Recurrent/metastatic H&N cancer patient

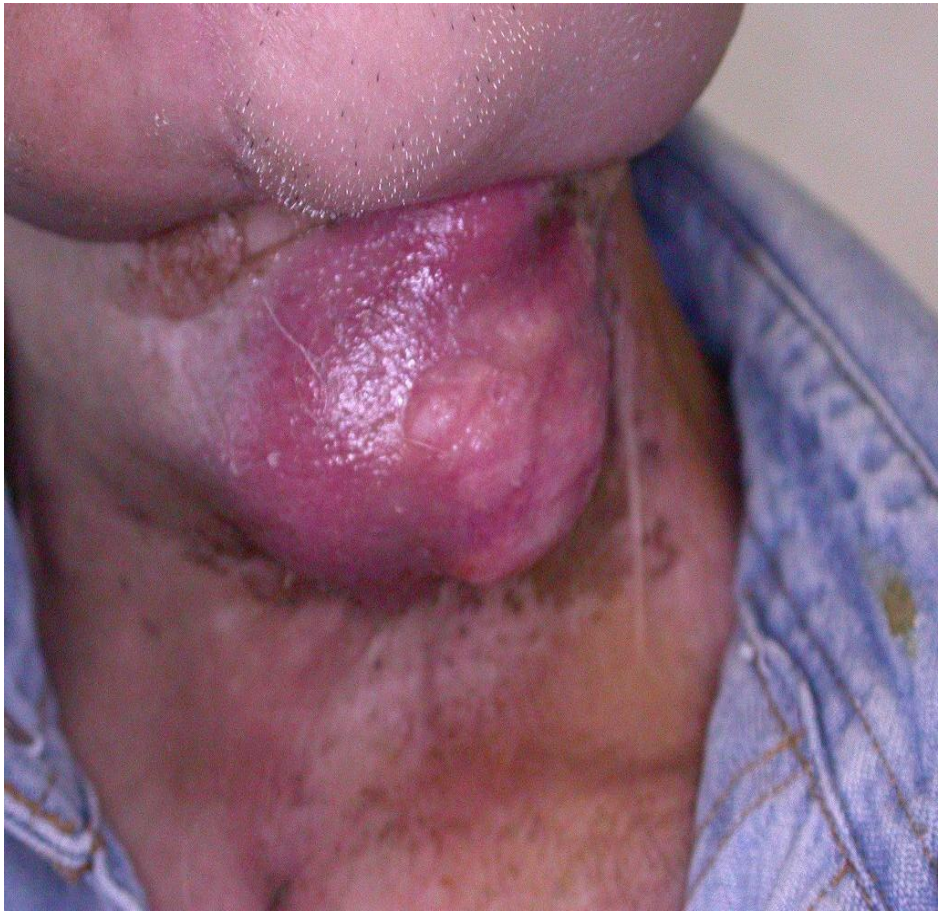
Lisa Licitra

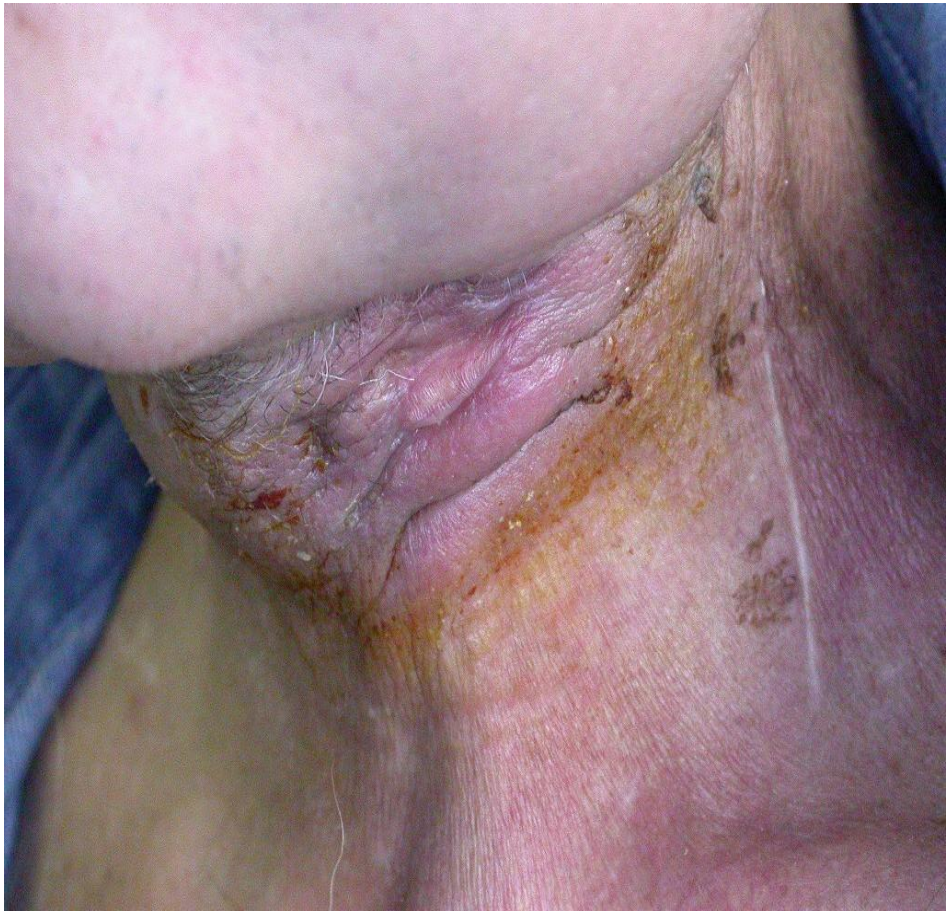
Head & Neck Cancer Medical Oncology Dept
Istituto Nazionale Tumori Milan,
and University of Milan
Italy

Recurrent and/or metastatic SCCHN

Treatment options:

- Chemotherapy (CT) or immunotherapy
- Re-irradiation
- Salvage surgery
- Best supportive care (BSC)





Prognostic Factors and Long-Term Survivorship in Patients with Recurrent or Metastatic Carcinoma of the Head and Neck

An Analysis of Two Eastern Cooperative Oncology Group Randomized Trials

Argiris A 2004

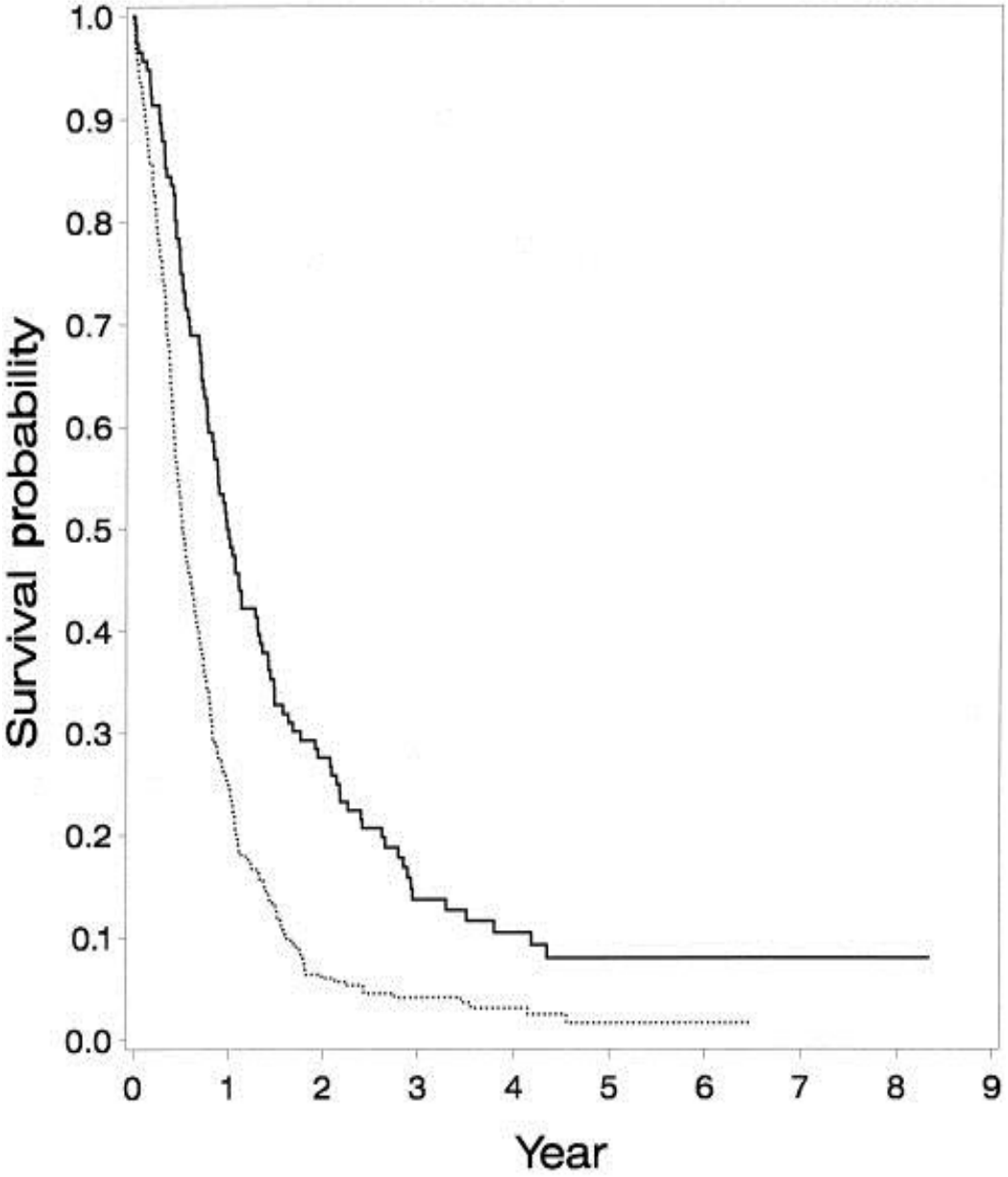
Factors affecting response…

	OR response (95% CI)	*P* value
Weight loss (> 5% vs. 5%)	**0.44 (0.27-0.73)**	**0.001**
ECOG PS 1 vs 0	**0.55 (0.34-0.88)**	**0.012**
Tumor differentiation (poor vs. well/moderate)	**1.59 (0.97-2.60)**	**0.067**
Residual tumor at the primary site	**0.39 (0.17-0.89)**	**0.024**
Oropharyngeal vs. other sites	**1.90 (1.16-3.10)**	**0.010**
Prior RT vs. no	**0.57 (0.32-1.01)**	**0.056**

Survivors at 2 yrs….

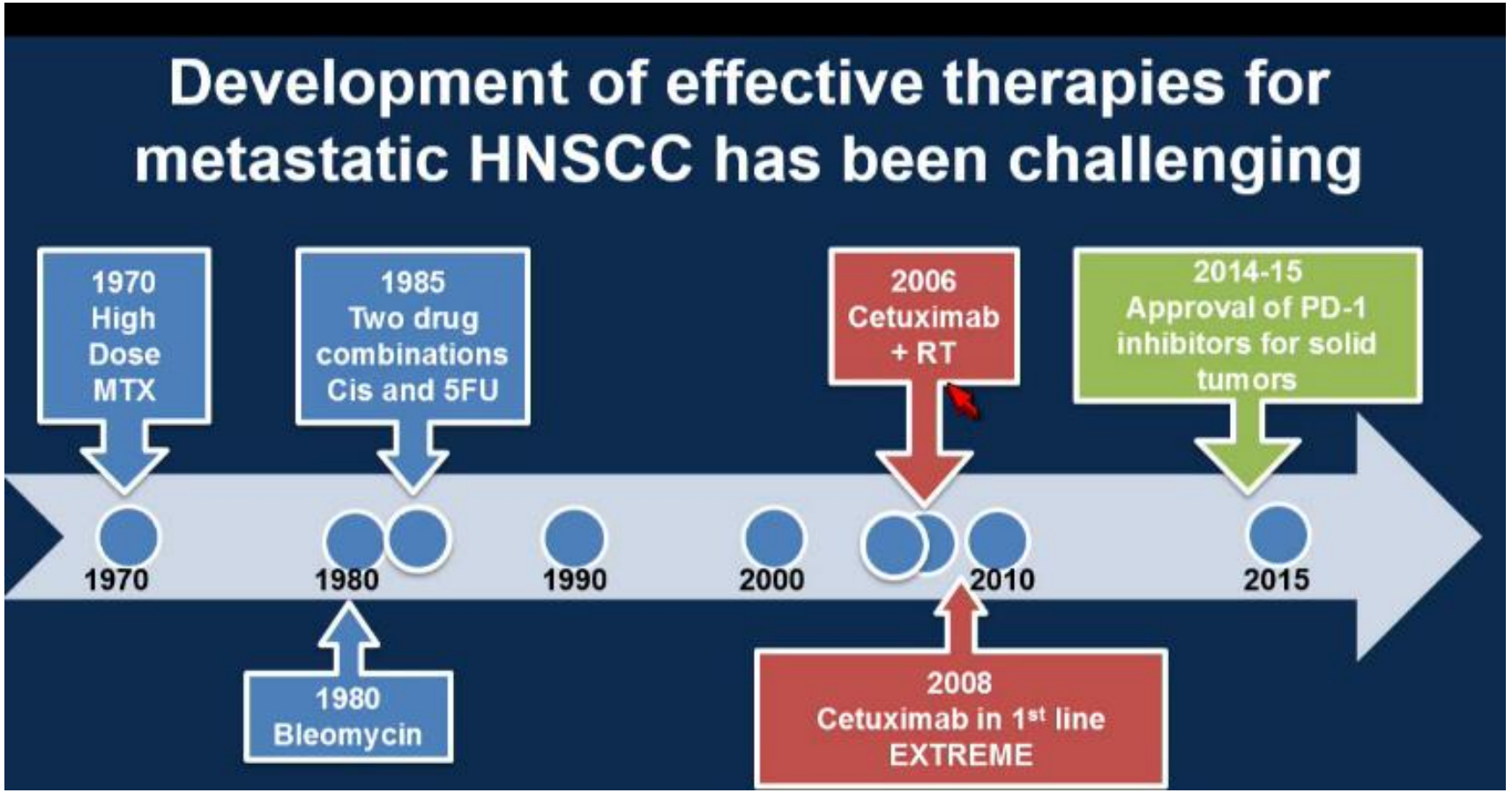
	OR (95% CI)	p-value
Response to chemotherapy vs. no response	**9.05 (4.23-19.15)**	**< 0.0001**
White race vs. others	**6.91 (1.52-31.36)**	**0.012**
ECOG performance status of 1 (vs. 0)	**0.45 (0.22-0.90)**	**0.024**
Cell differentiation (poor vs. well/moderate)	**2.55 (1.26-5.13)**	**0.009**
Prior RT (yes vs. no)	**0.34 (0.16-0.74)**	**0.006**

Survival by adverse factors (log-rank test P value of <0.0001)



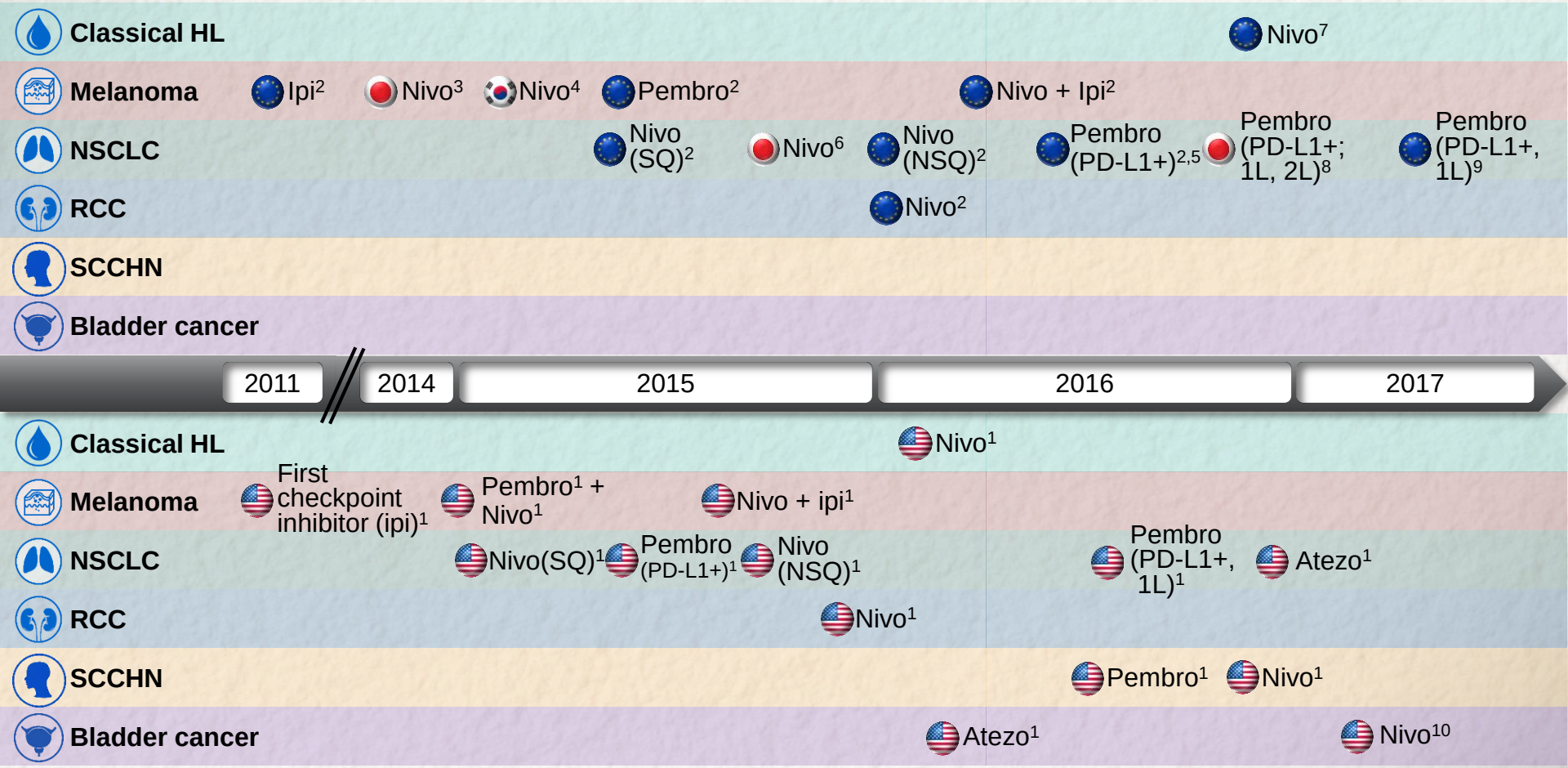
Category	Total	Dead	Alive	Median
0–2 adverse factor	116	104	12	1.0
≥ 3 adverse factors	283	274	9	0.5

HNSCC


Development of effective therapies for metastatic HNSCC has been challenging
1970 High Dose MTX
1985 Two drug combinations Cis and 5FU
2006 Cetuximab + RT
2014-15 Approval of PD-1 inhibitors for solid tumors
1970
1980
1990
2000
2010
2015
1980 Bleomycin
2008 Cetuximab in 1st line EXTREME

History of Checkpoint Inhibitors: Key Milestones

- Checkpoint inhibitors, discovered in the 1990s, have had a major impact on the treatment of multiple cancer types, particularly over the past 6 years



1. U.S. Food and Drug Administration. http://www.fda.gov. Accessed November 11, 2016. 2. European Medicines Agency. http://www.ema.europa.eu. Accessed November 11, 2016. 3. ONO Pharmaceutical Co., Ltd. [press release] July 4, 2014. 4. ONO Pharmaceutical Co, Ltd. [press release]. March 23, 2015. 5. Merck [press release]. June 27, 2016. Accessed August 8, 2016. 6. ONO Pharmaceutical Co, Ltd. [press release]. December 17, 2015. 7. Bristol-Myers Squibb Company [press release]. November 22, 2016. 8. Merck [press release]. December 19, 2016. 9. Merck [Press Release]. January 31, 2017. 10. Bristol-Myers Squibb Company [press release]. February 2, 2017.

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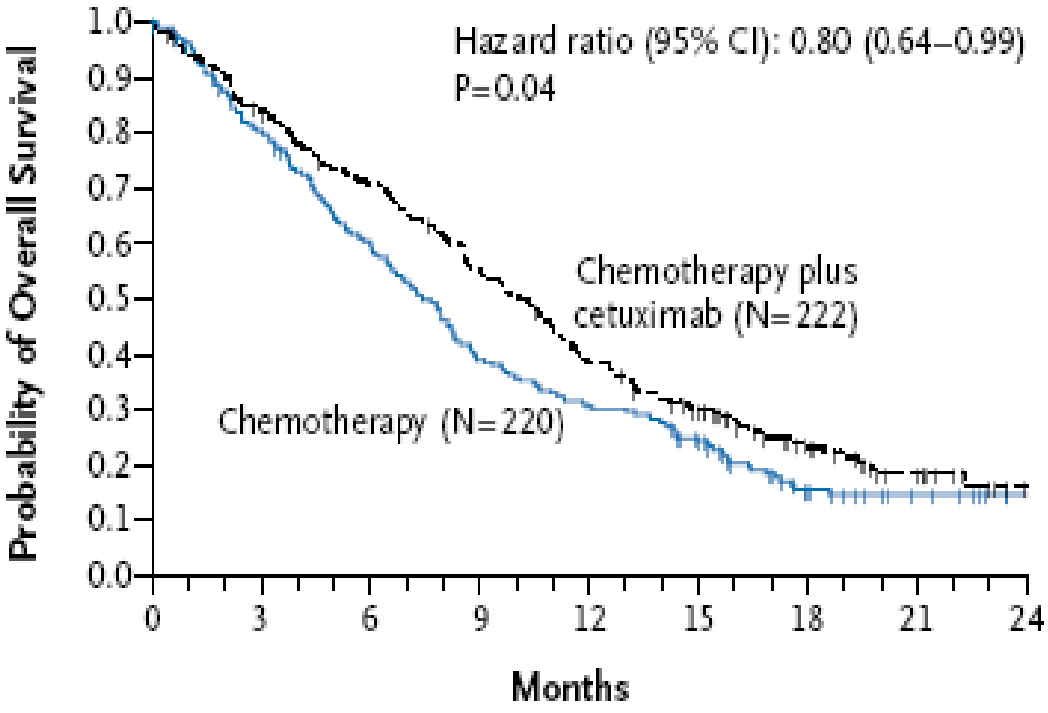
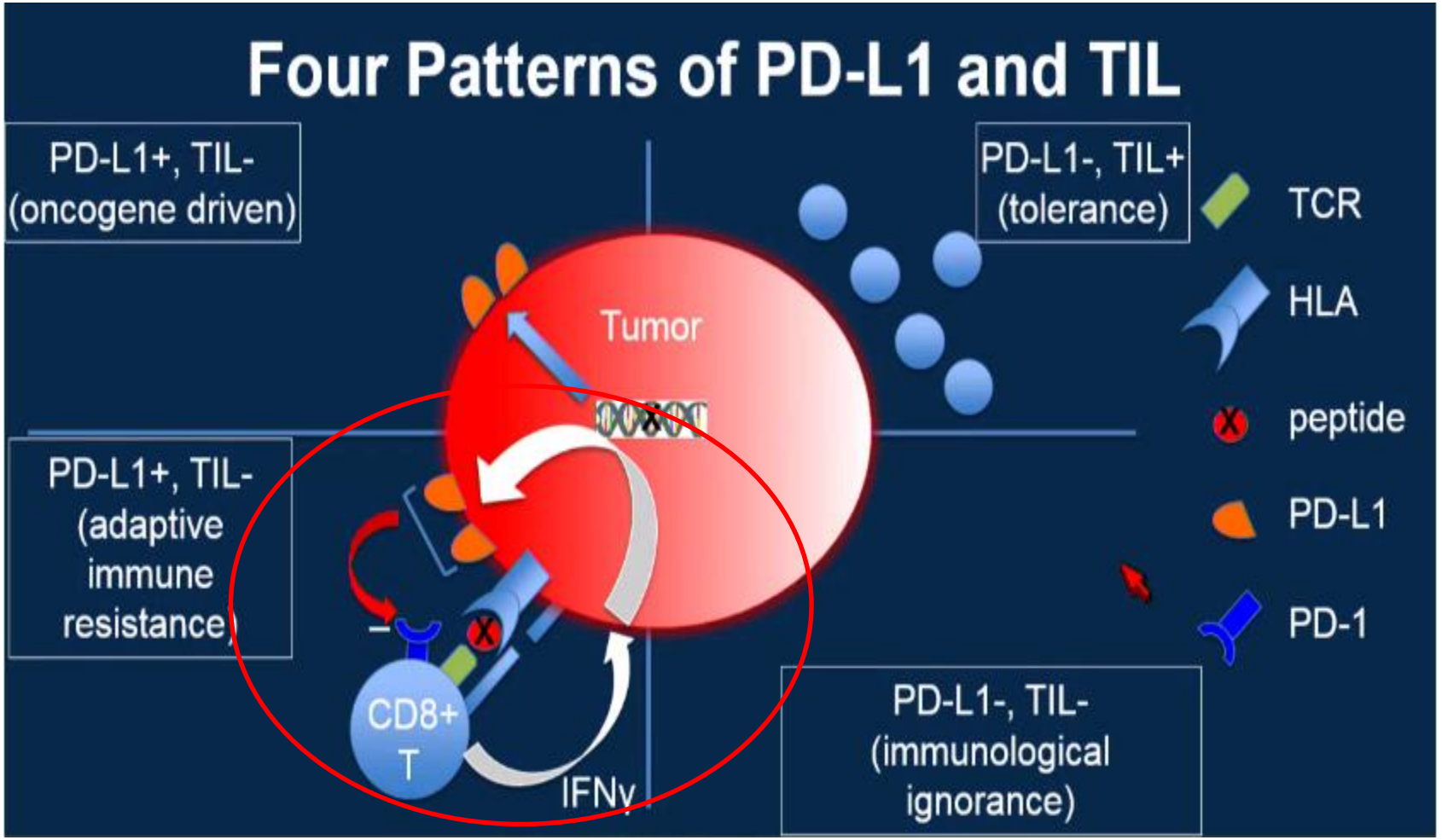


No. at Risk

Chemotherapy	220	173	127	83	65	47	19	8	1
Chemotherapy plus cetuximab	222	184	153	118	82	57	30	15	3

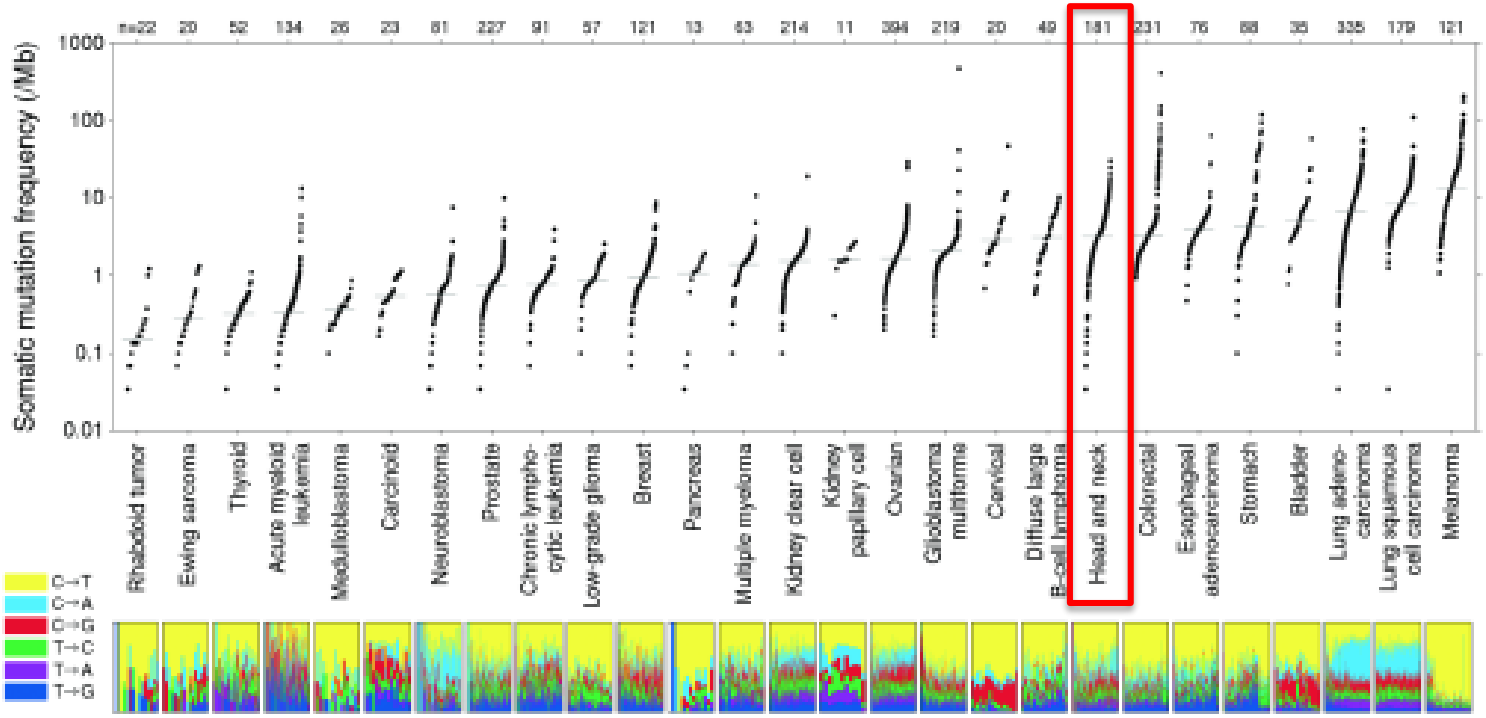
RATIONALE FOR IMMUNOTHERAPY IN HNSCC



Taube JM et al, Sci. Transl. Med. 2012

Higher Mutational Load in HNC

Somatic mutation frequencies



- Higher responses rate to PD-1/PDL-1 inhibitor in former and current smokers in lung cancer patients.

➢ Higher mutational load in smoking-associated lung cancer, leading to more tumor neoantigens and increased immunogenicity.

Nature. 2013 July 11; 499(7457): 214–218

Published OnlineFirst December 28, 2016; DOI: 10.1158/2159-8290.CD-16-0828

RESEARCH BRIEF

Evolution of Neoantigen Landscape during Immune Checkpoint Blockade in Non–Small Cell Lung Cancer

Valsamo Anagnostou[1,2], Kellie N. Smith[1,2], Patrick M. Forde[1,2], Noushin Niknafs[3], Rohit Bhattacharya[3], James White[1], Theresa Zhang[4], Vilmos Adleff[1], Jillian Phallen[1], Neha Wali[1], Carolyn Hruban[1], Violeta B. Guthrie[3], Kristen Rodgers[5], Jarushka Naidoo[1,2], Hyunseok Kang[1], William Sharfman[1], Christos Georgiades[6], Franco Verde[7], Peter Illei[1,8], Qing Kay Li[8], Edward Gabrielson[1,8], Malcolm V. Brock[1,5], Cynthia A. Zahnow[1], Stephen B. Baylin[1], Robert B. Scharpf[1], Julie R. Brahmer[1,2], Rachel Karchin[3], Drew M. Pardoll[1,2], and Victor E. Velculescu[1,2,3,8]

PD-L1 Expression in HNC

			PD-L1 expression%		
Author	subsite	N	total	HPV+	HPV -
Strome	OC,HP, L,PNS	24	66	NA	NA
Ukpo	OP	181	46.4	49.2	34.1
Lyford-pike	OP	27	59	70	29
Badoual	OC,OP,HP	64	51.5	62.5	40
Cho	OC	45	87	NA	NA
Zhang	NP	59	67.8	NA	NA
Hsu	NP	25	100	NA	NA

OC: oral cavity, HP: hypopharnx, L: larynx, PNS: parapharynx, OP: oropharynx, NP: nasopharynx

PD-L1 Expression Across Head and Neck Trials

Summary of PD-L1 Expression Across HNSCC Trials											
	Positive					Negative					N/E
	≥1% n (%)	≥5% n (%)	≥10% n (%)	≥25% n (%)	≥50% n (%)	<1% n (%)	<5% n (%)	<10% n (%)	<25% n (%)	<50% n (%)	n (%)
KN012 (N=188) [TPS]	123 (65.4)	--	--	--	--	65 (34.6)	--	--	--	--	--
KN012 (N=188) [CPS]	152 (80.9)	--	--	--	--	36 (19.1)	--	--	--	--	--
KN055 (N=171) [CPS]	140 (82)	--	--	--	48 (28)	26 (15)	--	--	--	118 (69)	5 (3)
CM141 (N=361) [TPS]	149 (41.3)	97 (26.9)	77 (21.3)	--	--	111 (30.7)	163 (45.1)	183 (50.7)	--	--	101 (28)
AZ 1108 (N=62) [TPS]	--	--	--	21 (34)	--	--	--	--	38 (61)	--	3 (5)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

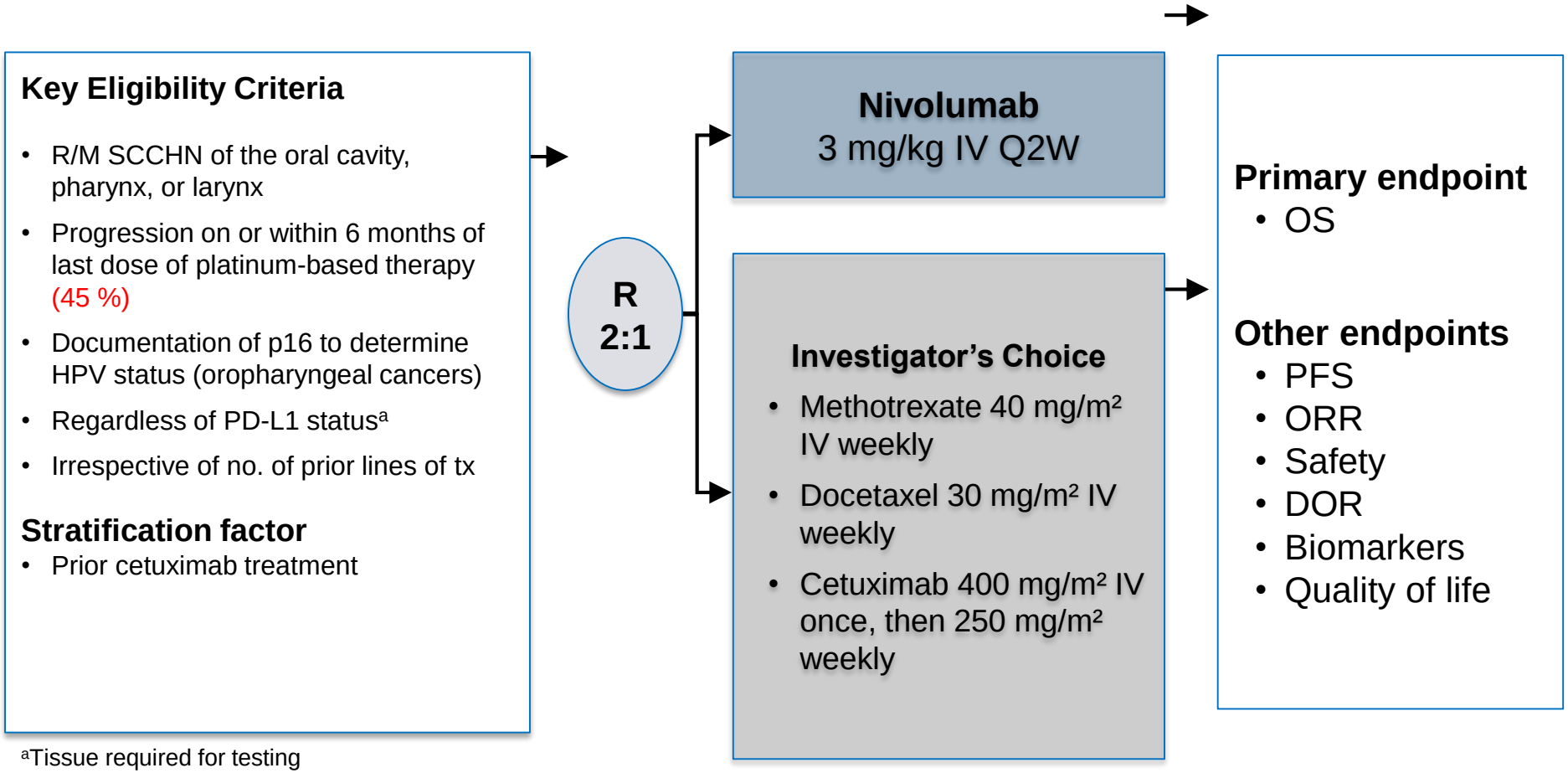
Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck

R.L. Ferris, G. Blumenschein, Jr., J. Fayette, J. Guigay, A.D. Colevas, L. Licitra, K. Harrington, S. Kasper, E.E. Vokes, C. Even, F. Worden, N.F. Saba, L.C. Iglesias Docampo, R. Haddad, T. Rordorf, N. Kiyota, M. Tahara, M. Monga, M. Lynch, W.J. Geese, J. Kopit, J.W. Shaw, and M.L. Gillison

2016

CheckMate-141 Study

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

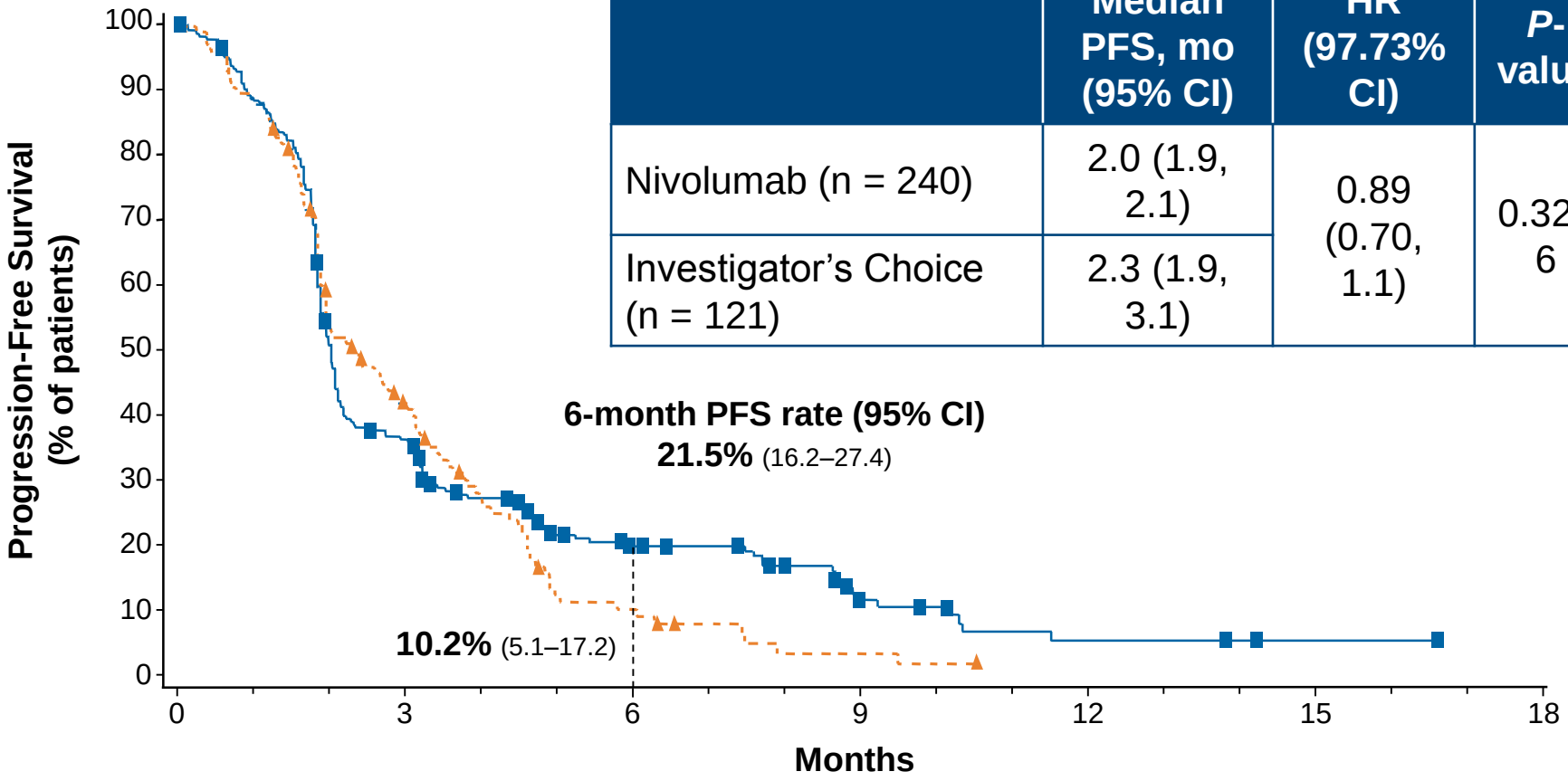


[a]Tissue required for testing

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

Progression-Free Survival

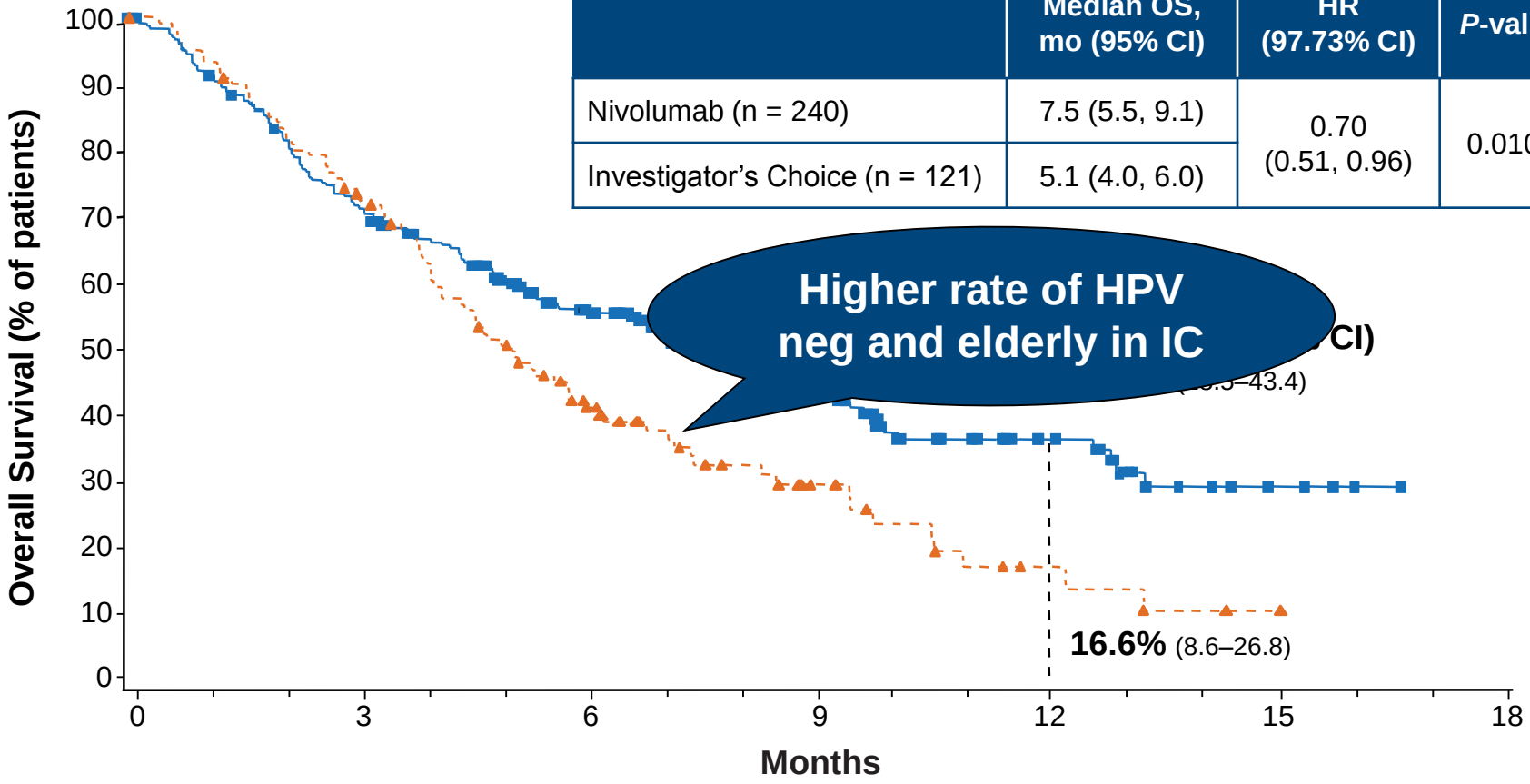
	Median PFS, mo (95% CI)	HR (97.73% CI)	*P*-value
Nivolumab (n = 240)	2.0 (1.9, 2.1)	0.89 (0.70, 1.1)	0.3236
Investigator's Choice (n = 121)	2.3 (1.9, 3.1)		



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

Overall Survival

	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

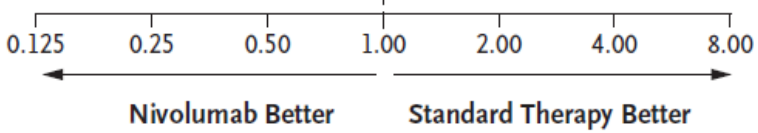
Nivolumab	240	167	109	52	24	7	0
Investigator's Choice	121	87	42	17	5	1	0

Objective Response Rate

	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)

C Treatment Effect on Overall Survival, According to Subgroup

Subgroup	Nivolumab	Standard Therapy	Unstratified Hazard Ratio (95% CI)
	no. of patients		
Overall	240	121	0.69 (0.53–0.91)
Age			
<65 yr	172	76	0.64 (0.45–0.89)
≥65 yr and <75 yr	56	39	0.93 (0.56–1.54)
≥75 yr	12	6	—
ECOG performance-status score			
0	49	23	0.60 (0.30–1.23)
≥1	190	97	0.71 (0.53–0.96)
Not reported	1	1	—
Previous cetuximab use			
Yes	147	74	0.81 (0.57–1.15)
No	93	47	0.55 (0.35–0.86)
Intended standard therapy			
Cetuximab	33	15	0.47 (0.22–1.01)
Methotrexate	119	52	0.64 (0.43–0.96)
Docetaxel	88	54	0.82 (0.53–1.28)
Site of primary tumor			
Larynx	34	15	0.75 (0.36–1.59)
Oral cavity	108	67	0.73 (0.51–1.07)
Pharynx	92	36	0.71 (0.42–1.19)
Other	6	3	—
No. of previous lines of systemic therapy			
1	106	58	0.72 (0.48–1.07)
2	80	45	0.64 (0.40–1.00)
≥3	54	18	0.77 (0.38–1.57)
Platinum-refractory disease in context of primary therapy			
Yes	52	26	0.63 (0.35–1.12)
No	188	95	0.71 (0.52–0.97)

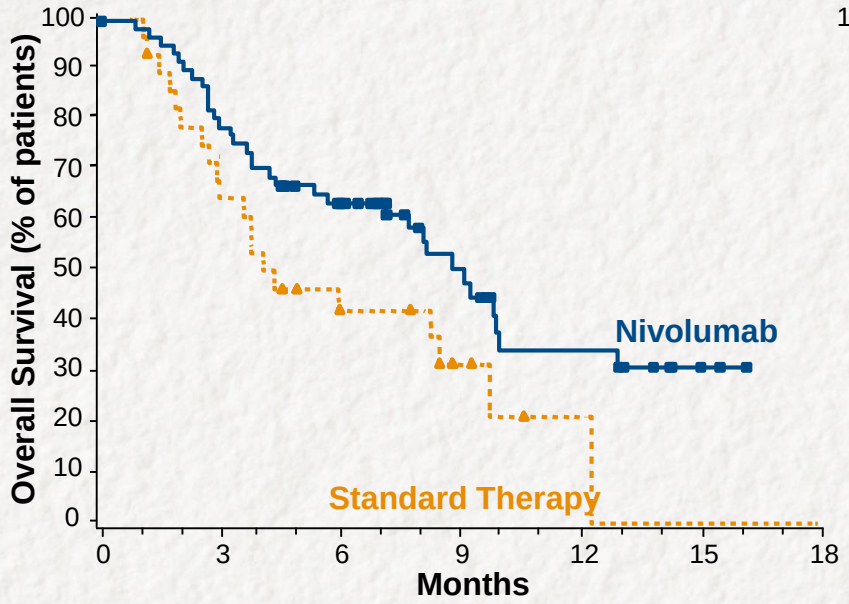


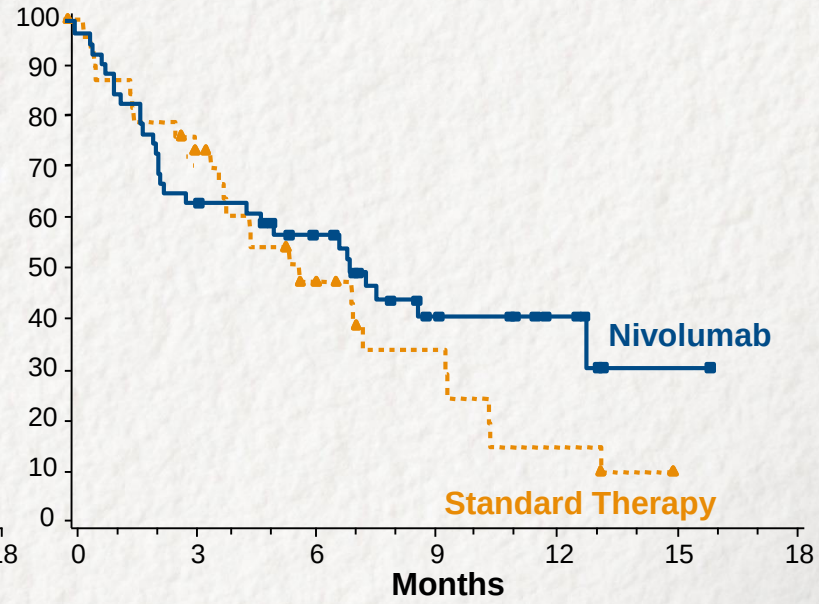
PHASE 3 CHECKMATE 141 OS BY P16 STATUS

NIVOLUMAB MONOTHERAPY

p16-Positive	Nivolumab	Standard Therapy
No. of Patients	63	29
Median OS mo (95% CI)	9.1 (7.2–10.0)	4.4 (3.0–9.8)
HR (95% CI)	0.56 (0.32–0.99)	

p16-Negative	Nivolumab	Standard Therapy
No. of Patients	50	36
Median OS mo (95% CI)	7.5 (3.0–NA)	5.8 (3.8–9.5)
HR (95% CI)	0.73 (0.42–1.25)	





Nivolumab	63	49	35	18	10	3	0	50	32	25	12	6	1	0
Standard Therapy	29	20	11	4	1	0	0	36	26	13	7	3	1	0

In a robust phase 3 trial, nivolumab demonstrated improved OS in both p16+ and p16- patients compared to standard therapy

CI=confidence interval; HR=hazard ratio; p16=cyclin-dependent kinase inhibitor 2A; OS=overall survival.

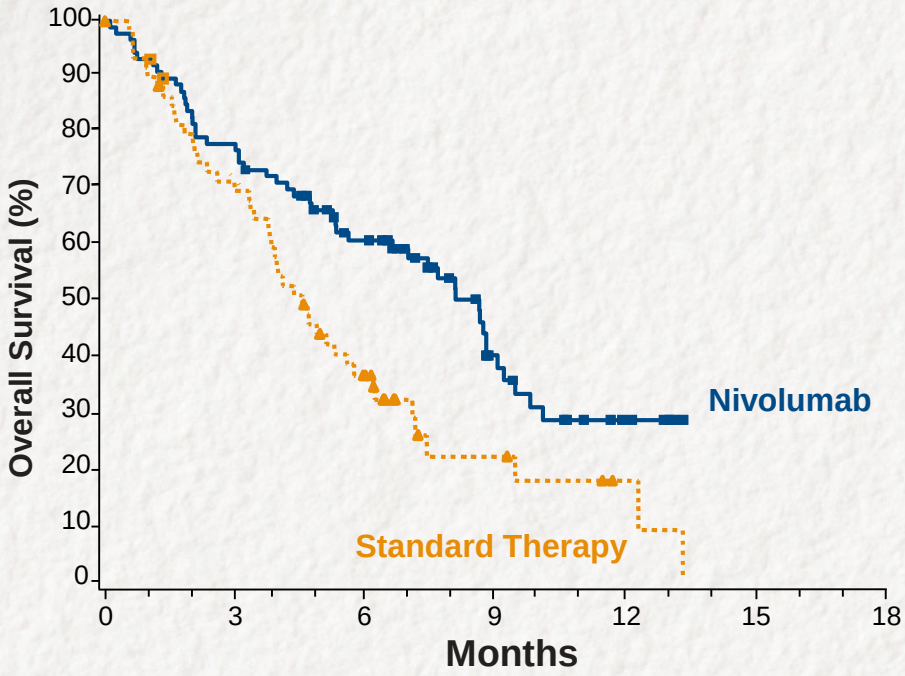
Ferris RL et al. *N Engl J Med*. 2016;375(19):1856-1867.

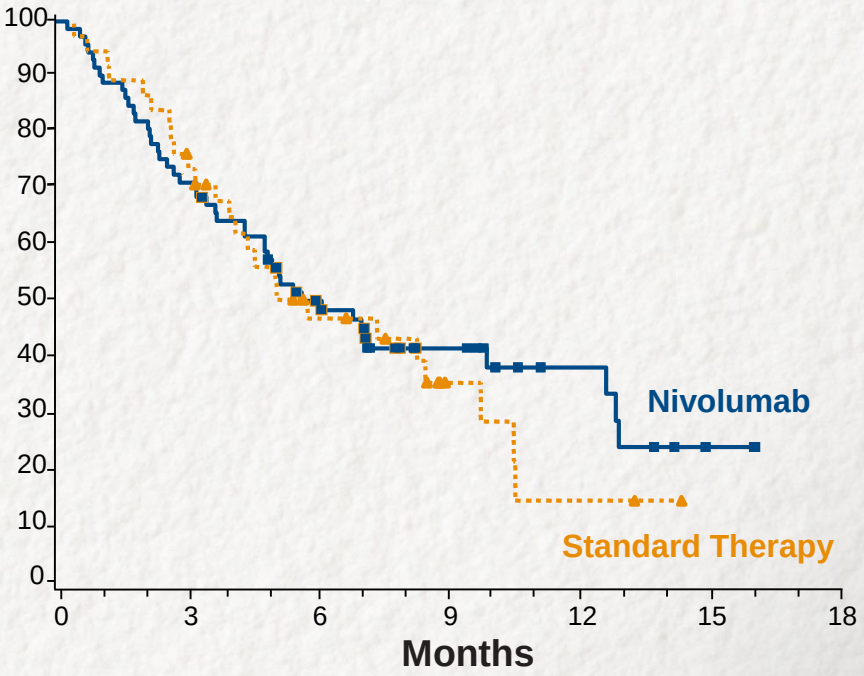
Phase 3 CheckMate 141 OS by PD-L1 Expression

Nivolumab Monotherapy

PD-L1 Baseline ≥1%	Nivolumab	Standard Therapy
No. of Patients	88	61
Median OS mo (95% CI)	8.7 (5.7–9.1)	4.6 (3.8–5.8)
HR (95% CI)	0.55 (0.36–0.83)	

PD-L1 Baseline <1%	Nivolumab	Standard Therapy
No. of Patients	73	38
Median OS mo (95% CI)	5.7 (4.4–12.7)	5.8 (4.0–9.8)
HR (95% CI)	0.89 (0.54–1.45)	





Nivolumab	88	67	44	18	6	0	73	52	33	17	8	3	0
Standard Therapy	61	42	20	6	2	0	38	29	14	6	2	0	0

CI=confidence interval; PD-L1=programmed death ligand 1; OS=overall survival.

Ferris RL et al. *N Engl J Med*. 2016;375(19):1856-1867.

PHASE 3 CHECKMATE 141 OS BY PD-L1 AND P16 EXPRESSION

NIVOLUMAB MONOTHERAPY

	Nivolumab		Standard Therapy		HR for Death (95% CI)
Combined Subgroup	n (%)	mOS, months	n (%)	mOS, months	
PD-L1 ≥1% and p16-positive	23 (9.6)	8.8	14 (11.6)	3.9	**0.50** (0.21-1.19)
PD-L1 ≥1% and p16-negative	17 (7.1)	8.8	16 (13.2)	5.6	**0.44** (0.18-1.10)
PD-L1 <1% and p16-positive	24 (10.0)	10.0	10 (8.3)	6.4	**0.55** (0.22-1.39)
PD-L1 <1% and p16-negative	14 (5.8)	7.1	12 (9.9)	7.4	**0.82** (0.31-2.19)

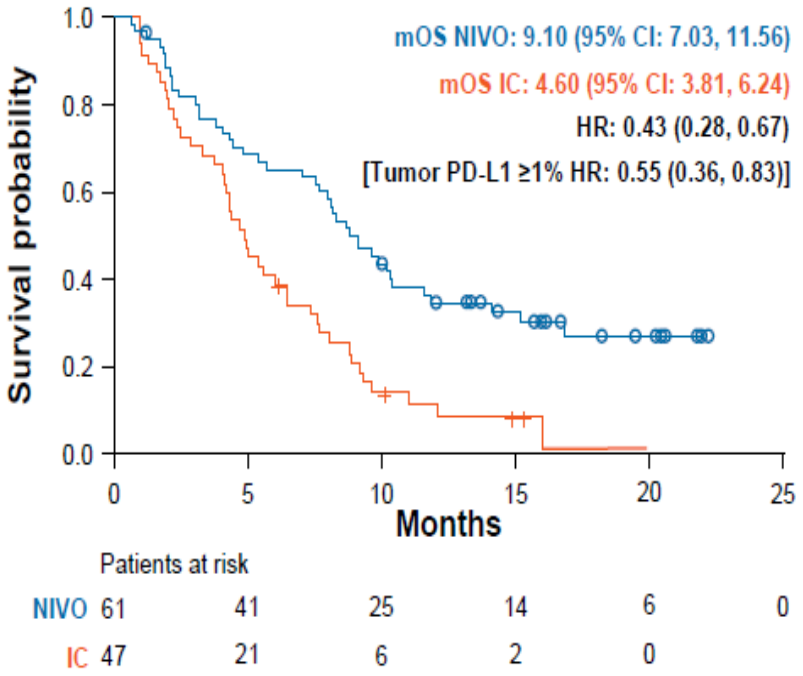
- **Hazard ratios for death in the analysis of OS with nivolumab vs standard therapy were less than 1 in all four subgroups**

CI=confidence interval; HR=hazard ratio; mOS=median overall survival; p16=cyclin-dependent kinase inhibitor 2A; PD-L1=programmed death ligand 1; OS=overall survival.

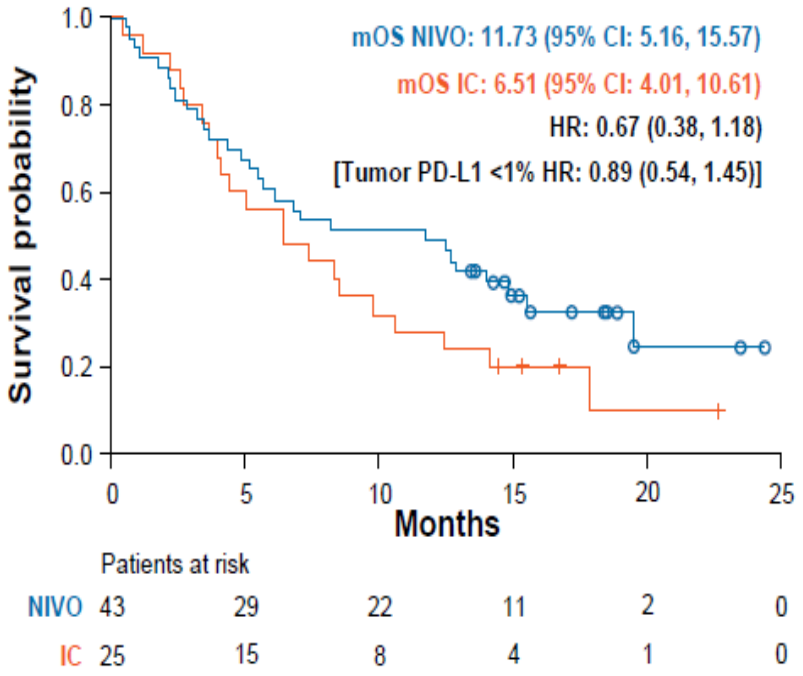
Ferris RL et al. *N Engl J Med*. 2016;375(19):1856-1867.

Overall Survival by Tumor PD-L1 Expression and PD-L1+ TAIC Abundance

Tumor PD-L1 ≥1% & PD-L1+ TAIC Abundance



Tumor PD-L1 <1% & PD-L1+ TAIC Abundance



- Tumor PD-L1 ≥1% and rare PD-L1+ TAICs: mOS increased with NIVO vs IC (6.7 vs 4.9 months, HR 0.89 [0.44, 1.80])
- Tumor PD-L1 <1% and rare PD-L1+ TAICs: no difference mOS with NIVO vs IC (3.7 vs 4.9 months, HR 1.09 [0.50, 2.36])

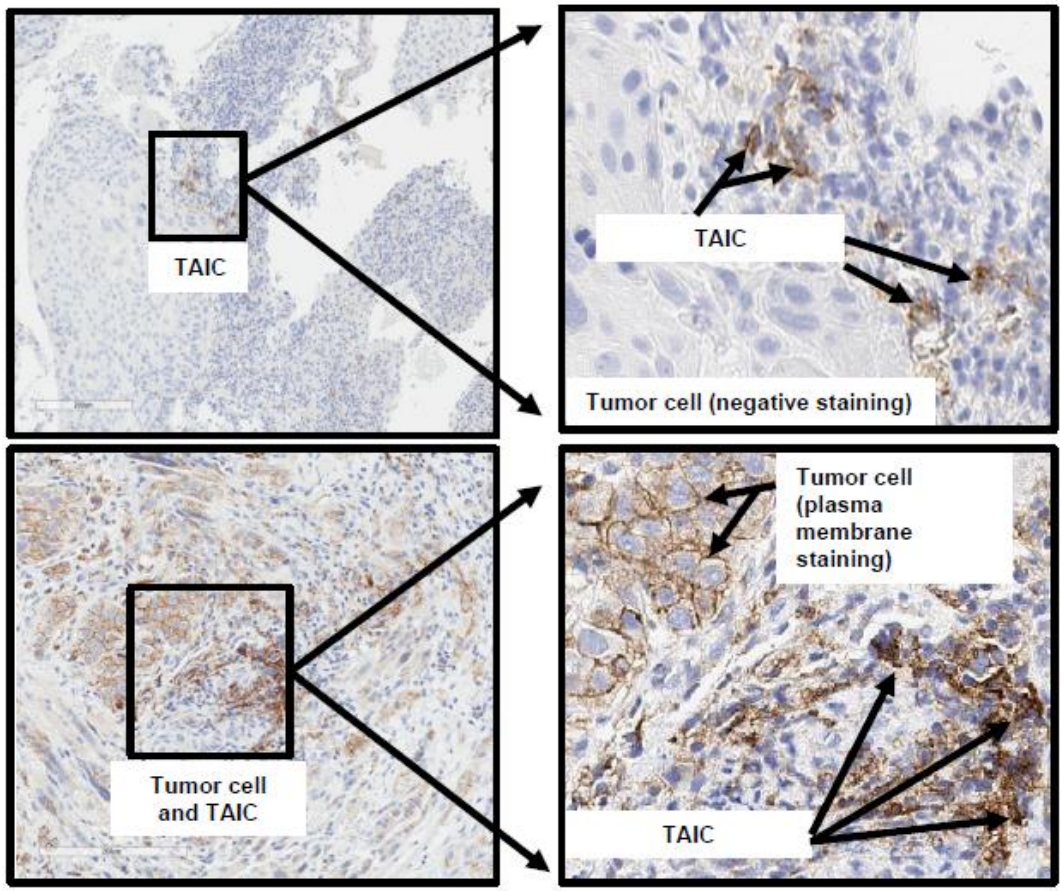
Overall Response by Tumor PD-L1 Expression and PD-L1+ TAIC Abundance

	ORR % (95% CI)	
	NIVO	IC
Tumor PD-L1 ≥1% and abundant PD-L1+ TAICs	n = 61	n = 47
	19.7 (10.6, 31.8)	0 (0, 7.5)
Tumor PD-L1 ≥1% and rare PD-L1+ TAICs	n = 27	n = 14
	11.1 (2.4, 29.2)	7.1 (0.2, 33.9)
Tumor PD-L1 <1% and abundant PD-L1+ TAICs	n = 43	n = 25
	18.6 (8.4, 33.4)	12.0 (2.5, 31.2)
Tumor PD-L1 <1% and rare PD-L1+ TAICs	n = 27	n = 10
	3.7 (<0.1, 19.0)	10.0 (0.3, 44.5)

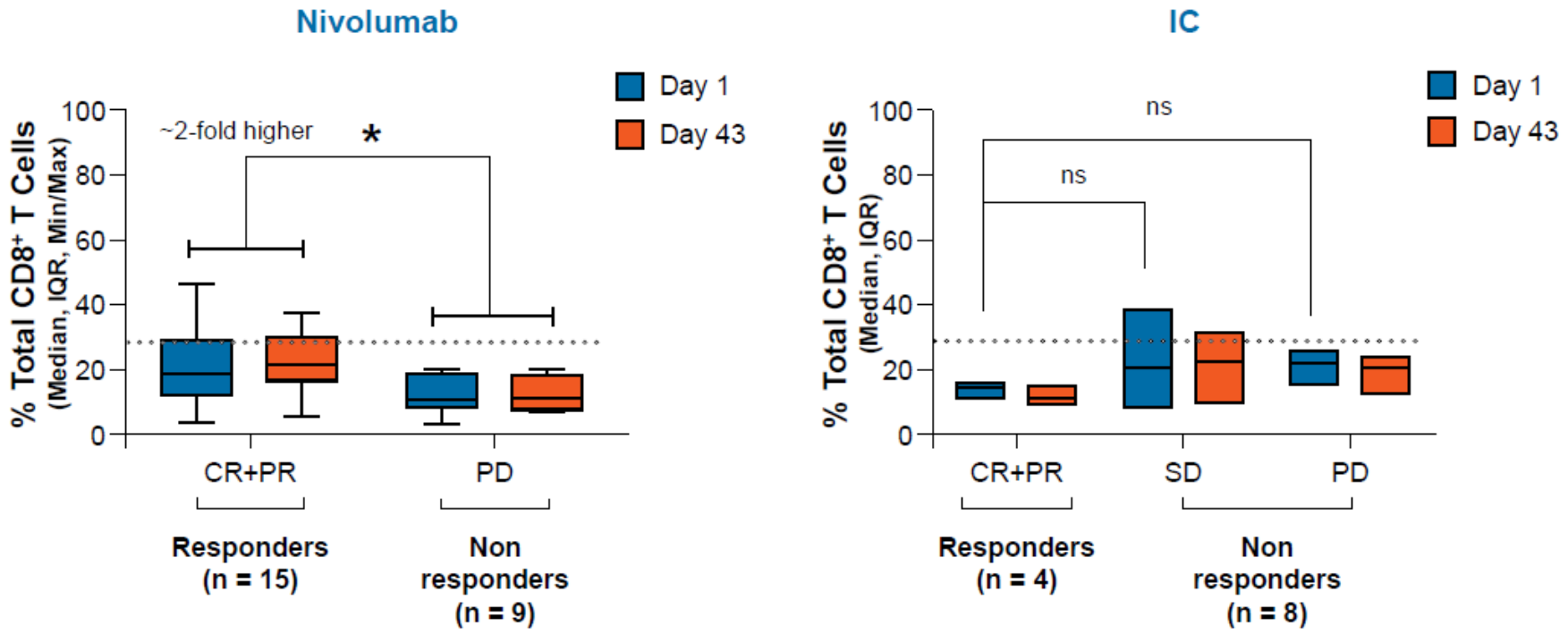
TAIC PD-L1 Evaluation: SCCHN CheckMate 141

Patient example 1

Patient example 2



Frequency of Total PBL CD8+ T Cells in Nivolumab and IC Responders vs Non-responders at Baseline and Day 43



*$P<0.05$

Response to nivolumab may be associated with higher circulating CD8+ T cells and Ki67+ Tregs, and lower PD-1+ Tregs at baseline

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.

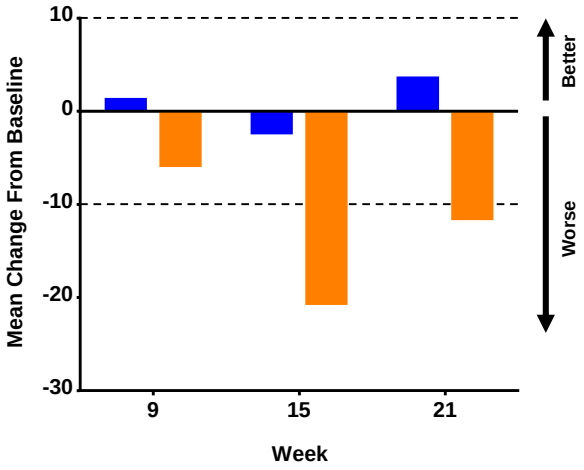
Treatment-Related Adverse Events

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)

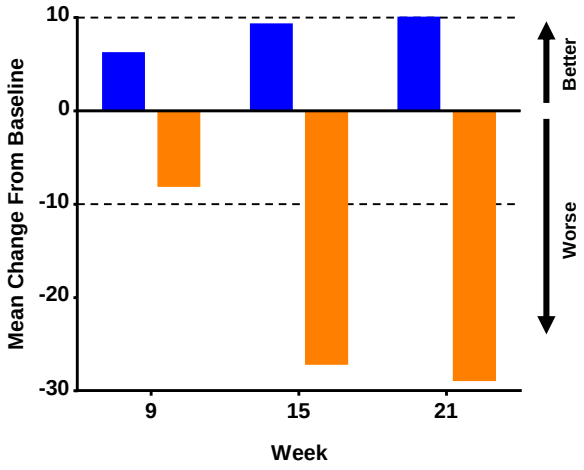
[a]One Grade 5 event (hypercalcemia) in the nivolumab arm and one grade 5 event (lung infection) in the investigator's choice arm were reported. A second death occurred in the nivolumab arm subsequent to pneumonitis.

Patient-Reported Outcomes

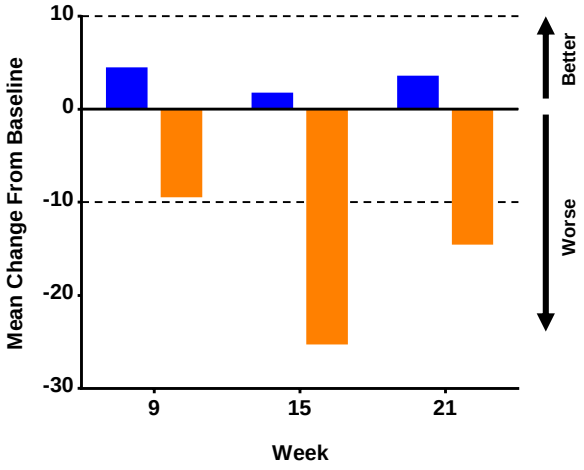
EORTC QLQ-C30 Physical Function



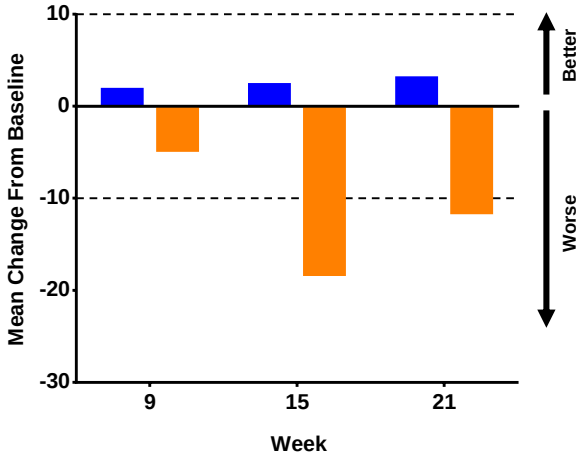
EORTC QLQ-C30 Social Function



EORTC QLQ-H&N35 Absence of Sensory Problems



EORTC QLQ-H&N35 Absence of Trouble With Social Contact



Nivolumab

Investigator's Choice

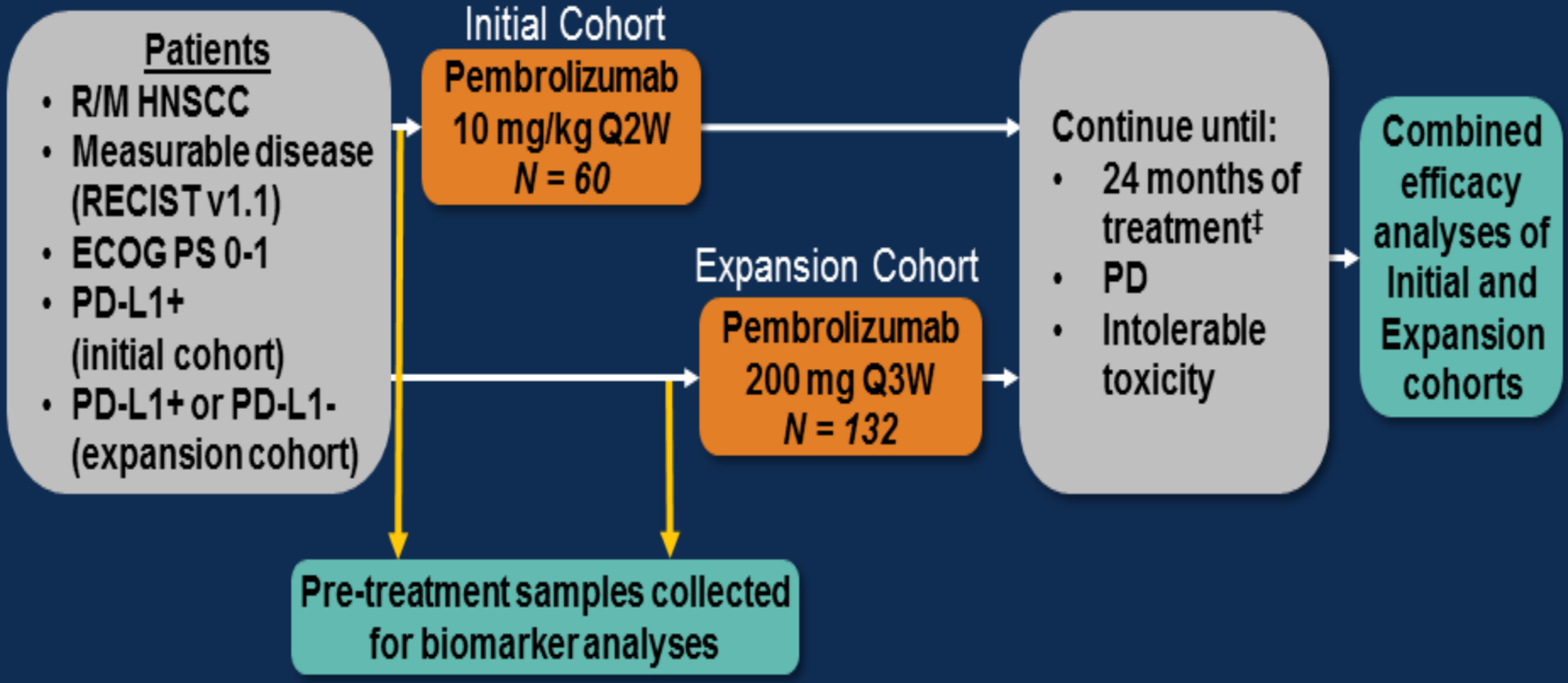
- Nivolumab was associated with generally stable PROs, while investigator's choice was associated with meaningful declines in function and worsening of symptoms

Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial

Tanguy Y Seiwert, Barbara Burtness, Ranee Mehra, Jared Weiss, Raanan Berger, Joseph Paul Eder, Karl Heath, Terrill McClanahan, Jared Lunceford, Christine Gause, Jonathan D Cheng, Laura Q Chow

2016

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



- Pre-treatment biomarker levels were correlated with efficacy outcomes (ORR, PFS, OS; central imaging vendor review)

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

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

Patients
- Recurrent/ metastatic HNSCC
- Resistant to platinum and cetuximab†
- Measurable disease (RECIST v1.1)
- ECOG PS 0-1

→ **Pembrolizumab 200 mg Q3W Flat Dose**

→ **Continue until:**
- 24 months of treatment
- PD
- Intolerable toxicity
- Investigator/patient decision

→ **Safety and Survival Follow-up**

Received ≥1 dose of pembrolizumab n = 171 (99%)

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

≥6 months of follow-up† n = 92 (54%)

†Resistance and cetuxima… latinum

…Matching the two studies with Pembro…

Demographics

Characteristic	KEYNOTE 055 N=171	KEYNOTE 012 N=192
Age	61 (33–90)	60 (20–84)
Male	138 (81)	159 (83)
ECOG PS 0	48 (28)	57 (30)
ECOG PS 1	120 (70)	135 (70)
HPV Status		
Positive	71 (41)	45 (23)
Negative	100 (59)	147 (77)
Median no. of prior (chemotherapy)	2 (1–6)	2 (0–7)
1	28 (16)	47 (24)
2	71 (42)	56 (29)
≥ 3	72 (42)	86 (45)

…Matching the two studies with Pembro…

Overall Response Rate (subgroup analysis)

	Keynote 055 (N=92)		Keynote 012 (N=192)	
	BEST OVERALL RESPONSE			
	n	%	n	%
HPV	(total HPV+ n= 18)		(total HPV+ n=45)	
HPV +	4	22	11	20
HPV -	12	16	23	16
PDL1	(PDL1+ n=76)		(PDL1+ n=123)	
PDL1 +	13	17	22	18
PDL1 -	1	7	12	18.5

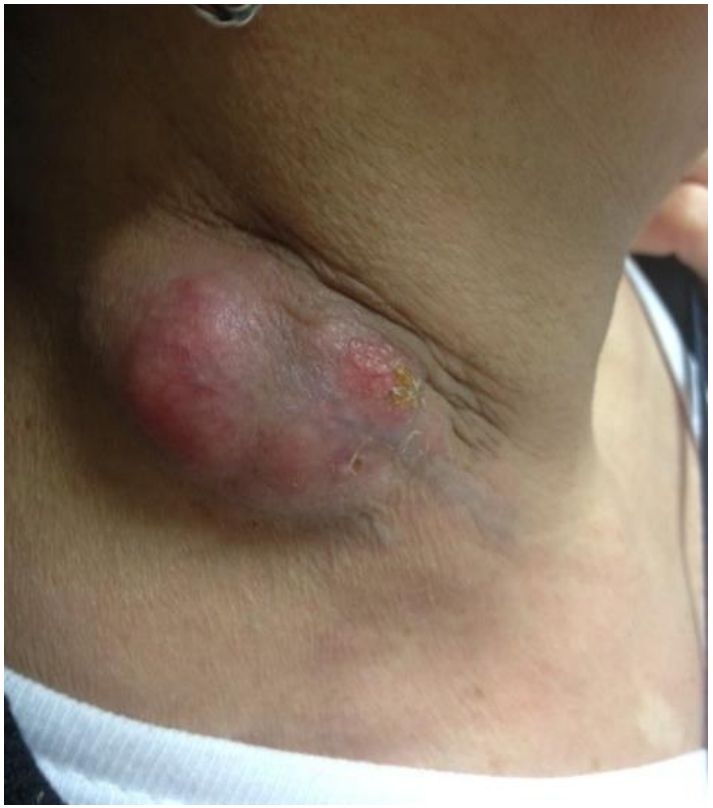
…Matching the two studies with Pembro…

Overall Response Rate

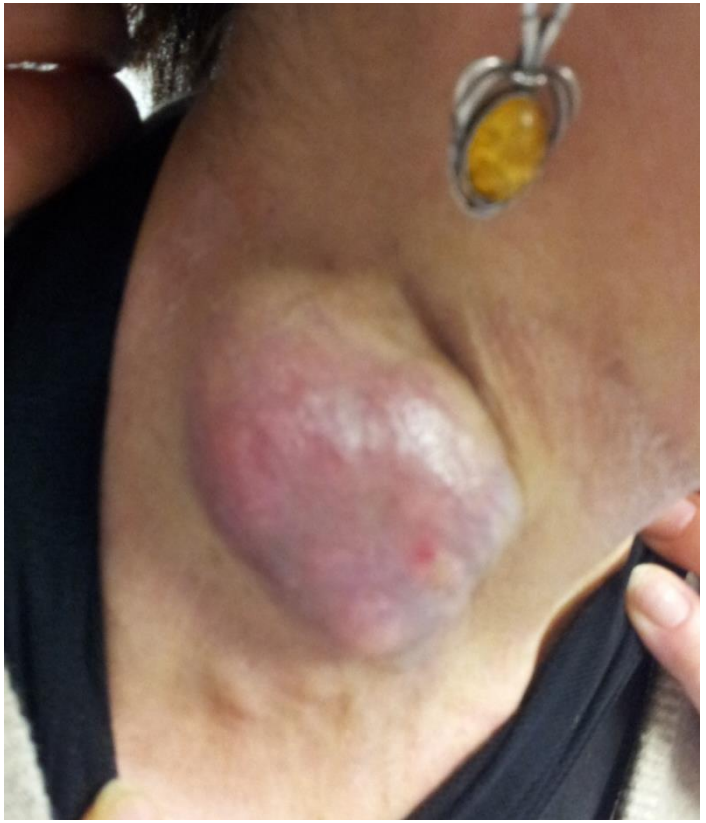
	Keynote 055		Keynote 012	
Best Overall Response	Patients With ≥6 Month Follow up N = 92		Total N = 192	
	n	%	n	%
ORR*	16	17	34	18
CR	-	-	8	4
PR	16	17	25	13
SD	17	18	33	17
PD	51	55	93	48
NA†	8	9	33	17

Case #1

Dec 2014

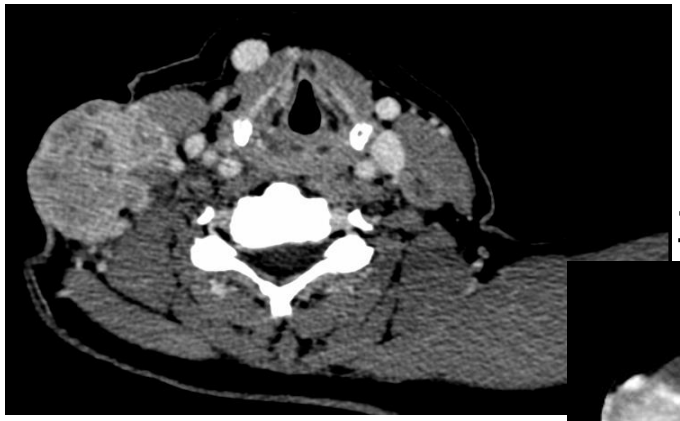


Dec 2014

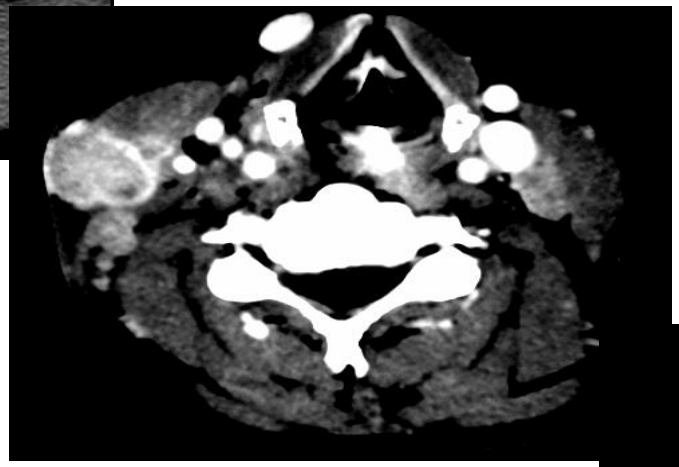


Case #1

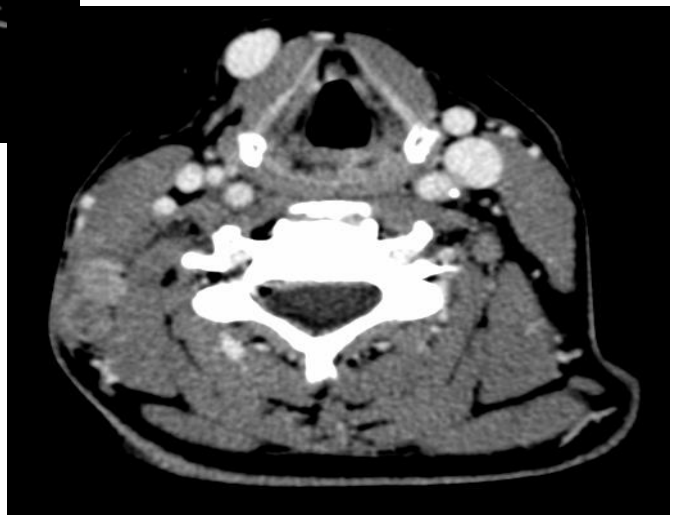
Baseline Nov 2014



1° Evaluation Jan 2015



Apr 2015



R&M disease

Trial	pts	phase	eligibility	target	TX	endpoint	Status
KEYNOTE-012	224	I	Solid tumors (including a HNSCC cohort)	Anti-PD-1	Pembrolizumab 10mg/k q 2w	ORR, safety	Compl
KEYNOTE-040	446	III	Planitum refractory HNSCC	Anti-PD-1	Pembrolizumab vs. Centuximab, Methotrexate or Docetaxel	PFS, OS	Recr
KEYNOTE-055	150	II	Platinum & Cetuximab refractory HNSCC	Anti-PD-1	Pembrolizumab	ORR, AEs	Compl
KEYNOTE-048	750	III	R/M HNSCC, first line, >6 months from curative therapy	Anti-PD-1	Pembrolizumab vs pembrolizumab + platinum/5-FU vs. Cetuximab + Platinum/5-FU	PFS	Recr
NCT02289209	48	II	Locoregional relapse/2 primary	Anti-PD-1	Reirradiation + Pembrolizumab	PFS	Recr
NCT02253992	200	I	Multiple tumors, including HNSCC	Anti-PD-1 CD137 agonist	Nivolumab + Urelumab	ORR, safety	Recr
CHECKMATE 141	360	III	Platinum refractory HNSCC (progression or relapse >6 months of last platinum dose)	Anti-PD-1	Nivolumab vs Centuximab or methotrexate or Docetaxel	OS at 28 months	Compl
NCT01693562	1038	I/II	Advanced solid tumors including HNSCC	Anti-PD-L1	Durvalumab (MEDI4736)	ORR, AEs	Recr

R&M disease

Trial	pts	phase	eligibility	target	TX	endpoint	Status
HAWK	112	II	Platinum refractory HNSCC	Anti-PD-L1	Durvalumab in PD-L1+	ORR, AEs	Compl
CONDOR	240	II	Platinum refractory R/M HNSCC PD-L1 negative	Anti-PD-1, anti-CTL4	Durvalumab vs Tremelumumab vs Durvalumab+ Tremelimumab	ORR	Compl
EAGLE	720	III	Platinum refractory R/M HNSCC <6 months from therapy containing platinum PD-L1+ or -	Anti-PD-L1, anti CTL4	Durvalumab vs Durvalumab + Tremelimumab vs standard of care	PFS, OS	Recr
KESTREL	628	III	R/M HNSCC first line	Anti-PD-L1, Anti CTL4	Durvalumab vs Durvalumab + Tremelimumab vs Cetuximab/Platinum /5-FU	PFS, OS	Compl
NCT02554812	147	Ib/II	Advanced solid tumors (HNSCC cohort)	Anti-PD-L1, anti-41BB	Avelumab + PF-05082566	ORR, AEs	Recr
NCT02110082	104	I	Advanced/metastatic HNSCC or CRC	CD137 agonist	Urelumab + Cetuximab	ORR, AEs	Recr
NCT01836029	175	II	R/M first line	TLR8 agonist	Platinum/FU/Cetuximab ≠ VTX-2337	PFS	Compl
NCT01585428	73	II	HPV – associated cancers	Adoptive T cell	Fludarabine + Cyclophos phamide followed by TILs and Adesleukin	ORR	Recr

R&M disease

Trial	pts	phase	eligibility	target	TX	endpoint	Status
NCT02280811	61	I/II	Metastatic/refractory HPV16+concers	TCR gene therapy targeting E6	Fludarabine+Cyclophosphamide followed by E6-TCR and Adesleukin	ORR, duration of response	Recr
NCT02526316	10	I	Advanced HPV + Cancer s	Vaccine	P16_37-63 peptide plus Montanide ISA-51+ cisplatin-based chemotherapy	Immune response	Recr
NCT01462838	26	I/II	Advanced HPV – induced cancers	Vaccine	P16_37-63 peptide plus Montanide ISA-51	Immune response	Compl
NCT02291055	66	I/II	R/M Cervical or HNSCC, ≤3 lines of therapy	Vaccine, anti-PD-1	ADXS11-001 vs Durvalumab vs ADXS11-001 + durvalumab	PFS at 2 years, AEs	Active
NCT02426892	28	II	HPV-16+ advanced solid tumors includingOPC	Vaccine, anti-PD-1	Nivolumab+ISA-101	ORR at 11 weeks	Not yet recr
NCT02544880	54	I/II	Stage III/IV recurrent or 2 primary HNSCC	Vaccine	Tadalafil+ Anti-MUC1 vaccine + Anti Influenza Vaccine	AEs , tumor specific immune response	Not yet recr

LA disease

Trial	pts	phase	eligibility	target	TX	endpoint	status
NCT02002182	30	II	OPC HPV+	vaccine	ADXS11-001 +TORS	CTL response	Recr
NCT01860430	18	I	Stage III-IV HNSCC p16 – or interm p16+	Anti-CTL4	Centuximab + IMRT + ipilimumab	Safety	Recr
NCT02586207	39	Ib	Stage III-IV (non metastatic) HNSCC	Anti-PD-1	Pembrolizumab + weekly cisplatin + RT	AEs	Recr
NCT02764593	120	II-III	SCHNC HR and IR	Anti-PD-1	CDDP+RT +/- Nivolumab	OS	Recr
NCT02609386	200	II	Stage II-III-IV oral cavity	Cell derived	IRX2	EFS	Recr

Phase 1/2 Study of Lirilumab + Nivolumab (NCT01714739)

Dose Escalation (3 + 3 + 3 design)
Advanced Solid Tumors
Progression/intolerance on ≥ 1 standard treatment in the advanced setting
(except patients with Mel); primary CNS tumors excluded

Dose Expansion
SCCHN: Progression/recurrence ≤6 mo after platinum-based chemotherapy (adjuvant, primary, recurrent, or advanced setting)
CRC, HCC, MEL, NSCLC

Liri IV Q4W
Nivo IV Q2

- Liri 0.1 mg/kg + Nivo 3 mg/kg
- Liri 0.3 mg/kg + Nivo 3 mg/kg
- Liri 1 mg/kg + Nivo 3 mg/kg
- Liri 3 mg/kg + Nivo 3 mg/kg

Liri 3 mg/kg + Nivo 3 mg/kg

Primary endpoints
- Safety/tolerability
  - DLTs/MTD
- Preliminary antitumor activity (RECIST 1.1)
  - ORR/DOR

Key secondary/exploratory endpoints
- Biomarkers
  - Response by PD-L1 expression
  - Gene expression
- Overall survival

Liri, lirilumab; MEL, melanoma; Nivo,

Patient Demographics and Disease Characteristics in All Patients Treated With Lirilumab + Nivolumab

	All Patients (N = 159)
Median age (range), years	60 (21–85)
Male, n (%)	98 (61.6)
ECOG performance status, n (%) 0 1 2	 57 (35.8) 101 (63.5) 1 (0.6)
Tumor type, n (%) Melanoma SCCHN NSCLC* HCC CRC Other	 55 (34.6) 41 (25.8) 37 (23.3) 9 (5.7) 9 (5.7) 8 (5.0)

*Open histology; 1 patient with squamous NSCLC was enrolled.

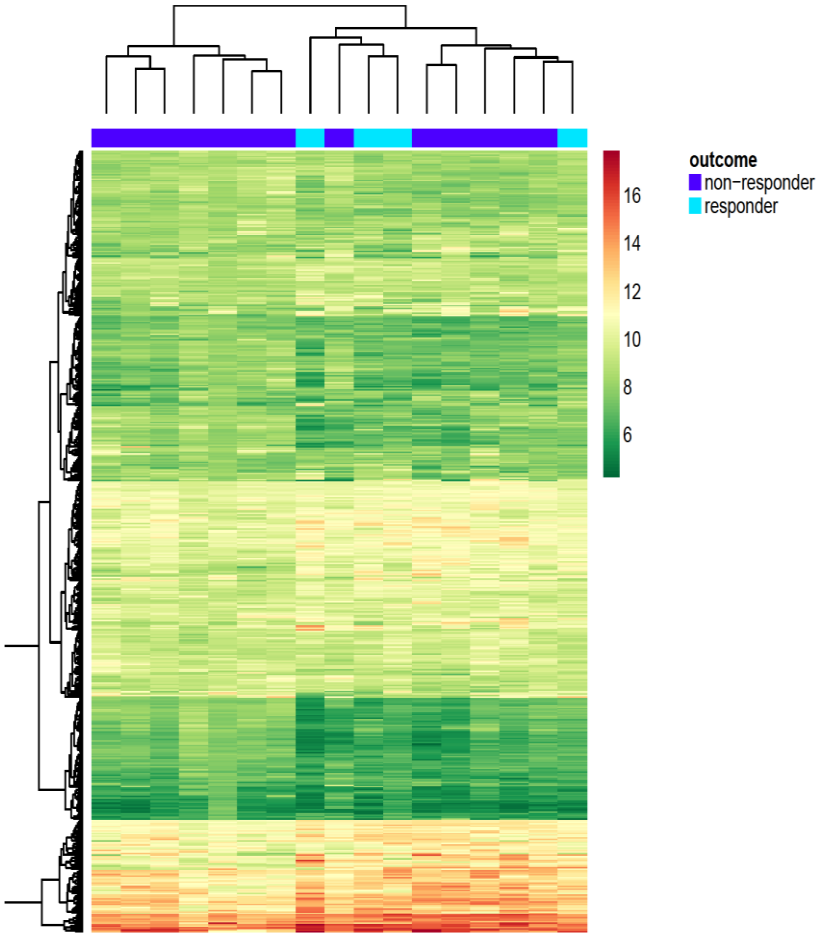
ORR and BOR With Lirilumab + Nivolumab (NCT01714739) or Nivolumab Monotherapy (CheckMate 141) in Evaluable Patients With SCCHN

	NCT01714739 (Phase 1/2) Lirilumab + Nivolumab	CheckMate 141 (Phase 3)[1,2] Nivolumab Monotherapy
ORR, n/N (%)	**7/29 (24.1)***	**32/240 (13.3)**
Complete response	3 (10.3)*	6 (2.5)
Partial response	4 (13.8)*	26 (10.8)
DCR, n/N (%)	15/29 (51.7)	NR
Overall survival in all patients, % (95% CI)		
At 6 months	90‡	55.6 (48.9, 61.8)
At 12 months	60§	36.0 (28.5, 43.4)

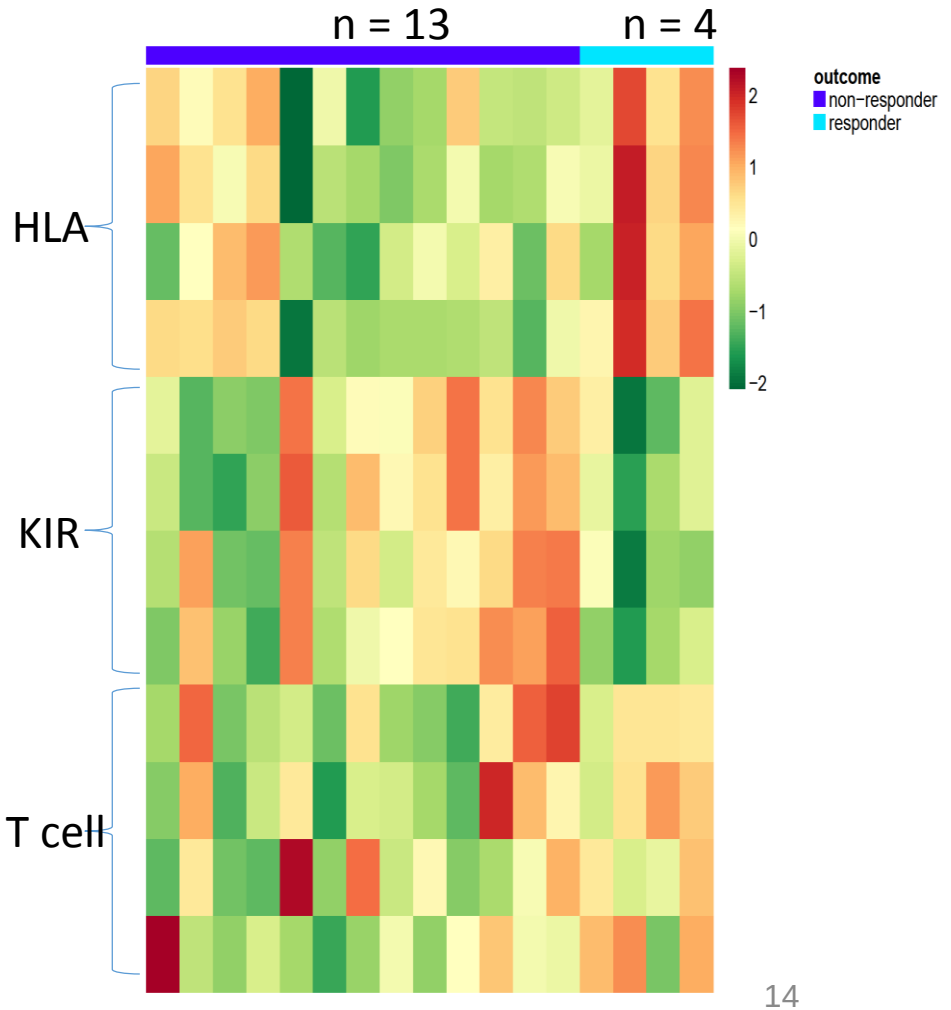
1.

Preliminary Heat Map Analysis in Patients With SCCHN (n = 17): Lirilumab + Nivolumab Responders, Non-Responders Have Distinct Expression Patterns

Unsupervised Cluster Analysis
549 Gene panel Edgeseq from FFPE



KIR, HLA, T-Cell Genes Differentially Expres



Latest from ASCO 2017

- ML and IFN-gamma signature predictor of response in HPV and EBV neg
- In IFN-gamma signature constitutive resistance through GM/CSF and Myeliod Derived Suppressor cell (MDSC) markers
- IDO1: resistance

Conclusions

- **Effective in H&N cancer**
- **Biomarkers?**
- **Best integration with curative modalities**