

# Immunotherapy for the Treatment of Head and Neck Cancer

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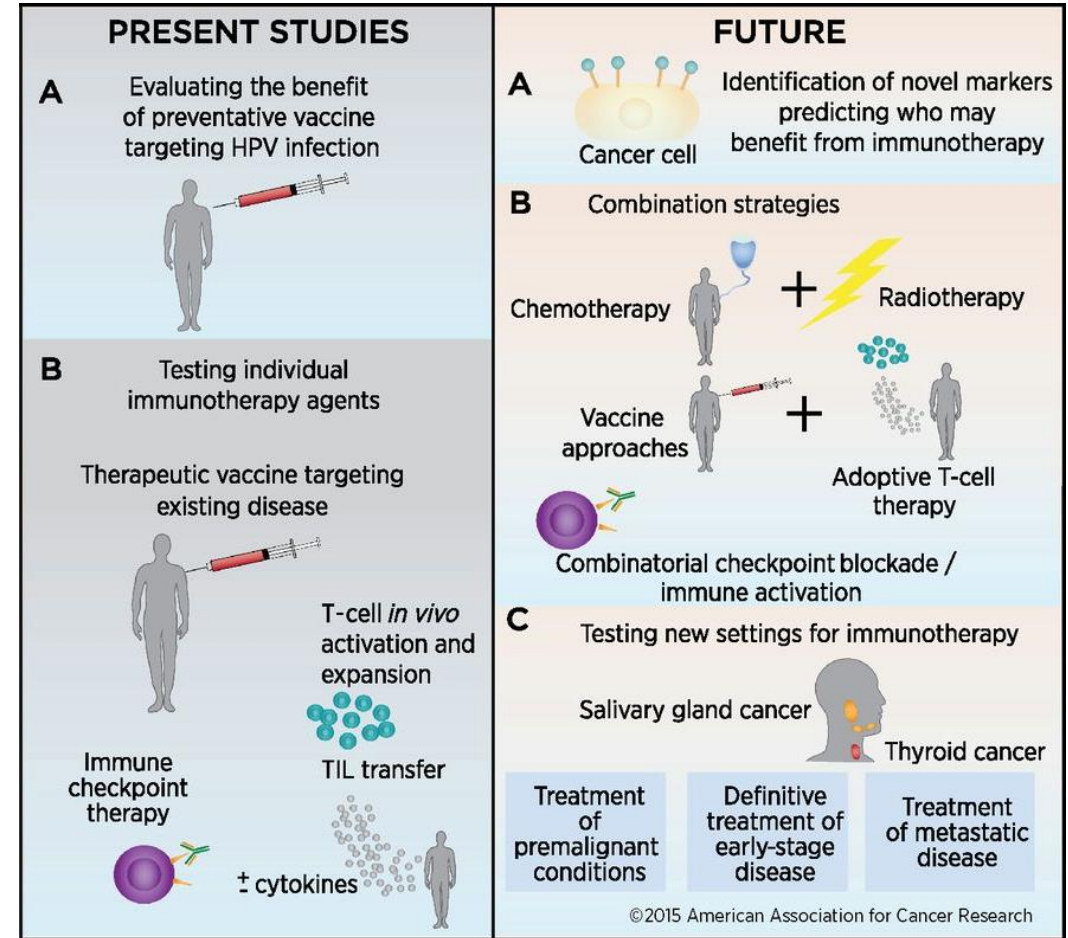
University of Colorado

# Disclosures

- No relevant disclosures
- I will not be discussing non-FDA approved indications during my presentation.

# Immunotherapy for the Treatment of Head and Neck Cancers

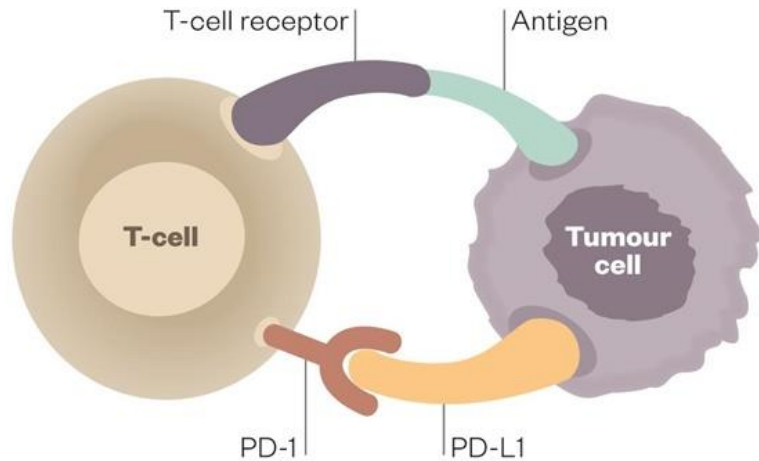
- Immuno-Oncology (I-O) developments in treatment of head and neck cancers
  - Expression of immunologic markers to guide treatment
  - Preventive vaccination against virally mediated cancers
  - PD-1 checkpoint inhibitors for the treatment of metastatic disease



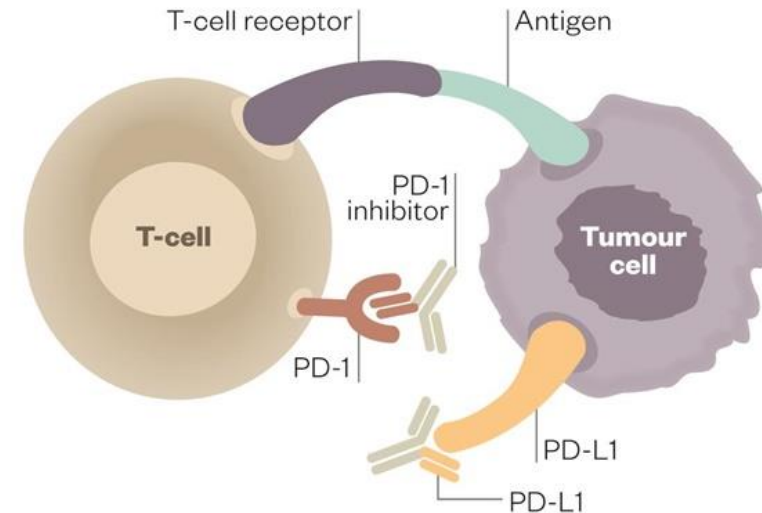
Schoenfeld JD, Cancer Immunol Res, 2015

# 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



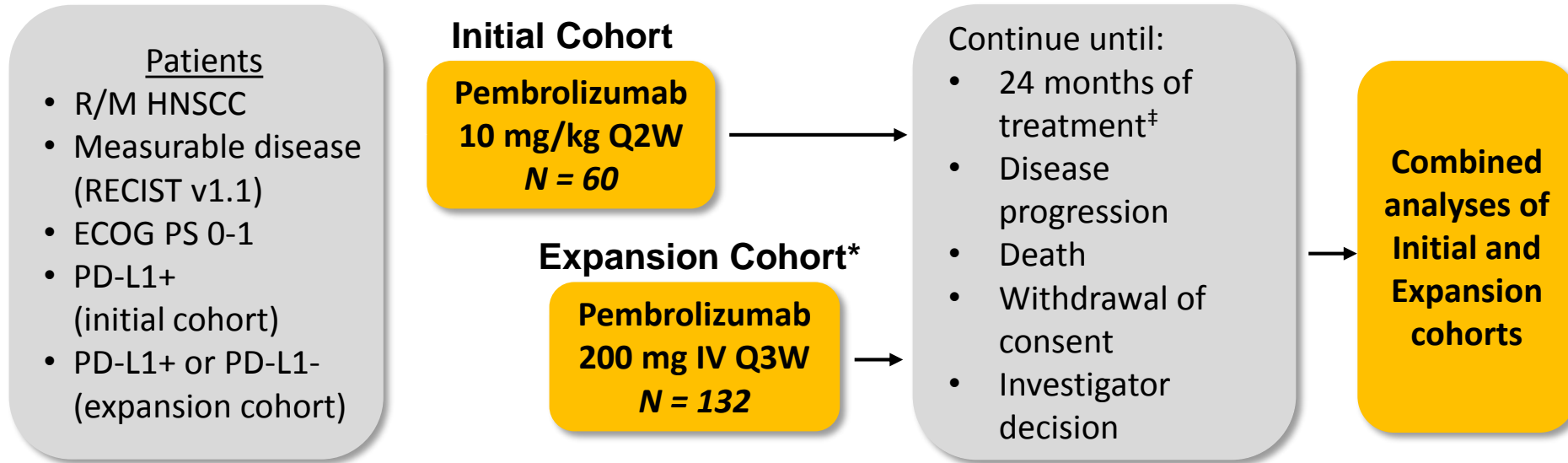
Antibodies against PD-1 and PD-L1 boost the immune response against cancer cells

# 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<sup>†</sup> 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<sup>§</sup>

<sup>†</sup>Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.

<sup>‡</sup>Treatment beyond progression was allowed.

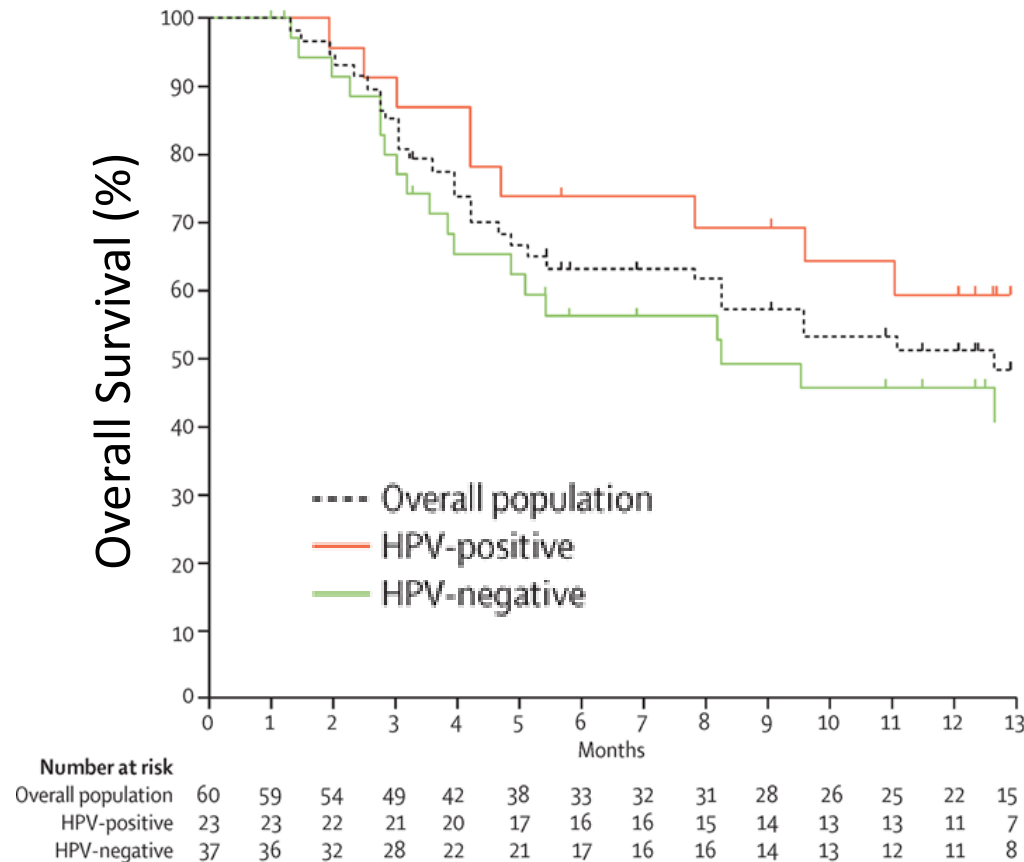
<sup>§</sup>Initial cohort only.

\*Median duration of disease not reached.



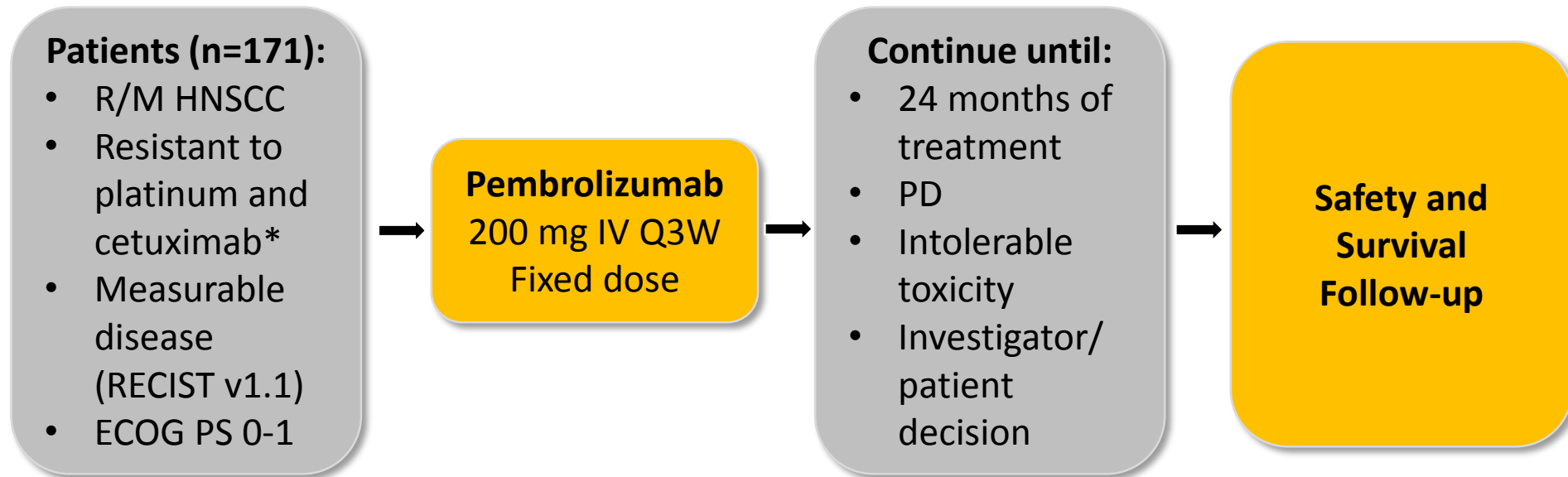
# KEYNOTE-012: Pembrolizumab in R/M HNSCC

Nonrandomized, Phase 1b Trial, Cohorts<sup>†</sup> 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  $\geq 2$  prior lines of therapy for metastatic disease



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

## Phase II Trial, Single Arm

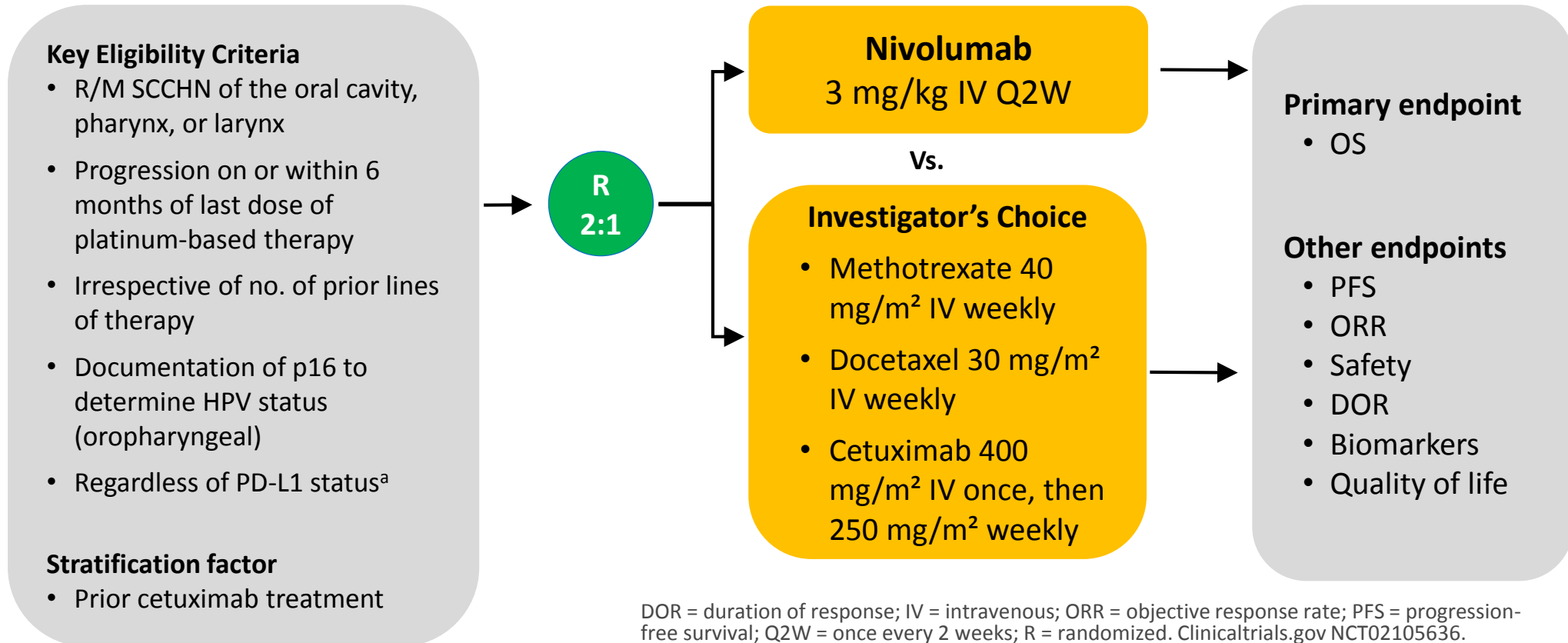
Outcome	All Patients	HPV Status		PD-L1 Status		
	N=171	Positive n=37	Negative n=131	≥1% n=140	<1% n=26	≥50% n=48
ORR, %	16	16	15	18	12	27
mPFS, mo	2.1					
6-mo PFS, %	23	25	21	24	20	31
6-mo OS, %	59	72	55	59	56	60

- 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

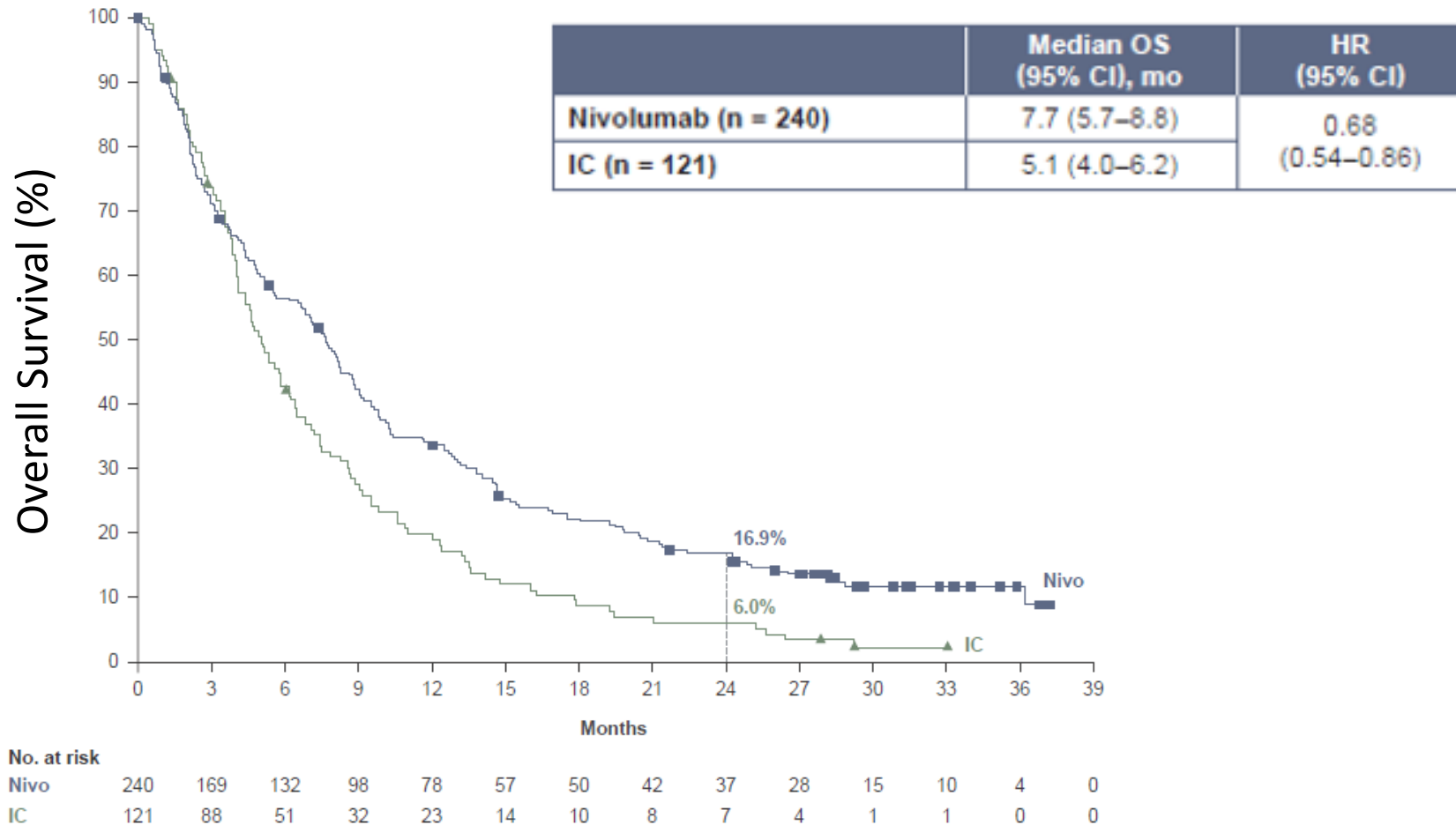


<sup>a</sup>Tissue required for testing

Ferris & Gillison, NEJM, 2016

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

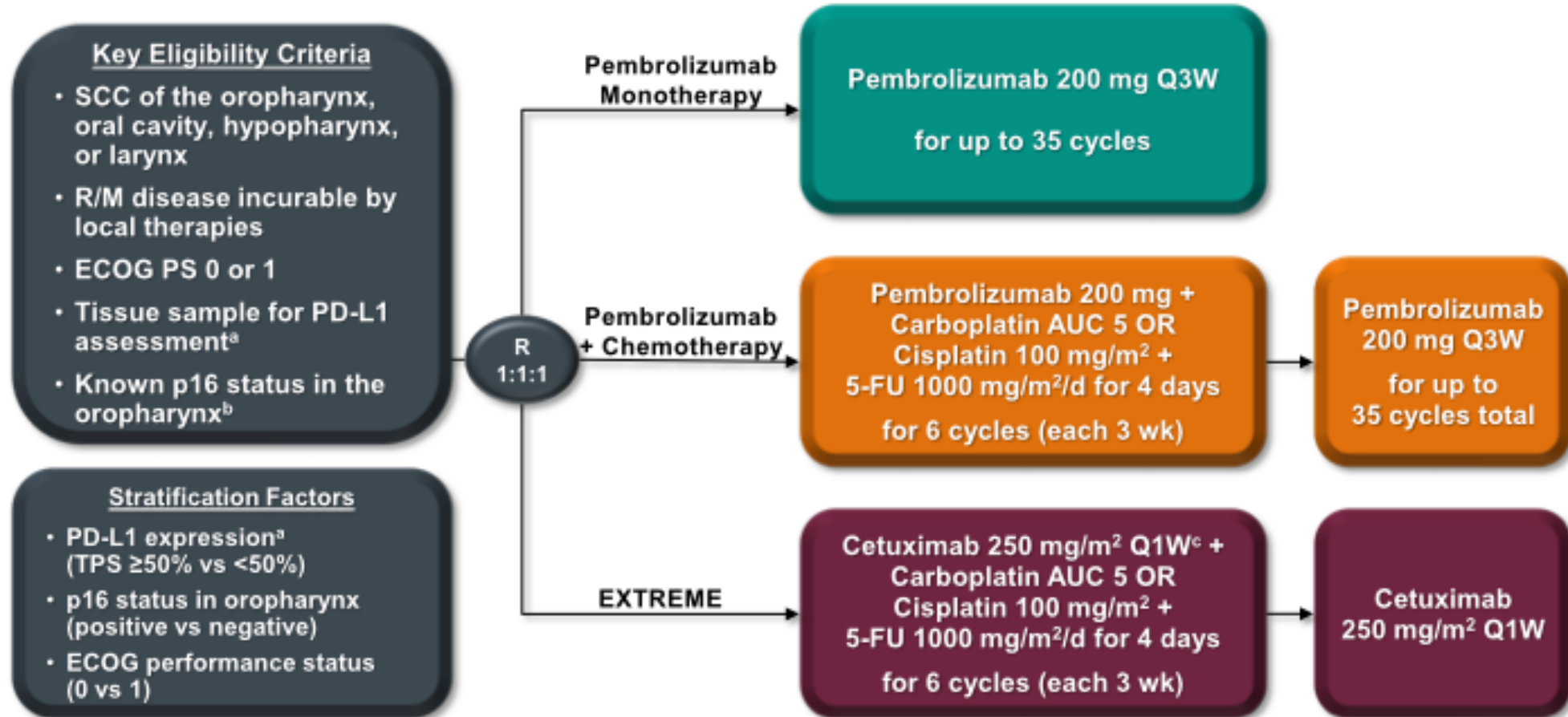
## Overall Survival: 2 year report



Ferris RL. Oral Oncology, 2018

# In Development: KEYNOTE-048

## Pembrolizumab +/- Chemotherapy in Newly diagnosed R/M HNSCC

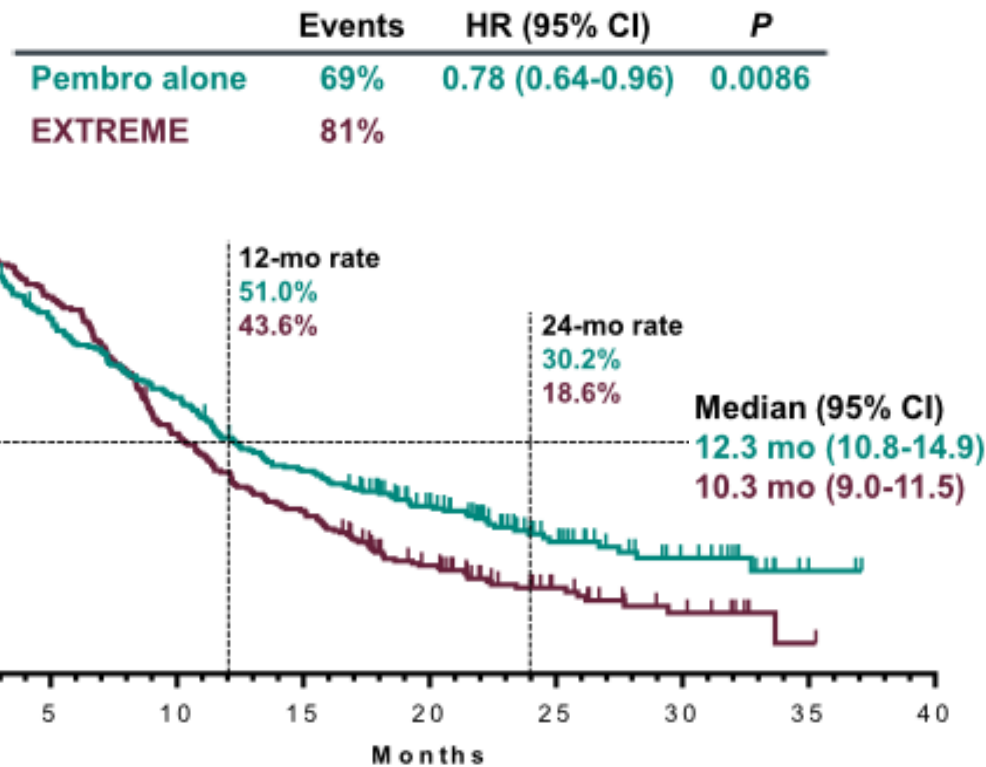


<sup>a</sup>Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. <sup>b</sup>Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. <sup>c</sup>Following a loading dose of 400 mg/m<sup>2</sup>.

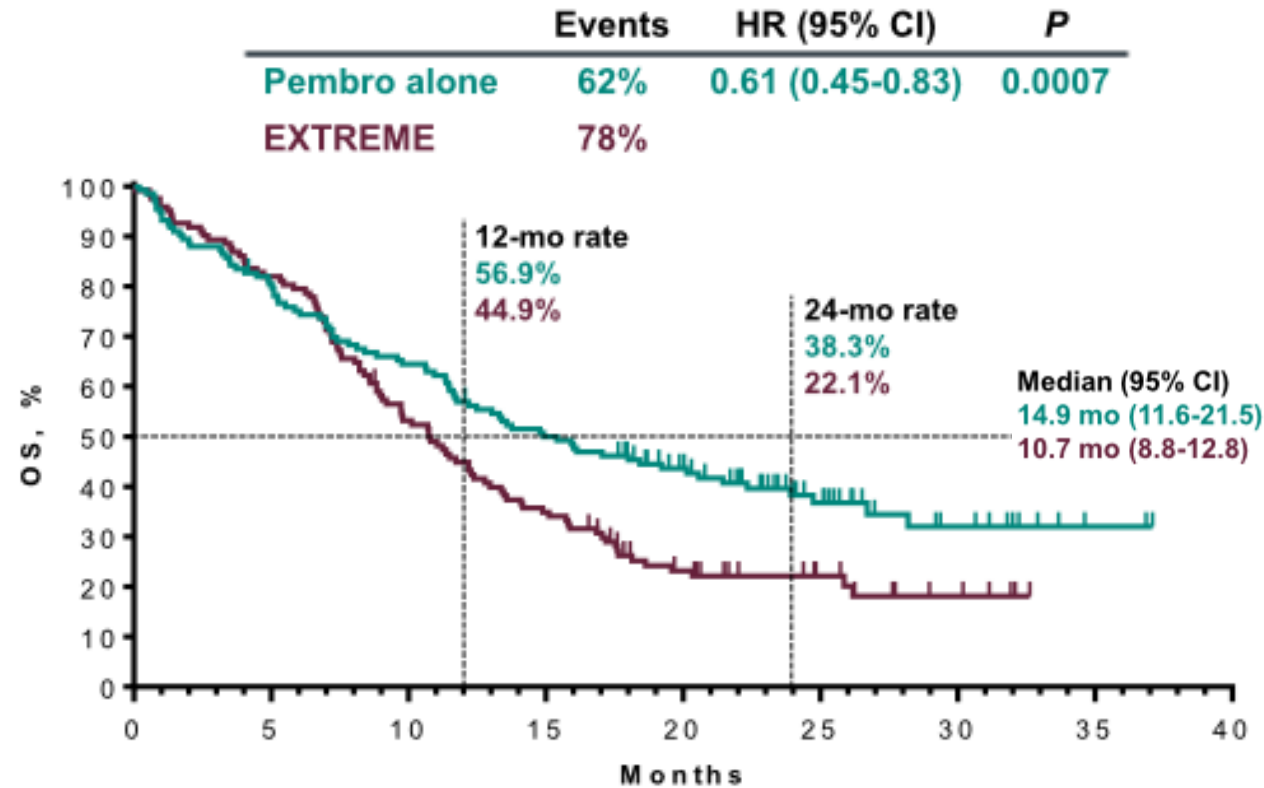
# In Development: KEYNOTE-048

## Pembrolizumab +/- Chemotherapy in Newly diagnosed R/M HNSCC

PD-L1 CPS  $\geq 1\%$



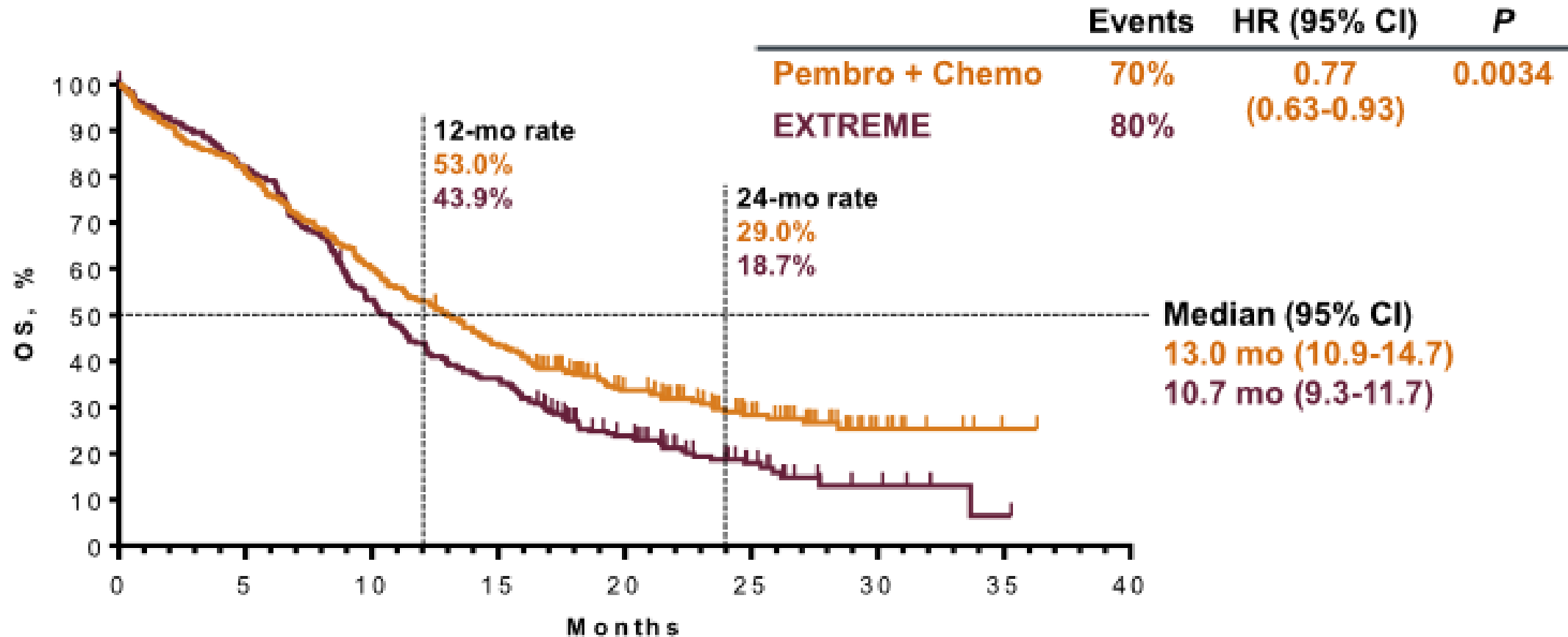
PD-L1 CPS  $\geq 20\%$



# In Development: KEYNOTE-048

## Pembrolizumab +/- Chemotherapy in Newly diagnosed R/M HNSCC

### All Patients

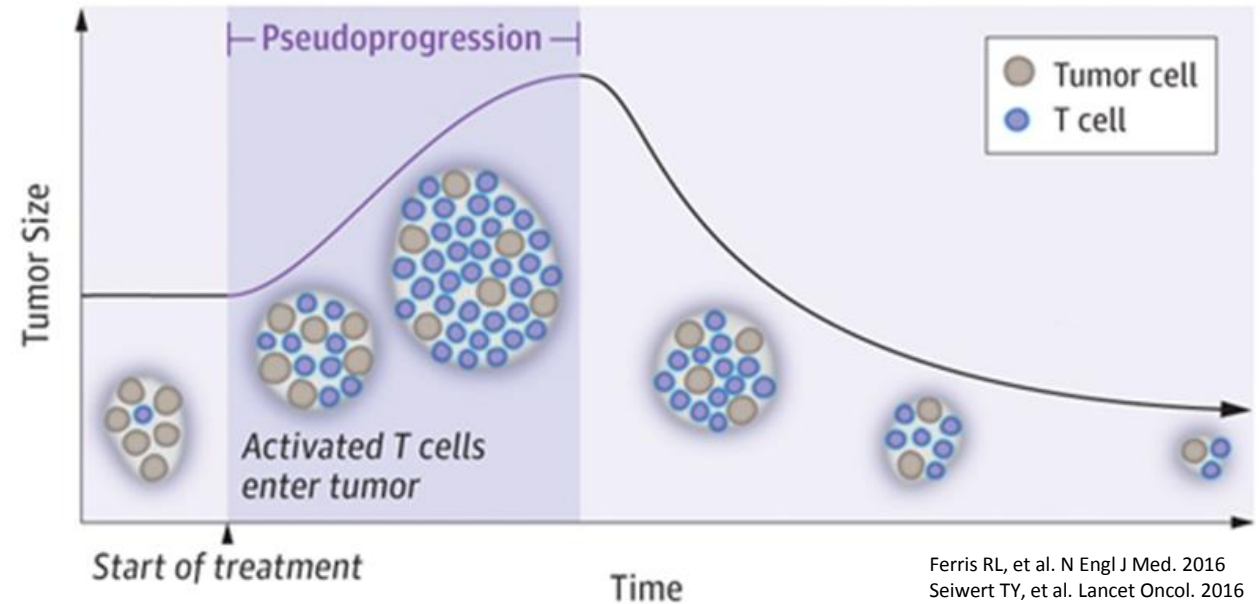




# Response to Immune Checkpoint Inhibitor Treatment with Brief Increase in Tumor Size

## 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.

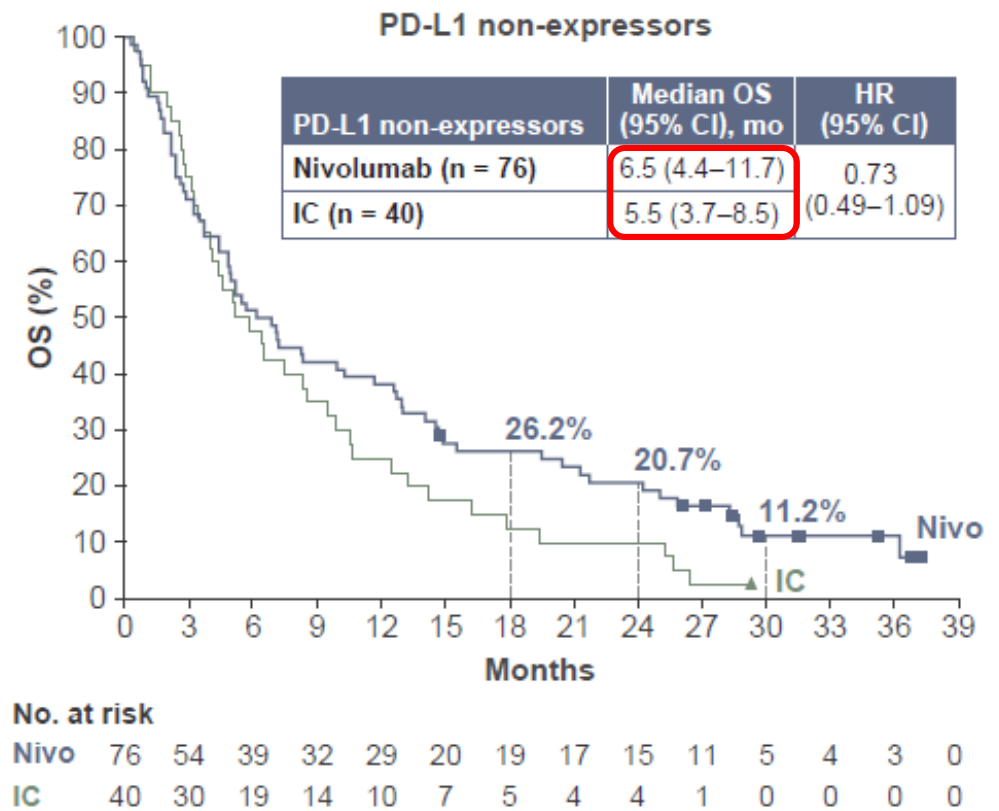
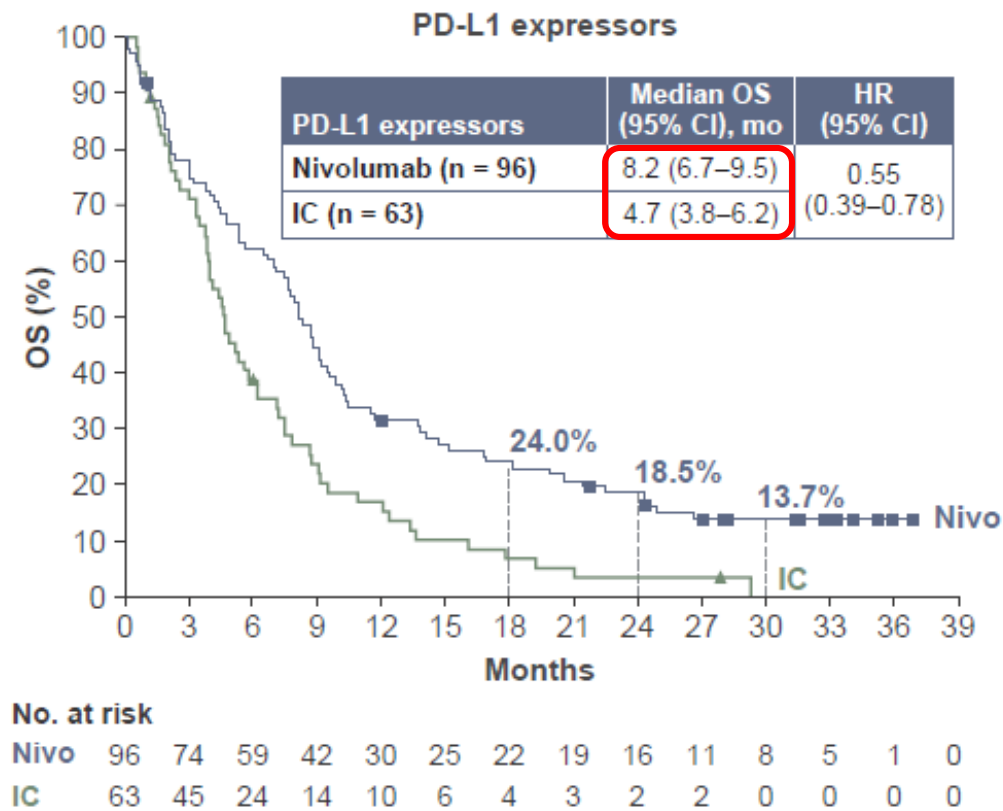
Ferris RL, et al. N Engl J Med. 2016  
Seiwert TY, et al. Lancet Oncol. 2016

# 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



# Immune-related Adverse Events

## KEYNOTE-012 and CheckMate 141

### 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)

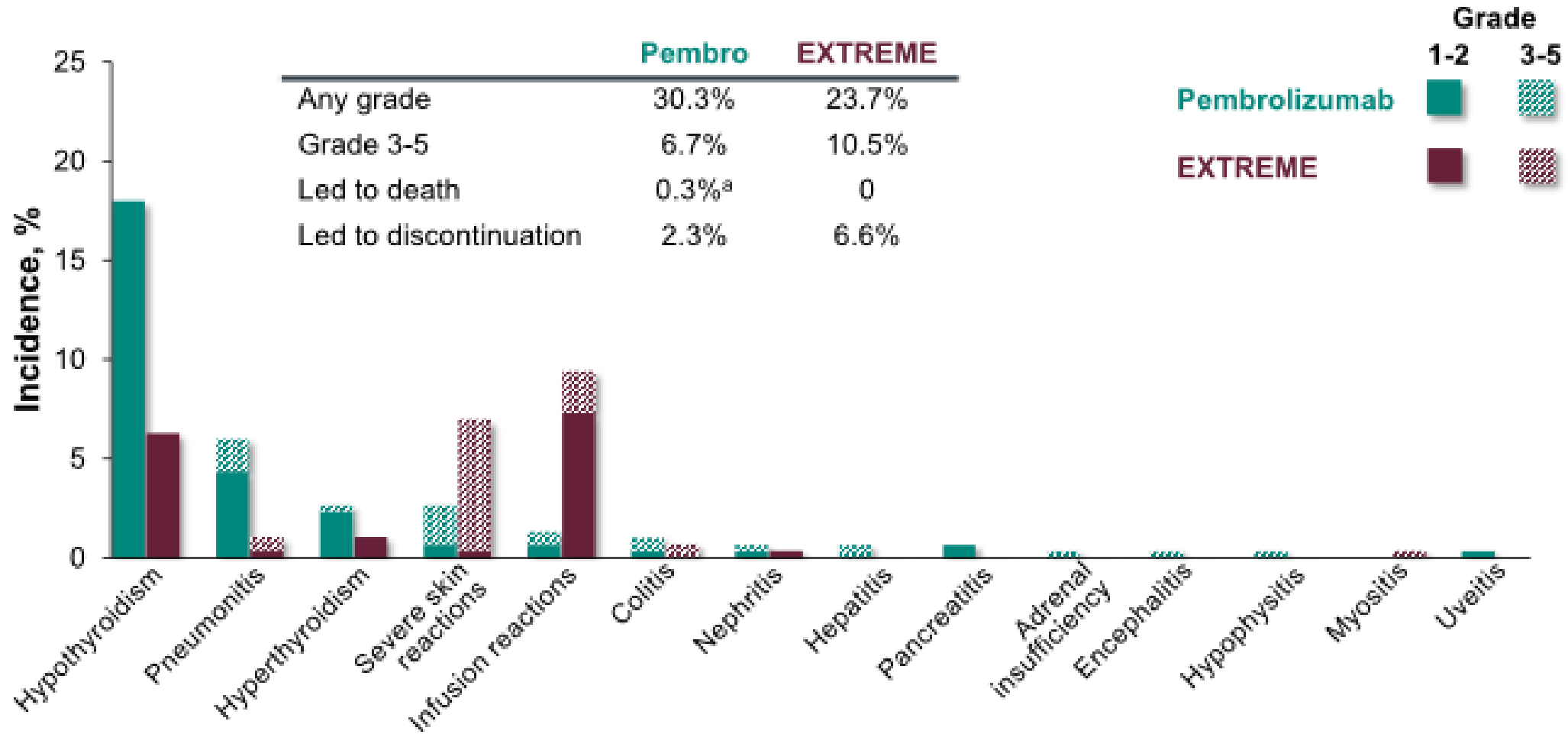
### CheckMate 141

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

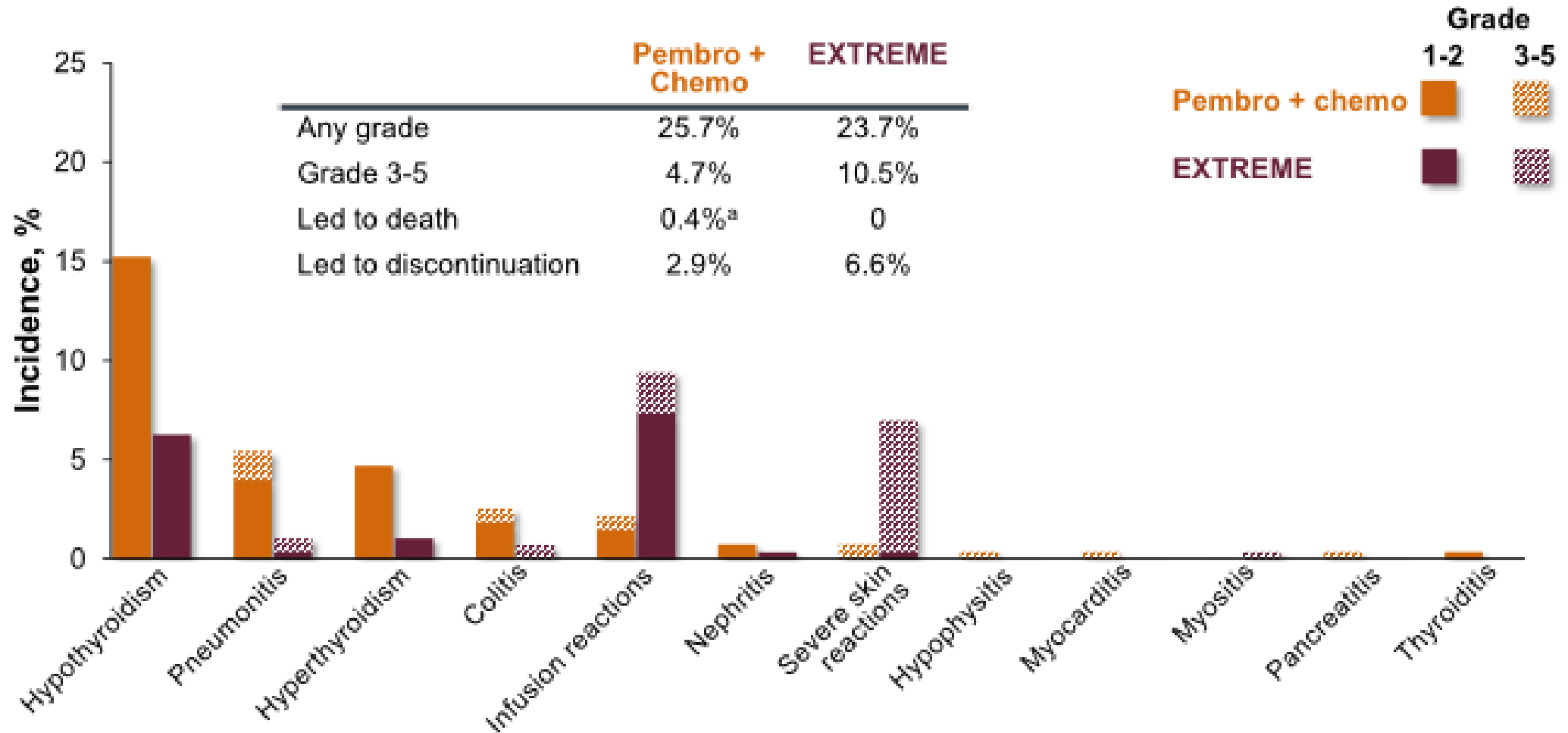
## KEYNOTE-048 – Pembrolizumab monotherapy





# Immune-related Adverse Events

## KEYNOTE-048 – Pembrolizumab + Chemotherapy



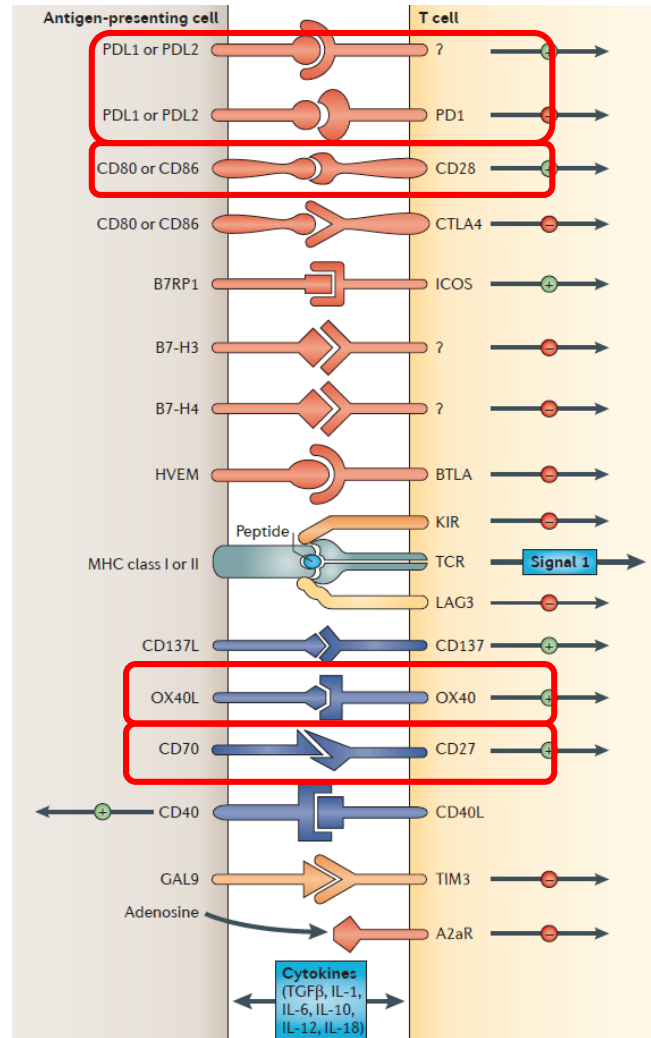
# Immune-related Adverse Events

**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"> <li>Corticosteroids not usually indicated</li> </ul>	<ul style="list-style-type: none"> <li>Continue immunotherapy</li> </ul>
2	<ul style="list-style-type: none"> <li>If indicated, start oral prednisone 0.5-1 mg/kg/day if patient can take oral medication.</li> <li>If IV required, start methylprednisolone 0.5-1 mg/kg/day IV</li> <li>If no improvement in 2–3 days, increase corticosteroid dose to 2 mg/kg/day</li> <li>Once improved to ≤grade 1 AE, start 4–6 week steroid taper</li> </ul>	<ul style="list-style-type: none"> <li>Hold immunotherapy during corticosteroid use</li> <li>Continue immunotherapy once resolved to ≤grade 1 and off corticosteroids</li> <li>Start proton pump inhibitor for GI prophylaxis</li> </ul>
3	<ul style="list-style-type: none"> <li>Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone)</li> <li>If no improvement in 2–3 days, add additional/alternative immune suppressant</li> <li>Once improved to ≤ grade 1, start 4–6-week steroid taper</li> <li>Provide supportive treatment as needed</li> </ul>	<ul style="list-style-type: none"> <li>Hold immunotherapy; if symptoms do not improve in 4–6 weeks, discontinue immunotherapy</li> <li>Consider intravenous corticosteroids</li> <li>Start proton pump inhibitor for GI prophylaxis</li> <li>Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (&gt;30 mg prednisone or equivalent/day)</li> </ul>
4	<ul style="list-style-type: none"> <li>Start prednisone 1-2 mg/kg/day (or equivalent dose of methylprednisolone)</li> <li>If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., infliximab</li> <li>Provide supportive care as needed</li> </ul>	<ul style="list-style-type: none"> <li>Discontinue immunotherapy</li> <li>Continue intravenous corticosteroids</li> <li>Start proton pump inhibitor for GI prophylaxis</li> <li>Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (&gt;30 mg prednisone or equivalent/day)</li> </ul>

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)

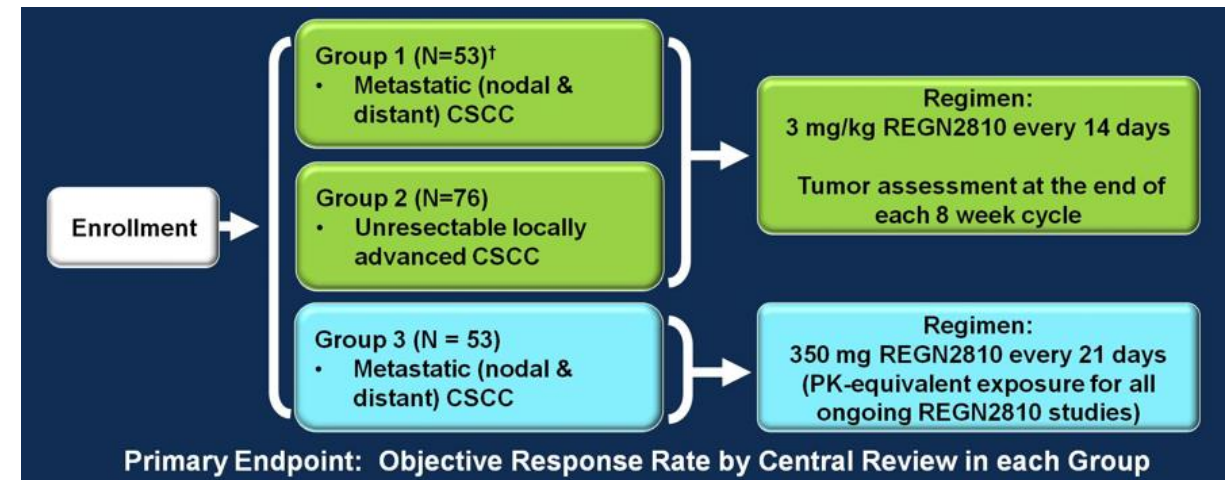
# Developmental Immunotherapies for HNSCC

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  $\geq 10$  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

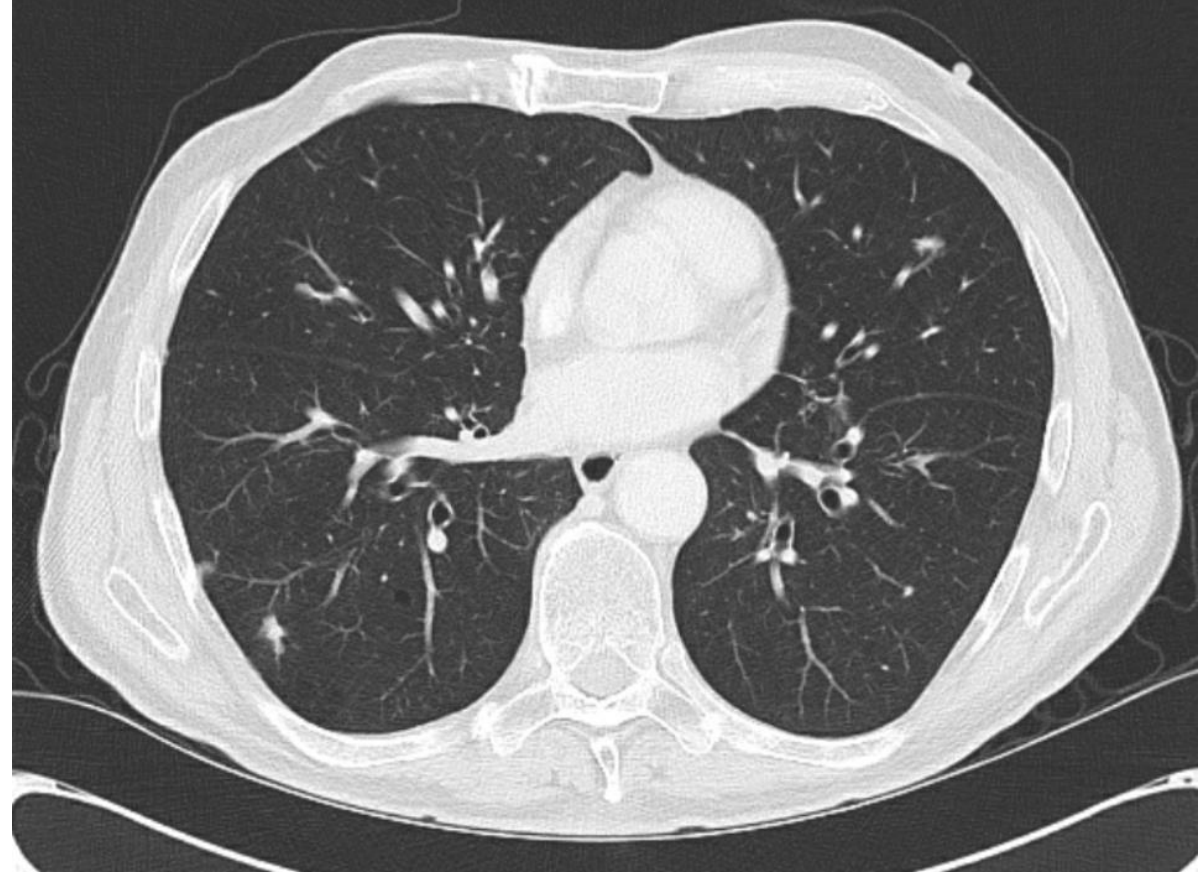
# Case Study 1

- 66 y/o man with a 50 pack year smoking history
  - 2015 dx cT2cN0cM0 glottic larynx SCC treated with RT alone
  - 2017 local recurrence treated with laryngectomy: local relapse with 1 node positive and positive margins
  - Late 2017/early 2018: adjuvant cisplatin-based chemo-RT
  - 3 months after CRT conclusion patient's PET shows new lung nodules c/w metastatic disease

# Case Study 1



# Case Study 1



# Case Study 1

- Finishes 7 cycles of nivolumab
- Complains of fatigue and wants to stop therapy. What do you do?

## Case study 2

- 56 man with 30 year pack year smoking history
- Diagnosed with stage 1 (cT1 cN1 cM0) HPV+ tonsil cancer
- Treated with cisplatin 100 mg/m<sup>2</sup> q3 weeks plus radiation but only gets one dose of cisplatin due to poor tolerance
- PET/CT 3 months after completion show complete response
- 5 months after CRT develops abdominal pain





