ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Head and Neck Cancers

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ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

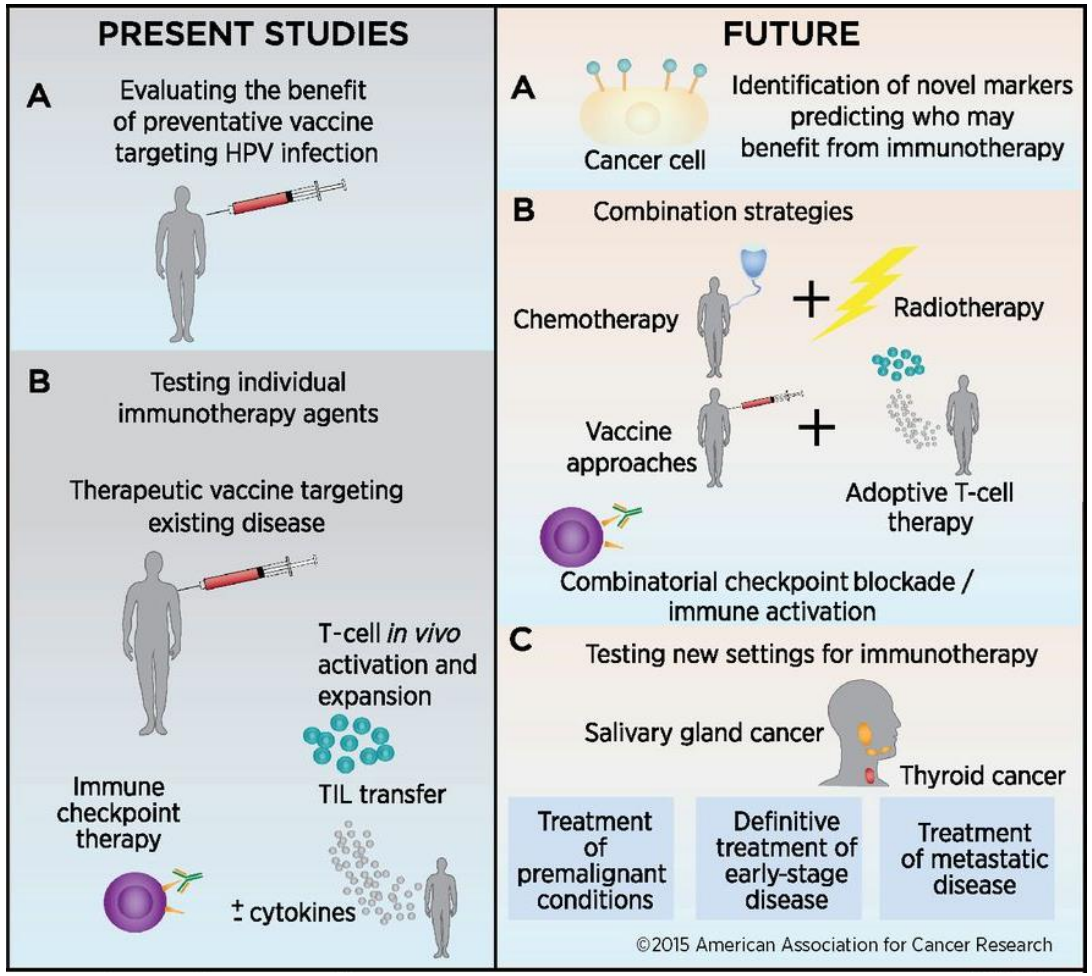
Disclosures

- Research support from Merck, Bristol Myers Squibb, AstraZeneca/Medimmune, Macrogenics, Gliknik,

Immunotherapy for the Treatment of Head and Neck Cancers

I-O Developments

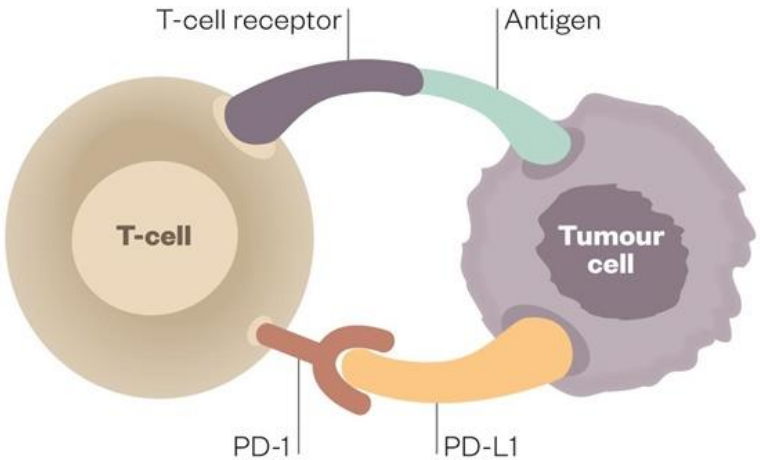
- Expression of immunologic markers to guide treatment
- Preventive vaccination against virally mediated cancers
- PD-1 checkpoint inhibitors for the treatment of metastatic disease



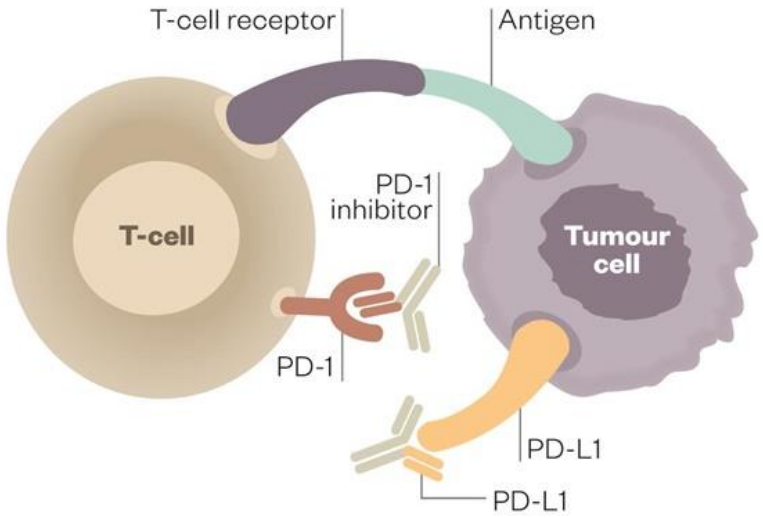
Schoenfeld JD, Cancer Immunol Res, 2015

Immunotherapy for the Treatment of Head and Neck Cancers

Immune Checkpoint Inhibitors (ICIs)



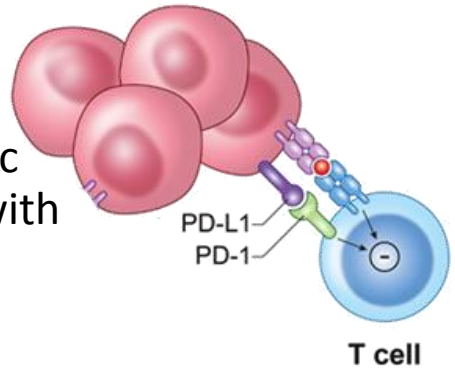
PD-1 acts as “off-switch” for T-Cells allowing cancer cells to evade immune attack



Antibodies against PD-1 and PD-L1 boost the immune response against cancer cells

Guha M, The Pharmaceutical Journal, 2014

FDA-approved Checkpoint Inhibitors for use in Head and Neck Cancers

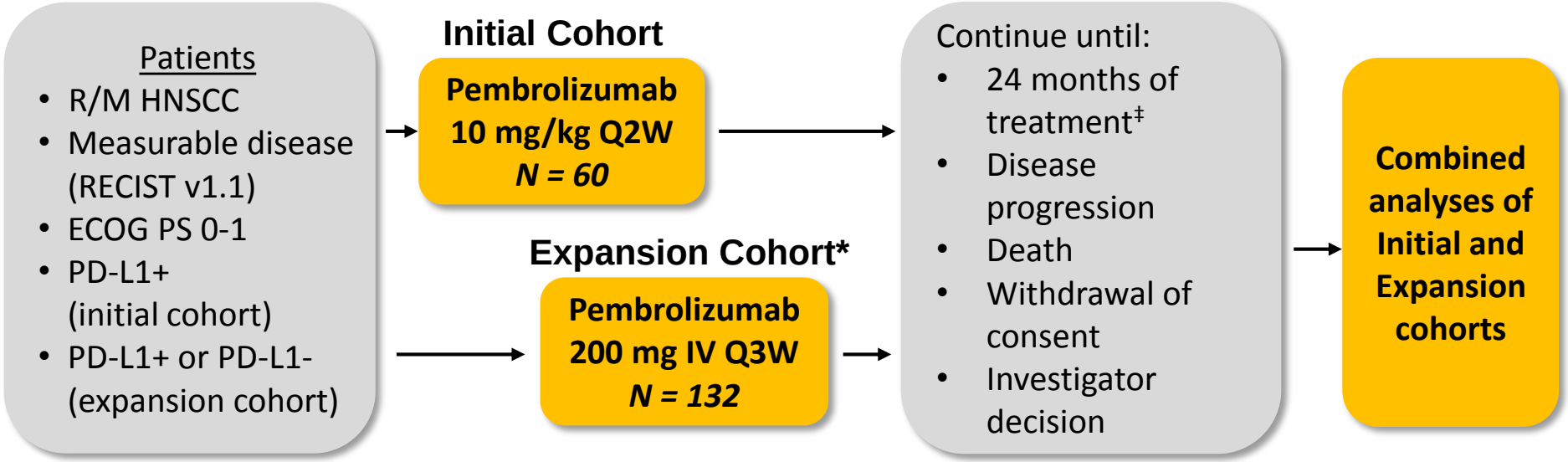


- Pembrolizumab (anti-PD-1)
  - KEYNOTE – 012/055: Patients with recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy
  - Accelerated Approval by FDA – August 5, 2016
- Nivolumab (anti-PD-1)
  - CheckMate – 141: Patients with R/M HNSCC with disease progression on or after a platinum-based therapy
  - Breakthrough Therapy Designation by FDA – April, 2016
  - Approval – November 10, 2016

In Development/Trials ongoing:

- Durvalumab, Atezolizumab, Avelumab (anti-PD-L1)
- R2810, PRD001, Tesaro (anti-PD-1)
- Ipilimumab, Tremelimumab (anti-CTLA-4)

KEYNOTE-012: Pembrolizumab in R/M HNSCC
Phase 1b trial, Cohorts† B, B2



Response assessment: Every 8 weeks until disease progression

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

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

†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§ Initial cohort only.
*Median duration of disease not reached.

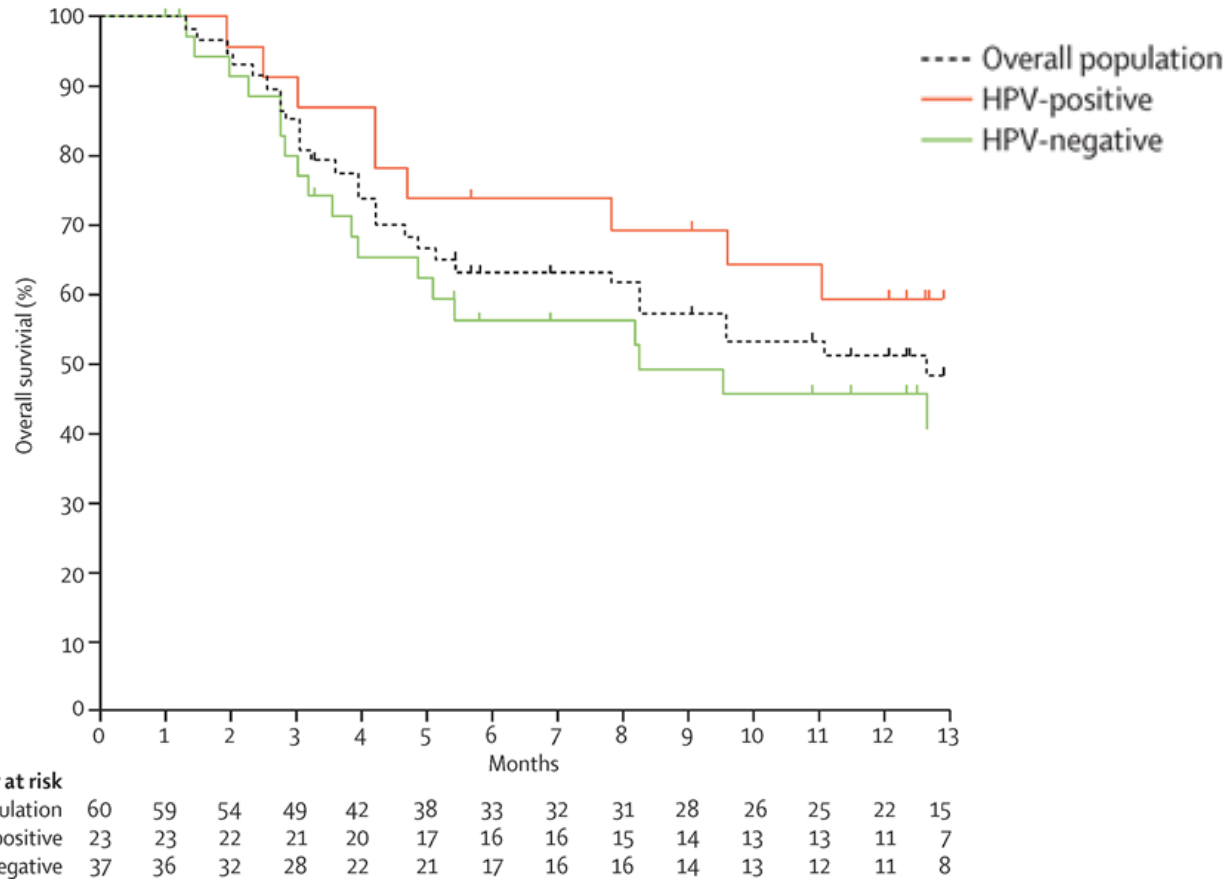
KEYNOTE-012: Pembrolizumab in HNSCC Cohort
Tumor Shrinkage

- *Demonstrated activity in both HPV-positive and HPV-negative tumors*

Seiwert TY Lancet Oncol 2016

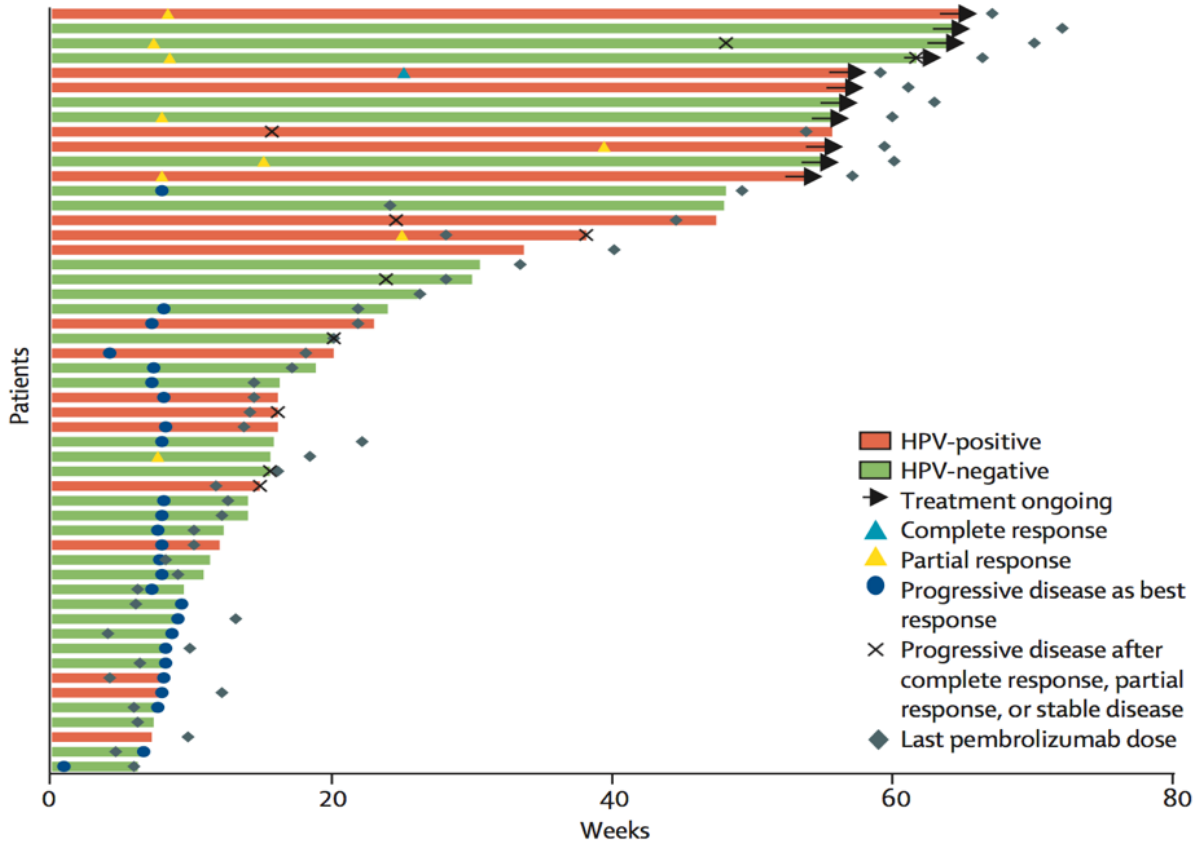
KEYNOTE-012: Pembrolizumab in HNSCC Cohort
Overall Survival

- *ORR = 18%*
- *mOS = 8.0 months*
- *mPFS = 2.2 months*



Seiwert TY, Lancet Oncol, 2016

KEYNOTE-012: Pembrolizumab in HNSCC Cohort
Durability of Response

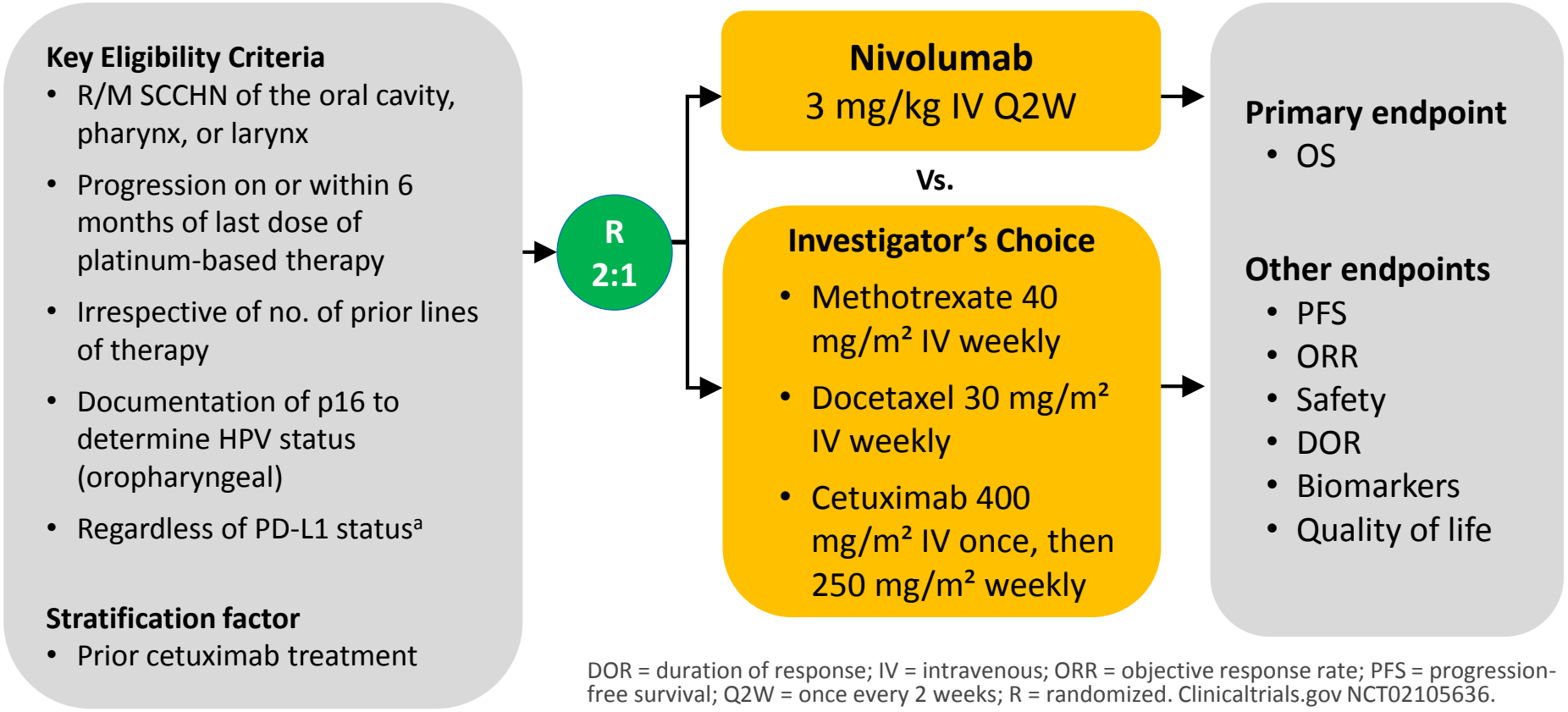


*Those patients that do respond show prolonged duration of response, most responses early

Seiwert TY, Lancet Oncol, 2016

CheckMate 141: Nivolumab vs. Investigator's Choice in R/M HNSCC after Platinum Therapy

Phase 3 Randomized, Safety and Efficacy trial



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

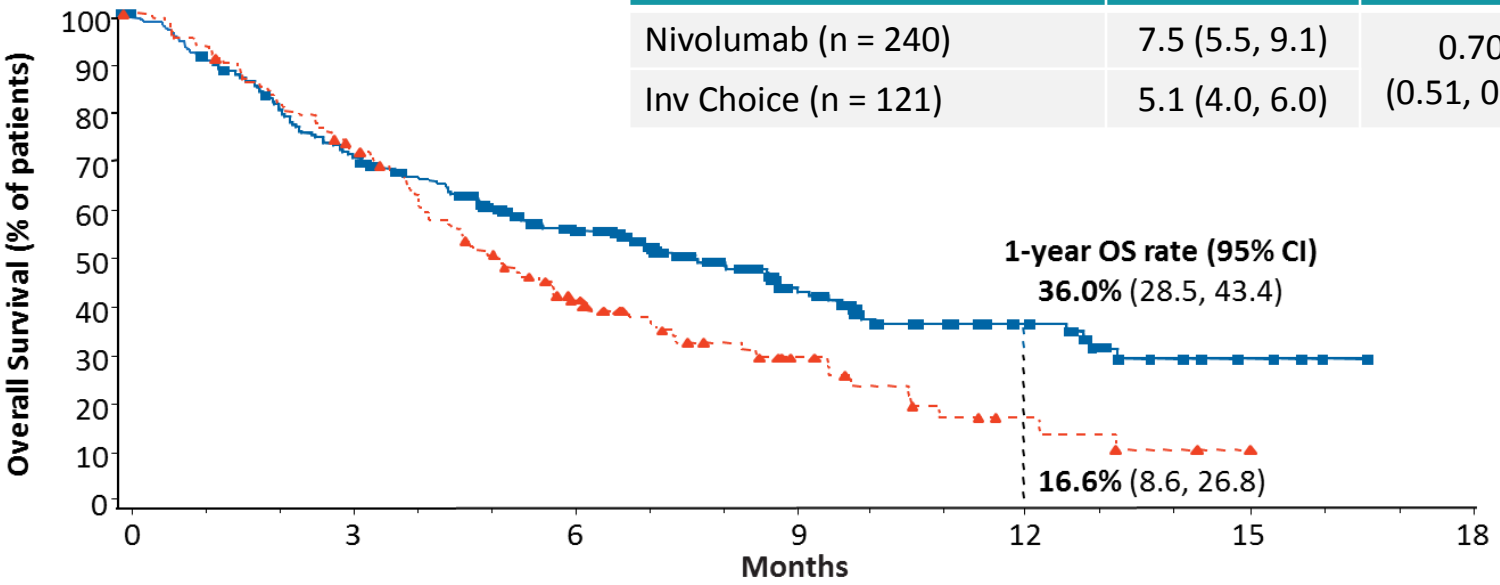
[a]Tissue required for testing

Ferris & Gillison, NEJM, 2016

CheckMate 141: Nivolumab vs. Investigator's Choice in R/M HNSCC after Platinum Therapy

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
Inv Choice (n = 121)	5.1 (4.0, 6.0)		



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

Ferris & Gillison, NEJM, 2016

*Response Rate only 13%, but major impact on **Survival***

CheckMate 141: Nivolumab vs. Investigator's Choice in R/M HNSCC after Platinum Therapy

Toxicity

Table 3. Treatment-Related Adverse Events Occurring in at Least 5% of the Patients in Either Group.

Event	Nivolumab (N=236)		Standard Therapy (N=111)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any event	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)
Rash	18 (7.6)	0	5 (4.5)	1 (0.9)
Decreased appetite	17 (7.2)	0	8 (7.2)	0
Pruritus	17 (7.2)	0	0	0
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)
Vomiting	8 (3.4)	0	8 (7.2)	0
Dry skin	7 (3.0)	0	10 (9.0)	0
Stomatitis	5 (2.1)	1 (0.4)	10 (9.0)	3 (2.7)
Weight loss	4 (1.7)	0	6 (5.4)	0
Mucosal inflammation	3 (1.3)	0	14 (12.6)	2 (1.8)
Peripheral neuropathy	1 (0.4)	0	7 (6.3)	0
Alopecia	0	0	14 (12.6)	3 (2.7)
Neutropenia	0	0	9 (8.1)	8 (7.2)

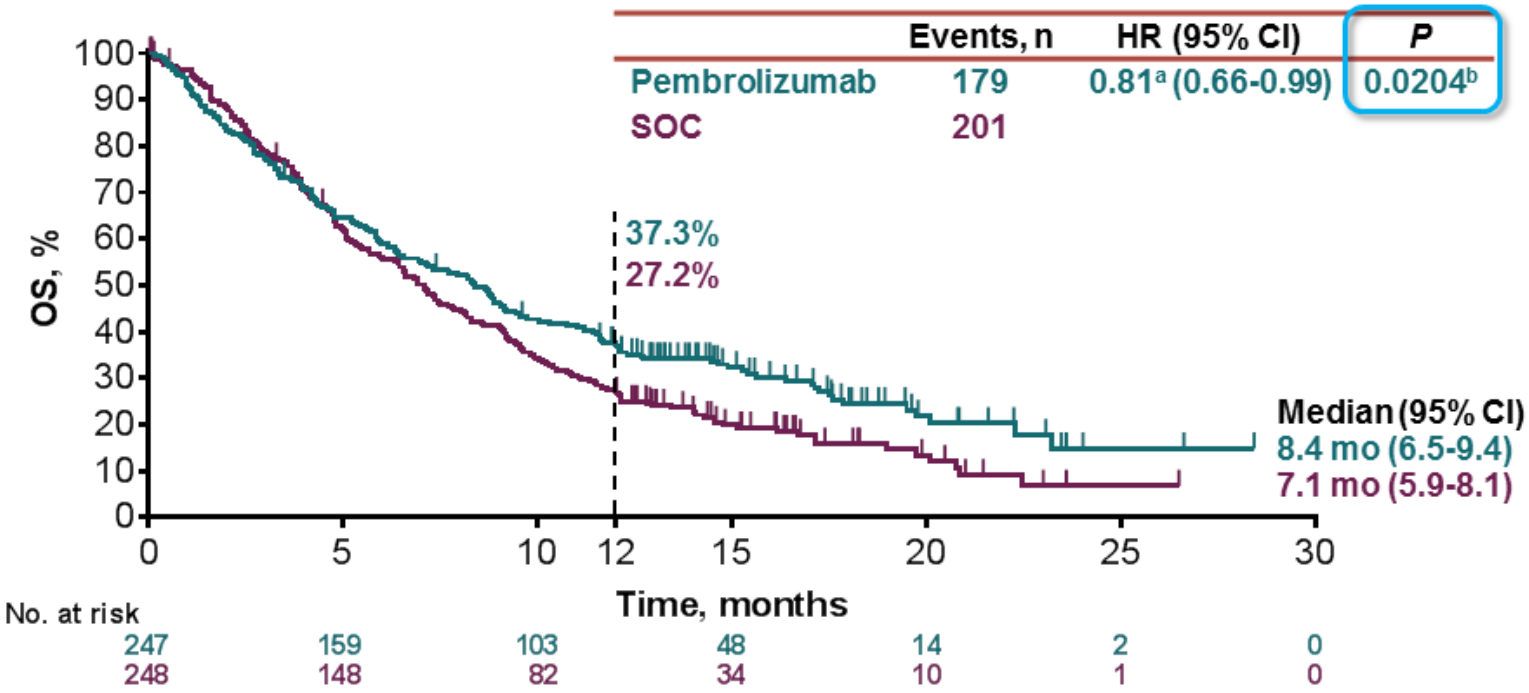
Ferris & Gillison, NEJM, 2016

Keynote 040: Pembrolizumab vs. Investigator's Choice in R/M HNSCC after Platinum Therapy

Overall Survival

E Cohen_ESMO 2017

Overall Survival in ITT Population

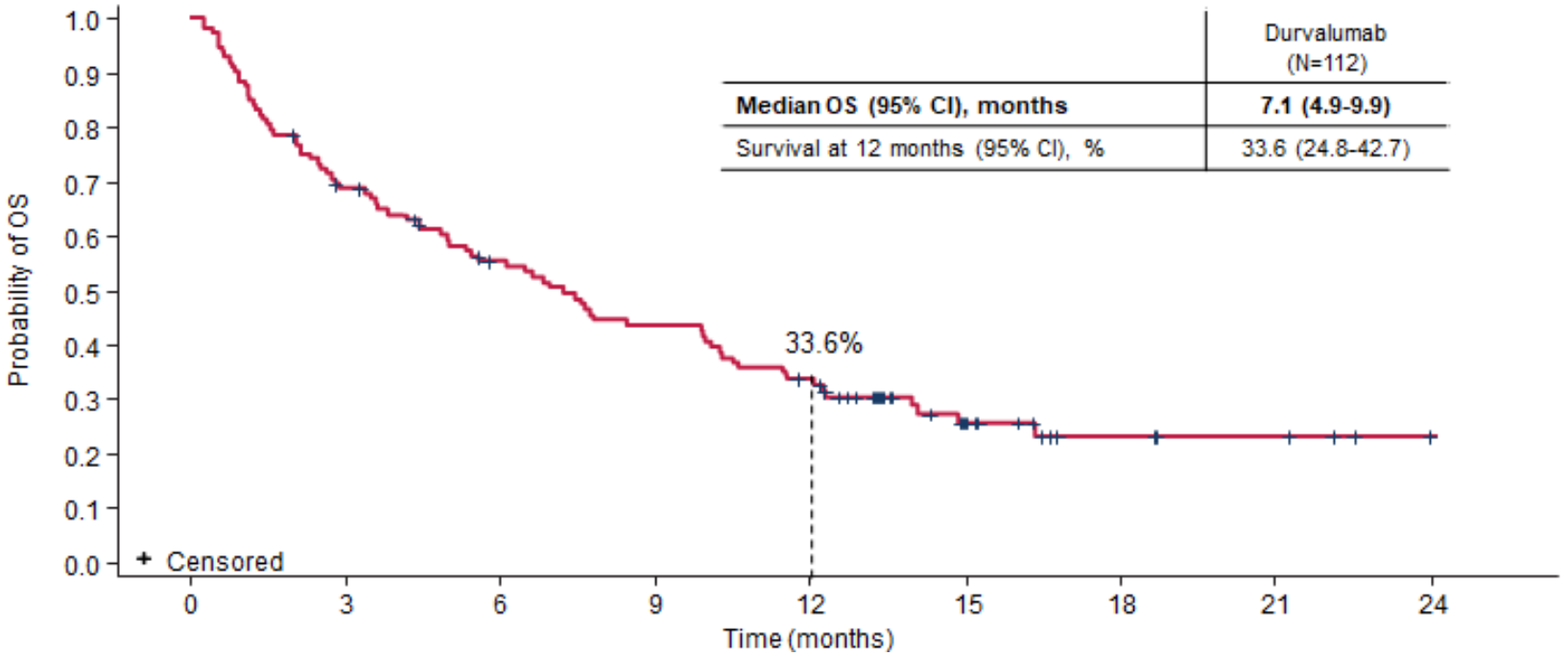


[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. Initially reported data: HR 0.82 (95% CI, 0.67-1.01), *P* = 0.0316. After the initial report, updated survival data were obtained for 4 patients. [b]One-sided *P* value based on the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

Cohen et al. ESMO annual congress 2017 LBA45

Hawk Trial: Durvalumab in PD-L1 high R/M HNSCC after failure of platinum based therapy

Overall Survival



	N=111
ORR, n (%)	18 (16.2 [95% CI, 9.90-24.41])
DCR at 24 weeks n (%)	26 (23.4)

Zandberg et al. ESMO Annual Congress 2017 #1042O

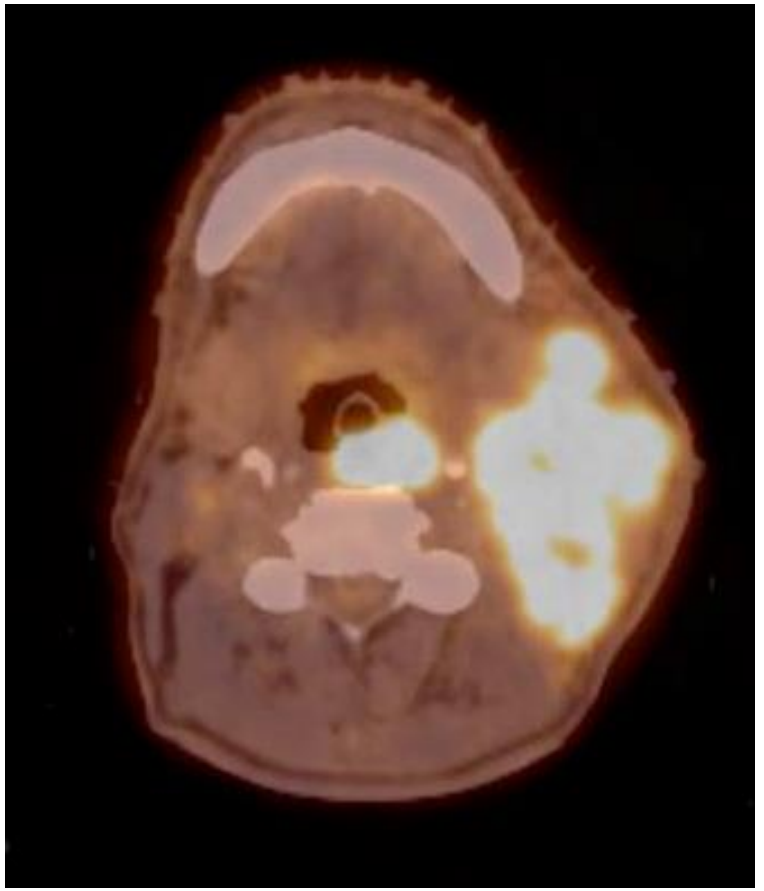
Patient Case Study 1

Patient Background Information:

- 78 yo M with a history of CAD, HTN, HLD
- Presents with painful L sided neck mass
- Lost 30 lbs due to anorexia

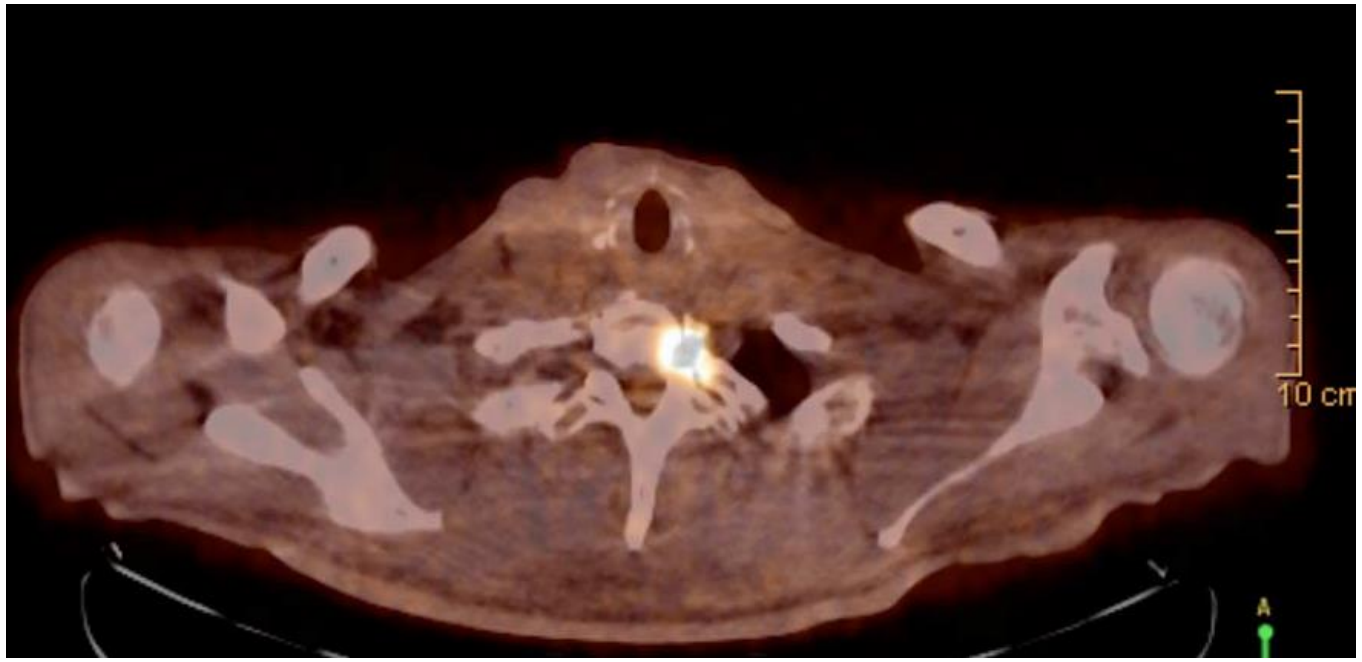
Patient Case Study 1
November 2014

- PET CT
  - Large L sided cervical mass
  - Periepiglottic tumor with no airway compromise
  - Multiple cervical osseous metastases
- Palliative hypofractionated XRT initiated



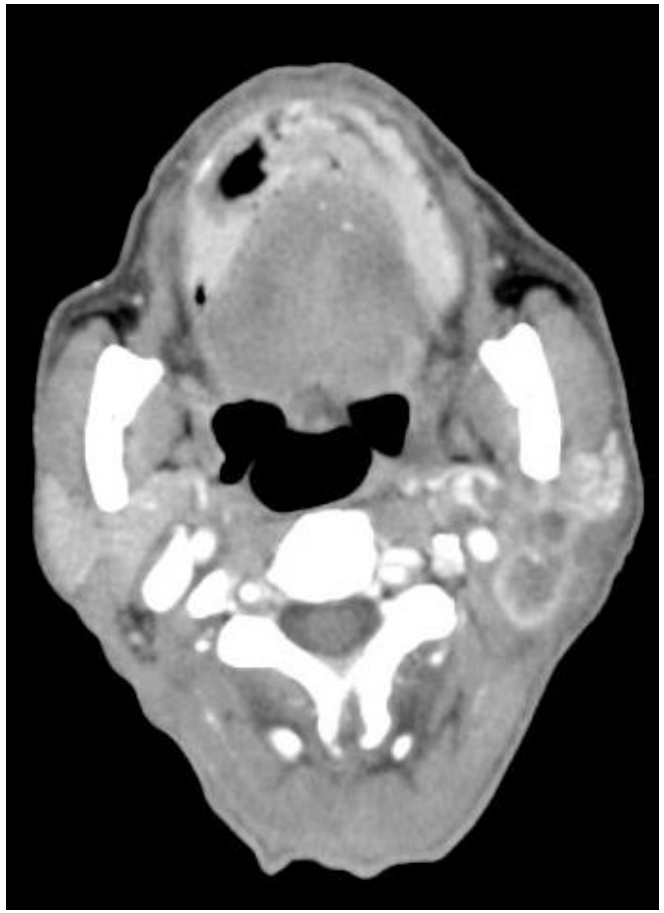
Patient Case Study 1
January 2015

- Cervical disease decreased – pain improved
  - Carboplatin/paclitaxel 1st line
- PET CT revealed new osseous and axillary mets
  - Started on cetuximab 2nd line



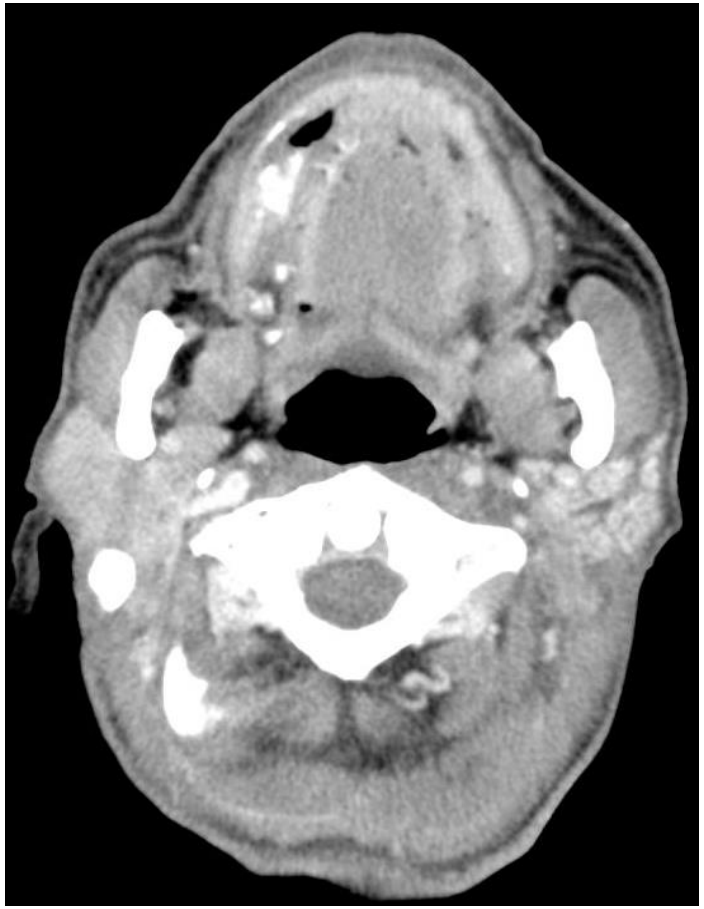
Patient Case Study 1
June 2015

- Progression in cervical nodes
  - Re-irradiation not an option
- Enrolled in KEYNOTE-055
  - Started on pembrolizumab



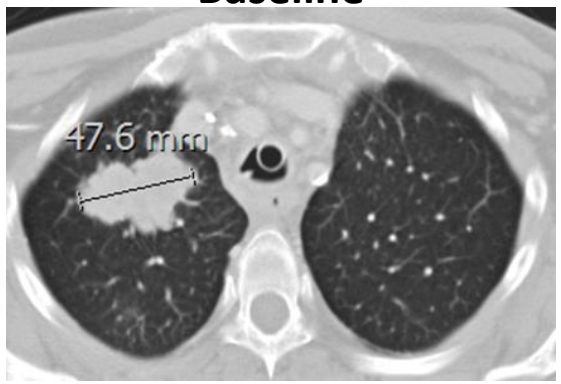
Patient Case Study 1
October 2015

- Patient experienced near CR
  - Response lasted 1 year
  - No side effects of note

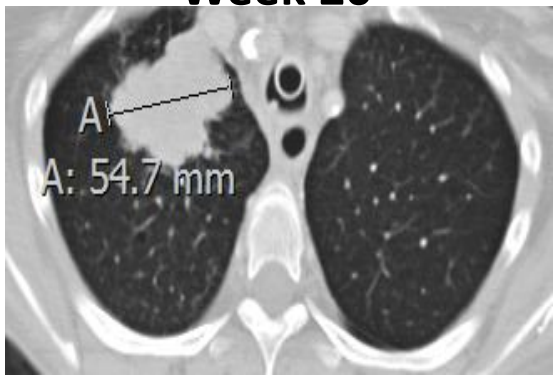


Patient Case Study 2
Durvalumab in HNSCC

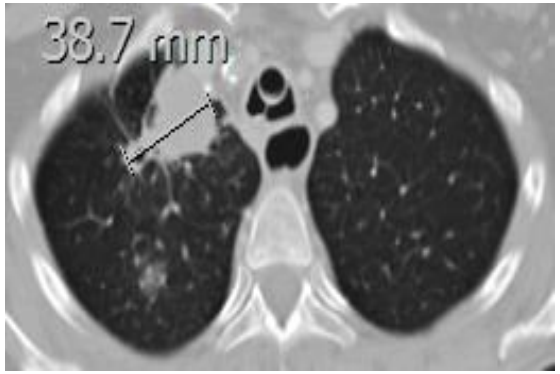
Baseline



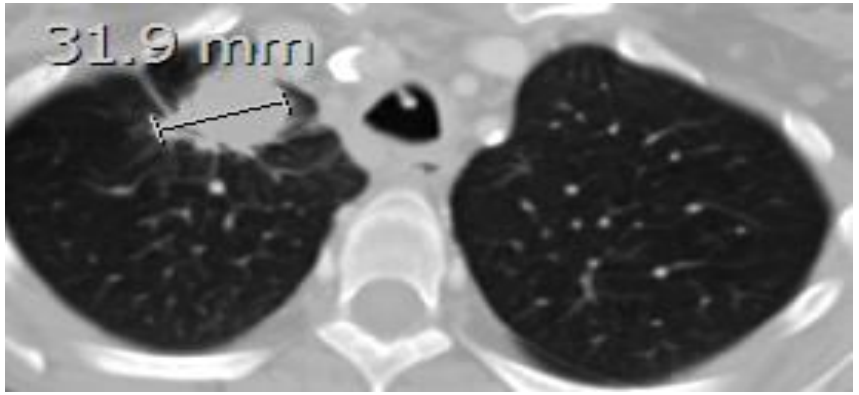
Week 20



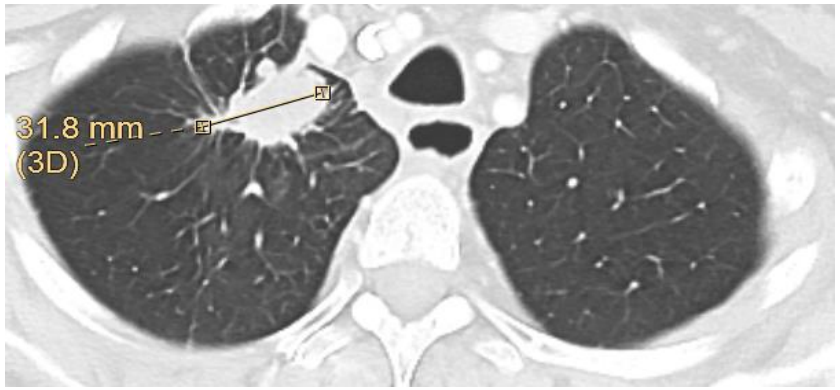
End of Treatment - Month 12



Post Treatment – Month 27



Post Treatment – Month 43



Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Next Steps: Evaluating Biomarkers in HNSCC

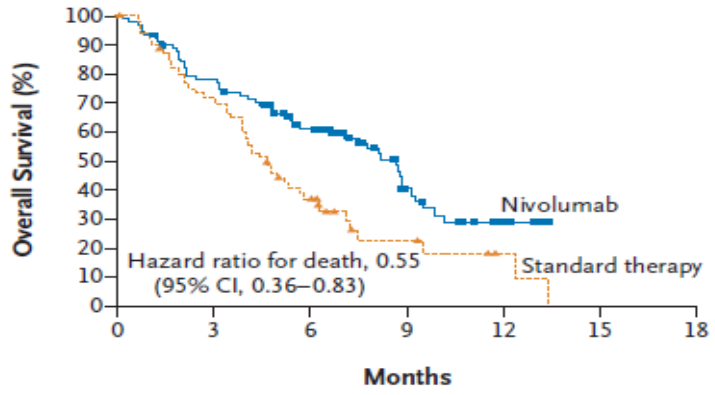
Association of Community Cancer Centers

Society for Immunotherapy of Cancer

Biomarkers: PD-L1 on Tumor Cells

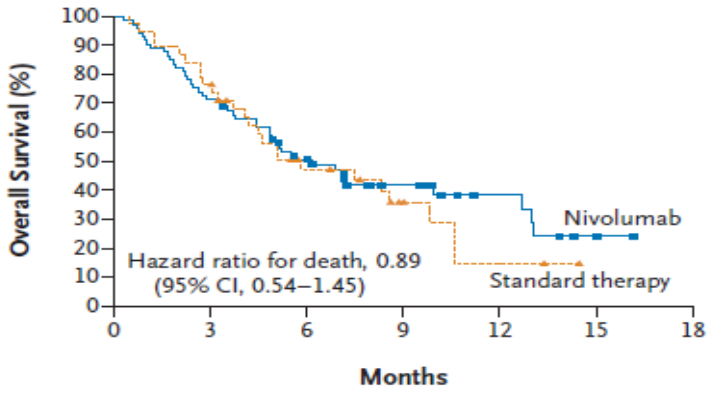
A Overall Survival among Patients with Baseline PD-L1 ≥1%

	No. of Patients	No. of Deaths	Median Overall Survival *mo (95% CI)*
Nivolumab	88	49	8.7 (5.7–9.1)
Standard Therapy	61	45	4.6 (3.8–5.8)



B Overall Survival among Patients with Baseline PD-L1 <1%

	No. of Patients	No. of Deaths	Median Overall Survival *mo (95% CI)*
Nivolumab	73	45	5.7 (4.4–12.7)
Standard Therapy	38	25	5.8 (4.0–9.8)

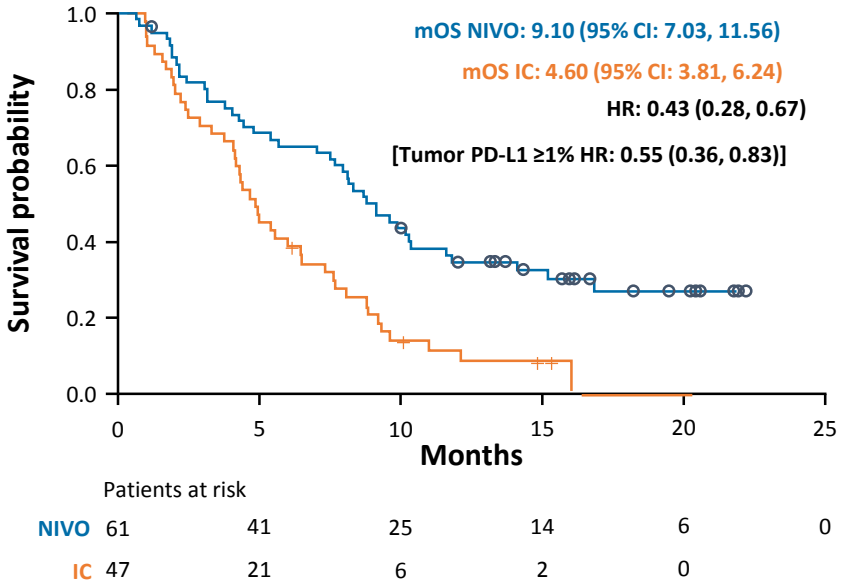


Variable	Nivolumab (N=240)		Standard Therapy (N=121)		Hazard Ratio for Death (95% CI)
	Patients	Median Survival	Patients	Median Survival	
	no. (%)	*mo*	*no. (%)*	*mo*	
All patients	240 (100.0)	7.5	121 (100.0)	5.1	0.69 (0.53–0.91)
PD-L1 expression level					
≥1%	88 (36.7)	8.7	61 (50.4)	4.6	0.55 (0.36–0.83)
≥5%	54 (22.5)	8.8	43 (35.5)	4.6	0.50 (0.30–0.83)
≥10%	43 (17.9)	8.7	34 (28.1)	5.2	0.56 (0.31–1.01)

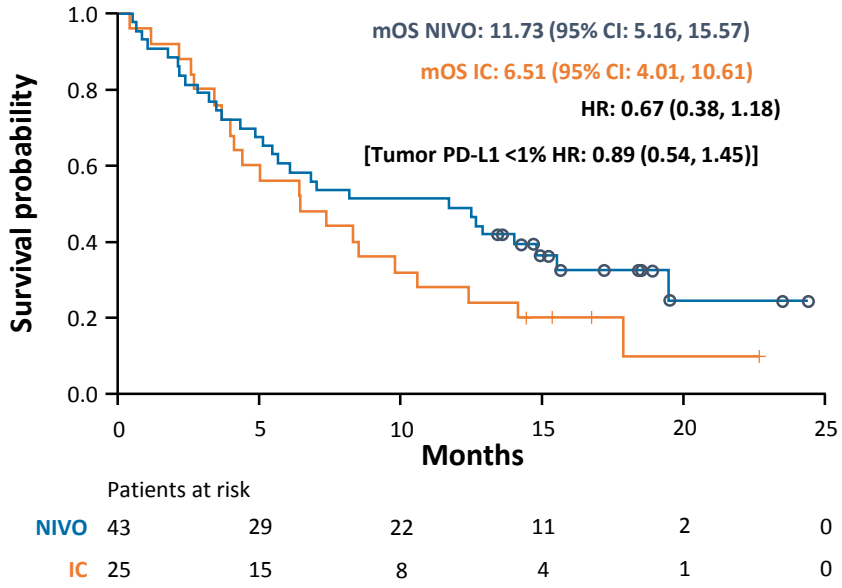
Ferris et al. N Engl J Med. 2016 Nov 10;375(19):1856-1867

Biomarkers: PD-L1 on Tumor and Immune Cells

Tumor PD-L1 ≥1% & PD-L1^{+} TAIC Abundance

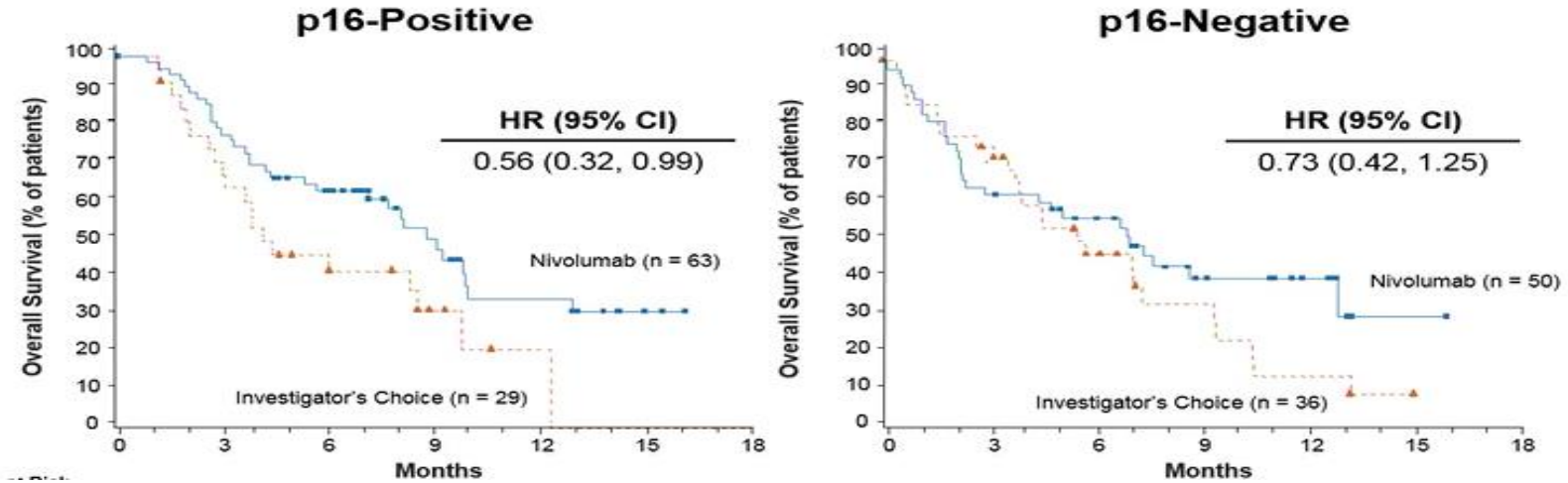


Tumor PD-L1 <1% & PD-L1^{+} TAIC Abundance



Ferris et al. AACR Annual Meeting 2017 #CT021

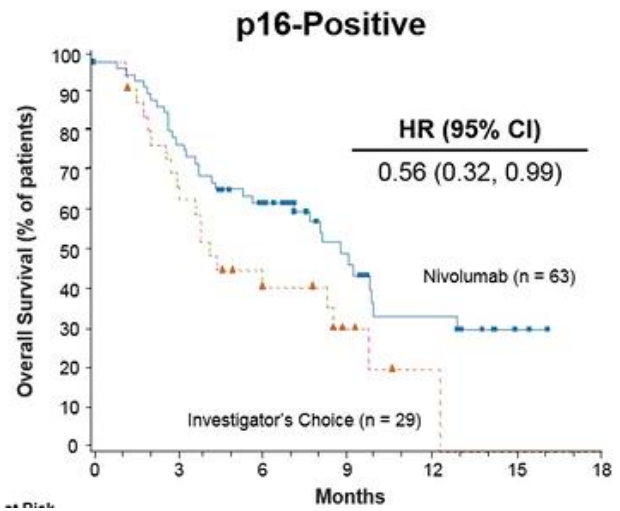
HPV positive vs. Negative

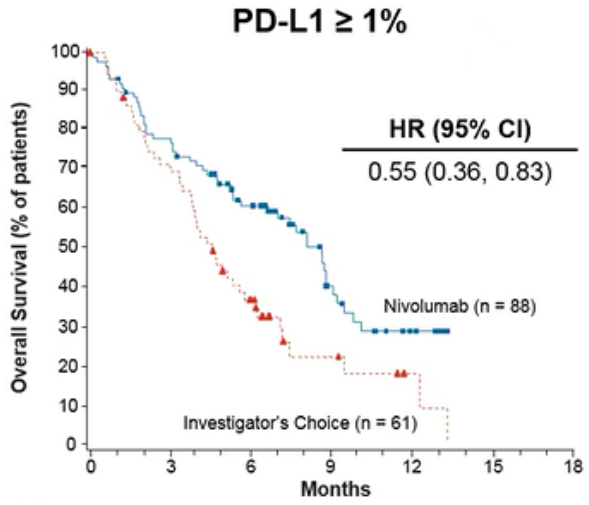


Study	HPV (+)	HPV (-)
Durvalumab (HAWK)	29% (10/34)	10.8% (7/65)
Pembrolizumab (012)	25% (4/16)	14% (4/29)
Pembrolizumab (055)	16% (6/37)	15% (20/131)
Durvalumab (1108)	4% (1/25)	16% (4/25)

Ferris et al. J Clin Oncol 34, 2016 (suppl; abstr 6009)

HPV and PD-L1 Status



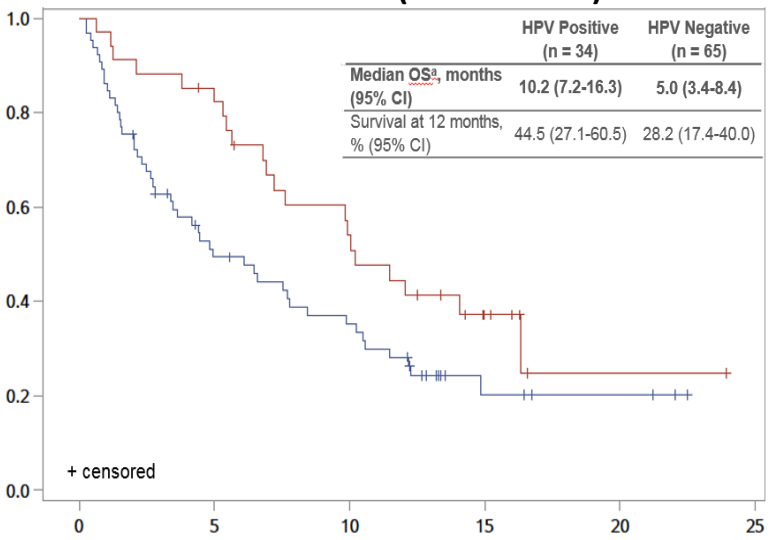


	Nivolumab		Investigator's Choice		
	n	Median OS, mo	n	Median OS, mo	Hazard ratio (95% CI)
PD-L1 ≥ 1%/p16-positive	23	8.8	14	3.9	0.50 (0.21, 1.19)
PD-L1 ≥ 1%/p16-negative	17	8.8	16	5.6	0.44 (0.18, 1.10)
PD-L1 < 1%/p16-positive	24	10.0	10	6.4	0.55 (0.22, 1.39)
PD-L1 < 1%/p16-negative	14	7.1	12	7.4	0.82 (0.31, 2.19)

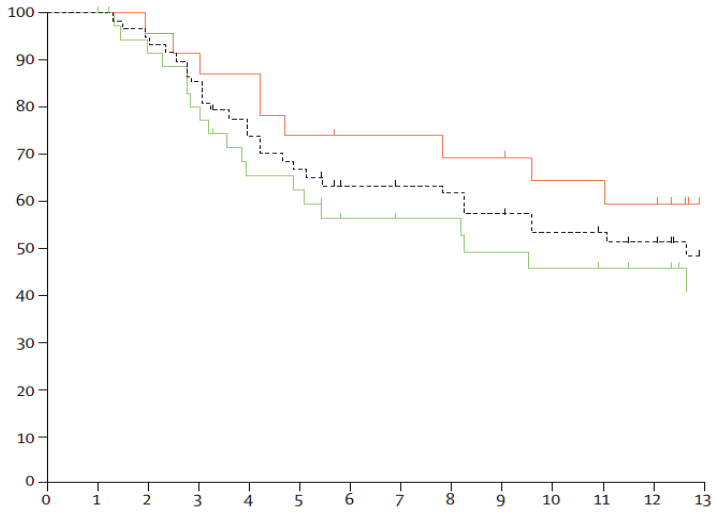
Ferris et al. J Clin Oncol 34, 2016 (suppl; abstr 6009)

HPV Positive vs. Negative

Durvalumab (PD-L1 >25%)



Pembrolizumab (PD-L1 >1%)



Study	PD-L1 Status	HPV (+)	HPV (-)
Durvalumab (HAWK)	**PD-L1 > 25%**	**29% (10/34)**	**10.8% (7/65)**
Pembrolizumab (012)	**PD-L1 > 1%**	**25% (4/16)**	**14% (4/29)**
Pembrolizumab (055)	Mixed	16% (6/37)	15% (20/131)
Durvalumab (1108)	Mixed	4% (1/25)	16% (4/25)

Next Steps: Evaluating Biomarkers in HNSCC

Current FDA approval of Pembrolizumab and Nivolumab

is NOT contingent upon PD-L1 IHC or HPV status

Next Steps: Ongoing Trials

- Checkpoint inhibitors in first line treatment of R/M HNSCC
- Checkpoint inhibitors as part of definitive therapy in the locally advanced setting
- Combination Immunotherapy trials

Conclusions

1. Chemotherapy offers short survival with many side effects
2. PD-1 antibodies nivolumab and pembrolizumab are approved in *platinum-refractory* recurrent / metastatic HNSCC.
3. Most patients have fewer side effects on PD-1 Abs than on chemotherapy
4. Clinical trials are underway to improve immunotherapy response rates
5. SITC Clinical Immunotherapy Guidelines are currently in development for HNSCC