

Immunotherapy for the Treatment of Head and Neck Cancer

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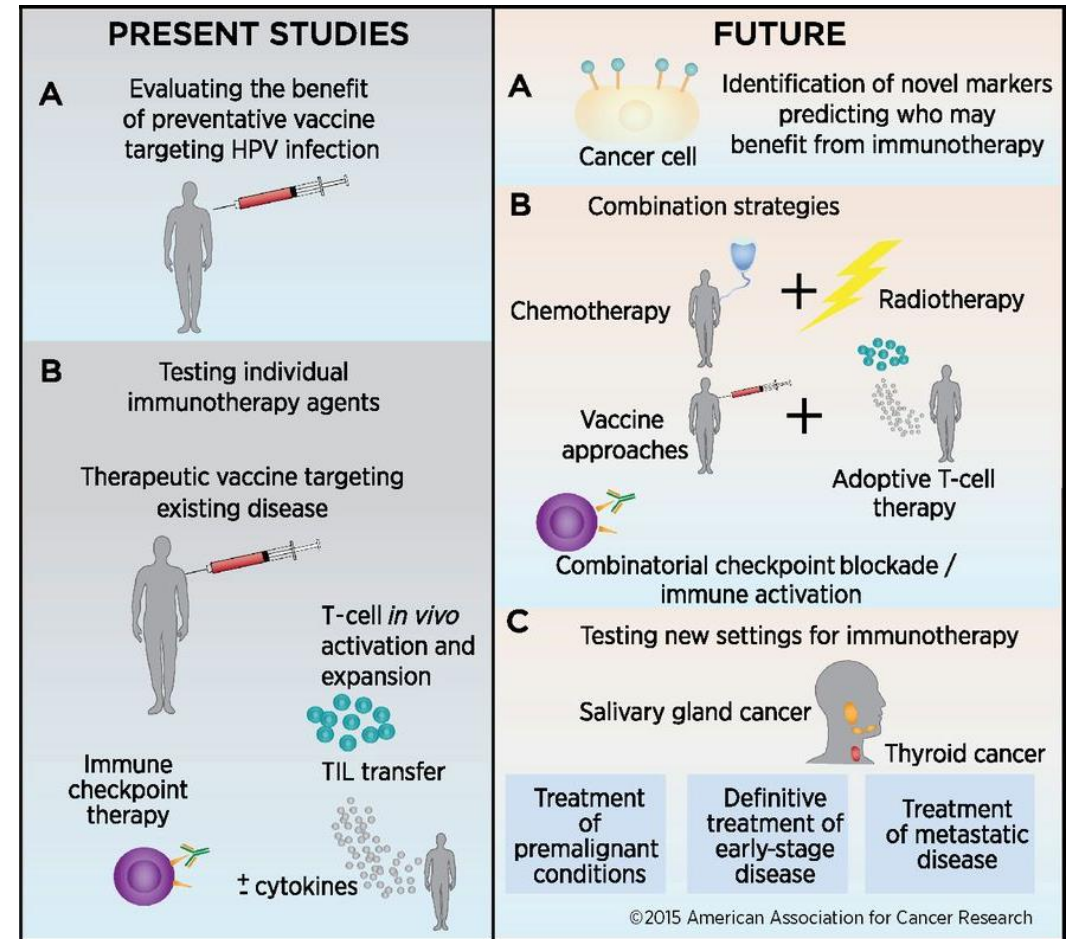
Norton Cancer Institute

Disclosures

- Institutional PI for Javelin B9991016.
 - No salary support /royalties/honoraria.
- I will not be discussing non-FDA approved indications during my presentation.

Immunotherapy for the Treatment of Head and Neck Cancers

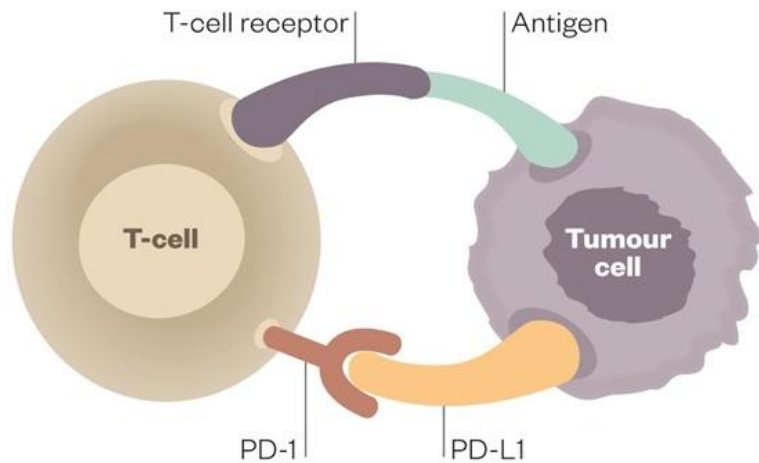
- Immuno-Oncology (I-O) developments in treatment of head and neck cancers
 - Expression of immunologic markers to guide treatment
 - Preventive vaccination against virally mediated cancers
 - PD-1 checkpoint inhibitors for the treatment of metastatic disease



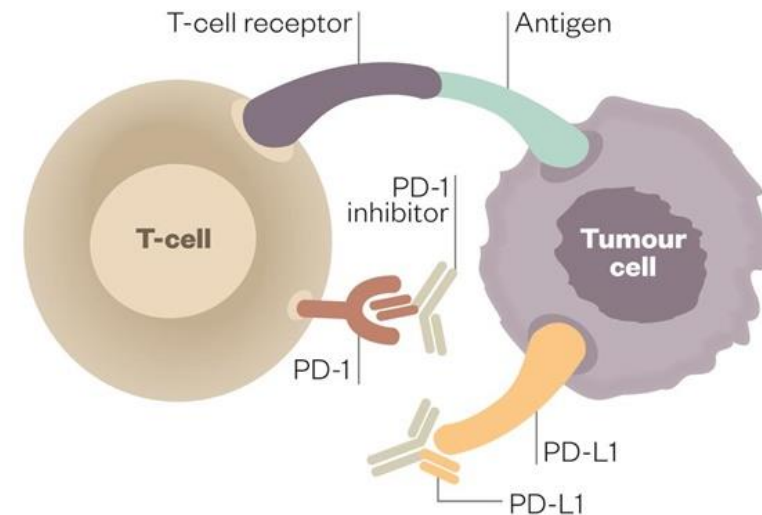
Schoenfeld JD, Cancer Immunol Res, 2015

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



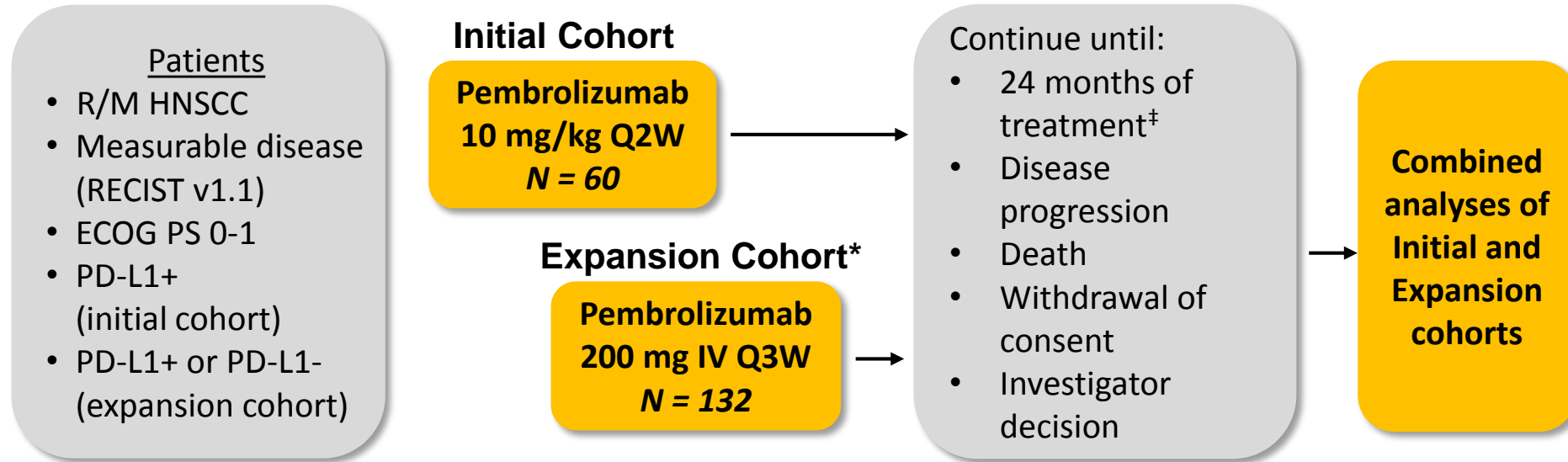
Antibodies against PD-1 and PD-L1 boost the immune response against cancer cells

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.

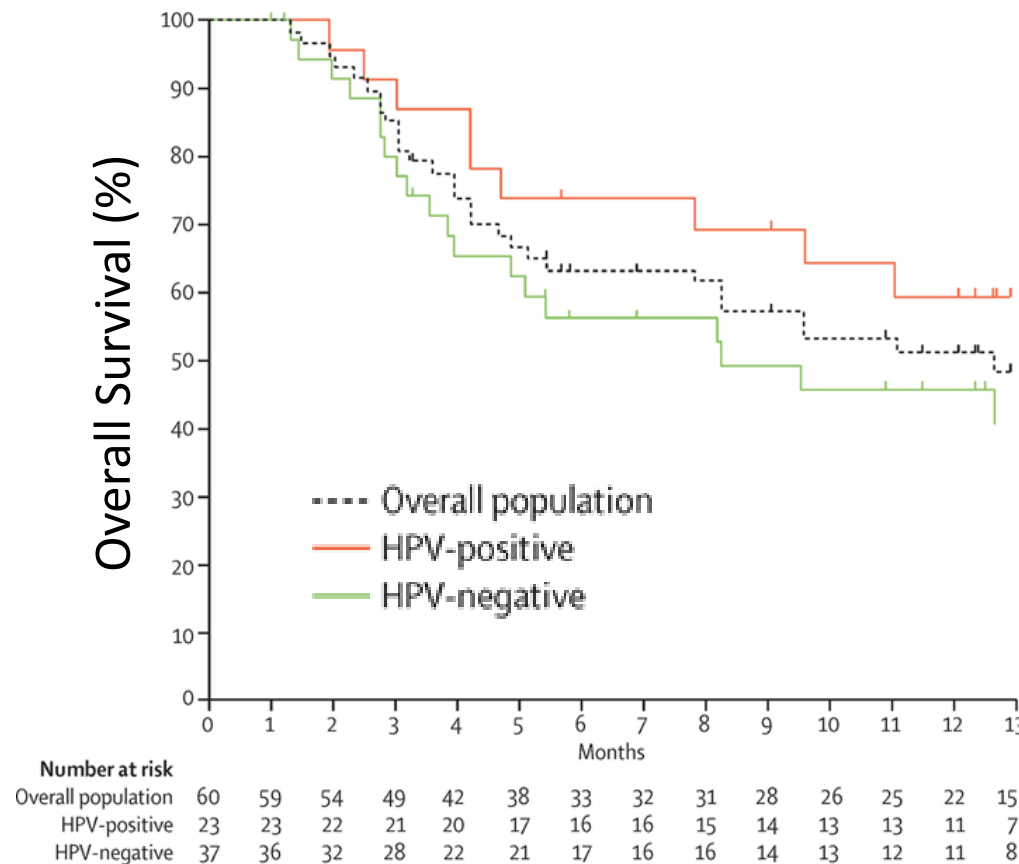
[‡]Treatment beyond progression was allowed.

[§]Initial cohort only.

*Median duration of disease not reached.

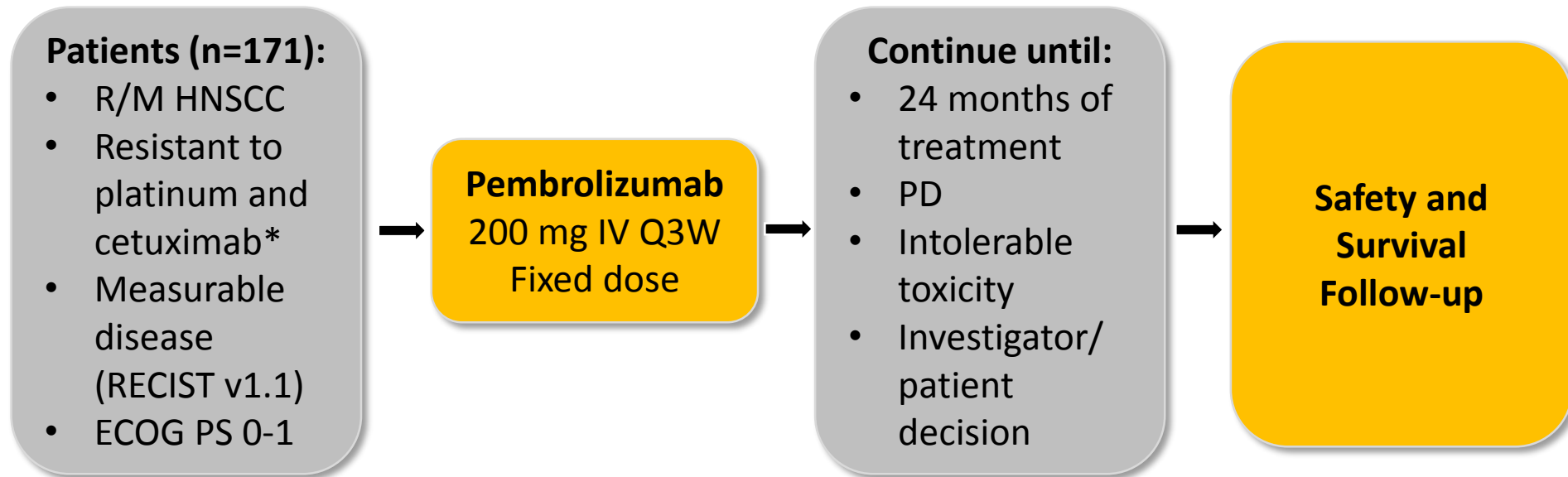
KEYNOTE-012: Pembrolizumab in R/M HNSCC

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

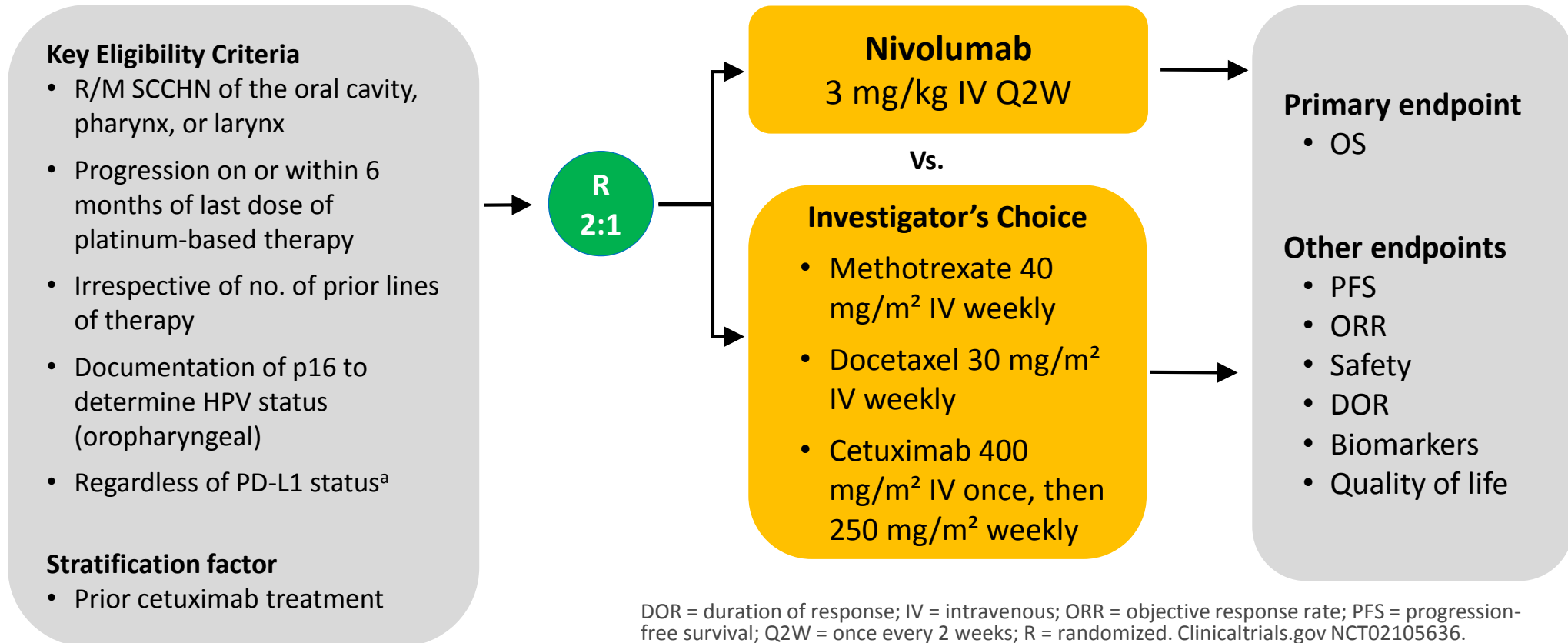
Outcome	All Patients	HPV Status		PD-L1 Status		
	N=171	Positive n=37	Negative n=131	≥1% n=140	<1% n=26	≥50% n=48
ORR, %	16	16	15	18	12	27
mPFS, mo	2.1					
6-mo PFS, %	23	25	21	24	20	31
6-mo OS, %	59	72	55	59	56	60

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

Bauml J, et al, J Clin Oncol. 2017

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

Phase III Randomized, Safety and Efficacy Trial

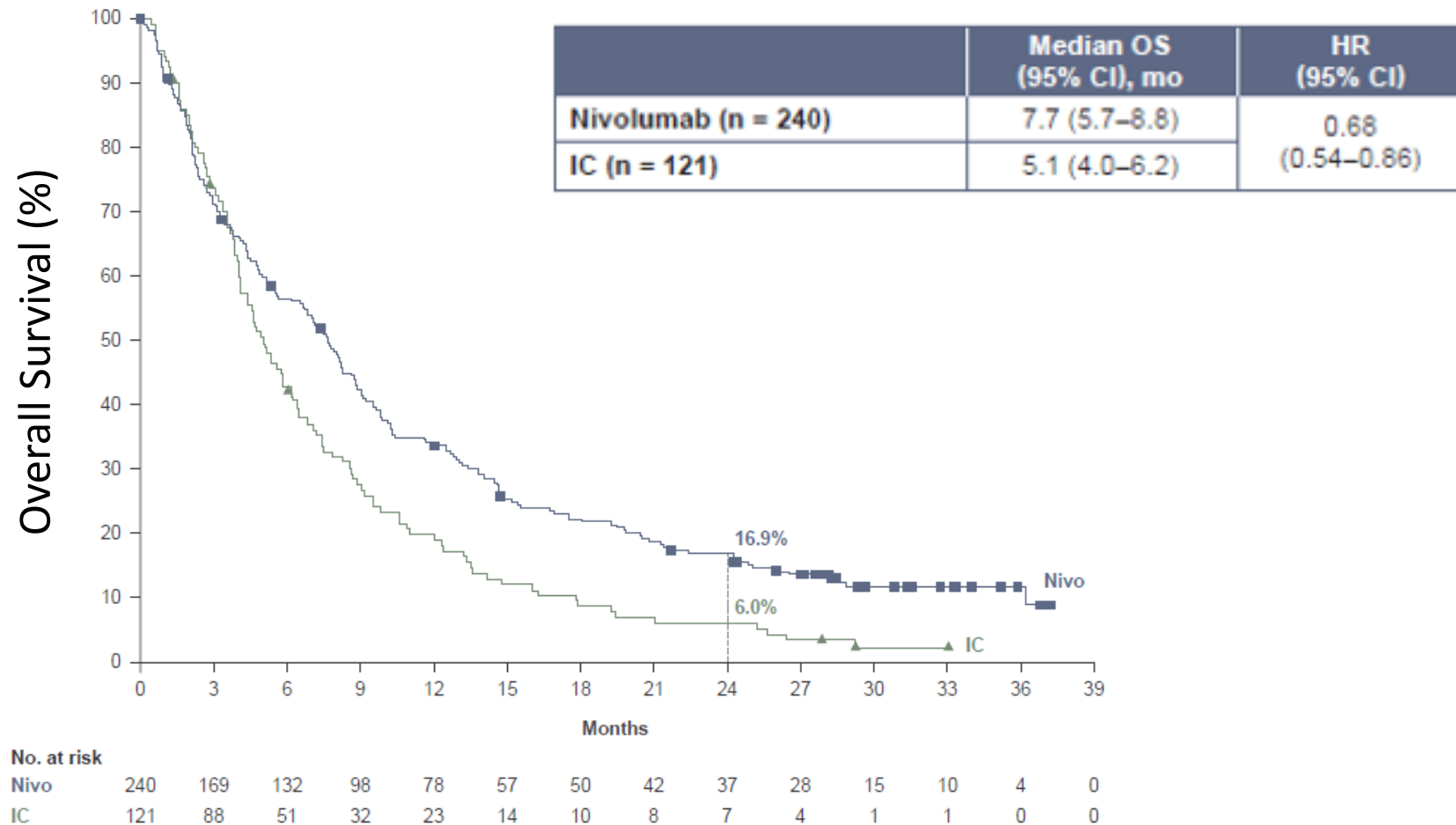


^aTissue required for testing

Ferris & Gillison, NEJM, 2016

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

Overall Survival: 2 year report

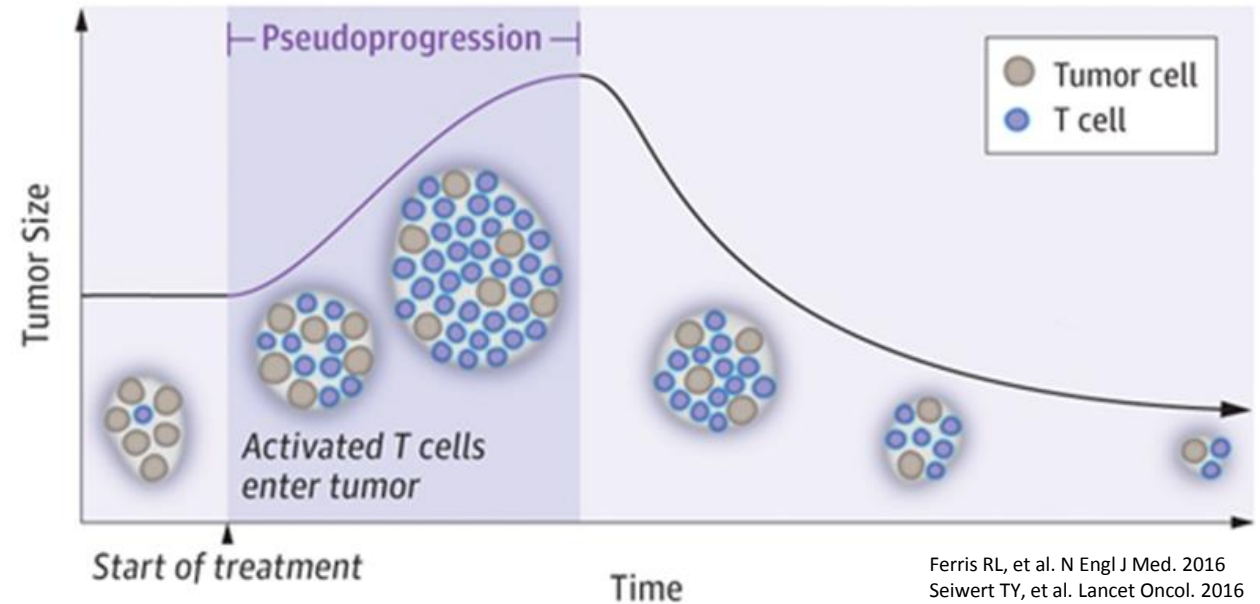


Ferris RL. Oral Oncology, 2018

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

Pseudoproggression

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



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.

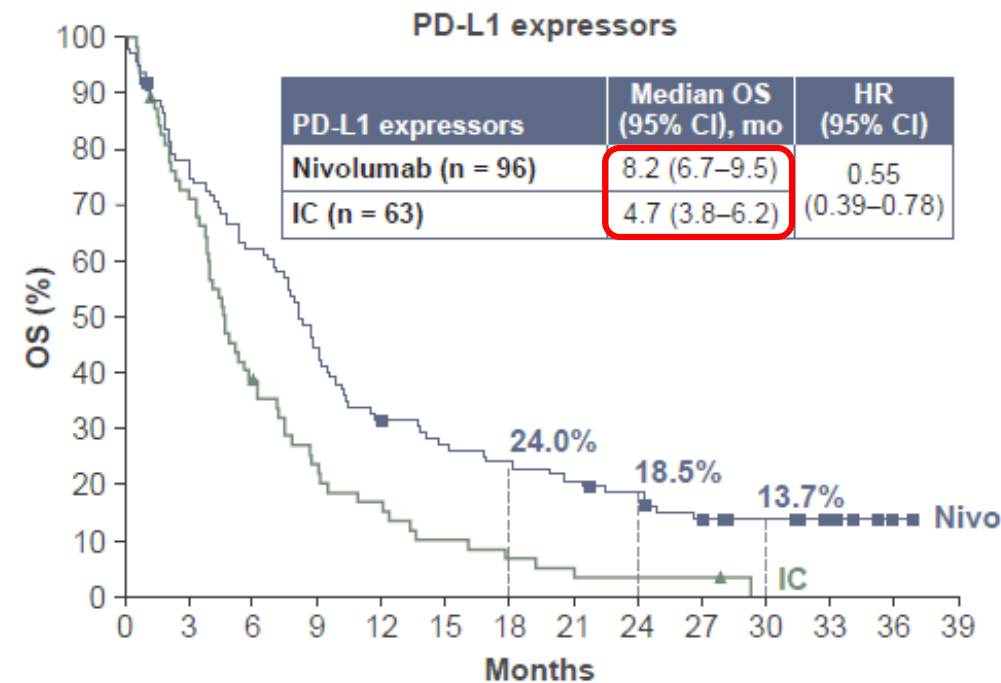
Ferris RL, et al. N Engl J Med. 2016
Seiwert TY, et al. Lancet Oncol. 2016

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

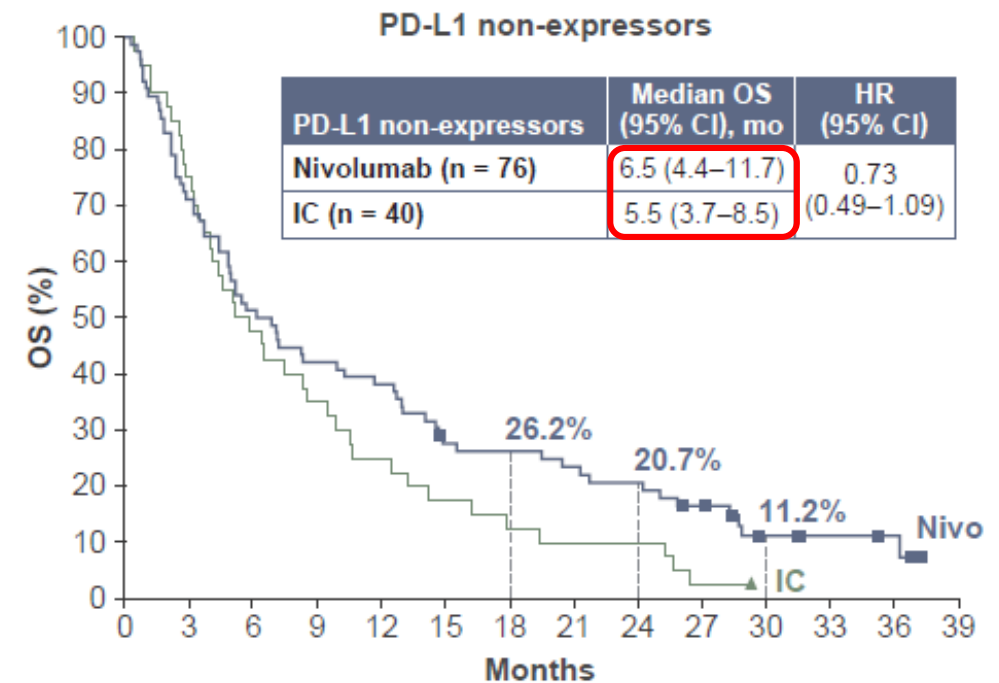
Evaluating Biomarkers in HNSCC

CheckMate 141: 2 year update



No. at risk

Nivo	96	74	59	42	30	25	22	19	16	11	8	5	1	0
IC	63	45	24	14	10	6	4	3	2	2	0	0	0	0



No. at risk

Nivo	76	54	39	32	29	20	19	17	15	11	5	4	3	0
IC	40	30	19	14	10	7	5	4	4	1	0	0	0	0

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

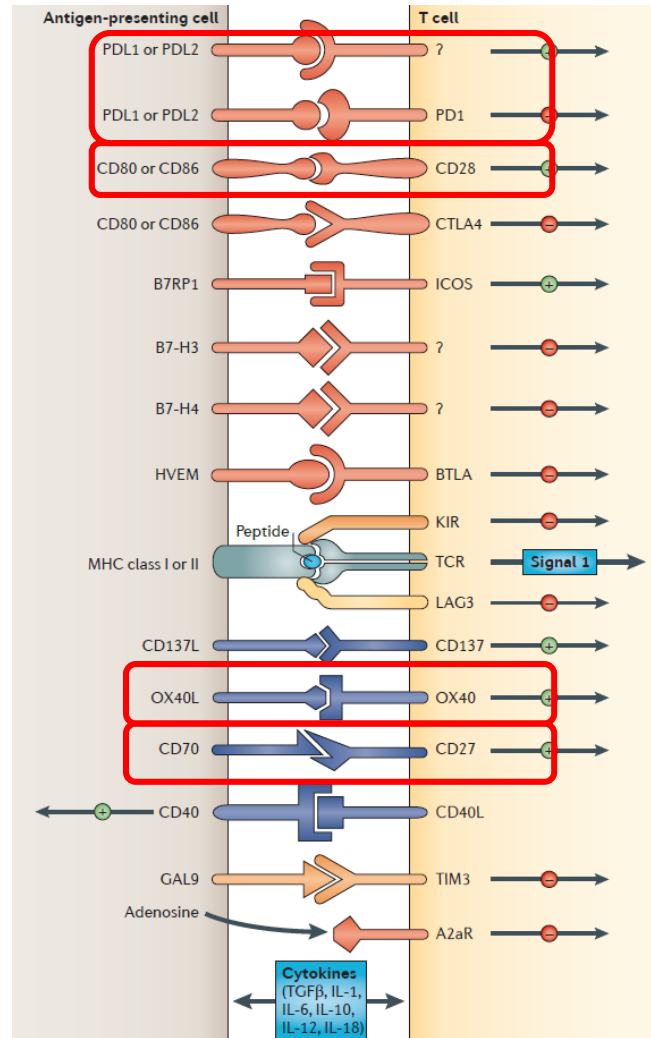
Immune-related Adverse Events

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

Grade of immune-related AE (CTCAE/equivalent)	Corticosteroid management	Additional notes
1	<ul style="list-style-type: none"> Corticosteroids not usually indicated 	<ul style="list-style-type: none"> Continue immunotherapy
2	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Hold immunotherapy during corticosteroid use Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids Start proton pump inhibitor for GI prophylaxis
3	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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)

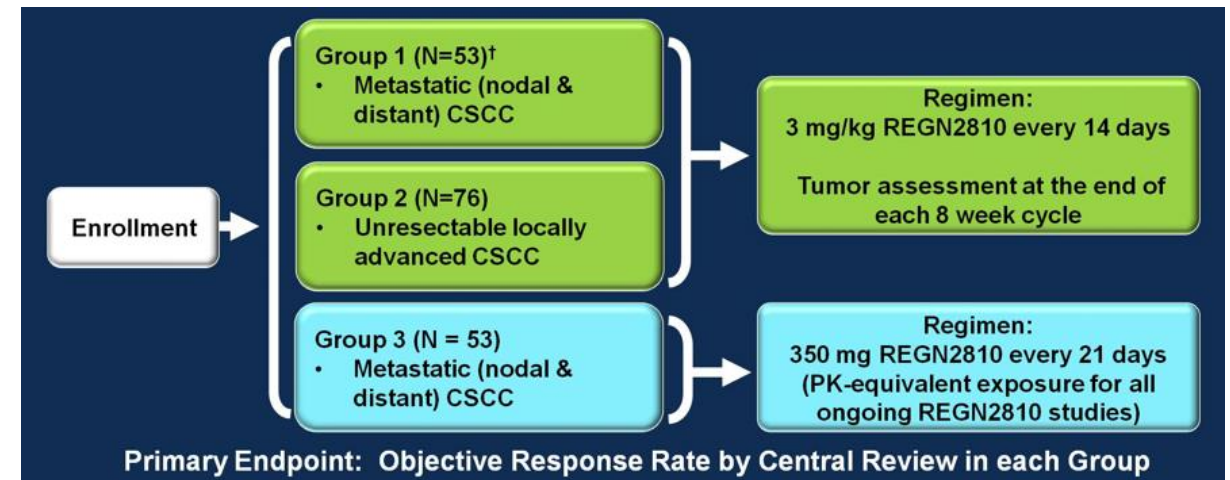
Developmental Immunotherapies for HNSCC

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

FDA approved – 09/28/2018

- Patients with metastatic cSCC
- Patients with locally advanced cSCC who are not candidates for radiation or surgery

NCT02760498



- ORR 46% in 82 patients in study
- Responses durable, median DOR not reached

Developmental Immunotherapies for HNSCC

KEYNOTE – 048 (NCT02358031)

Key Eligibility Criteria

- R/M SCCHN of the oropharynx, oral cavity, hypopharynx, or larynx considered incurable by local therapies
- No prior systemic therapy in the R/M setting
- ECOG 0-1
- Results from HPV testing (oropharyngeal)
- Tissue for PD-L1 biomarker analysis



Pembrolizumab
200 mg IV Q3W

Vs.

**Pembrolizumab +
Platinum + 5-FU**

Vs.

**Cetuximab + Platinum
+ 5-FU**

Primary endpoint

- PFS
- OS

Other endpoints

- PFS at 6 months
- ORR
- Biomarkers
- Quality of life

Developmental Immunotherapies for HNSCC

MASTERKEY 232/KEYNOTE-137

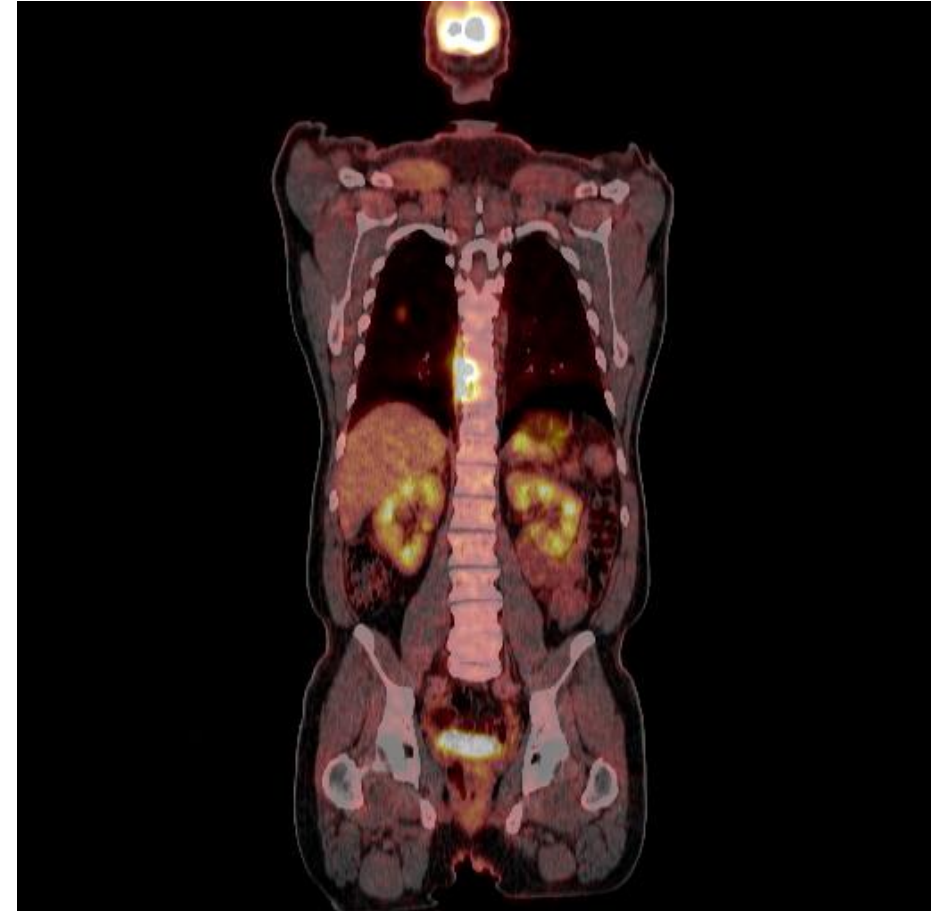
- Talimogene laherparepvec (T-Vec)
 - Genetically engineered herpes virus
- T-Vec 10^6 PFU/mL intratumoral injection followed by 10^8 PFU/mL Q3W
- Pembrolizumab 200 mg IV Q3W
- Eligibility:
 - R/M HNSCC not suitable for curative therapy
 - Progressed after platinum treatment
 - At least 1 injectable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

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

Case Study 1

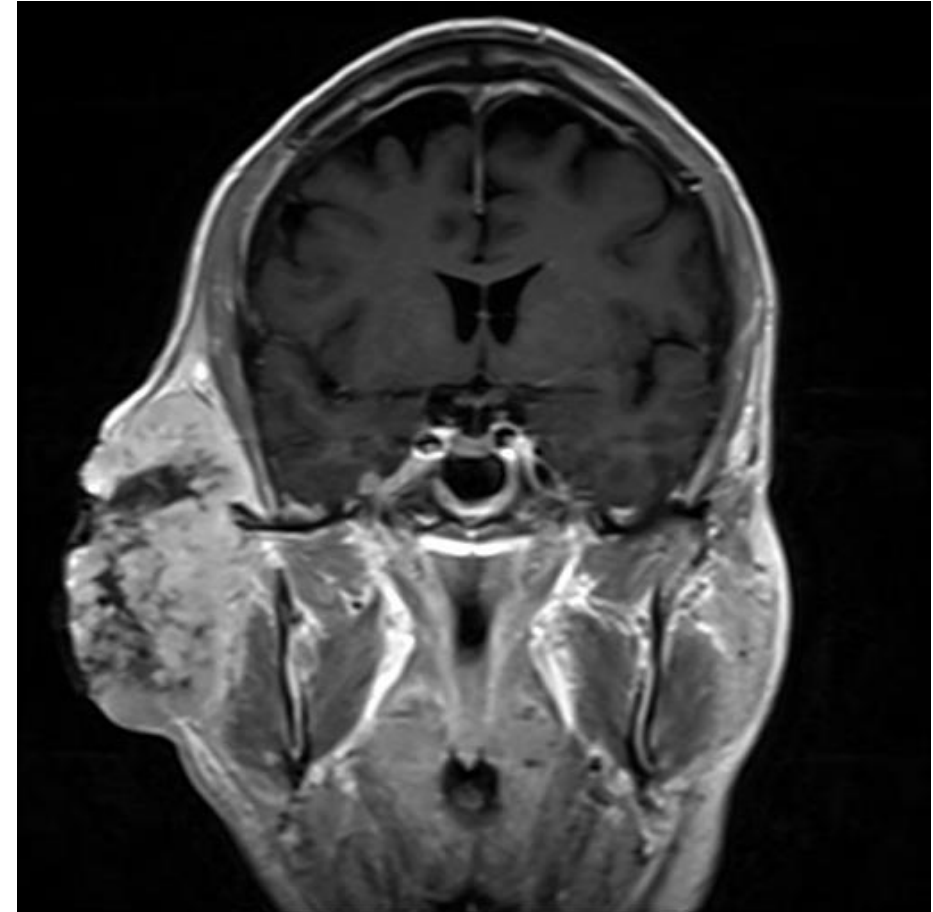
- 45 yo patient T2N2M0 SCC RT BOT treated with cisplatin + RT three years prior.
- HPV status unknown.
- Non smoker.
- He develops mid thoracic back pain.
- CT/PET done with lesions in the bilateral lungs and vertebrae.



- CT guided biopsy was done of the thoracic lesion
 - Pathology revealed SCC.
 - HPV (+) by PCR
- Patient underwent irradiation to the thoracic spine metastases, the left mainstem bronchus lesion, and rib lesion.
 - Initiated pembrolizumab due to recurrent metastatic SCC.

Case study 2

- 59 yo with prior local excision of SCC right preauricular skin.
- Develops mass with pain and ulceration.
- Right V2 and VII impaired. Remainder CN intact.
- MRI was obtained.



- What would next steps be?
 - Additional History, Physical Examination including flexible laryngoscopy.
 - Staging studies.
 - Biopsy

- Answer: All of them
 - Additional History, Physical Examination including flexible laryngoscopy.
 - Staging studies.
 - Biopsy
- No neck masses.
- Upper aerodigestive surfaces without lesion.
- CT/PET negative.
- Pathology “Poorly Differentiated Squamous Cell Carcinoma.”

- What would next steps be?
 - PD-1 pathway blockade
 - Radiation
 - Cytotoxic chemotherapy

Case study 2

- Answer:
- Concurrent irradiation (70Gy) in 35 fractions.
- Concurrent PD1 pathway blockade
- Scan six months later

