ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Head and Neck Cancers

Saad A. Khan, MD

UT Southwestern Medical Center

American Academy of Emergency Medicine

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Disclosures

- Guardant Health, Foundation Medicine, Takeda Oncology, Oak Ridge Associated University, Novartis, Merck, Threshold Pharm, Gilead Sciences, Bayer/Onyx, Celldex, Abbvie

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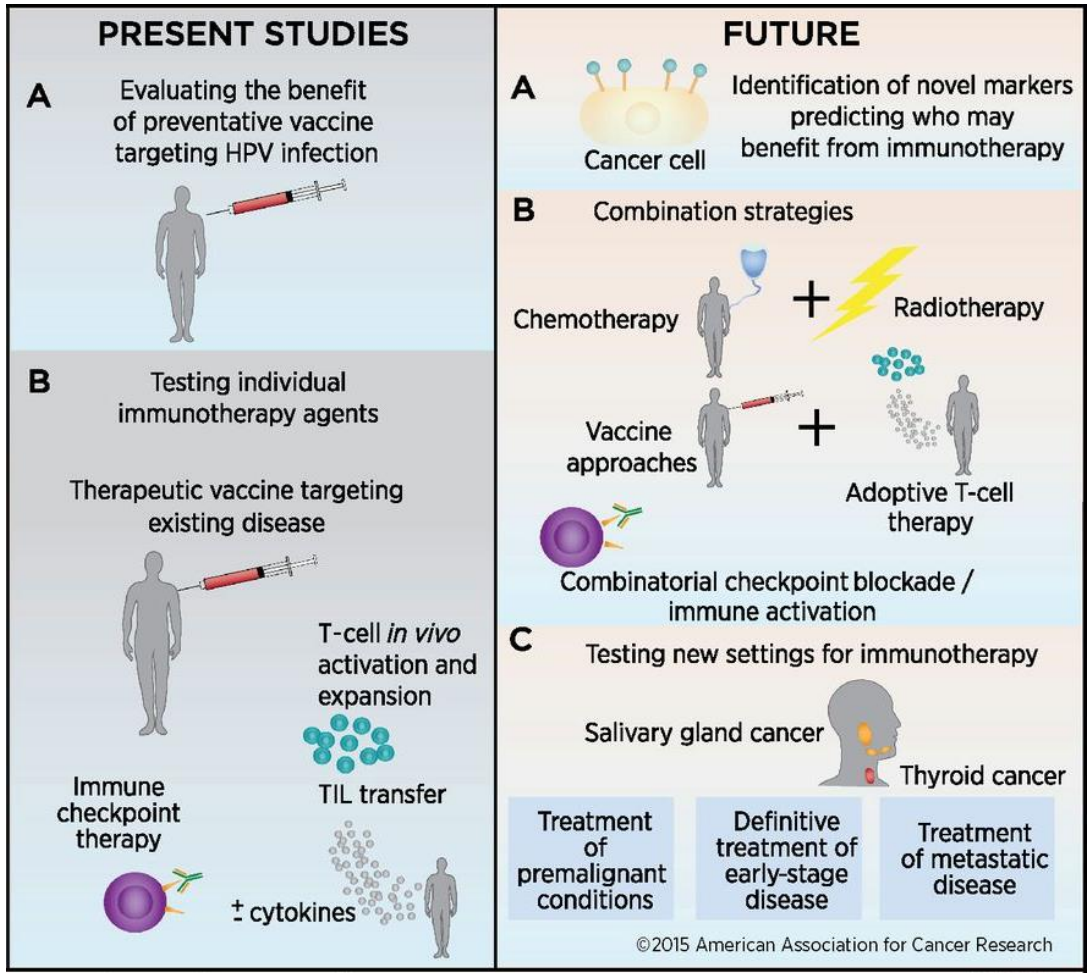
Immunotherapy for the Treatment of Head and Neck Cancers

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

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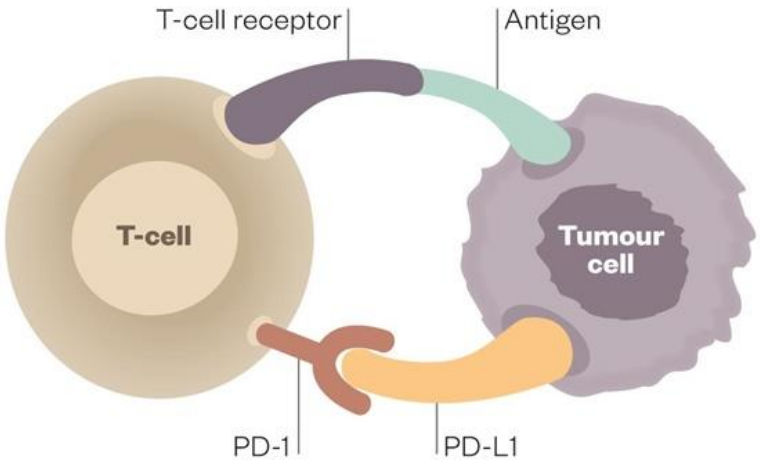
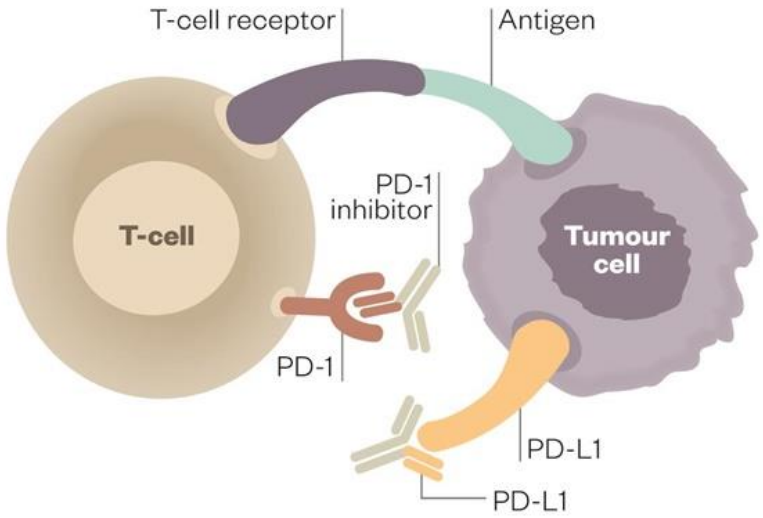
Immunotherapy for the Treatment of Head and Neck Cancers

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

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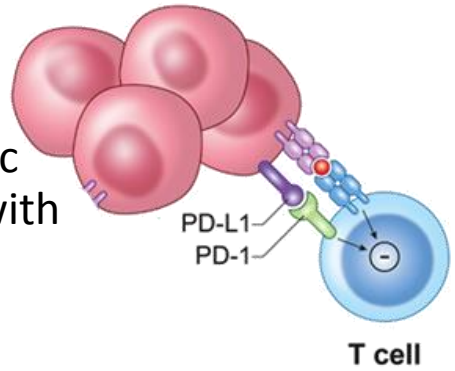
FDA-approved Checkpoint Inhibitors for use in Head and Neck Cancers



- 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:

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

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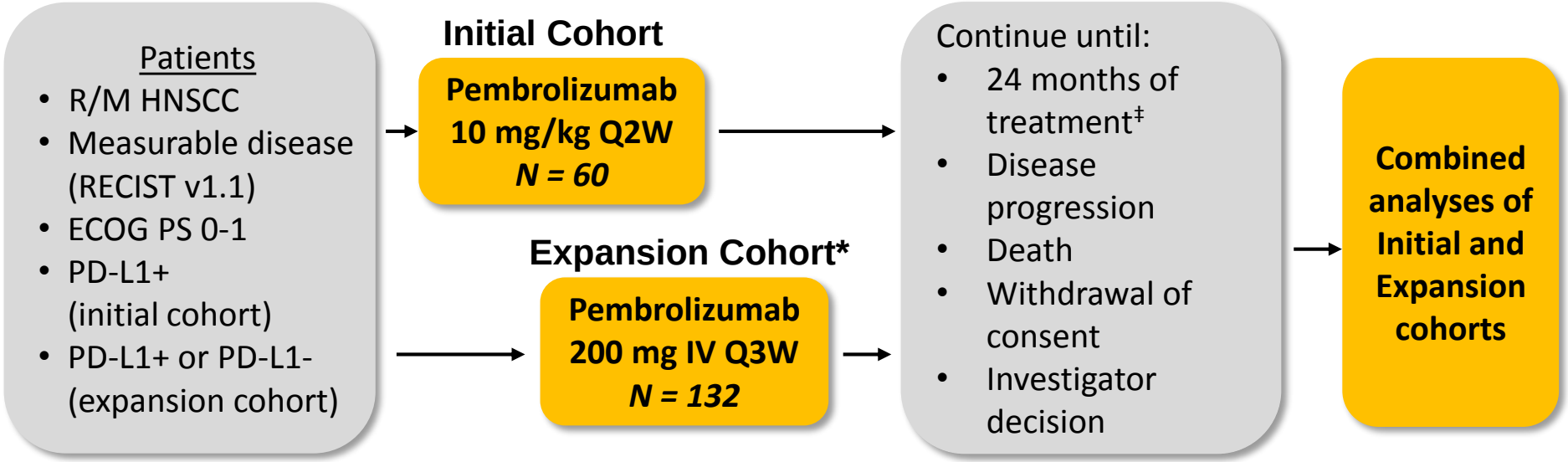
KEYNOTE-012: Pembrolizumab in R/M HNSCC
Phase 1b trial, Cohorts† B, B2



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.

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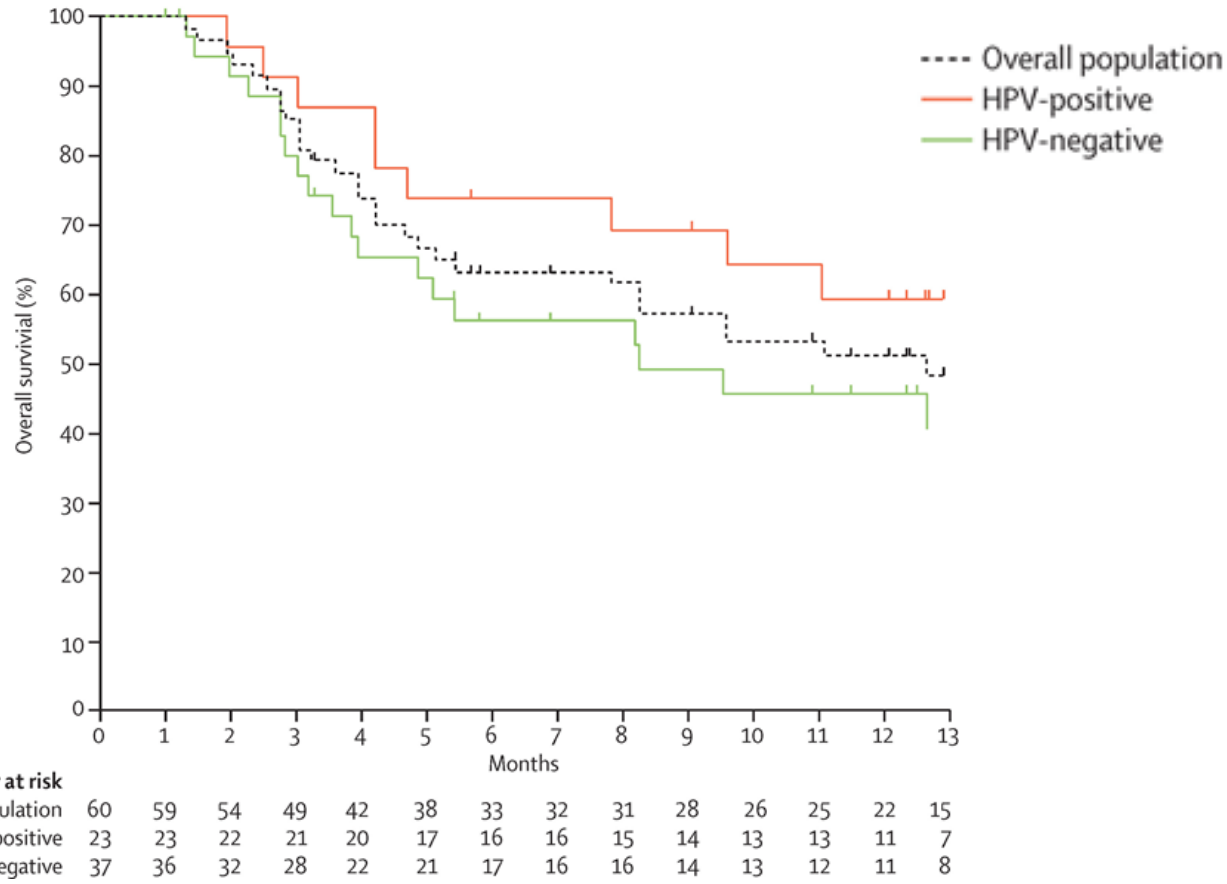
KEYNOTE-012: Pembrolizumab in HNSCC Cohort
Overall Survival

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



Seiwert TY, Lancet Oncol, 2016

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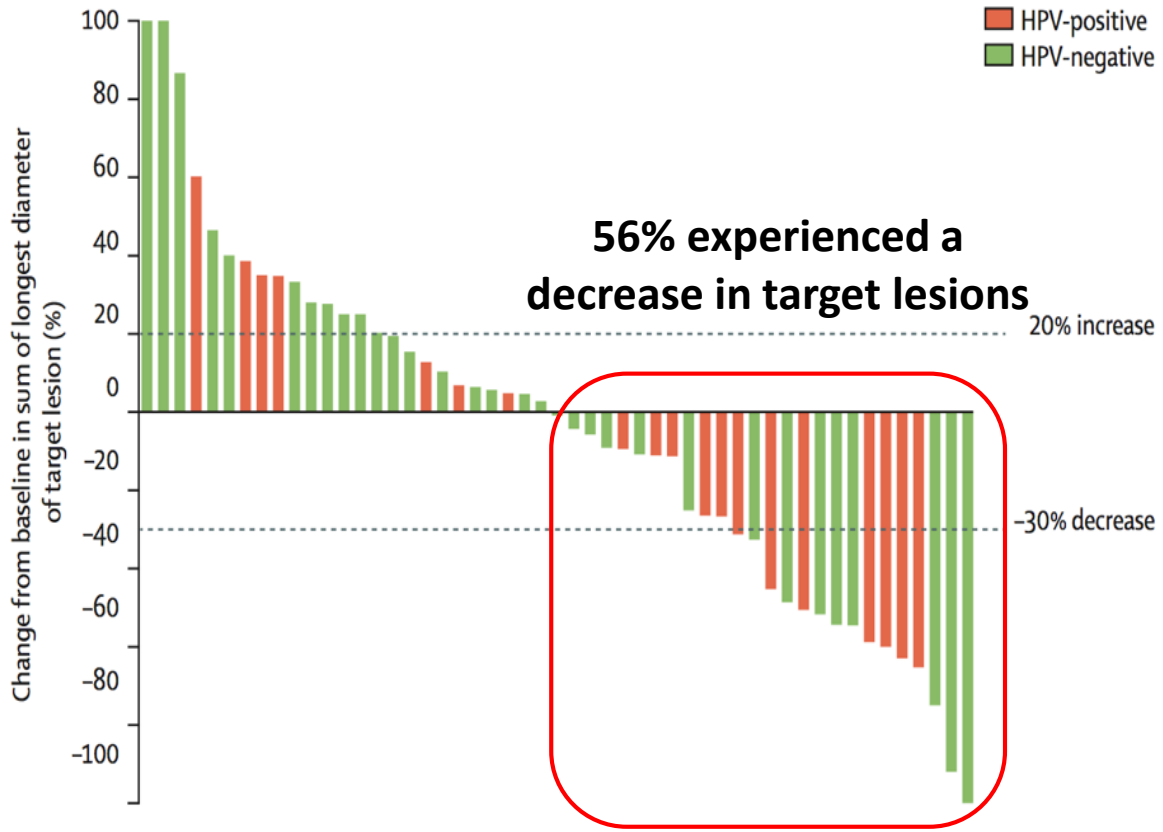
KEYNOTE-012: Pembrolizumab in HNSCC Cohort
Tumor Shrinkage

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



Seiwert TY Lancet Oncol 2016

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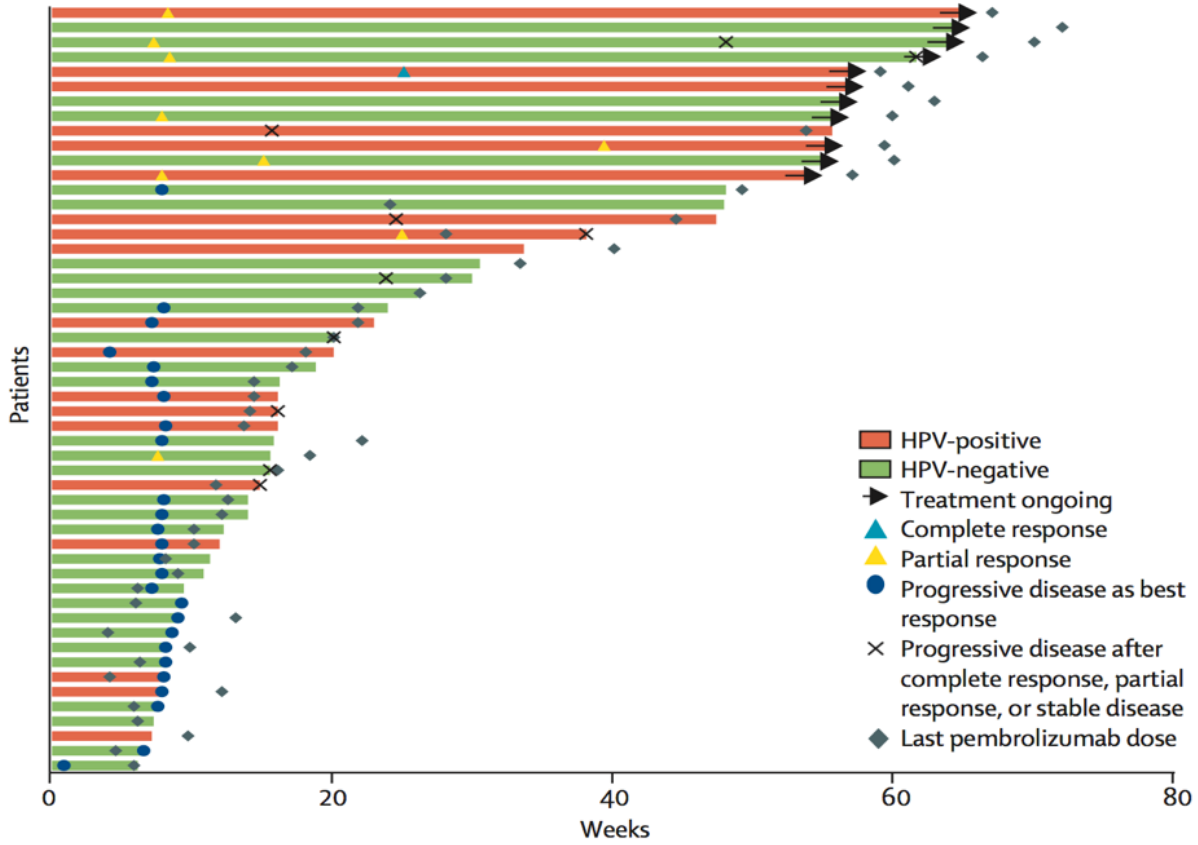
KEYNOTE-012: Pembrolizumab in HNSCC Cohort
Durability of Response



*Those patients that do response show prolonged duration of response, most seen early on

Seiwert TY, Lancet Oncol, 2016

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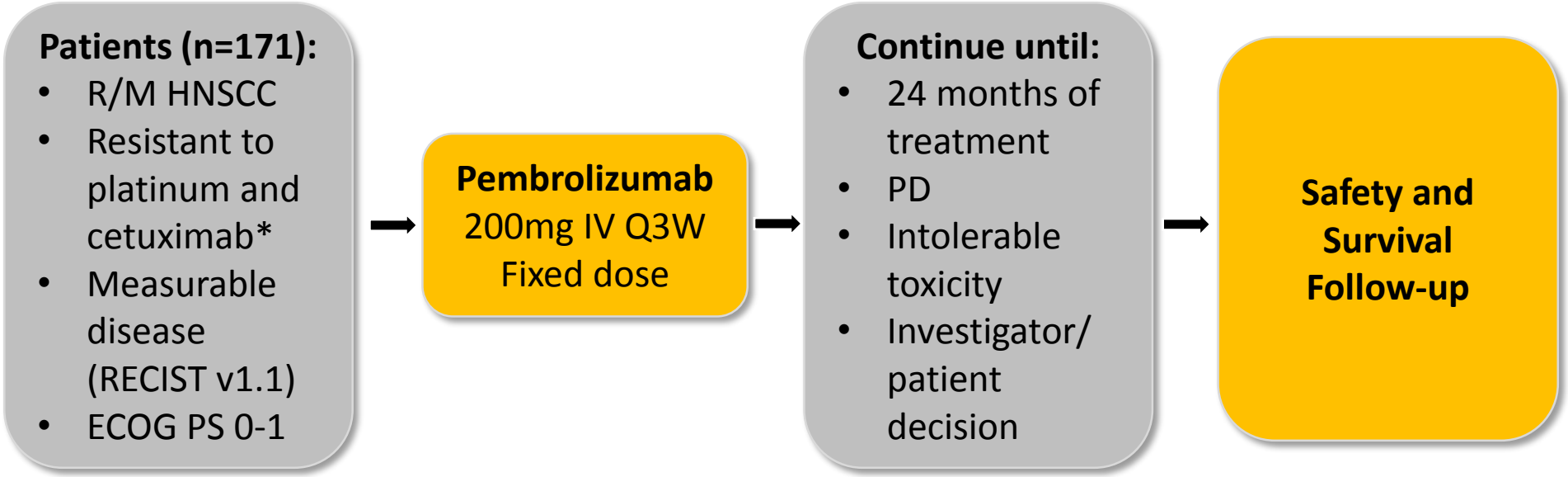
KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum and Cetuximab
Phase 2 Trial, Single Arm



Bauml, JCO 2017

Response assessment: Imaging every 6 to 9 weeks (central radiology review)

Primary end points: ORR (RECIST v1.1) by Response Evaluation Criteria in Solid Tumors and safety

Secondary end points: ORR (RECIST v1.1) in all dosed patients, ORR for HPV+, PD-L1+, DOR, PFS, OS

*75% of patients had ≥2 prior lines of therapy for metastatic disease

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

ORR = 16%
mDOR = 8 months
mOS = 8 months

Outcome	All Patients N=171	HPV Status Positive n=37	HPV Status Negative n=131	PD-L1 Status ≥1% n=140	PD-L1 Status <1% n=26	PD-L1 Status ≥50% n=48
ORR, %	16	16	15	18	12	27
mPFS, mo	2.1					
6-mo PFS,%	23	25	21	24	20	31
6-mo OS, %	59	72	55	59	56	60

ORR: overall response; mDOR: median duration of response; mOS: median overall survival; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease

1% combined positive score (CPS) cutoff:

- Most patients (82%) were PD-L1 positive as determined by combined positive score (CPS) ≥1, and 28% of PD-L1-positive patients had a CPS ≥50%.
- Response rates were similar regardless of PD-1 expression.
- The 1 complete response recorded in the study occurred in a patient with a CPS of ≥50%.

Bauml J, et al, J Clin Oncol. 2017

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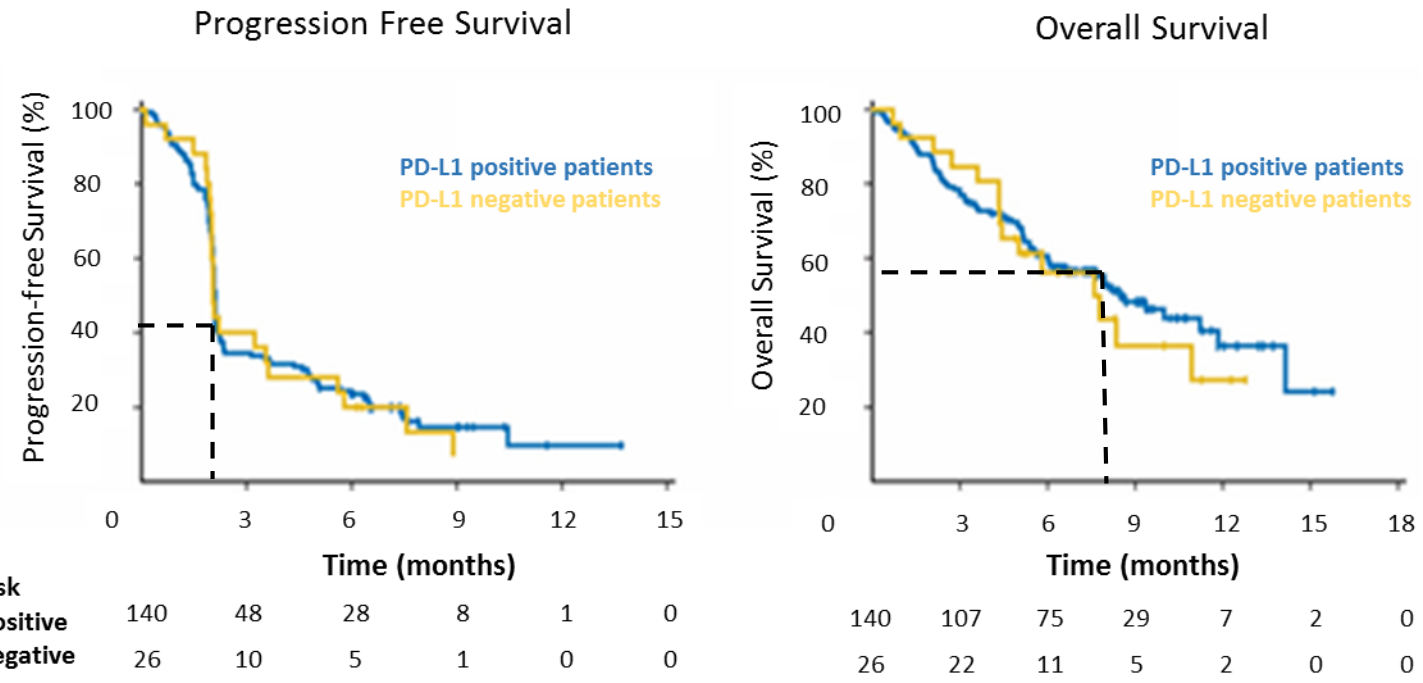
KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum and Cetuximab
Phase 2 Trial, Single Arm

*Neither the effects of tumor PD-L1 expression nor HPV status are sufficiently robust in guiding the use of ICI therapy at this time.



Bauml J, et al, J Clin Oncol. 2017

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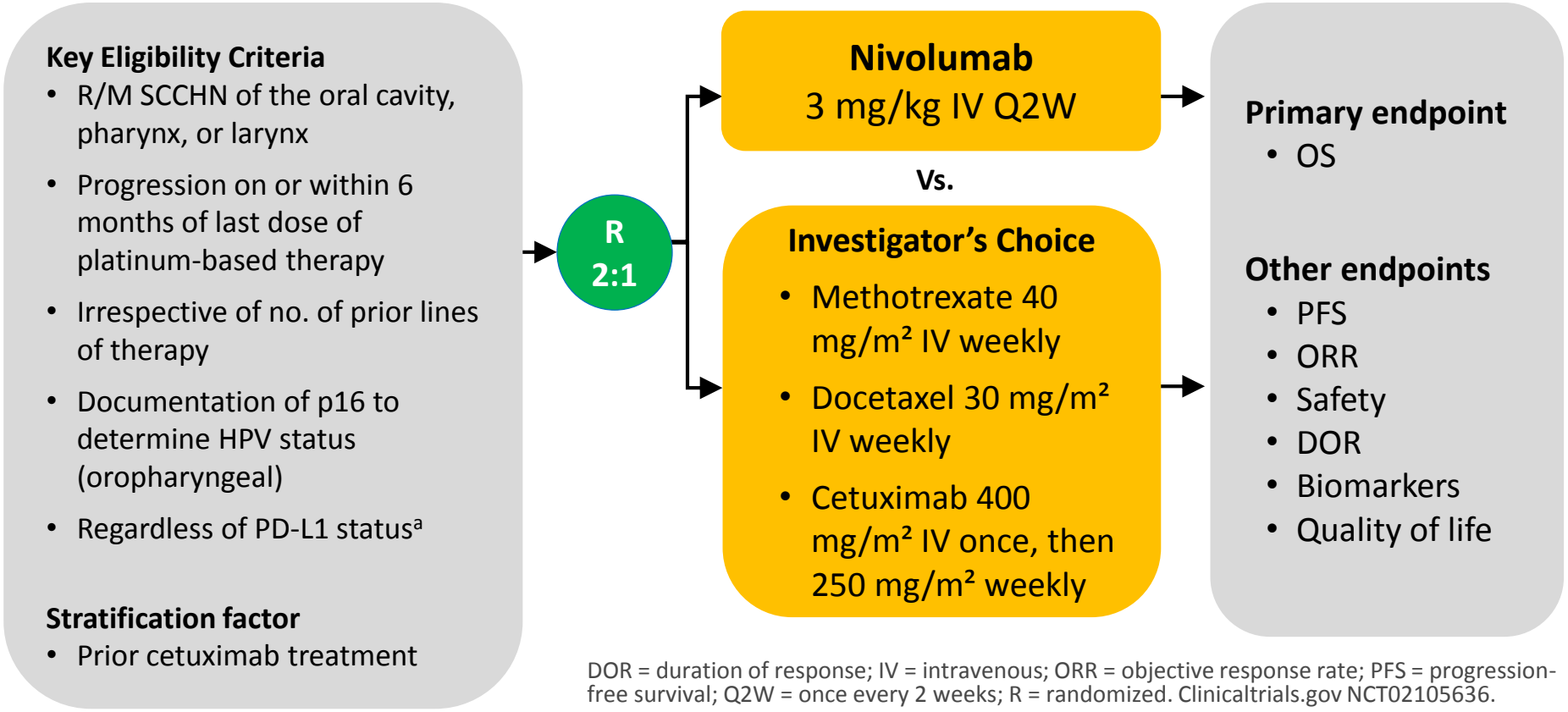
CheckMate 141: Nivolumab vs. Investigator's Choice in R/M HNSCC after Platinum Therapy

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

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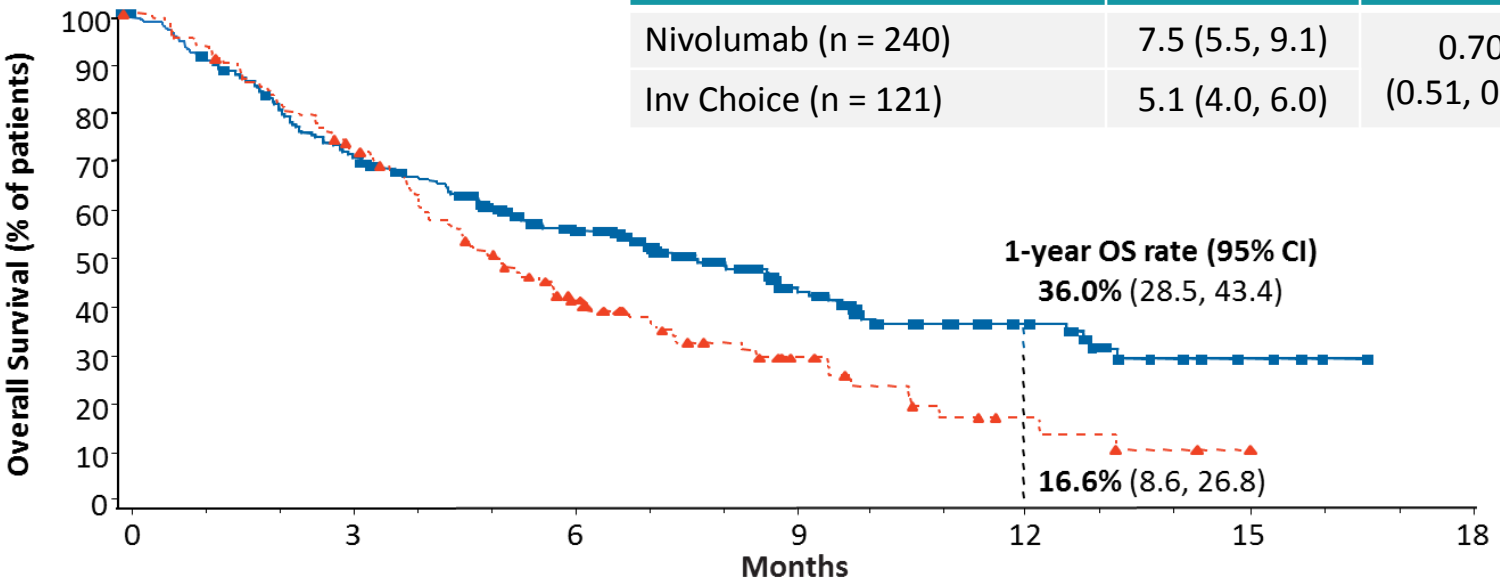
CheckMate 141: Nivolumab vs. Investigator's Choice in R/M HNSCC after Platinum Therapy

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***

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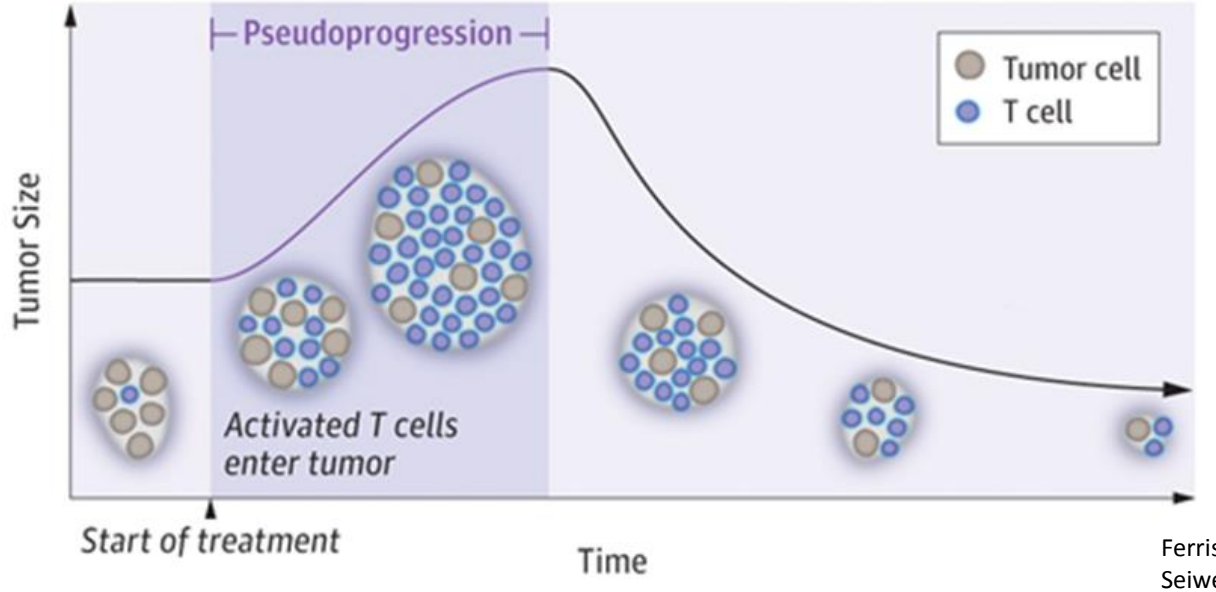
Response to Immune Checkpoint Inhibitor Treatment with Brief Increase in Tumor Size

Pseudoprogression



Ferris RL, et al. N Engl J Med. 2016
Seiwert TY, et al. Lancet Oncol. 2016

- Early appearance of an increase in tumor burden, subsequently followed by tumor regression
- Initially recognized in the melanoma trials, with incidence up to 10%

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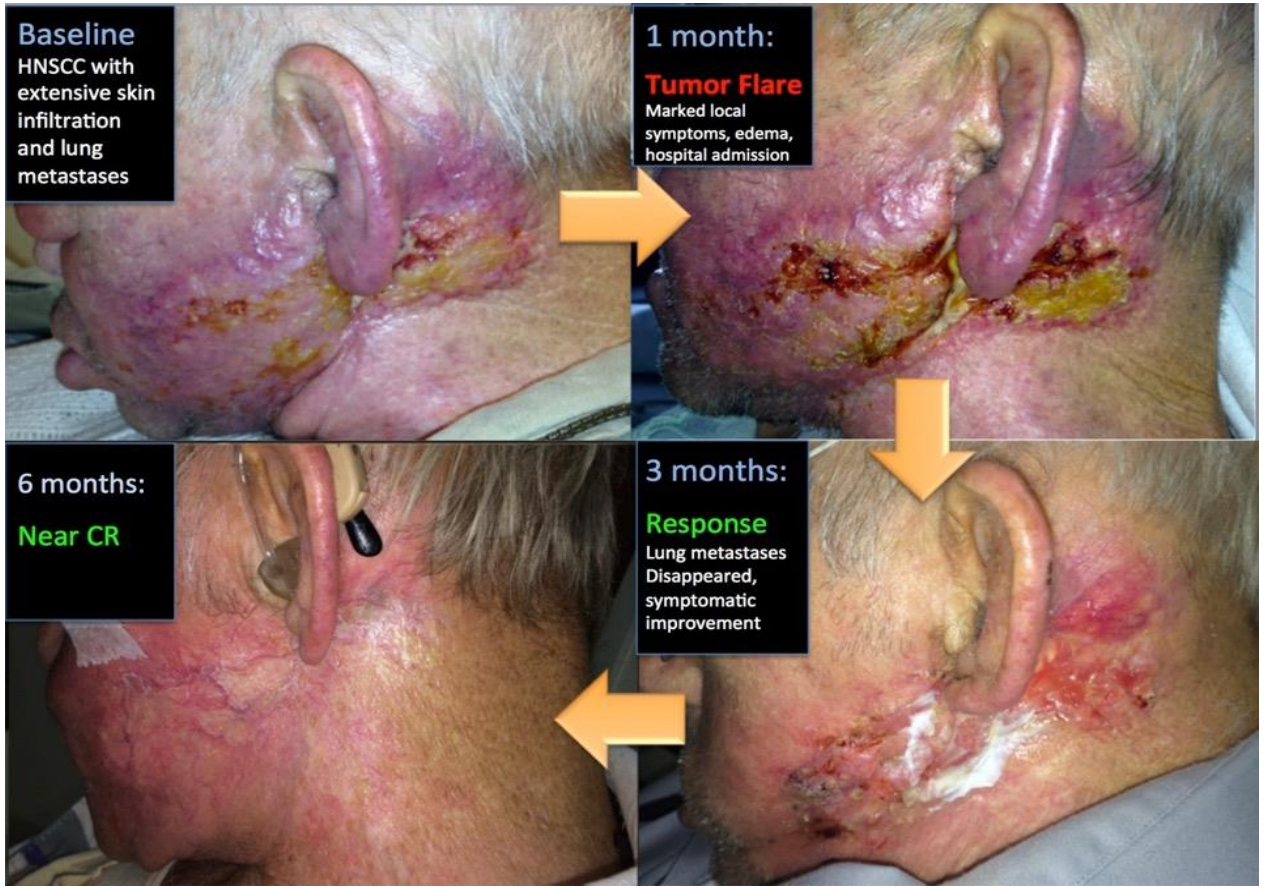
Response to Immune Checkpoint Inhibitor Treatment with Brief Increase in Tumor Size

Pseudoprogression: Case Report from Keynote-012

*KEYNOTE-012 and CHECKMAKE-141 trials of pembrolizumab and nivolumab showed an exceedingly rare rate of pseudoprogression.



Ferris RL, et al. N Engl J Med. 2016
Seiwert TY, et al. Lancet Oncol. 2016

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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

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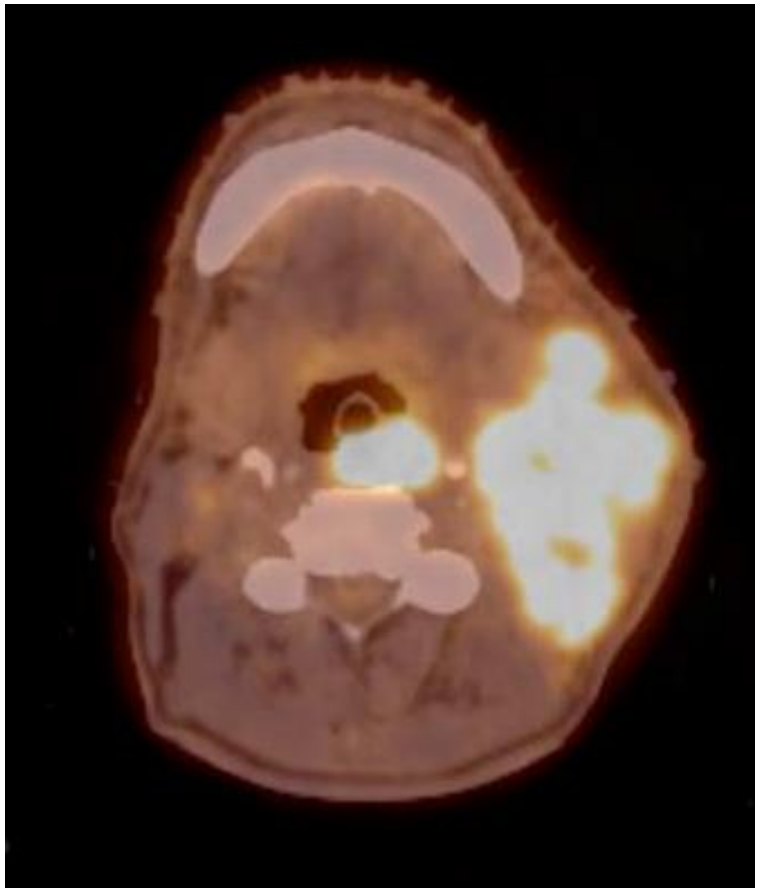
Patient Case Study 1
November 2014

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



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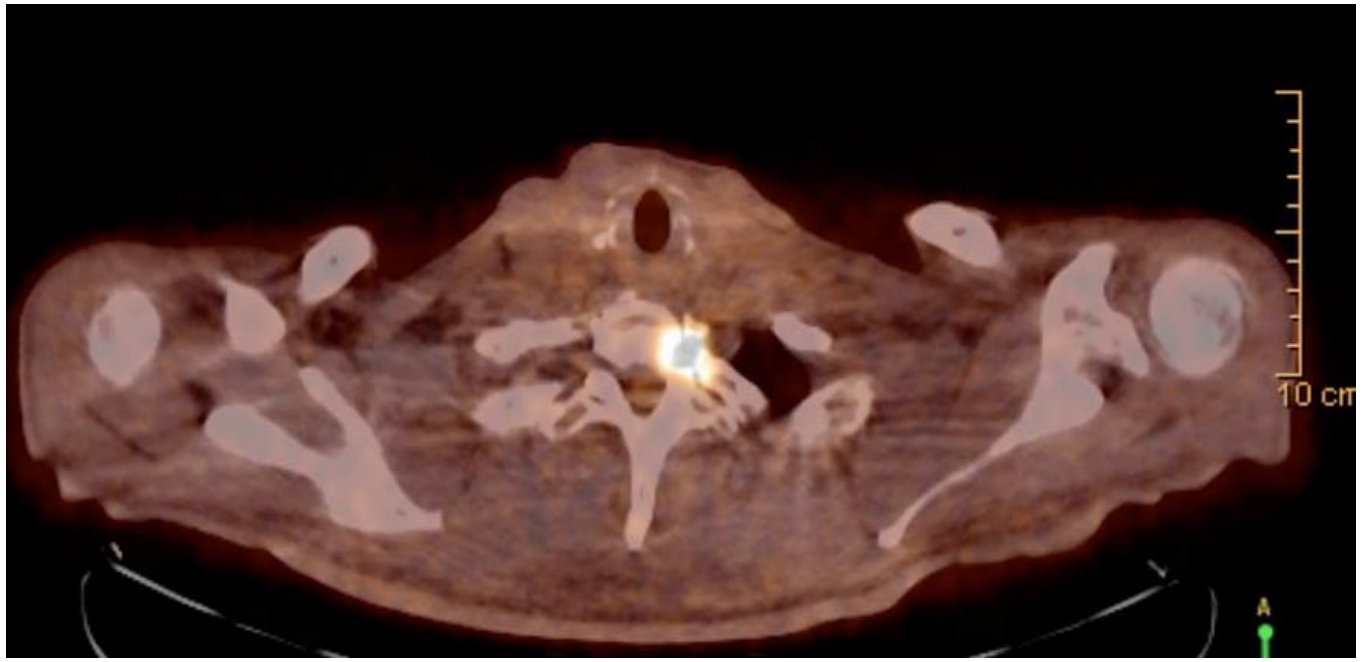
Patient Case Study 1
January 2015

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



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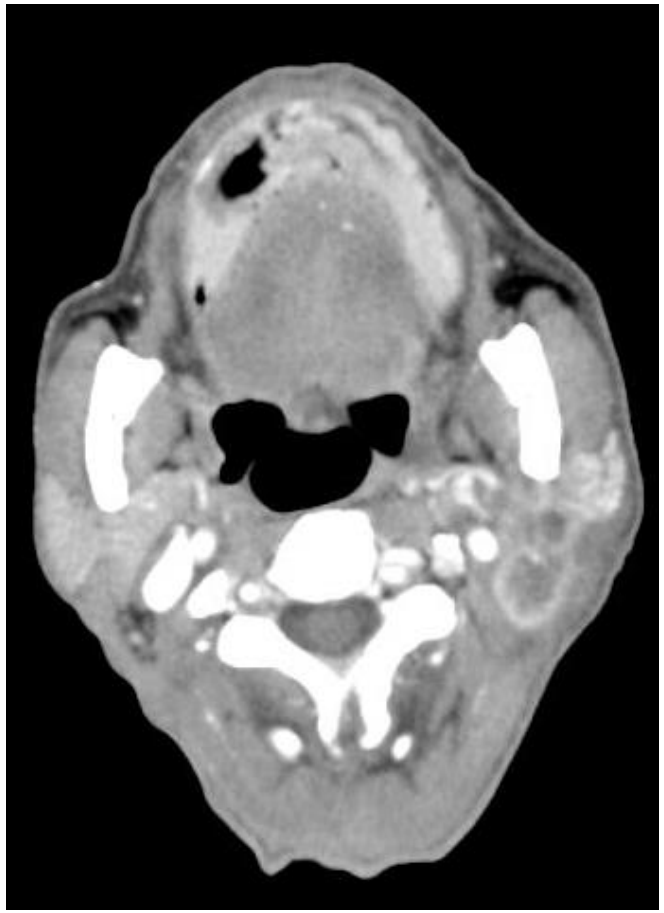
Patient Case Study 1
June 2015

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



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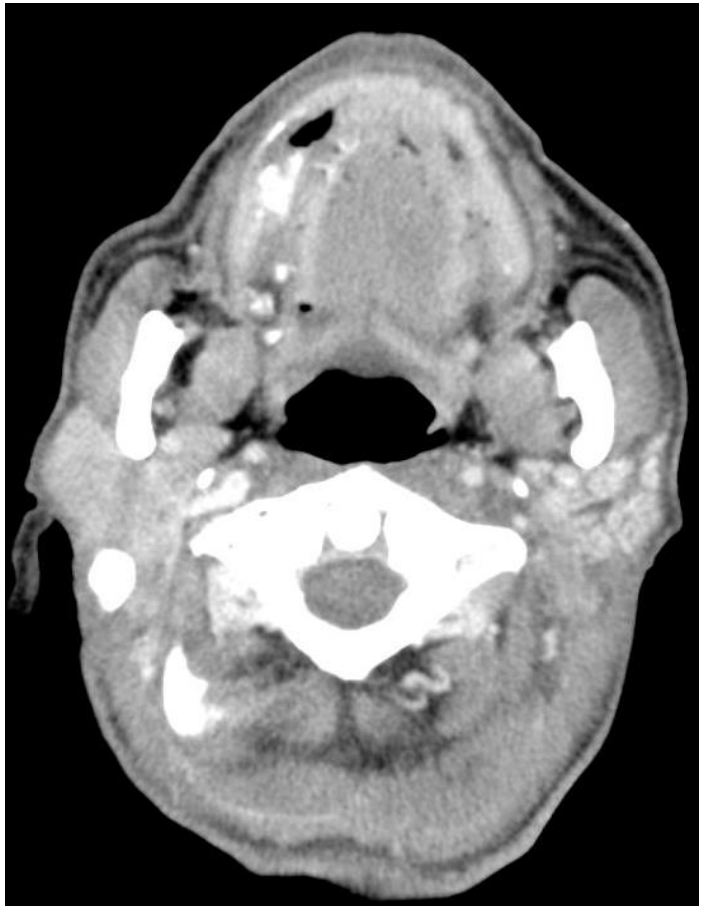
Patient Case Study 1
October 2015

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



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Patient Case Study 2

Patient Background Information:

- 65 yo, prior smoker (10ppy)
- Presented with a large mass in the R oropharynx
- Underwent carboplatin/paclitaxel/cetuximab induction
- Concurrent Chemoradiotherapy with high dose cisplatin
- 3 months after CRT, presented with multiple pulmonary nodules
- Cetuximab in metastatic setting

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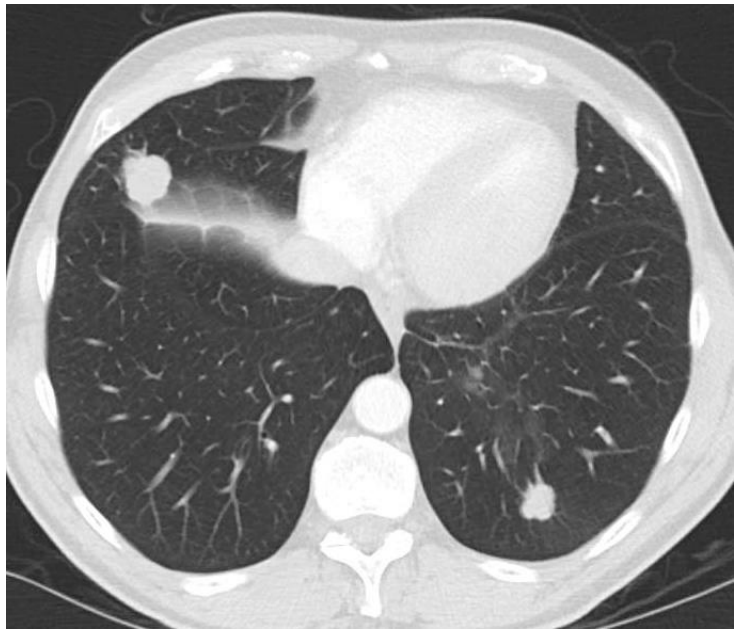
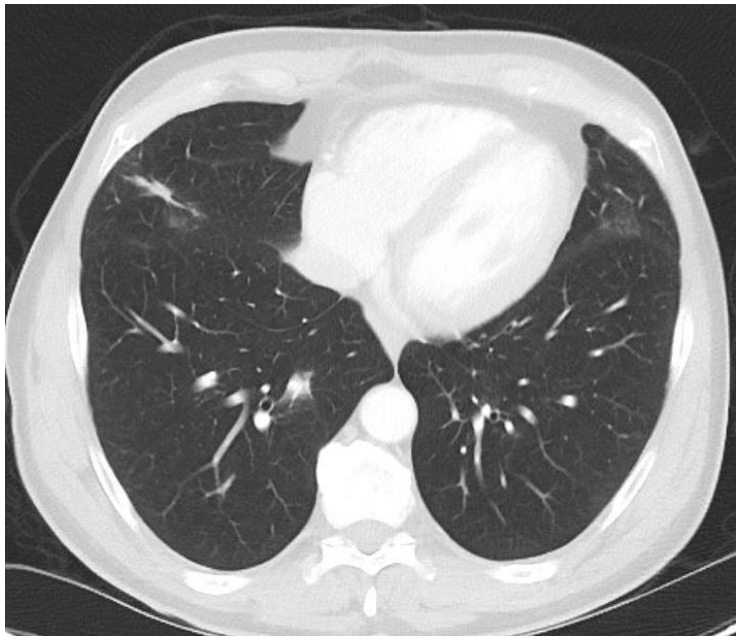
Patient Case Study 2
February 2015

- Enrolled in KEYNOTE 055
  - Started on pembrolizumab
- Experienced a near CR





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Next Steps: Evaluating Biomarkers in HNSCC

Current FDA approval of pembrolizumab and nivolumab is NOT contingent upon PD-L1 IHC

- KEYNOTE-012 and -055: response rates were not significantly different on the basis of tumor PD-L1 staining
- CHECKMATE-141: most benefit was seen in PD-L1 positive tumors

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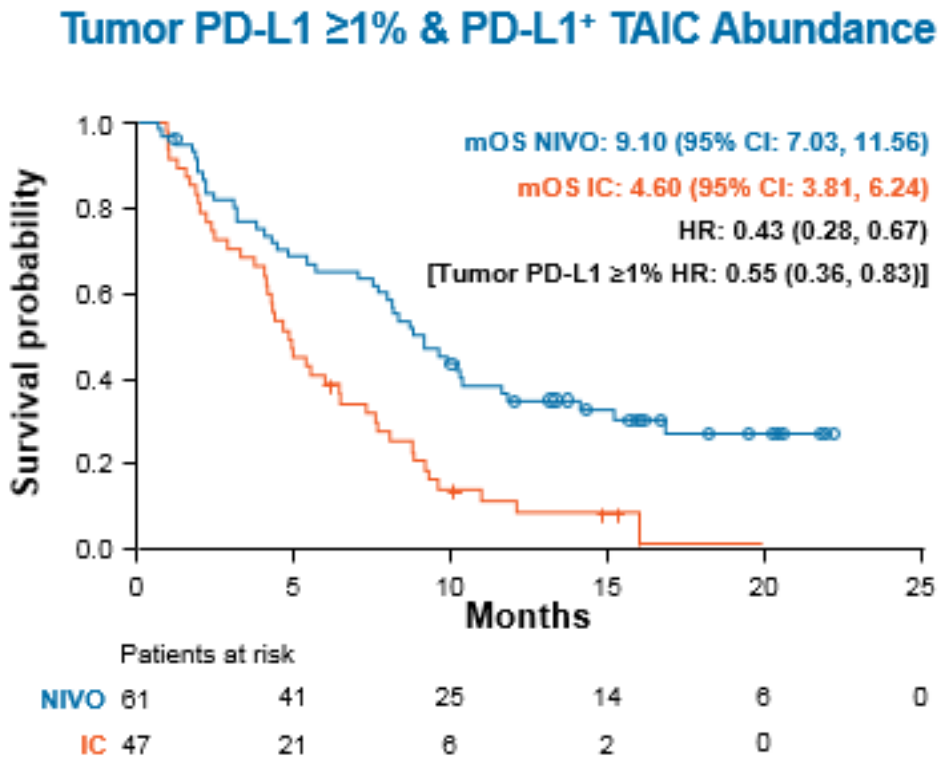
Next Steps: PD-L1 Staining Outside of the tumor

How can we improve on these methods?

- PD-L1 staining is not limited to tumor, though the approved assays only look there
- In KEYNOTE and CHECKMATE 141, inclusion of tumor associated PD-L1+ immune cells improves diagnostic performance



Ferris et al AACR 2017

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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

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