Society for Immunotherapy of Cancer

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Immunotherapy for the Treatment of Head and Neck Cancer

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

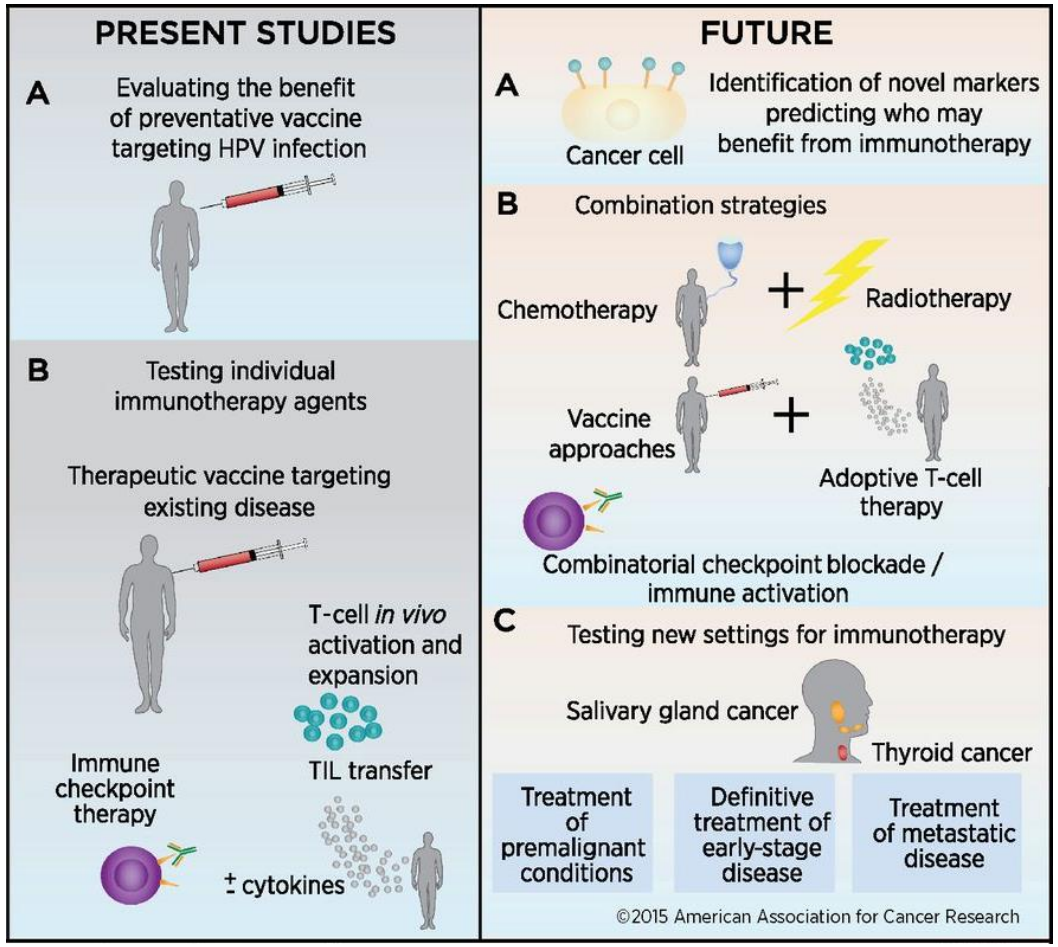
Society for Immunotherapy of Cancer

Disclosures

- Relevant financial relationships to disclose: institutional support from BMS and EMD Serono
- I will not be discussing non-FDA approved indications during my presentation.

Immunotherapy for the Treatment of Head and Neck Cancers

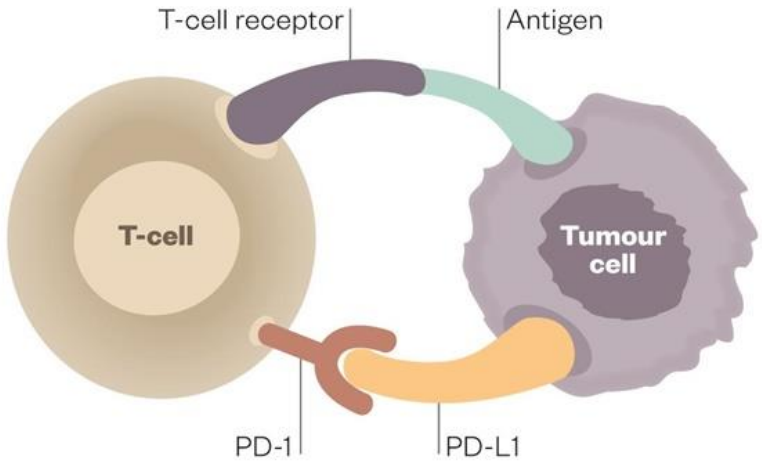
- Immuno-Oncology (I-O) developments in treatment of head and neck cancers
  - Expression of immunologic markers to guide treatment
  - Vaccination strategies against virally mediated cancers
  - PD-1 checkpoint inhibitors for the treatment of metastatic disease



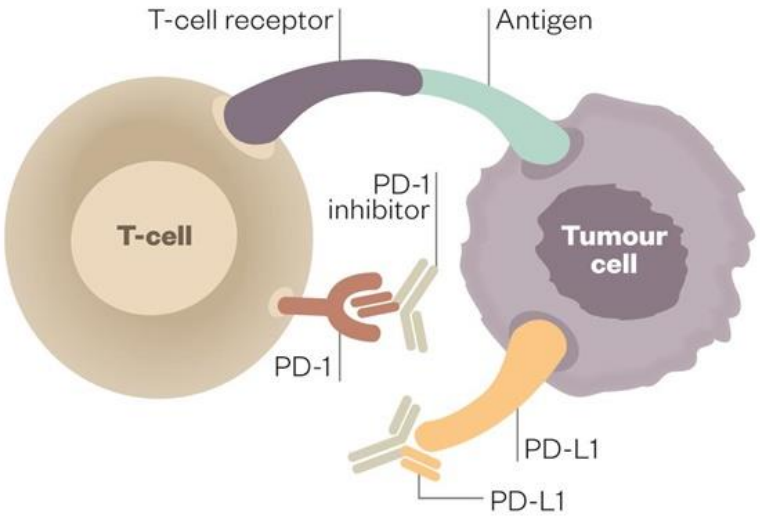
Schoenfeld JD, Cancer Immunol Res, 2015

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

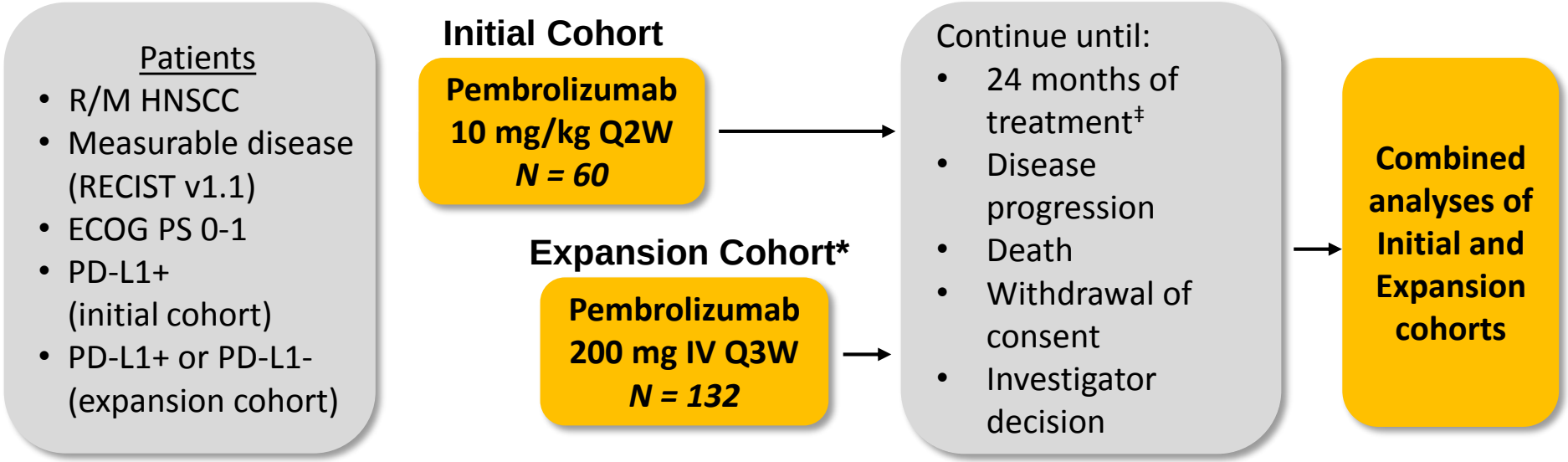
FDA-approved Checkpoint Inhibitors for Use in Head and Neck Cancers

- 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

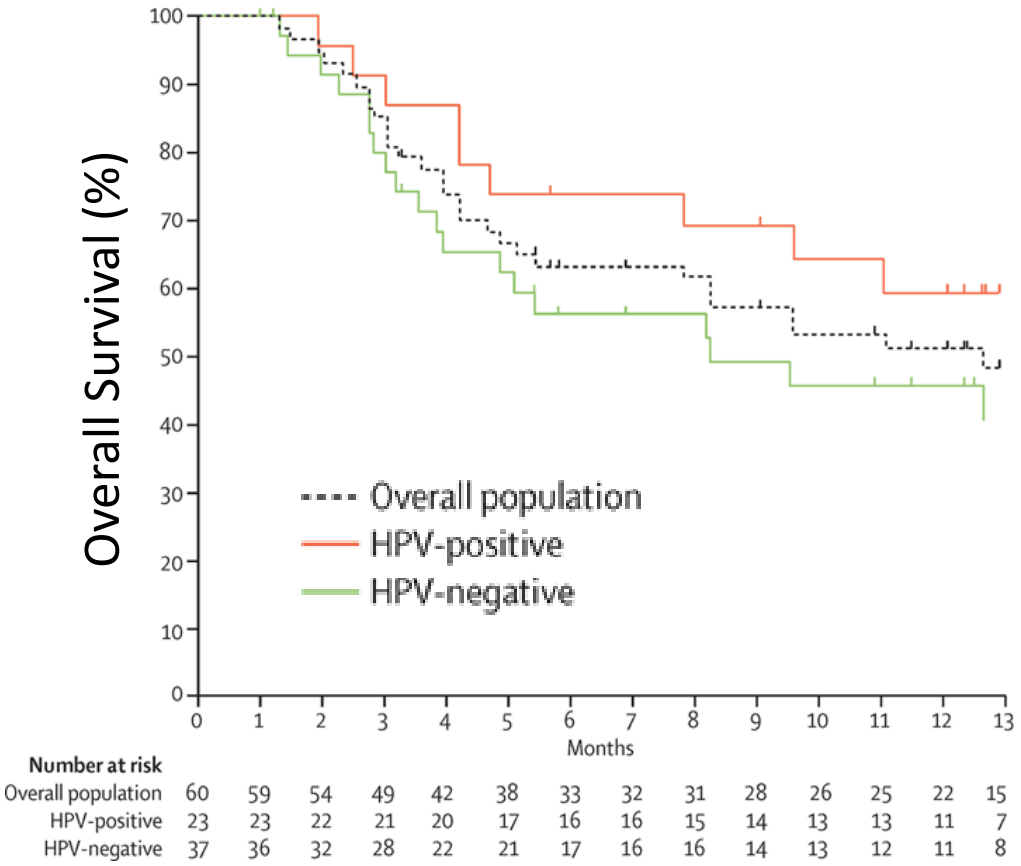
Primary end points: ORR (RECIST v1.1, central imaging vendor review), safety

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

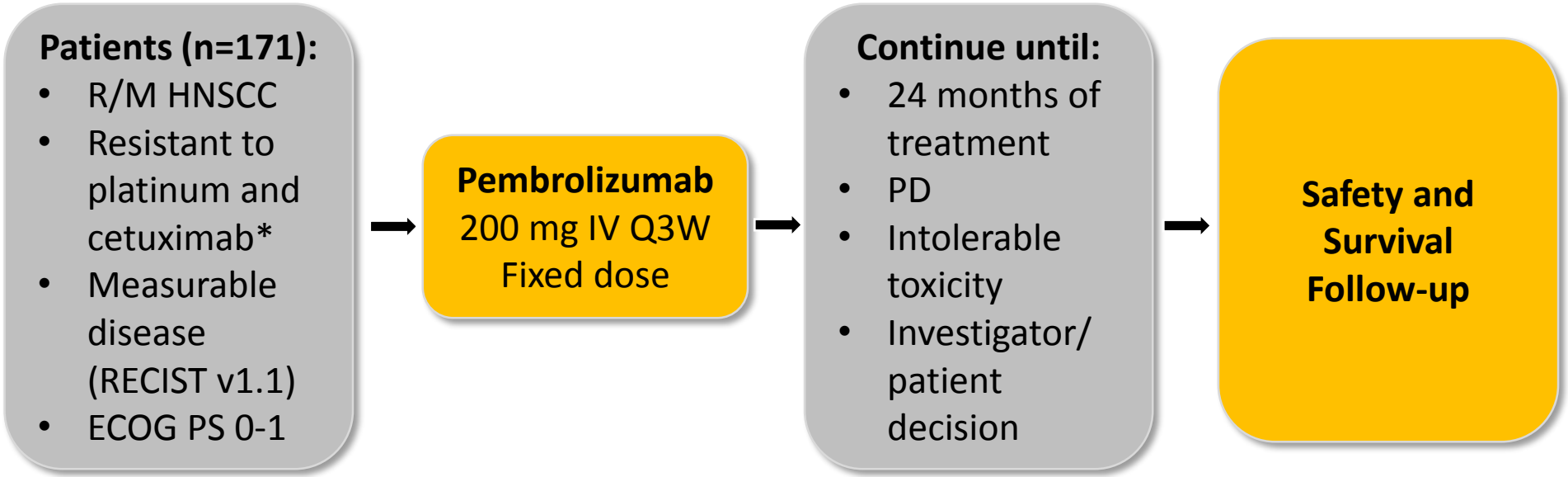
Nonrandomized, Phase 1b Trial, Cohorts† B, B2



- 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.

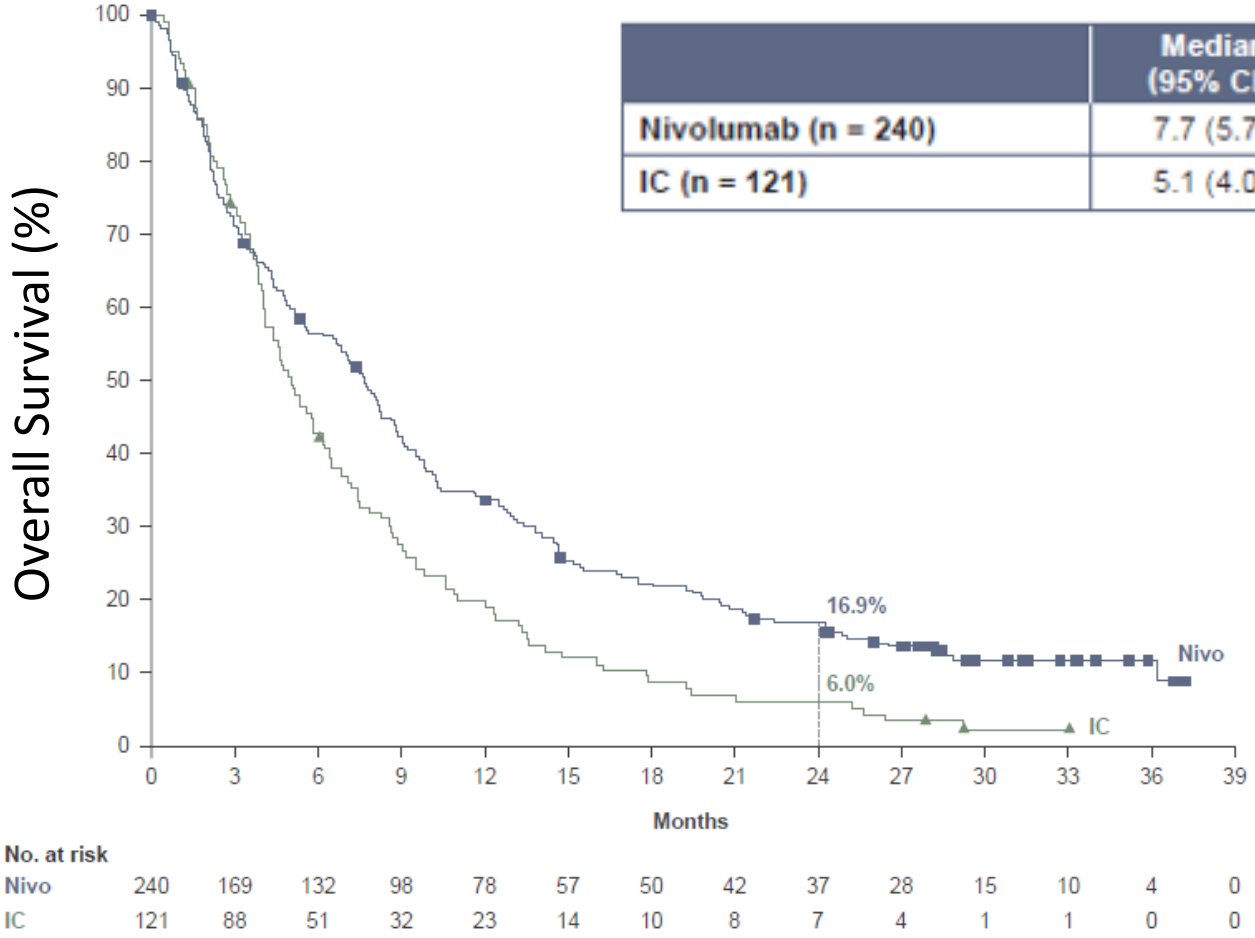
[a]Tissue required for testing

Ferris & Gillison, NEJM, 2016

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

Overall Survival: 2 year report

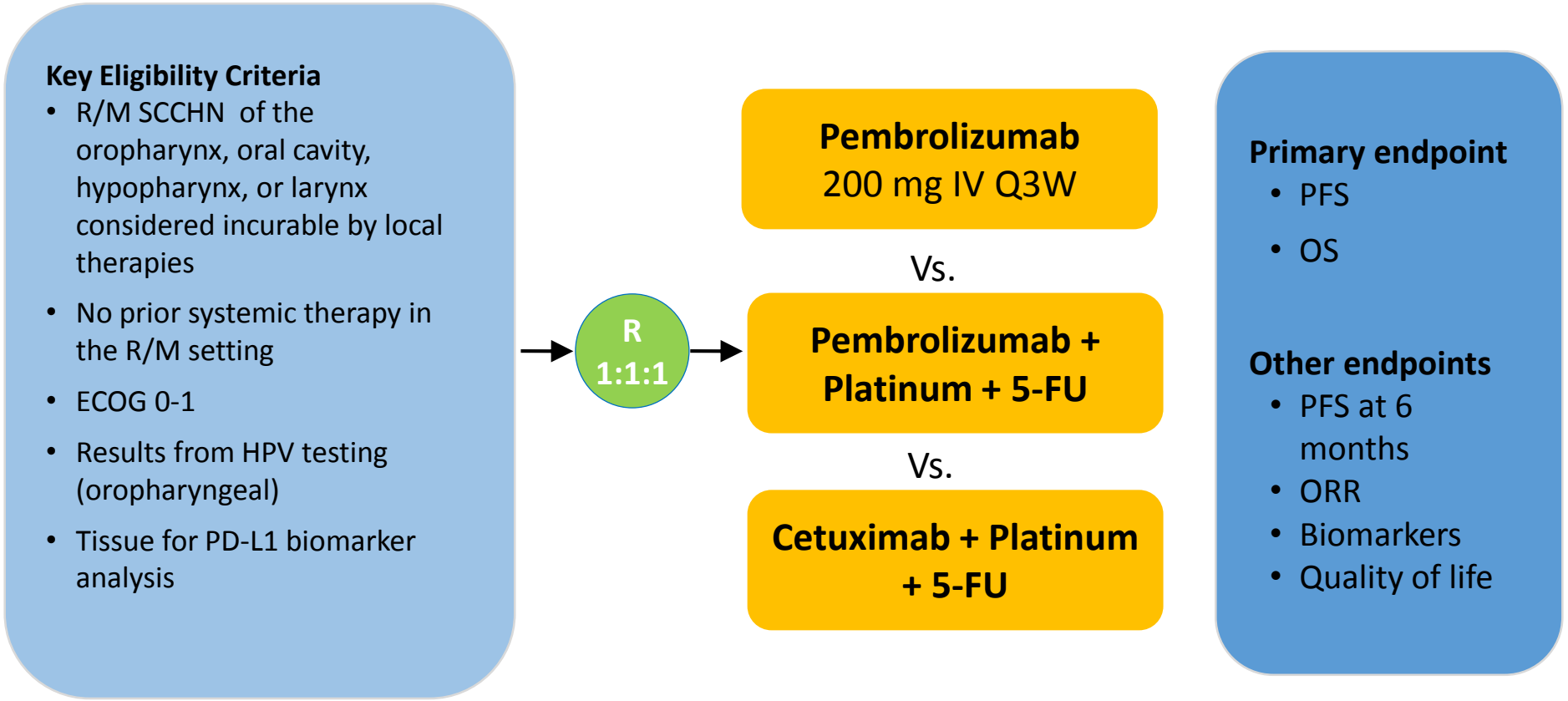
	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 240)	7.7 (5.7–8.8)	0.68 (0.54–0.86)
IC (n = 121)	5.1 (4.0–6.2)	



Ferris RL. Oral Oncology, 2018

Developmental Immunotherapies for HNSCC

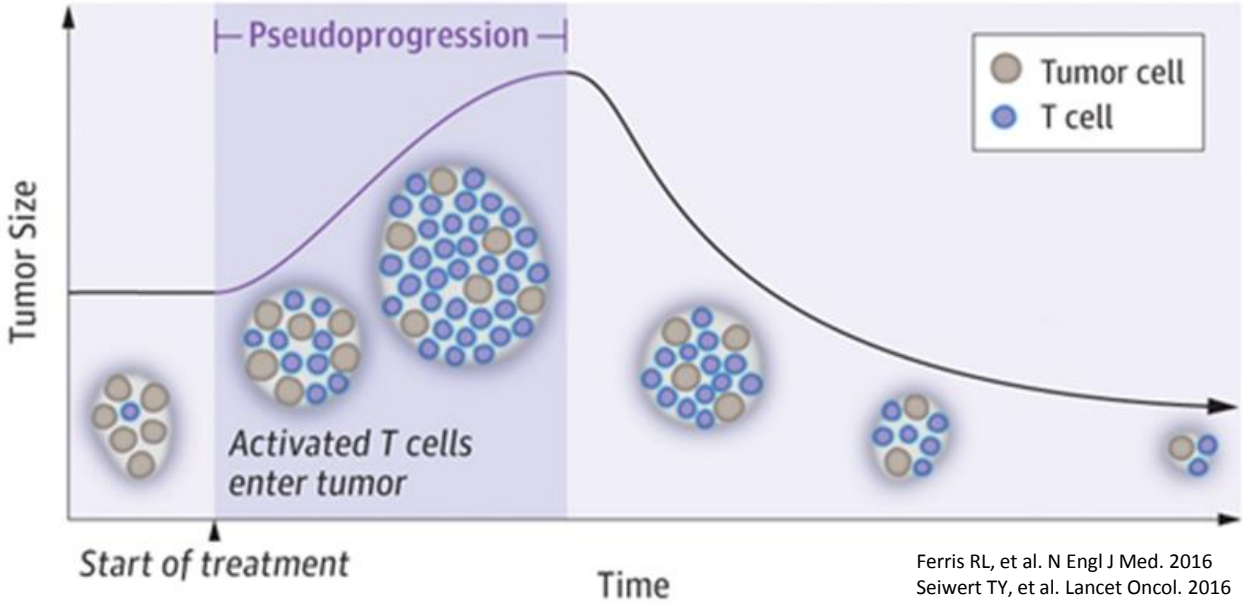
KEYNOTE – 048 (NCT02358031)



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

Pseudoprogression

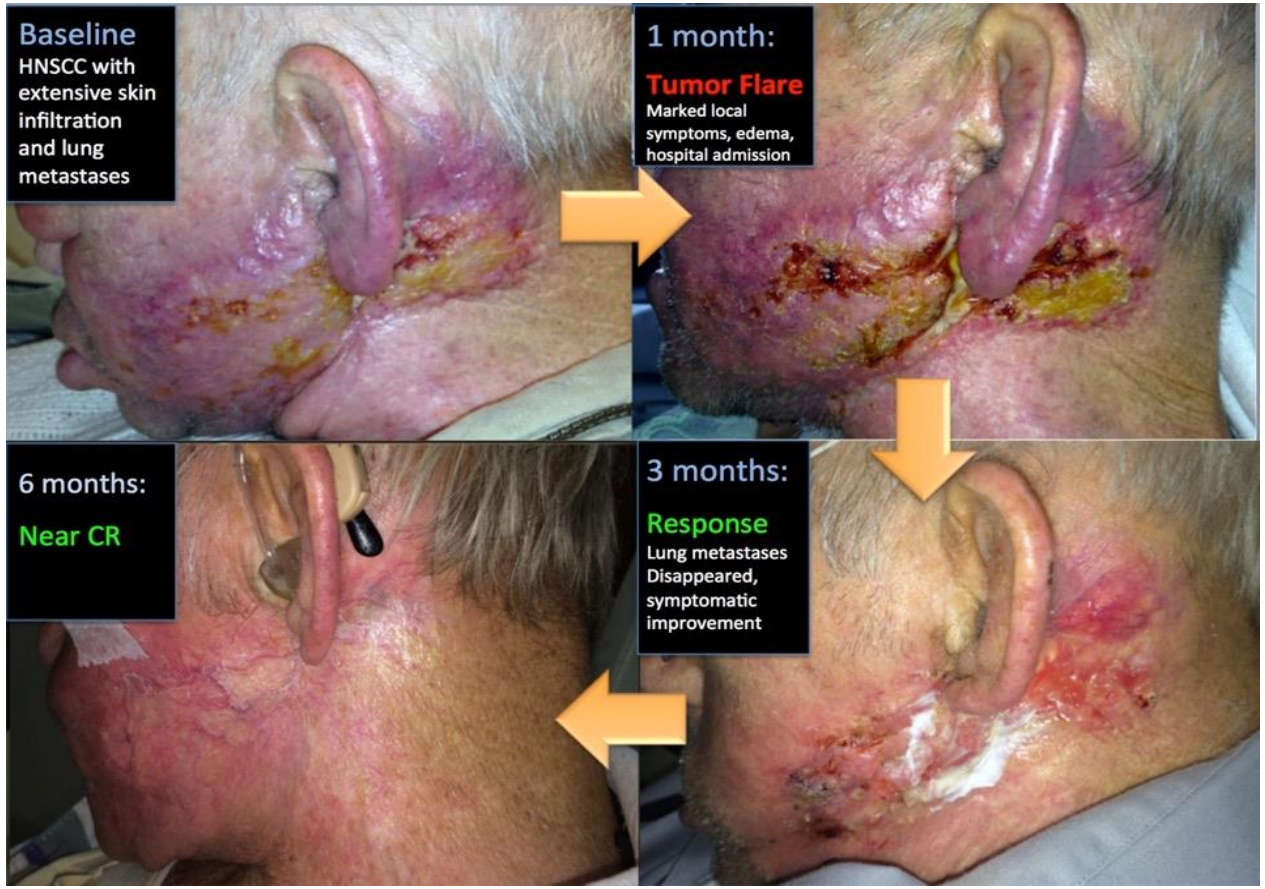
- Early appearance of an increase in tumor burden, subsequently followed by tumor regression
- Initially recognized in the melanoma trials, with incidence up to 10%



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.

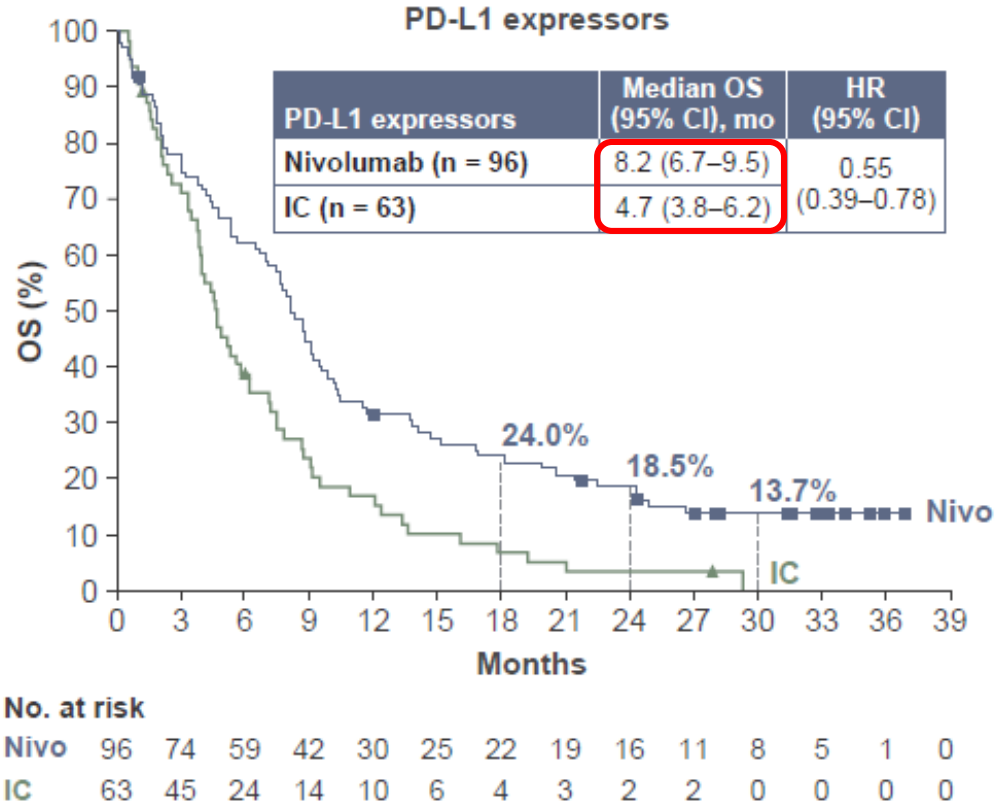
Ferris RL, et al. N Engl J Med. 2016
Seiwert TY, et al. Lancet Oncol. 2016

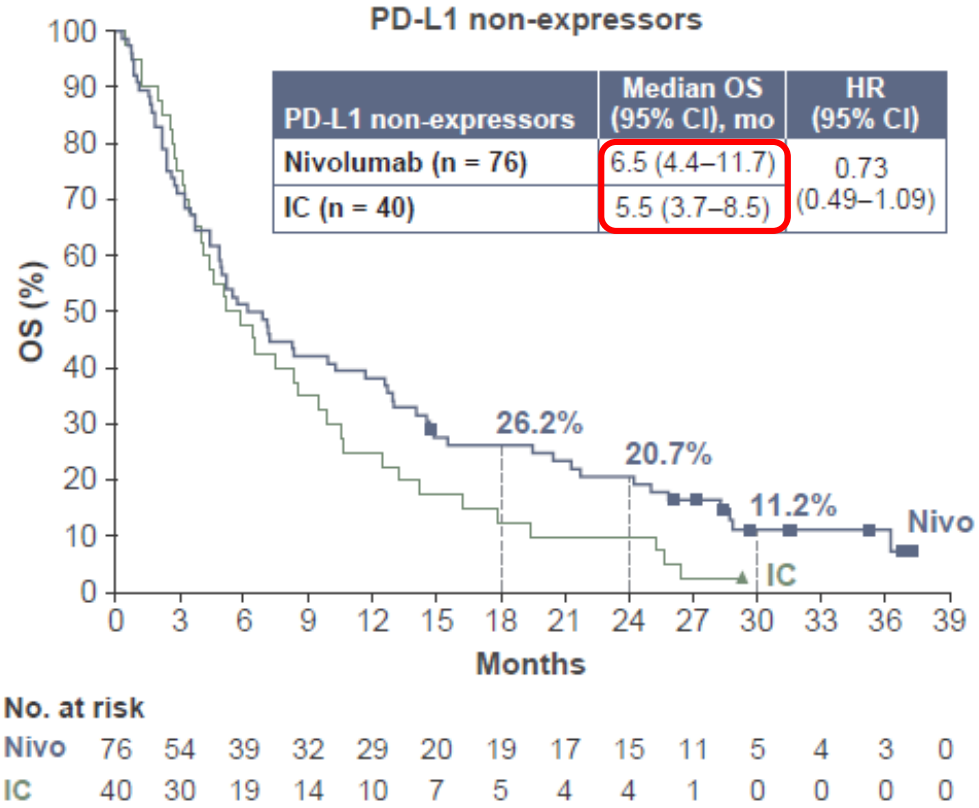
Evaluating Biomarkers in HNSCC

- 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 (as of AACR presentation in April 2018, the OS endpoint was reached with a HR 0.8 and p = 0.016)
  - CheckMate 141: Most benefit was seen in PD-L1-positive tumors

Evaluating Biomarkers in HNSCC

CheckMate 414: 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

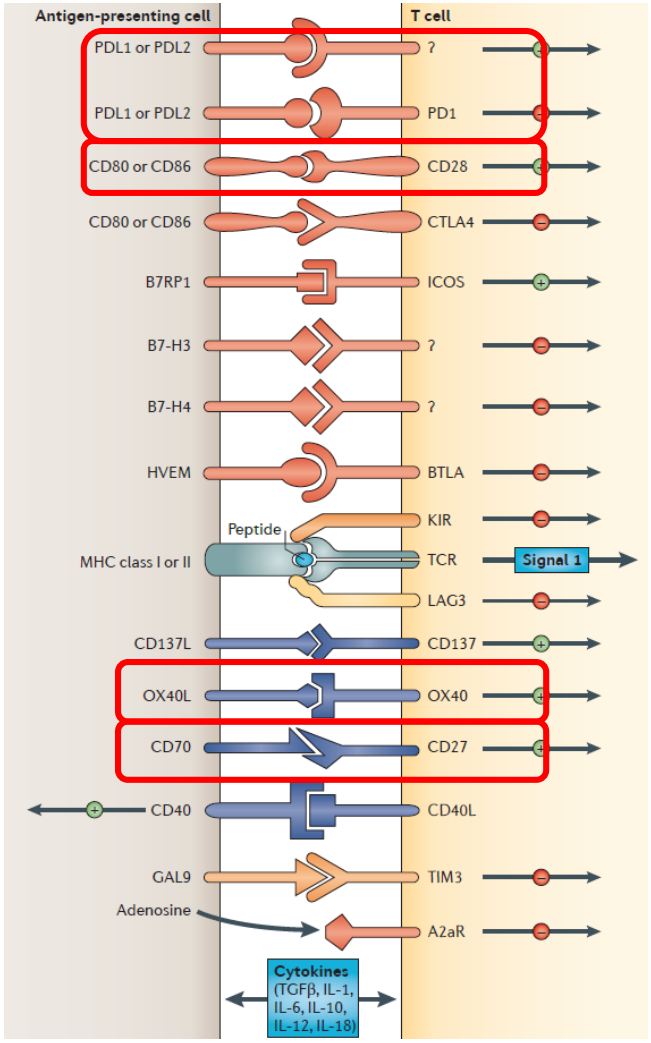
Immune-related Adverse Events

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



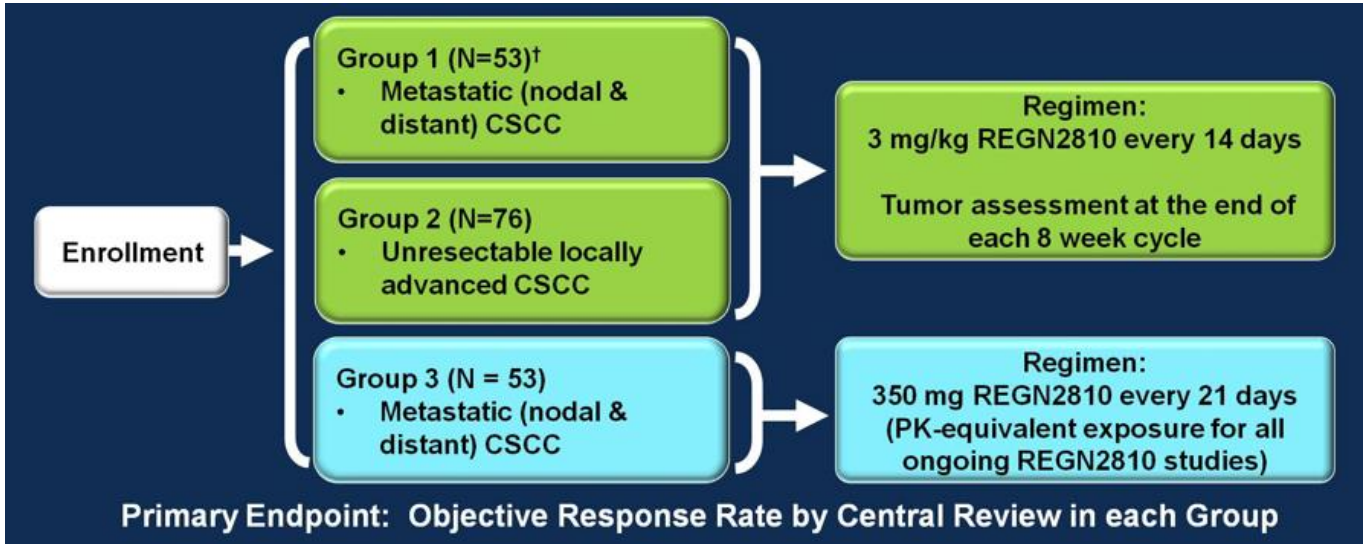
Pardoll DM Nature 2012

- 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 47% in 82 patients in study
  - Much higher than RR in mucosal HNSCC as per KEYNOTE and CheckMate studies
- Responses durable, median DOR not reached

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

Case Studies

Case 1

54M (never smoker) diagnosed in December 2017 with metastatic HPV+ SCC arising in the right oropharynx involving several osseous sites

Staging: cT3N2M1 (stage IV, AJCC 2017 8th ed)

He started first-line platinum-based chemotherapy plus cetuximab in **January 2018**

Case 1

54M (never smoker) diagnosed in December 2017 with metastatic HPV+ SCC arising in the right oropharynx involving several osseous sites

He started first-line platinum-based chemotherapy plus cetuximab in January 2018

Clinical exam and restaging scans confirmed an initial PR but he later developed both locoregional and distant progression

He switched to palliative nivolumab in **March 2018**

Case 1

54M (never smoker) diagnosed in December 2017 with metastatic HPV+ SCC arising in the right oropharynx involving several osseous sites

He switched to palliative nivolumab in March 2018

By **June 2018** restaging scans had shown stable disease at all sites

Case 1

54M (never smoker) diagnosed in December 2017 with metastatic HPV+ SCC arising in the right oropharynx involving several osseous sites

He switched to palliative nivolumab in March 2018 with SD

Event: call on 6/20 that he was brought to a local ED for an irregular heartbeat and palpitations followed by syncope or LOC…

Case 1

54M (never smoker) with metastatic HPV+ SCC arising in the right oropharynx involving several osseous sites on nivolumab with SD

Event: call on 6/20 that he was brought to a local ED for an irregular heartbeat and palpitations followed by syncope or LOC

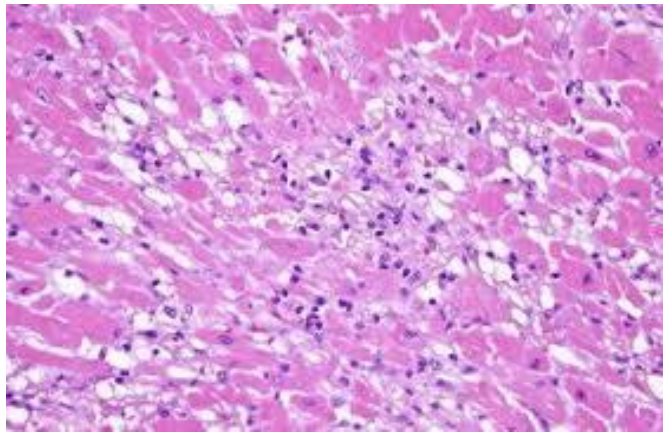
- admitted to CCU for a junctional rhythm with frequent pauses and hypotension requiring a PPM
- Trop T-hs Gen5 peaked at 19, pro-BNP 949, CRP 2.1
- TTE shows an LVEF 62%, normal RV/LV function, normal valves
- Cath was without significant CAD, endomyocardial biopsy performed

Case 1

54M (never smoker) with metastatic HPV+ SCC arising in the right oropharynx involving several osseous sites on nivolumab with SD

Event: developed cardiac nodal dysfunction and syncope with biopsy confirming focal lymphocytic myocarditis with macrophages and myocyte injury

Immune checkpoint inhibitor associated myocarditis



Case 1

54M (never smoker) with metastatic HPV+ SCC arising in the right oropharynx involving several osseous sites on nivolumab with SD

Immune checkpoint inhibitor associated myocarditis

Management:

- High dose corticosteroids with slow taper
- Trend cardiac biomarkers, cardiac MRI or TTE
- Onco-cardiology consultation required
- Permanent discontinuation of checkpoint blockade

Case 2

55M (never smoker) initially diagnosed with HPV+ SCC of the left base of tongue with ipsilateral level II/III cervical adenopathy in October 2016

Staging: cT4N1M0 (stage III, AJCC 2017 8th ed)

Treatment: definitive concurrent chemoradiation with weekly cisplatin ending February 2017

Case 2

55M (never smoker) initially diagnosed with HPV+ SCC of the left base of tongue with ipsilateral level II/III cervical adenopathy in October 2016

Staging: cT4N1M0 (stage III, AJCC 2017 8th ed)

Treatment: definitive concurrent chemoradiation with weekly cisplatin ending February 2017

Restaging: PET-CT in June 2017 shows local residual disease and new lung metastases

Case 2

55M (never smoker) with platinum-refractory, locoregionally persistent and now metastatic HPV+ SCC of the left base of tongue with pulmonary involvement

Restaging: PET-CT in June 2017 shows local residual disease and new lung metastases

What would be your next line of therapy outside of a clinical trial?

A. Platinum-based chemotherapy with cetuximab

B. Nivolumab

C. Methotrexate

Case 2

55M (never smoker) with platinum-refractory, locoregionally persistent and now metastatic HPV+ SCC of the left base of tongue with pulmonary involvement

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Case 2

55M (never smoker) with platinum-refractory, locoregionally persistent and now metastatic HPV+ SCC of the left base of tongue with pulmonary involvement

Restaging: PET-CT in June 2017 shows local residual disease and new lung metastases

Started nivolumab (3 mg/kg IV D1, 15) q28d **in July 2017**

Interval scan: in September 2017 his lung lesions had resolved and his local disease showed regression (partial response)

Case 2

55M (never smoker) with platinum-refractory, locoregionally persistent and now metastatic HPV+ SCC of the left base of tongue with pulmonary involvement

Started nivolumab (3 mg/kg IV D1, 15) q28d in July 2017

Interval scan: in September 2017 his lung lesions had resolved and his local disease showed regression (partial response)

In **January 2018** he has new left neck pain and a PET-CT is obtained

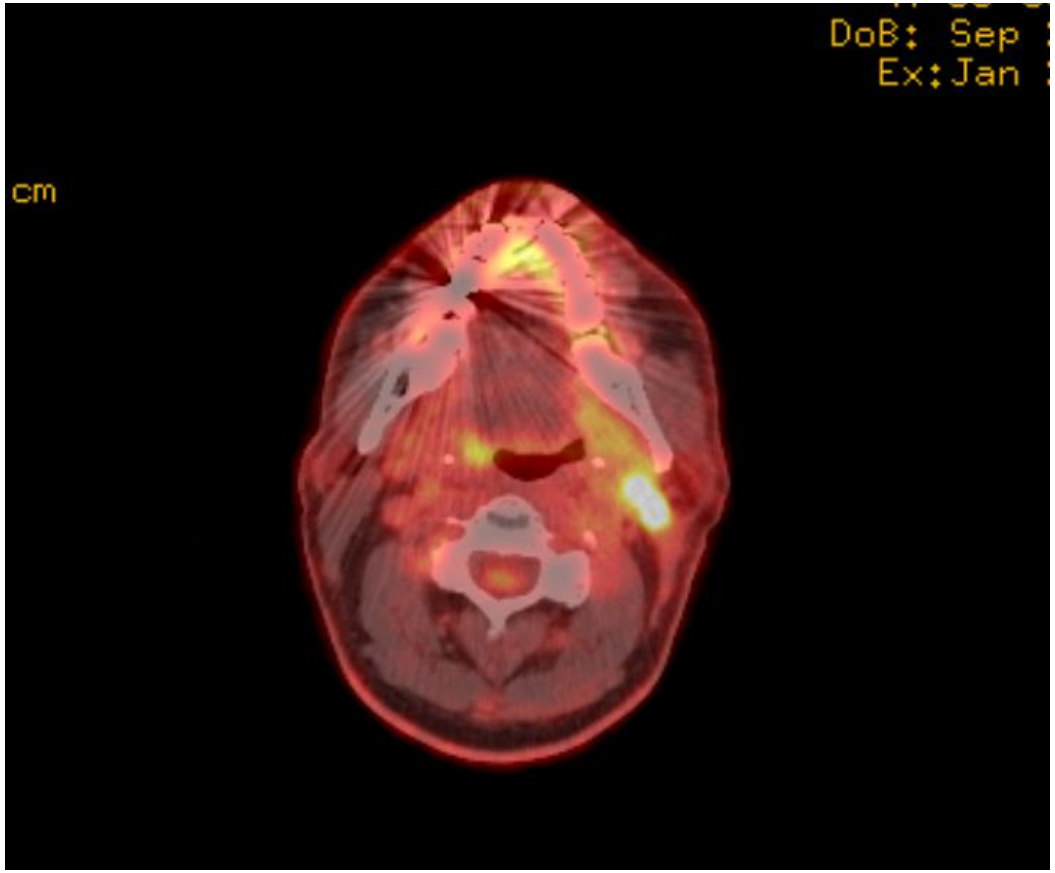
Case 2

What would be your best next step?

A. US-guided left neck biopsy

B. Discontinue PD-1 blockade and start second line chemotherapy or clinical trials

C. Consider palliative radiation



Case 2

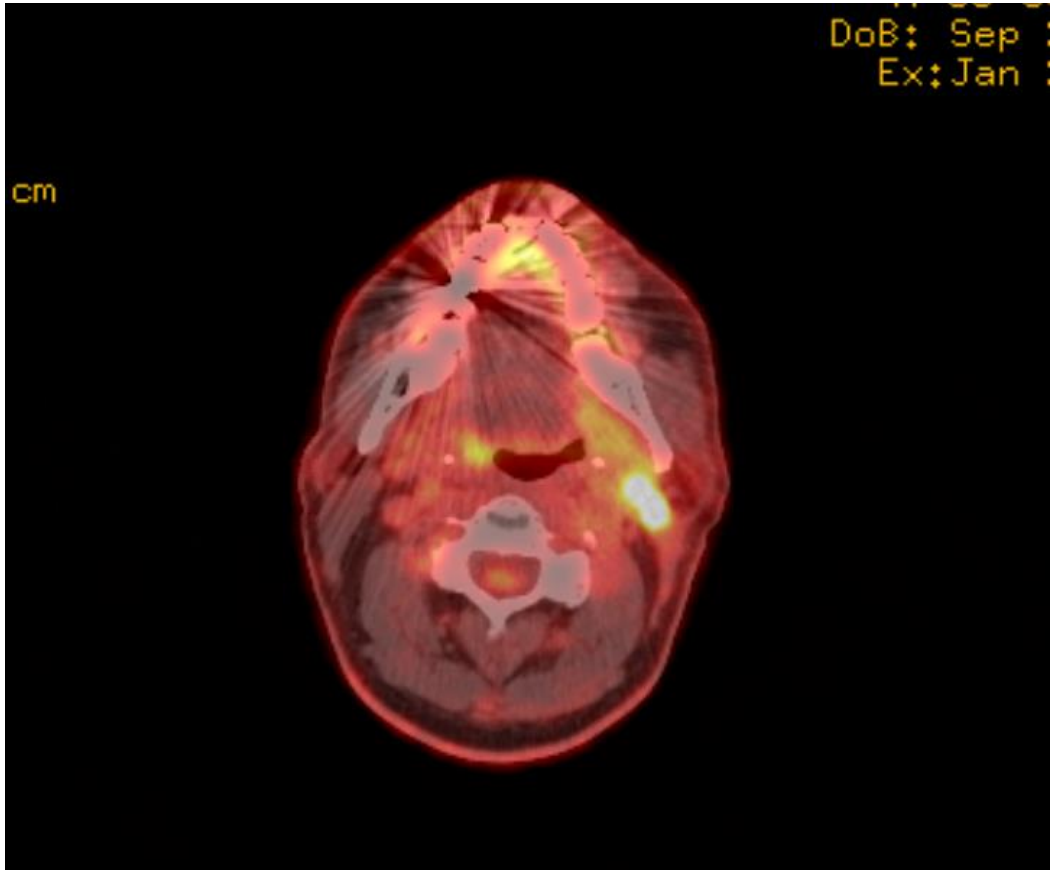
What would be your best next step?

A. US-guided left neck biopsy

B. Discontinue PD-1 blockade and start second line chemotherapy or clinical trials

C. Consider palliative radiation

- Localized disease with slow progression
- Clear clinical benefit from PD-1i at distant site
- Would continue PD-1 blockade during or after SBRT or IMRT



Case 2

55M (never smoker) with platinum-refractory, locoregionally persistent and now metastatic HPV+ SCC of the left base of tongue with pulmonary involvement

Started nivolumab (3 mg/kg IV D1, 15) q28d in July 2017 with PR

In January 2018 imaging shows focal regional node progression and he receives SBRT

He has continued on nivolumab (now **August 2018**) with no further disease progression

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 and testing immunotherapy in other settings