

Immunotherapy for the Treatment of Head and Neck Cancer

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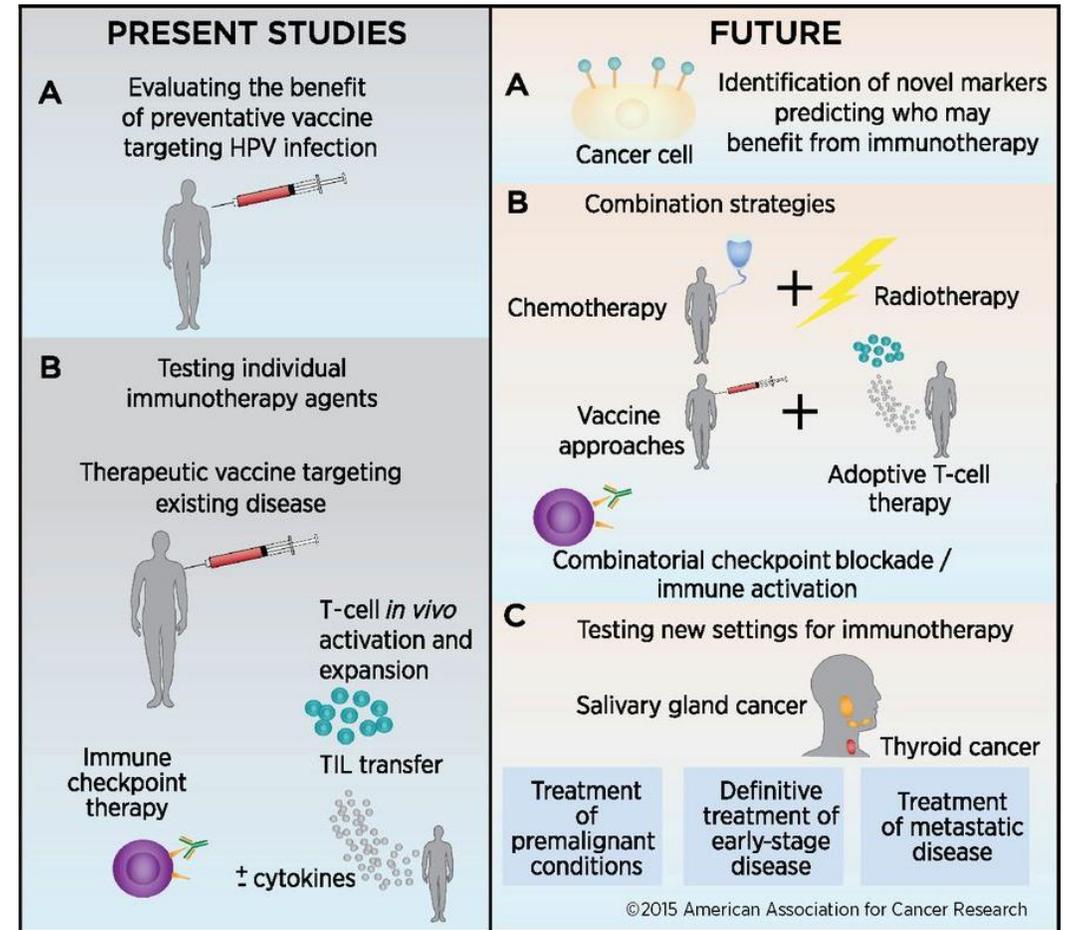
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Disclosures

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

Immunotherapy for the Treatment of Head and Neck Cancers

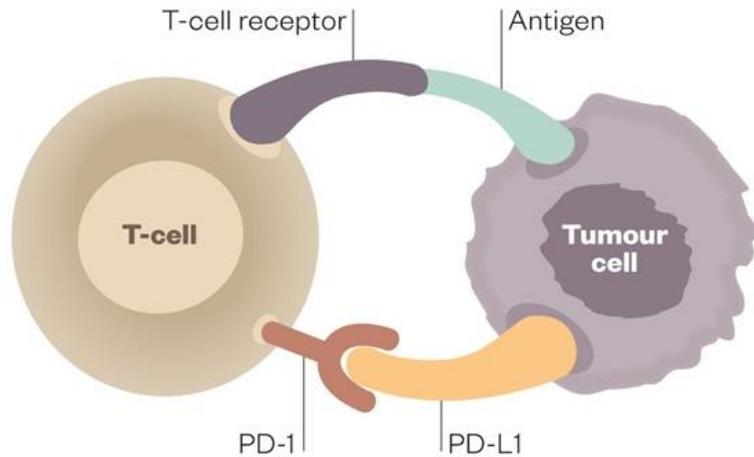
- Immuno-Oncology (I-O) developments in treatment of head and neck cancers
 - Expression of immunologic markers to guide treatment
 - Preventive vaccination against virally mediated cancers
 - PD-1 checkpoint inhibitors for the treatment of metastatic disease



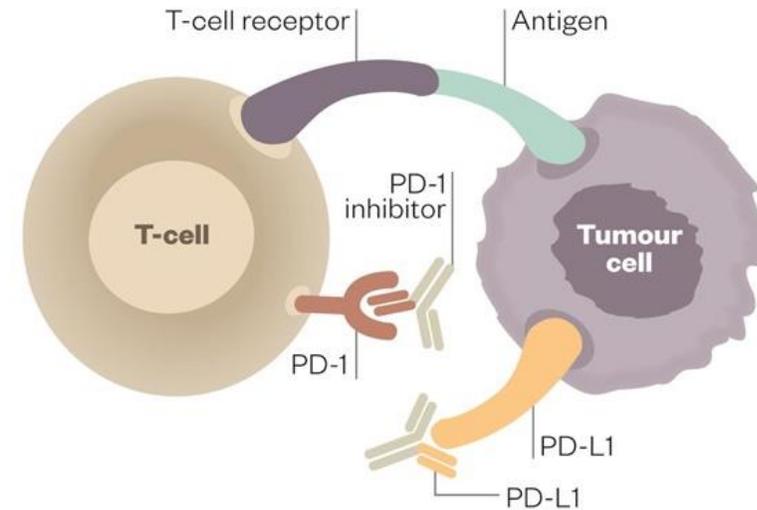
Schoenfeld JD, Cancer Immunol Res, 2015

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



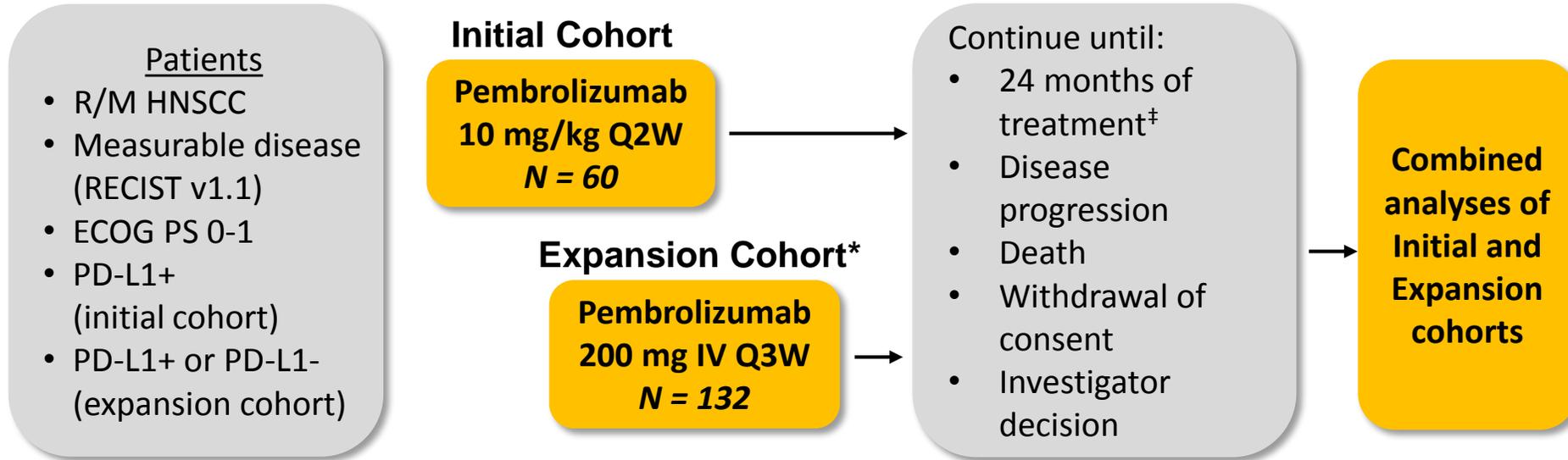
Antibodies against PD-1 and PD-L1 boost the immune response against cancer cells

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

- Pembrolizumab 200 mg IV Q3W
 - 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
 - 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[§]

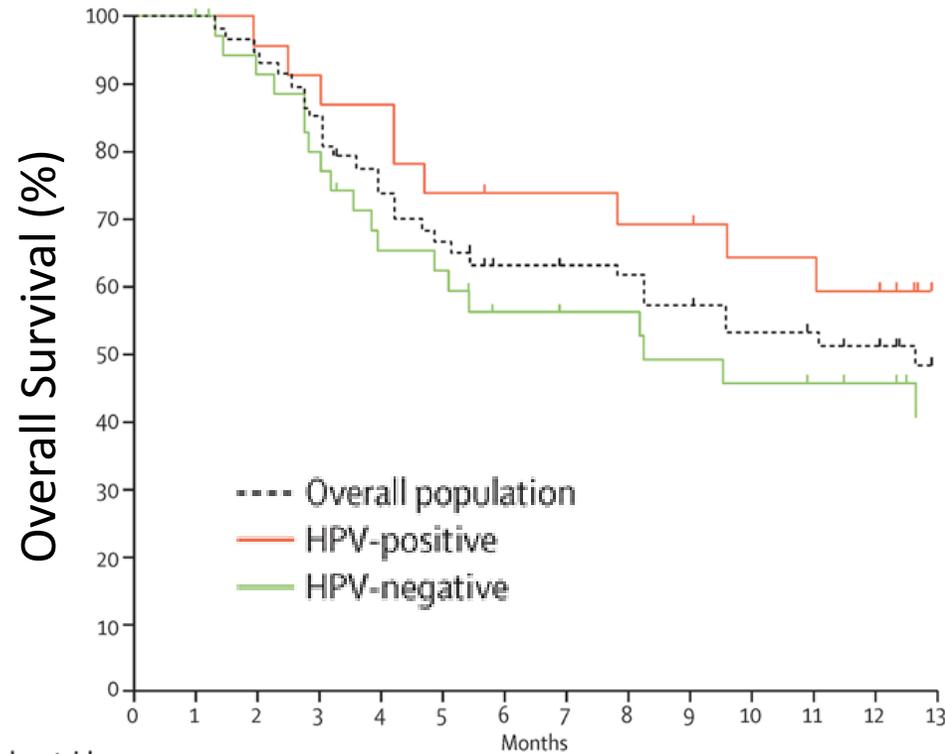
[†]Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.

[‡]Treatment beyond progression was allowed.

[§] Initial cohort only.

*Median duration of disease not reached.

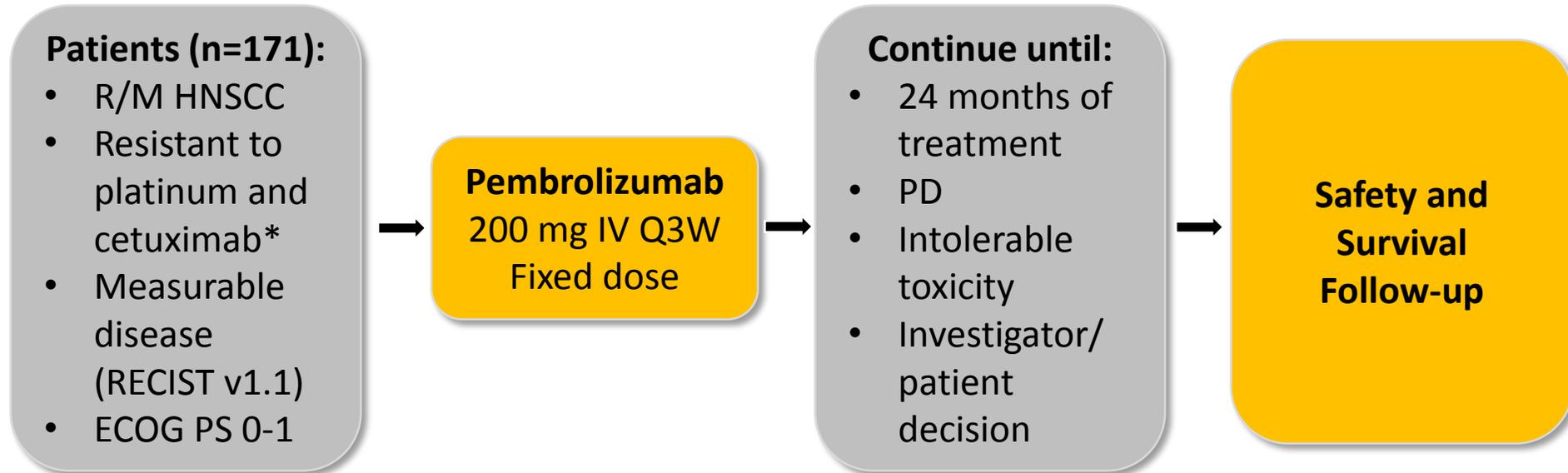
KEYNOTE-012



Number at risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Overall population	60	59	54	49	42	38	33	32	31	28	26	25	22	15
HPV-positive	23	23	22	21	20	17	16	16	15	14	13	13	11	7
HPV-negative	37	36	32	28	22	21	17	16	16	14	13	12	11	8

- 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

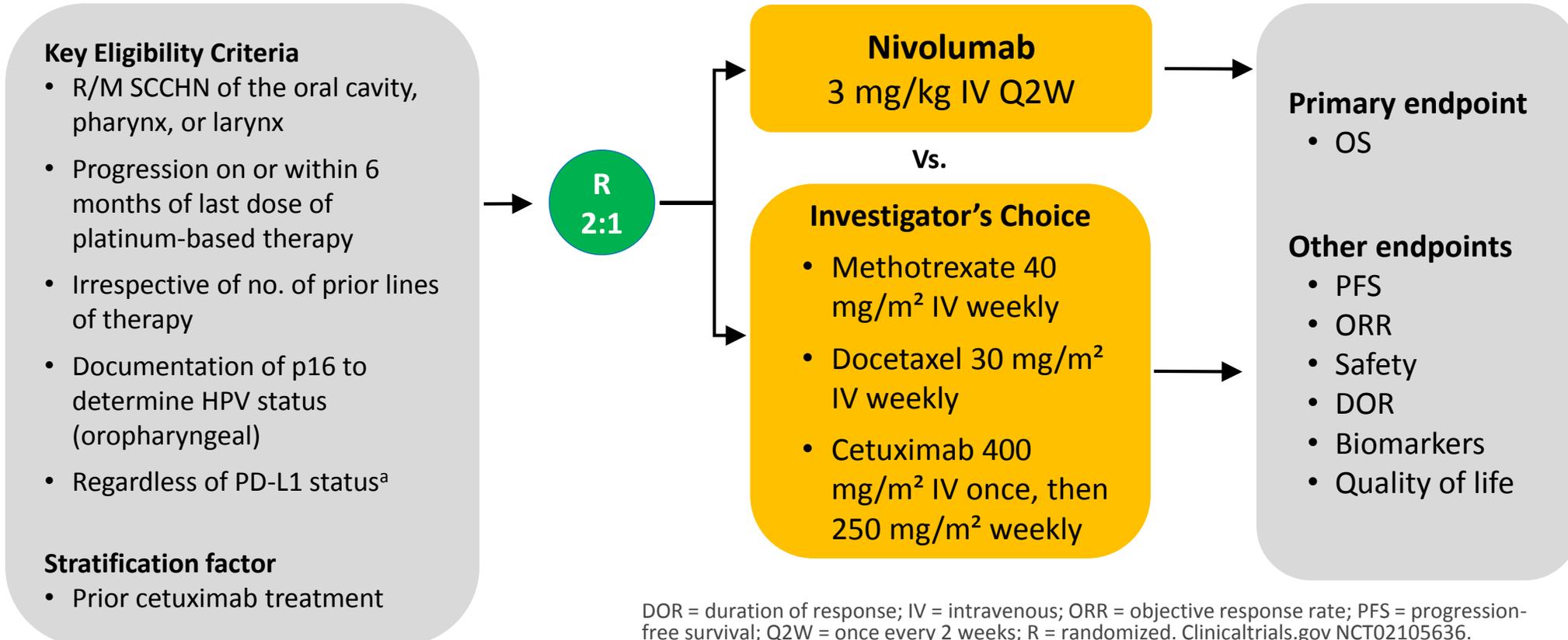
Outcome	All Patients	HPV Status		PD-L1 Status		
	N=171	Positive n=37	Negative n=131	≥1% n=140	<1% n=26	≥50% n=48
ORR, %	16	16	15	18	12	27
mPFS, mo	2.1					
6-mo PFS, %	23	25	21	24	20	31
6-mo OS, %	59	72	55	59	56	60

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



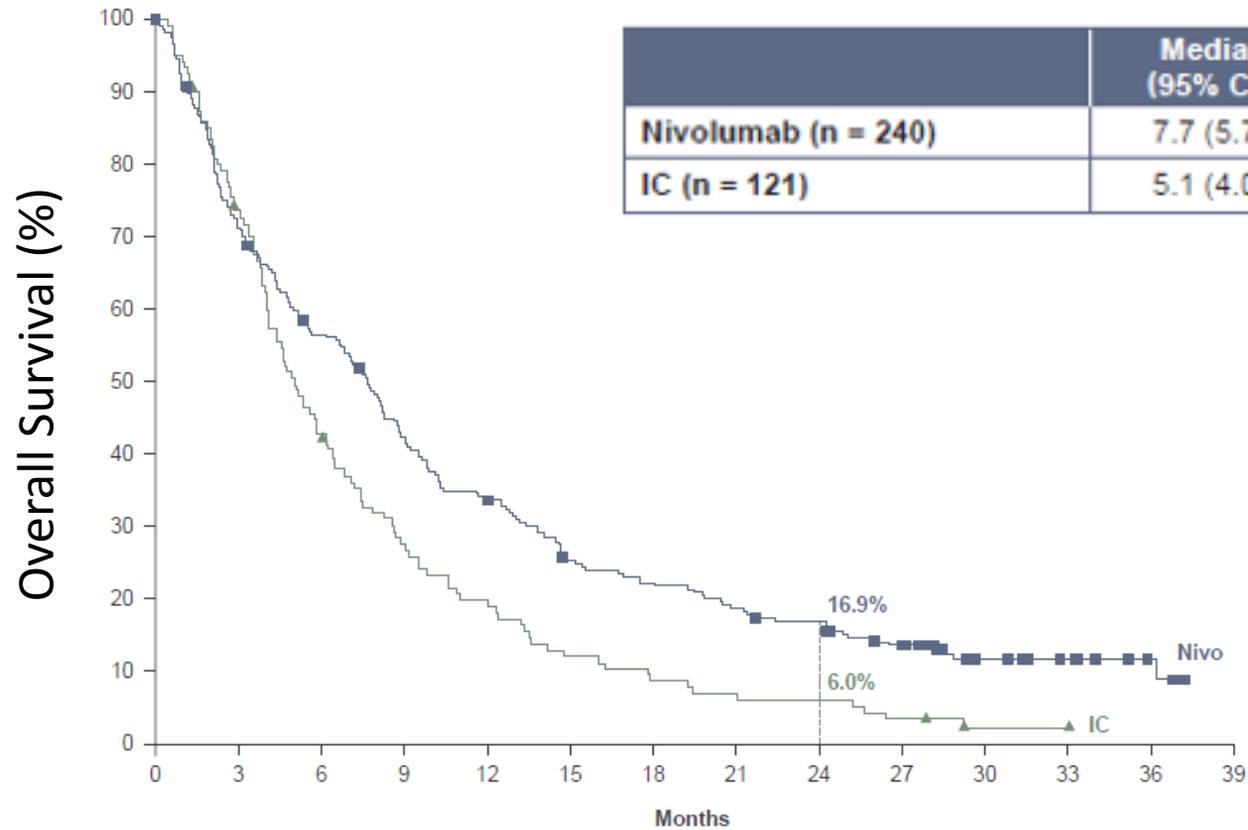
DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

^aTissue required for testing

Ferris & Gillison, NEJM, 2016

Checkmate 141

2 year Overall Survival

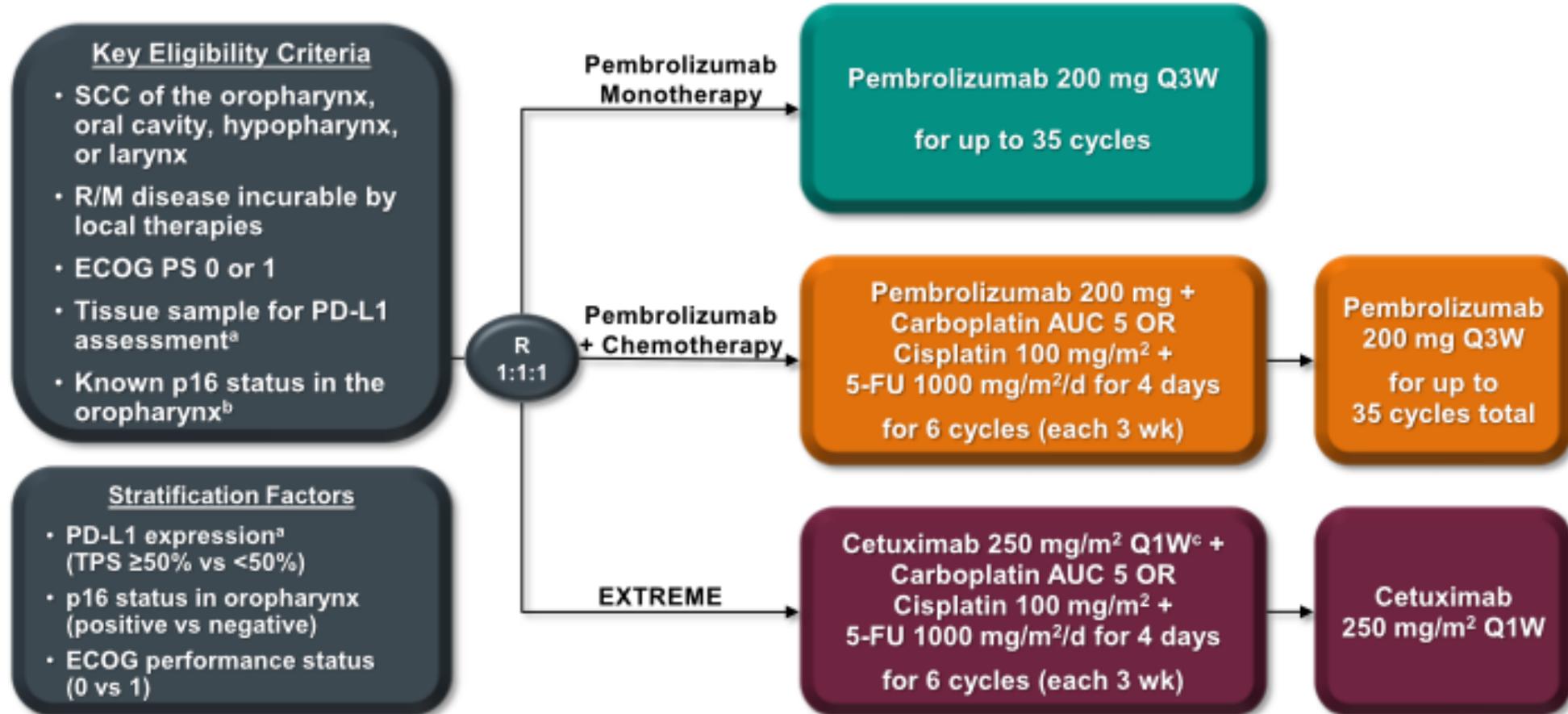


No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Nivo	240	169	132	98	78	57	50	42	37	28	15	10	4	0
IC	121	88	51	32	23	14	10	8	7	4	1	1	0	0

Ferris RL. Oral Oncology, 2018

In Development: KEYNOTE-048

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

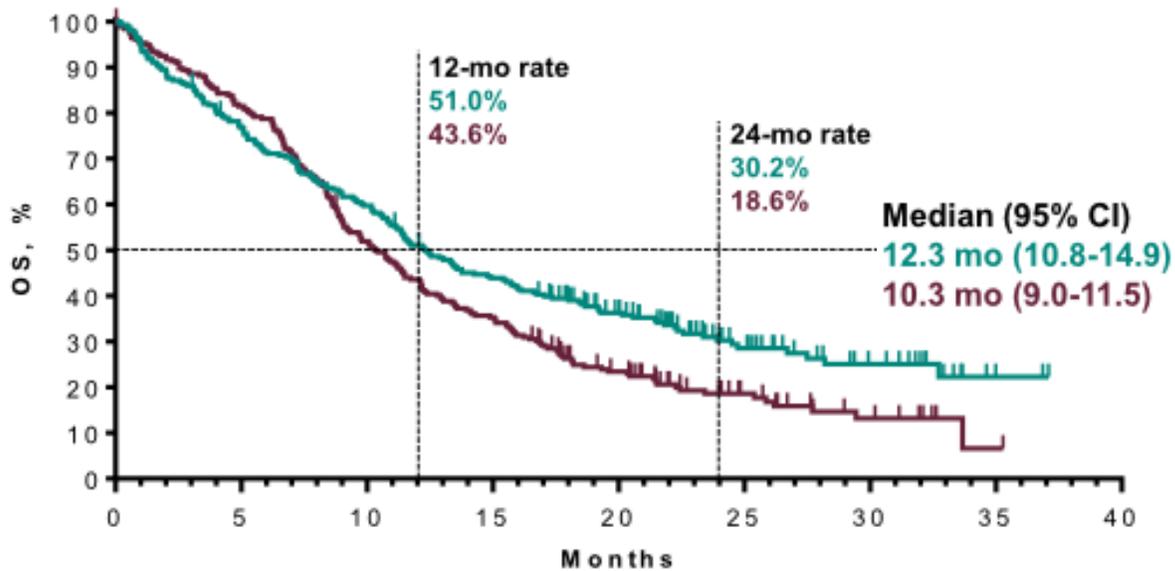


^aAssessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. ^bAssessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. ^cFollowing a loading dose of 400 mg/m².

KEYNOTE-048

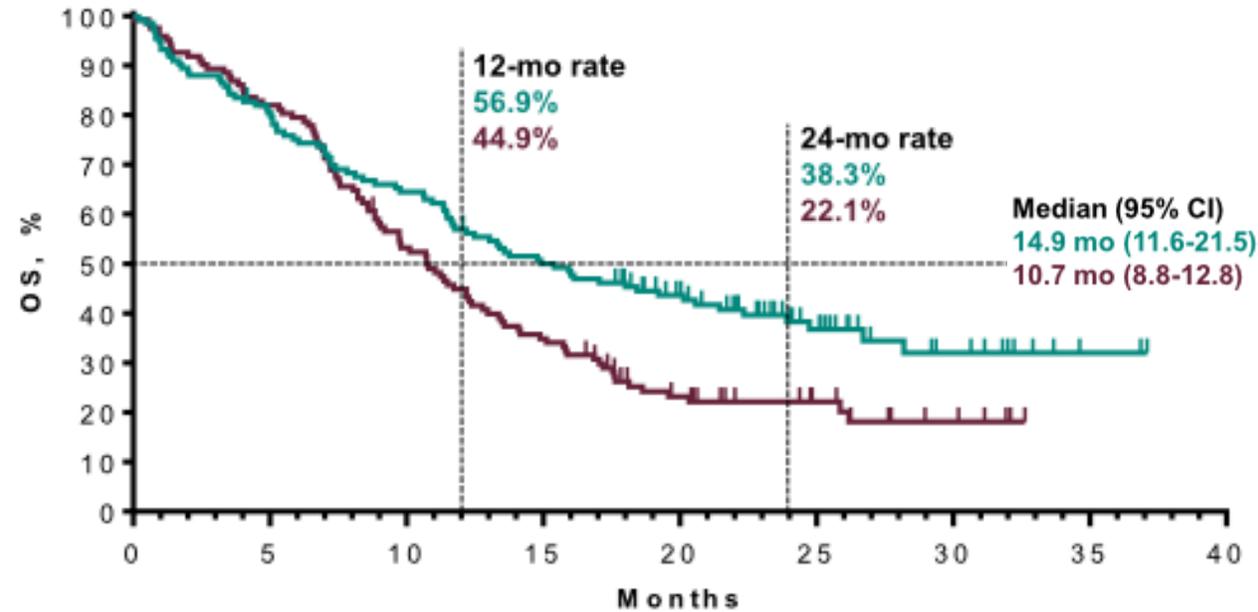
PD-L1 CPS ≥ 1%

	Events	HR (95% CI)	P
Pembro alone	69%	0.78 (0.64-0.96)	0.0086
EXTREME	81%		



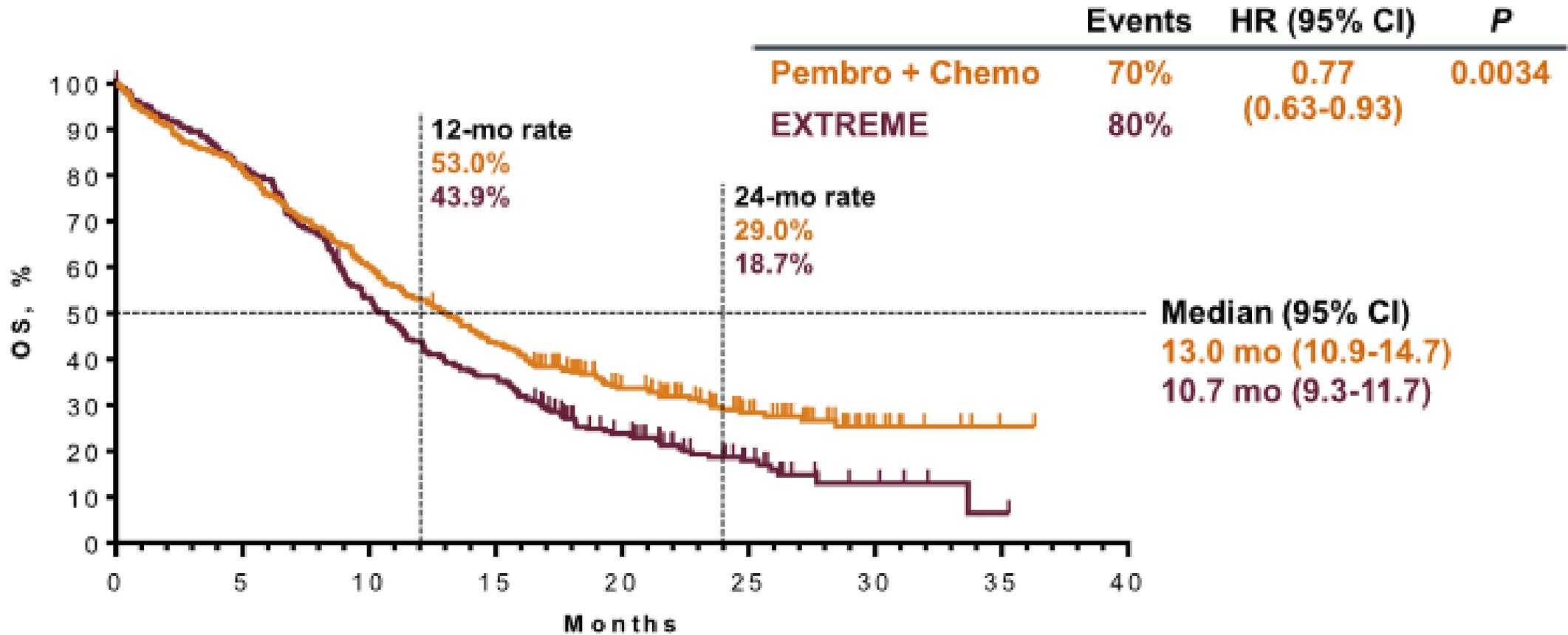
PD-L1 CPS ≥ 20%

	Events	HR (95% CI)	P
Pembro alone	62%	0.61 (0.45-0.83)	0.0007
EXTREME	78%		



KEYNOTE-048

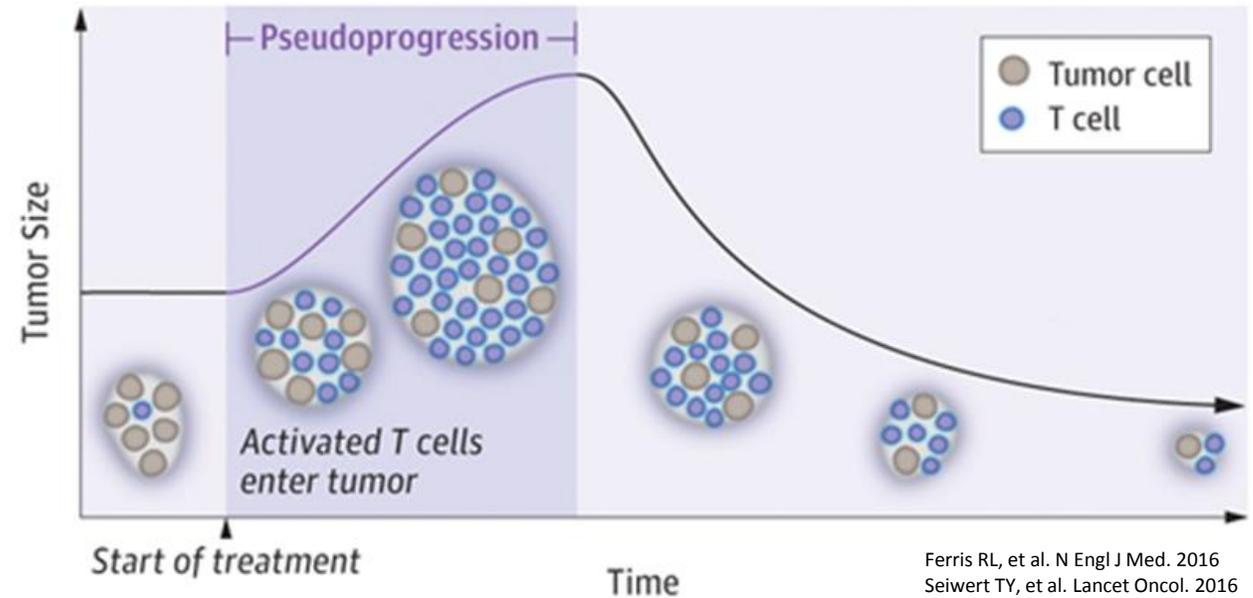
All Patients



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

Pseudoprogession

- Early appearance of an increase in tumor burden, followed by tumor regression
- Initially recognized in melanoma trials, 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 rare rates of pseudoprogression with pembrolizumab and nivolumab, respectively.

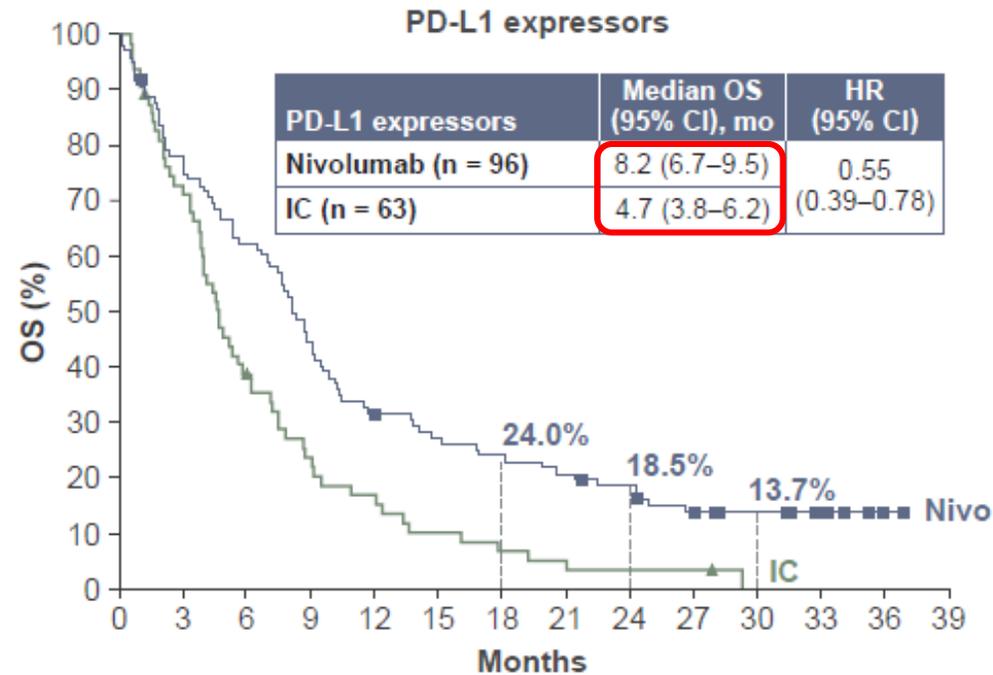
Ferris RL, et al. N Engl J Med. 2016
Seiwert TY, et al. Lancet Oncol. 2016

Evaluating Biomarkers in HNSCC

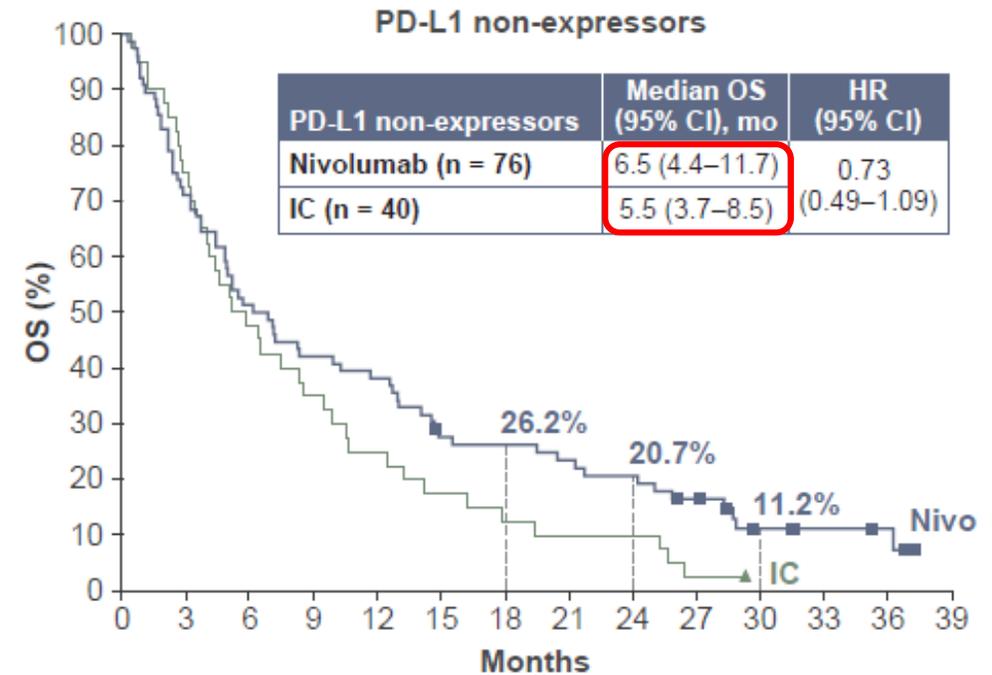
- Current FDA approvals of pembrolizumab and nivolumab are NOT contingent upon tumor PD-L1 status
 - KEYNOTE - 012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
 - KEYNOTE - 040: Phase III pembrolizumab vs. investigator's choice chemotherapy
 - Did not meet survival 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		0	3	6	9	12	15	18	21	24	27	30	33	36	39
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		0	3	6	9	12	15	18	21	24	27	30	33	36	39
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 and CheckMate 141

KEYNOTE 012

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

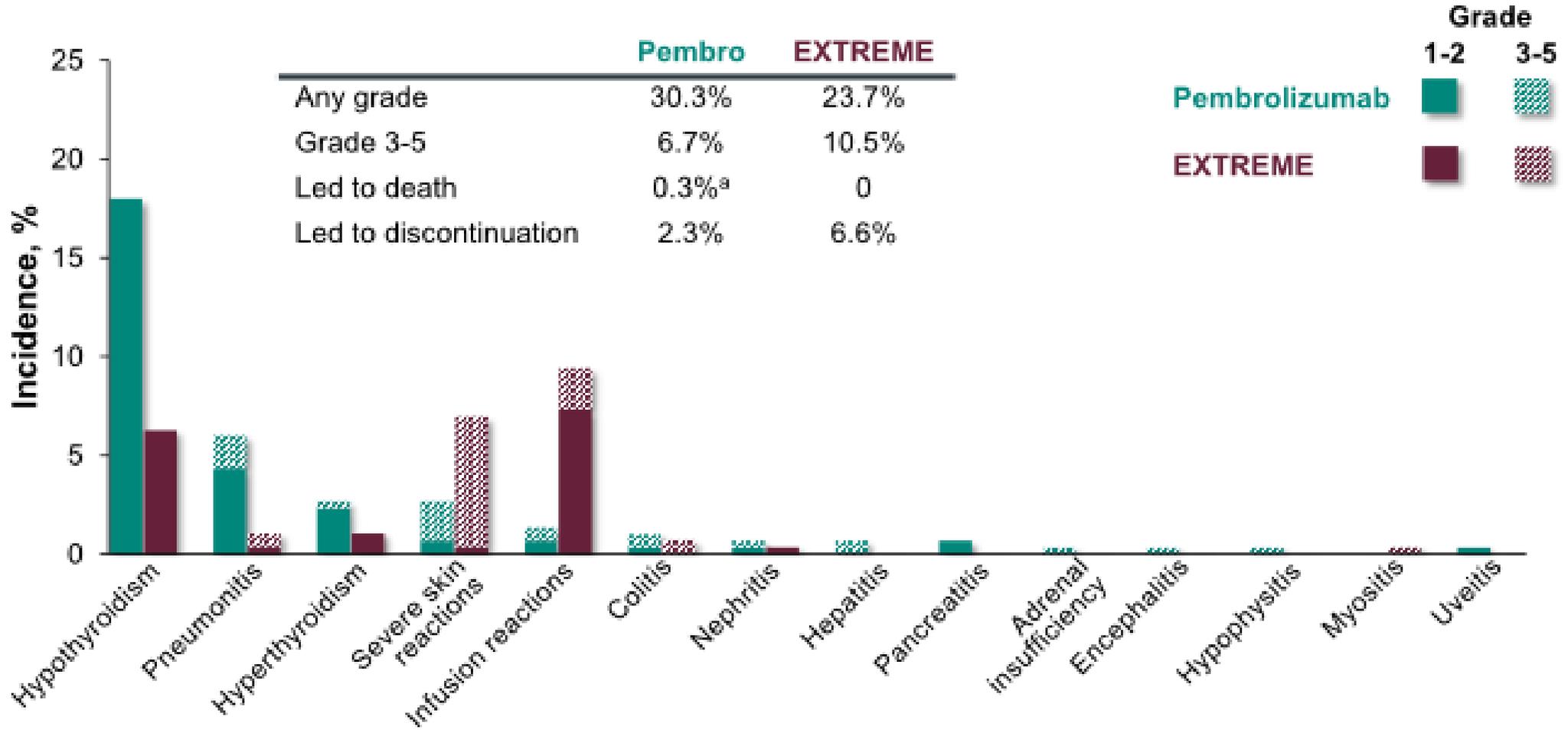
Treatment-Related Adverse Event	Grade 1 or 2 (≥ 10% of patients), No. (%)	Grade 3 (any occurrence), No. (%)	Grade 4 (any occurrence), No. (%)
Patients with ≥ 1 event	70 (53)	8 (6)	4 (3)
Hypothyroidism	14 (11)	0	0
Immune thrombocytopenic purpura	0	0	1 (1)
Abdominal pain	1 (1)	1 (1)	0
Colitis	0	1 (1)	0
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

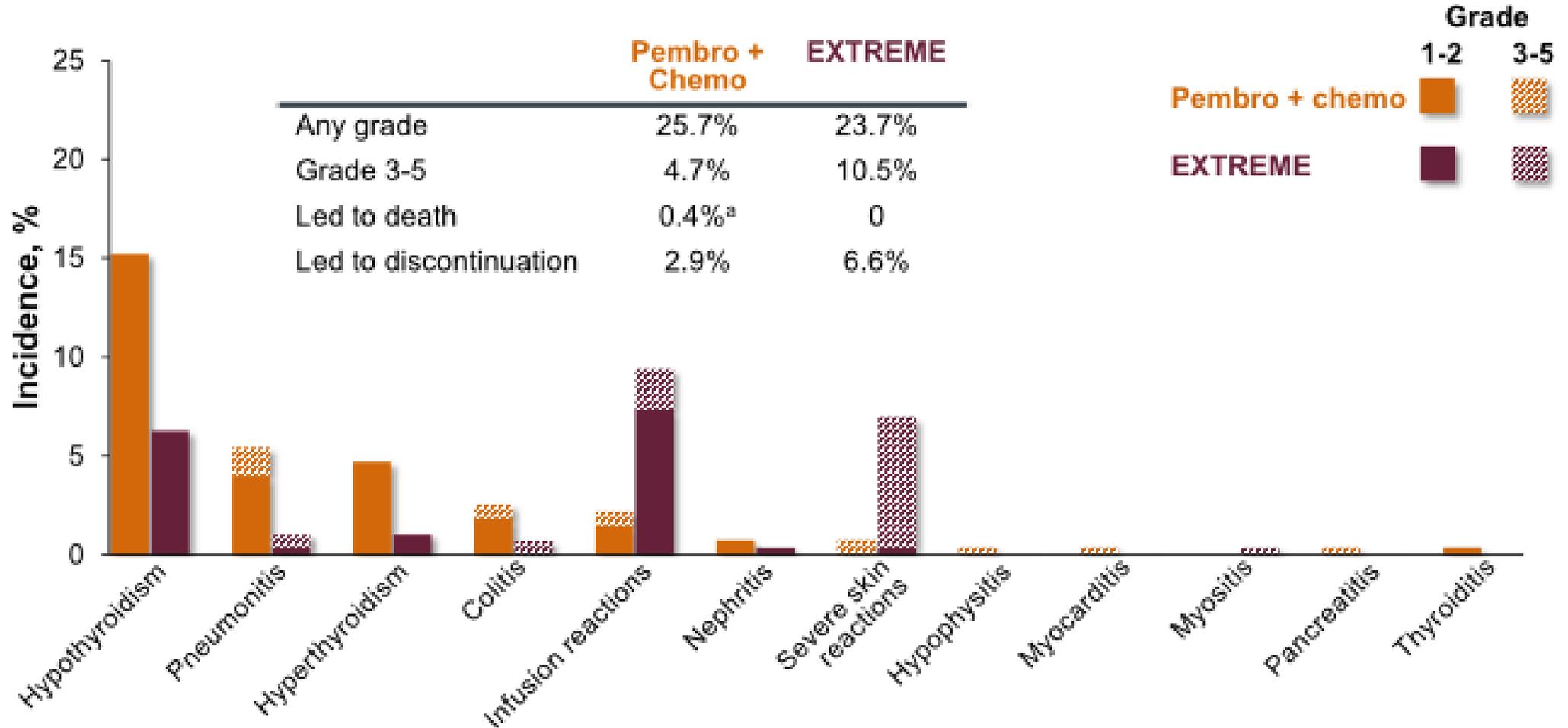
Immune-related Adverse Events

KEYNOTE-048 – Pembrolizumab monotherapy



Immune-related Adverse Events

KEYNOTE-048 – Pembrolizumab + Chemotherapy

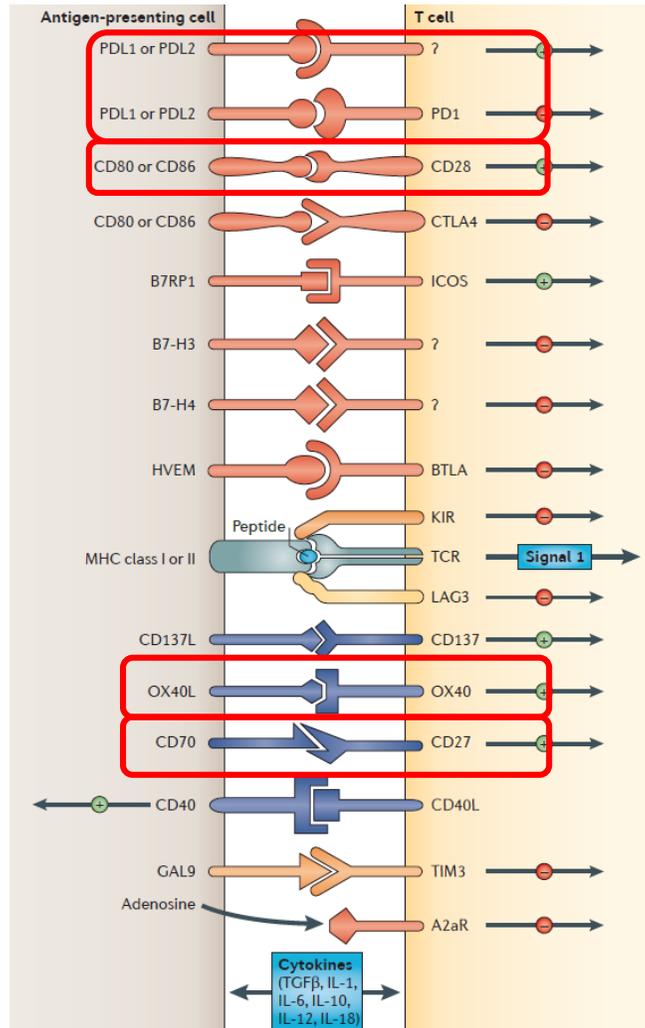


Immune-related Adverse Events

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)

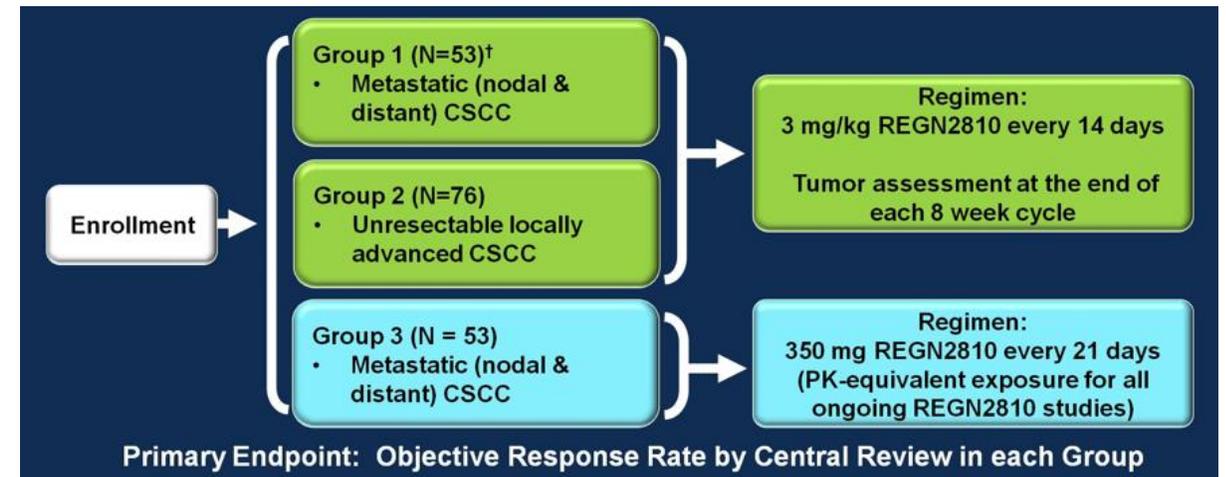
Developmental Immunotherapies for HNSCC

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

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 with anti-PD1 therapy versus chemotherapy
4. Clinical trials are underway to improve immunotherapy response rates and testing immunotherapy in other settings

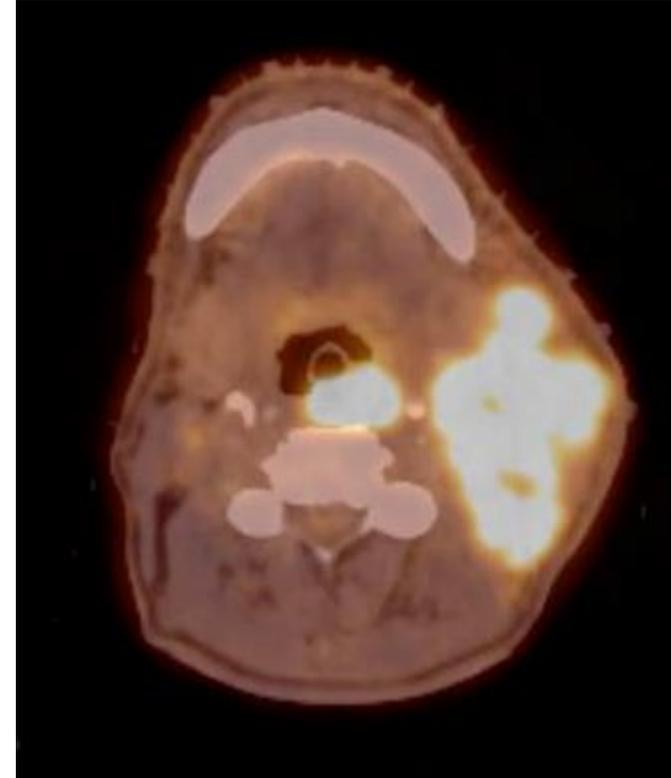
Patient Case Study 1

- Patient Background Information:
 - 78 yo M with a history of CAD, HTN, HLD
 - Presents with painful left sided neck mass
 - Lost 30 lbs due to anorexia

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



Patient Case Study 1

January 2015

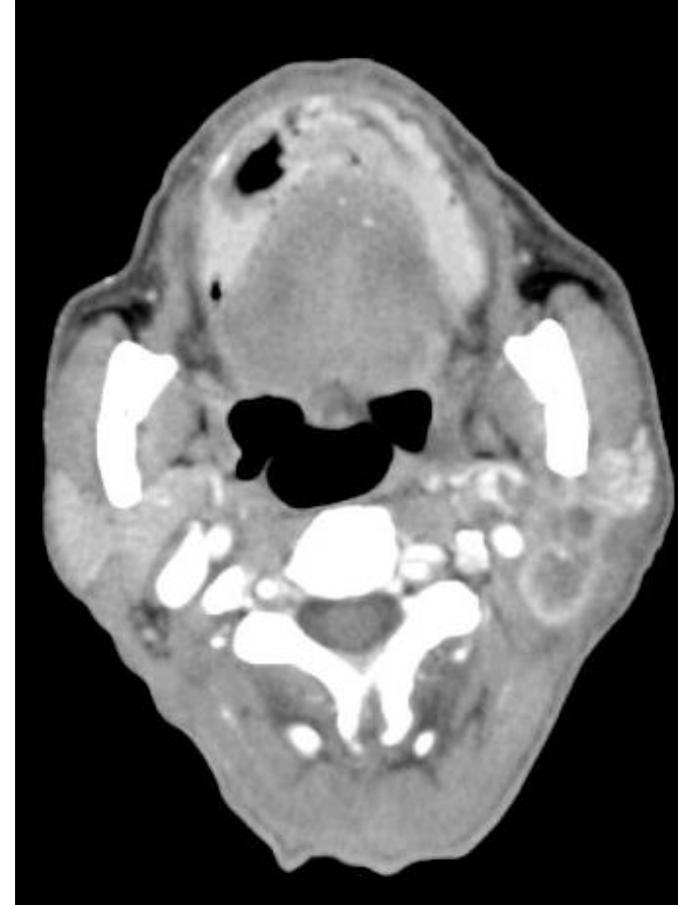
- Cervical disease decreased – pain improved
 - Carboplatin/paclitaxel 1st line
- PET CT revealed new osseous and axillary mets
 - Started on cetuximab 2nd line



Patient Case Study 1

June 2015

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



Patient Case Study 1

October 2015

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

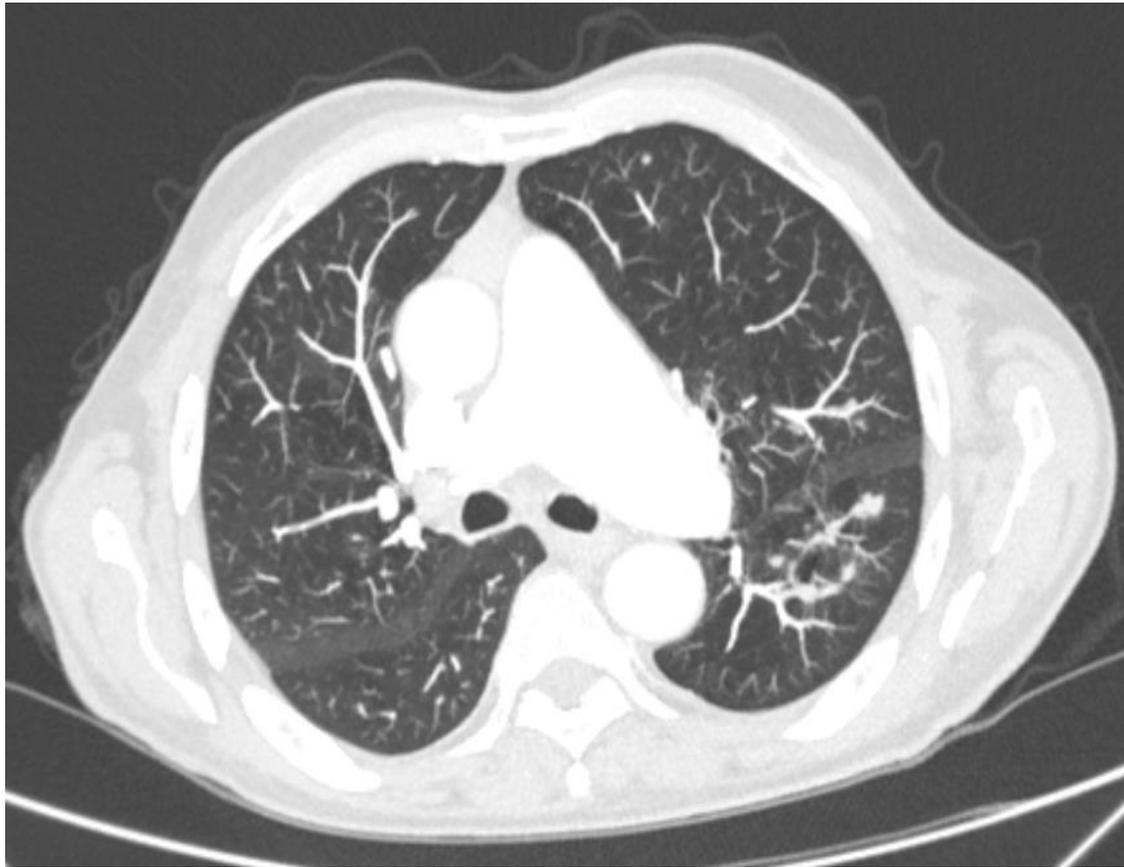


Patient Case 2

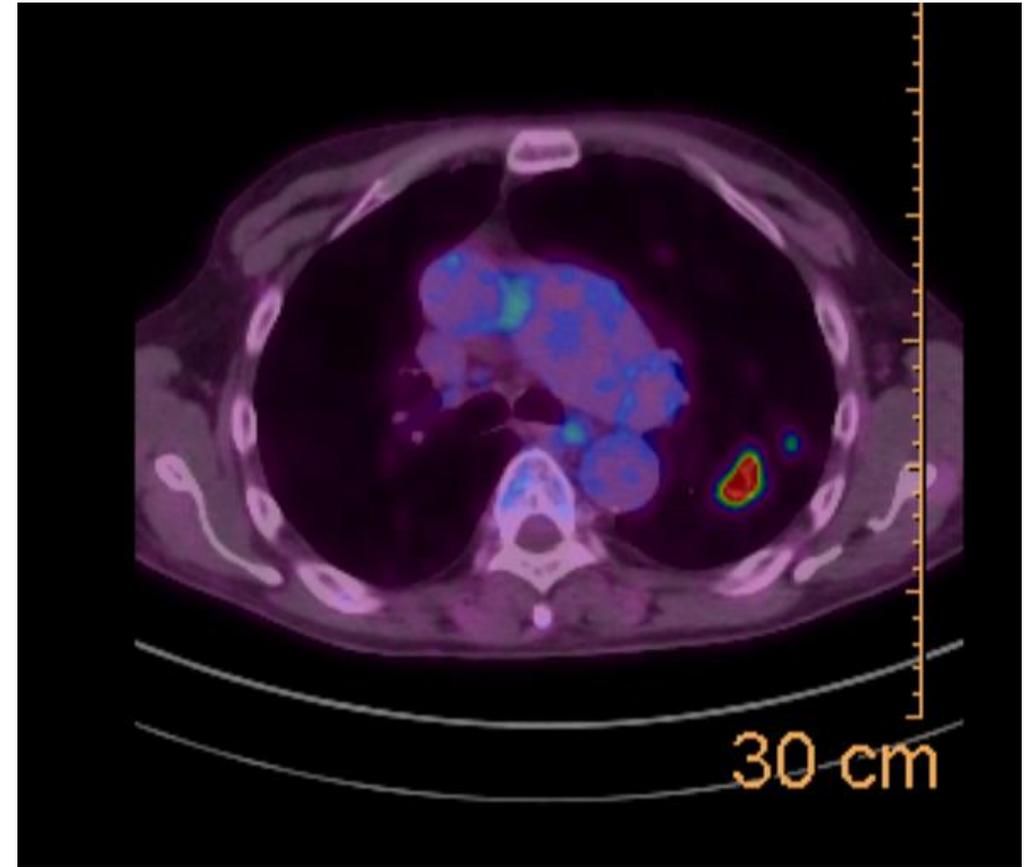
- pT4pN2cM0 squamous cell carcinoma of the larynx in 2017
- Laryngectomy
- Adjuvant chemoradiotherapy

Patient Case 2

CT Thorax at recurrence:



PET/CT

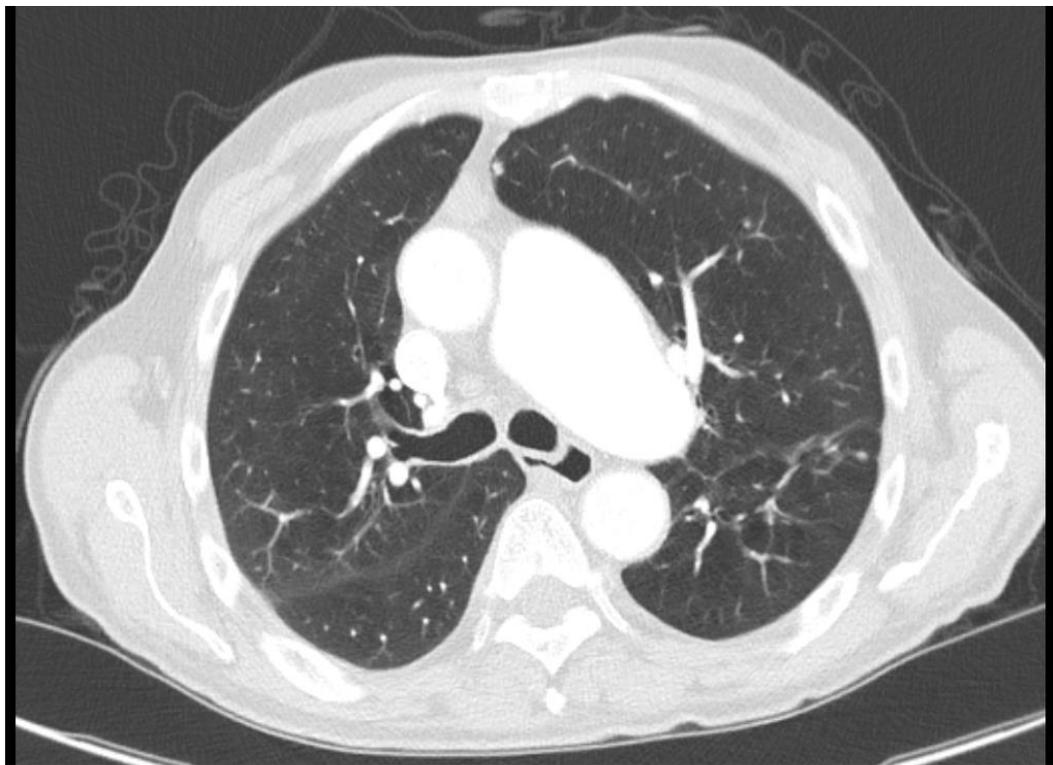


Patient Case 2

- Patient started on nivolumab, as per Checkmate- 141
- No subjective adverse events
- Developed hypothyroidism
 - Unclear association with nivolumab
 - Possibly secondary to prior radiotherapy

Patient Case 2

- CT Thorax after three months:



- CT thorax after ten months:

