ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Head and Neck Cancers

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AMERICAN ACADEMY OF EMERGENCY MEDICINE

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Disclosures

- Principle Investigator and Sponsor of an Investigator Initiated Phase II Trial of Nivolumab as a Novel Neoadjuvant Pre-Surgical Therapy for Locally Advanced Oral Cavity Cancer that funded by Bristol Myers Squibb

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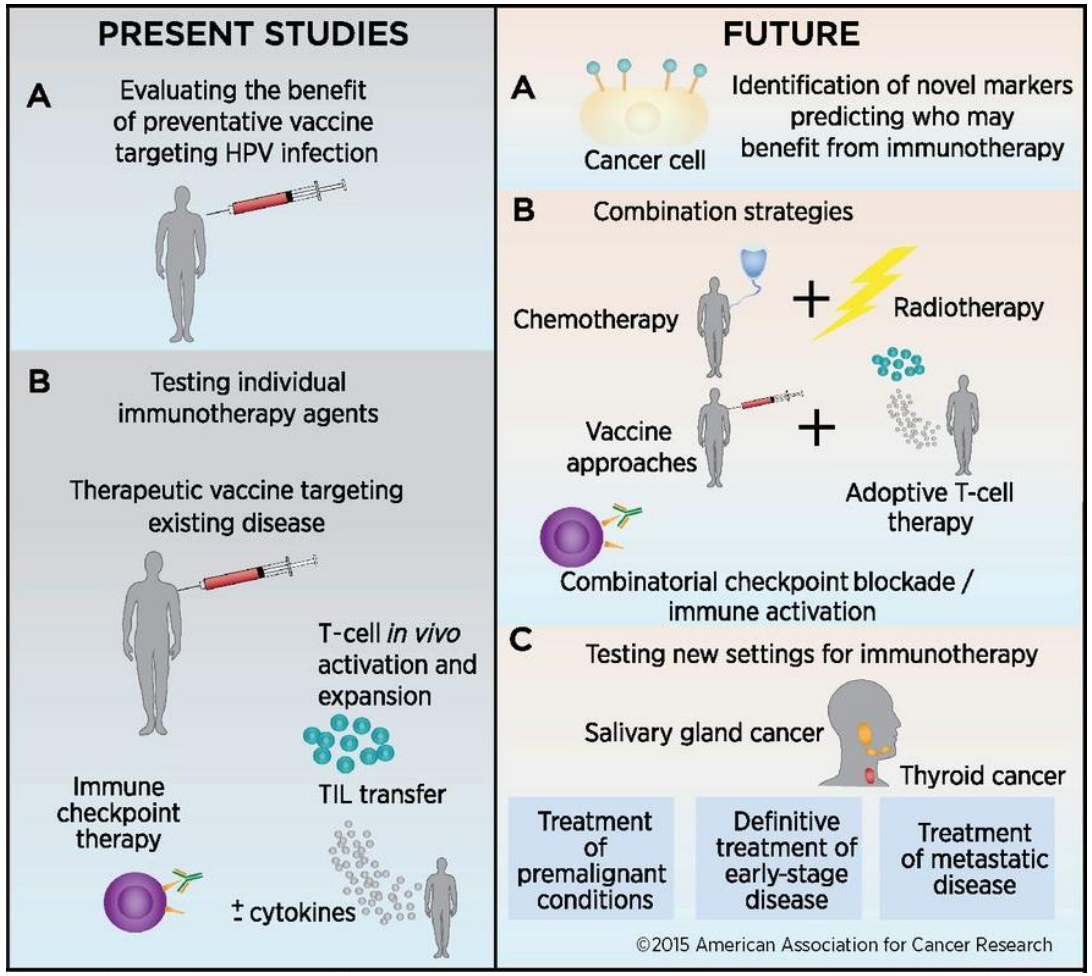
Immunotherapy for the Treatment of Head and Neck Cancers

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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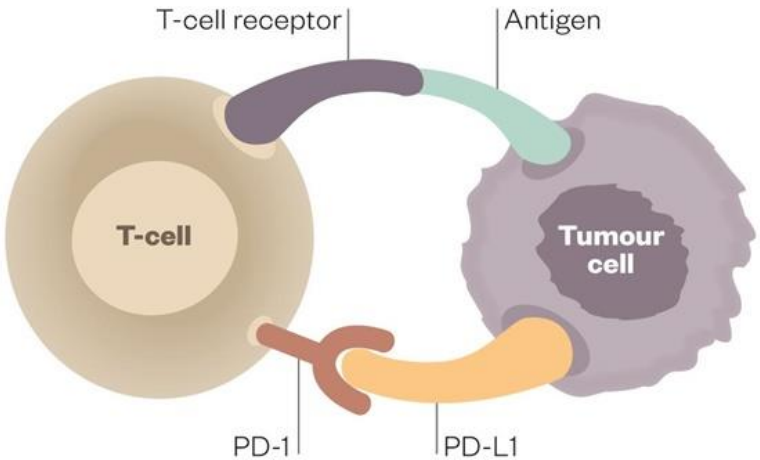
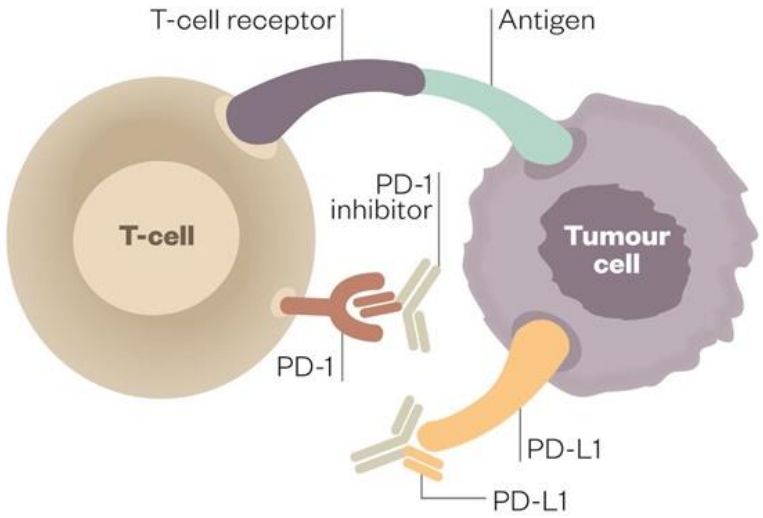
Immunotherapy for the Treatment of Head and Neck Cancers

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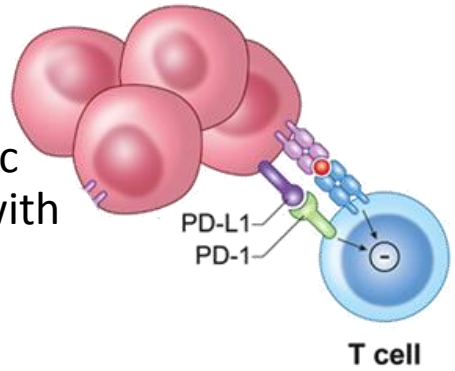
FDA-approved Checkpoint Inhibitors for use in Head and Neck Cancers



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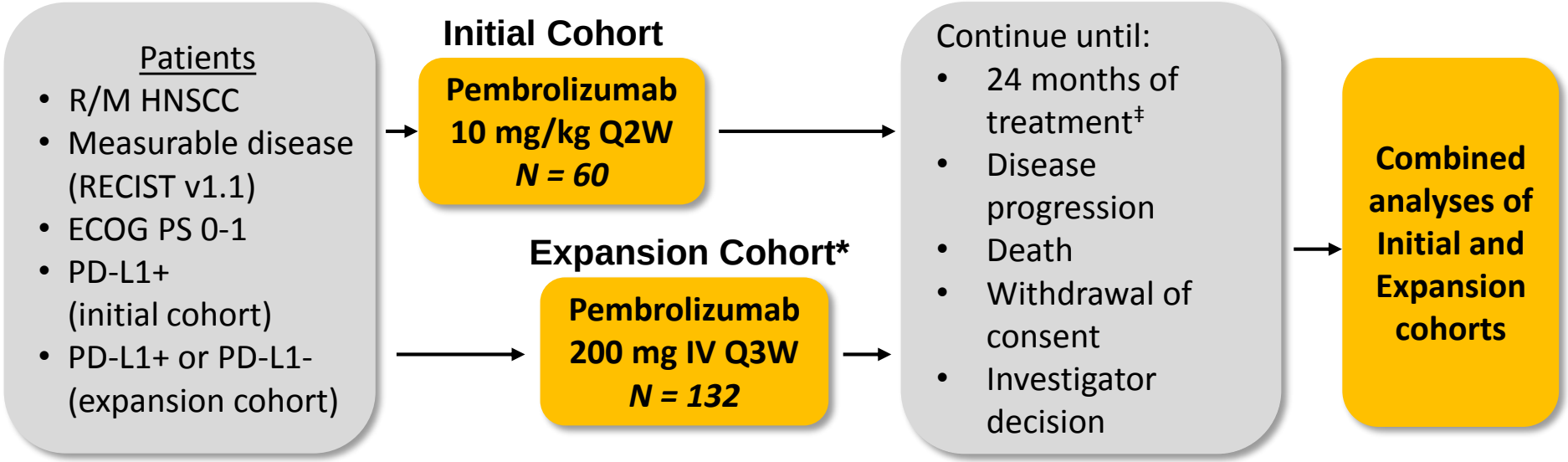
KEYNOTE-012: Pembrolizumab in R/M HNSCC
Phase 1b trial, Cohorts† B, B2



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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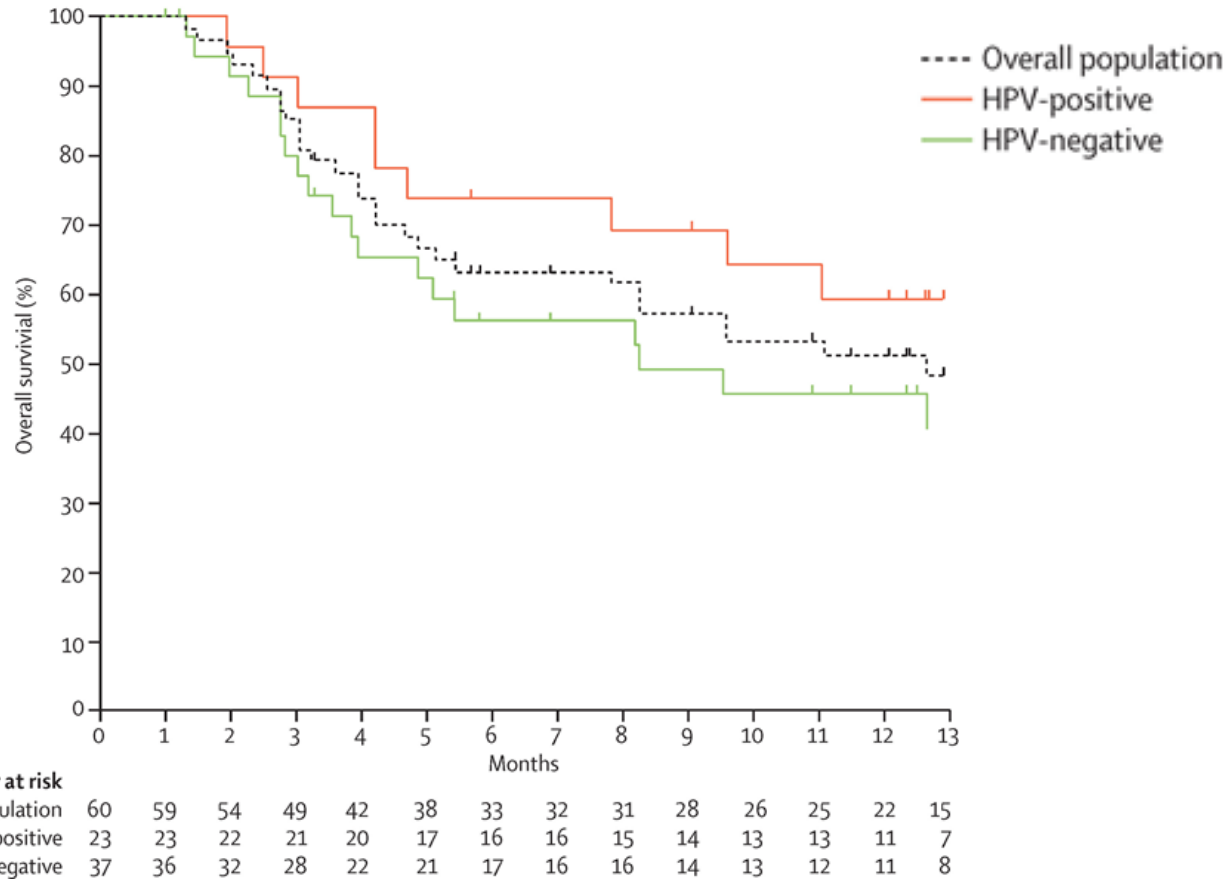
KEYNOTE-012: Pembrolizumab in HNSCC Cohort
Overall Survival

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



Seiwert TY, Lancet Oncol, 2016

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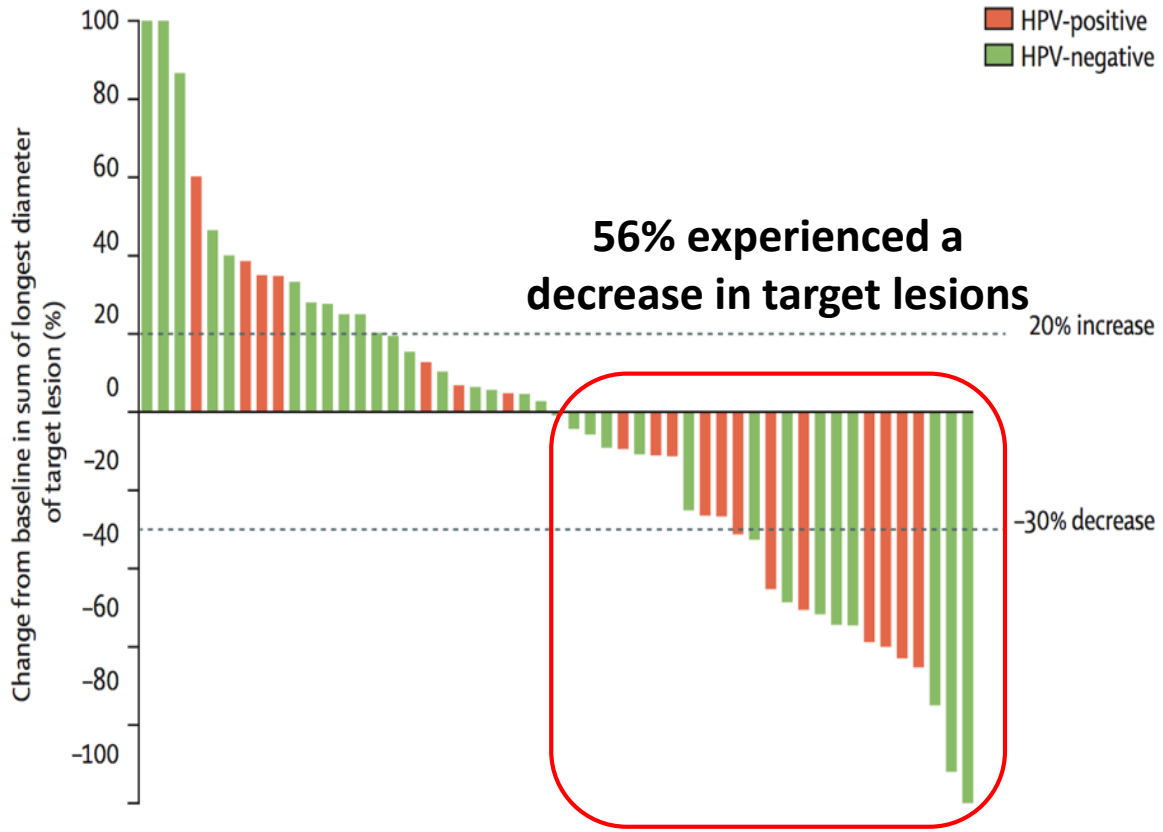
KEYNOTE-012: Pembrolizumab in HNSCC Cohort
Tumor Shrinkage

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



Seiwert TY Lancet Oncol 2016

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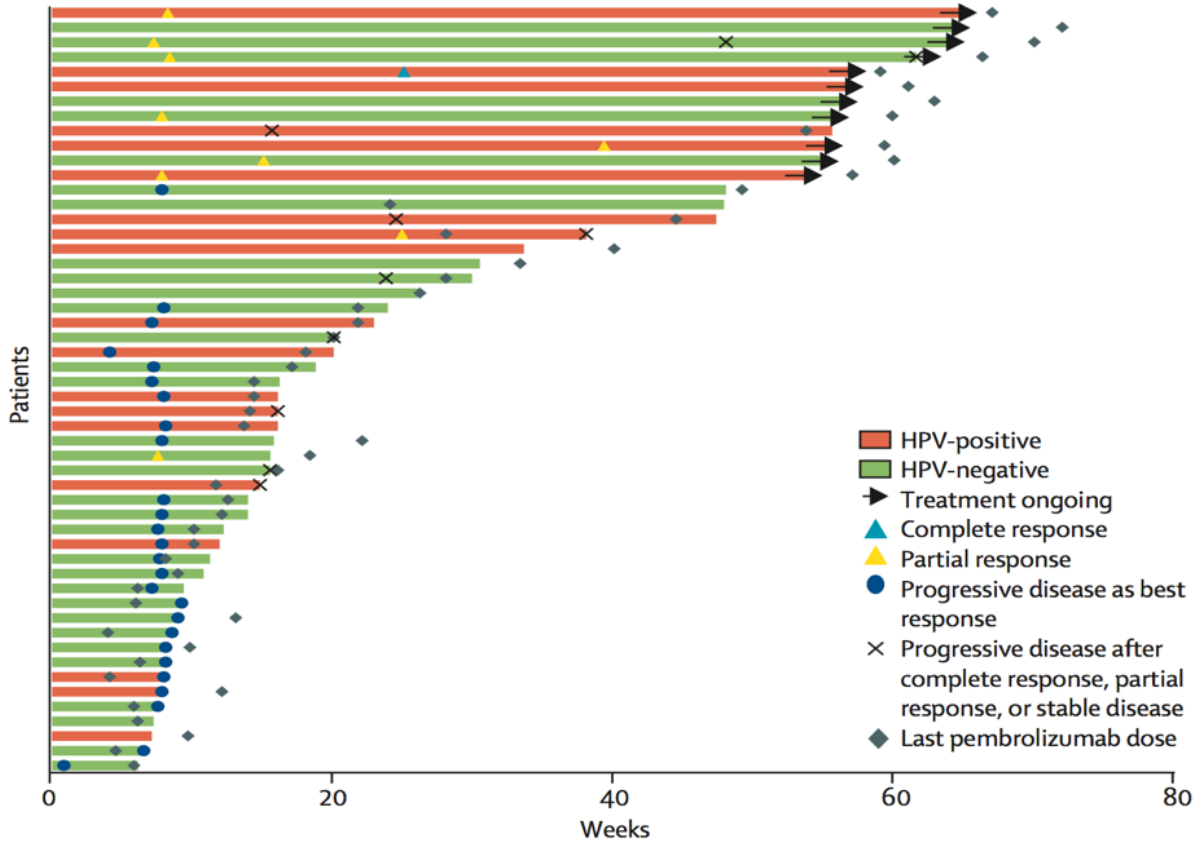
KEYNOTE-012: Pembrolizumab in HNSCC Cohort
Durability of Response



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

Seiwert TY, Lancet Oncol, 2016

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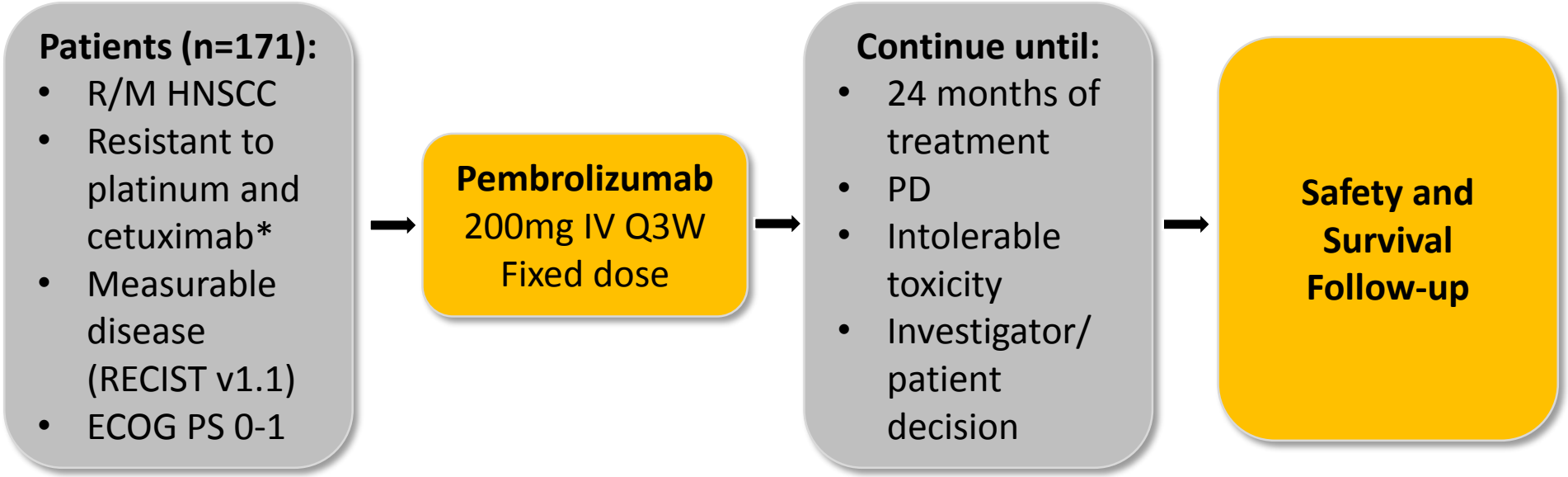
KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum and Cetuximab
Phase 2 Trial, Single Arm



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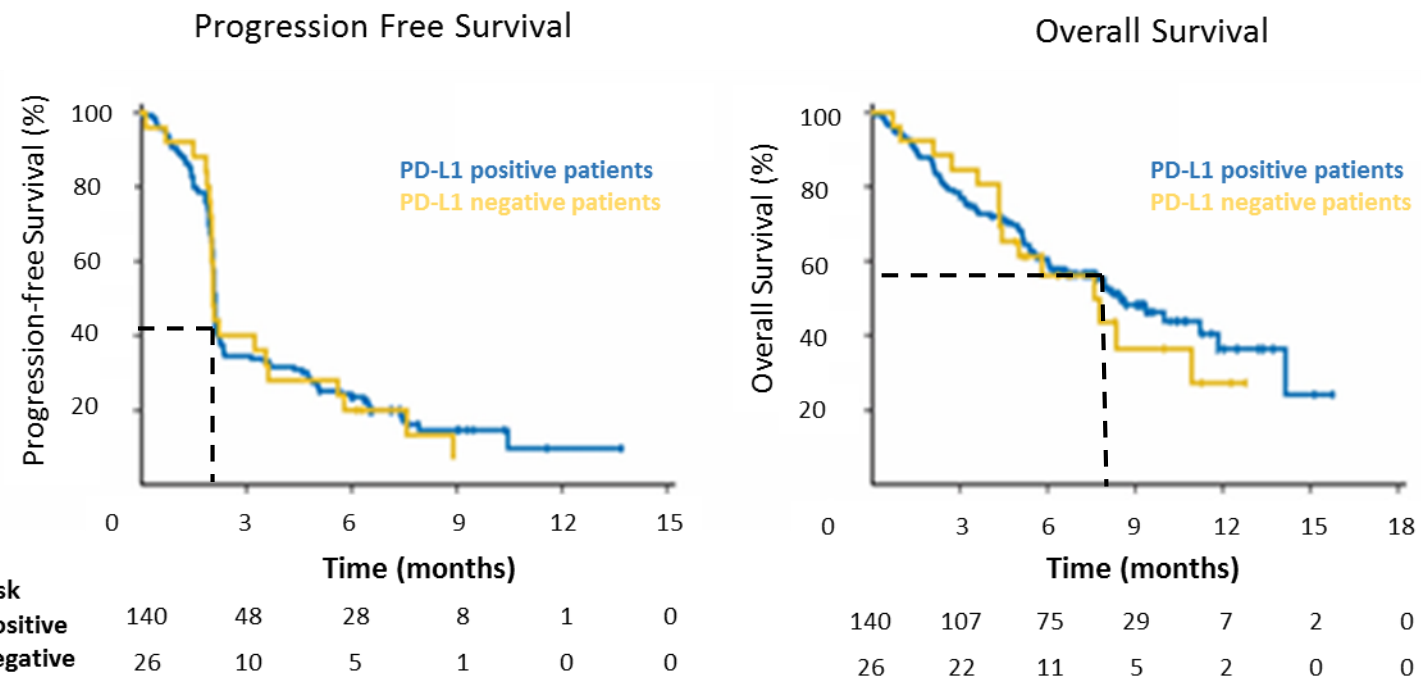
KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum and Cetuximab
Phase 2 Trial, Single Arm

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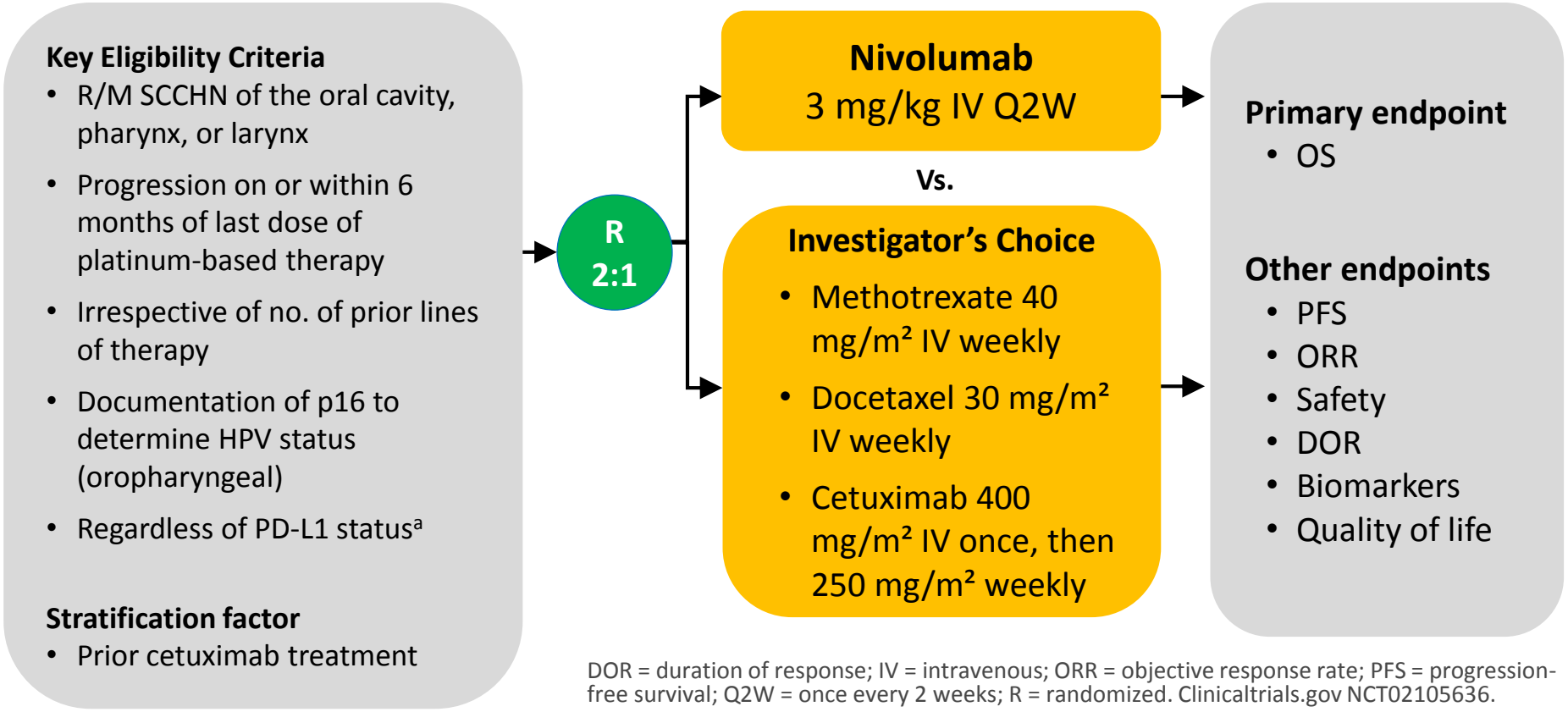
CheckMate 141: Nivolumab vs. Investigator's Choice in R/M HNSCC after Platinum Therapy

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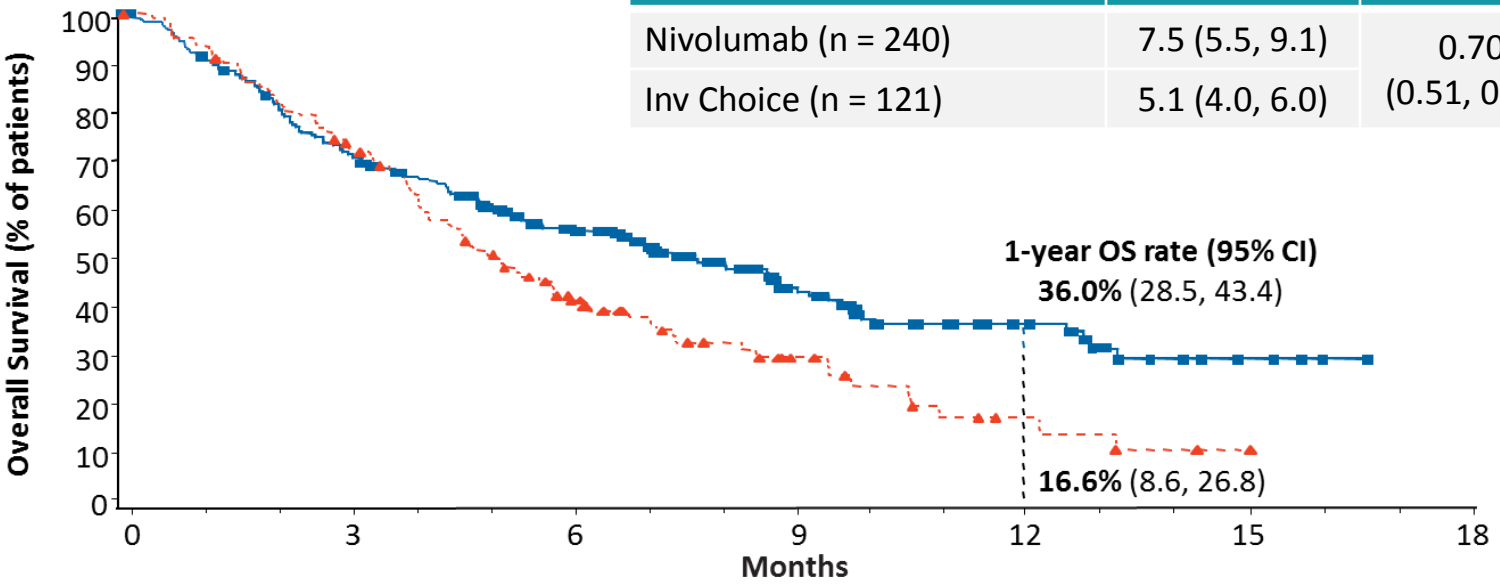
CheckMate 141: Nivolumab vs. Investigator's Choice in R/M HNSCC after Platinum Therapy

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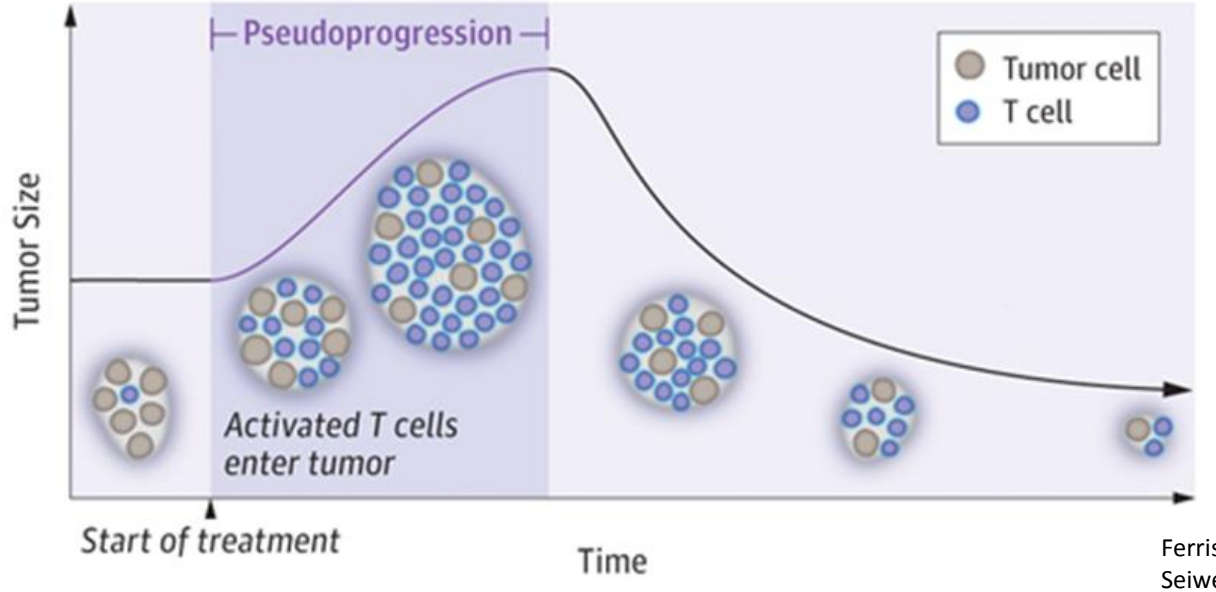
Response to Immune Checkpoint Inhibitor Treatment with Brief Increase in Tumor Size

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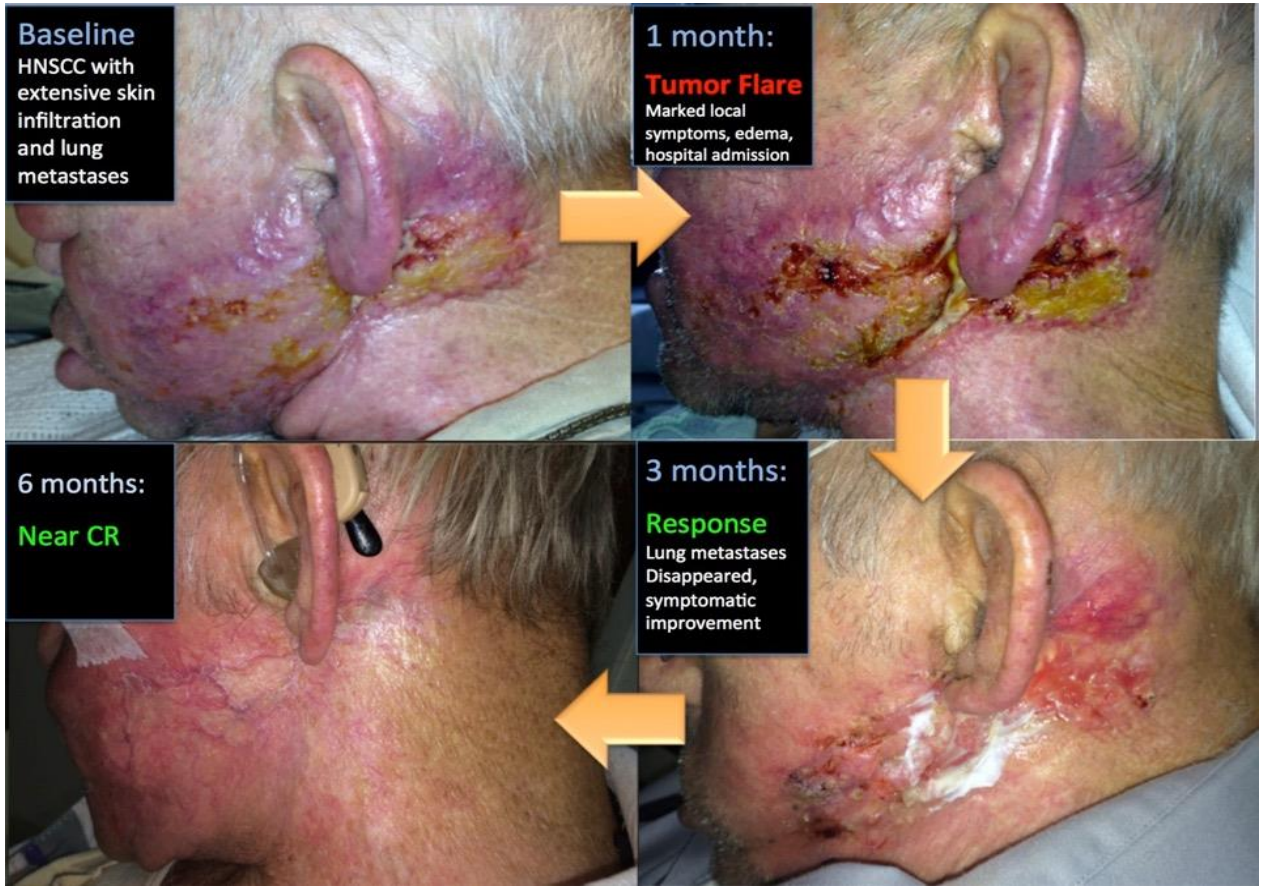
Response to Immune Checkpoint Inhibitor Treatment with Brief Increase in Tumor Size

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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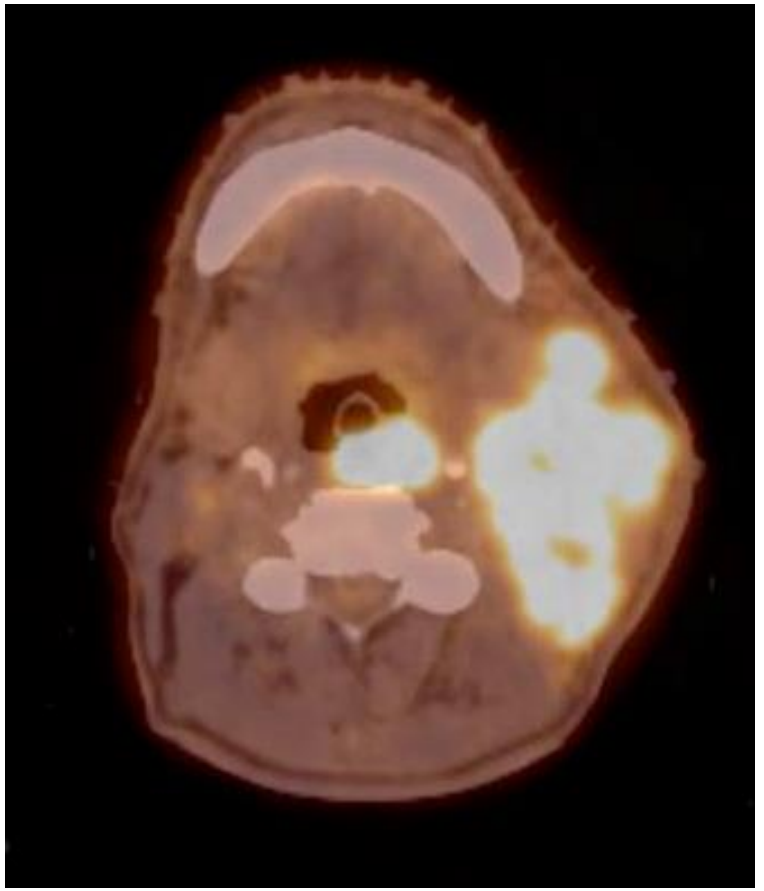
Patient Case Study 1
November 2014

- 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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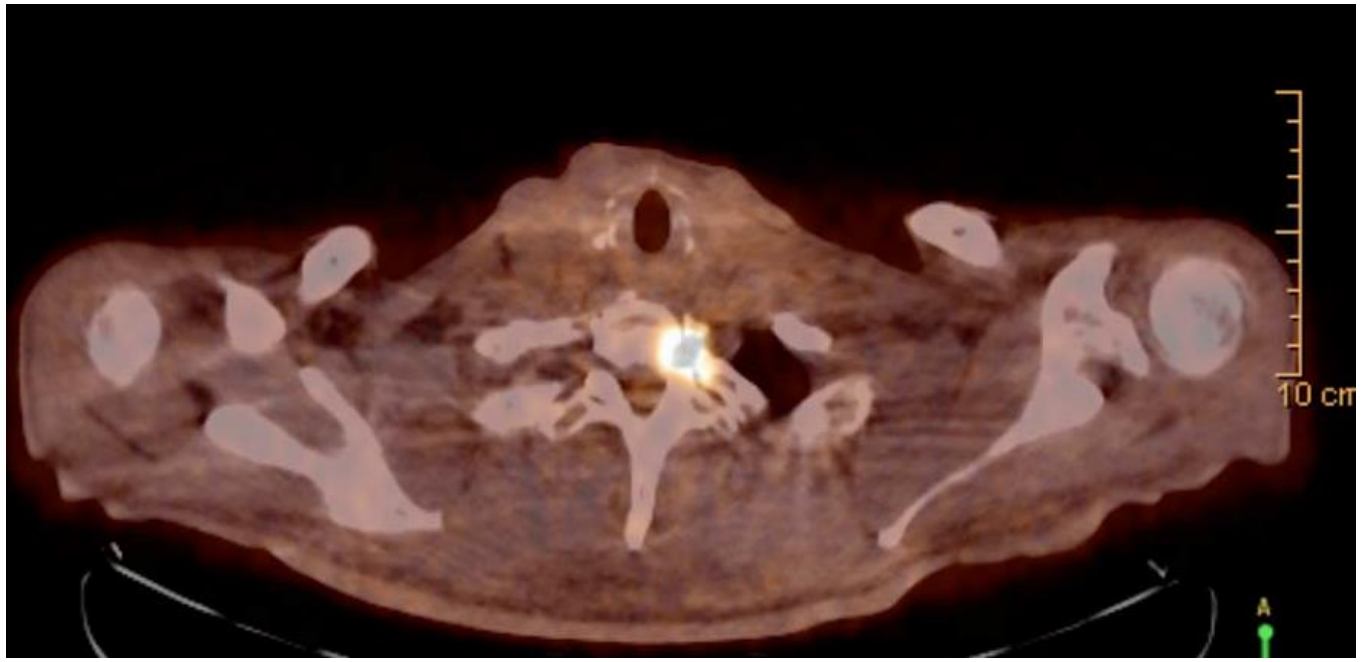
Patient Case Study 1
January 2015

- 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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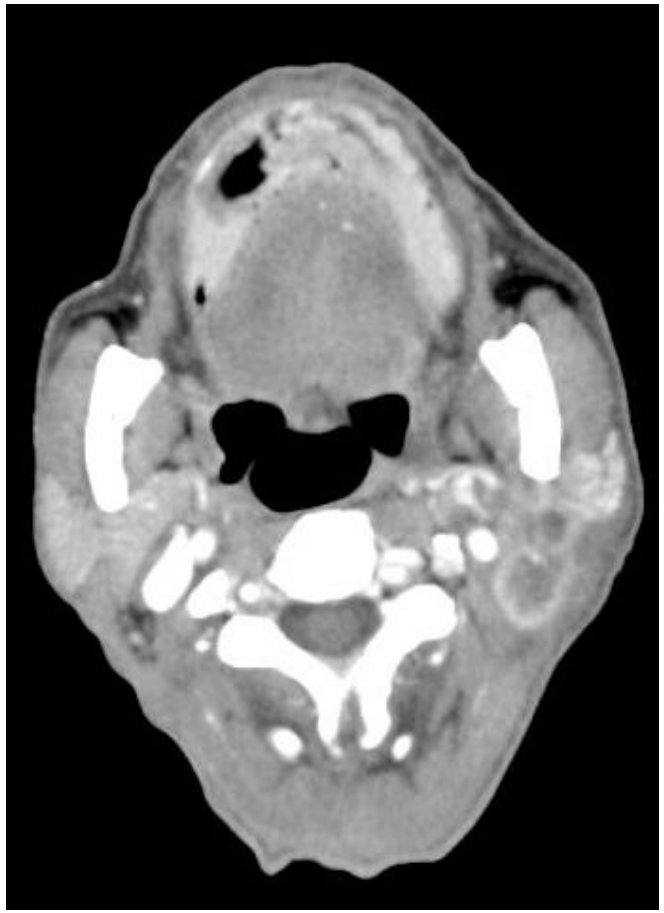
Patient Case Study 1
June 2015

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



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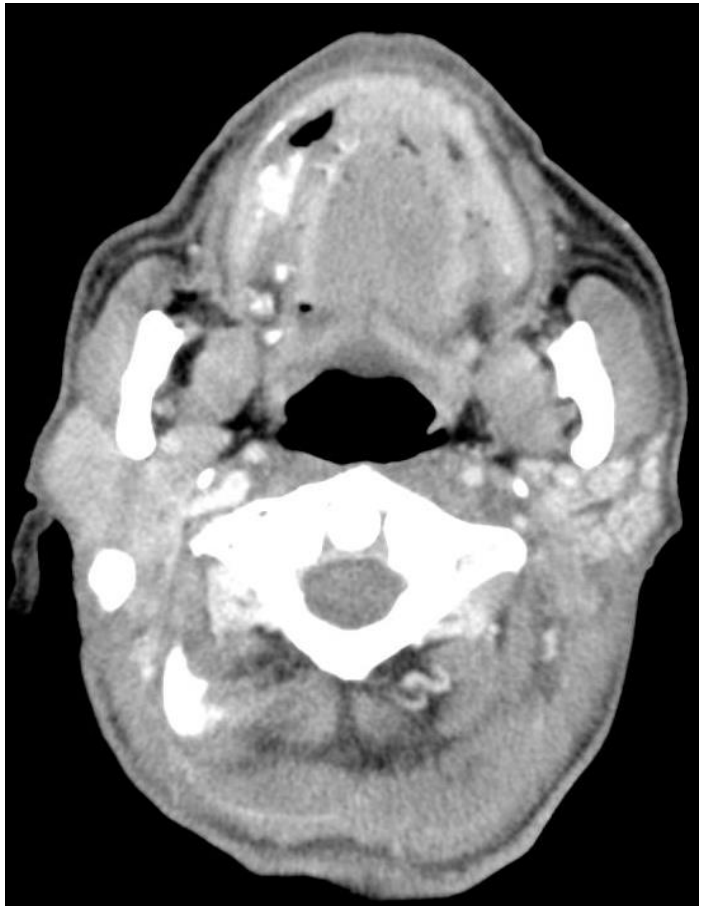
Patient Case Study 1
October 2015

- 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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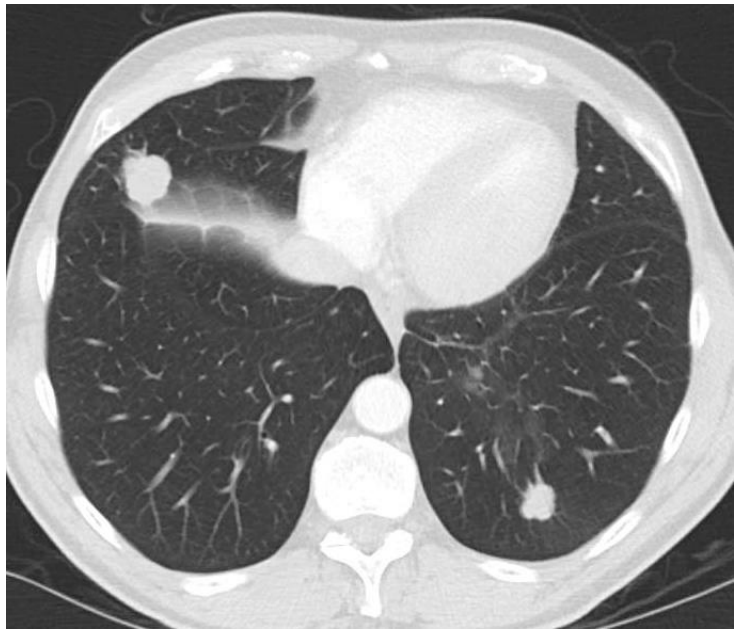
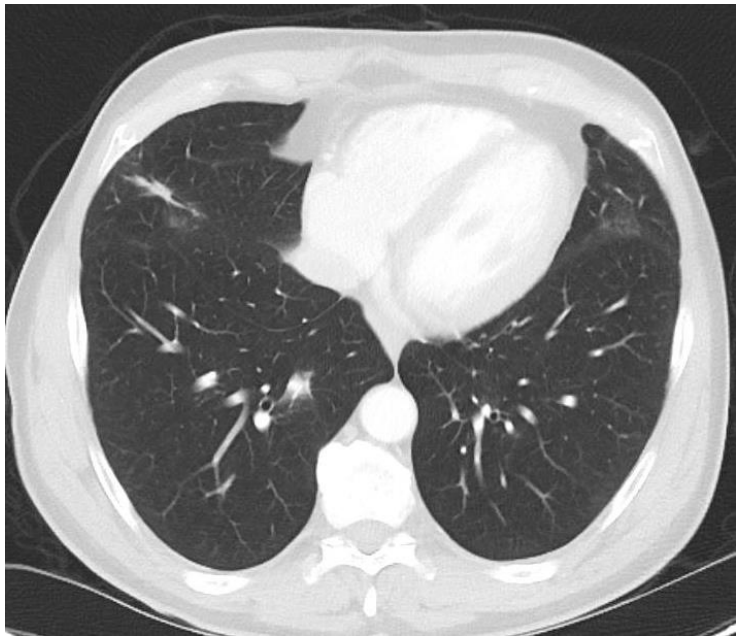
Patient Case Study 2
February 2015

- 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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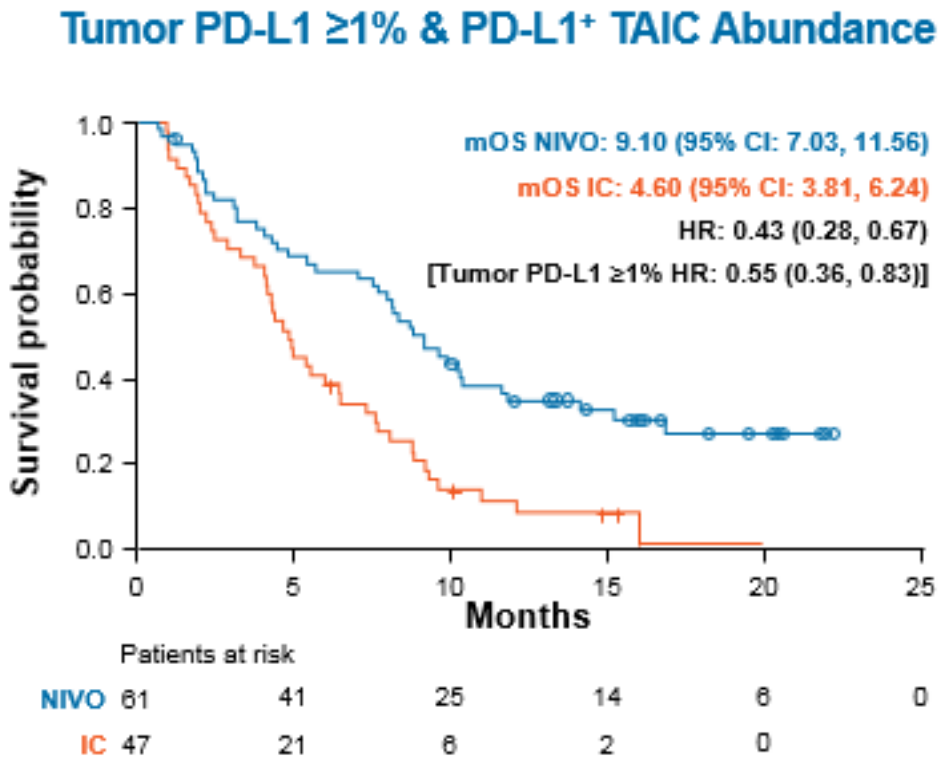
Next Steps: PD-L1 Staining Outside of the tumor

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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