Immune Checkpoint Inhibitors for Head and Neck Cancers

William N. William Jr.

Diretor de Onco-Hematologia
Hospital BP, A Beneficência Portuguesa

Outline

- Immunotherapy for recurrent / metastatic HNSCC
    - Keynote-012 clinical data (pembrolizumab)
    - Keynote-055 (pembrolizumab)
    - Keynote-012 biomarker data (pembrolizumab)
    - Keynote-040
    - Checkmate 141 (nivolumab)

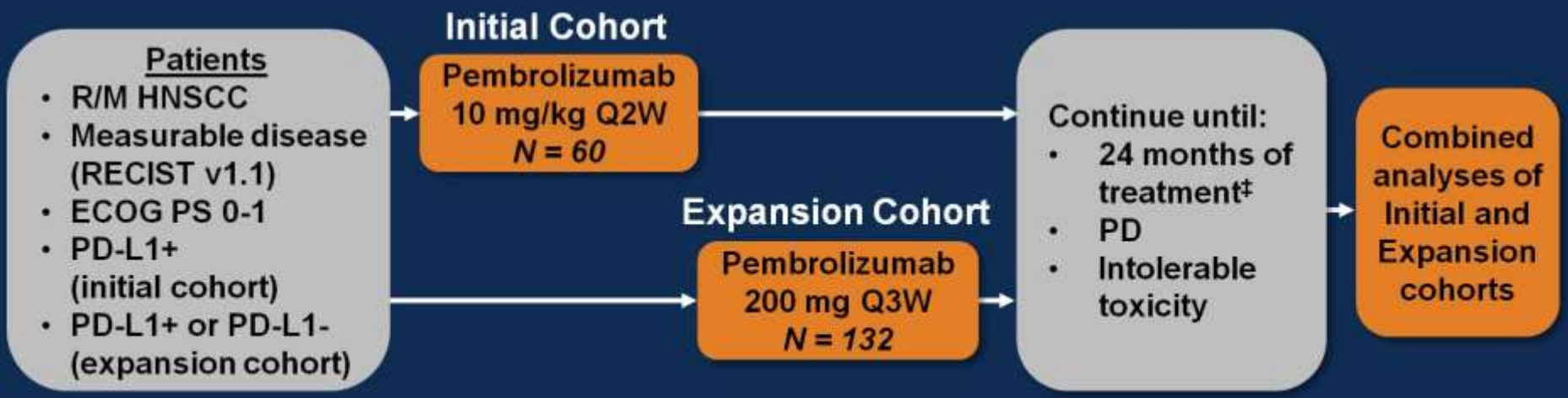
- Immunotherapy for recurrent / metastatic NPC
    - Pembrolizumab and nivolumab

Outline

- Immunotherapy for recurrent / metastatic HNSCC
  - Keynote-012 clinical data (pembrolizumab)
  - Keynote-055 (pembrolizumab)
  - Keynote-012 biomarker data (pembrolizumab)
  - Keynote-040
  - Checkmate 141 (nivolumab)

- Immunotherapy for recurrent / metastatic NPC
  - Pembrolizumab and nivolumab

HNSCC Cohorts of Nonrandomized, Phase 1b, Multi-cohort KEYNOTE-012 Trial†



Response assessment: Every 8 weeks

Primary end points: ORR (RECIST v1.1, central imaging vendor), safety

Secondary end points: ORR (investigator), PFS, OS, response duration, ORR in HPV+ patients§

†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§Initial cohort only.

Baseline Characteristics All HNSCC Patients

Characteristic	N = 192† n (%)
Median age (range), years	60 (20–84)
Male	159 (83)
ECOG performance status	
0	57 (30)
1	135 (70)
Metastatic stage M1	165 (86)
HPV status‡	
Positive	45 (23)
Negative	147 (77)

Characteristic	N = 192† n (%)
Median prior systemic therapies (range)	2 (0-7)
Prior lines of systemic therapy§	
1	47 (24)
2	56 (29)
≥3	86 (45)
Prior platinum therapy	174 (91)
Prior platinum and cetuximab therapy	110 (57)

Data cutoff date: Apr 26, 2016. †Includes patients who received ≥1 dose of pembrolizumab in the initial or expansion cohort. ‡HPV status was determined by the local institution. Cancers outside the oropharynx, identified from primary diagnosis/prior radiation/prior surgery, were considered HPV negative. §3 patients received 0 systemic therapies.

Overall Response Rate

Best Overall Response	Total N = 192†			HPV+ n = 45‡			HPV– n = 147‡		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
ORR	**34**	**18**	**13–24**	**11**	**24**	**13–40**	**23**	**16**	**10–23**
CR	8	4	–	4	9	–	4	3	–
PR	26	14	–	7	16	–	19	13	–
SD	33	17	–	7	16	–	26	18	–
PD	93	48	–	19	42	–	74	50	–
NA§	32	17	–	8	18	–	24	16	–

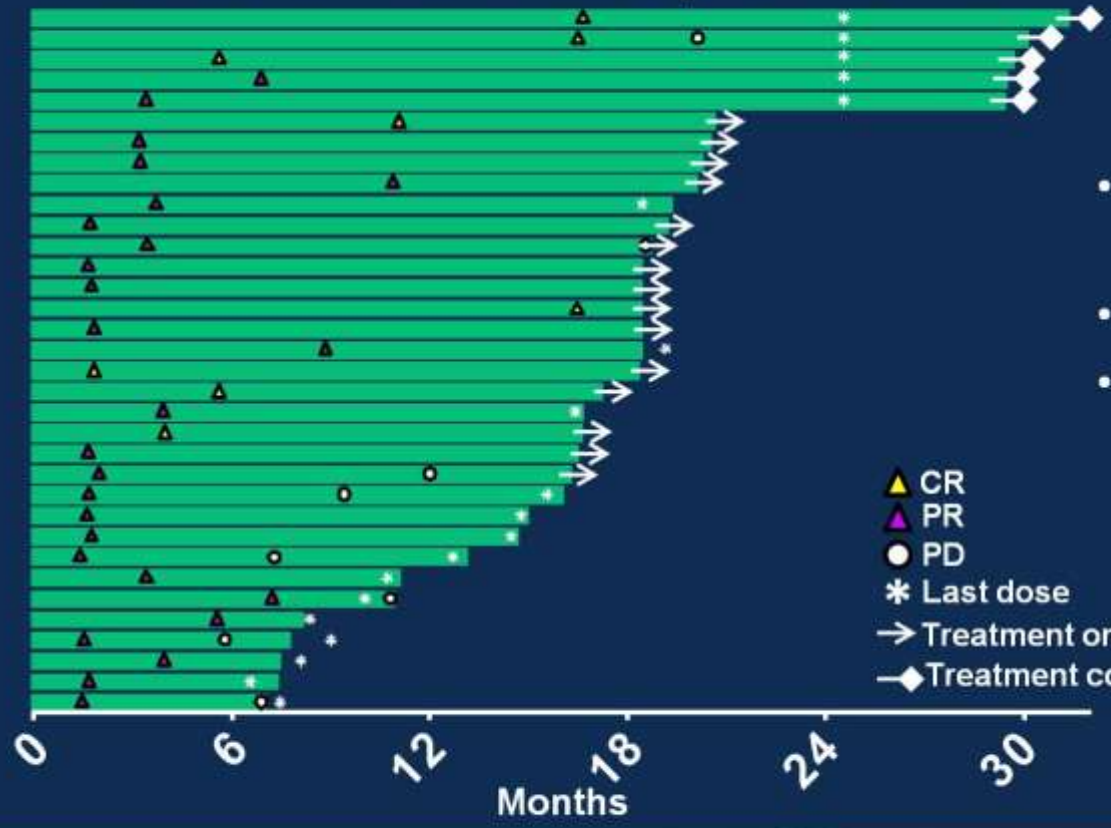
Data cutoff date: Apr 26, 2016. Response assessed per RECIST v1.1 (central imaging vendor review, all patients as treated). Only confirmed responses are included.
†Includes patients who received ≥1 dose of pembrolizumab in the initial or expansion cohort.
‡HPV status was determined by the local institution. Cancers outside the oropharynx, identified from primary diagnosis/prior radiation/prior surgery, were considered HPV negative.
§No assessment because patient did not have central imaging review data or images were not evaluable.

Overall Response Rate by Prior Treatment

Best Overall Response	Prior Platinum n = 174			Prior Platinum and Cetuximab† n = 110		
	n	%	95% CI	n	%	95% CI
ORR	29	17	12–23	16	15	9–23
CR	8	5	–	5	5	–
PR	21	12	–	11	10	–
SD	31	18	–	18	16	–
PD	86	49	–	57	52	–
NA‡	28	16	–	19	17	–

Data cutoff date: Apr 26, 2016. Response assessed per RECIST v1.1 (central imaging vendor review). Only confirmed responses are included. †Subset of "prior platinum" patients. ‡No assessment because patient did not have central imaging review data or images were not evaluable.

Duration of Response in Responders

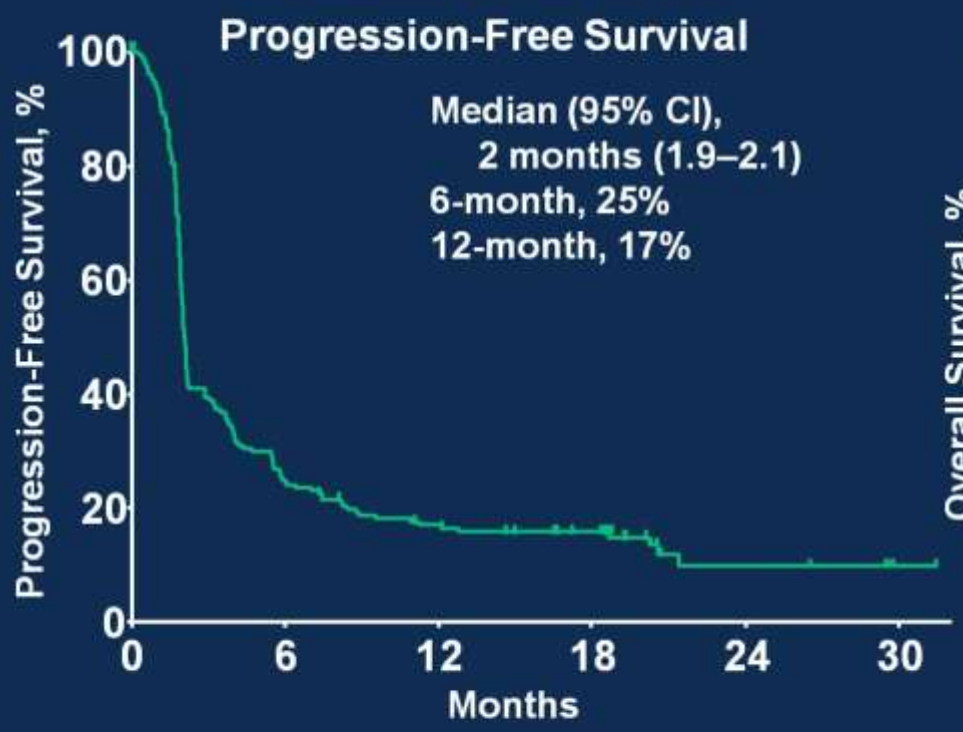


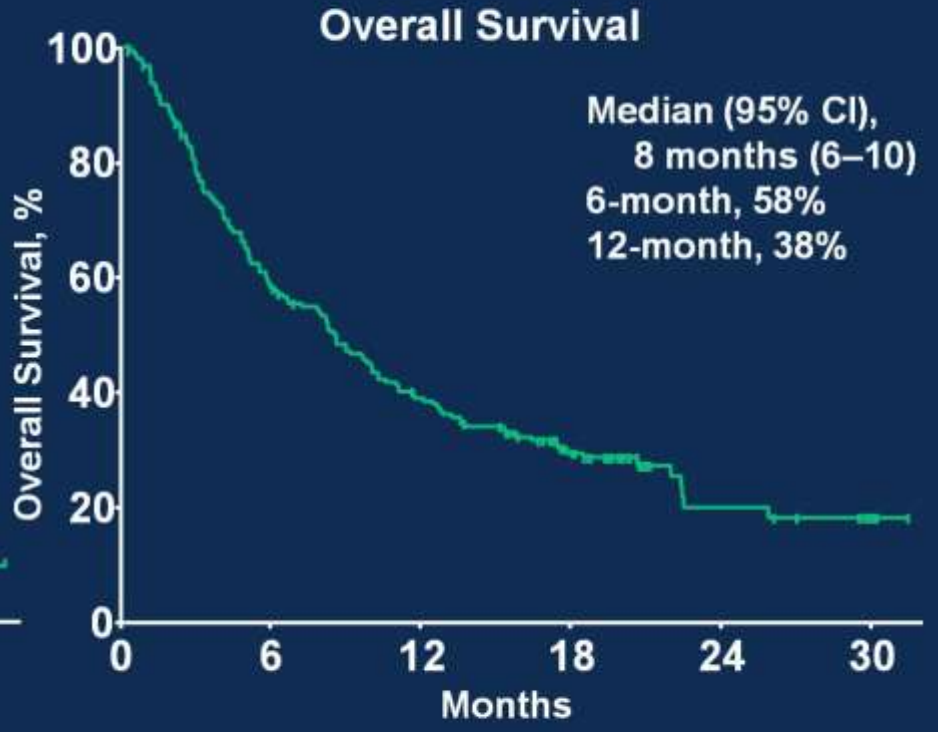
- Median time to response
  - 2 months (range, 2–17)
- 24% of responders had CR
- 65% (22/34) of responders remain in response
  - 85% responses lasted ≥6 months
  - 71% responses lasted ≥12 months

PRESENTED AT: ASCO ANNUAL MEETING '16

Data cutoff date: Apr 26, 2016.
Based on RECIST v1.1 per central imaging vendor review (swimlane plot).
Only confirmed responses shown.

Progression-Free Survival† and Overall Survival





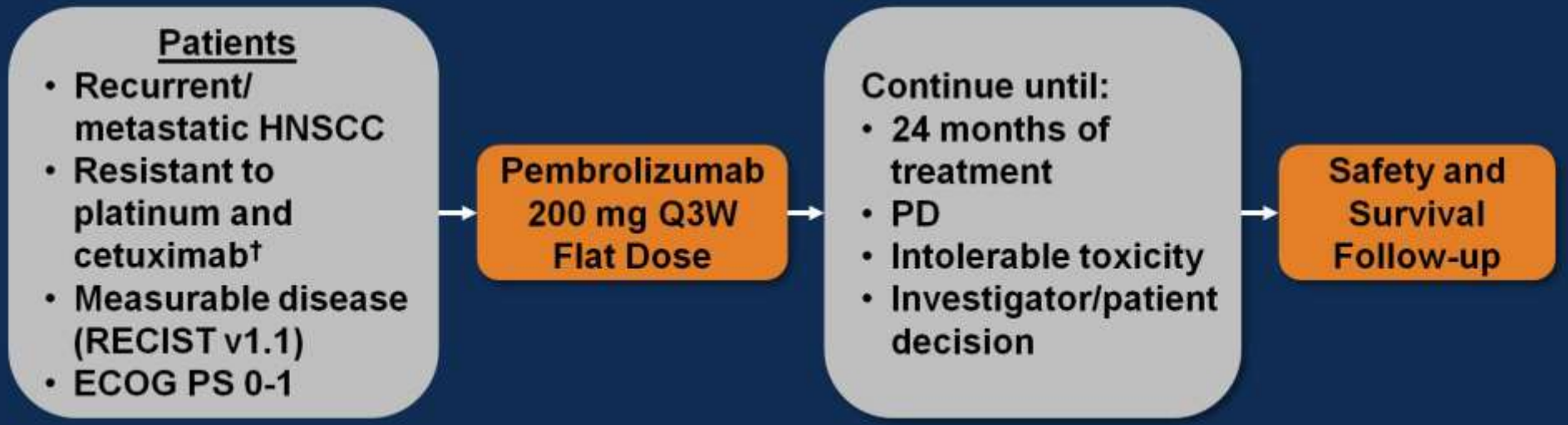
Data cutoff date: Apr 26, 2016.
†RECIST v1.1 by central imaging vendor review.

Outline

- Immunotherapy for recurrent / metastatic HNSCC
  - Keynote-012 clinical data (pembrolizumab)
  - Keynote-055 (pembrolizumab)
  - Keynote-012 biomarker data (pembrolizumab)
  - Keynote-040
  - Checkmate 141 (nivolumab)

- Immunotherapy for recurrent / metastatic NPC
  - Pembrolizumab and nivolumab

KEYNOTE-055: Single Arm, Phase 2 Trial in R/M HNSCC After Progression on Platinum/Cetuximab



Response assessment: Every 6-9 weeks

Primary end points: ORR (RECIST v1.1, central imaging vendor) in all patients and PD-L1+ patients, safety

Secondary end points: ORR in HPV+ patients, PFS, OS, duration of response

†Resistance defined as tumor progression or recurrence within 6 months of last platinum and cetuximab dose.

Baseline Characteristics

Characteristic	N = 171† n (%)
Median age (range), years	61 (33–90)
Male	138 (81)
ECOG performance status	
0	48 (28)
1	120 (70)
2	3 (2)
HPV status‡	
Positive	71 (41)
Negative	100 (59)

Characteristic	N = 171† n (%)
Median prior systemic therapies (range)	2 (1–6)
Prior lines of systemic therapy	
1	28 (16)
2	71 (42)
≥3	72 (42)

Data cutoff date: Jan 29, 2016. †Includes patients who received ≥1 dose of pembrolizumab. ‡HPV status determined by the local institution. Patients with nonoropharyngeal disease were considered HPV negative.

Keynote-055 Response Rates

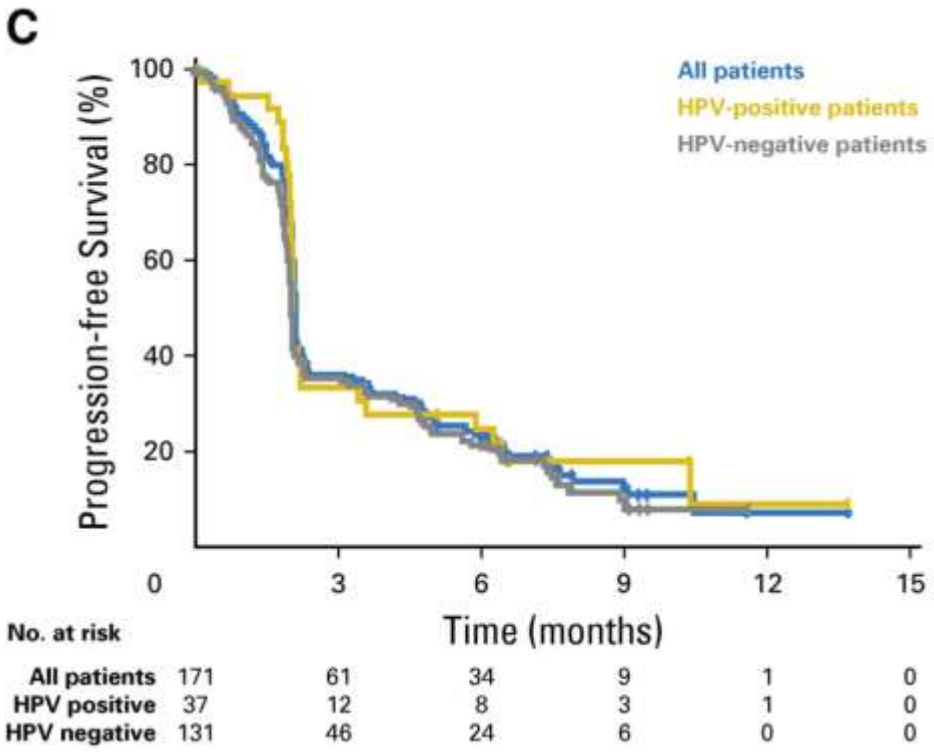
Table 3. Antitumor Activity of Pembrolizumab

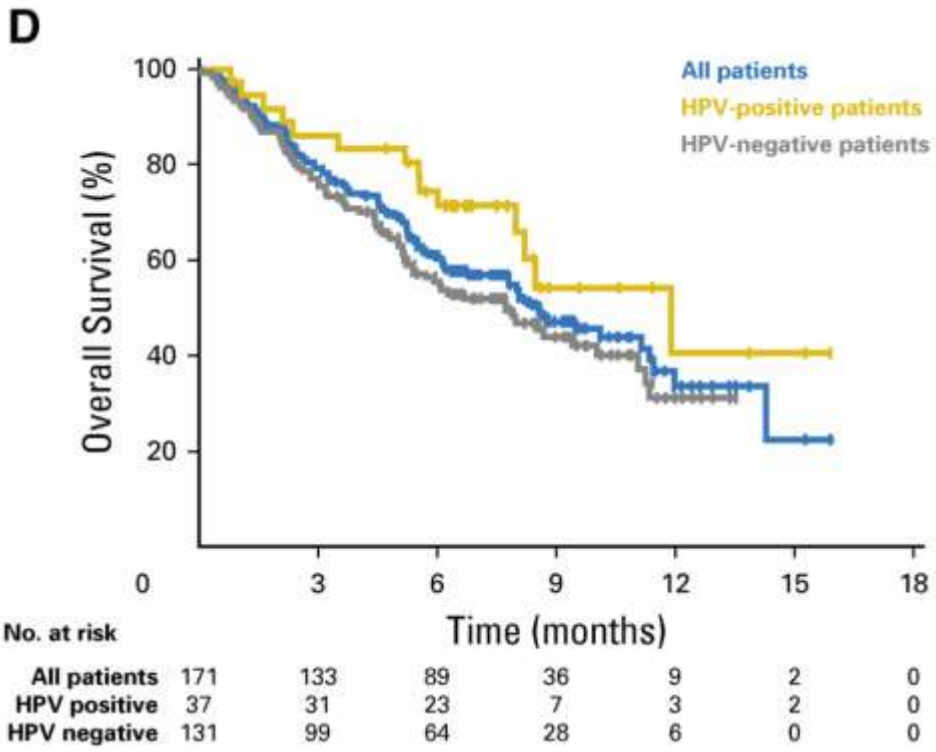
Response Evaluation	All Patients* (N = 171)		HPV Positive† (n = 37)		HPV Negative† (n = 131)	
	No.	% (95% CI)‡	No.	% (95% CI)‡	No.	% (95% CI)‡
Overall response rate	28	16 (11 to 23)	6	16 (6 to 32)	20	15 (10 to 23)
Complete response	1	1 (0 to 3)	0	0 (0 to 10)	1	1 (0 to 4)
Partial response	27	16 (11 to 22)	6	16 (6 to 32)	19	15 (9 to 22)
Stable disease	33	19 (14 to 26)	6	16 (6 to 32)	26	20 (13 to 28)
Progressive disease	87	51 (43 to 59)	21	57 (40 to 73)	66	50 (42 to 59)
Nonevaluable§	4	2 (1 to 6)	0	0 (0 to 10)	4	3 (1 to 8)
Data unavailable‖	19	11 (7 to 17)	4	11 (3 to 25)	15	12 (7 to 18)

NOTE. Confirmed responses per Response Evaluation Criteria in Solid Tumors, version 1.1, per central imaging vendor review.
Abbreviation: HPV, human papillomavirus.
*Patients who received one or more doses of pembrolizumab.
†HPV status determined using p16 immunohistochemistry for tumors of the oropharynx. Nonoropharyngeal tumors were considered HPV negative.
‡On the basis of binomial exact confidence interval method.
§Images were not evaluable.
‖Data were unavailable because of death or withdrawal from the study before the first scheduled scan.

Bauml et al., ASCO 2016; JCO 2017

Keynote-055 PFS and OS





Median PFS: 2.1 months

Median OS: 8 months

Bauml et al., ASCO 2016; JCO 2017

Keynote-055 Efficacy According to PD-L1

Table 4. Antitumor Activity on the Basis of PD-L1 Expression Status

	CPS ≥ 1% (n = 140)		CPS < 1% (n = 26)		CPS ≥ 50% (n = 48)		CPS < 50% (n = 118)	
Response Evaluation	No.	% (95% CI)*	No.	% (95% CI)*	No.	% (95% CI)*	No.	% (95% CI)*
Overall response rate	25	18 (12 to 25)	3	12 (2 to 30)	13	27 (15 to 42)	15	13 (7 to 20)
Complete response	1	1 (0 to 4)	0	0 (0 to 13)	1	2 (0 to 11)	0	0 (0 to 3)
Partial response	24	17 (11 to 24)	3	12 (2 to 30)	12	25 (14 to 40)	15	13 (7 to 20)
Stable disease	23	16 (11 to 24)	7	27 (12 to 48)	7	15 (6 to 28)	23	20 (13 to 28)
Progressive disease	73	52 (44 to 61)	13	50 (30 to 70)	18	38 (24 to 53)	68	58 (48 to 67)
Nonevaluable	2	1 (0 to 5)	2	8 (1 to 25)	0	0 (0 to 7)	4	3 (1 to 9)
Data unavailable	17	12 (7 to 19)	1	4 (0 to 20)	10	21 (11 to 35)	8	7 (3 to 13)

NOTE. Confirmed responses per Response Evaluation Criteria in Solid Tumors, version 1.1, per central imaging vendor review.
Abbreviations: CPS, combined positive score; PD-L1, programmed death ligand 1.
*On the basis of binomial exact confidence interval method.

Bauml et al., ASCO 2016; JCO 2017

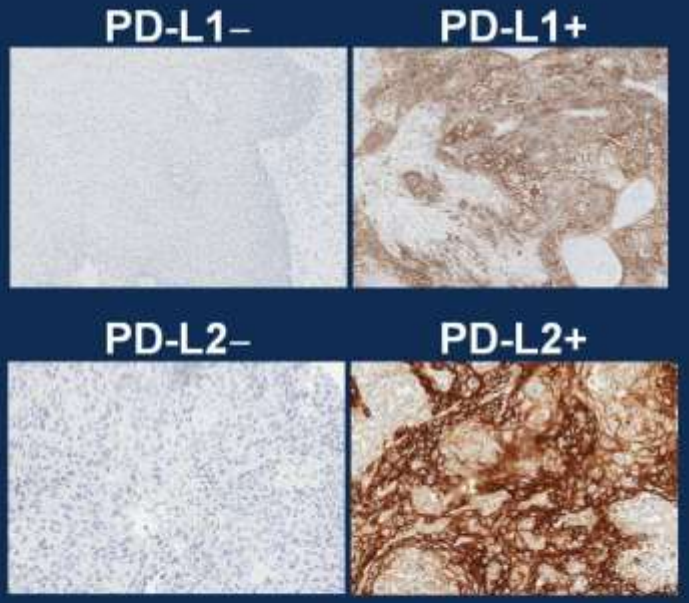
Outline

- Immunotherapy for recurrent / metastatic HNSCC
  - Keynote-012 clinical data (pembrolizumab)
  - Keynote-055 (pembrolizumab)
  - Keynote-012 biomarker data (pembrolizumab)
  - Keynote-040
  - Checkmate 141 (nivolumab)

- Immunotherapy for recurrent / metastatic NPC
  - Pembrolizumab and nivolumab

PD-L1 and PD-L2 Analyses in Pre-treatment Samples

- Determine the correlation of PD-L1 and PD-L2 expression in FFPE pre-treatment samples† with clinical outcomes in HNSCC patients who received ≥1 dose of pembrolizumab
  - **PD-L1** (n = 188)
    - IHC‡ using 22C3 (Merck) anti-PD-L1 antibody
    - Tumor proportion score (TPS) = tumor cells only
    - Combined positive score (CPS) = tumor and inflammatory cells
  - **PD-L2** (n = 172)
    - IHC using 3G2 (Merck) anti-PD-L2 antibody
    - CPS = tumor and inflammatory cells
  - **Scored 0%-100%**
    - Positive, ≥1%
    - Negative, <1%



FFPE, formalin fixed paraffin embedded.
†Newly obtained or archival tissue. ‡Investigational version of PD-L1 IHC 22C3 pharmDx assay (Dako North America, Carpinteria, CA, USA).

Overall Response by PD-L1 Status

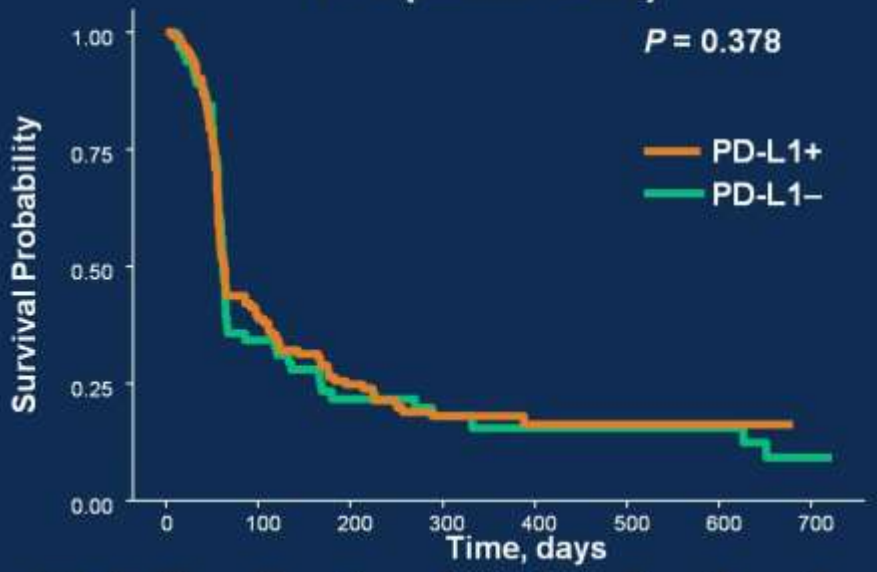
	PD-L1 Status	Non-responders n	Responders n	ORR % (95% CI)	P-value
TPS (tumor cells)	PD-L1+	101	22	18 (12–26)	0.461
	PD-L1–	53	12	19 (10–30)	
CPS (tumor and inflammatory cells)	PD-L1+	120	32	21 (15–28)	0.023
	PD-L1–	34	2	6 (1–19)	

Incorporation of inflammatory cells improves ability to detect responders

P-values based on logistic regression one-sided testing.

Progression-Free Survival by PD-L1 Status

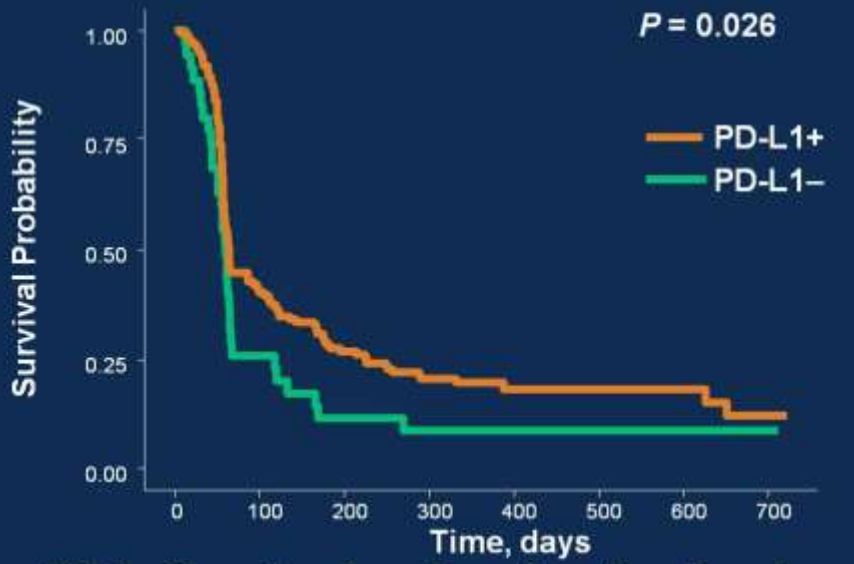
TPS (tumor cells)



TPS <1	65	22	14	8	5	5	5	2
TPS ≥1	123	48	30	21	3	3	3	0

Median (95% CI)
- PD-L1+, 63 days (58-98)
- PD-L1–, 62 days (59-67)

CPS (tumor and inflammatory cells)



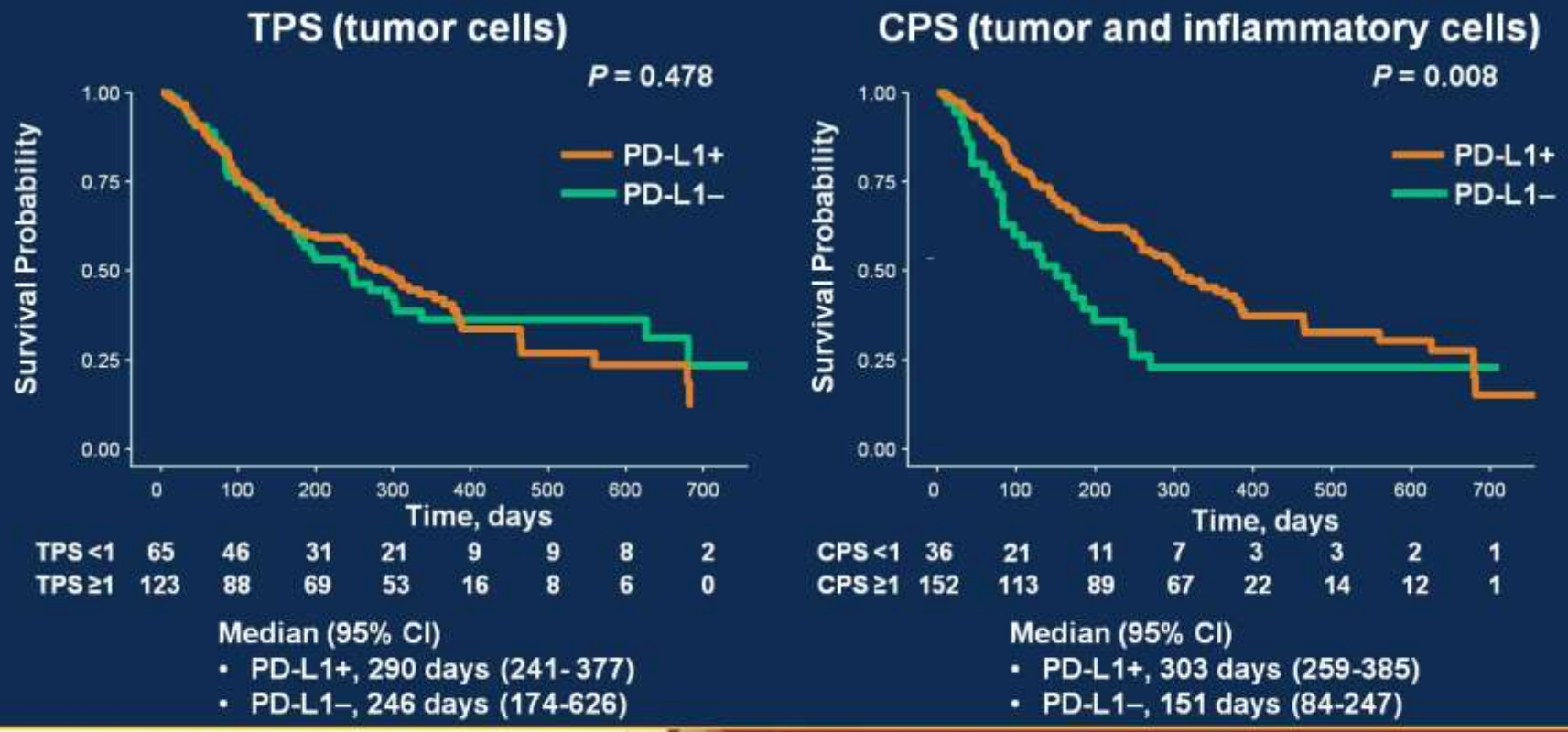
CPS <1	36	9	4	3	2	2	2	1
CPS ≥1	152	61	40	26	6	6	6	1

Median (95% CI)
- PD-L1+, 64 days (59-98)
- PD-L1–, 60 days (51-66)

P-values based on Cox regression one-sided testing.

Presented By Laura Chow at 2016 ASCO Annual Meeting

Overall Survival by PD-L1 Status



PRESENTED AT: ASCO ANNUAL MEETING '16

P-values based on Cox regression one-sided testing.

Presented By Laura Chow at 2016 ASCO Annual Meeting

Overall Response Rate by PD-L2 Status

		Non-responders n	Responders n	ORR % (95% CI)	P-value
CPS (tumor and inflammatory cells)	PD-L2+	86	25	**23 (15–31)**	0.022
	PD-L2–	55	6	**10 (4–20)**	

PD-L2 expression on tumor and inflammatory cells is predictive of response to pembrolizumab

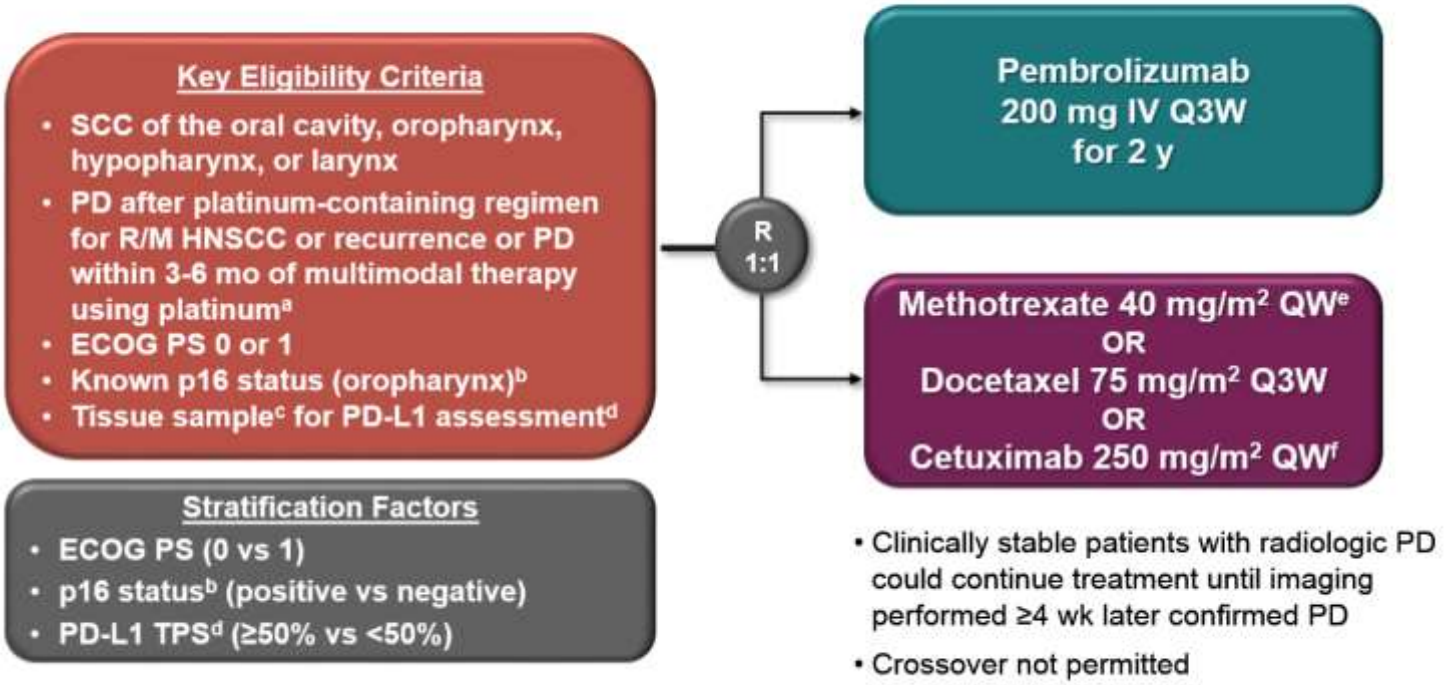
P-values based on logistic regression one-sided testing.

Outline

- Immunotherapy for recurrent / metastatic HNSCC
  - Keynote-012 clinical data (pembrolizumab)
  - Keynote-055 (pembrolizumab)
  - Keynote-012 biomarker data (pembrolizumab)
  - Keynote-040
  - Checkmate 141 (nivolumab)

- Immunotherapy for recurrent / metastatic NPC
  - Pembrolizumab and nivolumab

Phase 3 KEYNOTE-040 Study (NCT02252042)



[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/m^2 QW in the absence of toxicity. [f]Following a loading dose of 400 mg/m^2.

Analysis Populations and End Points

Analysis Populations

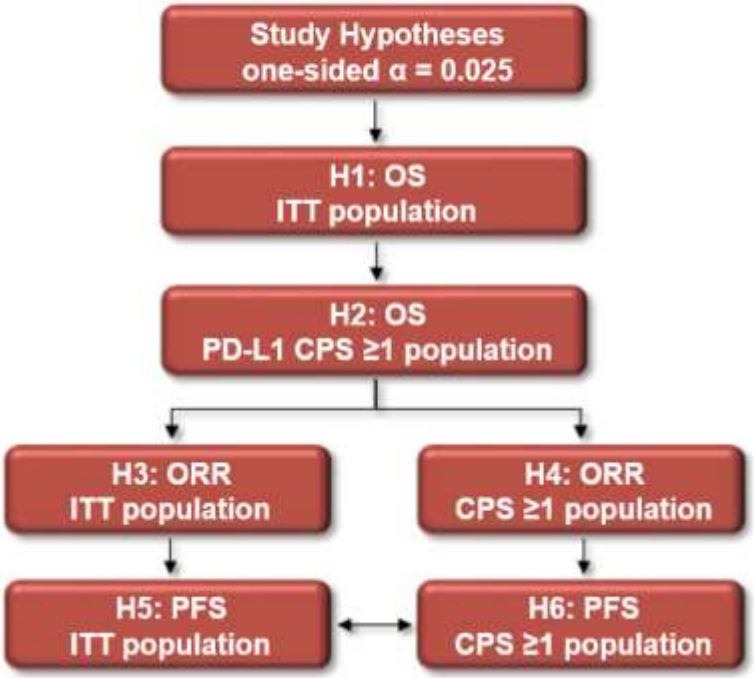
- Intention-to-treat (ITT)
- PD-L1 combined positive score (CPS) ≥1[a]
  - Previously reported as and equivalent to CPS ≥1%
  - CPS = number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells 100
- PD-L1 tumor proportion score (TPS) ≥50%[a]
  - TPS = percentage of tumor cells with membranous PD-L1 expression

Key End Points

- Primary: OS in the ITT population
- Secondary
  - OS in the CPS ≥1 population
  - PFS[b] in the ITT and CPS ≥1 populations
  - ORR[b] in the ITT and CPS ≥1 populations
  - DOR[b] in the ITT and CPS ≥1 populations
  - Safety and tolerability
- Predefined exploratory
  - OS, PFS,[b] ORR,[b] and DOR[b] in the TPS ≥50% population

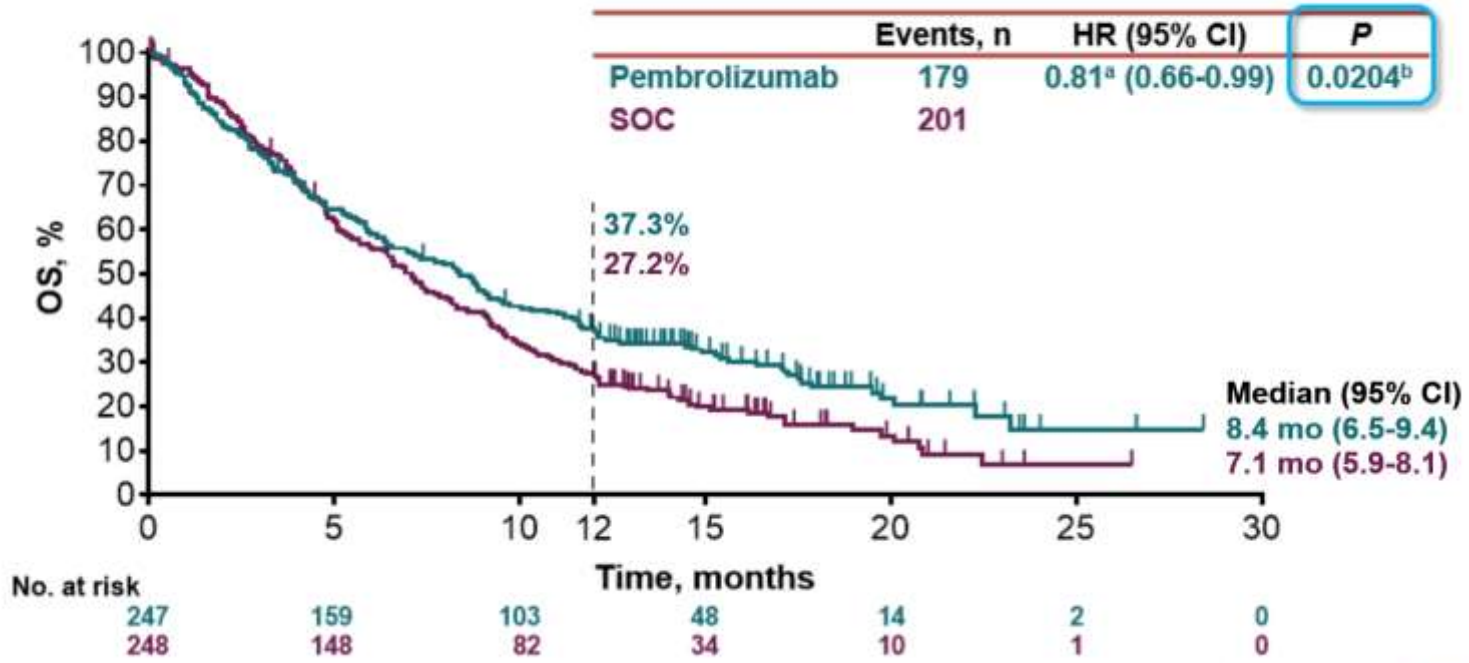
[a]PD-L1 assessed at a central laboratory in newly collected (preferred) or archival tumor samples using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies).
[b]Assessed per RECIST v1.1 by blinded, independent radiology review.

Statistical Considerations



- Multiplicity strategy
  - Family-wise alpha strictly controlled at **0.025 (one sided)**
  - Alpha allocated in stepwise fashion
- Final analysis
  - Performed after **380 OS** events in 495 patients
  - Data cutoff date: May 15, 2017
  - **Efficacy boundary**
    - OS, ITT: one-sided **α = 0.0175**, HR ~0.80
    - OS, CPS ≥1: one-sided α = 0.0178, HR ~0.78
      - Tested only if efficacy boundary in ITT population reached

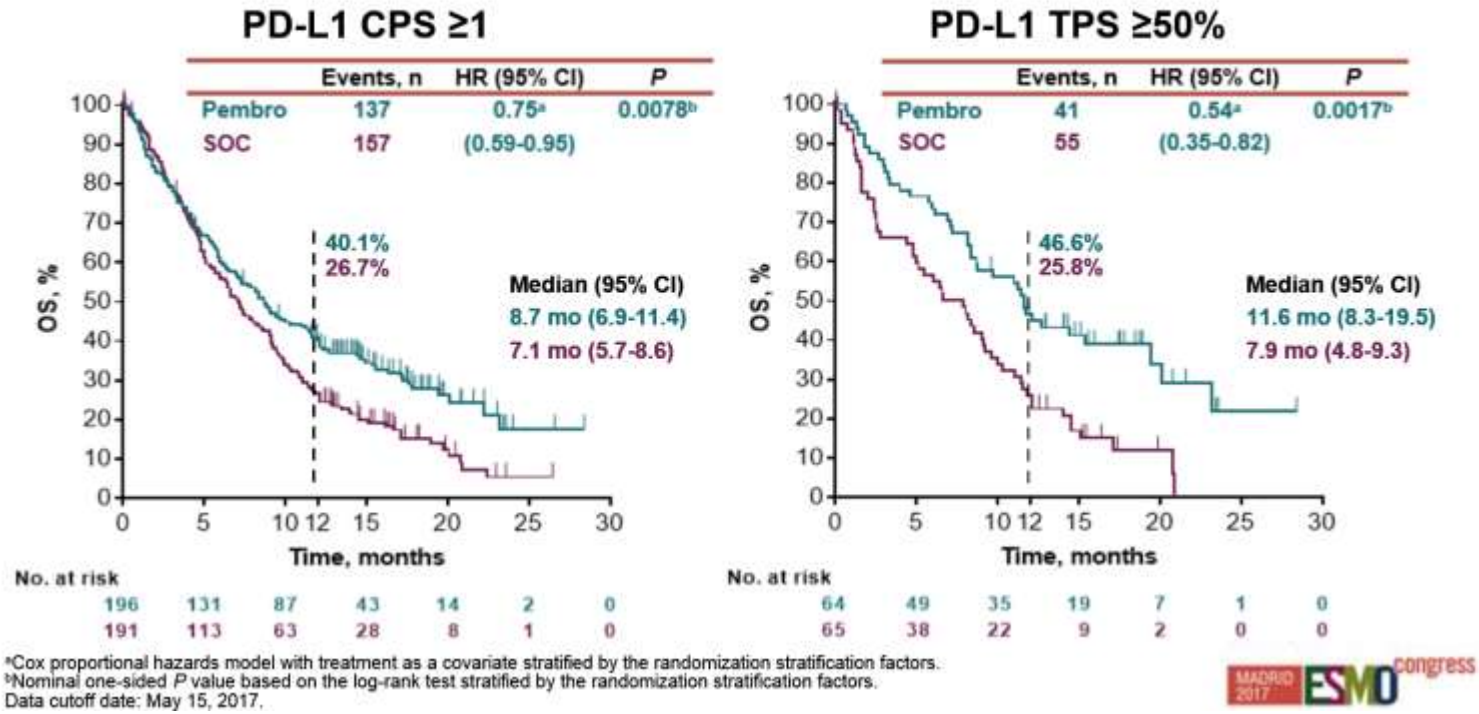
Overall Survival in ITT Population



[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. Initially reported data: HR 0.82 (95% CI, 0.67-1.01), $P = 0.0316$. After the initial report, updated survival data were obtained for 4 patients. [b]One-sided P value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

ESMO congress

Overall Survival by PD-L1 Expression



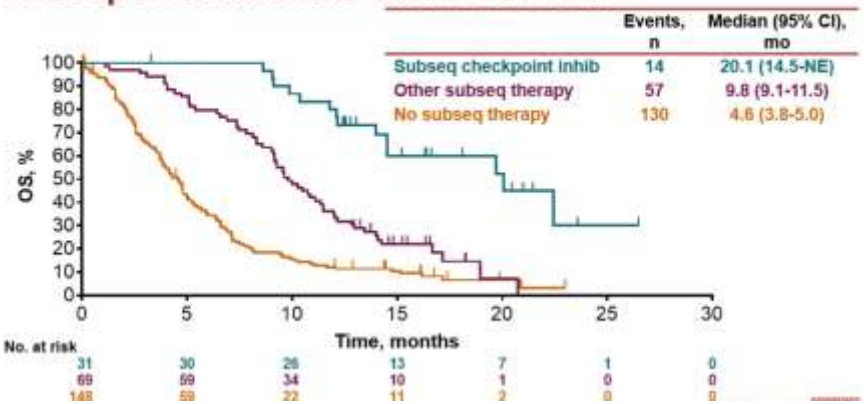
[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors.
[b]Nominal one-sided *P* value based on the log-rank test stratified by the randomization stratification factors.
Data cutoff date: May 15, 2017.

MADRID 2017 ESMO congress

Subsequent Therapy

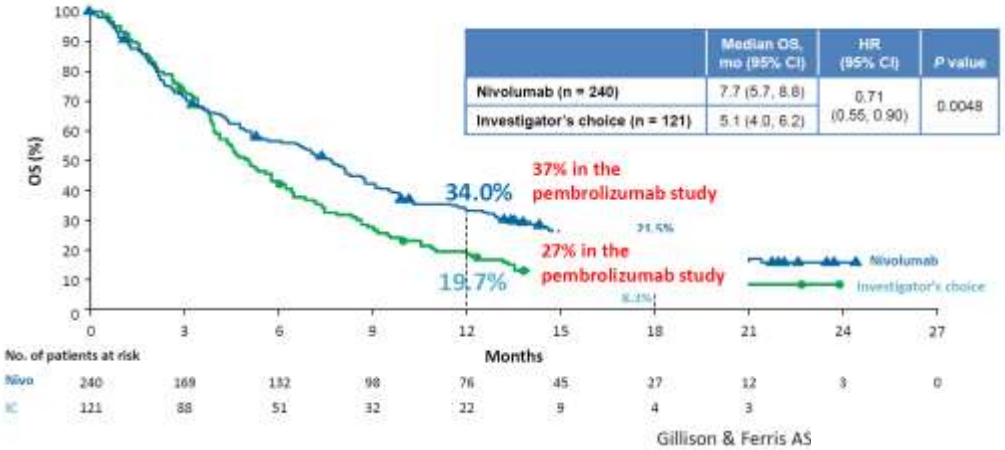
Type, n (%)	Pembrolizumab N = 247	SOC N = 248
Any[a]	84 (34.0)	100 (40.3)
Chemotherapy	70 (28.3)	76 (30.6)
EGFR inhibitor	20 (8.1)	19 (7.7)
Kinase inhibitor	4 (1.6)	8 (3.2)
Immune checkpoint inhibitor	11 (4.5)	31 (12.5)
Other immunotherapy	5 (2.0)	1 (0.4)
Other	2 (0.8)	2 (0.8)

Overall Survival: Effect of Subsequent Immune Checkpoint Inhibitors in the SOC Arm



Educação e Pesquisa

Overall survival



	Median OS, mo (95% CI)	HR (95% CI)	*P* value
Nivolumab (n = 240)	7.7 (5.7, 8.8)	0.71 (0.55, 0.90)	0.0048
Investigator's choice (n = 121)	5.1 (4.0, 6.2)		

Gillison & Ferris AS

Standard arm

	Pembrolizumab	Nivolumab
Cetuximab	30%	10%
Docetaxel	42%	43%
Methotrexate	27%	38%

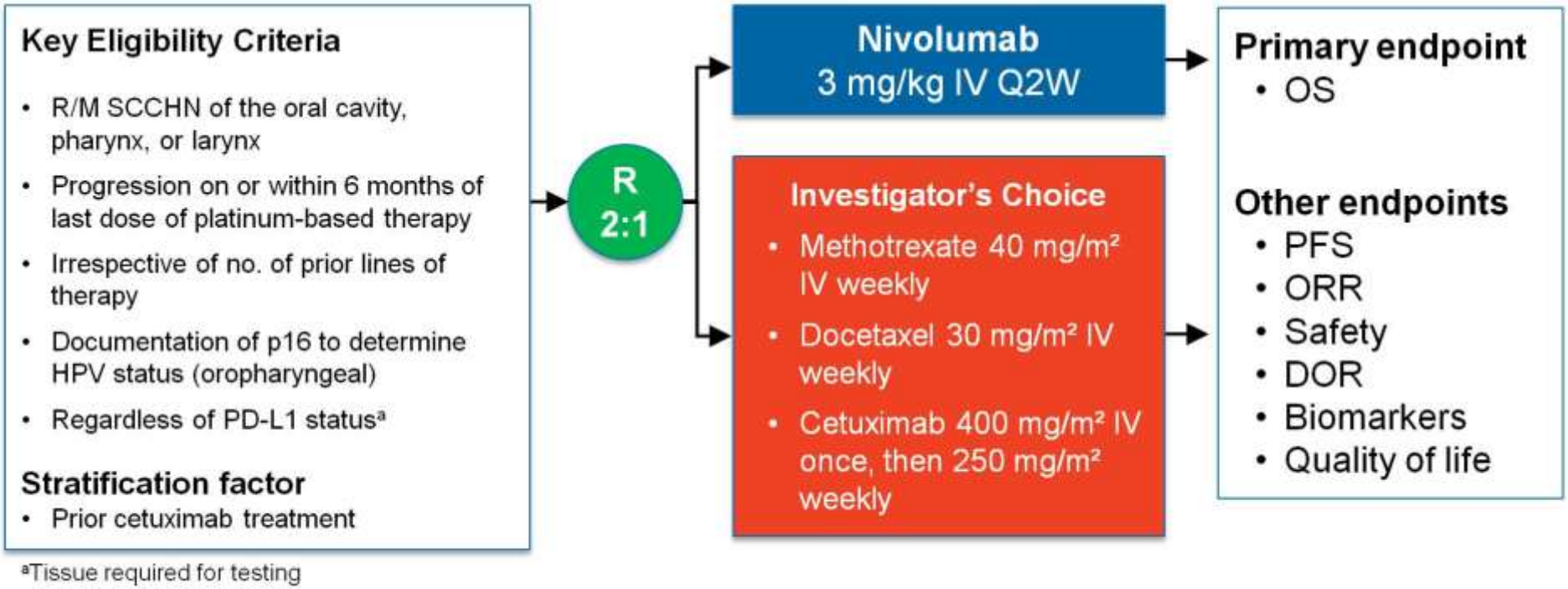
Outline

- Immunotherapy for recurrent / metastatic HNSCC
  - Keynote-012 clinical data (pembrolizumab)
  - Keynote-055 (pembrolizumab)
  - Keynote-012 biomarker data (pembrolizumab)
  - Keynote-040
  - Checkmate 141 (nivolumab)

- Immunotherapy for recurrent / metastatic NPC
  - Pembrolizumab and nivolumab

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.

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)

ECOG = Eastern Cooperative Oncology Group.

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

Treatment Administration and Patient Disposition

Nivolumab in R/M SCCHN After Platinum Therapy

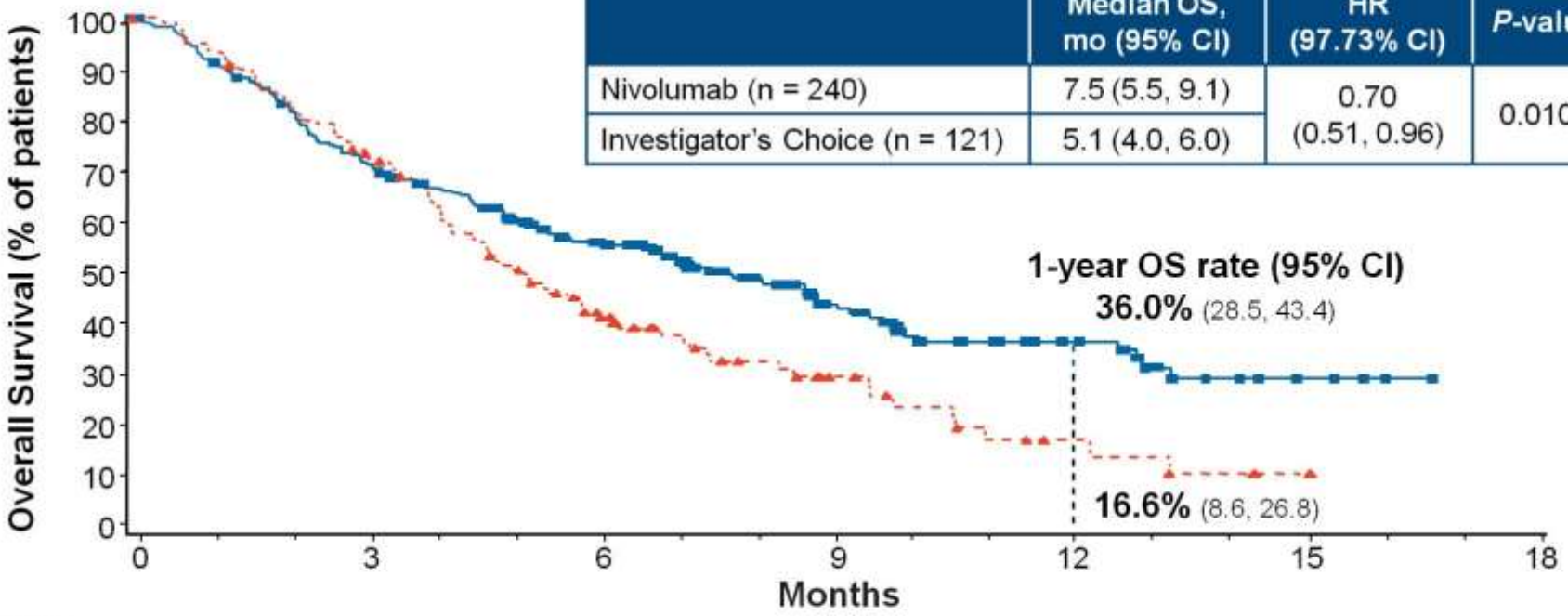
	Nivolumab (n = 240)	Investigator's Choice (n = 121)	Total (N = 361)
Investigator's choice therapy, n (%)			
Methotrexate	–	52 (43.0)	–
Docetaxel	–	54 (44.6)	–
Cetuximab	–	15 (12.4)	–
Ongoing treatment, n (%)	41 (17.4)	3 (2.7)	44 (12.7)
Not continuing treatment, n (%)	195 (82.6)	108 (97.3)	303 (87.3)
Disease progression	162 (68.6)	83 (74.8)	245 (70.6)
Study drug toxicity	9 (3.8)	11 (9.9)	20 (5.8)
Adverse event not related to study drug	12 (5.1)	3 (2.7)	15 (4.3)
Other[a]	9 (3.8)	11(9.9)	20 (5.8)
Not reported	3 (1.3)	0	3 (0.9)

[a]Other includes patient request to discontinue, withdrawal of consent, non-compliance and maximum clinical benefit.

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)		

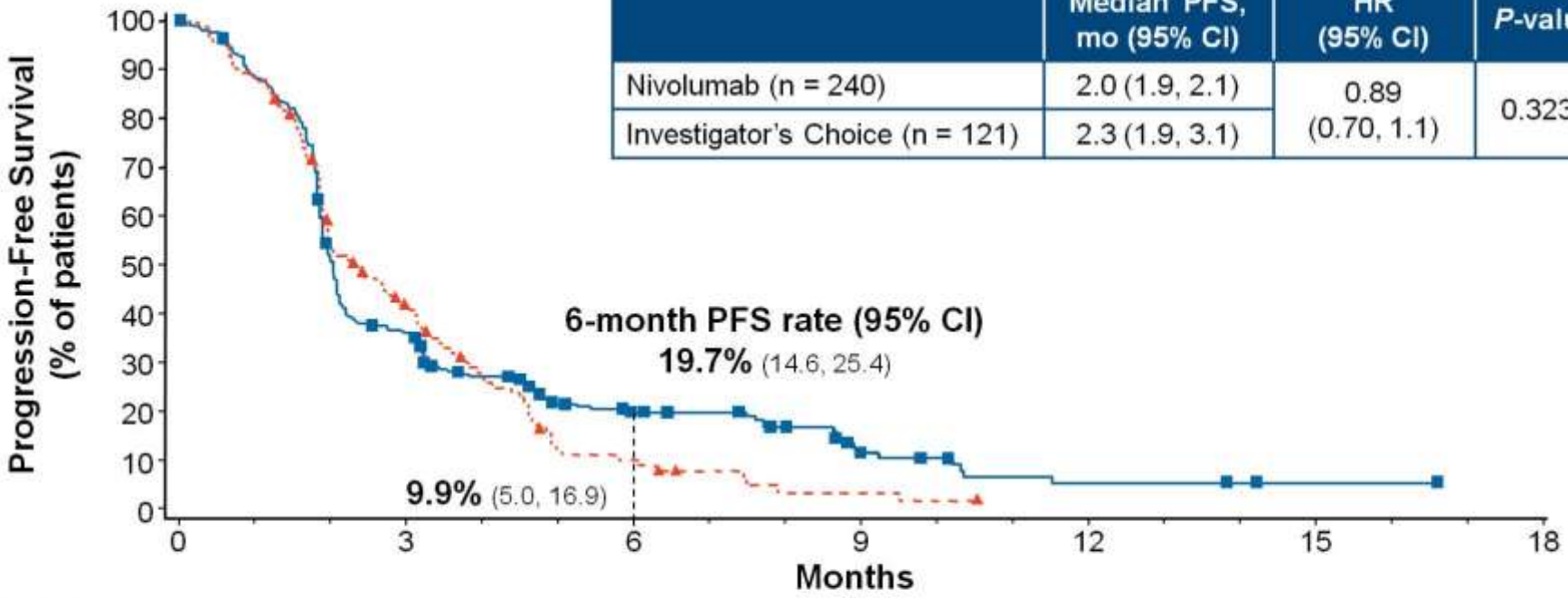


No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Investigator's Choice	121	87	42	17	5	1	0

Progression-Free Survival

Nivolumab in R/M SCCHN After Platinum Therapy

	Median PFS, mo (95% CI)	HR (95% 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

Presented By Robert Ferris at 2016 ASCO Annual Meeting

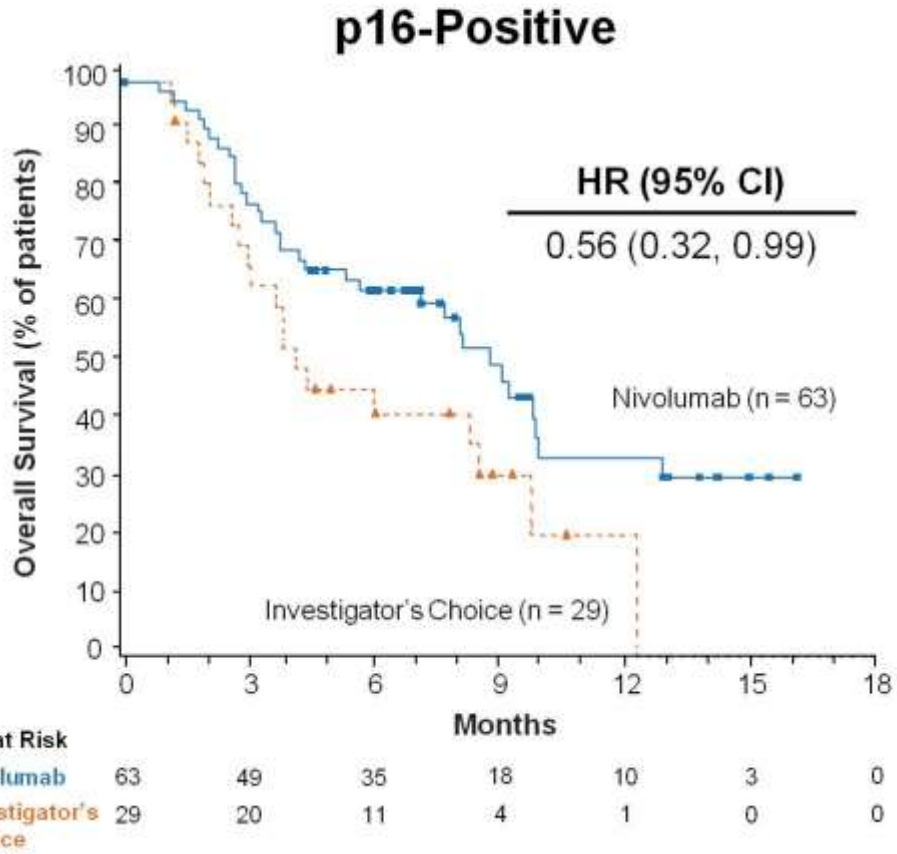
Objective Response Rate

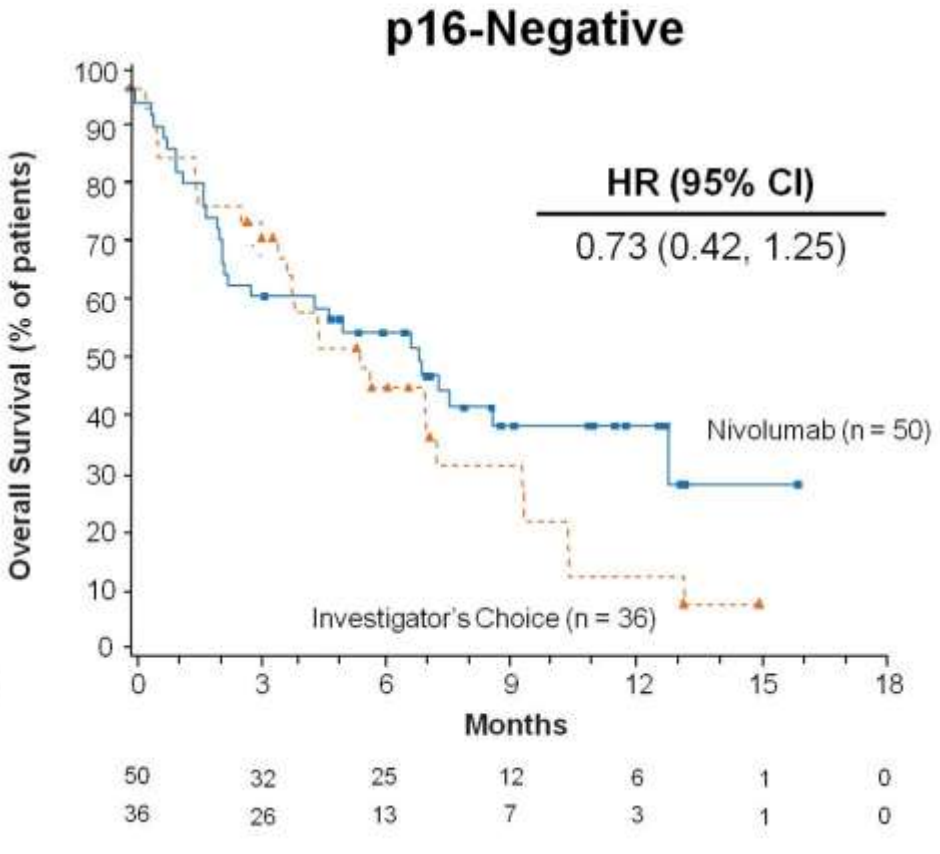
Nivolumab in R/M SCCHN After Platinum Therapy

	Nivolumab (n = 240)	Investigator's Choice (n = 121)
Objective response rate, n (%)	32 (13.3)	7 (5.8)
95% CI	9.3, 18.3	2.4, 11.6
Best overall response, n (%)		
Complete response	6 (2.5)	1 (0.8)
Partial response	26 (10.8)	6 (5.0)
Stable disease	55 (22.9)	43 (35.5)
Progressive disease	100 (41.7)	42 (34.7)
Not determined	53 (22.1)	29 (24.0)
Time to response, mo		
Median (range)	2.1 (1.8–7.4)	2.0 (1.9–4.6)

Overall Survival by p16 Status

Nivolumab in R/M SCCHN After Platinum Therapy

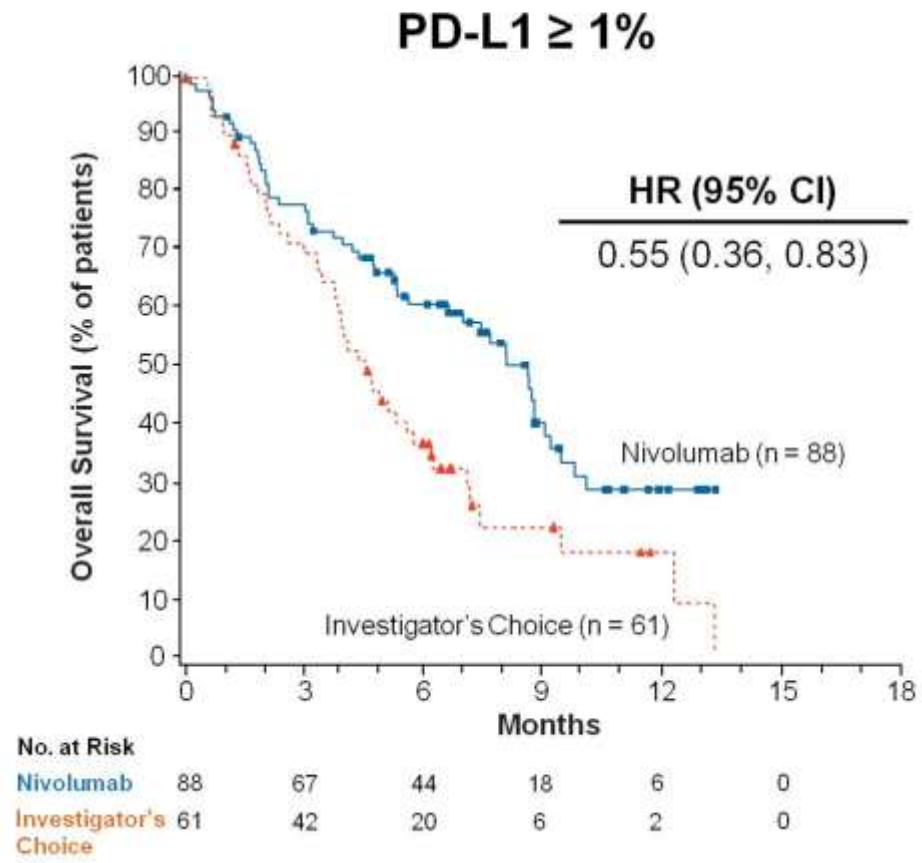


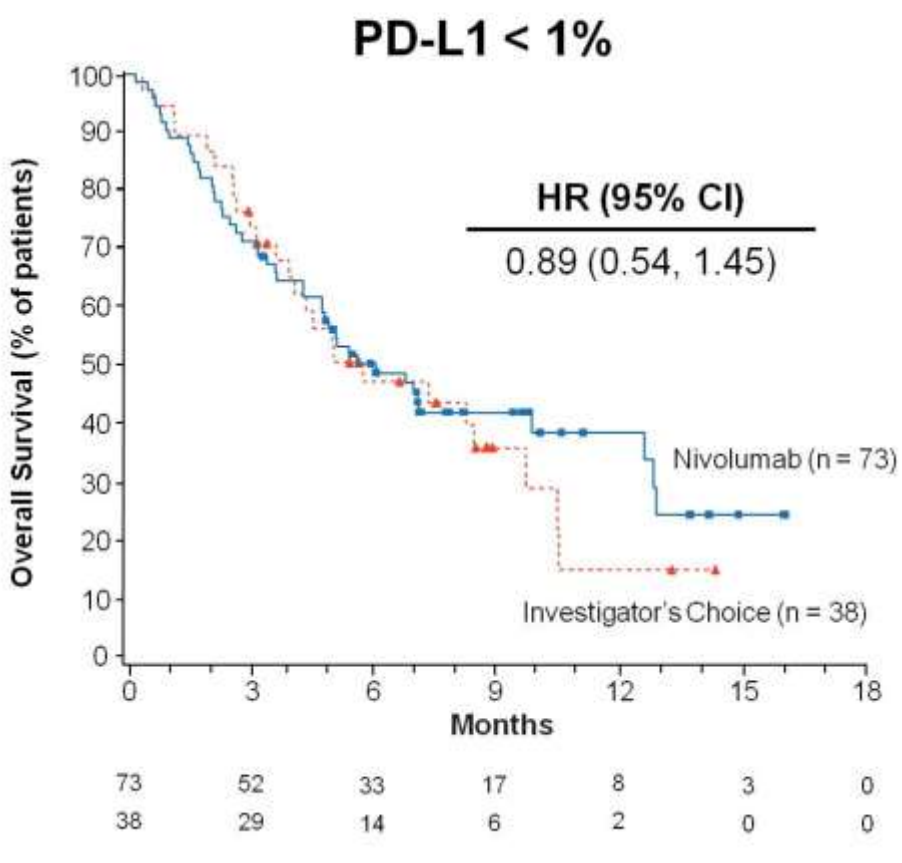


Presented By Robert Ferris at 2016 ASCO Annual Meeting

Overall Survival by Tumor PD-L1 Expression at 1%

Nivolumab in R/M SCCHN After Platinum Therapy



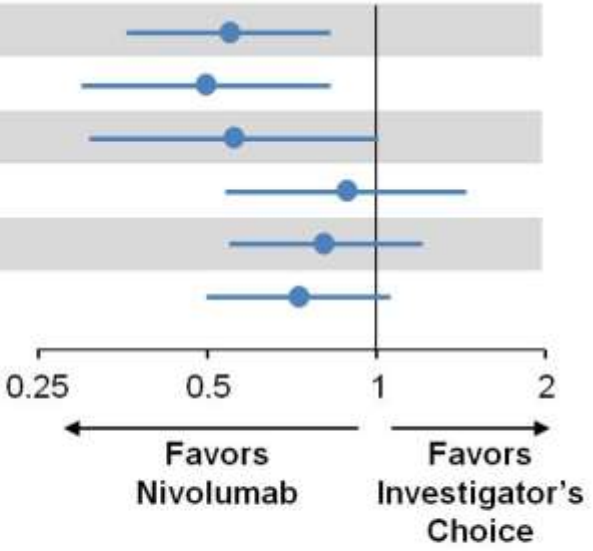


Presented By Robert Ferris at 2016 ASCO Annual Meeting

Overall Survival by Tumor PD-L1 Expression Level

Nivolumab in R/M SCCHN After Platinum Therapy

	Nivolumab n = 240		Investigator's Choice n = 121		
PD-L1 Expression	n	Median OS, mo	n	Median OS, mo	Unstratified Hazard Ratio (95% CI)
≥ 1%	88	8.7	61	4.6	0.55 (0.36, 0.83)
≥ 5%	54	8.8	43	4.6	0.50 (0.30, 0.83)
≥ 10%	43	8.7	34	5.2	0.56 (0.31, 1.01)
< 1%	73	5.7	38	5.8	0.89 (0.54, 1.45)
< 5%	107	7.0	56	5.1	0.81 (0.55, 1.21)
< 10%	118	7.2	65	4.6	0.73 (0.50, 1.06)



- The magnitude of OS benefit of nivolumab vs investigator's choice was greater in patients with tumor PD-L1 expression
- Increasing PD-L1 expression did not result in further OS benefit

Objective Response Rate by PD-L1 Expression

Nivolumab in R/M SCCHN After Platinum Therapy

PD-L1 Expression Level	Objective Response Rate			
	Nivolumab		Investigator's Choice	
	n/N	%	n/N	%
≥ 1%	15/88	17.0	1/61	1.6
≥ 5%	12/54	22.2	1/43	2.3
≥ 10%	12/43	27.9	1/34	2.9
< 1%	9/73	12.3	4/38	10.5
< 5%	12/107	11.2	4/56	7.1
< 10%	12/118	10.2	4/65	6.2

Treatment-Related Adverse Events

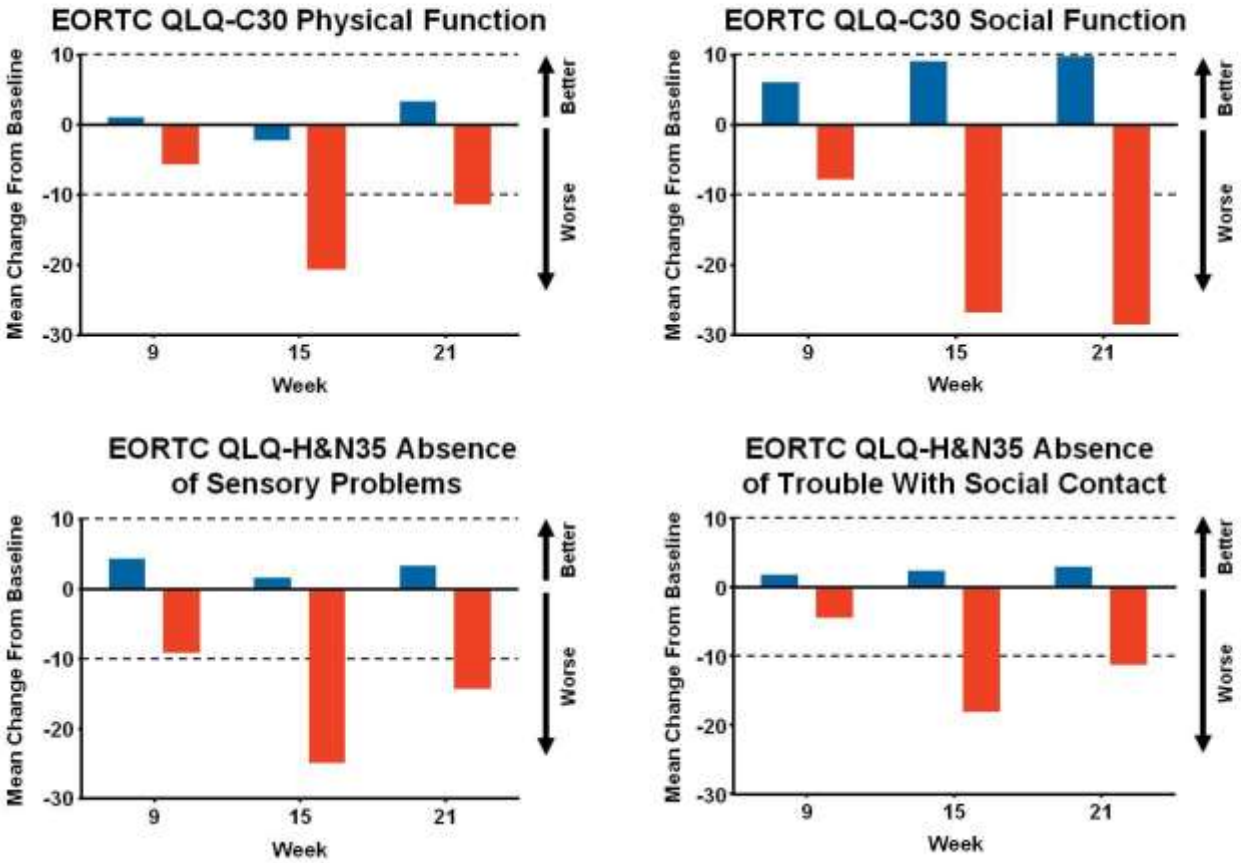
Nivolumab in R/M SCCHN After Platinum Therapy

Event	Nivolumab (n = 236)		Investigator's Choice (n = 111)	
	Any grade n (%)	Grade 3–4 n (%)	Any grade n (%)	Grade 3–4 n (%)
Any treatment-related AE in ≥ 10% of patients[a]	139 (58.9)	31 (13.1)	86 (77.5)	39 (35.1)
Fatigue	33 (14.0)	5 (2.1)	19 (17.1)	3 (2.7)
Nausea	20 (8.5)	0	23 (20.7)	1 (0.9)
Diarrhea	16 (6.8)	0	15 (13.5)	2 (1.8)
Anemia	12 (5.1)	3 (1.3)	18 (16.2)	5 (4.5)
Asthenia	10 (4.2)	1 (0.4)	16 (14.4)	2 (1.8)
Mucosal inflammation	3 (1.3)	0	14 (12.6)	2 (1.8)
Alopecia	0	0	14 (12.6)	3 (2.7)
Treatment-related select AEs				
Skin	37 (15.7)	0	14 (12.6)	2 (1.8)
Endocrine	18 (7.6)	1 (0.4)	1 (0.9)	0
Gastrointestinal	16 (6.8)	0	16 (14.4)	2 (1.8)
Hepatic	5 (2.1)	2 (0.8)	4 (3.6)	1 (0.9)
Pulmonary	5 (2.1)	2 (0.8)	1 (0.9)	0
Hypersensitivity/infusion reaction	3 (1.3)	0	2 (1.8)	1 (0.9)
Renal	1 (0.4)	0	2 (1.8)	1 (0.9)

[a]One Grade 5 event (hypercalcemia) in the nivolumab arm and one Grade 5 event (lung infection) in the investigator's choice arm were reported. A second death occurred in the nivolumab arm subsequent to pneumonitis.

Quality of Life and Symptom Burden

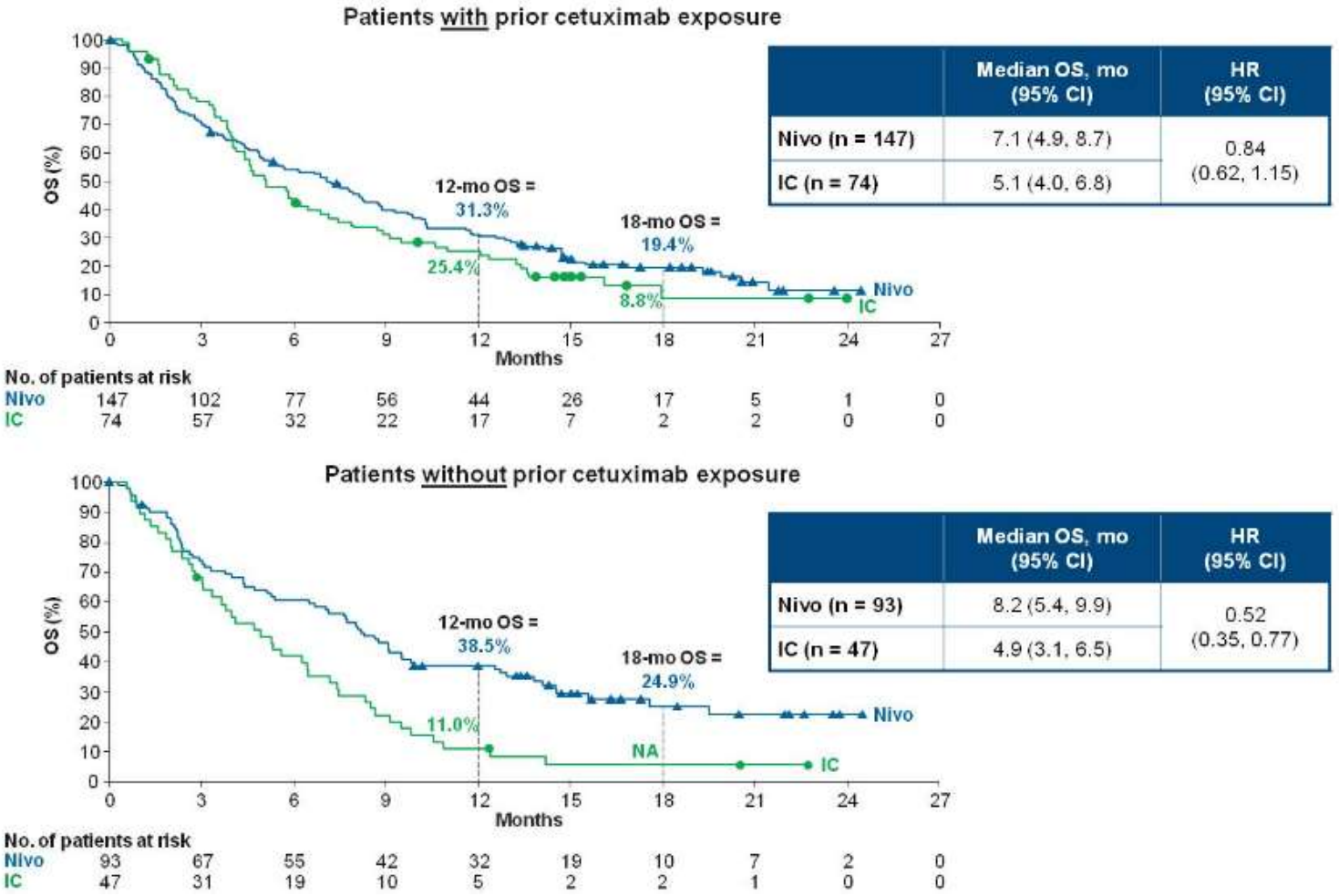
Nivolumab in R/M SCCHN After Platinum Therapy



- Nivolumab stabilized PROs while investigator's choice led to meaningful declines in function and worsening of symptoms

Presented By Robert Ferris at 2016 ASCO Annual Meeting

Figure 2. OS by prior cetuximab exposure



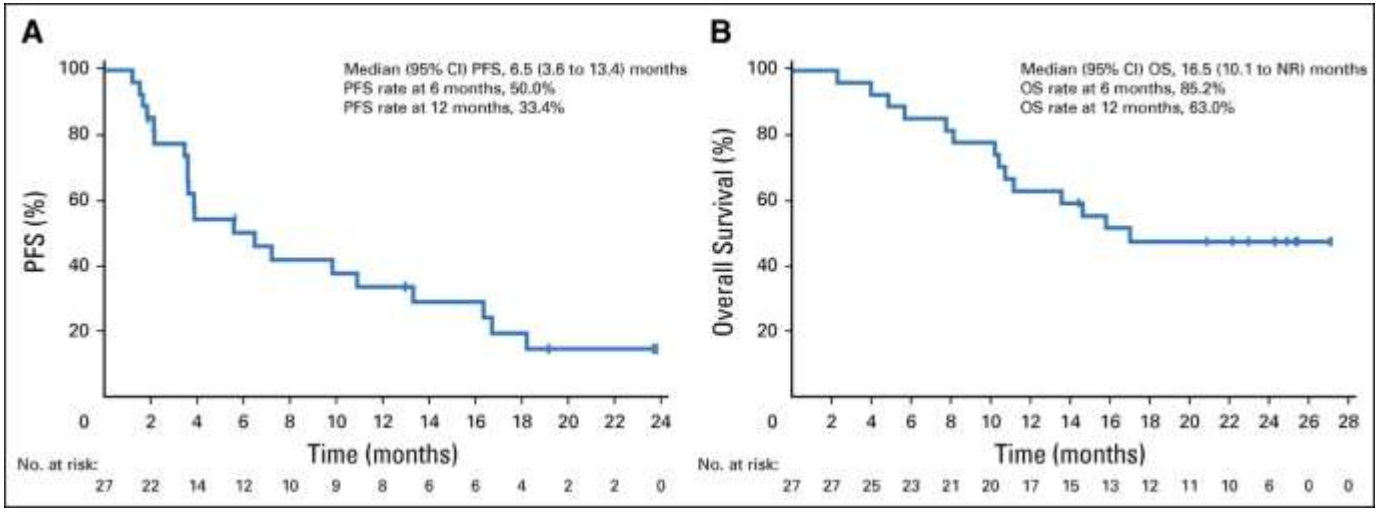
Outline

- Immunotherapy for recurrent / metastatic HNSCC
  - Keynote-012 clinical data (pembrolizumab)
  - Keynote-055 (pembrolizumab)
  - Keynote-012 biomarker data (pembrolizumab)
  - Checkmate 141 (nivolumab)

- Immunotherapy for recurrent / metastatic NPC
  - Pembrolizumab

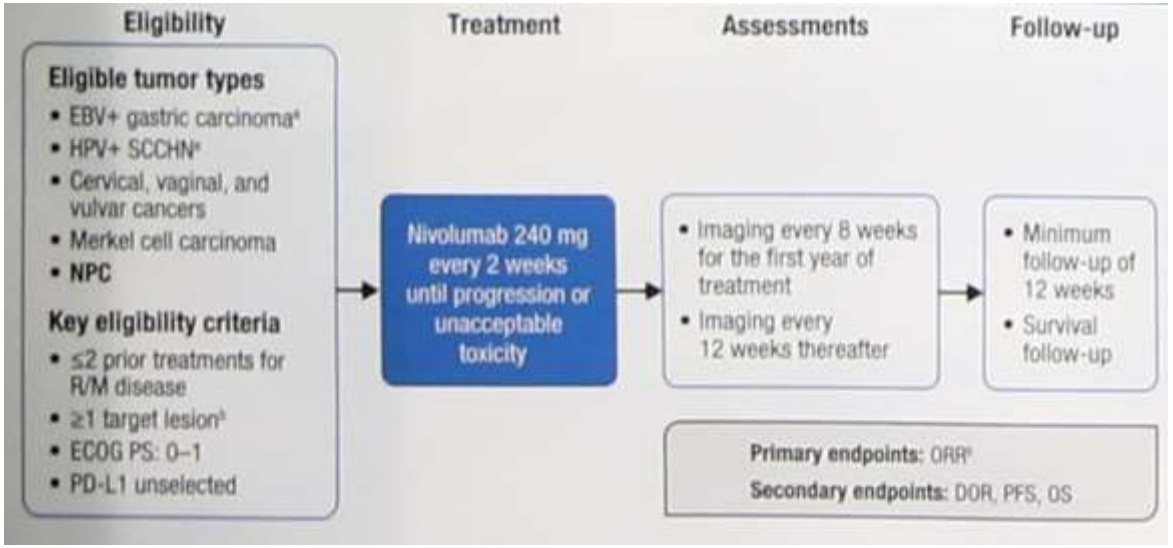
Pembrolizumab in NPC – Keynote 028

- Phase Ib, multicenter, open-label study
- Previously treated NPC - PD-L1 positive by IHC (CPS ≥1%)
- Pembrolizumab 10 mg/kg IV every 2 weeks
- 27 patients
  - 63% Asian
  - 22% keratinizing carcinomas
- **Efficacy:**
  - 26% response rate
  - Median duration of response 17 months



Hsu et al. JCO 2017

Checkmate-358
Nivolumab in Non-Keratinizing NPC



	Patients (N = 24)
Best overall response, n (%)	
Complete response	0
Partial response	5 (20.8)
Stable disease	6 (25.0)
Progressive disease	13 (54.2)
ORR, n (%) [95% CI]	5 (20.8) [7.1, 42.2]
Disease control rate, n (%)	11 (45.8)
Time to response, range, months	1.4–5.7
Duration of response, median (range), months	NR (0–5.5+)

+ Response ongoing
CI = confidence interval; NR = not reached

Delord et al. ASCO 2017

Summary

- Pembrolizumab with 14-18% response rate in heavily pre-treated patient population, and clinically meanigful (but not statistically different) improvements in overall survival compared to stadard therapy

- Nivolumab with 13% response rate in heavily pre-treated patient population and significant improvent in overall survival and quality of life compared to standard therapy

- Efficacy of PD-1 inhibitors may be slightly higher in HPV-positive patients, but this is up for debate

- PD-L1 expression predicts for better outcomes, in general

- Pembrolizumab and nivolumab active in recurrent/metastatic NPC