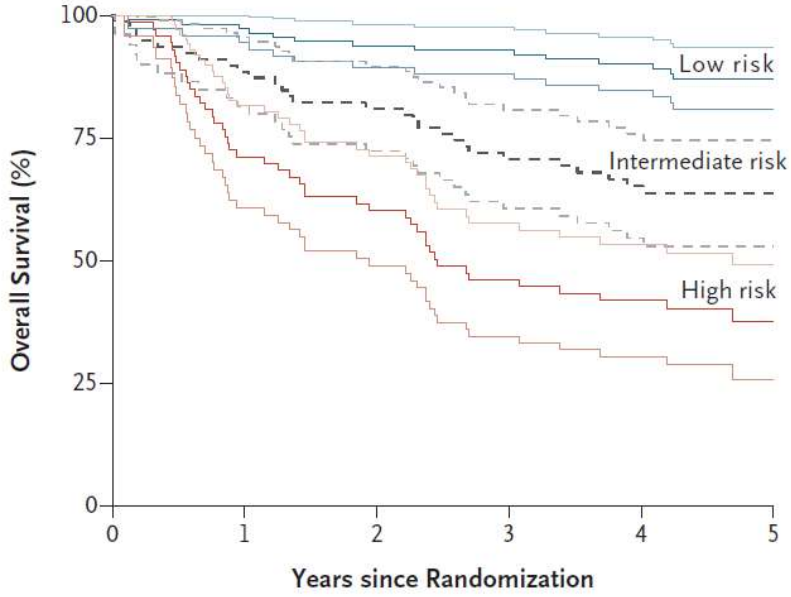
- The classic causative factors for ~80% of HNSCCs are heavy tobacco usage and/or excessive alcohol consumption
- HPV as a causative factor account for ~20% of HNSCC patients in the Western world
- HPV (+) and HPV-negative (-) HNSCCs are distinct subtypes in regard to molecular signatures, clinical presentation, and responses to therapy.
- The immune landscape of HPV (+) HNSCCs differs from HPV (-) tumors in that the HPV (+) Tumor Micro-Environment is associated with abundant immune infiltrates, whereas the HPV (-) TME incurs high mutational load.

Head and Neck Cancer

- Approximately 10% of HNSCC patients present with metastatic disease
- Median OS for patients with recurrent/metastatic (R/M) disease is 10–13 months
- Standard of care has been Platinum/5FU + Cetuximab: EXTREME - extended survival by ~ 3 months compared to chemo alone
  - Very toxic regimen

Head and Neck Cancers in 2019

B



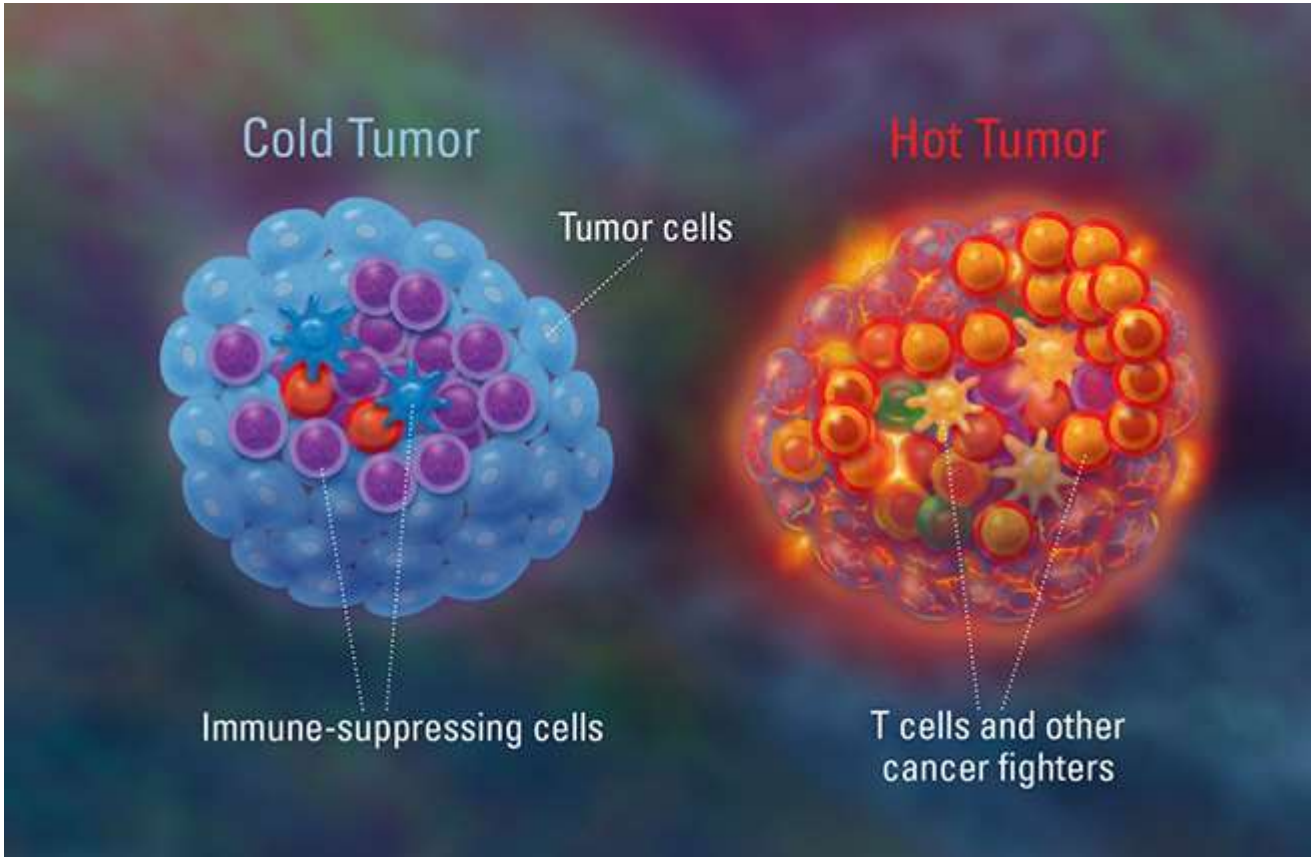
No. at Risk						
Low risk	114	111	106	102	95	46
Intermediate risk	79	70	64	54	44	24
High risk	73	52	43	33	28	8

OS >90% →HPV+ (T1-2, <N2b, non smokers)

OS >70-80% →HPV+ (T4, N2b-3, smokers)
HPV- (T2-3, non-smoker)

OS 40-50% → HPV-, T4, N3

Head and neck cancer: Micro-environment



HPV+ tumors
Have a more
favorable
TME

Head and Neck Cancers: Immunotherapy

- Initial role for IO was studied in second line
- Immunotherapy in second line was shown to improve survival
- Approved after failure of platinum-based first line therapy (nivolumab and pembrolizumab)
- Approved for PDL-1 > 1% (need to specify antibody)
- In 2019: First line immunotherapy– Approved

PDL-1 expression and prognosis

- In early stage H&N cancers treated for cure, PDL-1 expression has no prognostic value

- In a cohort of 303 patients treated with RT
  - Median follow-up was 5.3 years
  - With 199 deaths, there was no difference in overall survival between patients with PD-L1+ and PD-L1− tumors
  - locoregional failure was similar between the two groups

Jacob K. et al. Prognostic impact of PD-L1 in oropharyngeal cancer after primary curative radiotherapy and relation to HPV and tobacco smoking, Acta Oncologica, Feb 20, 2020DOI: 10.1080/0284186X.2020.1729407

PDL-1 expression and prognosis

- Tumors were PD-L1+ in 76% of cases, significantly more among HPV p16+ tumors (82% vs. 70%, $p = .01$)
- higher prevalence of PD-L1+ expression was seen in HPV p16+ patients with <10 pack-years of tobacco-smoking

Jacob K. et al. Prognostic impact of PD-L1 in oropharyngeal cancer after primary curative radiotherapy and relation to HPV and tobacco smoking, Acta Oncologica, Feb 20, 2020DOI: 10.1080/0284186X.2020.1729407

AACR American Association for Cancer Research
ANNUAL MEETING
2018 CHICAGO, IL
CheckMate 141
CT116

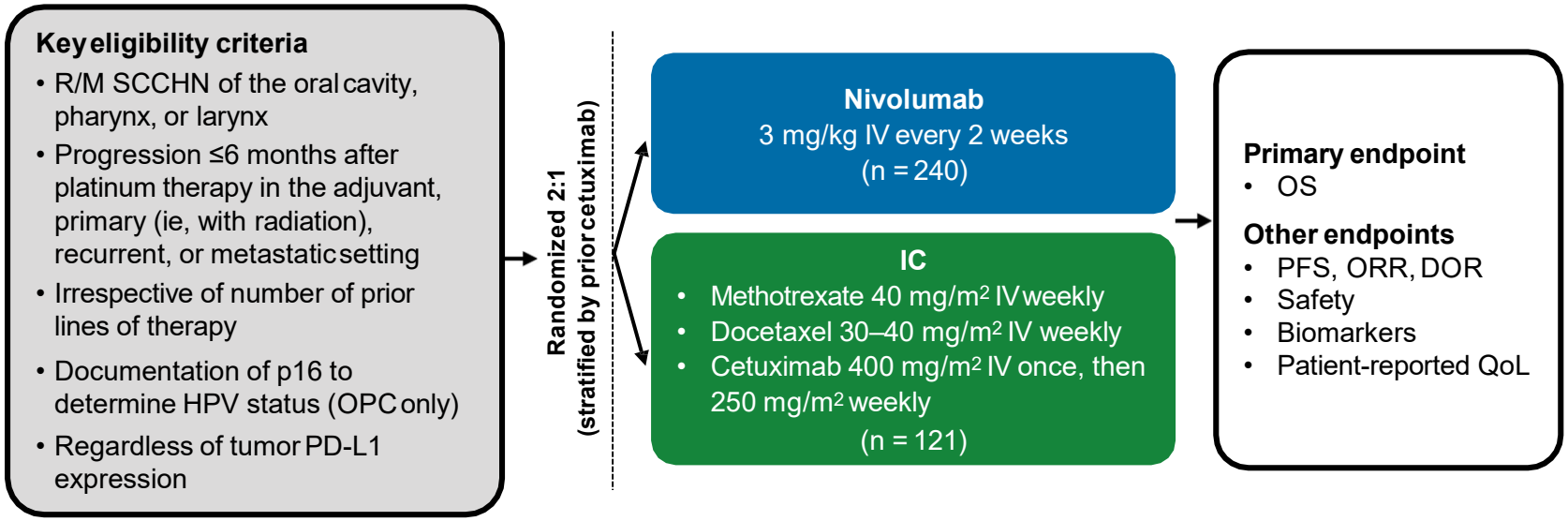
Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-yr outcomes in the overall population and PD-L1 subgroups of CheckMate 141

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]

[1]University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]Centre Leon Berard, Lyon, France; [4]Centre Antoine Lacassagne, FHU OncoAge, Université Côte d'Azur, Nice, France; [5]Stanford University, Stanford, CA, USA; [6]Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy; [7]Royal Marsden NHS Foundation Trust/The Institute of Cancer Research, London, UK; [8]West German Cancer Center, University Hospital, Essen, Germany; [9]University of Chicago Medical Center, Chicago, IL, USA; [10]Gustave Roussy, Villejuif Cedex, France; [11]University of Michigan, Ann Arbor, MI, USA; [12]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [13]Hospital Universitario 12 de Octubre, Madrid, Spain; [14]Dana-Farber/Harvard Cancer Center, Boston, MA, USA; [15]Universitätsspital Zurich, Zurich, Switzerland; [16]Kobe University Hospital, Kobe, Japan; [17]National Cancer Center Hospital East, Kashiwa, Japan; [18]Bristol-Myers Squibb, Princeton, NJ, USA

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

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)

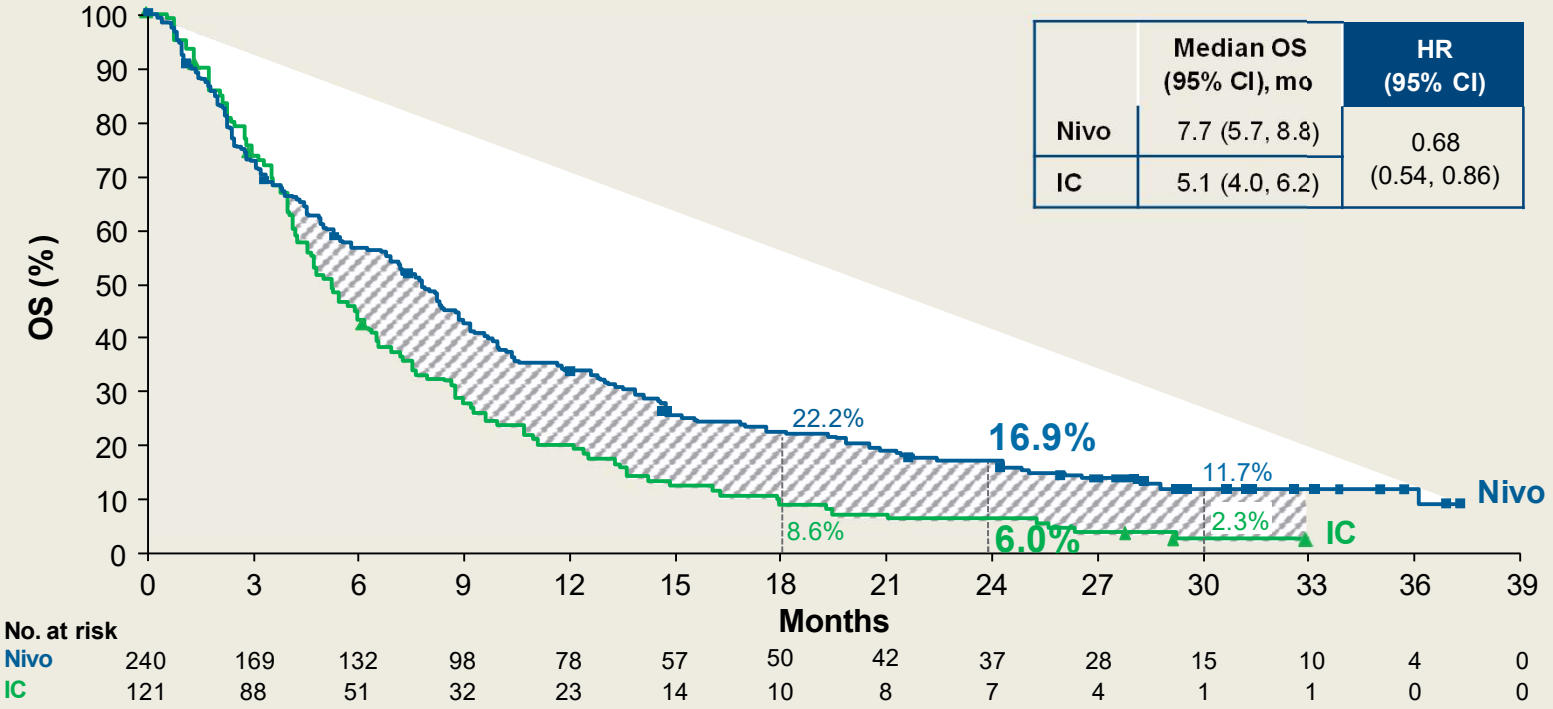
[a]PD-L1 status was determined using the Dako PD-L1 IHC 28-8 pharmDx test

[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

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



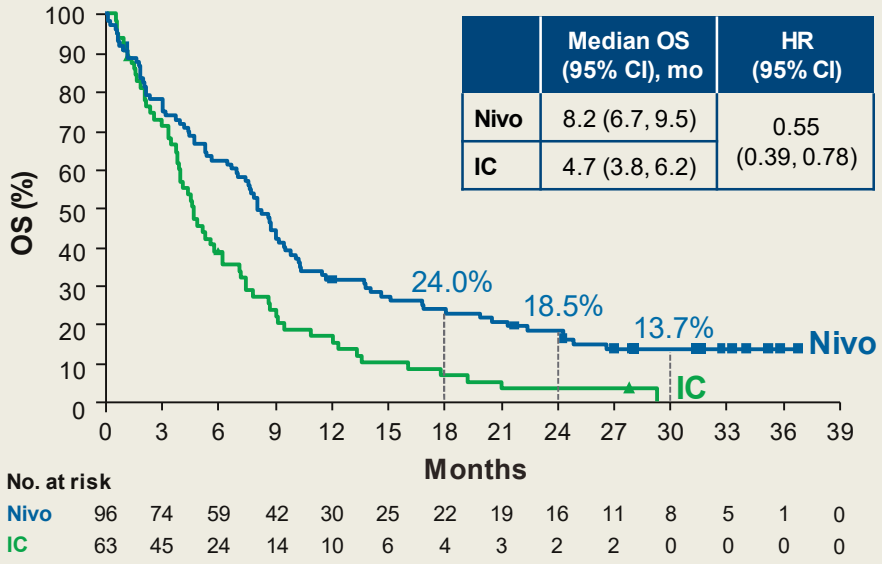
	Median OS (95% CI), mo	HR (95% CI)
Nivo	7.7 (5.7, 8.8)	0.68 (0.54, 0.86)
IC	5.1 (4.0, 6.2)	

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

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

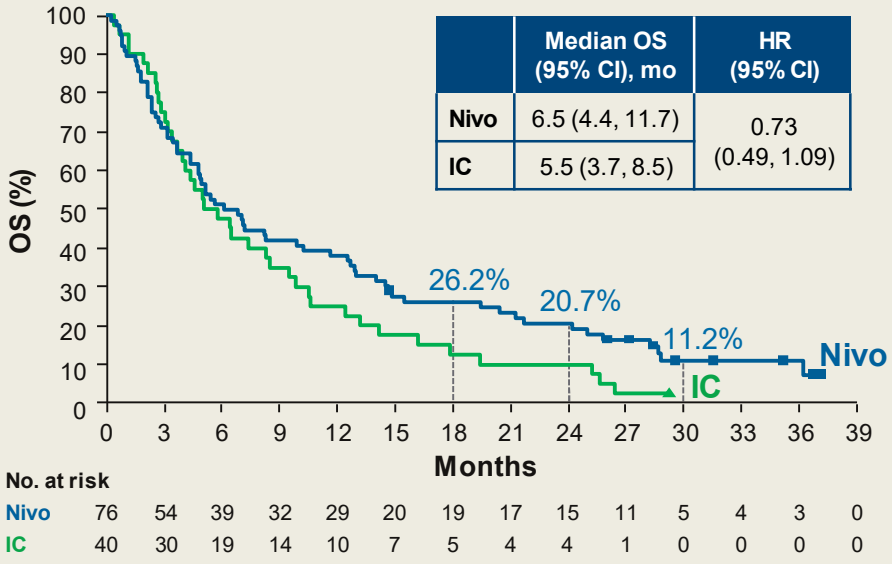
PD-L1 Expressors (≥1%)



	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

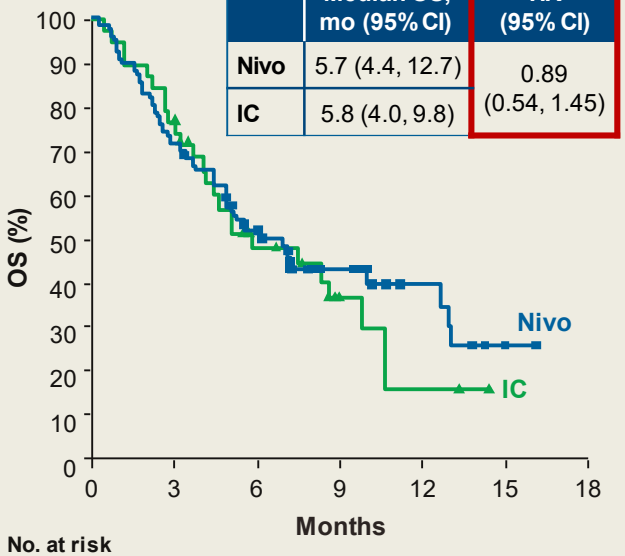
Symbols represent censored observations

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)	

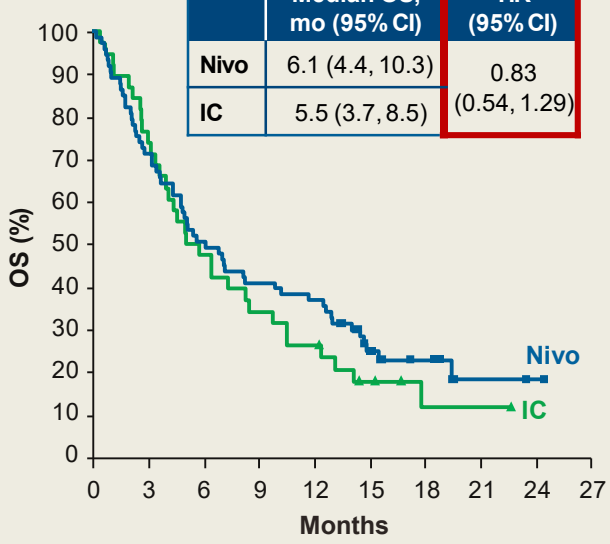


No. at risk

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

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

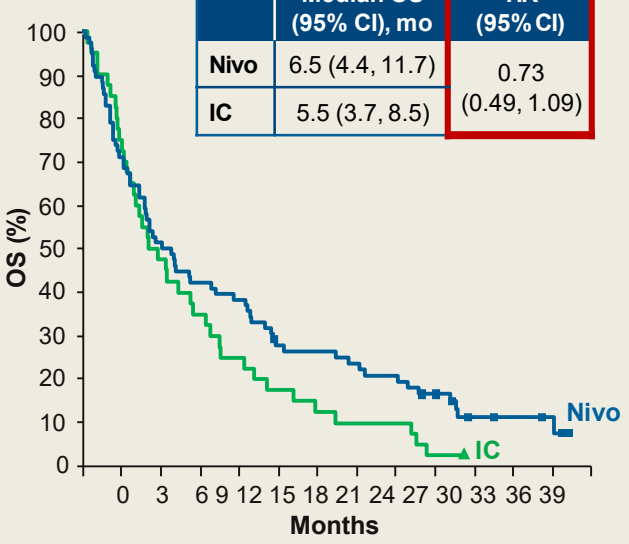
	Median OS, mo (95% CI)	HR (95% CI)
Nivo	6.1 (4.4, 10.3)	0.83 (0.54, 1.29)
IC	5.5 (3.7, 8.5)	



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)	



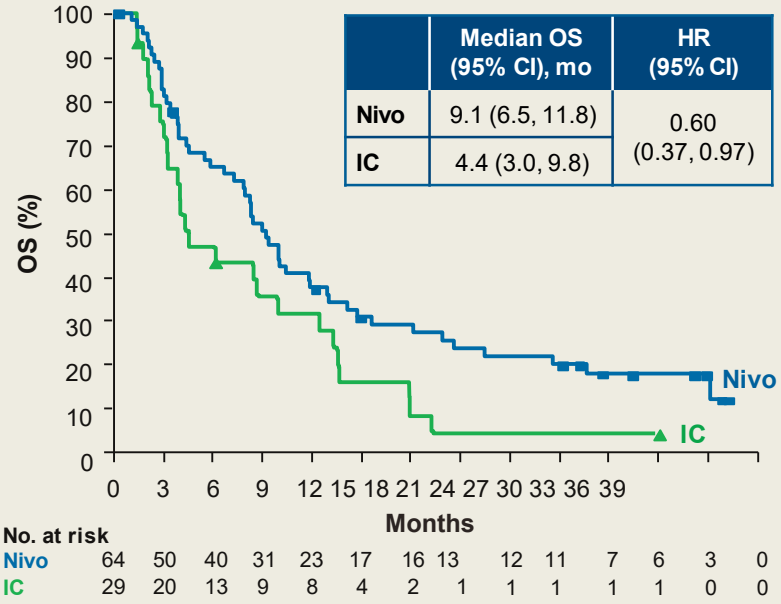
Nivo	76	54	39	32	29	20	19	17	15	11	5	4	3	0
IC	40	30	19	14	10	7	5	4	4	1	0	0	0	0

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 with permission from Massachusetts Medical Society.

OS by HPV Status[a]

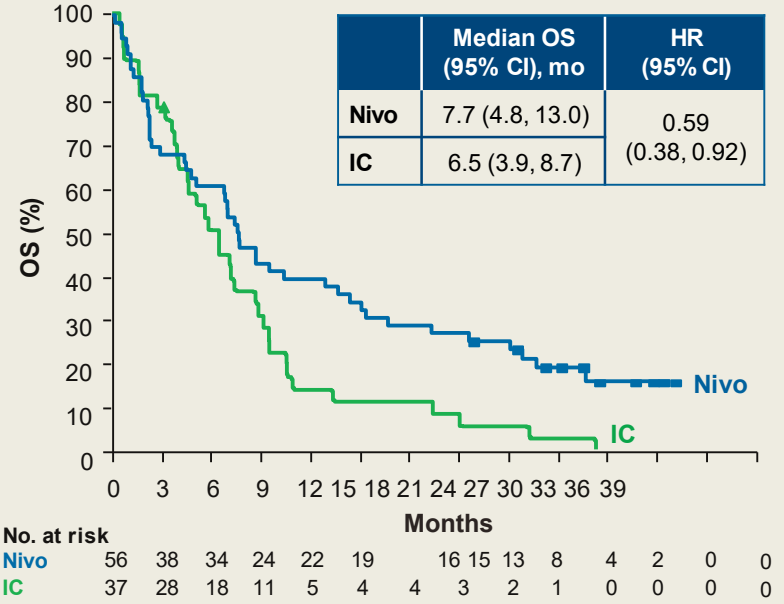
- Nivolumab demonstrated survival benefit in patients with HPV-positive and HPV-negative tumors, with comparable HRs for risk of death vs IC

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

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)

Tumor Response

- In the nivolumab arm, complete responses were observed in both PD-L1 expressors and PD-L1 non-expressors
  - Seven complete responders (2 PD-L1 expressors, 2 PD-L1 non-expressors, and 3 with no data on tumor PD-L1 expression)
  - One patient had a partial response, which later converted to a complete response

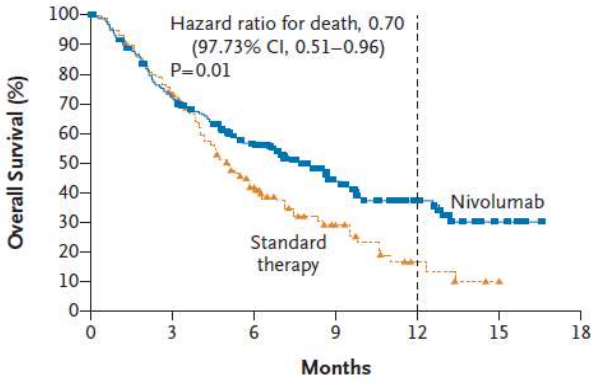
	Nivolumab (n = 240)	IC (n = 121)
ORR, % (95% CI)	13.3 (9.3, 18.3)	5.8 (2.4, 11.6)
Time to response, median (range), months	2.1 (1.8 to 7.4)	2.0 (1.9 to 4.6)
Duration of response, median (range), months	9.7 (2.8 to 32.8+)	4.0 (1.5+ to 11.3)

Checkpoint Inhibitors in R/M SCCHN After Platinum Therapy

CheckMate 141: Phase III trial of Nivolumab versus chemotherapy

A Overall Survival

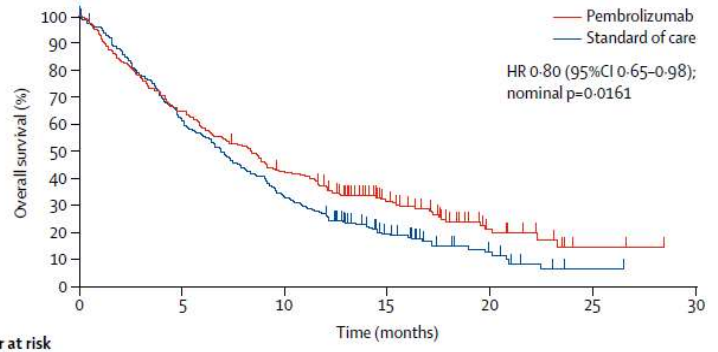
	No. of Patients	No. of Deaths	1–Yr Overall Survival Rate % (95% CI)	Median Overall Survival mo (95% CI)
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard Therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



13% ORR, but more than doubled OS at 2 years (16 vs. 6%).

KEYNOTE-040: Pembrolizumab vs. investigator's choice Phase III trial

A



Number at risk (number censored)							
Pembrolizumab	247 (0)	160 (0)	103 (2)	48 (33)	14 (55)	2 (64)	0 (66)
Standard of care	248 (0)	151 (3)	82 (3)	34 (19)	10 (35)	1 (40)	0 (41)

Borderline positive, clinically meaningful (mOS 8.4 vs 6.9 months).

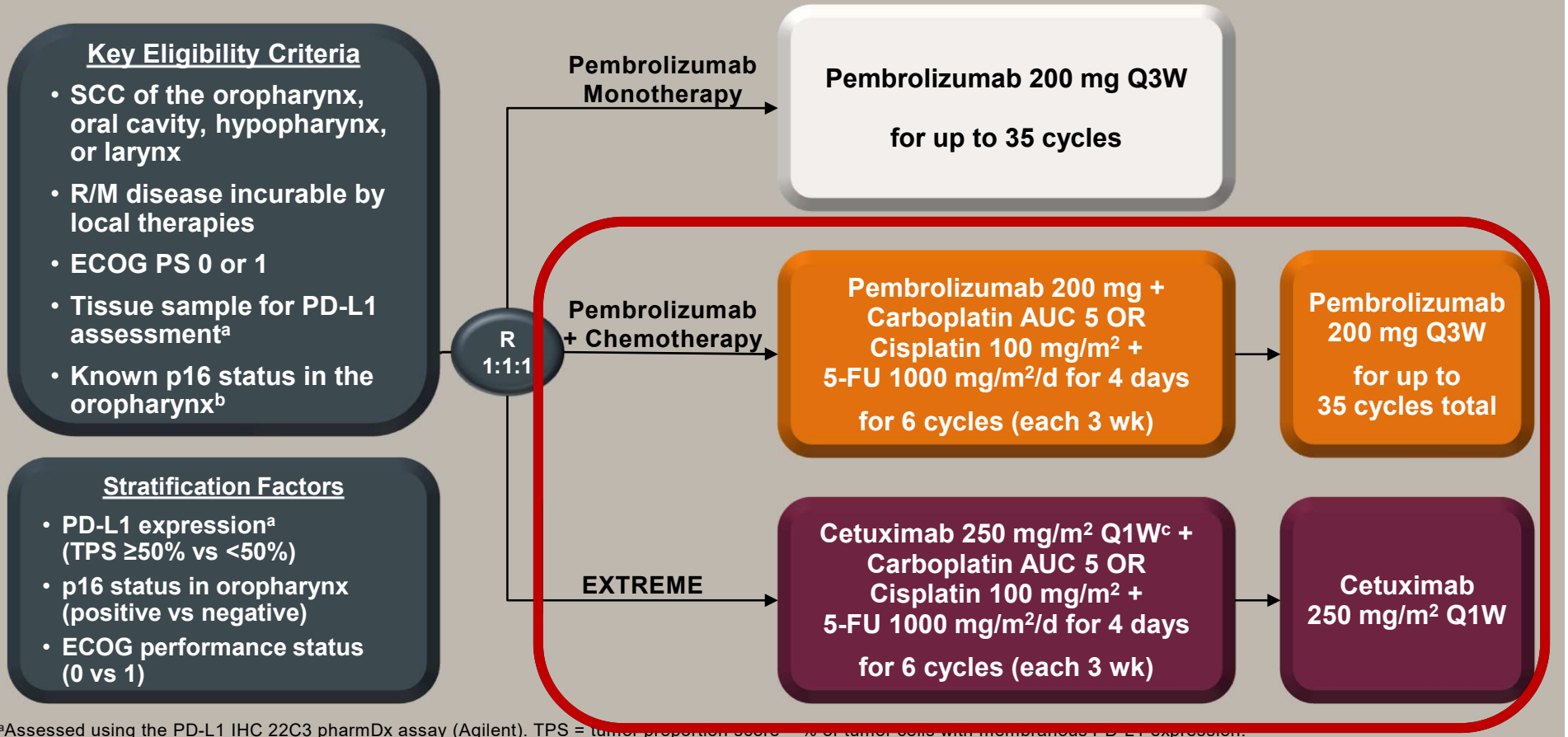
Protocol-Specified Final Results of the KEYNOTE-048 Trial of Pembrolizumab as First-Line Therapy for Recurrent/ Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC)

Danny Rischin[1], Kevin Harrington,[2] Richard Greil,[3] Denis Soulières,[4] Makoto Tahara,[5] Gilberto de Castro,[6] Amanda Psyrri,[7] Neus Basté,[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] Yayan Zhang,[17] Fan Jin,[17] Burak Gumuscu,[17] Barbara Burtness[18]

[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [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; [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]Yale School of Medicine and Yale Cancer Center, New Haven, CT, USA

Presented By Danny Rischin at 2019 ASCO Annual Meeting

KEYNOTE-048 Study Design (NCT02358031)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score [illegible] % 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]

CPS= number of PDL-1 + cells (tumor, lymphs, macros) divided by number of tumor cells

Secondary

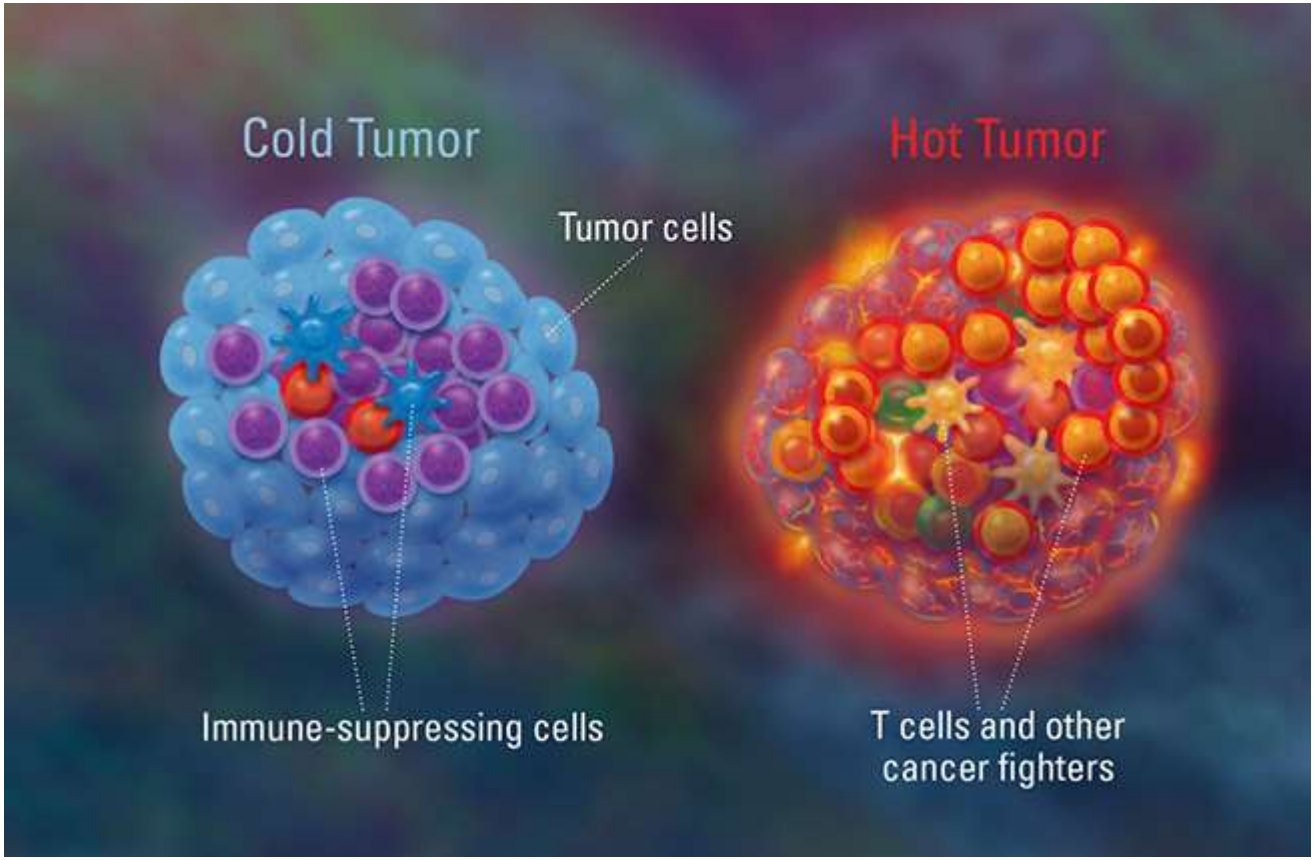
- CPS ≥20,[a] CPS ≥1,[a] and total populations
  - PFS[b] rates at 6 and 12 mo
  - ORR[b]
  - Change from baseline and time to deterioration in quality of life (EORTC QLQ-C30 and H&N-35)[c]
- Total population
  - Safety and tolerability

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.

Head and neck cancer: Micro-environment



HPV+ tumors Have a more favorable TME

Importance of CPS

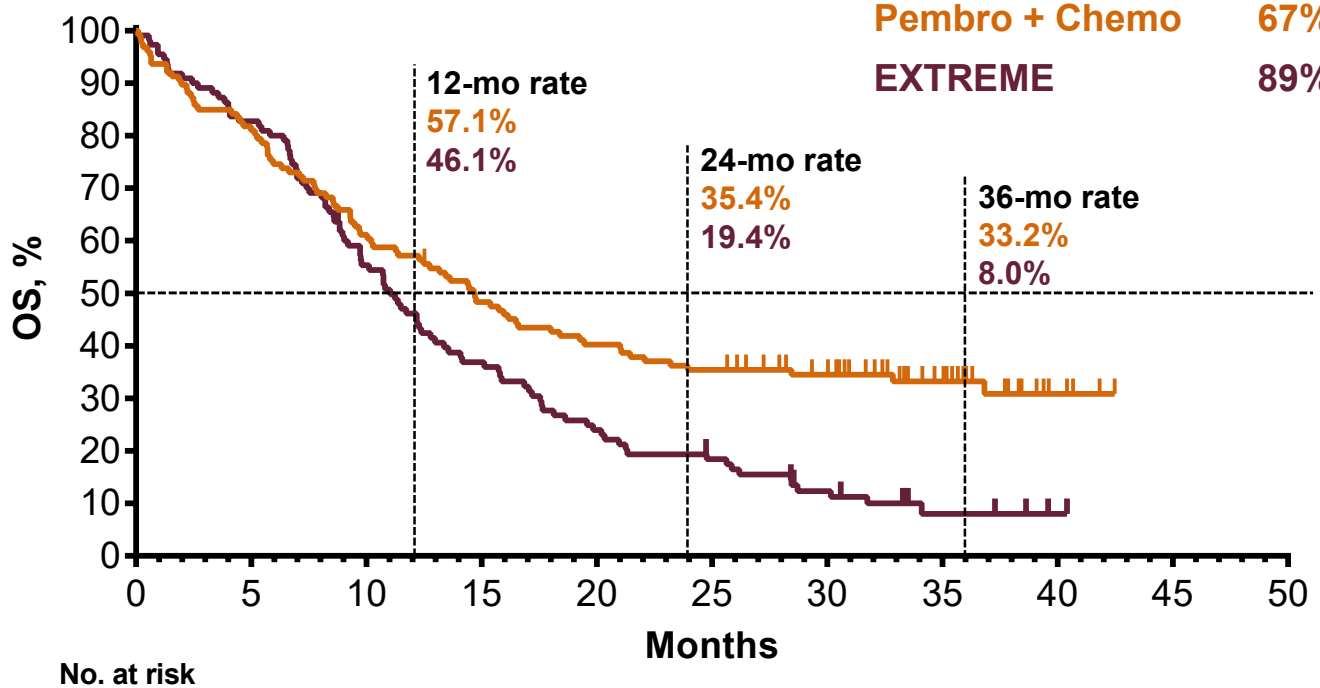
Baseline Characteristics, ITT Population

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)
Locoregional recurrence only	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.
FA (data cutoff date: Feb 25, 2019).

OS, P+C vs E, CPS ≥20 Population

	Events	HR (95% CI)	*P*
Pembro + Chemo	67%	0.60 (0.45-0.82)	0.0004[a]
EXTREME	89%		



Median (95% CI)
14.7 mo (10.3-19.3)
11.0 mo (9.2-13.0)

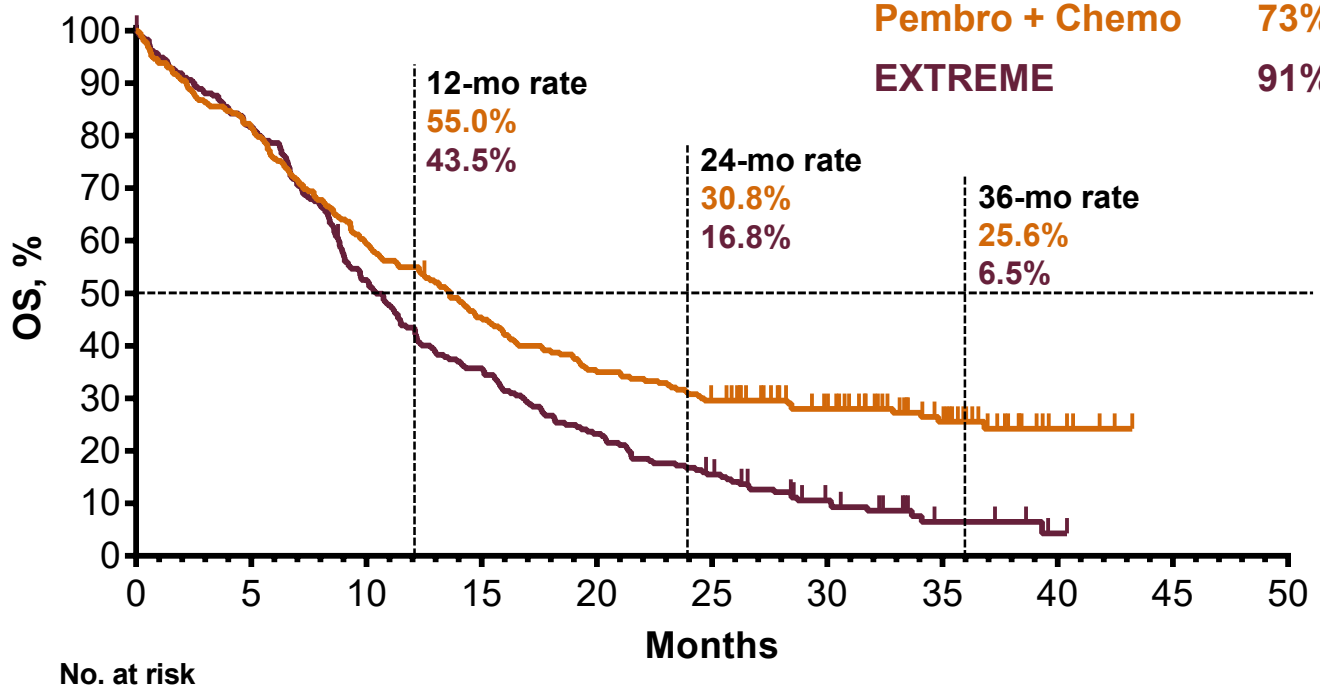
No. at risk

126	102	77	60	50	44	36	21	4	0	0
110	91	60	40	26	19	11	4	1	0	0

[a]Statistically significant at the superiority threshold of *P* = 0.0023.
FA (data cutoff date: Feb 25, 2019).

OS, P+C vs E, CPS ≥1 Population

	Events	HR (95% CI)	*P*
Pembro + Chemo	73%	0.65 (0.53-0.80)	<0.0001[a]
EXTREME	91%		



Median (95% CI)
13.6 mo (10.7-15.5)
10.4 mo (9.1-11.7)

No. at risk

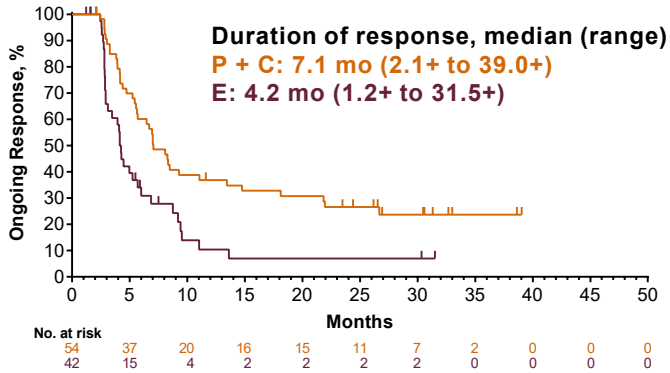
242	197	144	109	84	70	52	29	5	0	0
235	191	122	83	54	35	17	5	1	0	0

[a]Statistically significant at the superiority threshold of *P* = 0.0026.
FA (data cutoff date: Feb 25, 2019).

Response Summary, P+C vs E

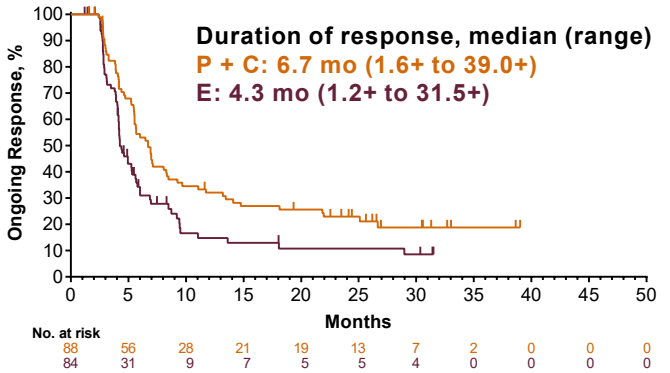
CPS ≥20

Confirmed Response, n (%)	P + C N = 126	E N = 110
ORR	**54 (42.9)**	**42 (38.2)**
CR	12 (9.5)	4 (3.6)
PR	42 (33.3)	38 (34.5)
SD	29 (23.0)	38 (34.5)
PD	19 (15.1)	9 (8.2)
Non-CR/non-PD[a]	4 (3.2)	5 (4.5)
Not evaluable or assessed[b]	20 (15.9)	16 (14.5)



CPS ≥1

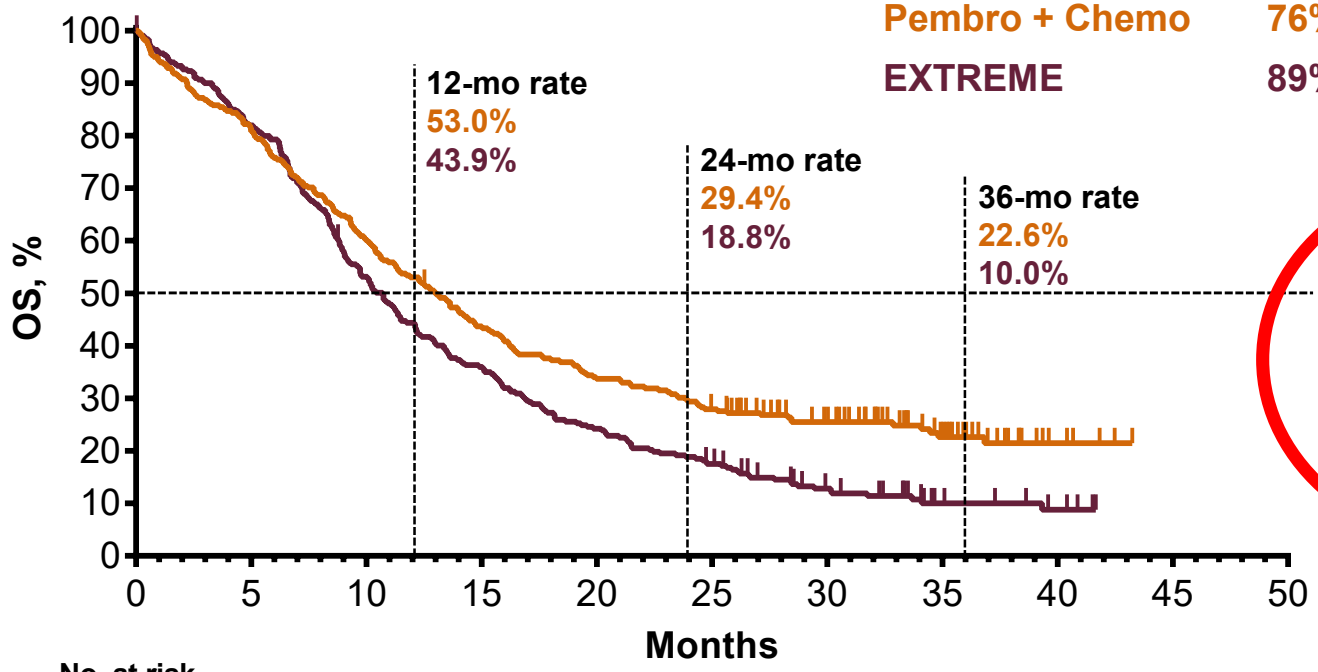
Confirmed Response, n (%)	P + C N = 242	E N = 235
ORR	**88 (36.4)**	**84 (35.7)**
CR	16 (6.6)	7 (3.0)
PR	72 (29.8)	77 (32.8)
SD	64 (26.4)	77 (32.8)
PD	42 (17.4)	29 (12.3)
Non-CR/non-PD[a]	11 (4.5)	9 (3.8)
Not evaluable or assessed[b]	37 (15.3)	36 (15.3)



[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. FA (data cutoff date: Feb 25, 2019).

OS, P+C vs E, Total Population

	Events	HR (95% CI)
Pembro + Chemo	76%	0.72[a] (0.60–0.87)
EXTREME	89%	



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

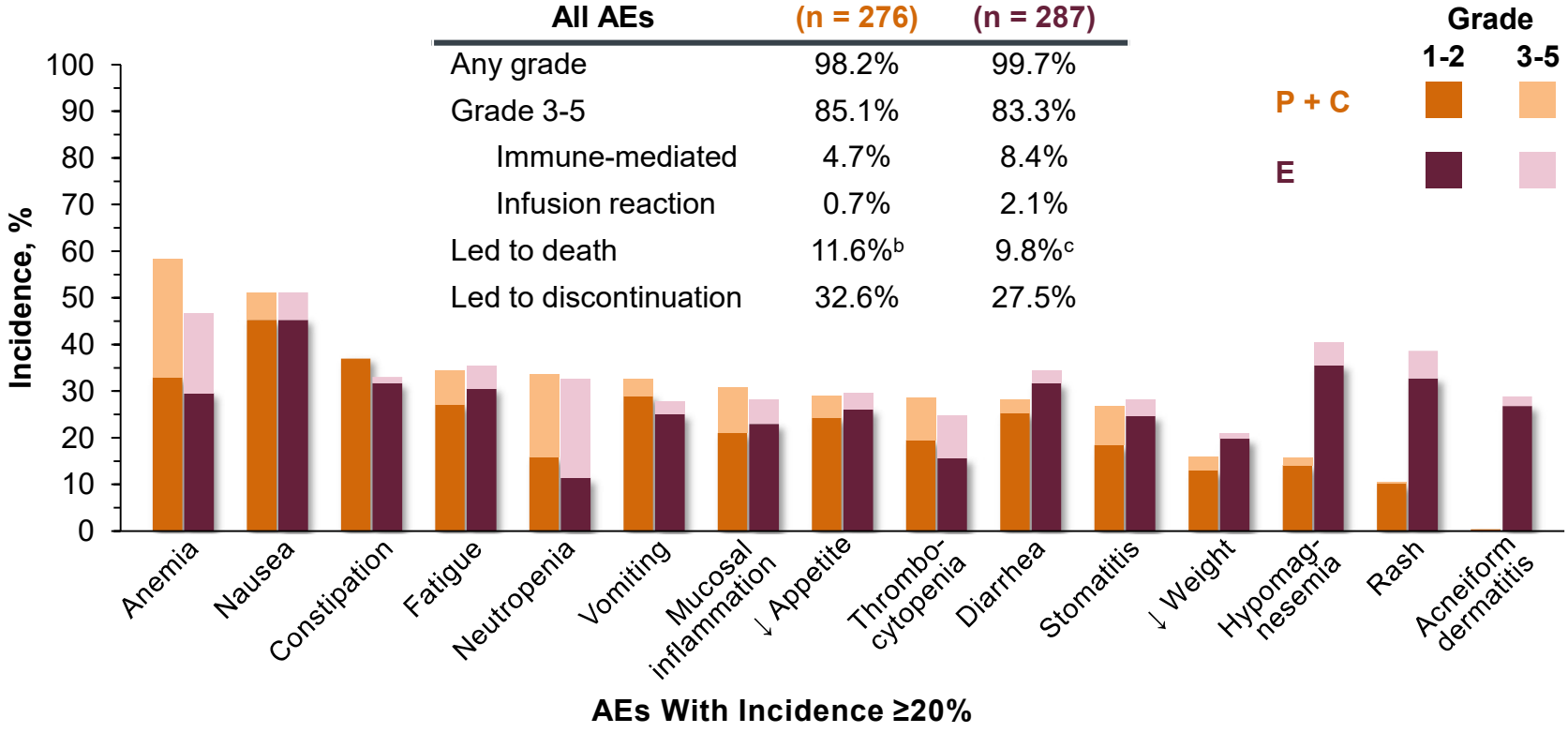
No. at risk

281	227	169	122	94	77	55	29	5	0	0
278	227	147	100	66	45	23	6	1	0	0

[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.77 (95% CI 0.53–0.93).
FA (data cutoff date: Feb 25, 2019).

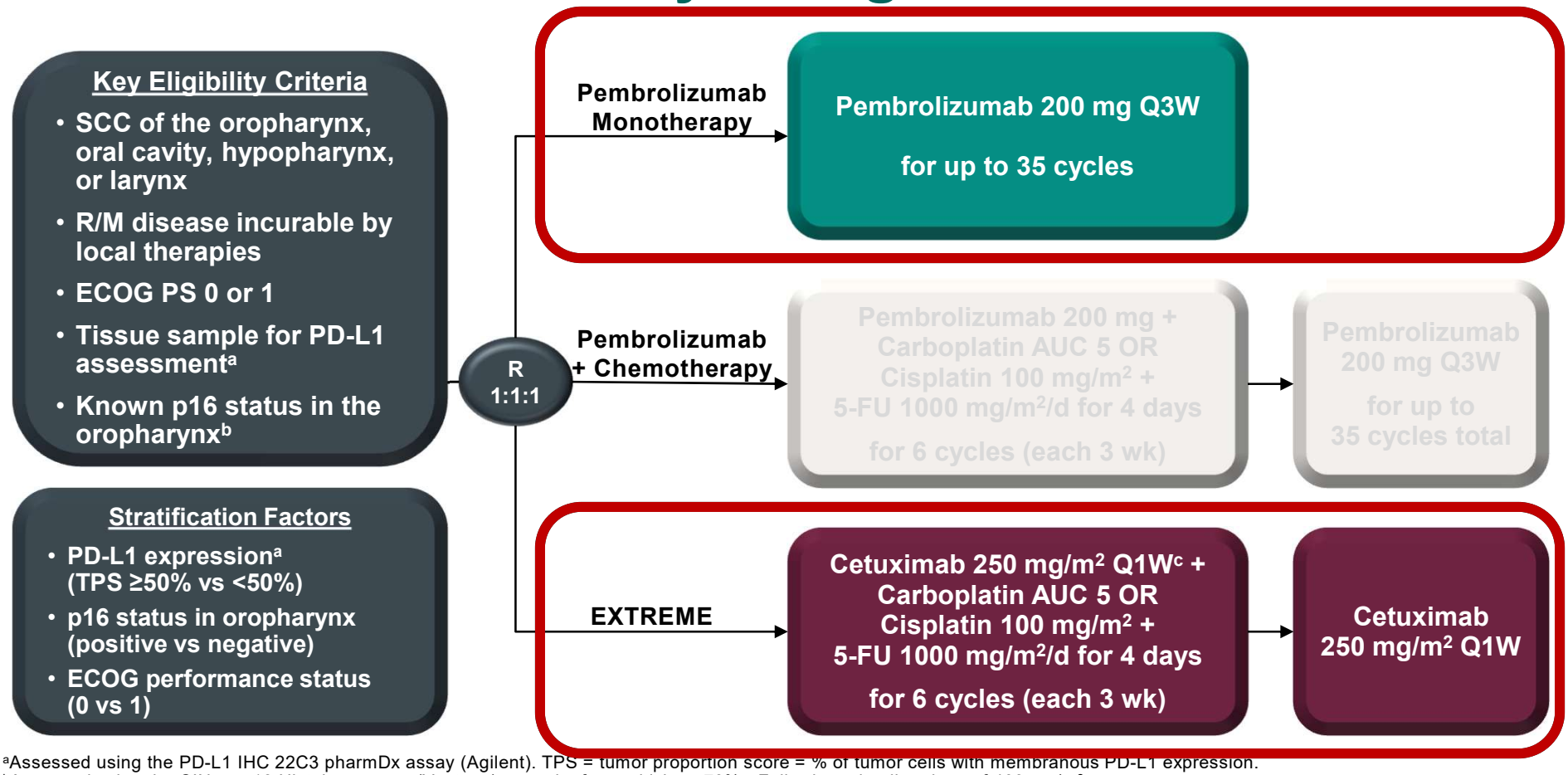
All-Cause AEs,[a] P + C vs E, Total Population

All AEs	P + C (n = 276)	E (n = 287)
Any grade	98.2%	99.7%
Grade 3-5	85.1%	83.3%
Immune-mediated	4.7%	8.4%
Infusion reaction	0.7%	2.1%
Led to death	11.6%[b]	9.8%[c]
Led to discontinuation	32.6%	27.5%



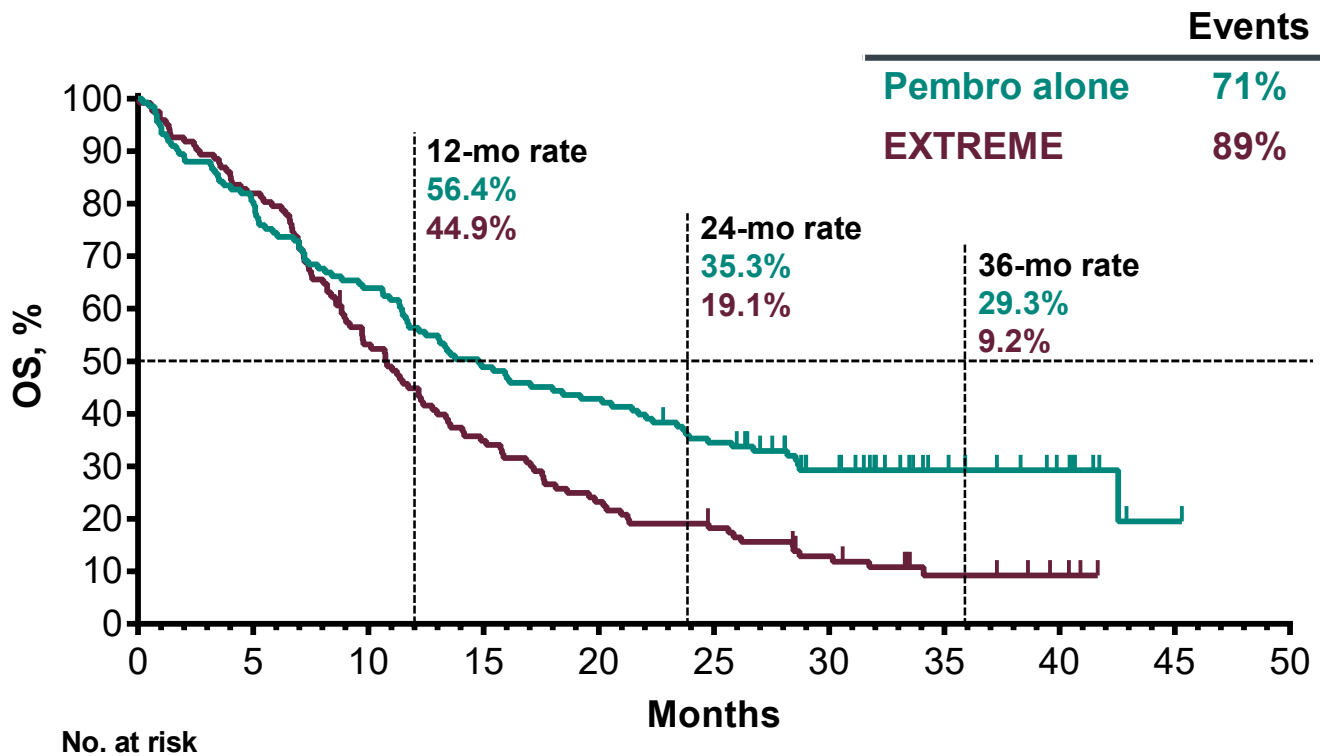
[a]Data for treatment-related AEs were presented at ESMO 2018. [b]Events were considered treatment related in 4.0%. [c]Events were considered treatment related in 2.8%.
FA (data cutoff date: Feb 25, 2019).

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.

OS, P vs E, CPS ≥20 Population

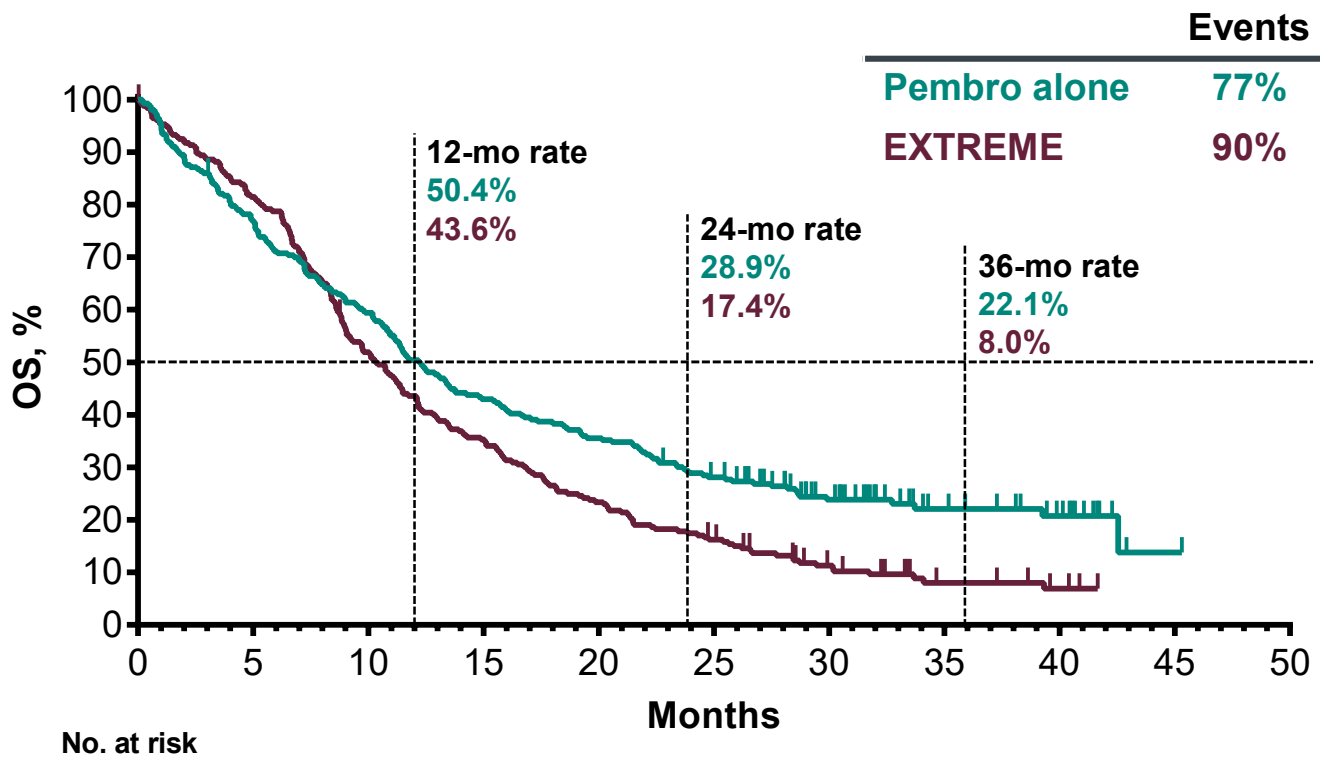


	Events	HR (95% CI)
Pembro alone	71%	0.58 (0.44-0.78)[a]
EXTREME	89%	

Median (95% CI)
14.8 mo (11.5-20.6)
10.7 mo (8.8-12.8)

[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.61 (95% CI 0.45–0.83).
FA (data cutoff date: Feb 25, 2019).

OS, P vs E, CPS ≥1 Population

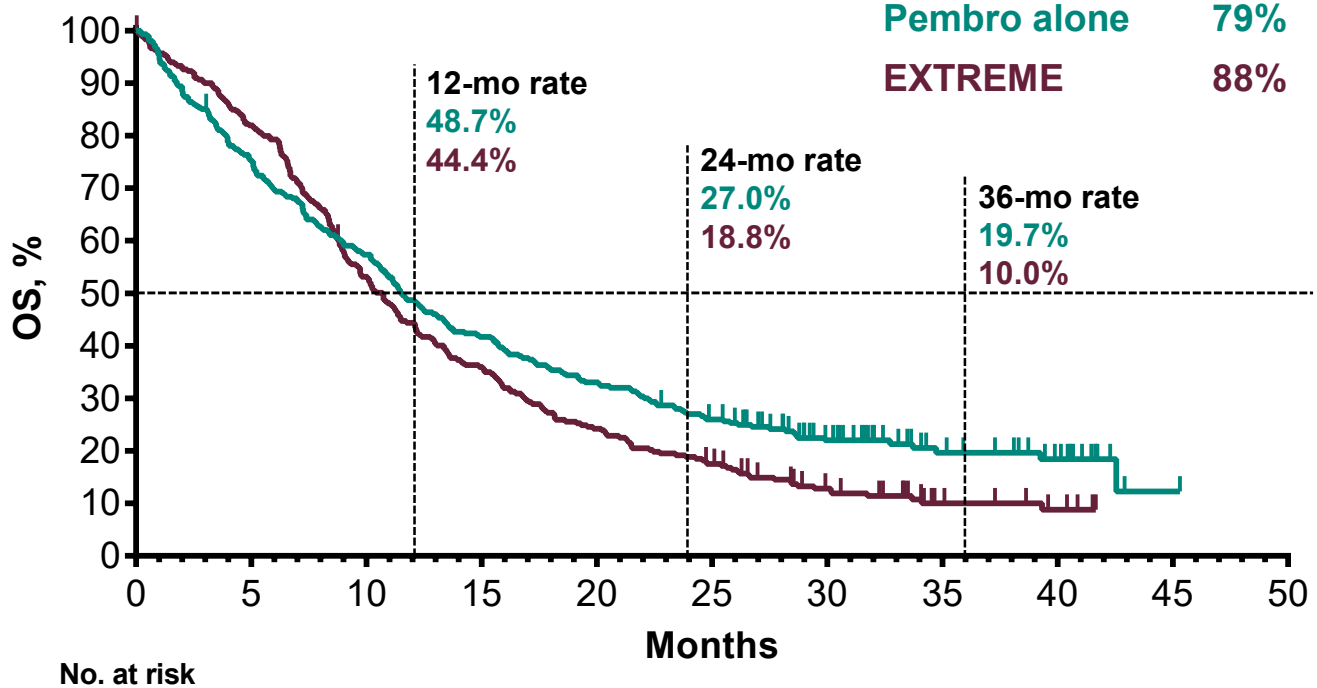


	Events	HR (95% CI)
Pembro alone	77%	0.74 (0.61-0.90)[a]
EXTREME	90%	

Median (95% CI)
12.3 mo (10.8-14.3)
10.3 mo (9.0-11.5)

[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.78 (95% CI 0.64–0.96).
FA (data cutoff date: Feb 25, 2019).

OS, P vs E, Total Population



	Events	HR (95% CI)	*P*
Pembro alone	79%	0.83 (0.70-0.99)	0.0199[a]
EXTREME	88%		

Not statistically significant at the superiority threshold of 0.0059

Median (95% CI)
11.5 mo (10.3-13.4)
10.7 mo (9.3-11.7)

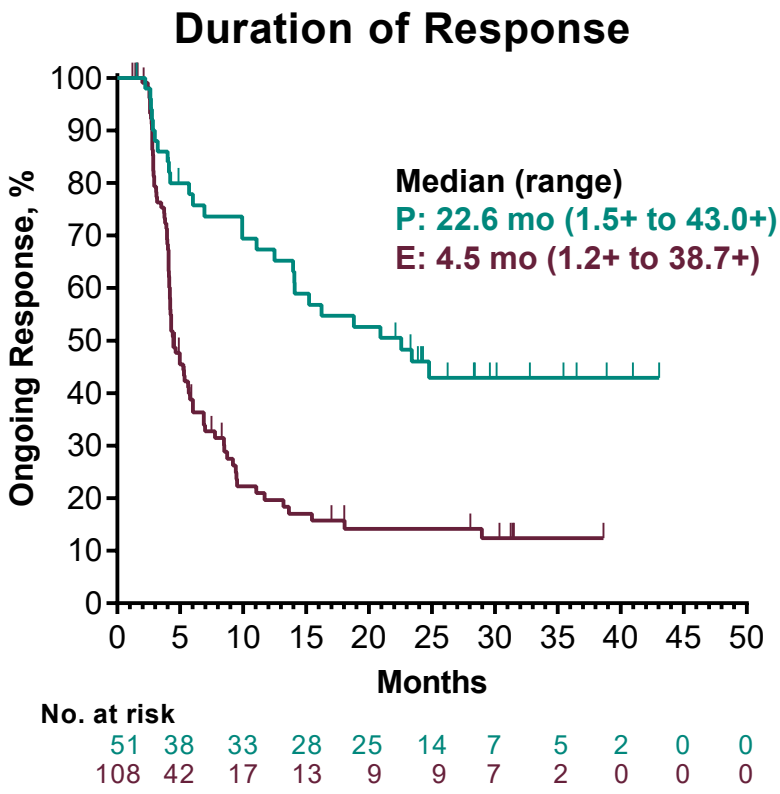
No. at risk

301	226	172	125	99	75	46	22	13	1	0
300	245	158	107	72	51	28	11	6	0	0

[a]Not statistically significant at the superiority threshold of $P = 0.0059$.
FA (data cutoff date: Feb 25, 2019).

Response Summary, P vs E, Total Population

Confirmed Response, n (%)	Pembro N = 301	EXTREME N = 300
ORR	**51 (16.9)**	**108 (36.0)**
CR	14 (4.7)	8 (2.7)
PR	37 (12.3)	100 (33.3)
SD	82 (27.2)	102 (34.0)
PD	122 (40.5)	37 (12.3)
Non-CR/non-PD[a]	14 (4.7)	11 (3.7)
Not evaluable or assessed[b]	32 (10.6)	42 (14.0)



[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. FA (data cutoff date: Feb 25, 2019).

Summary and Conclusions

- Pembrolizumab plus a platinum and 5-FU vs EXTREME
  - Superior OS for pembrolizumab + chemotherapy in the PD-L1 CPS ≥20 and CPS ≥1 and total populations
  - Longer duration of response for pembrolizumab + chemotherapy
  - Comparable safety profiles for pembrolizumab + chemotherapy and EXTREME
- Pembrolizumab monotherapy vs EXTREME
  - Superior OS for pembrolizumab in the CPS ≥20 and CPS ≥1 populations
  - Noninferior OS for pembrolizumab in the total population
  - Substantially longer duration of response for pembrolizumab
  - Favorable safety profile for pembrolizumab
- Data support pembrolizumab plus platinum-based chemotherapy and pembrolizumab monotherapy as new first-line standard-of-care therapies for R/M HNSCC

Phase 3 KEYNOTE-048 Trial
Pembrolizumab vs EXTREME

FDA approves pembrolizumab for first-line treatment of head and neck squamous cell carcinoma

On June 10, 2019, the Food and Drug Administration approved pembrolizumab (KEYTRUDA, Merck) for the first-line treatment of patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC).

Pembrolizumab was approved for use in combination with platinum and fluorouracil (FU) for all patients and as a single agent for patients whose tumors express PD-L1 (Combined Positive Score [CPS] ≥1) as determined by an FDA-approved test. The FDA also expanded the intended use for the PD-L1 IHC 22C3 pharmDx kit to include use as a companion diagnostic device for selecting patients with HNSCC for treatment with pembrolizumab as a single agent.

Resistance to Checkpoint Inhibitors In SCCHN
PD-1 + CTLA Inhibition in HN Cancer: Does it still make sense?

CONDOR -Phase 2, randomised, open-label study of durvalumab, tremelimumab, or the combination in platinum-resistant R/M HNSCC expressing low/negative levels of tumour PD-L1

- R/M HNSCC (oral cavity, oropharynx, hypopharynx, larynx)
- Failure of 1 platinum-based chemotherapy in the R/M setting
- PD-L1 low/negative (<25% TC)

N=267

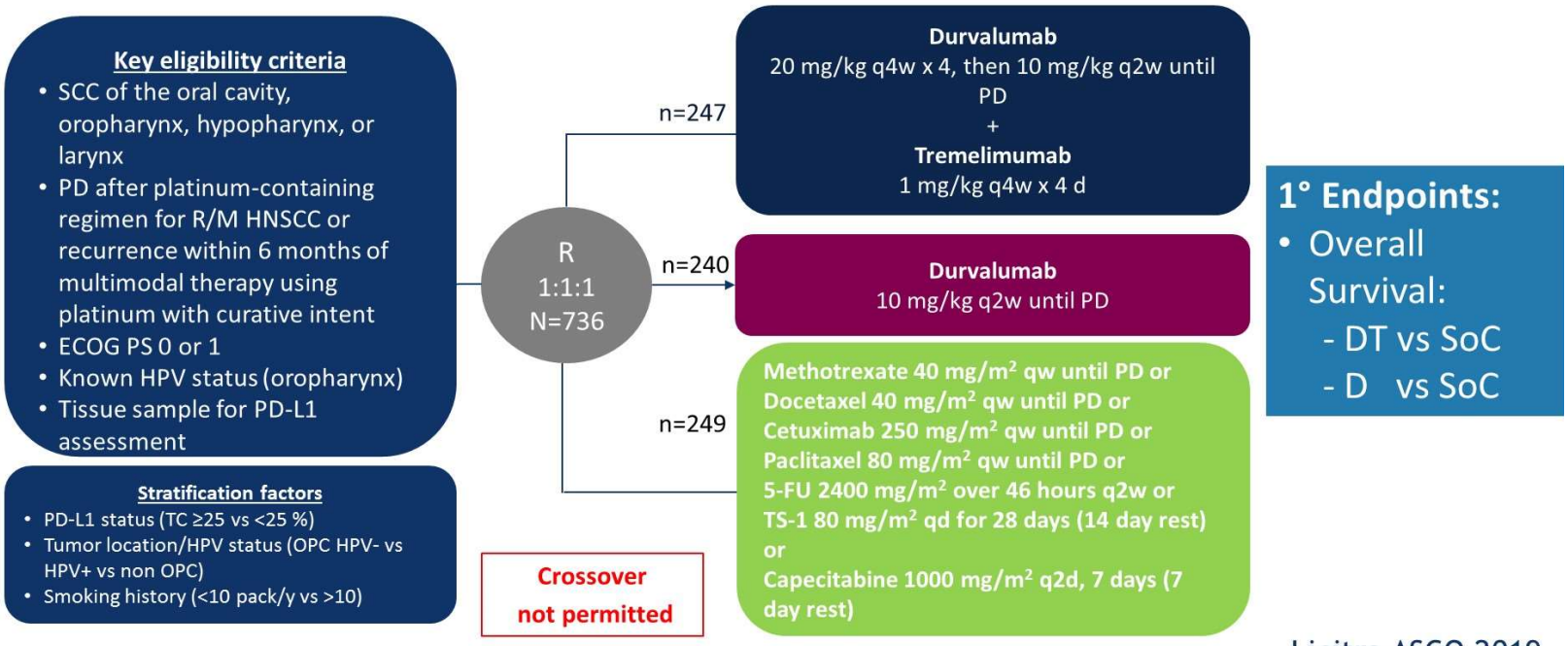
	ORR % [95% CI]
Durvalumab + tremelimumab n=133	7.8 [3.8-13.3]
Durvalumab n=67	9.2 [3.5-19]
Tremelimumab n=67	1.6 [0.04-8.5]

Primary endpoint: ORR

Siu et al JAMA Oncology 2018

Resistance to Checkpoint Inhibitors In SCCHN
PD-1 + CTLA Inhibition in HN Cancer: Does it still make sense?

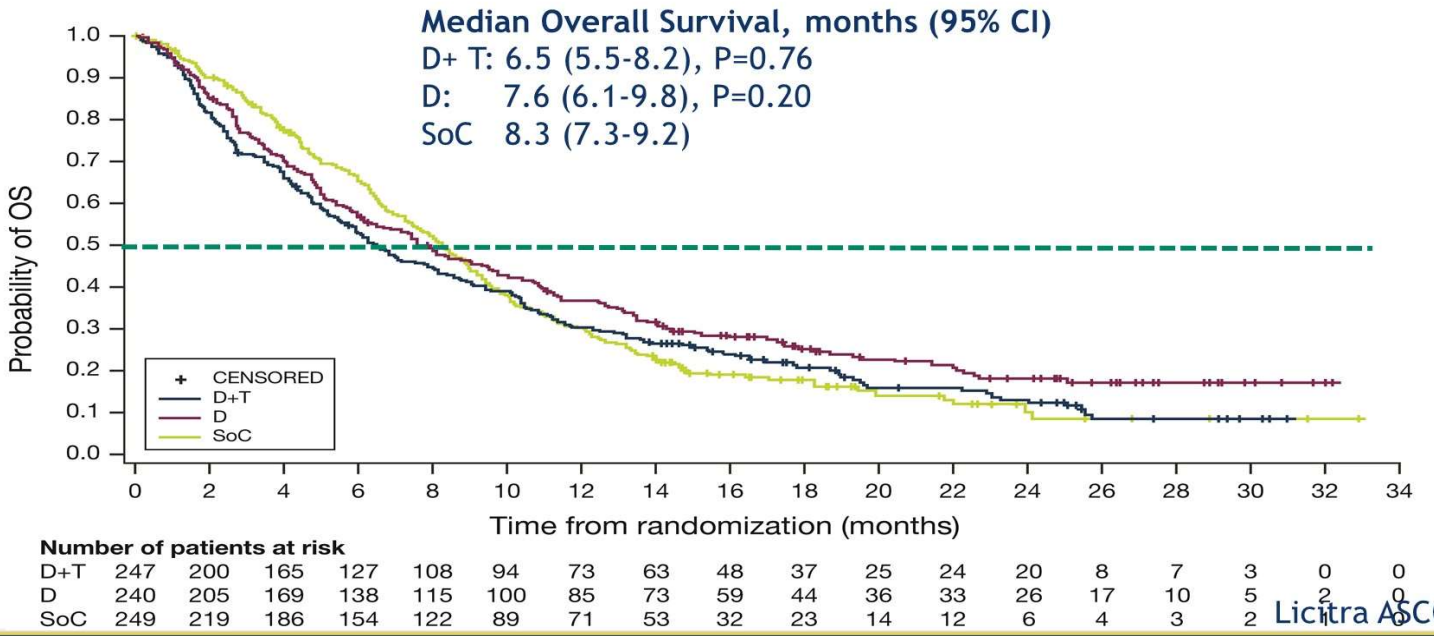
EAGLE : Phase 3 Trial of Durvalumab alone or Durvalumab + Tremelimumab compared with SOC as 2L Treatment for R/M HNSCC



Licitra ASCO 2019

Resistance to Checkpoint Inhibitors In SCCHN
PD-1 + CTLA Inhibition in HN Cancer: Does it still make sense?

EAGLE Primary Endpoint: Overall Survival for D+T vs SoC and D vs SOC



Licitra ASCO 2019

Conclusion

- Pembrolizumab with or without chemotherapy is now standard for R/M SCCHN (based on CPS PD-L1 score)
- Checkpoint inhibitors are being added to neoadjuvant, concurrent and adjuvant tx.
- PD-1 + CTLA might not be as effective (still being tested)
- Enrolling patients on clinical trials is the best option if possible