



Immunotherapy for the Treatment of Head and Neck Cancers

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Disclosures

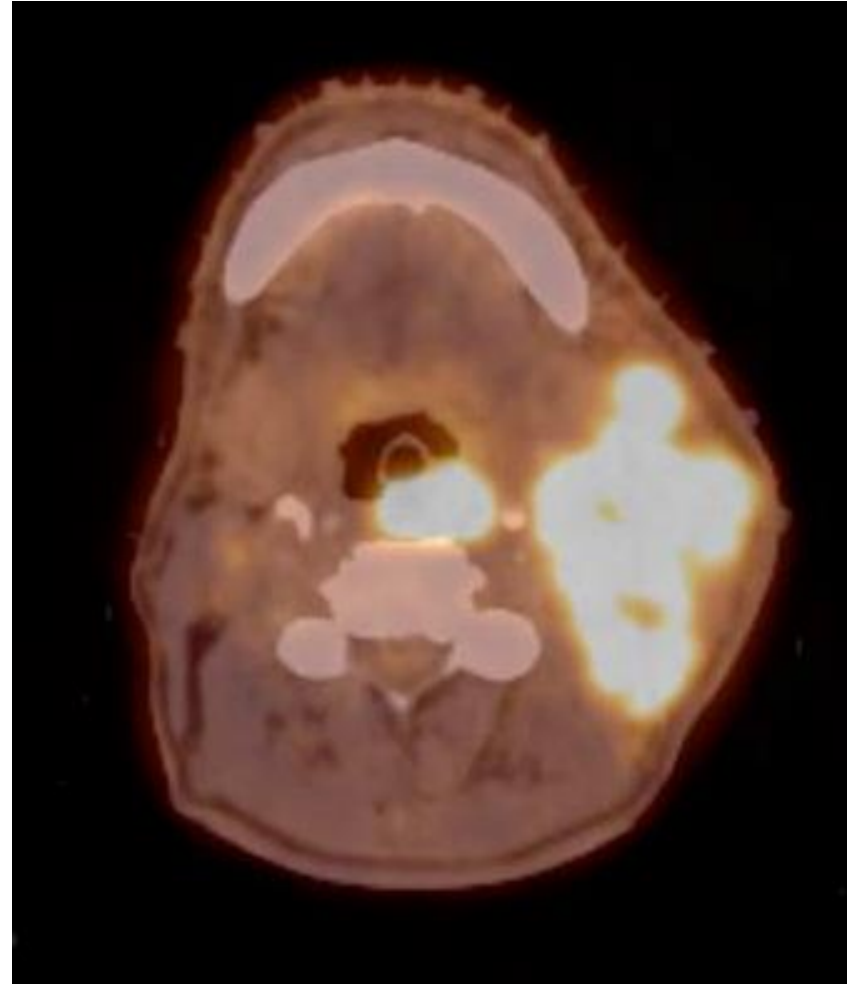
- Eisai Speakers Bureau
- I will be discussing non-FDA approved indications during my presentation.

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

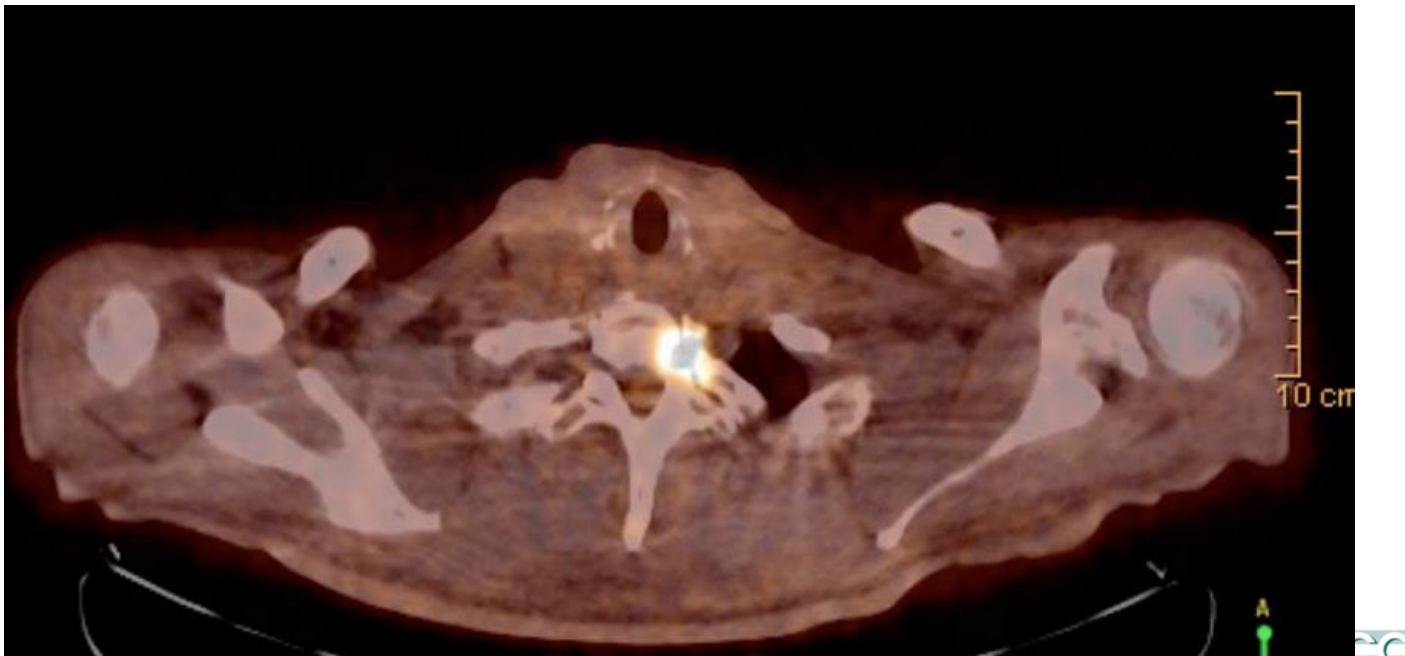
11/2014

- PET CT
 - Large L sided cervical mass
 - Periepiglottic tumor with no airway compromise
 - Multiple cervical osseous metastases
- Palliative hypofractionated XRT initiated
- Started on carboplatin/paclitaxel



1/2015

- Cervical disease decreased with XRT and carboplatin/paclitaxel
 - Pain improved
- PET CT revealed new osseous and axillary mets
- Started on cetuximab



6/2015

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



10/2015

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



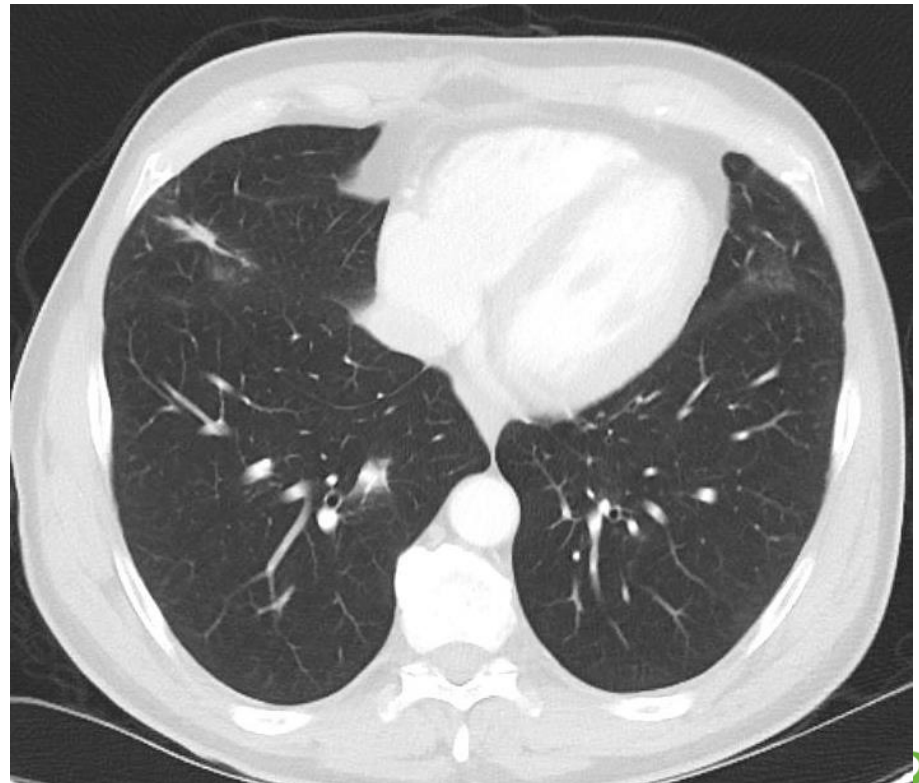
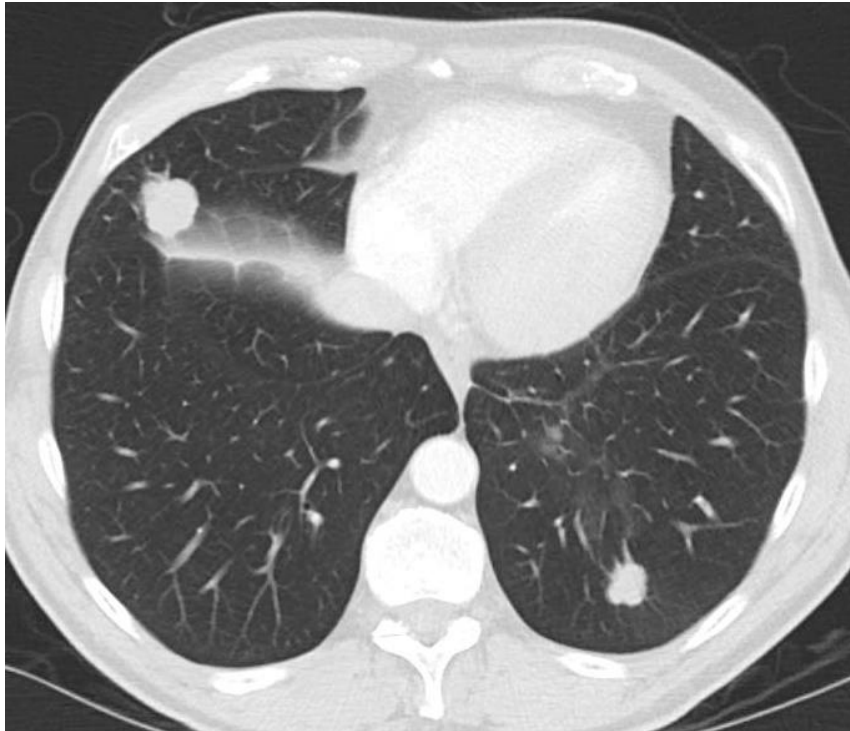
Pt SG

- Initially presented with a large mass in the R oropharynx
 - Underwent carboplatin/paclitaxel/cetuximab induction
 - Concurrent Chemoradiotherapy with high dose cisplatin
- 3 months after CRT, presented with multiple pulmonary nodules
- Cetuximab in metastatic setting



2/2015

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



An atypical cause of nausea

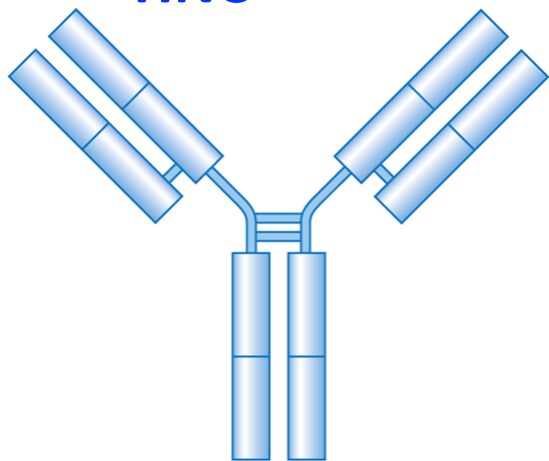
- 6 months into therapy presented with nausea/vomiting
- BMP revealed glucose 532, anion gap of 18
- Patient was diagnosed with autoimmune diabetes
- Started on insulin replacement
- Continued to enjoy an excellent response (ongoing) to pembrolizumab, 2.5 years on therapy

10 Agents approved and in development for HNC

1. Pembrolizumab

- IgG4
- Humanized
- High Affinity for PD-1 ($K_D \sim 29$ pM)
- Approved for Melanoma, NSCLC, Hodgkin Lymphoma, Gastric, Bladder, MSI-H,

HNC



2. Nivolumab

- IgG4
- Fully human
- High Affinity for PD-1 ($K_D \sim 2.6$ nM)
- Approved for Melanoma, NSCLC, RCC, Bladder, Hodgkin Lymphoma, MSI-H CRC, **HNC**

3. Durvalumab

- IgG1
- Humanized
- High Affinity for PD-L1 ($K_D \sim 29$ pM)
- Approved for urothelial; In Development for Head and Neck Cancer, Lung Cancer, others

5. CTLA-4 agents:

- Ipilimumab,
- Tremelimumab

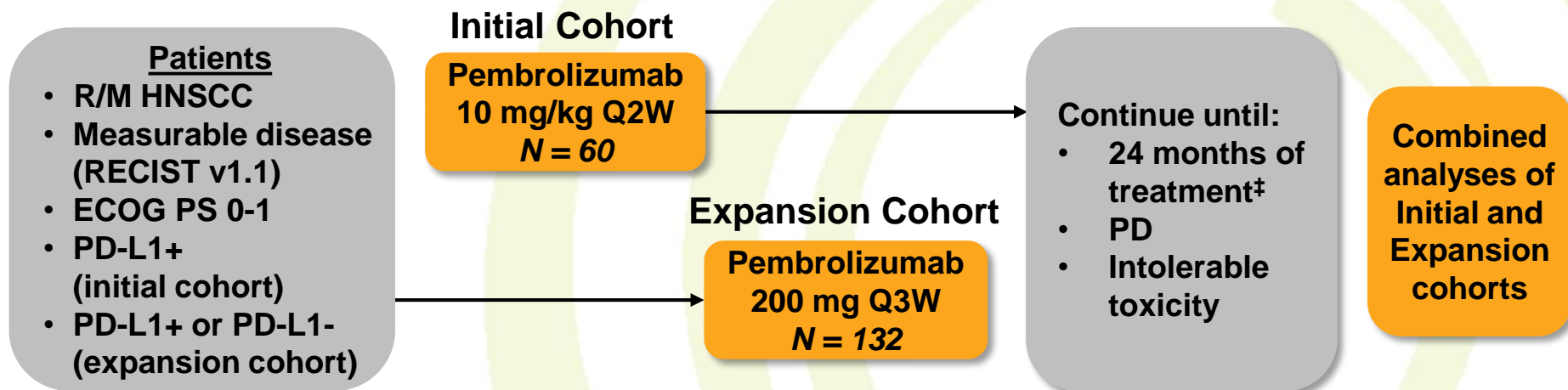
4. Other PD-1/PD-L1 agents in development:

- PD-L1 agents – Atezolizumab (bladder, NSCLC approval), Avelumab (urothelial, Merkel Cell approval)
- PD-1 agents: R2810, PRD001, Tesaro





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[§]

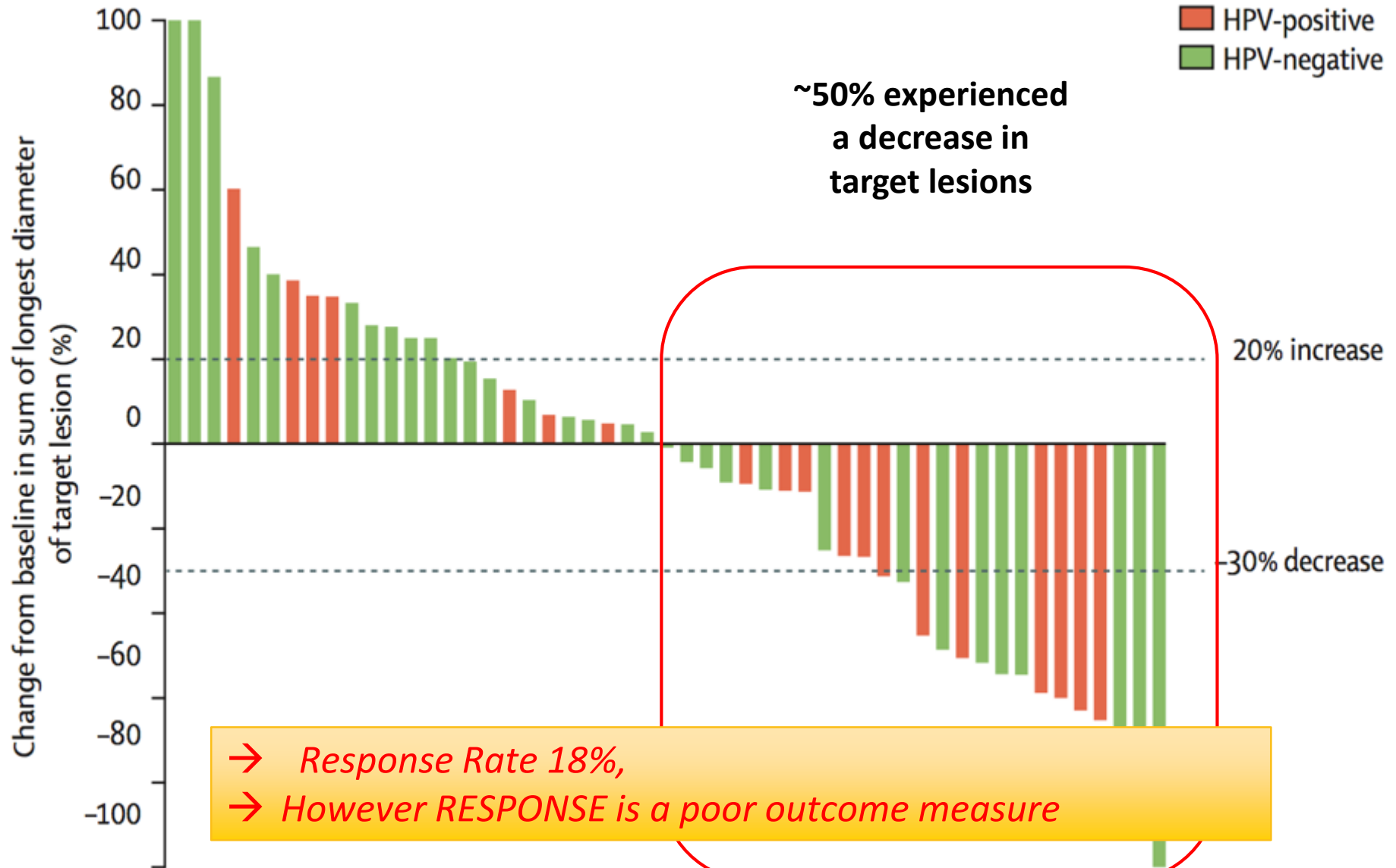
[†]Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.

[‡]Treatment beyond progression was allowed.

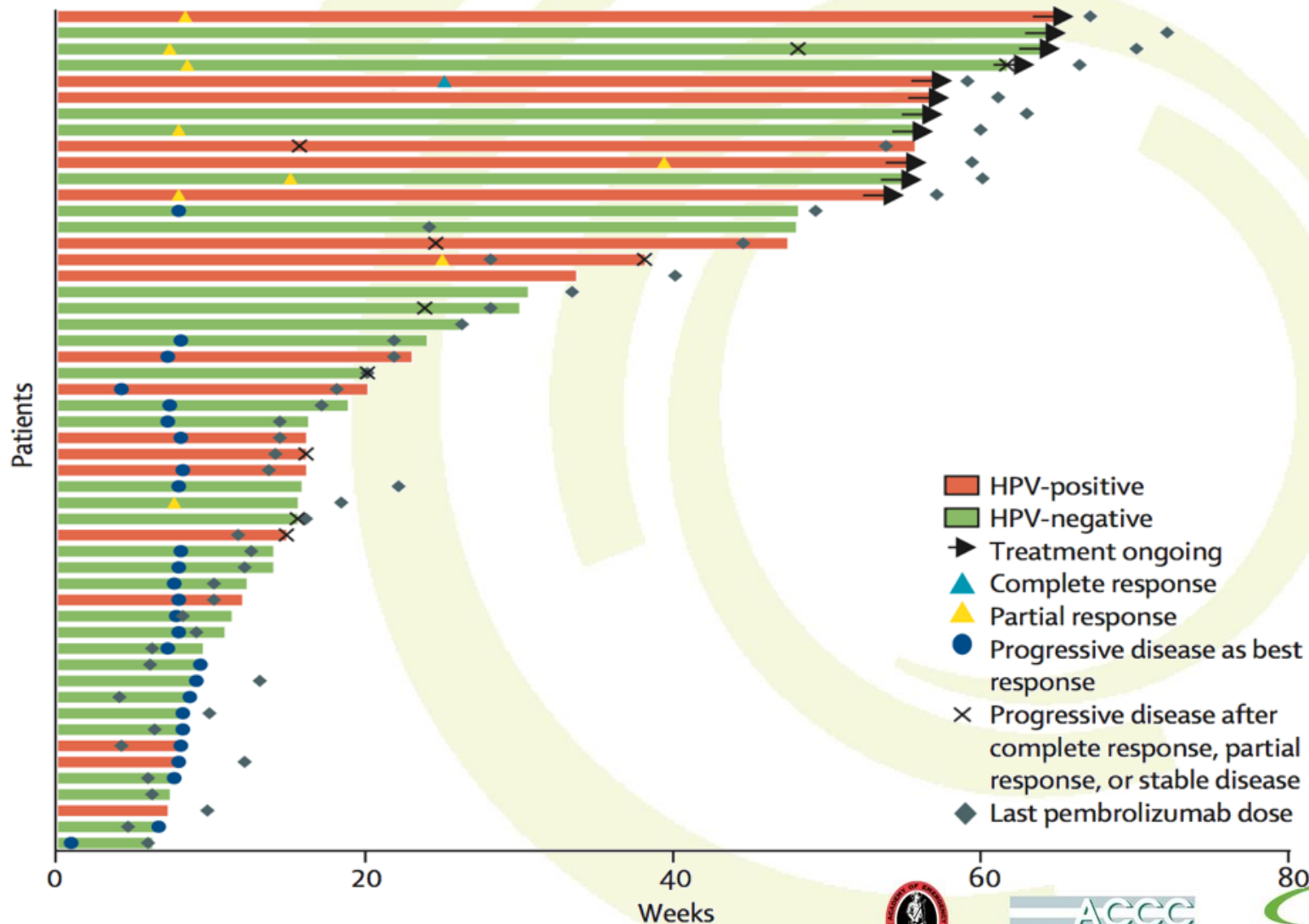
[§] Initial cohort only.



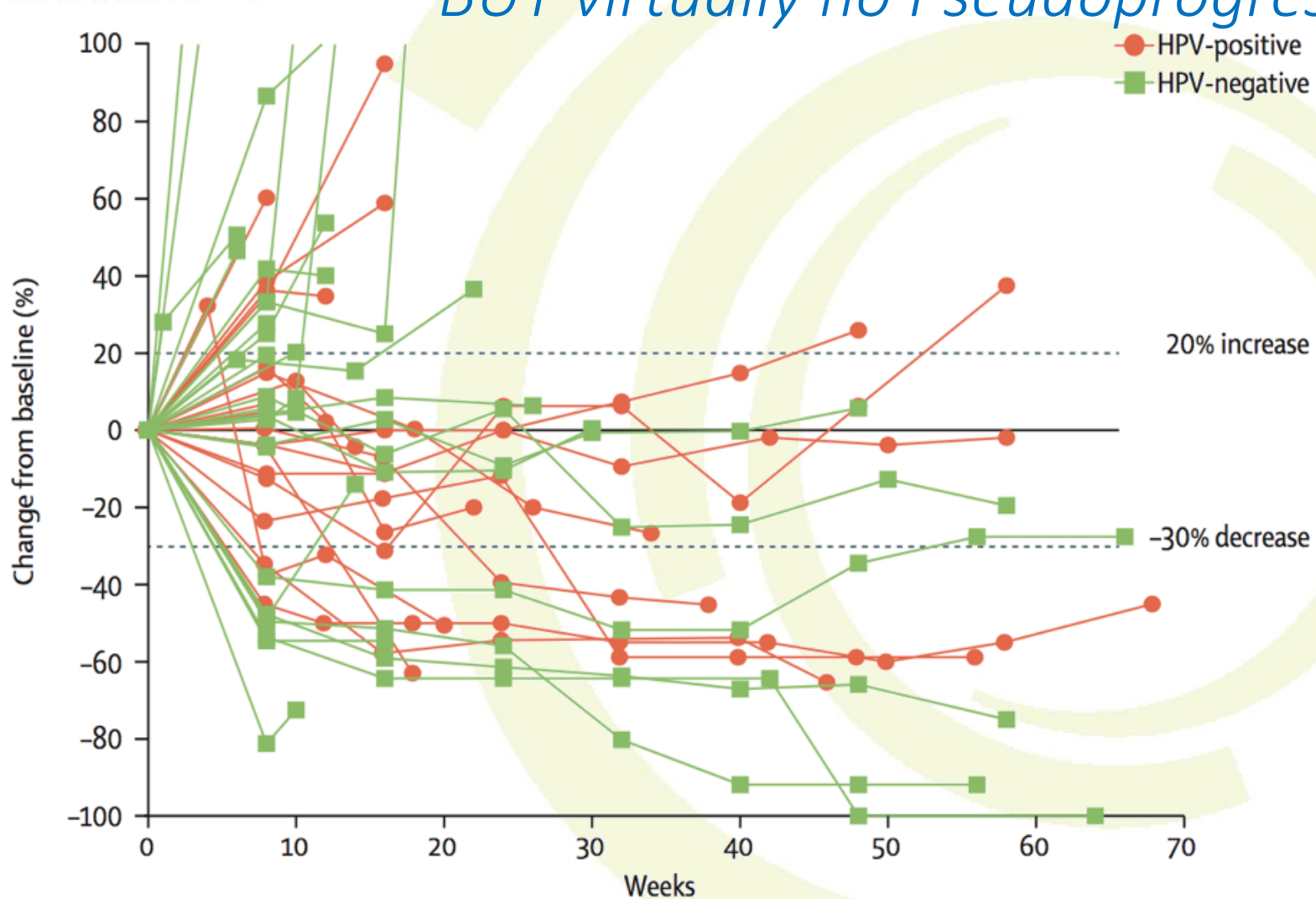
Tumor Shrinkage (KeyNote 12)



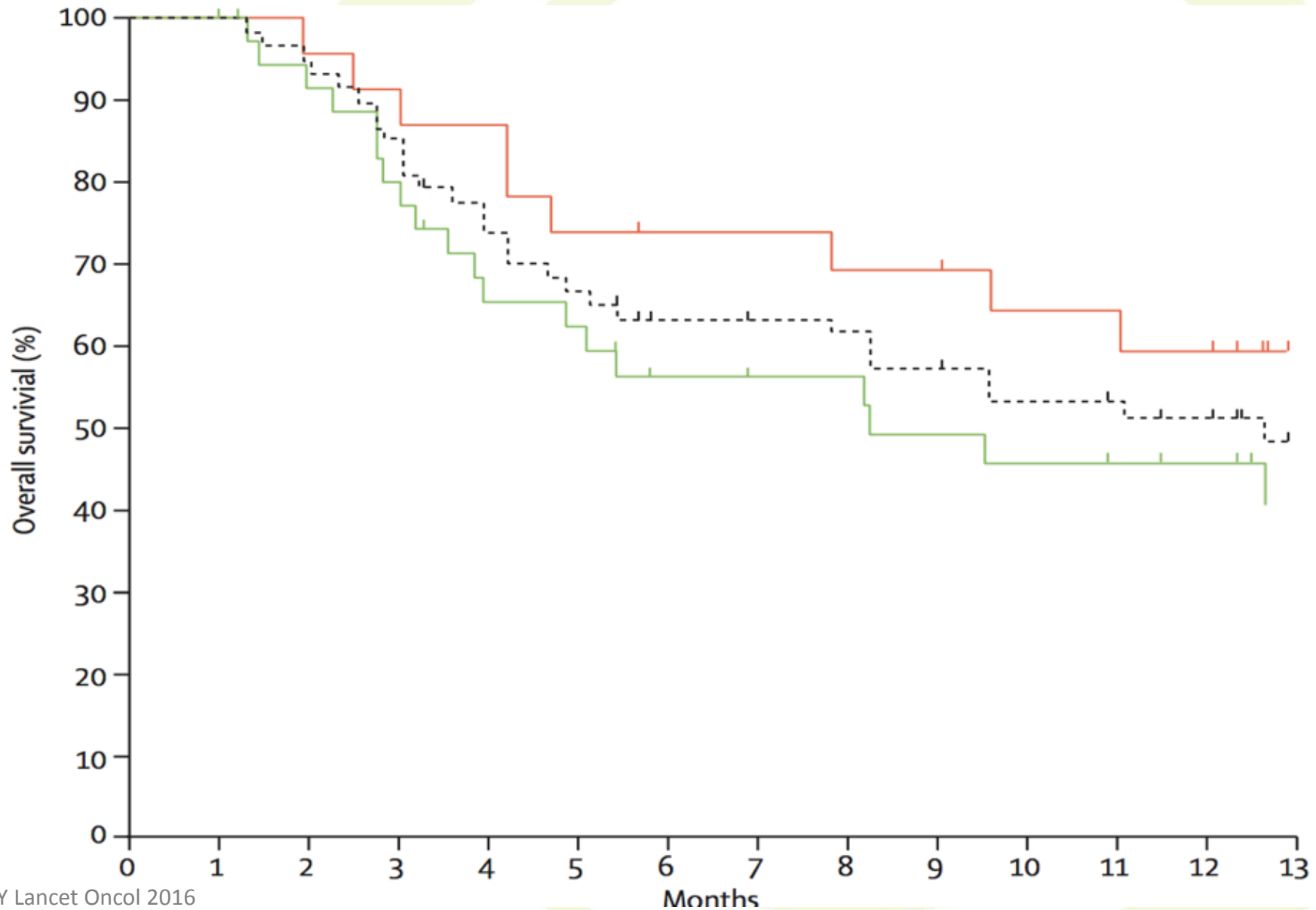
Durability (KeyNote 12)



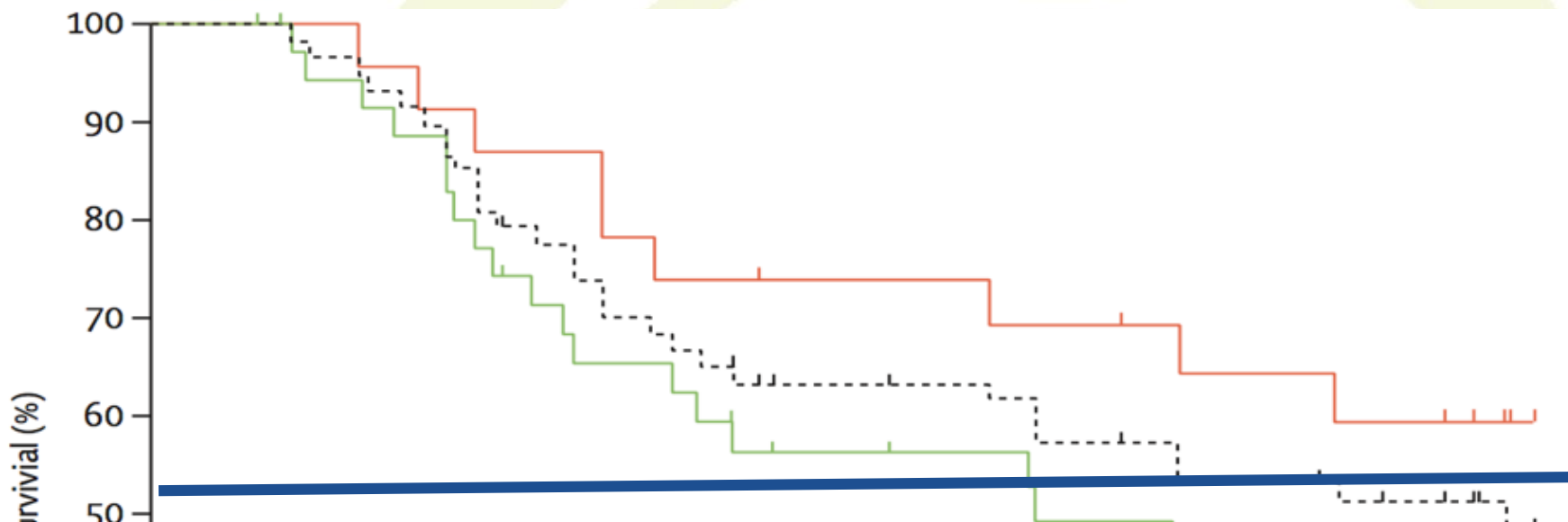
Most responses are early, *few delayed*,
BUT virtually no Pseudoprogression!



Major Impact on Overall Survival



Major Impact on Overall Survival



KEYNOTE-055: Single Arm Phase 2 Trial in R/M HNSCC After Progression on Platinum/Cetuximab

KN55: N=171

- RR = 16%
- mOS = 8 months
- DOR: 8 months

Baumli, et al JCO
2017

Patients

- Recurrent/metastatic HNSCC
- Resistant to platinum and cetuximab*
- Measurable disease (RECIST v1.1)
- ECOG PS 0-1

**Pembrolizumab
200 mg Q3W
Fixed Dose**

Continue until:

- 24 months of treatment
- PD
- Intolerable toxicity
- Investigator/patient decision

**Safety and
Survival
Follow-up**

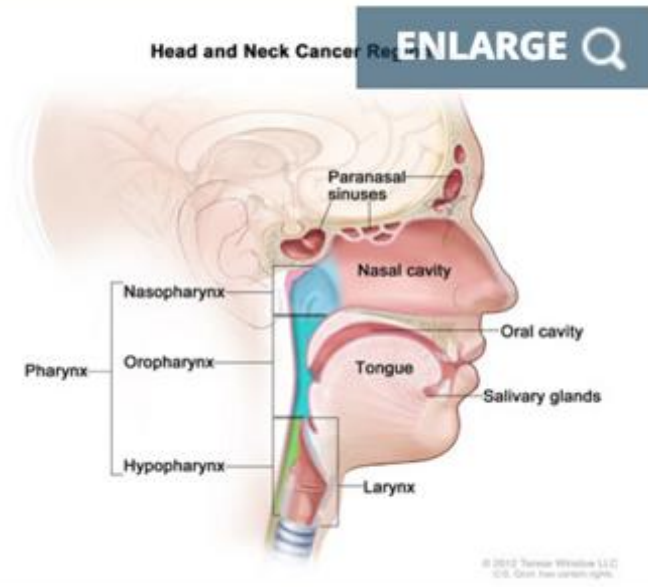


FDA Approves Pembrolizumab for Head and Neck Cancer

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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.



Baseline
HNSCC with
extensive skin
infiltration
and lung
metastases



1 month:
Tumor Flare
Marked local
symptoms, edema,
hospital admission



6 months:
Near CR

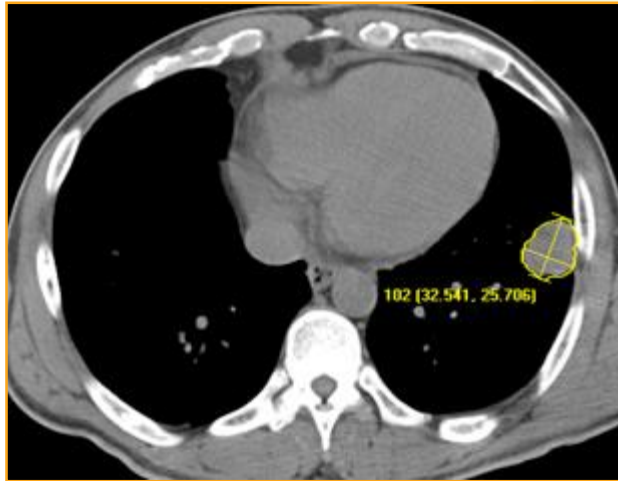


3 months:
Response
Lung metastases
Disappeared,
symptomatic
improvement

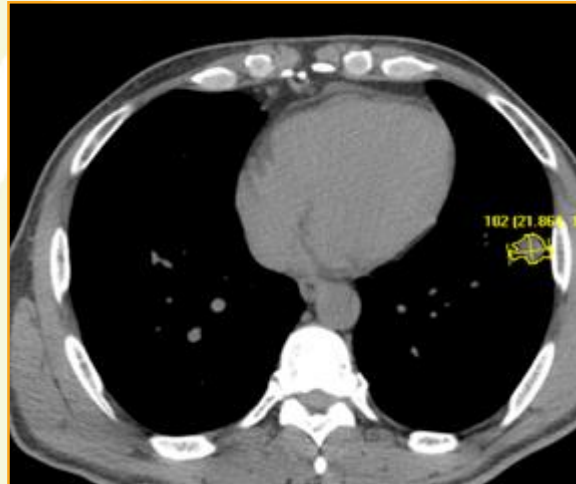


Patient Response *(central review)*

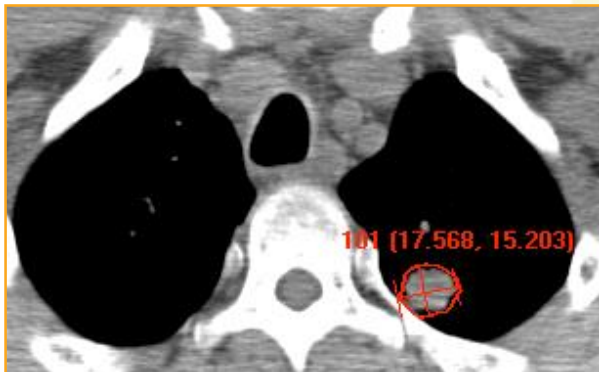
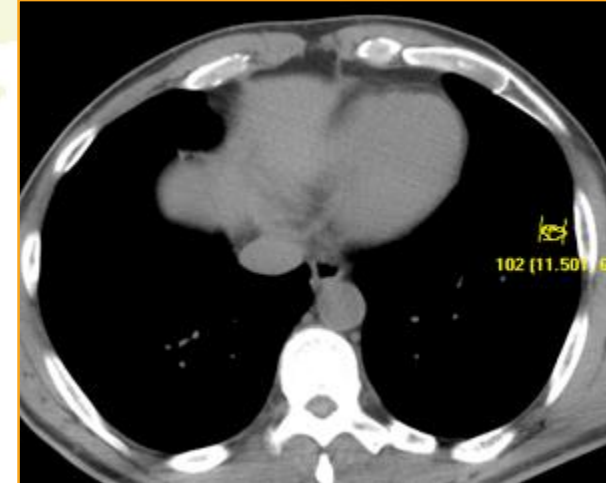
Baseline



Cycle 4 -28.3%



Cycle 8 -56.1%



Wk 8 SD



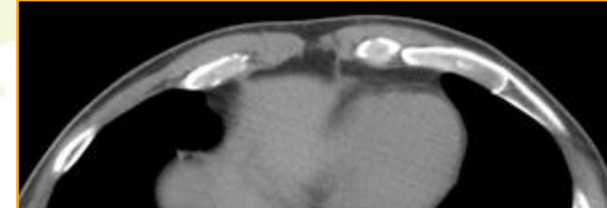
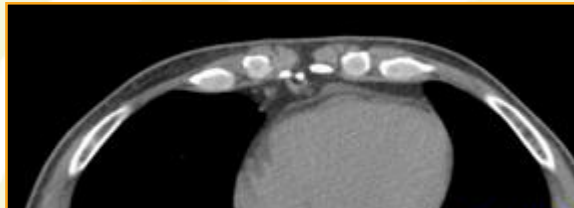
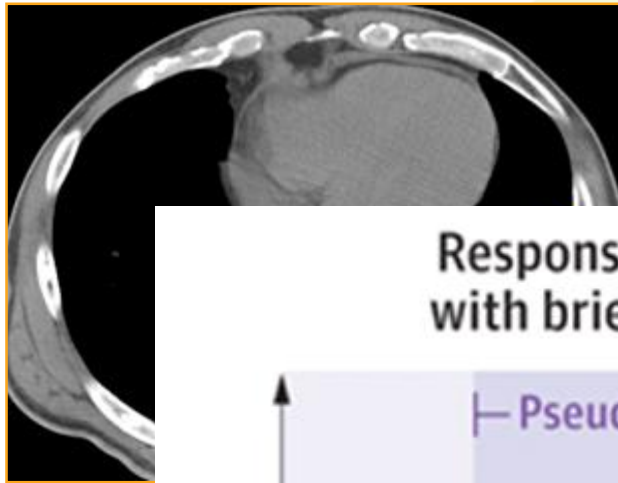
Wk 16 PR

Patient Response *(central review)*

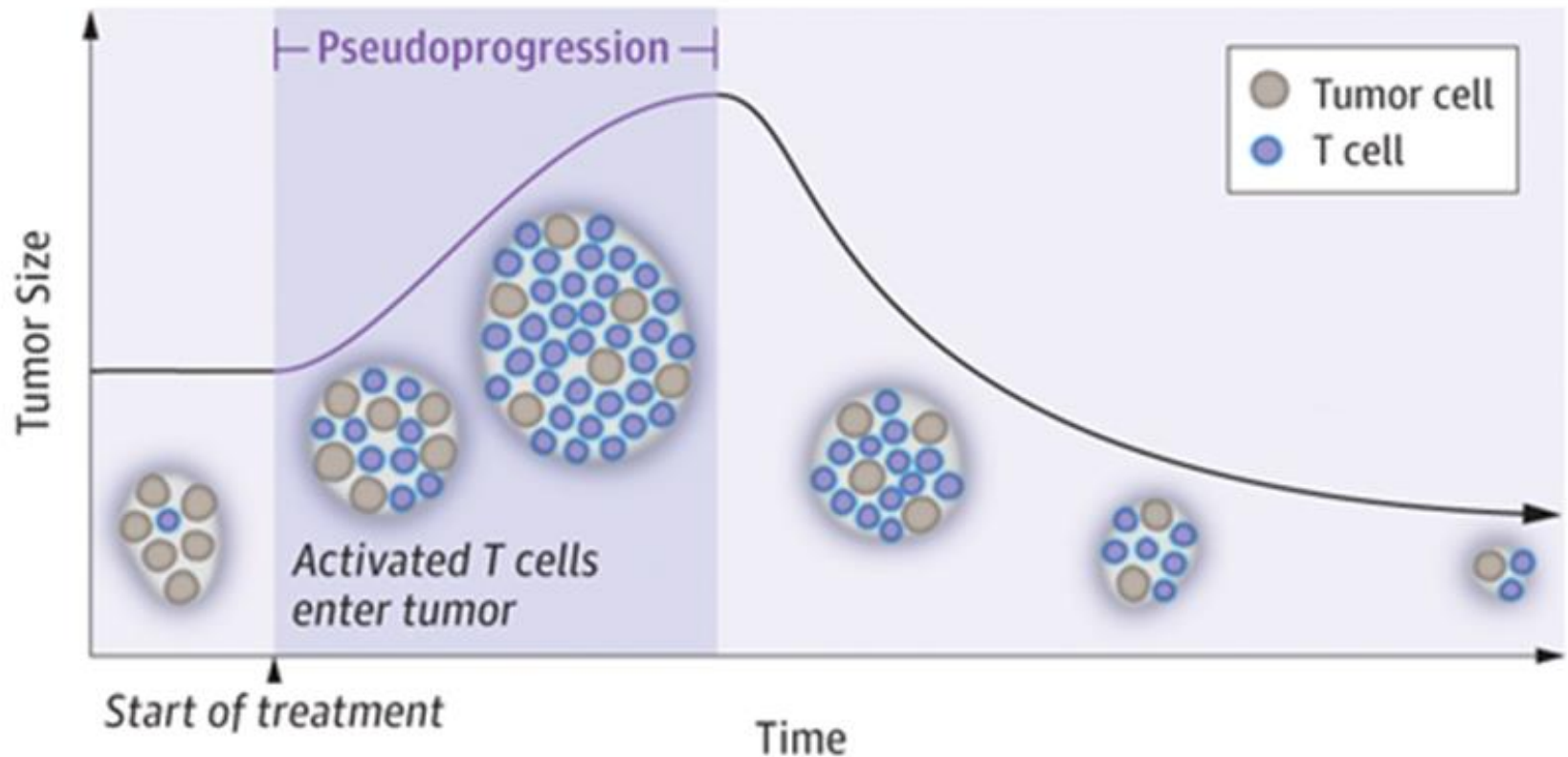
Baseline

Cycle 4 -28.3%

Cycle 8 -56.1%



Response to immune checkpoint inhibitor treatment
with brief increase in tumor size (pseudoprogression)



Phase 3 CheckMate 141 Study Design

Nivolumab in R/M SCCHN After Platinum Therapy

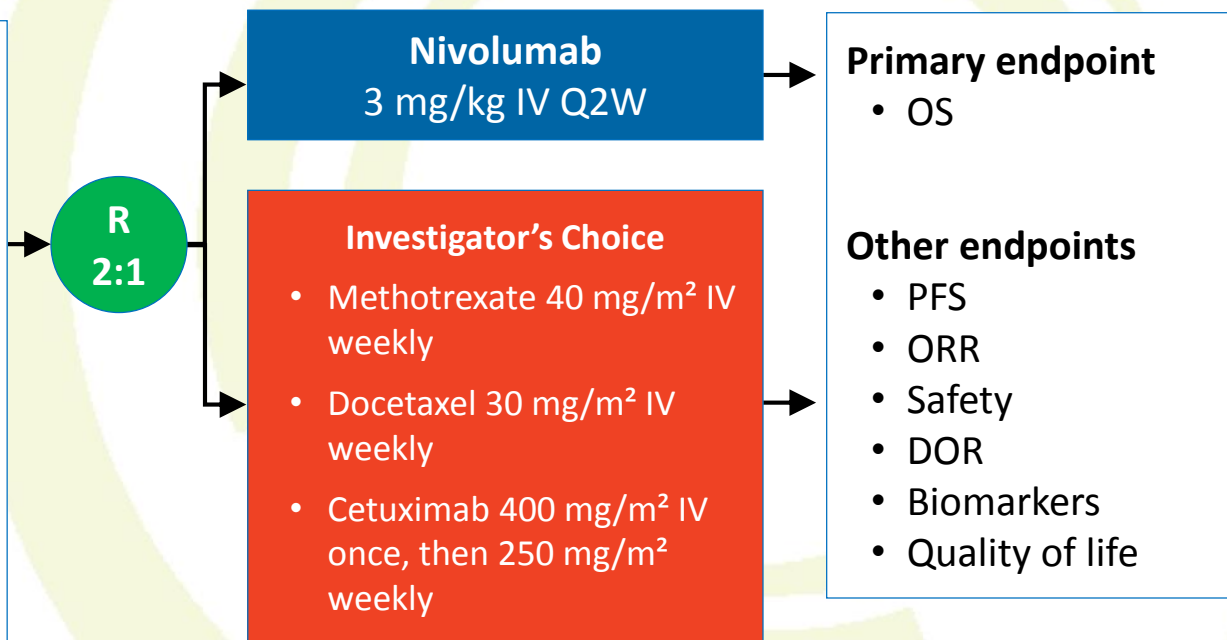
Randomized, global, phase 3 trial of the efficacy and safety of nivolumab vs investigator's choice in patients with R/M SCCHN

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



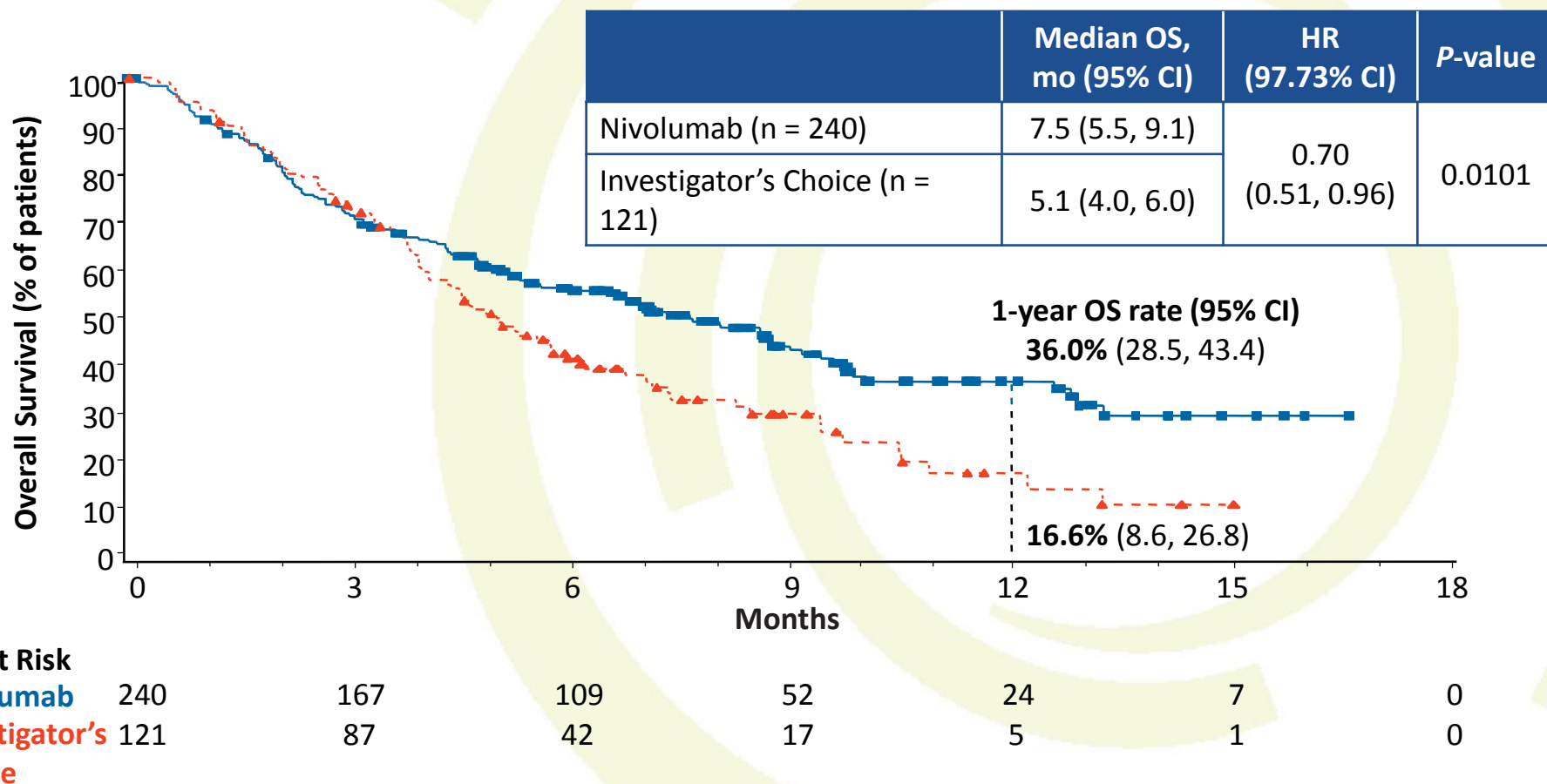
DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

^aTissue required for testing



Overall Survival

Nivolumab in R/M SCCHN After Platinum Therapy



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



FDA Approves Nivolumab for Head and Neck Cancer

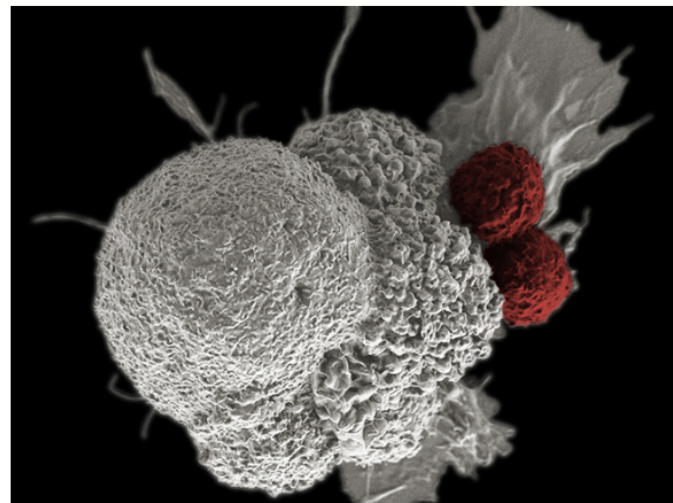
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December 1, 2016, by NCI Staff

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.



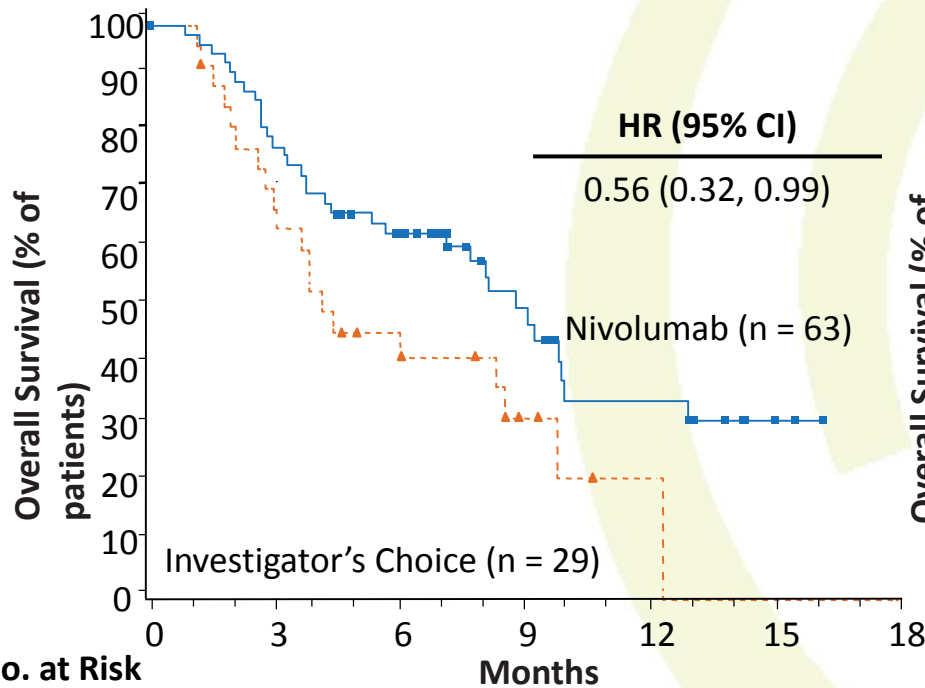
Cytotoxic T cells (red) attacking an oral squamous cancer cell (white). Immune checkpoint inhibitors like nivolumab prevent tumors from turning off T cells, allowing them to attack and kill the tumor cells.

Credit: National Cancer Institute

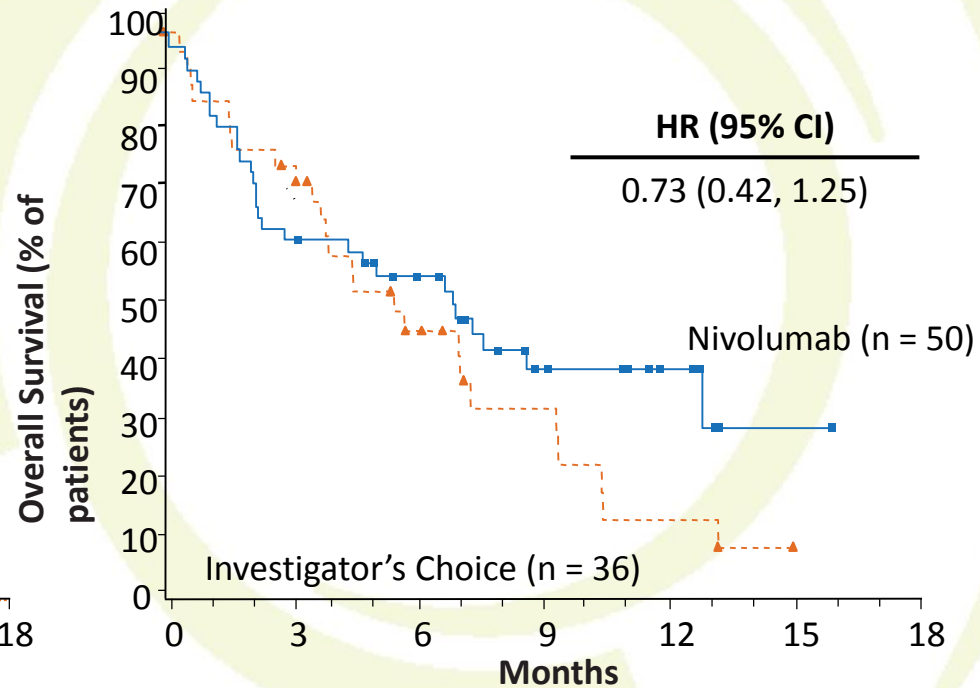
Overall Survival by p16 Status

Nivolumab in R/M SCCHN After Platinum Therapy

p16-Positive



p16-Negative



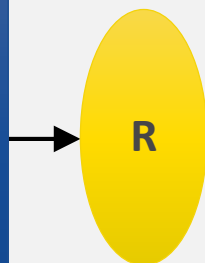
KEYNOTE 40: 2nd Line PIII

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



**Pembrolizumab
200 mg IV q3w**

**Methotrexate, or
Docetaxel, or
Cetuximab**

Start Date: November 2014

Estimated Study Completion Date:

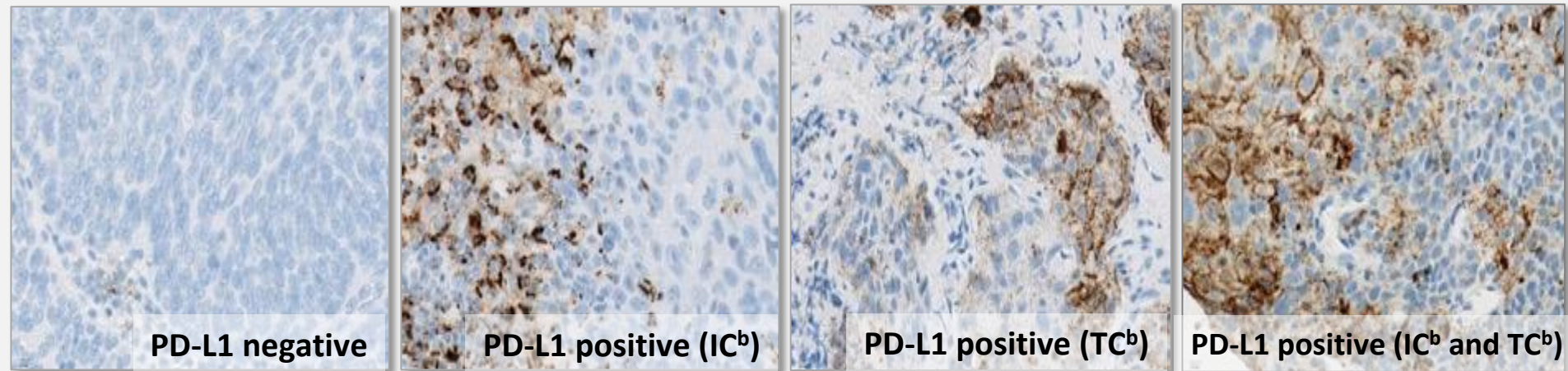
~March 2017

Primary Outcome Measure:

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

Inflamed tumor express PD-L1

PD-L1 Expression in HNC



PD-L1 expressing cells ^b	PD-L1 expression cut-off	All (n=135)	HPV(+) (n=49)	HPV(-) (n=86)	p-value* (HPV+ vs HPV-)
Tumor Cells (TC)	≥1%	21.5	26.5	18.6	0.27
	≥5%	11.9	16.3	9.3	
Immune Cells (IC)	≥1%	69.6	71.4	68.6	0.26
	≥5%	32.6	38.8	29.1	
Immune and/or Tumor Cells	≥1%	72.6	73.5	72.1	0.14
	≥5%	40.0	49.0	34.9	

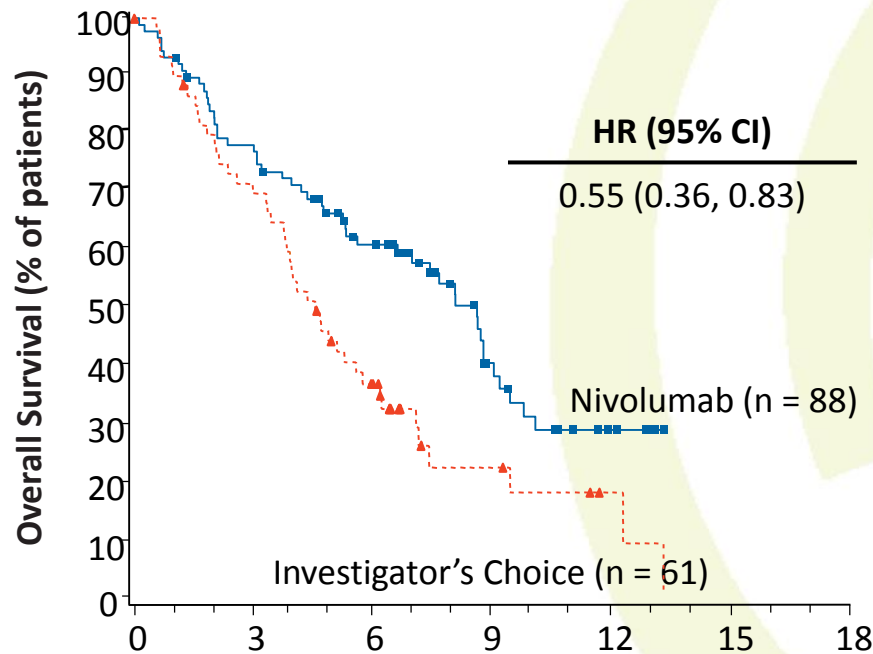
PD-L1 prevalence (TC^b & IC^b) by IHC was similar in HPV(+) vs HPV(-) tumors.

* Fisher's exact test

CM141: OS by PD-L1 Expression

TPS 1% cutpoint

PD-L1 \geq 1%

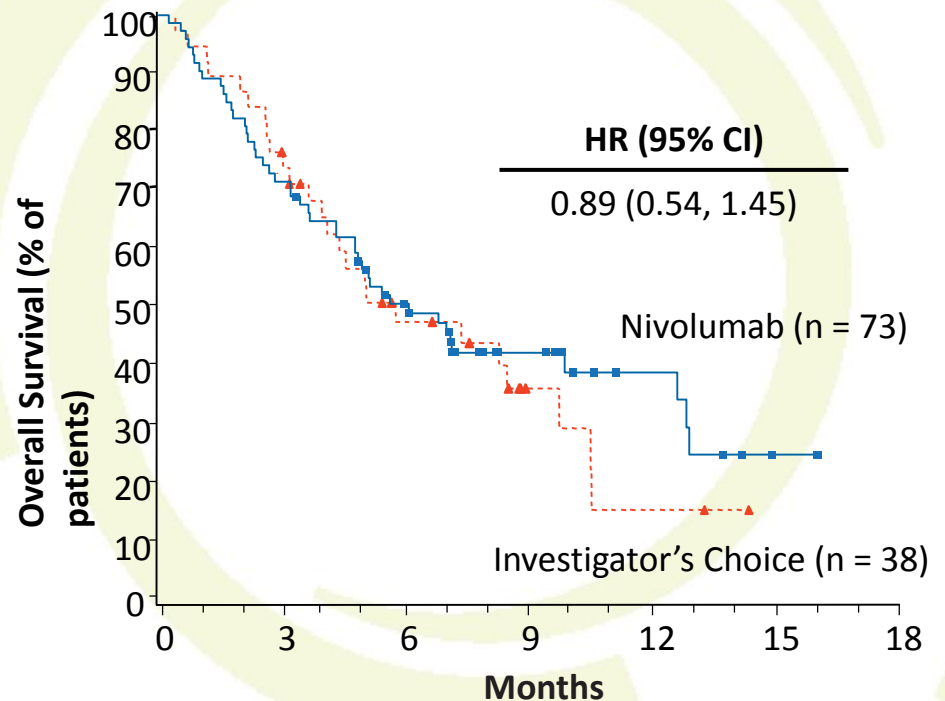


No. at Risk

Nivo	88	67	44	18	6	0
Inv	61	42	20	6	2	0

Choice

PD-L1 < 1%

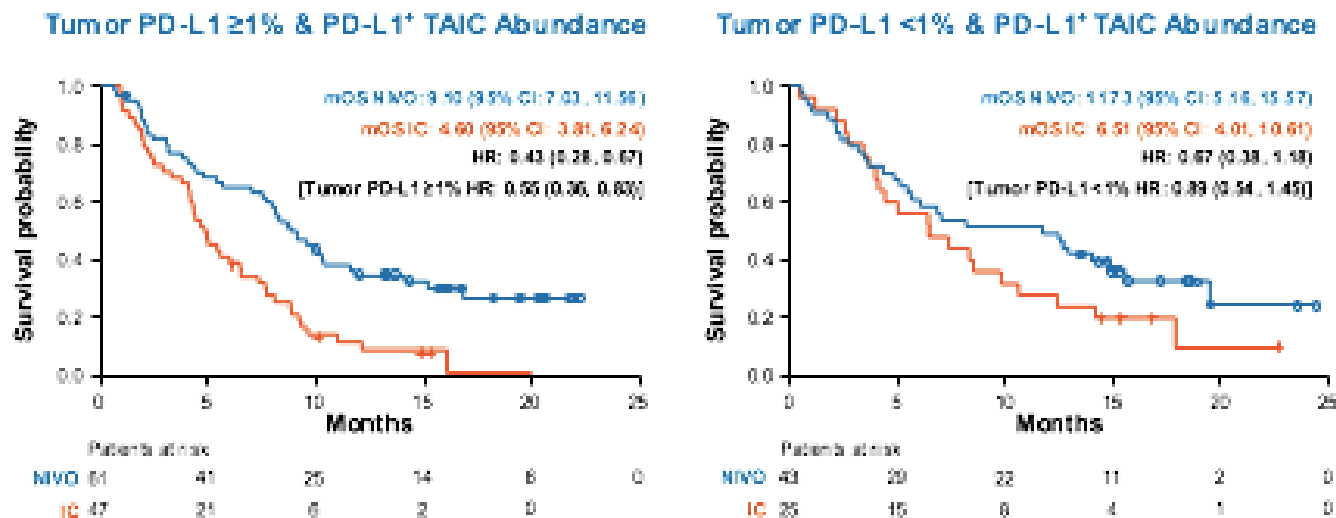


73	52	33	17	8	3	0
38	29	14	6	2	0	0

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

PD-L1 Staining: Think Outside the Tumor?

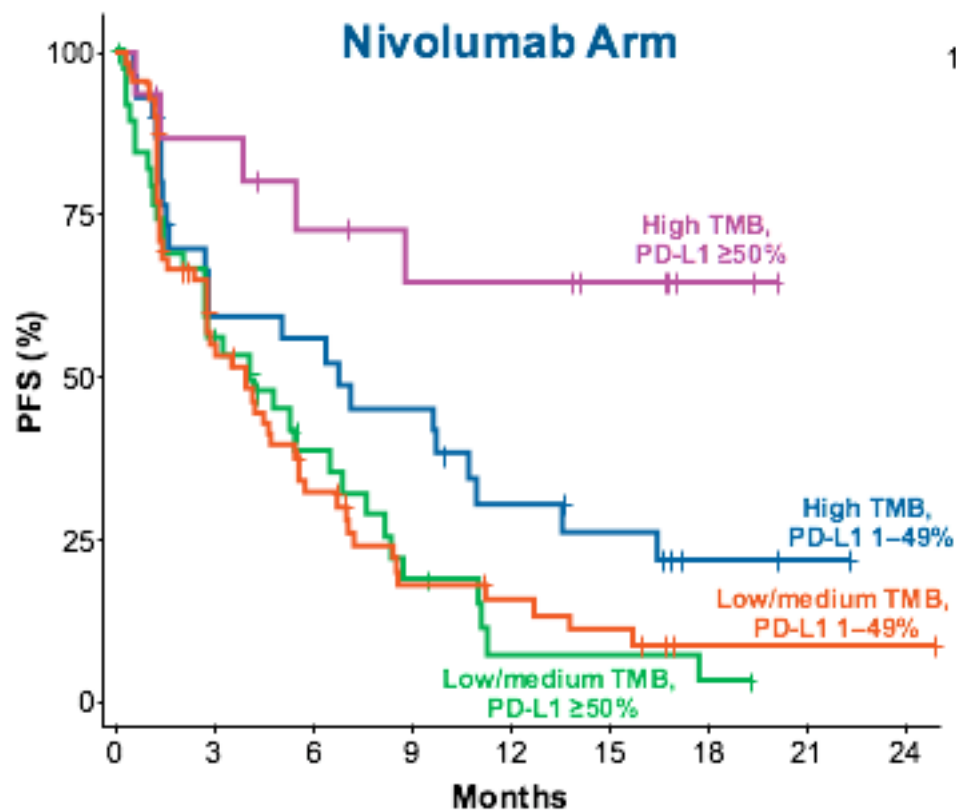
- PD-L1 staining is not limited to tumor, though the approved assays only look there
- In both KEYNOTE studies as well as CHECKMATE 141, inclusion of tumor associated PD-L1+ immune cells improves diagnostic performance



Biomarkers in Head and Neck Cancer

- 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

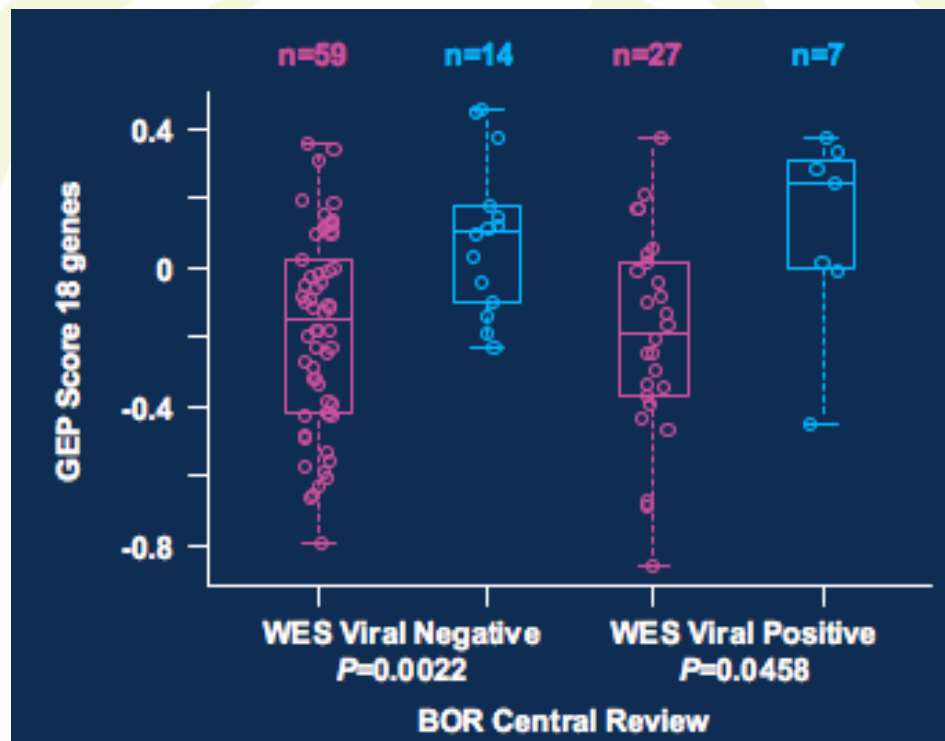
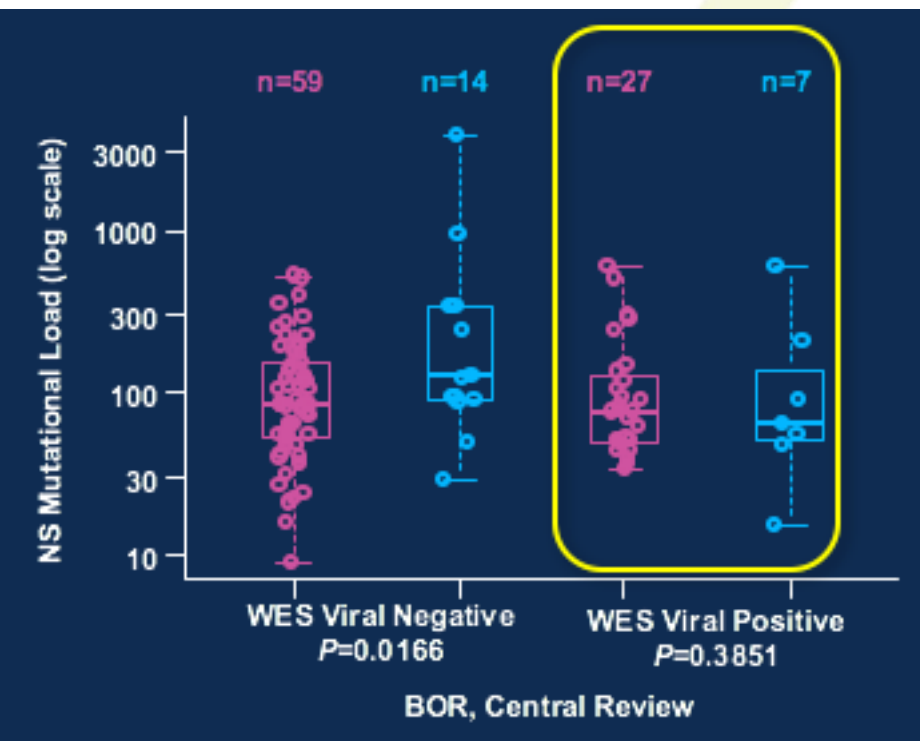
PD-L1 isn't Everything!



Peters et al AACR 2017



Various Biomarkers in HNC



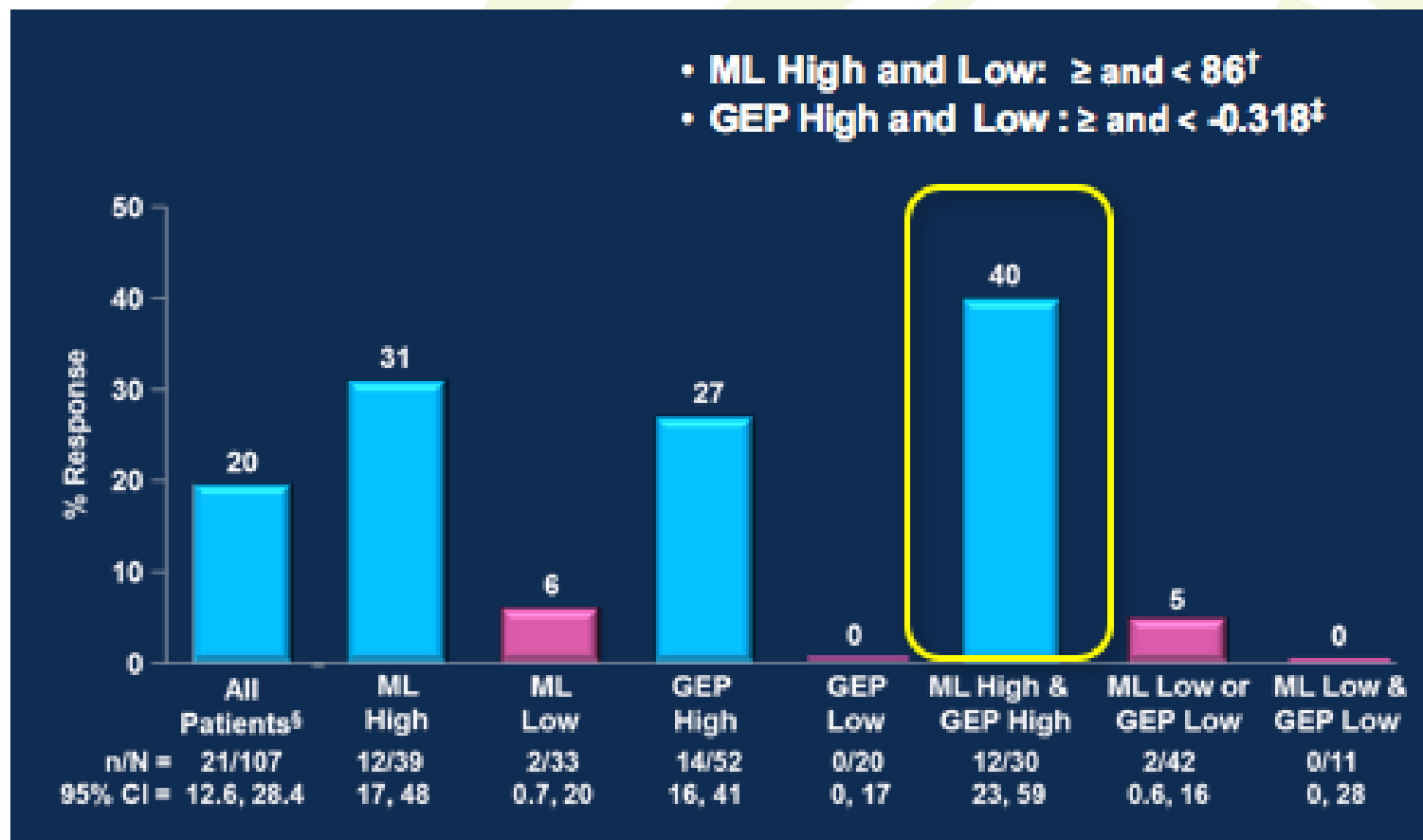
○ Not PR or CR
○ PR or CR

Haddad et al ASCO 2017





Combined GEP/ML



Haddad et al ASCO 2017

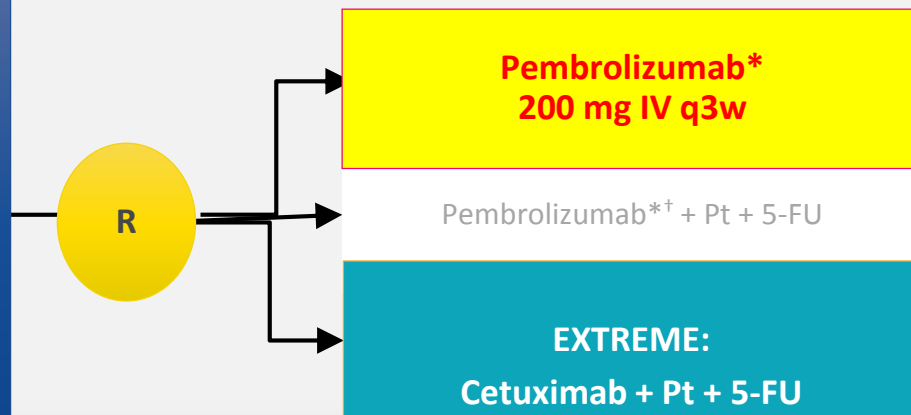


Randomized, phase III trial in 1st line R/M HNSCC:

N=825

Key Eligibility Criteria

- Recurrent or metastatic HNSCC (oral cavity, oropharynx, hypopharynx, larynx, or nasopharynx)
- No prior systemic therapy in recurrent/metastatic setting
- ECOG PS 0–1
- Ability to provide tissue for PD-L1 analysis
- No active CNS metastases
- No prior exposure to PD-1 pathway inhibitors



Start Date: March 2015

**20%, 10%, 1% successive cut points*
Composite Score (CPS)

- **Primary Outcome Measure:** PFS*, OS, (→PD-L1+ subgroup*)
- **Secondary Outcome Measures:** PFS, ORR

Conclusions for Head and Neck Cancer

1. Chemotherapy offers short survival with many side effects
2. PD-1 antibodies nivolumab and pembrolizumab are approved in *second line recurrent / metastatic HNSCC*:
 - Oral cavity
 - Oropharynx
 - Larynx
 - Hypopharynx
3. Most patients have fewer side effects on PD-1 Abs than on chemotherapy
4. Clinical trials are underway to improve immunotherapy response rates

New Approvals Affecting Various Disease States

On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to **pembrolizumab** for adult and pediatric patients with the following:

- Unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) **solid tumors** that have progressed following prior treatment and who have no satisfactory alternative treatment options OR
- MSI-H or dMMR **colorectal cancer** that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

