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Immunotherapy for the Treatment of Head and Neck Cancers

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AMERICAN ACADEMY OF EMERGENCY MEDICINE

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Disclosures

- No relevant financial relationships to disclose
- I will be discussing non-FDA approved indications during my presentation.

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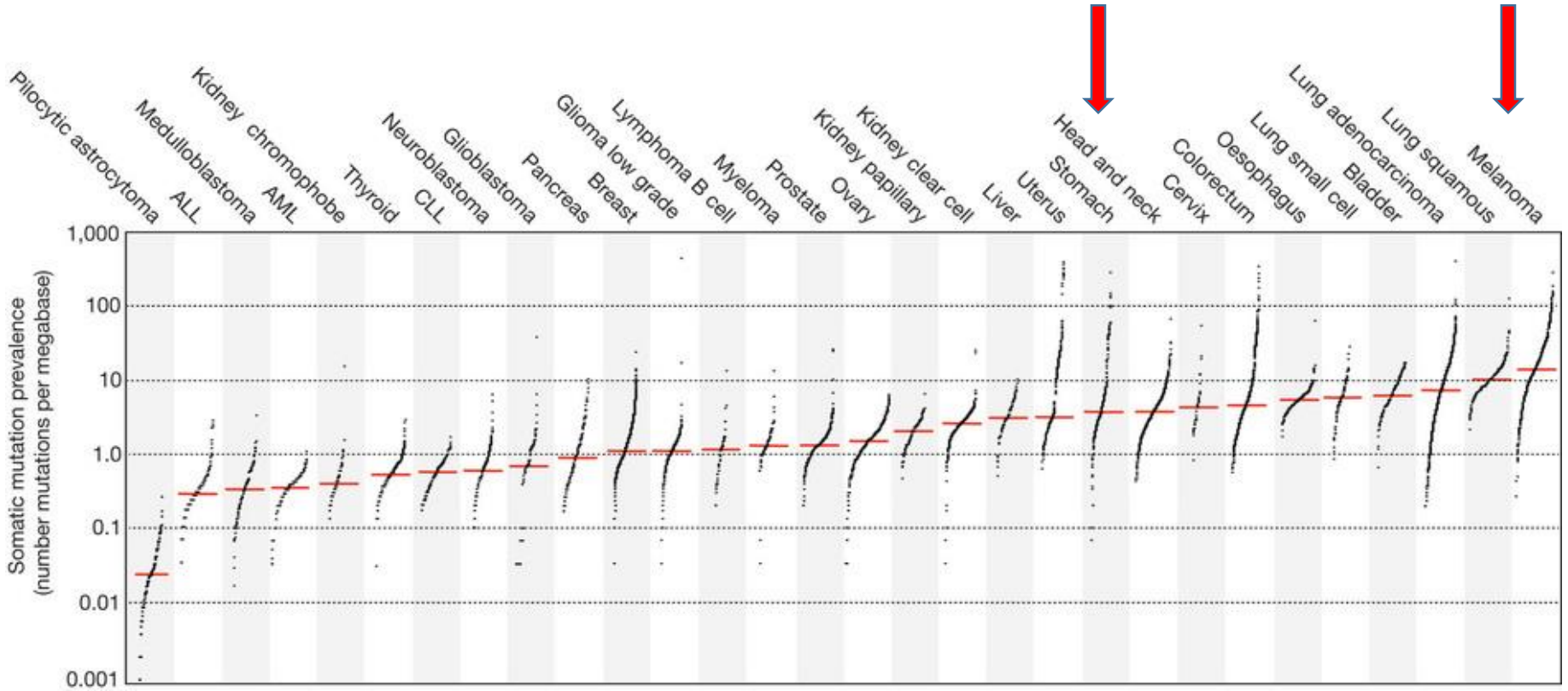
The prevalence of somatic mutations across human cancer types

Alexandrov et al. Nature 500, 415–421 (22 August 2013)



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Pt WS

- 78 yo M with a history of CAD, HTN, HLD
- Presents with painful L sided neck mass
- Lost 30 lbs due to anorexia
- Diagnosed with hypopharynx SCC

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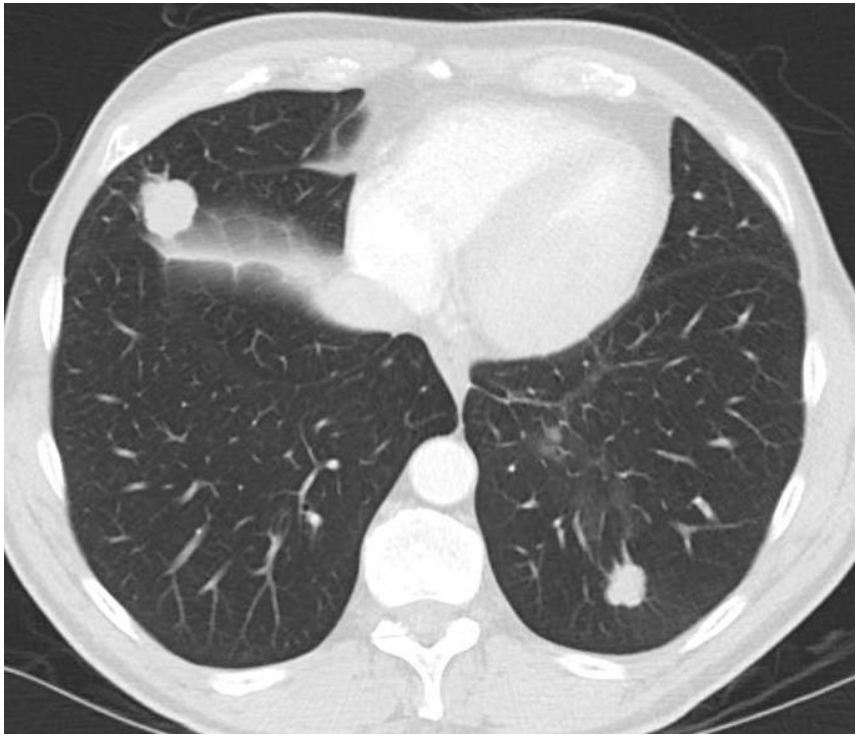
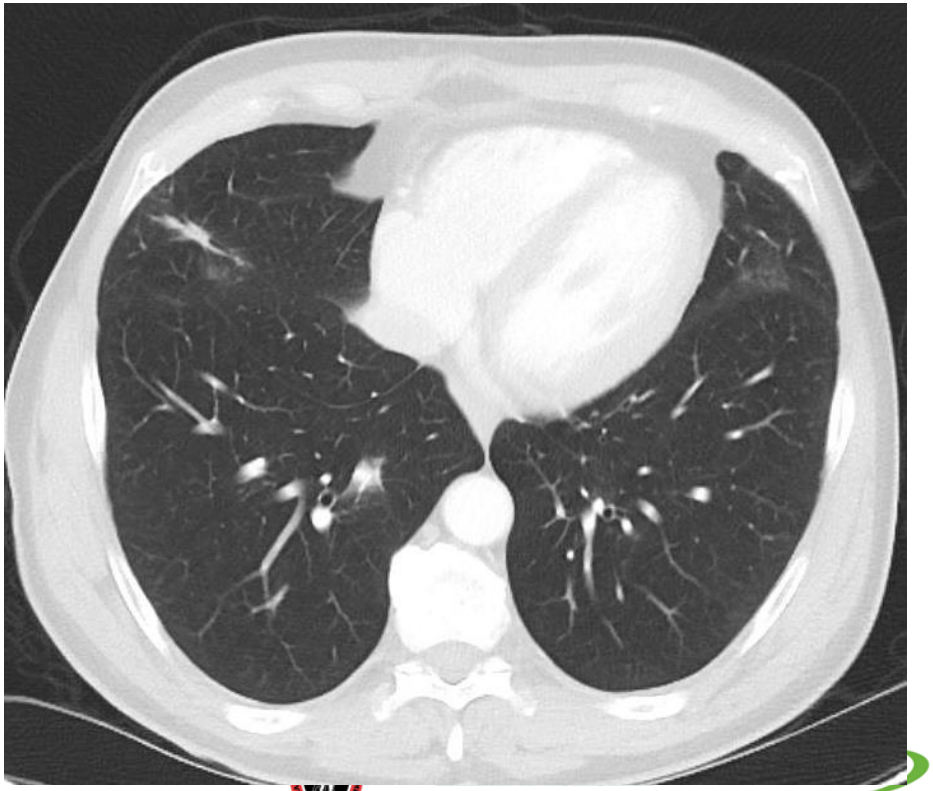
2/2015

- Started on pembrolizumab
  - Enrolled in KEYNOTE 055
- Experienced a near CR





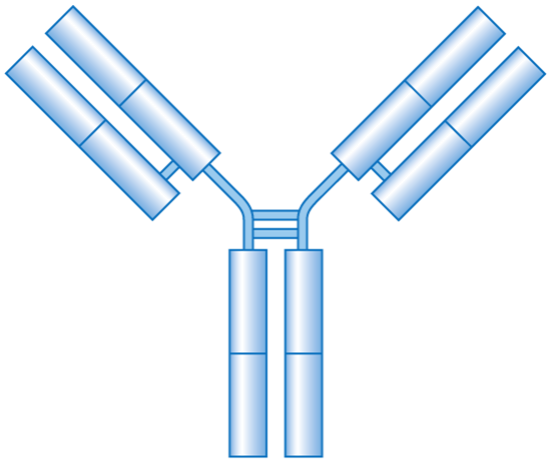
IO Agents approved and in development for HNC

1. **Pembrolizumab**
   - IgG4
   - Humanized
   - High Affinity for PD-1 (K_D ~ 29 pM)
   - Approved for Melanoma, NSCLC, **HNC**

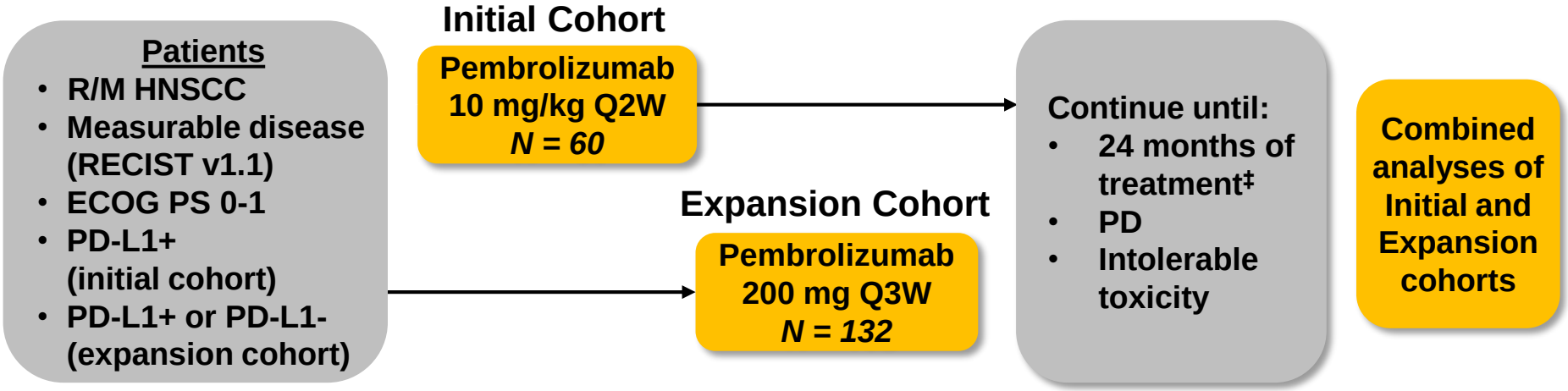
2. **Nivolumab**
   - IgG4
   - Fully human
   - High Affinity for PD-1 (K_D ~ 2.6 nM)
   - Approved for Melanoma, NSCLC, RCC, **HNC**

3. **PD-L1 agents in development:**
   - Atezolizumab (bladder, NSCLC),
   - Avelumab (Bladder, MCC)
   - Durvalumab (NSCLC, bladder)

4. **CTLA-4 agents:**
   - Ipilimumab,
   - Tremelimumab



HNSCC Cohorts of Nonrandomized, Phase 1b, Multi-cohort KEYNOTE-012 Trial



Response assessment: Every 8 weeks

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

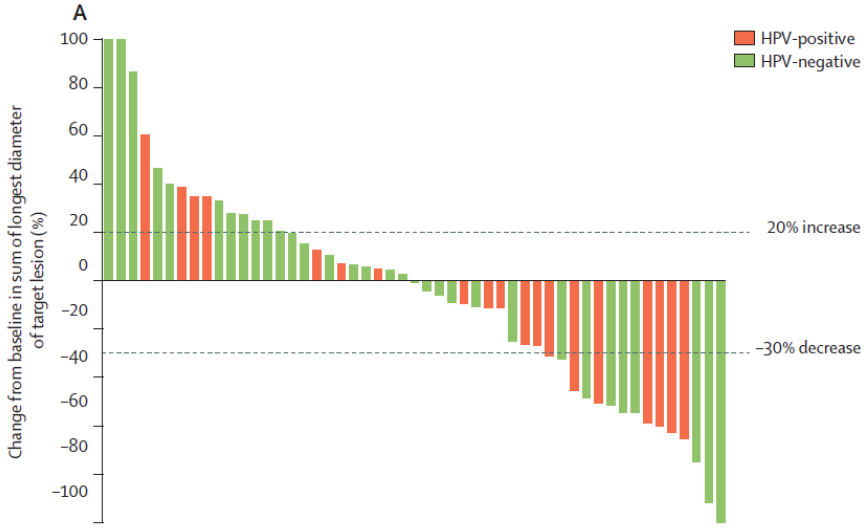
Secondary end points: ORR (investigator), PFS, OS, response duration, ORR in HPV+ patients§

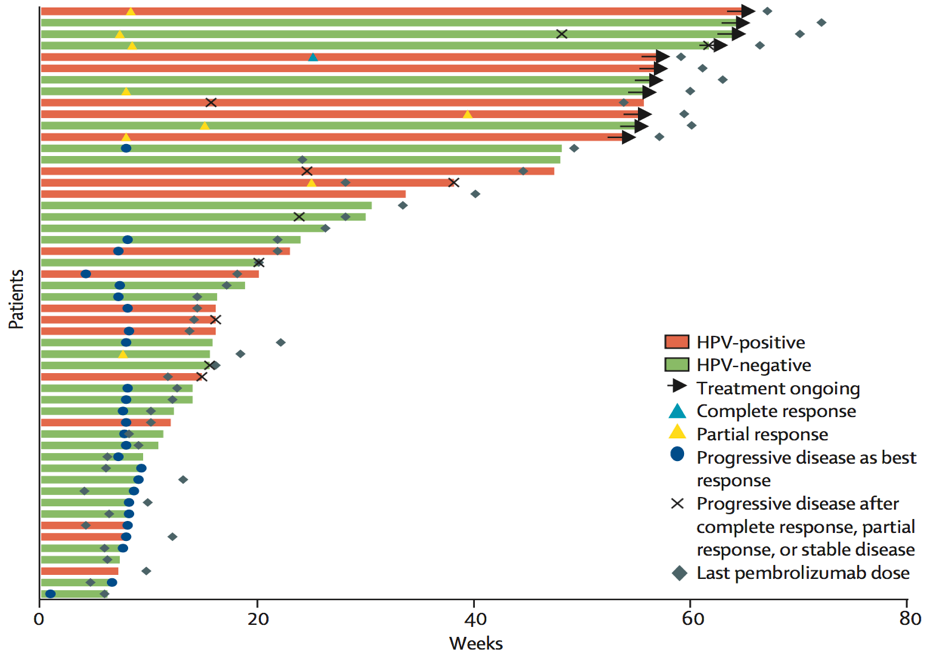
†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§Initial cohort only.

Tumor Shrinkage (KeyNote 12)

Pembrolizumab in Platinum-refractory R/M SCCHN

Lancet Oncol 2016; 17: 956–65

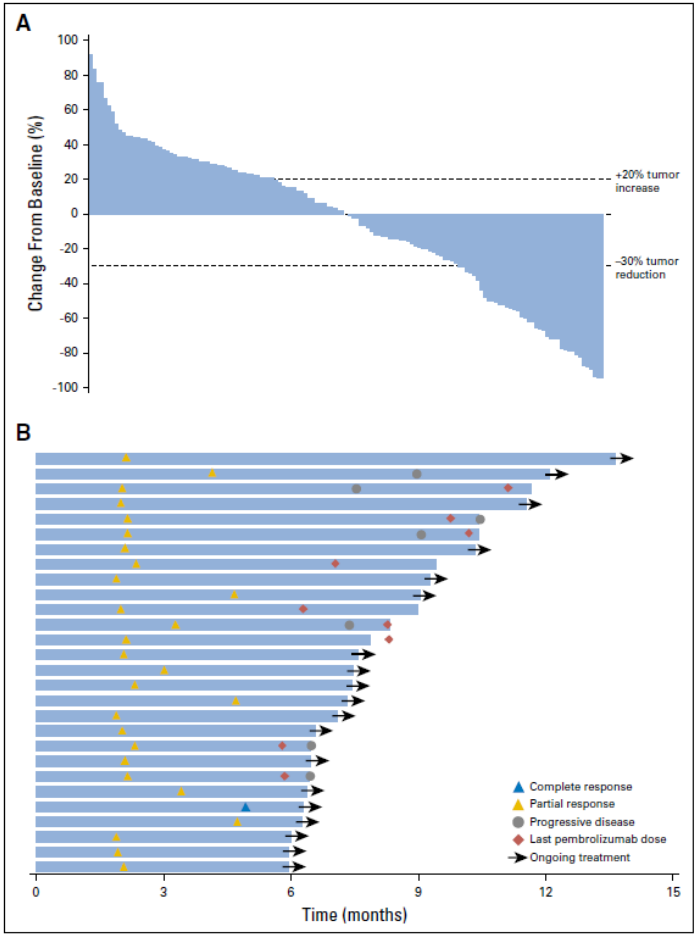


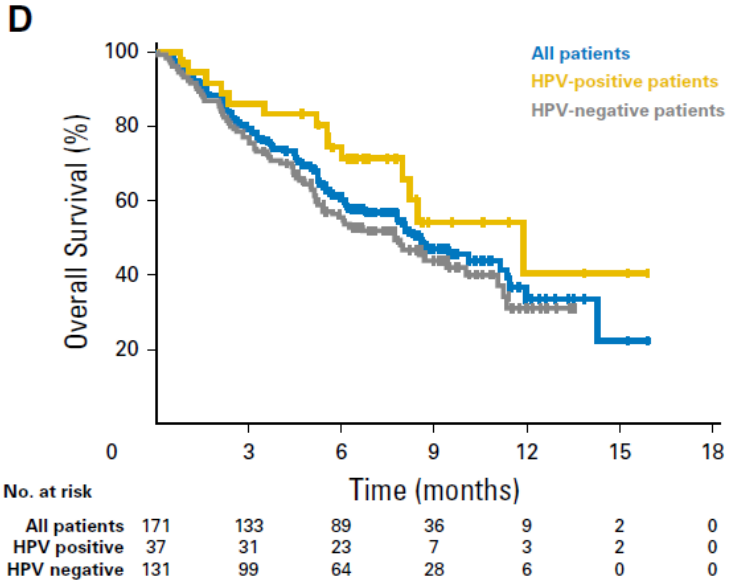


- Median Time to response 2 months (2-17 mo)
- ORR 18%
- 24% of the responders had CR
- 74% of the responses lasted ≥ 12 months

Pembrolizumab in Platinum-refractory R/M SCCHN – Phase II Keynote 55

J Clin Oncol 35:1542-1549.





- ORR 16% (28/171) plus 19% SD
- Median (range) response durations were 8 (2+ to 12+)
- Median OS of 8 months (95% CI, 6 to 11 months)

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FDA Approves Pembrolizumab for Head and Neck Cancer

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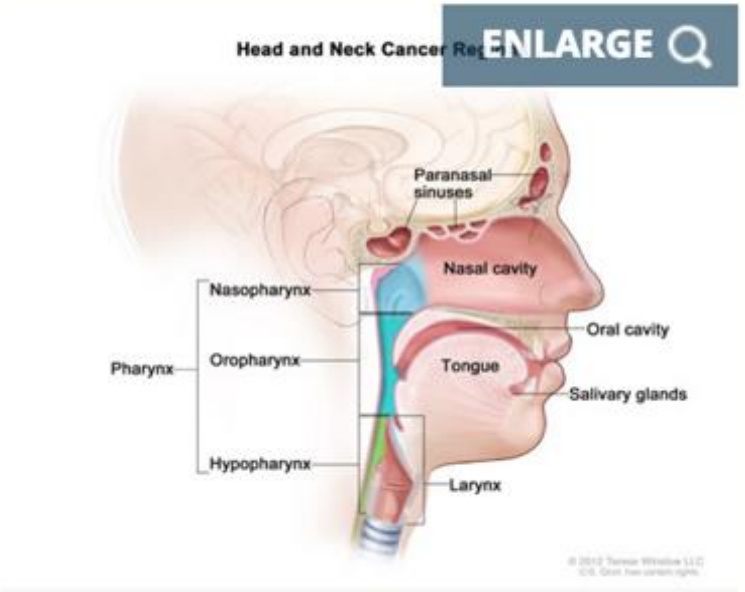
August 24, 2016 by NCI Staff

The Food and Drug Administration (FDA) approved pembrolizumab (Keytruda®) on August 5 for the treatment of some patients with an advanced form of head and neck cancer. The approval is for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) that has continued to progress despite standard-of-care treatment with chemotherapy.



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Phase 3 CheckMate 141 Study Design

Nivolumab in R/M SCCHN After Platinum Therapy

Randomized, global, phase 3 trial of the efficacy and safety of nivolumab vs investigator's choice in patients with R/M SCCHN

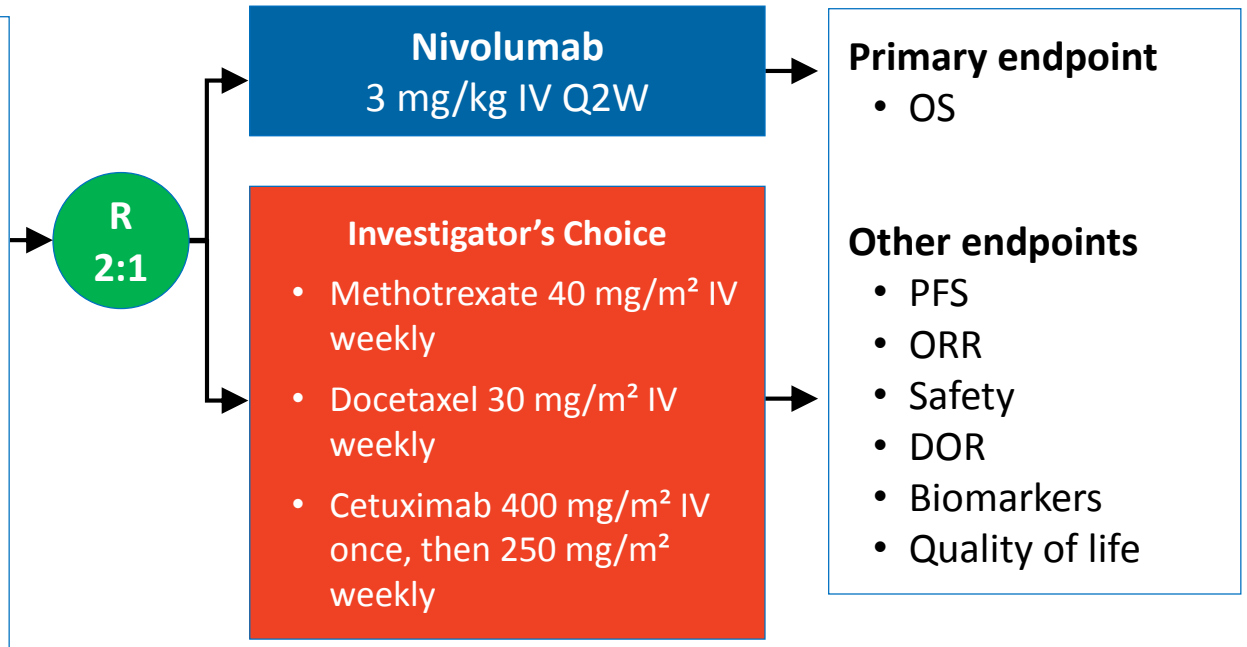
Key Eligibility Criteria

- 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

[a]Tissue required for testing



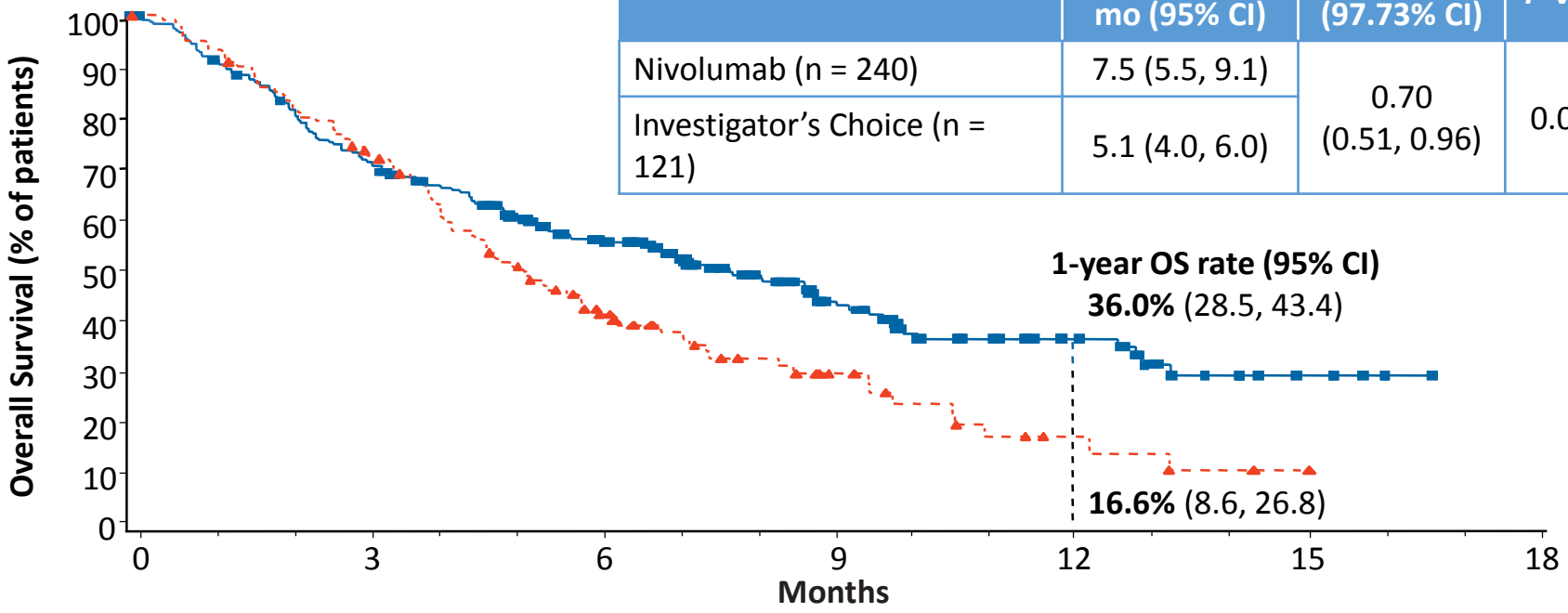
DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

Ferris/Gillison NEJM 2016

Overall Survival

Nivolumab in R/M SCCHN After Platinum Therapy

	Median OS, mo (95% CI)	HR (97.73% CI)	*P*-value
Nivolumab (n = 240)	7.5 (5.5, 9.1)	0.70 (0.51, 0.96)	0.0101
Investigator's Choice (n = 121)	5.1 (4.0, 6.0)		



No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Investigator's Choice	121	87	42	17	5	1	0

→ *Response Rate only 13%, but major impact on **Survival***

Ferris/Gillison NEJM 2016

FDA Approves Nivolumab for Head and Neck Cancer

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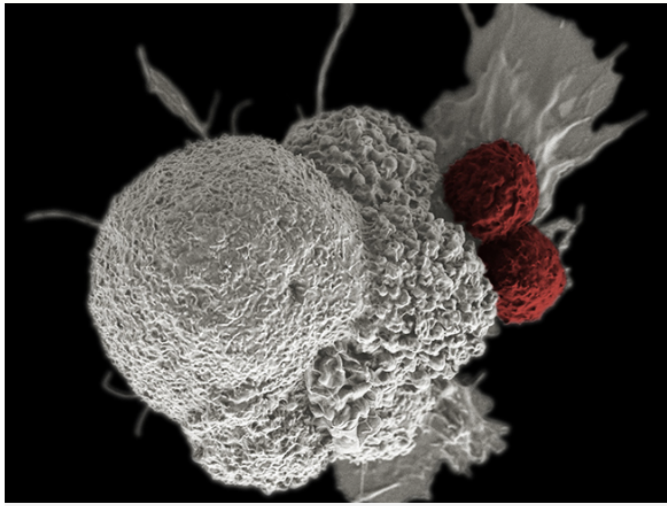
December 1, 2016, by NCI Staff

The Food and Drug Administration (FDA) approved nivolumab (Opdivo®) on November 10 for the treatment of squamous cell cancer of the head and neck (SCCHN).

Nivolumab is already approved for the treatment of several other cancers. This new approval is for the use of nivolumab in patients with SCCHN that has progressed during chemotherapy with a platinum-based drug or that has recurred or metastasized after platinum-based chemotherapy.

Nivolumab is the second immunotherapy drug approved to treat SCCHN. In August of this year, the FDA approved pembrolizumab (Keytruda®) for patients with SCCHN whose disease has progressed during or after platinum-containing chemotherapy. Both nivolumab and pembrolizumab are immune checkpoint inhibitors, drugs that prevent tumor cells from blocking attack by the immune system.

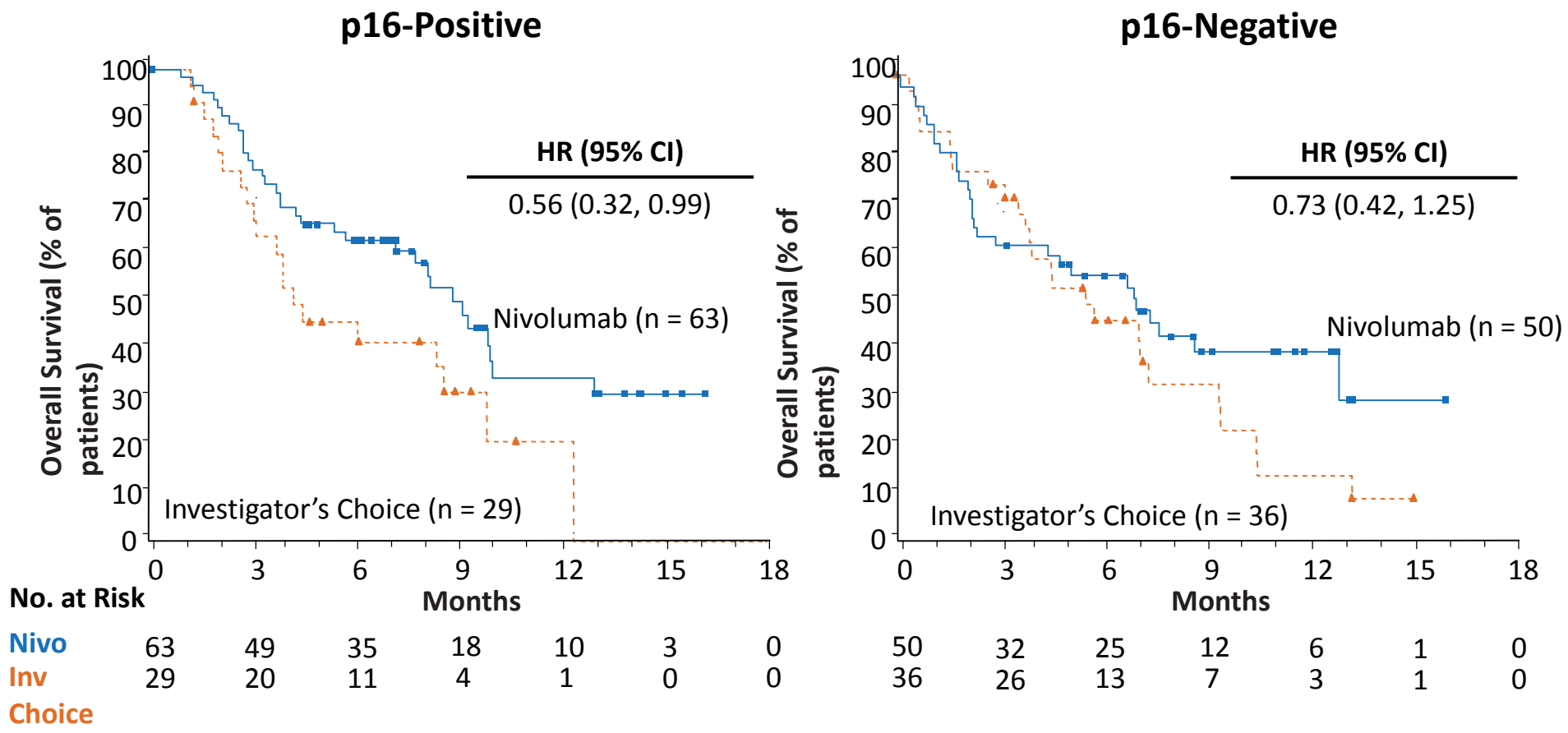


Cytotoxic T cells (red) attacking an oral squamous cancer cell (white). Immune checkpoint inhibitors like nivolumab prevent tumors from turning off T cells, allowing them to attack and kill the tumor cells.

Credit: National Cancer Institute

Overall Survival by p16 Status

Nivolumab in R/M SCCHN After Platinum Therapy



Ferris/Gillison NEJM 2016

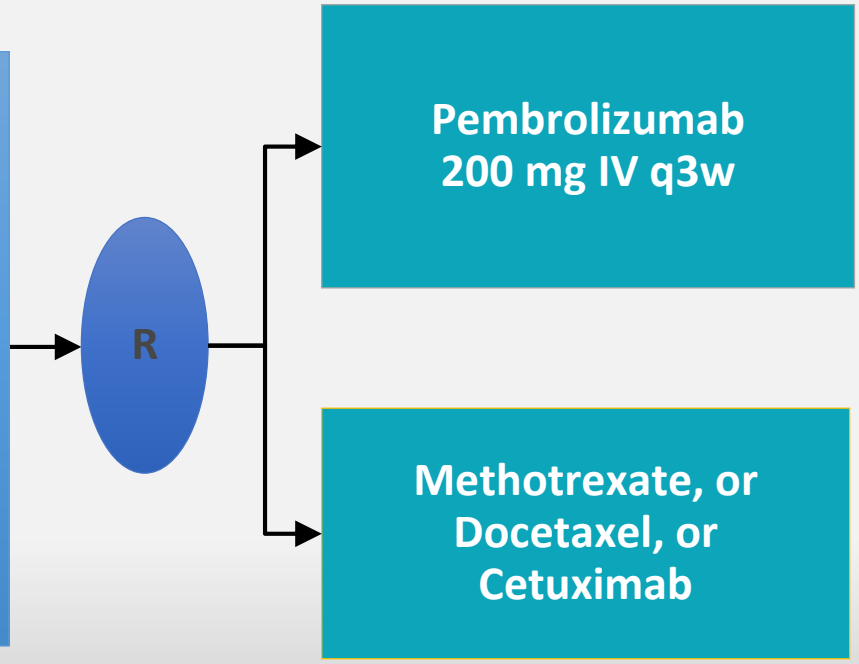
KEYNOTE 40:
Phase III Randomized Trial of *Pembrolizumab vs SOC*

Randomized, phase III trial of Pembrolizumab vs. Dealer's choice in R/M HNSCC following failure of platinum therapy

N=466

Key Eligibility Criteria

- Recurrent or metastatic HNSCC (oral cavity, oropharynx, hypopharynx, or larynx)
- Failure of prior platinum therapy
- ECOG PS 0–1
- No active CNS metastases
- No prior exposure to PD-1 pathway inhibitors

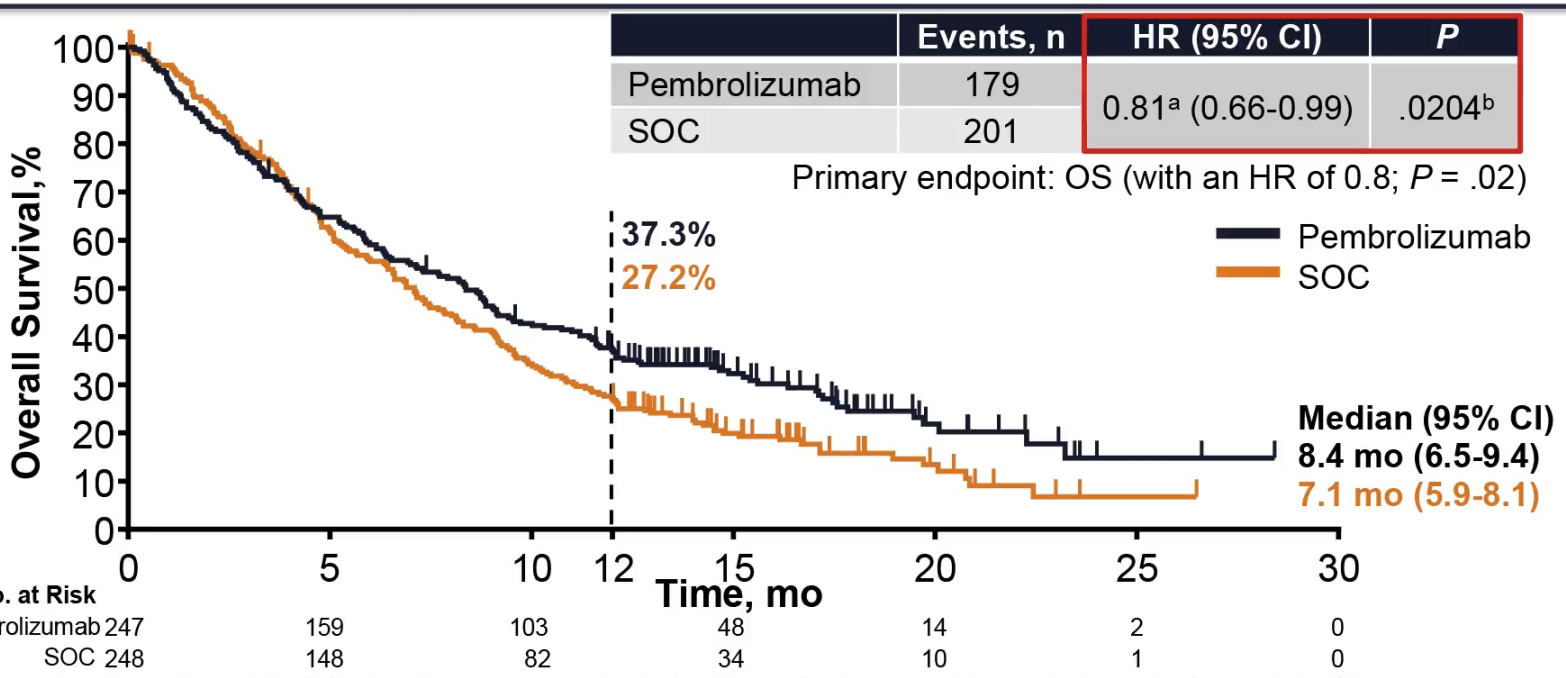


Start Date: November 2014
Estimated Study Completion Date:
~March 2017

Primary Outcome Measure:

- OS and PFS* in all patients
- OS and PFS* in strong PD-L1+ patients

Overall Survival in ITT Population[1]



	Events, n	HR (95% CI)	*P*
Pembrolizumab	179	0.81[a] (0.66-0.99)	.0204[b]
SOC	201		

Primary endpoint: OS (with an HR of 0.8; *P* = .02)

No. at Risk							
Pembrolizumab	247	159	103	48	14	2	0
SOC	248	148	82	34	10	1	0

[a] Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. Initially reported data: HR 0.82 (95% CI, 0.67-1.01), *P* = .0316. After the initial report, updated survival data were obtained for 4 patients.

[b] One-sided *P* value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

1. Cohen EE et al. ESMO 2017. Abstract LBA45_PR.

Trial is statistically NEGATIVE (HR 0.81)

Crossover?

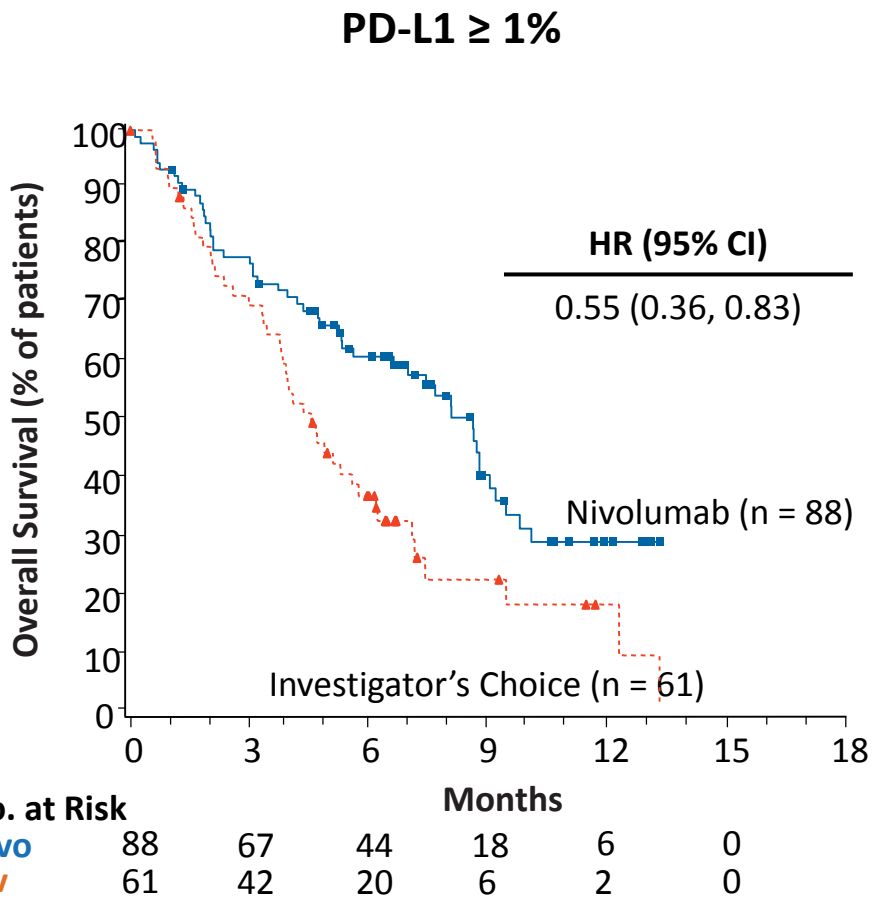
Immunotherapy for SCCHN

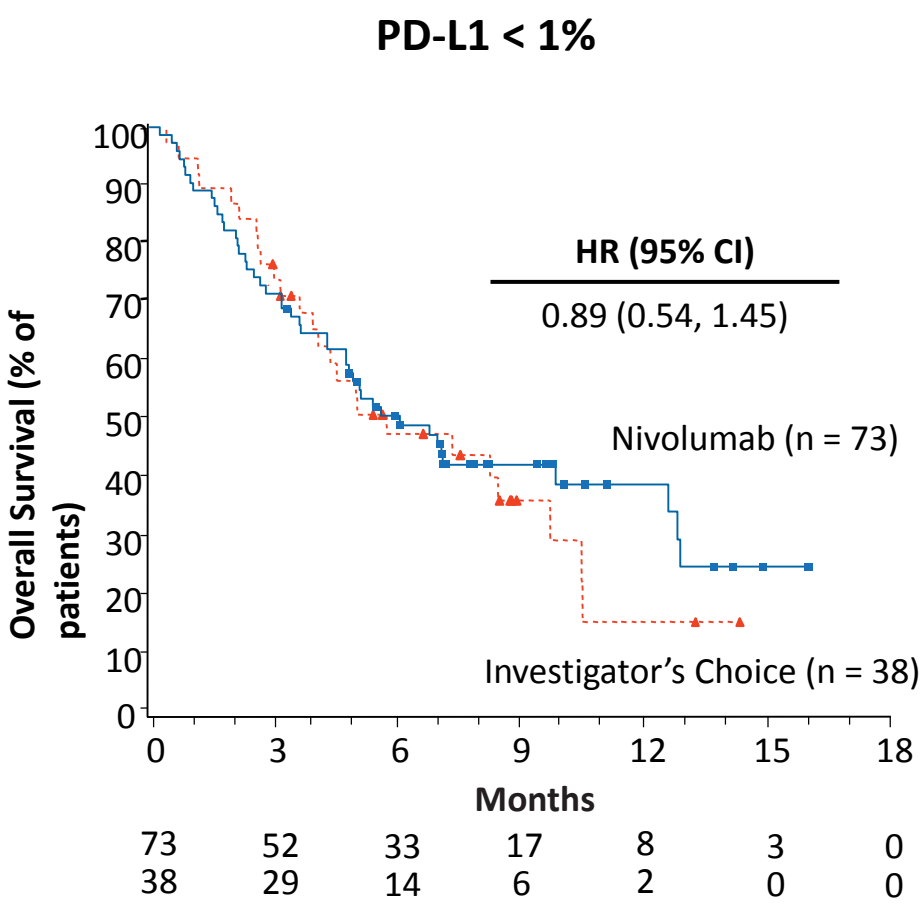
Predictive Biomarkers

- Current FDA approval of pembrolizumab and nivolumab is NOT contingent upon PD-L1 IHC
  - In KN012 and KN055 response rates were not significantly different on the basis of tumor PD-L1 staining
  - IN CM141 most benefit was seen in PD-L1 positive tumors

CM141: OS by PD-L1 Expression

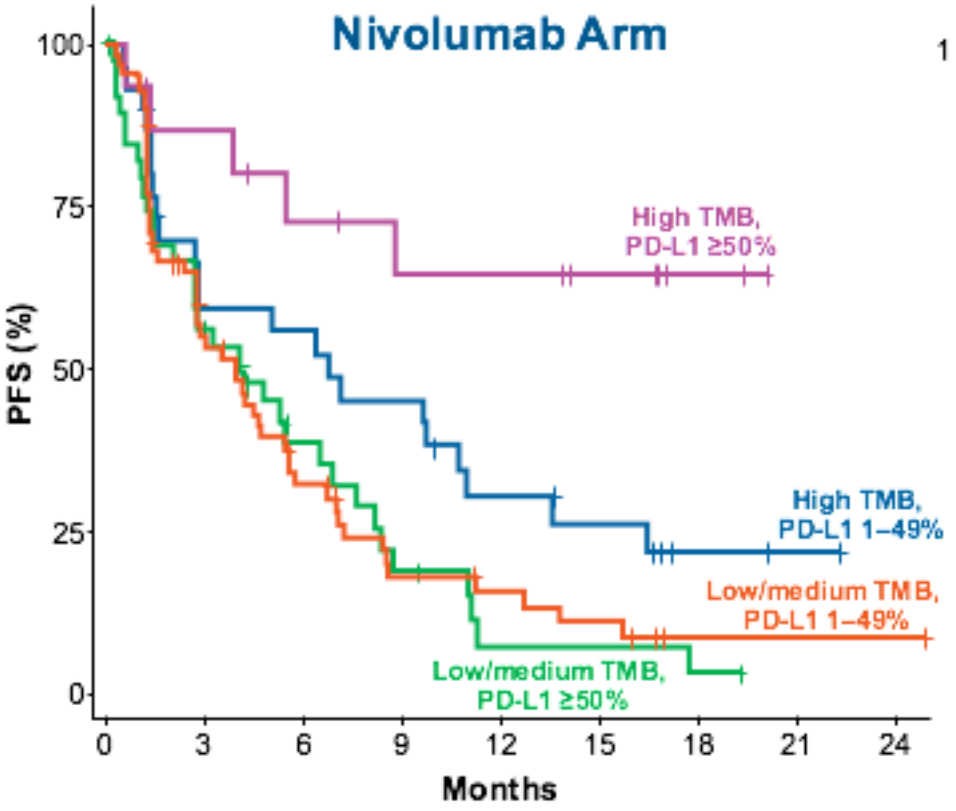
TPS 1% cutpoint





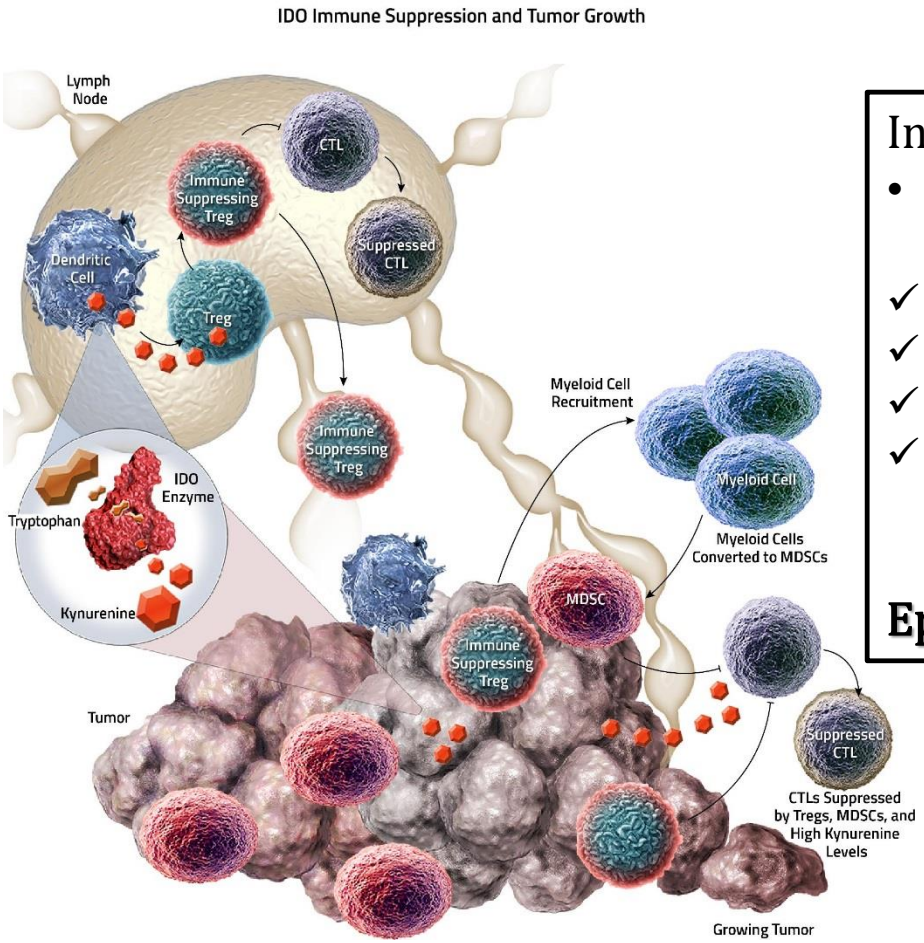
Similar data with *Pembrolizumab and Durvalumab*,
PENDING: measure **TUMOR (TPS)**, or **TUMOR + IMMUNE CELLS (CPS)** **?**

PD-L1 isn’t Everything!



Peters et al AACR 2017

IDO pathway



Indoleamine-pyrrole 2,3-dioxygenase (IDO)

- Enzyme encoded by the IDO1 gene

✓ Converts tryptophan into kynurenine
✓ Depletion of L-Trp in microenvironment
✓ Impairs the growth and survival of T cells
✓ Allows tumor cells to escape the immune system

Epacadostat is an IDO1 inhibitor

Epacadostat plus pembrolizumab in patients with SCCHN: Preliminary phase I/II results from ECHO-202/KEYNOTE-037.

- **36 efficacy-evaluable pts**, 81% (n = 29) received 1–2 prior lines of tx and 19% (n = 7) received ≥3 prior lines of tx.

- For patients tx with 1-2 prior tx:
  - ORR (CR+PR) 39% (10% CR) and DCR 65%

- For pts with ≥3 prior tx:
  - ORR 14% and DCR 29% (2 SD).

- At data cutoff, 9/11 responses were ongoing (range, 1+ to 563+ days).

JCO 2017:35; 15Suppl 6010

Treatment-Related AEs (≥5%)

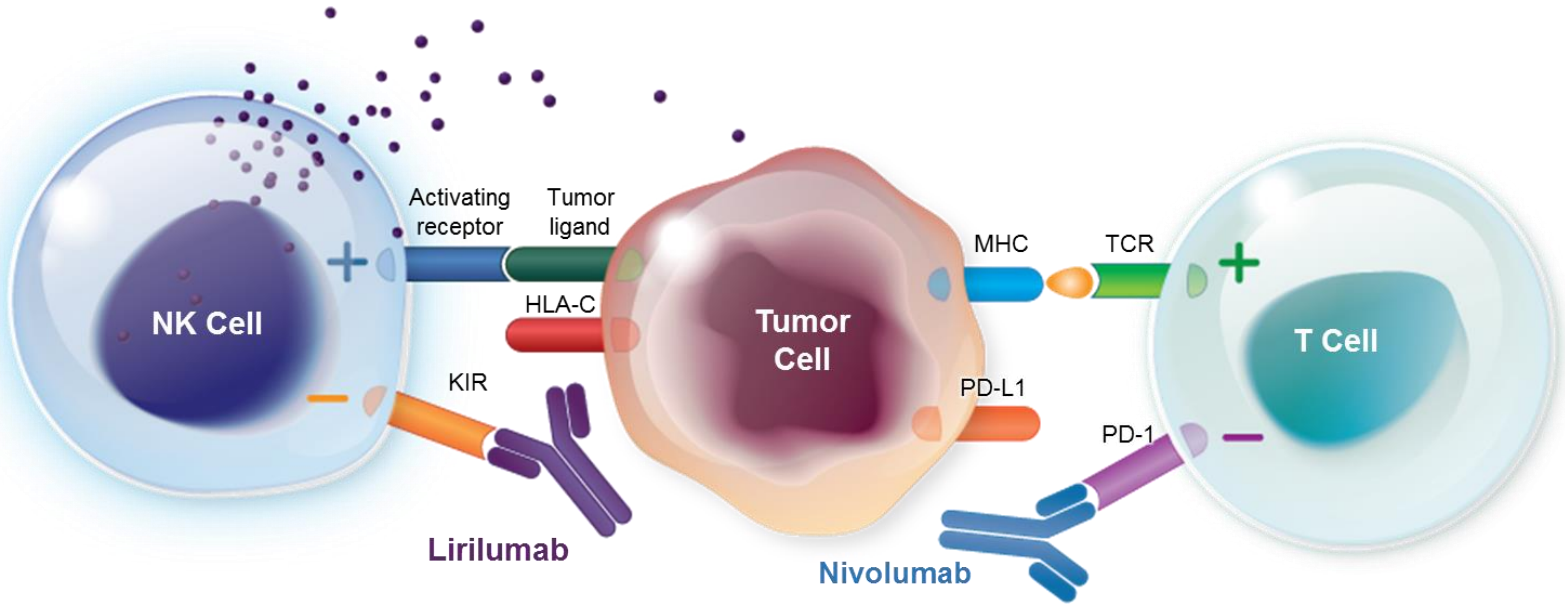
Epacadostat Plus Pembrolizumab
Phase 1/2 Metastatic or Recurrent SCCHN

AE, n (%)	All Grade (N=38)	Grade 3/4* (N=38)
Total	**24 (63)**	**7 (18)**
Fatigue	12 (32)	1 (3)
Rash†	5 (13)	0
Diarrhea	4 (11)	2 (5)
Nausea	4 (11)	0
Blood iron decreased	3 (8)	0
Dizziness	3 (8)	0
Pruritus‡	3 (8)	0
Vomiting	3 (8)	0
Weight decreased	3 (8)	1 (3)
Amylase increased	2 (5)	2 (5)
Asthenia	2 (5)	0
Decreased appetite	2 (5)	1 (3)
Dehydration	2 (5)	1 (3)
Erythema	2 (5)	0
Hypothyroidism	2 (5)	0
Lipase increased	2 (5)	2 (5)
Pyrexia	2 (5)	0

- Treatment-related AEs led to dose interruptions in 7 patients (18%)
  - The most common were fatigue and dizziness (n=2 [5%] each)
- One patient had a dose reduction due to a treatment-related AE (pneumonitis)
- One patient discontinued treatment due to treatment-related AEs (asymptomatic grade 3 amylase increased and grade 3 lipase increased); these were manageable with supportive care
- There was 1 treatment-related death due to respiratory failure (secondary to aspiration pneumonia; pneumonitis could not be ruled out)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
* Other grade 3/4 treatment-related AEs not included in the table: liver function test abnormal, facial pain, and respiratory failure (n=1 each). † Rash includes the following MedDRA preferred terms: rash, rash macular, and rash maculopapular. ‡ Pruritus includes the following MedDRA preferred term: pruritus generalized.

Preliminary efficacy from a phase 1/2 study of the natural killer cell–targeted antibody, lirilumab in combination with nivolumab in squamous cell carcinoma of the head and neck



Lirilumab→ Fully human IgG4 mAb
blocks **killer cell immunoglobulin-like receptor** (KIRs)on NK cells
Promotes NK-cell activation and tumor cell death

ORR With Lirilumab + Nivolumab (NCT01714739) VS Nivolumab Monotherapy (CheckMate 141) in Evaluable Patients With SCCHN

	NCT01714739 (Phase 1/2) Lirilumab + Nivolumab	CheckMate 141 (Phase 3)[1,2] Nivolumab Monotherapy
ORR, n/N (%)	**7/29 (24.1)***	**32/240 (13.3)**
Complete response	3 (10.3)*	6 (2.5)
Partial response	4 (13.8)*	26 (10.8)
DCR, n/N (%)	15/29 (51.7)	NR
ORR by PD-L1 expression, n/N (%)†		
<1%	0/9 (0)	9/73 (12.3)
≥1%	7/17 (41.2)	15/88 (17.0)
≥5%	6/11 (54.5)	12/54 (22.2)
≥50%	4/7 (57.1)	7/19 (36.8)

Responses > 40% in PD-L1+

1. Ferris RL, et al. *N Engl J Med.* 2016 Oct 8 [Epub ahead of print]; 2. BMS data on file.

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Clinical Protocol CA209714

A Double-Blind, Randomized, Two Arm Phase 2 Study of Nivolumab in Combination with Ipilimumab versus Nivolumab in combination with Ipilimumab placebo Squamous Cell Carcinoma of the Head and Neck (SCCHN)

(CheckMate 714: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation **714**)

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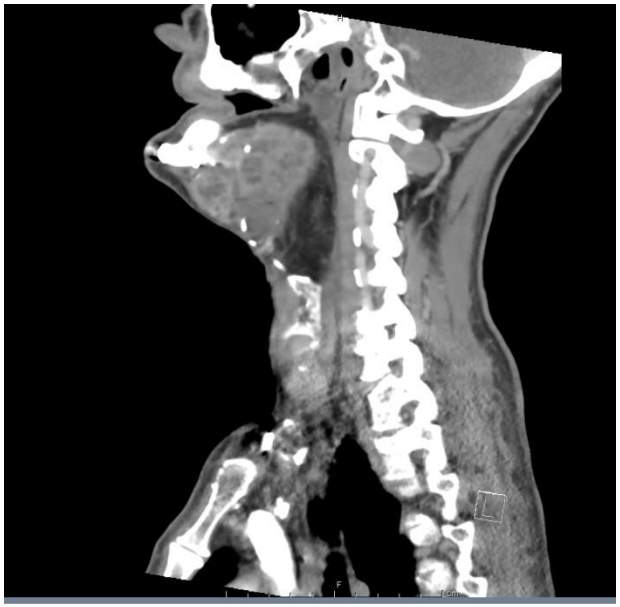
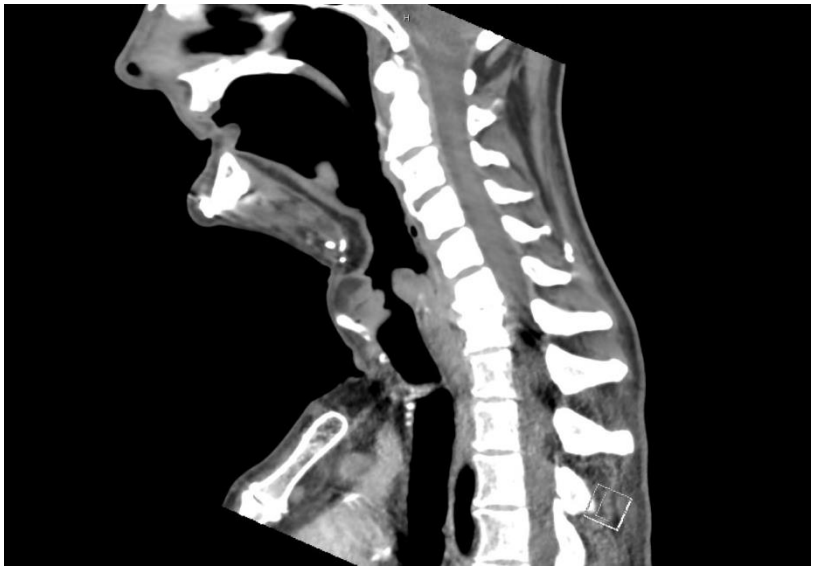
A Double-Blind, Randomized, Two Arm Phase 2 Study of Nivolumab in Combination With Ipilimumab Versus Nivolumab in Combination With Ipilimumab Placebo in R/M SCCHN



In 12 weeks



Conclusions for Head and Neck Cancer

1. Historical median survival with chemotherapy for R/M SCCHN is less than 1 year.

2. Nivolumab and Pembrolizumab are currently approved for second-line treatment of (unselected) SCCHN

3. Response rates with single agent checkpoint inhibitors 13-18% (DCR of 30-50%)

4. Agents more active in HPV+ than HPV negative
    1. But In HPV negative also probably better than chemo in 2nd/3rd line?

5. Doublet Immunotherapy regimens promising (IDO+ αPD-1, CTLA-4+PD-1/PD-L1, PD-1+αKIR)