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ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Head and Neck Cancers

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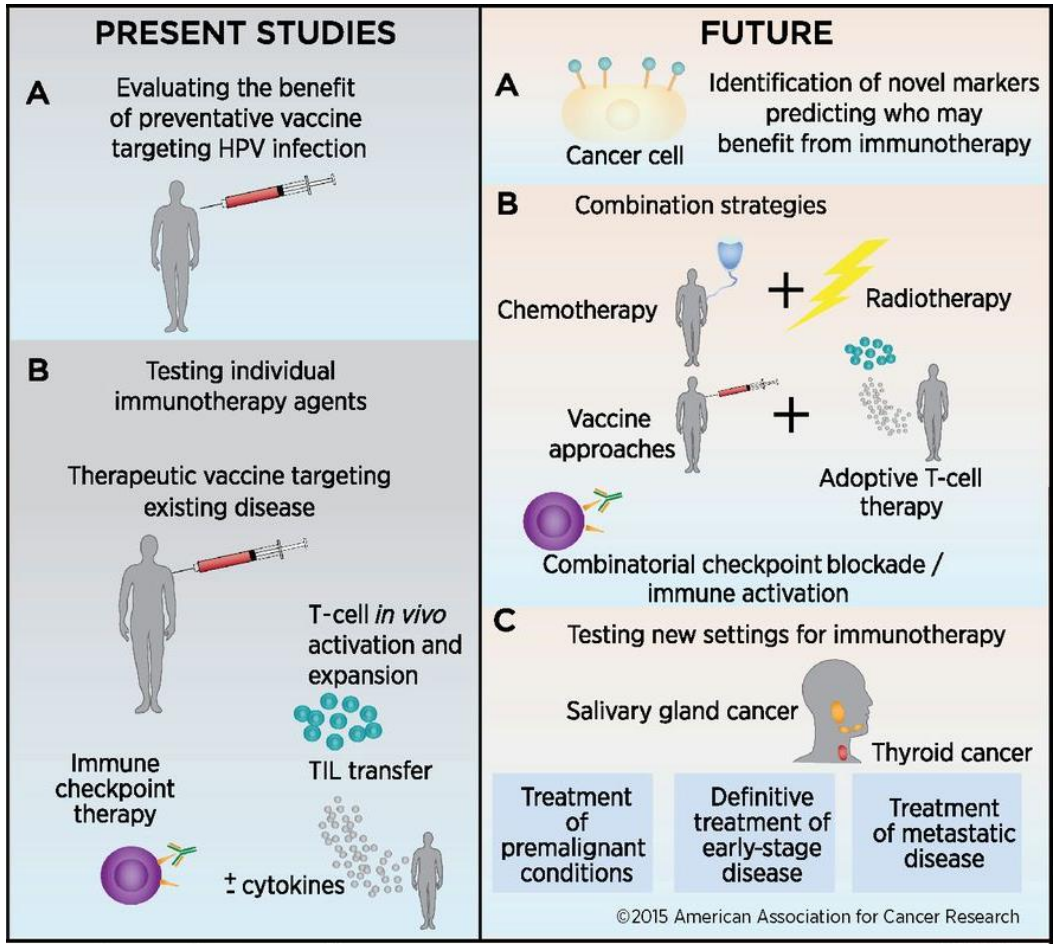
Disclosures

- Bristol-Myers Squibb, Consulting Fees
- ImageMoverMD, Ownership Interest
- I will *not* be discussing non-FDA approved indications during my presentation.

Immunotherapy for the Treatment of Head and Neck Cancers

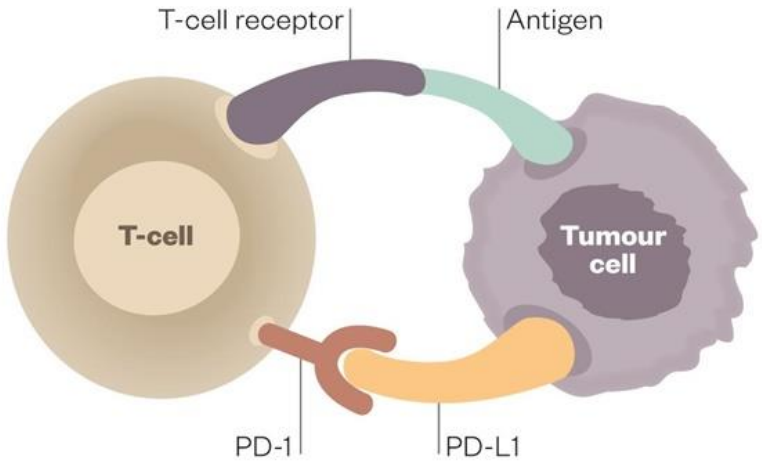
- Immuno-Oncology (I-O) developments in treatment of head and neck cancers
  - Expression of immunologic markers to guide treatment
  - Preventive vaccination against virally mediated cancers
  - PD-1 checkpoint inhibitors for the treatment of metastatic disease



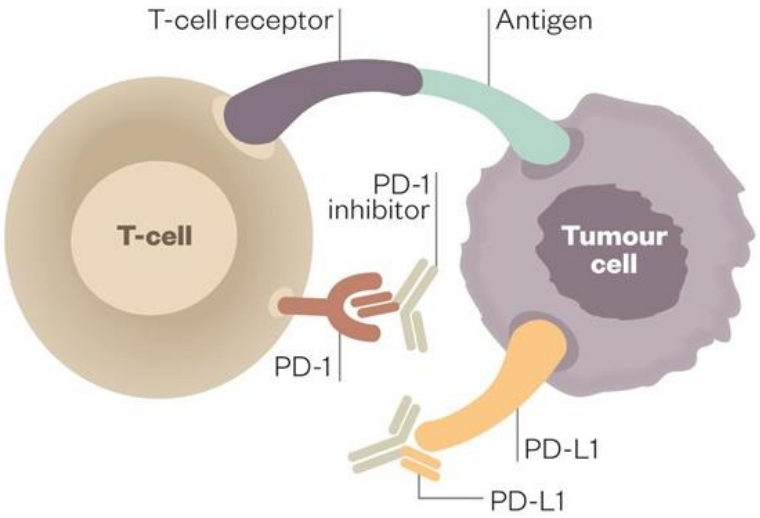
Schoenfeld JD, Cancer Immunol Res, 2015

Immunotherapy for the Treatment of Head and Neck Cancers

Immune Checkpoint Inhibitors (ICI)



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

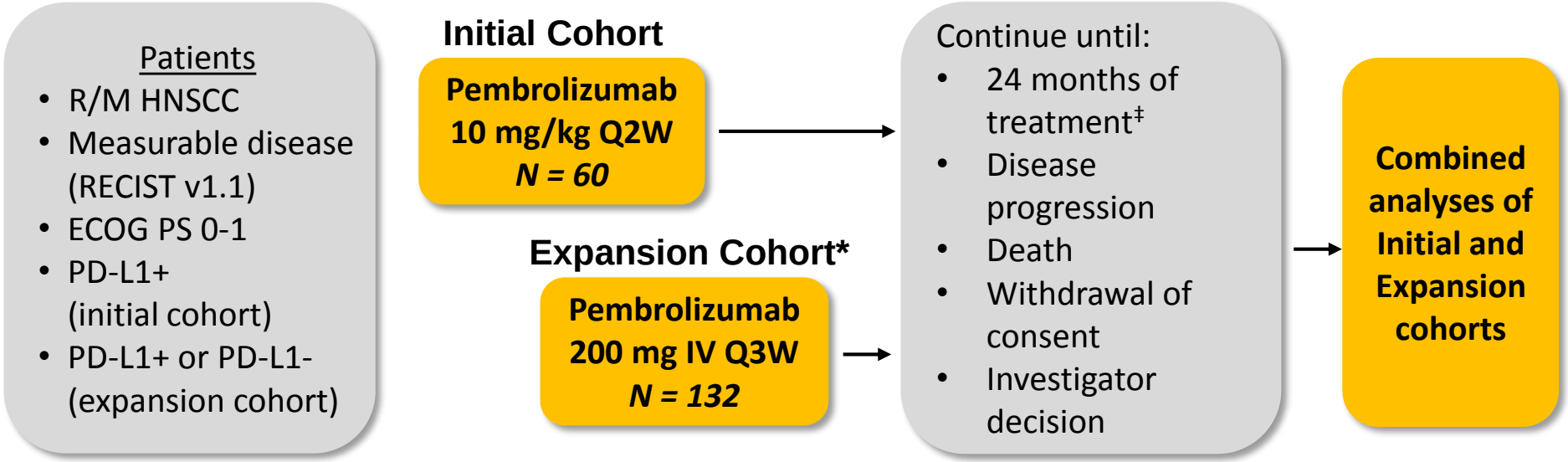
FDA-approved Checkpoint Inhibitors for Use in Head and Neck Cancers

- Pembrolizumab 200 mg IV Q3W(anti-PD-1)
  - KEYNOTE – 012/055: Patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (HNSCC) with disease progression on or after platinum-containing chemotherapy
  - Accelerated Approval by FDA – August 5, 2016

- Nivolumab 240 mg IV Q2W or 480 mg IV Q4W (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

KEYNOTE-012: Pembrolizumab in R/M HNSCC

Nonrandomized, Phase 1b Trial, Cohorts† B, B2



Response assessment: Every 8 weeks until disease progression

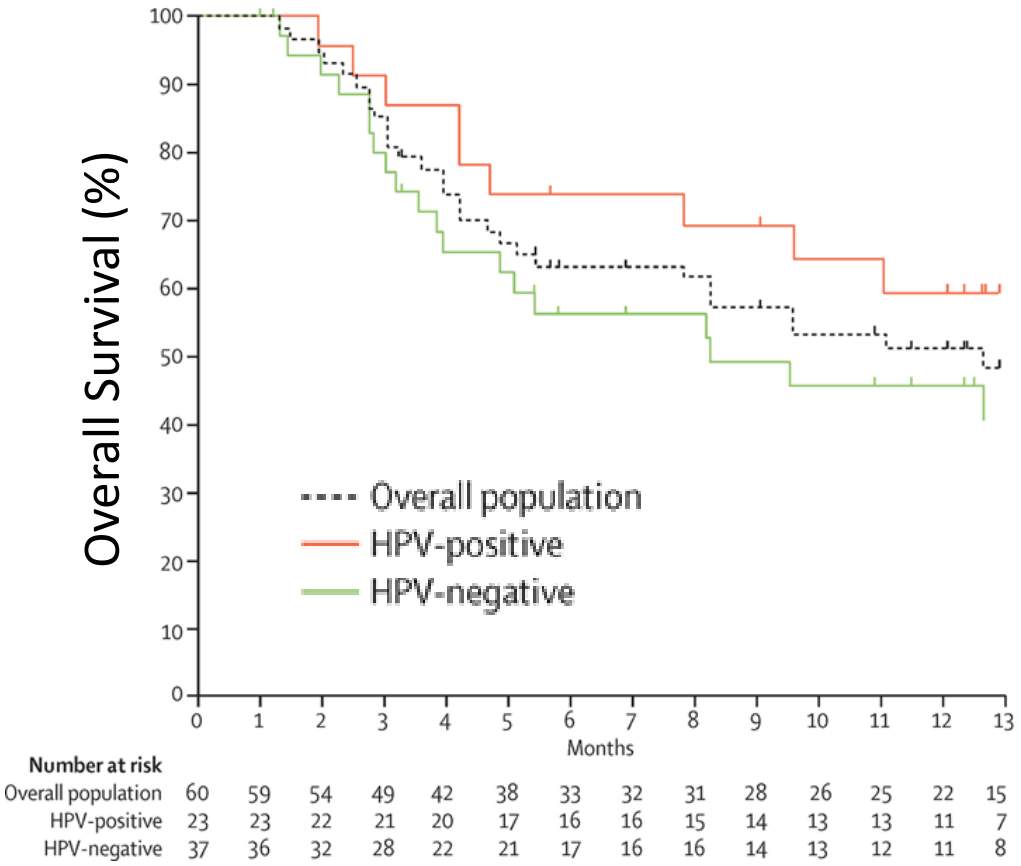
Primary end points: ORR (RECIST v1.1, central imaging vendor review), safety

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 R/M HNSCC

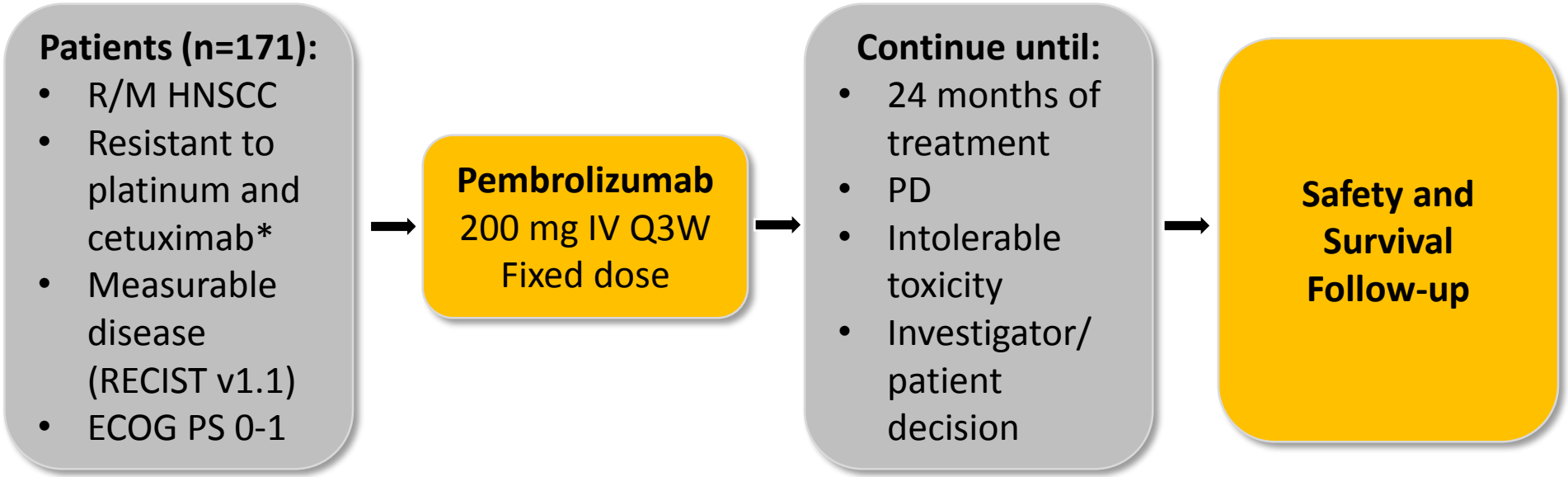
Nonrandomized, Phase 1b Trial, Cohorts† B, B2



- ORR = 18%
  - CR = 4%
  - PR = 14%
- mOS = 8.0 months
- mPFS = 2.2 months

KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum/Cetuximab

Phase II Trial, Single Arm



Bauml J 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

KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum/Cetuximab

Phase II Trial, Single Arm

Outcome	All Patients	HPV Status		PD-L1 Status		
	N=171	Positive n=37	Negative n=131	≥1% n=140	<1% n=26	≥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

Bauml J, et al, J Clin Oncol. 2017

- Neither tumor PD-L1 expression or HPV status are sufficiently robust in guiding the use of pembrolizumab at this time.

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

Phase III Randomized, Safety and Efficacy Trial

Key Eligibility Criteria

- R/M SCCHN of the oral cavity, pharynx, or larynx
- Progression on or within 6 months of last dose of platinum-based therapy
- Irrespective of no. of prior lines of therapy
- Documentation of p16 to determine HPV status (oropharyngeal)
- Regardless of PD-L1 status[a]

Stratification factor

- Prior cetuximab treatment

R 2:1

Nivolumab
3 mg/kg IV Q2W

Vs.

Investigator's Choice

- Methotrexate 40 mg/m² IV weekly
- Docetaxel 30 mg/m² IV weekly
- Cetuximab 400 mg/m² IV once, then 250 mg/m² weekly

Primary endpoint

- OS

Other endpoints

- PFS
- ORR
- Safety
- DOR
- Biomarkers
- Quality of life

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

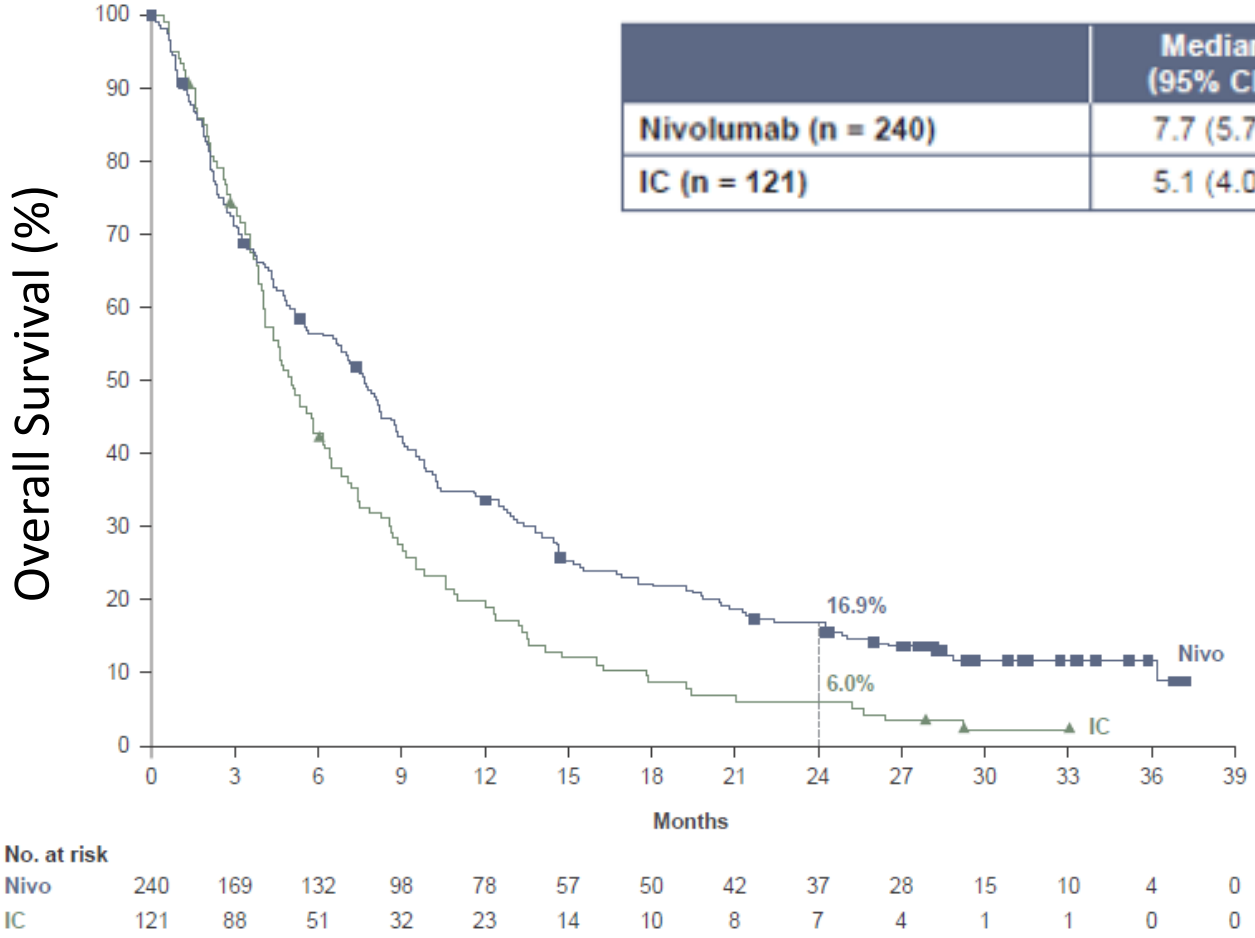
[a]Tissue required for testing

Ferris & Gillison, NEJM, 2016

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

Overall Survival: 2 year report

	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 240)	7.7 (5.7–8.8)	0.68 (0.54–0.86)
IC (n = 121)	5.1 (4.0–6.2)	

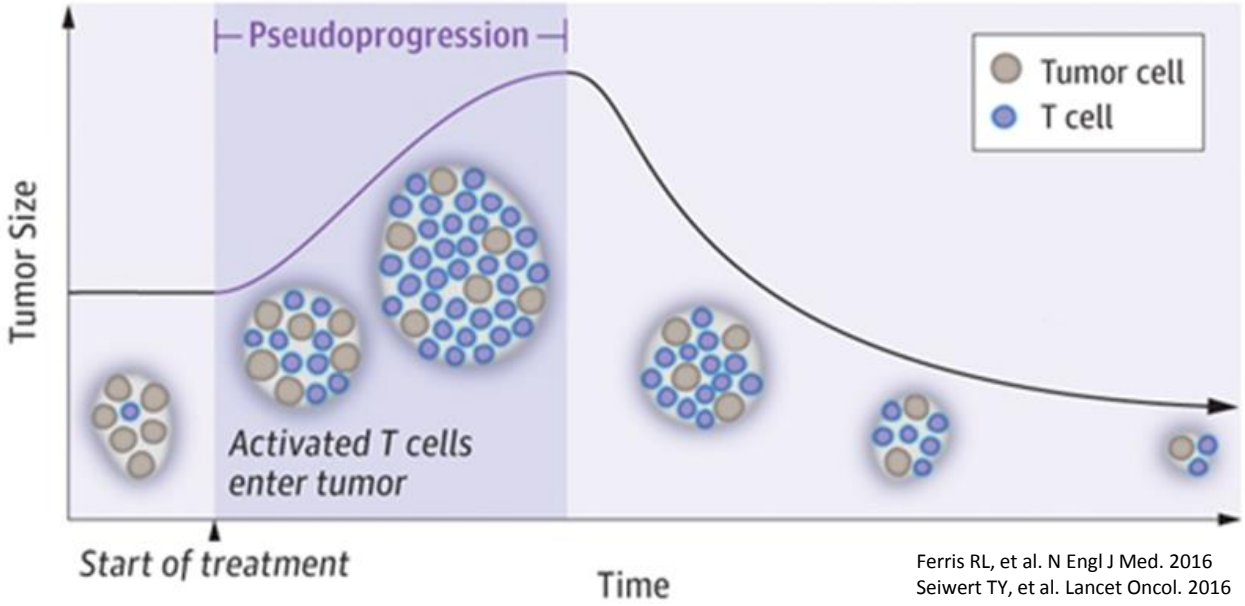


Ferris RL. Oral Oncology, 2018

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

Pseudoprogression

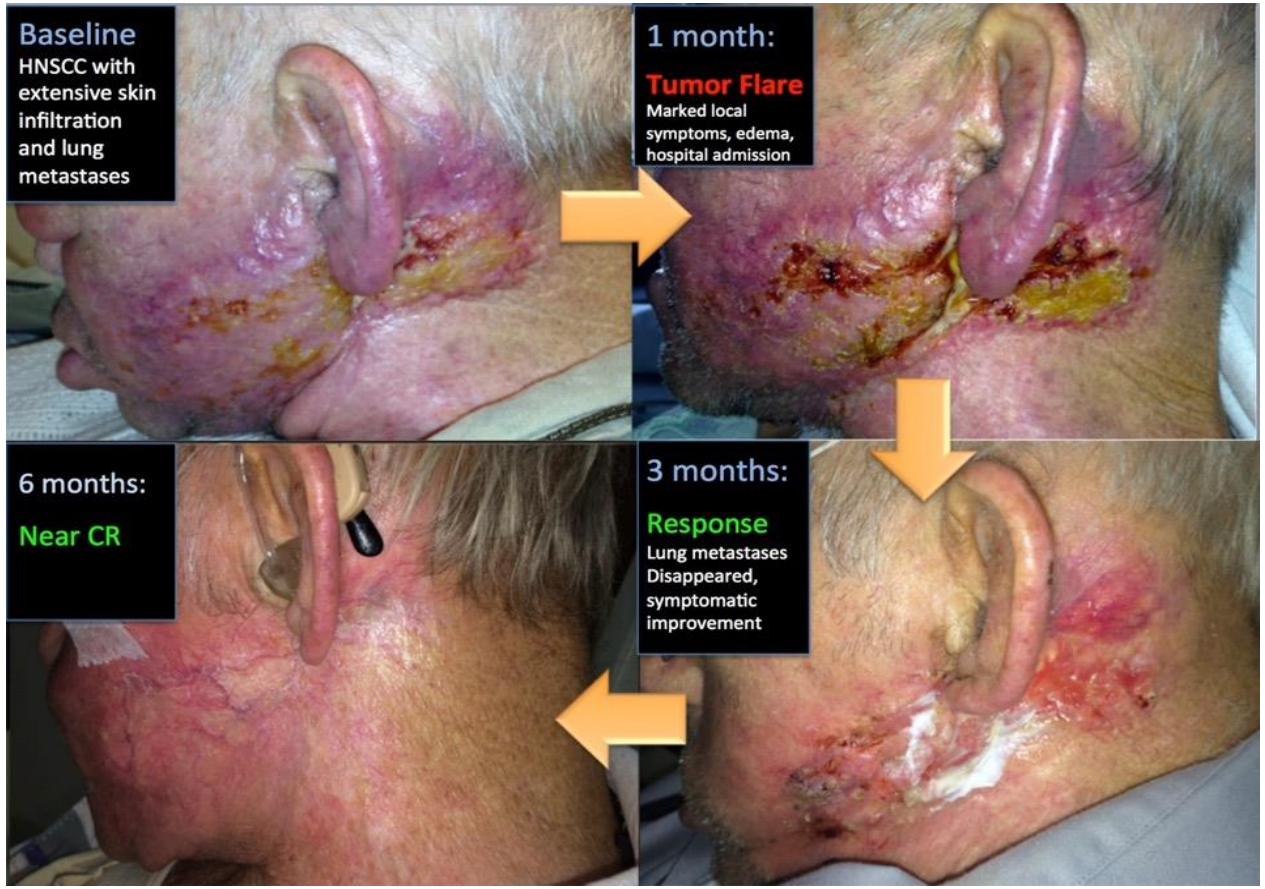
- Early appearance of an increase in tumor burden, subsequently followed by tumor regression
- Initially recognized in the melanoma trials, with incidence up to 10%



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

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

Case Report – KEYNOTE-012



- Both KEYNOTE-012 and CheckMate 141 trials showed an exceedingly rare rate of pseudoprogression with pembrolizumab and nivolumab, respectively.

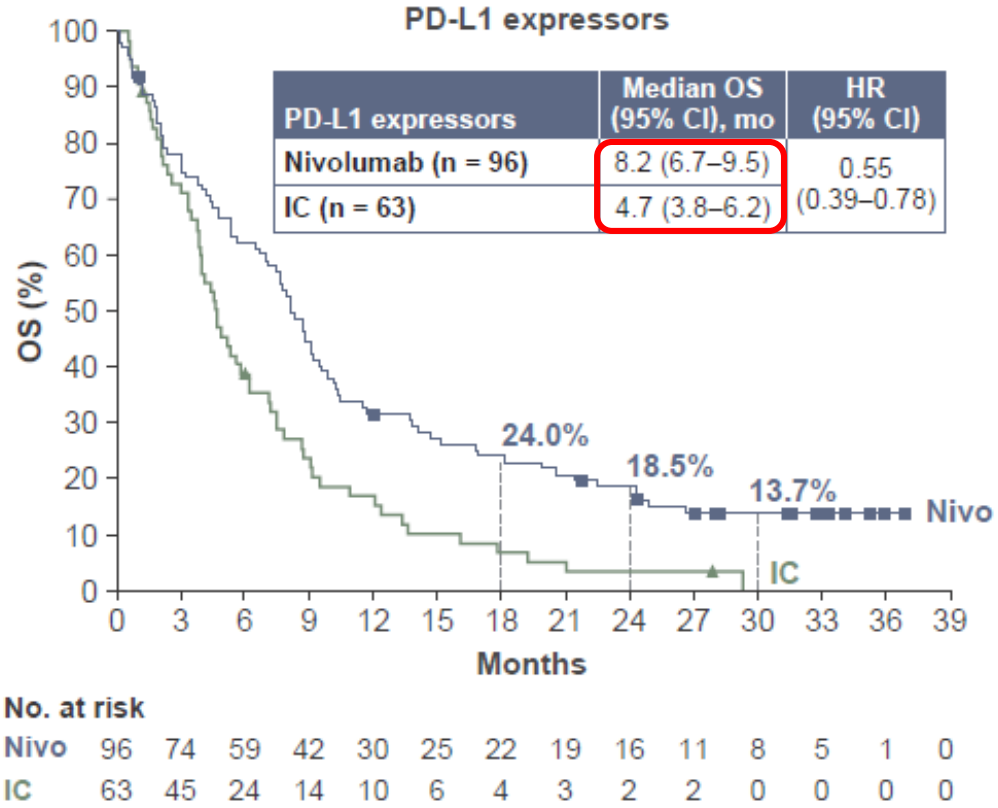
Ferris RL, et al. N Engl J Med. 2016
Seiwert TY, et al. Lancet Oncol. 2016

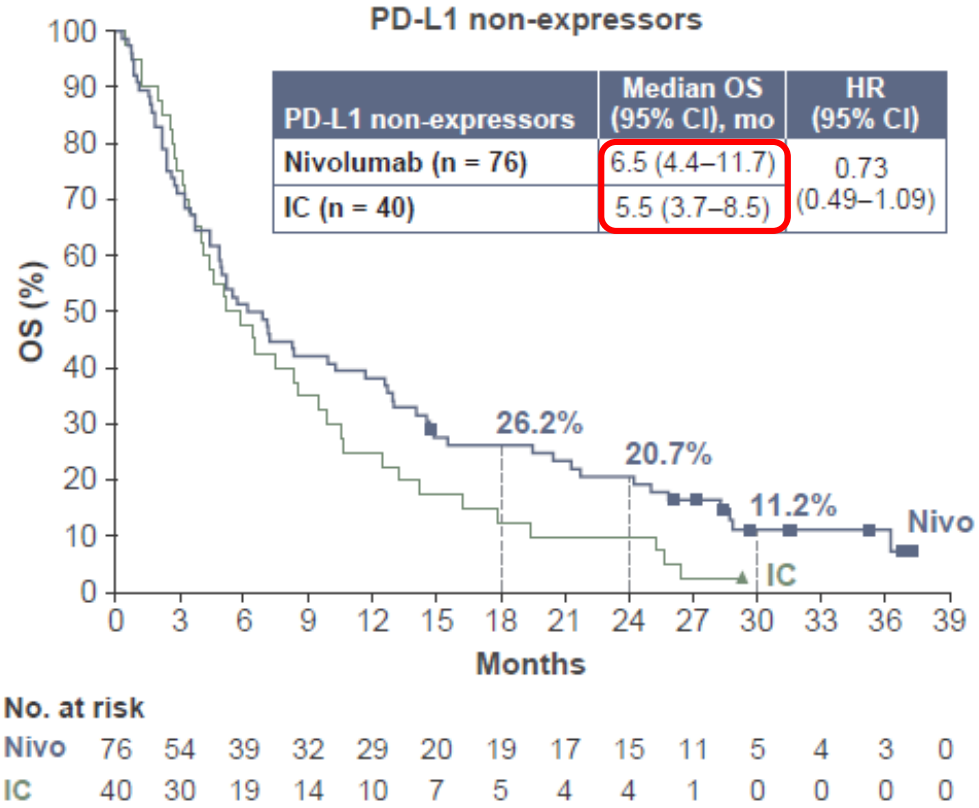
Evaluating Biomarkers in HNSCC

- Current FDA approvals of pembrolizumab and nivolumab are NOT contingent upon tumor PD-L1 status
  - KEYNOTE - 012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
  - KEYNOTE - 040: Phase III pembrolizumab vs. investigator's choice chemotherapy
    - Did not meet survival endpoints in total population but improved outcomes in patients with PD-L1 expressing tumor
  - CheckMate 141: Most benefit was seen in PD-L1-positive tumors

Evaluating Biomarkers in HNSCC

CheckMate 141: 2 year update





Immune-related Adverse Events

KEYNOTE 012

Table 2. Treatment-Related Adverse Events by Grade Severity (all-patients-as-treated population; N = 132)

Treatment-Related Adverse Event	Grade 1 or 2 (≥ 10% of patients), No. (%)	Grade 3 (any occurrence), No. (%)	Grade 4 (any occurrence), No. (%)
Patients with ≥ 1 event	70 (53)	8 (6)	4 (3)
Hypothyroidism	14 (11)	0	0
Immune thrombocytopenic purpura	0	0	1 (1)
Abdominal pain	1 (1)	1 (1)	0
Colitis	0	1 (1)	0
Dysphagia	1 (1)	1 (1)	0
Nausea	6 (5)	1 (1)	0
Stomatitis	1 (1)	1 (1)	0
Facial edema	0	1 (1)	0
Fatigue	28 (21)	0	0
Localized edema	0	1 (1)	0
Infection	0	1 (1)	0
Decreased appetite	9 (7)	2 (2)	0
Dehydration	0	1 (1)	0
Diabetic ketoacidosis	0	0	1 (1)
Hyperglycemia	1 (1)	0	1 (1)
Type I diabetes mellitus	0	1 (1)	0
Laryngeal edema	0	0	1 (1)
Pneumonitis	2 (2)	2 (2)	0
Respiratory distress	0	1 (1)	0
Facial swelling	3 (2)	1 (1)	1 (1)

CheckMate 141

Event	Nivolumab (N=236)	
	Any Grade	Grade 3 or 4
Any event	139 (58.9)*	31 (13.1)
Fatigue	33 (14.0)	5 (2.1)
Nausea	20 (8.5)	0
Rash	18 (7.6)	0
Decreased appetite	17 (7.2)	0
Pruritus	17 (7.2)	0
Diarrhea	16 (6.8)	0
Anemia	12 (5.1)	3 (1.3)
Asthenia	10 (4.2)	1 (0.4)
Vomiting	8 (3.4)	0
Dry skin	7 (3.0)	0
Stomatitis	5 (2.1)	1 (0.4)
Weight loss	4 (1.7)	0
Mucosal inflammation	3 (1.3)	0
Peripheral neuropathy	1 (0.4)	0
Alopecia	0	0
Neutropenia	0	0

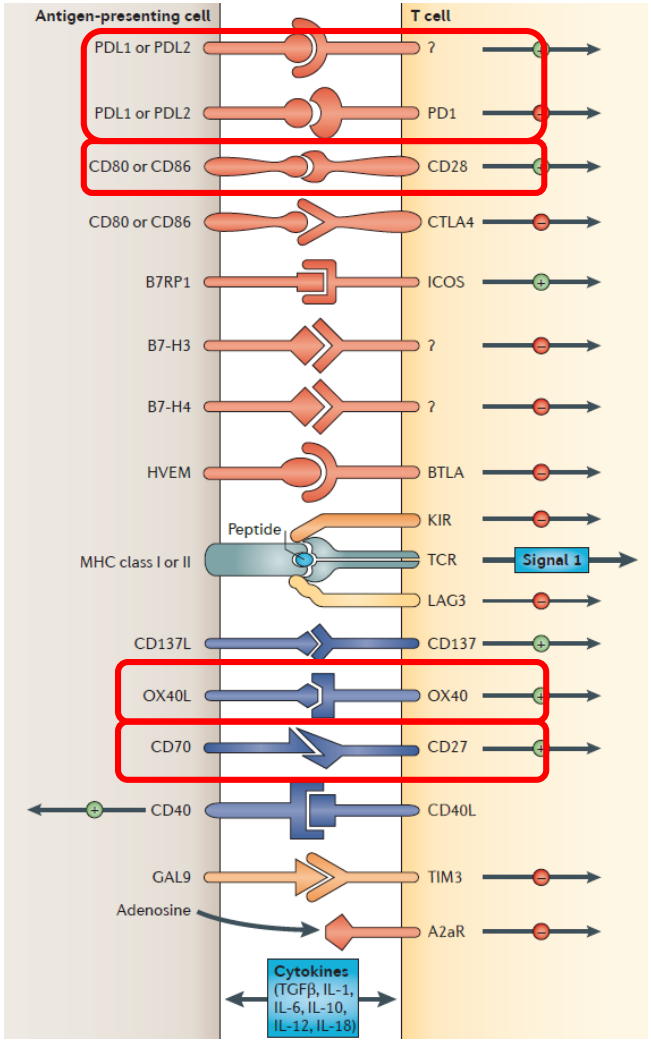
Immune-related Adverse Events

Table 2 General guidance for corticosteroid management of immune-related adverse events

Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	• Corticosteroids not usually indicated	• Continue immunotherapy
2	• If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication. • If IV required, start methylprednisolone 0.5-1 mg/kg/day IV • If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day • Once improved to ≤grade 1 AE, start 4–6 week steroid taper	• Hold immunotherapy during corticosteroid use • Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor for GI prophylaxis
3	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant • Once improved to ≤ grade 1, start 4–6-week steroid taper • Provide supportive treatment as needed	• Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy • Consider intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)
4	• Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab • Provide supportive care as needed	• Discontinue immunotherapy • Continue intravenous corticosteroids • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day)

Puzanov Journal for ImmunoTherapy of Cancer 2017

Developmental Immunotherapies for HNSCC



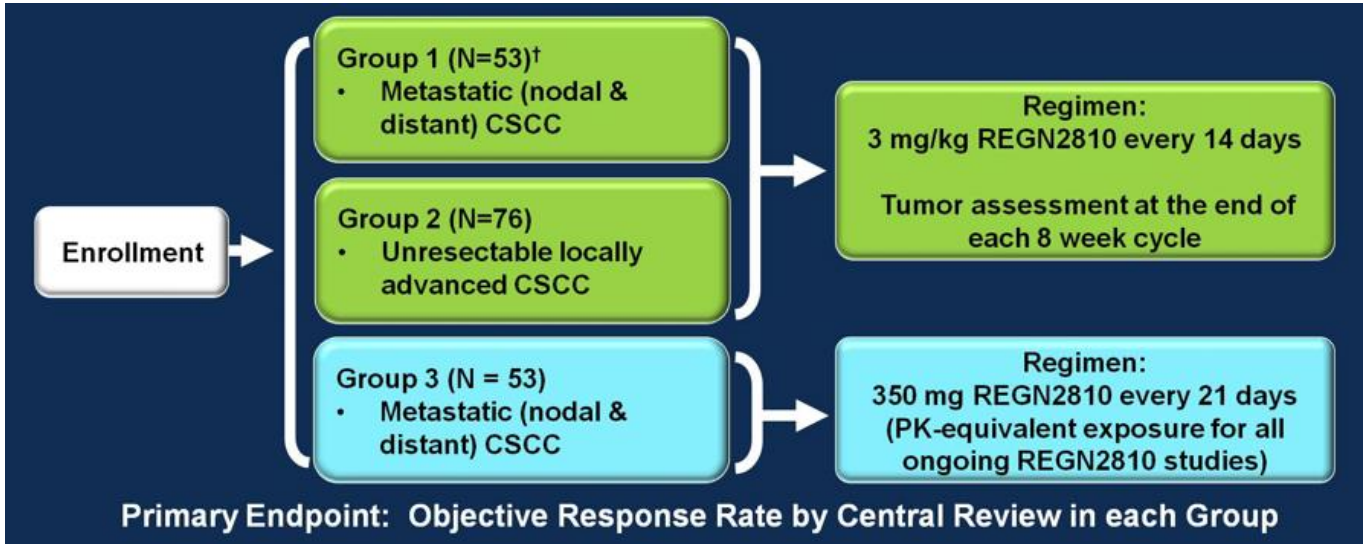
Pardoll DM Nature 2012

- Durvalumab, atezolizumab, avelumab, CK-301 (anti-PD-L1)
- Cemiplimab (anti-PD-1)
- Ipilimumab, tremelimumab (anti-CTLA-4)
- Varlilumab (anti-CD27)
- PF-04518600, tavolimab (anti-OX40)

Developmental Immunotherapies for HNSCC

Cemiplimab (REGN2810) for treatment of patients with cutaneous squamous cell carcinoma (cSCC)

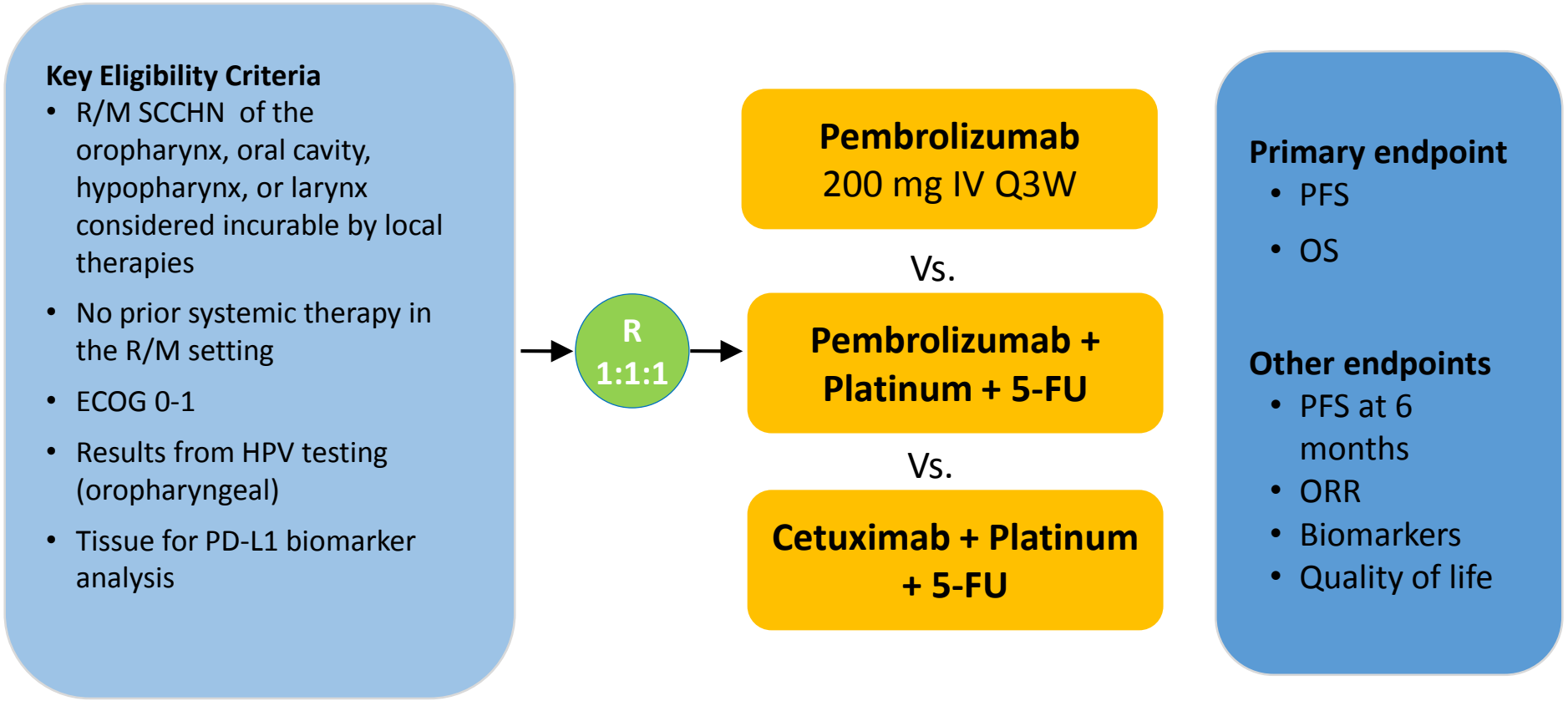
NCT02760498



- Largest prospective study in this disease
- ORR 46% in 82 patients in study
  - Much higher than RR in mucosal HNSCC as per KEYNOTE and CheckMate studies
- Responses durable, median DOR not reached
- Study ongoing

Developmental Immunotherapies for HNSCC

KEYNOTE – 048 (NCT02358031)



Developmental Immunotherapies for HNSCC

MASTERKEY 232/KEYNOTE-137

- Talimogene laherparepvec (T-Vec)
  - Genetically engineered herpes virus
- T-Vec 10^6 PFU/mL intratumoral injection followed by 10^8 PFU/mL Q3W
- Pembrolizumab 200 mg IV Q3W
- Eligibility:
  - R/M HNSCC not suitable for curative therapy
  - Progressed after platinum treatment
  - At least 1 injectable cutaneous, subcutaneous, or nodal tumor ≥ 10 mm in longest diameter

Patient Case Studies

Patient Case Study 1

- Patient 1 has metastatic squamous cell carcinoma of the hypopharynx to the lungs
- Past medical history of:
  - Hypertension
  - Hyperlipidemia
  - COPD
- Treated with pembrolizumab
- Presented to the ER with worsening and progressive shortness of breath

Patient 1 – in the ER

- Chest x-ray: no evidence of pneumonia, but small pleural effusions
- Oxygen supplementation with mild improvement
- Afebrile
- WBC 5.2

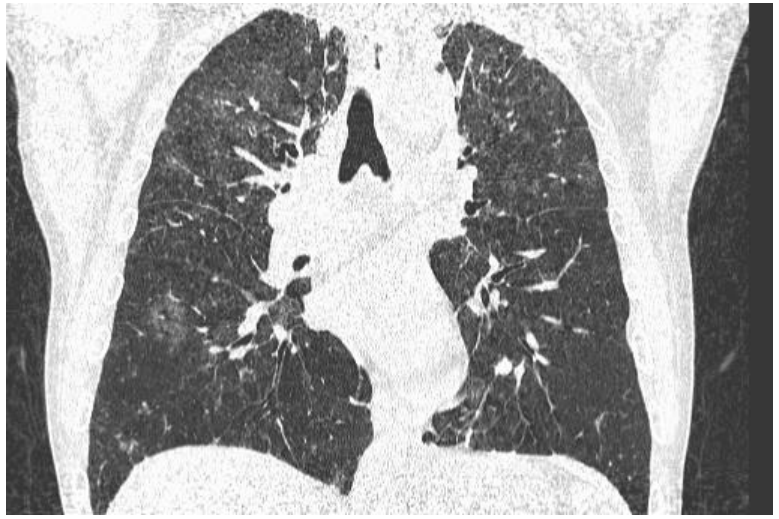
Patient 1 – Next Steps

- Raise your hand to indicate you would select option A, B or C
- **Option A:** CT chest, pulmonary consult, possible bronchoscopy
- **Option B:** initiation of corticosteroids (prednisone), oxygen supplementation, notify oncologist
- **Option C:** IV antibiotics, oxygen supplementation

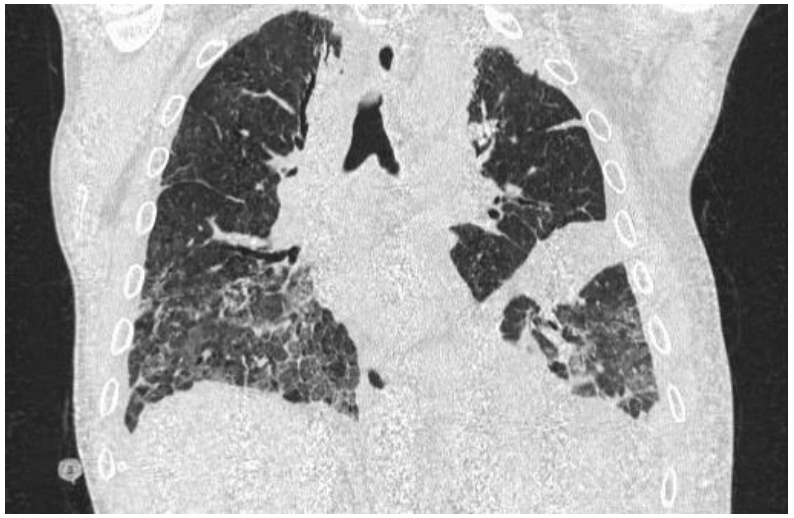
Patient 1 – Next Steps

- Pulmonary consulted
  - Thoracentesis: No malignant cells
  - Bronchoscopy: Negative for legionella, mycoplasma, chlamydia pneumonia, Haemophilus influenza
- CT chest:
  - Ground glass opacities noted throughout
  - Superimposed septal thickening

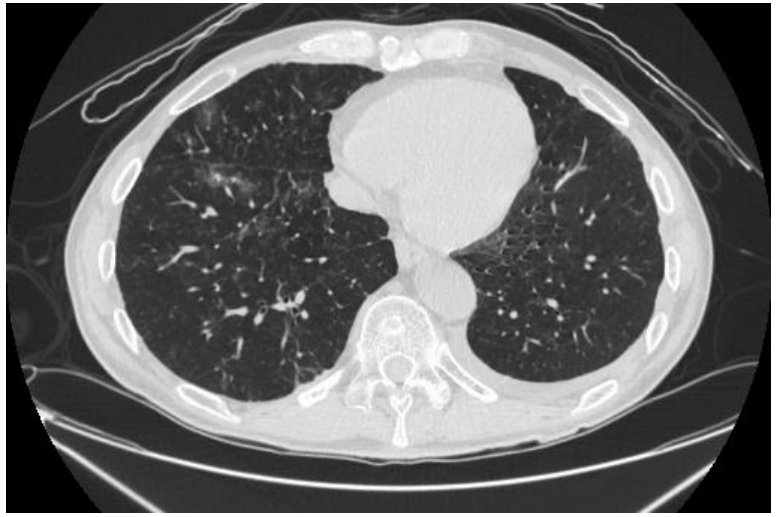
Patient 1 – Imaging Studies

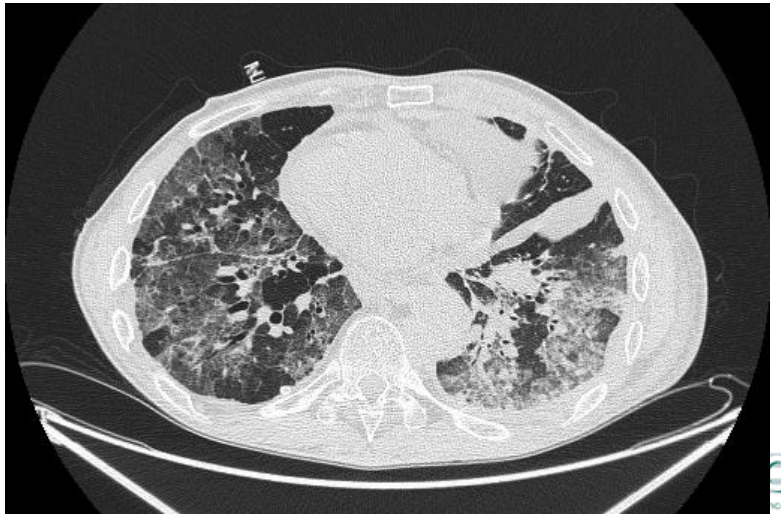


Before pembrolizumab



After pembrolizumab





Pneumonitis

- Uncommon but potentially severe/fatal complication
- Overall incidence is 5%
- Diagnosis of exclusion
  - Make sure that infection and malignancy are excluded
- Treatment:
  - Withholding the checkpoint inhibitor
  - Initiation of corticosteroids (prednisone 1-2 mg/kg daily)
  - Must have a slow steroid taper (typically 30-60 days)

Rechallenge?

- Could potentially rechallenge the patient after resolution of pneumonitis
  - Grade 2 (moderate) or less pneumonitis
  - Needs discussion with the patient regarding recurrence of pneumonitis
- Grade 3 or 4 pneumonitis (severe or life-threatening)
  - Permanent discontinuation of checkpoint inhibitor

Patient Case Study 2

- 62 year old with metastatic squamous cell carcinoma of the oropharynx (p16 positive)
- ECOG performance status 0
- Prior treatments include:
  - Cisplatin/radiotherapy
  - 5FU/carboplatin/cetuximab (EXTREME regimen) x 6 cycles with initial response, then progression
- Started nivolumab treatment for disease progression

Patient 2: In Clinic

- Here for cycle 2 treatment
- Asymptomatic

	Baseline	After cycle 1
AST	41	481
ALT	38	639
Alk Phos	135	148
Total Bilirubin	0.3	0.4
Amylase	74	61
Lipase	37	29

Patient 2: In clinic

- Raise you hand to indication your selection (option A, B or C)
- **Option A:** proceed with cycle 2
- **Option B:** hold Nivolumab
- **Option C:** hold Nivolumab and add corticosteroid

Patient 2: Treatment

- Nivolumab was withheld
- Patient initiated on prednisone 1 mg/kg
  - Tapered over 6 weeks

	Baseline	After cycle 1	2 weeks later On prednisone	8 weeks later Tapered off prednisone
AST	41	481	209	39
ALT	38	639	384	40
Alk Phos	135	148	102	117
Total Bilirubin	0.3	0.4	0.2	0.5
Amylase	74	61		72
Lipase	37	29		35

Immunotherapy Induced Hepatitis

- Elevated hepatic enzymes (AST, ALT) can be seen with checkpoint inhibitors
- Rarely elevated total bilirubin
- Most patients are asymptomatic
  - Could have associated fevers
- Typically occurs 8-12 weeks after initiation of treatment
- Incidence: <10% of patients on checkpoint inhibitors

Immunotherapy Induced Hepatitis

- Must exclude viral or drug induced causes of hepatitis
  - Check the hepatitis serologies
  - Have pharmacy double check concomitant medications
- Treatment
  - Hold checkpoint inhibitor
  - Initiate corticosteroids
    - Prednisone 0.5-1 mg/kg/day, if asymptomatic
    - Prednisone 1-2 mg/kg/day, if symptomatic
  - If LFTs are worsening, can use mycophenolate mofetil
    - Avoid infliximab
    - Consult hepatology

Patient 2: In Clinic

- Completely tapered off Prednisone
- LFTs returned to baseline
- Repeat CT imaging demonstrated disease response with significant shrinkage of metastatic lesions
- Given the disease response, patient elected to pursue surveillance
- 12 months later, noted to have increasing size of pulmonary lesions

Immunotherapy Induced Hepatitis

- Completely asymptomatic
- Patient previously responded to checkpoint inhibitors
  - Only received 1 cycle of Nivolumab
- Patient was a nurse and fully understood the risks
- Very motivated given significant disease burden

Patient 2: Disease Progression

- Who would rechallenge the patient?

Option A: Rechallenge the patient

Option B: No way!

Patient 2: Rechallenge?

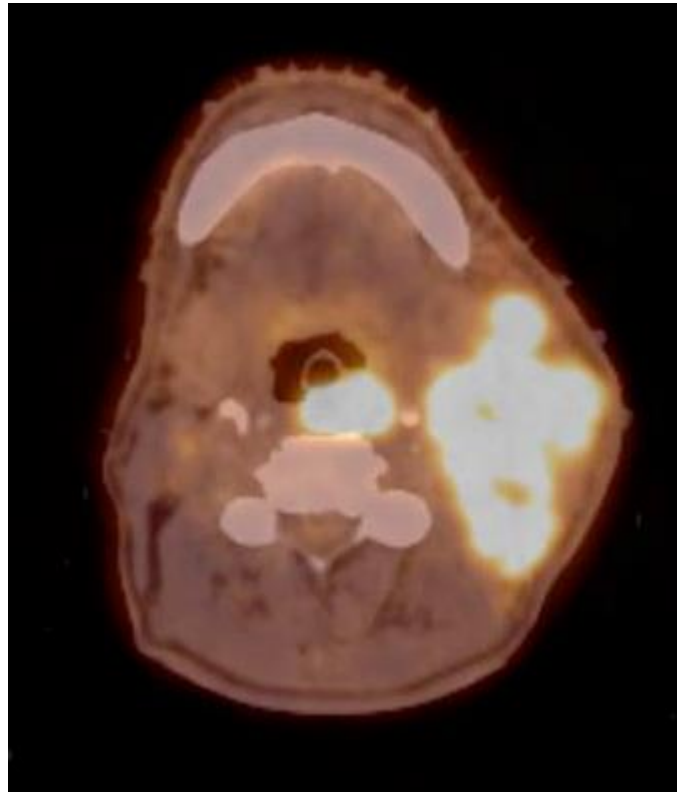
- Real struggle to decide the best treatment option
- Per FDA package insert, the hepatitis was considered grade 3 (5-20 x ULN)
  - Remember: After cycle 1
    - AST 481 (range 5-34)
    - ALT: 639 (range 0-55)
  - For patients without hepatocellular carcinoma, permanently discontinue Nivolumab for severe (grade 3) or life-threatening (grade 4) immune-mediated hepatitis
- Ultimately did not want to purse additional treatment → hospice

Patient Case Study 3

- 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

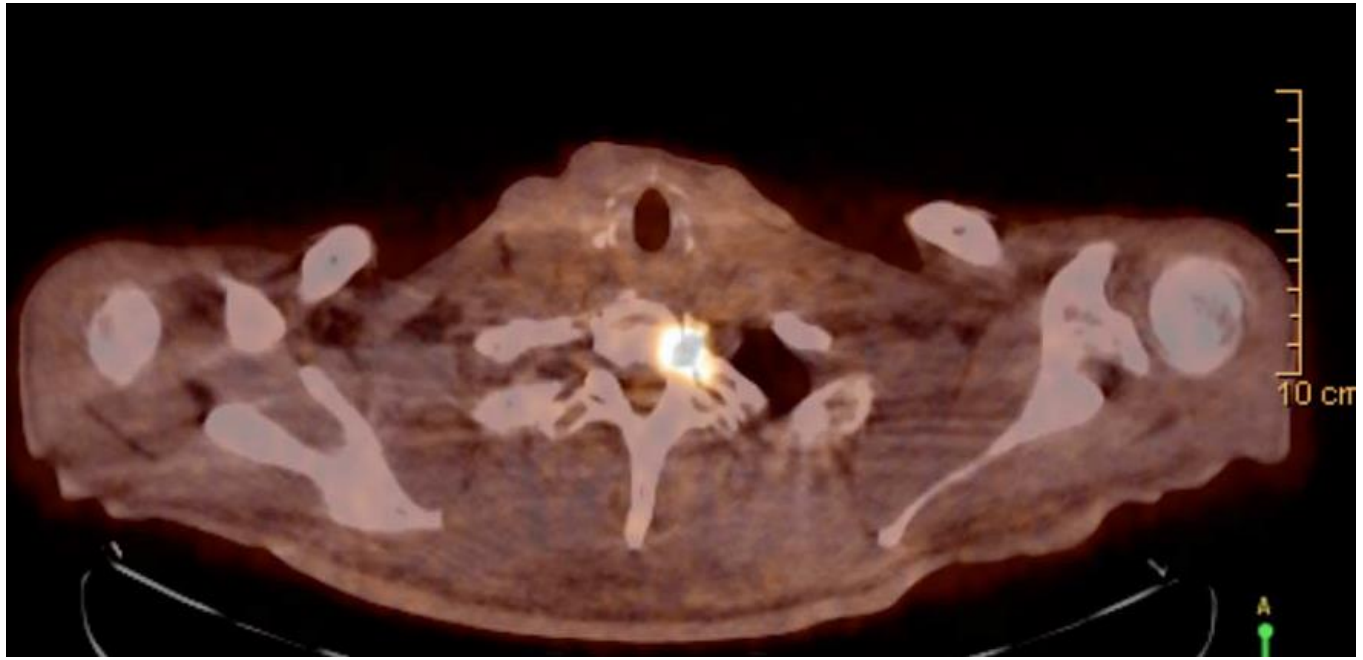
Patient Case Study 3
November 2014

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



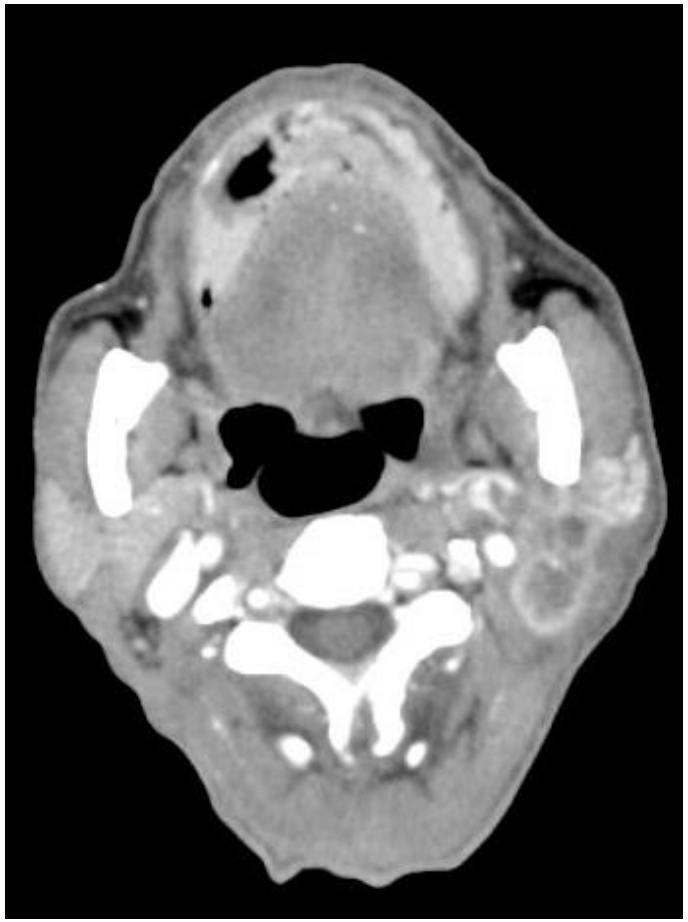
Patient Case Study 3
January 2015

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



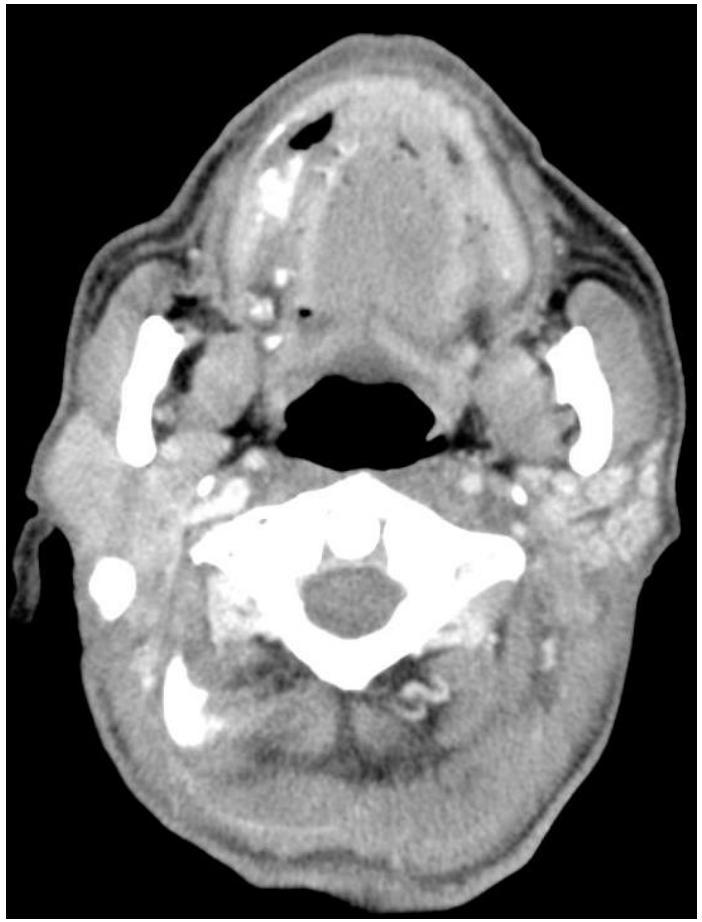
Patient Case Study 3
June 2015

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



Patient Case Study 3
October 2015

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



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 inhibitors than on chemotherapy
4. Clinical trials are underway to improve immunotherapy response rates and testing immunotherapy in other settings