ADVANCES IN Cancer IMMUNOTHERAPY™

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

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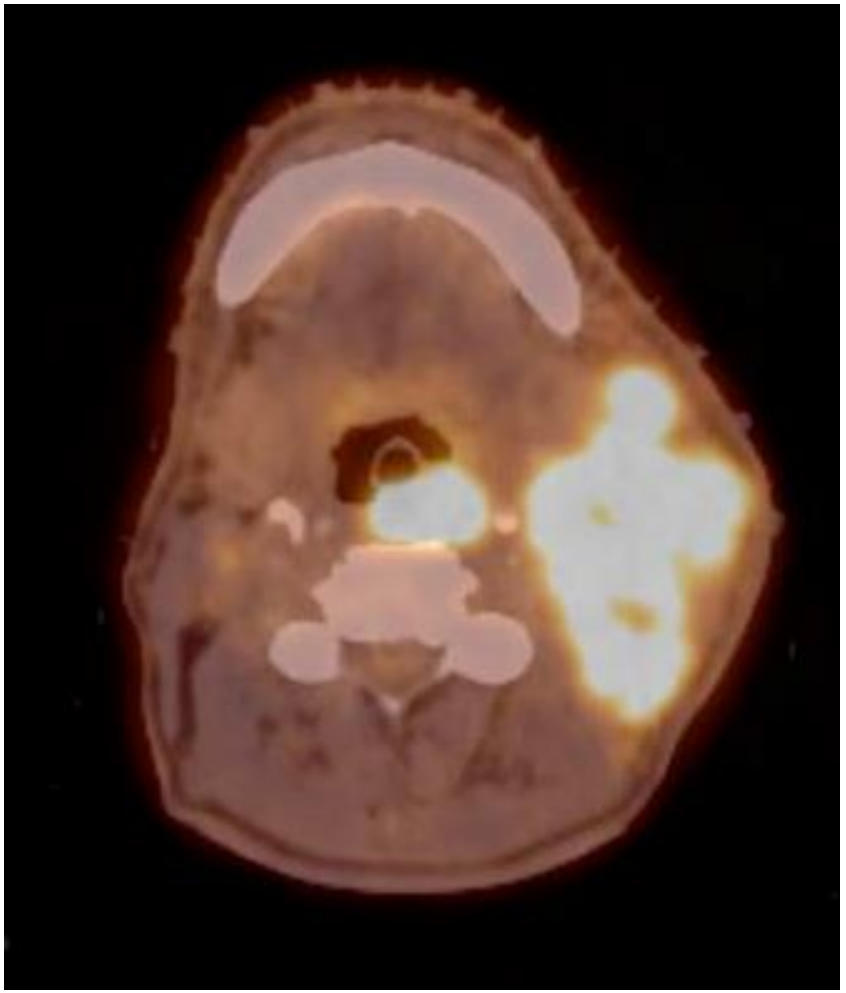
Pt WS

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

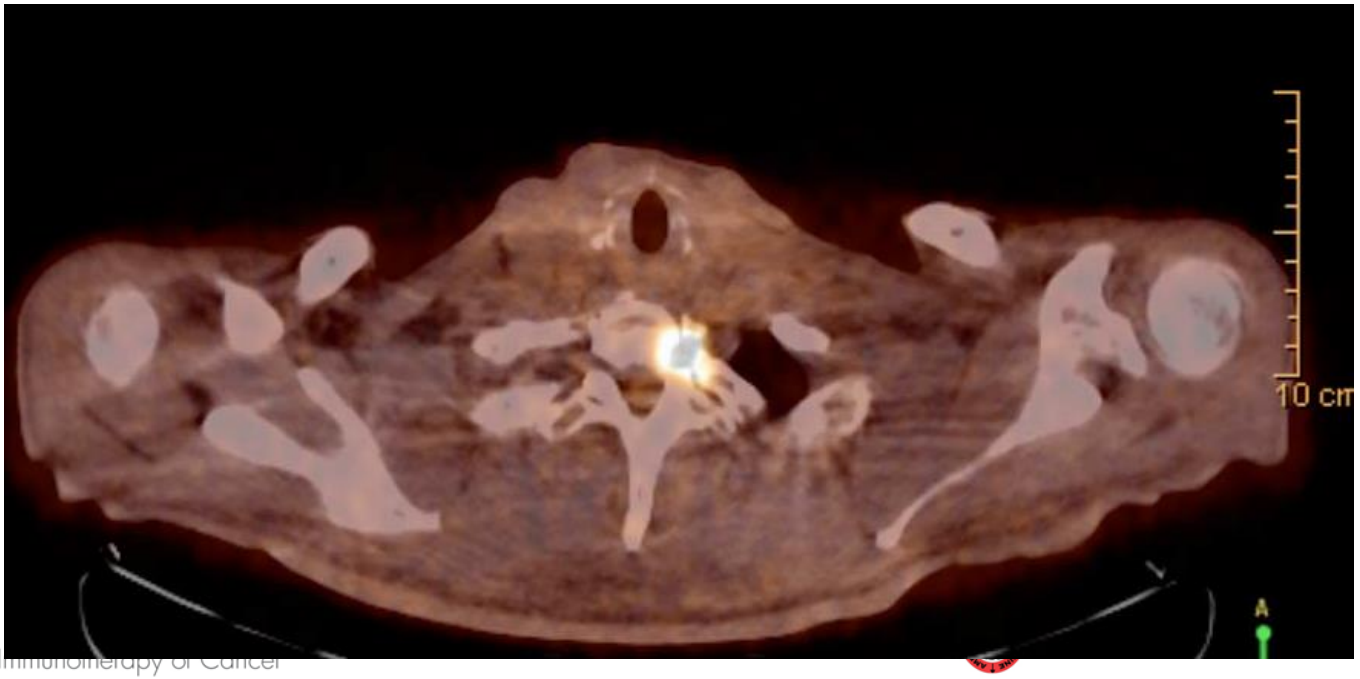
11/2014

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



1/2015

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



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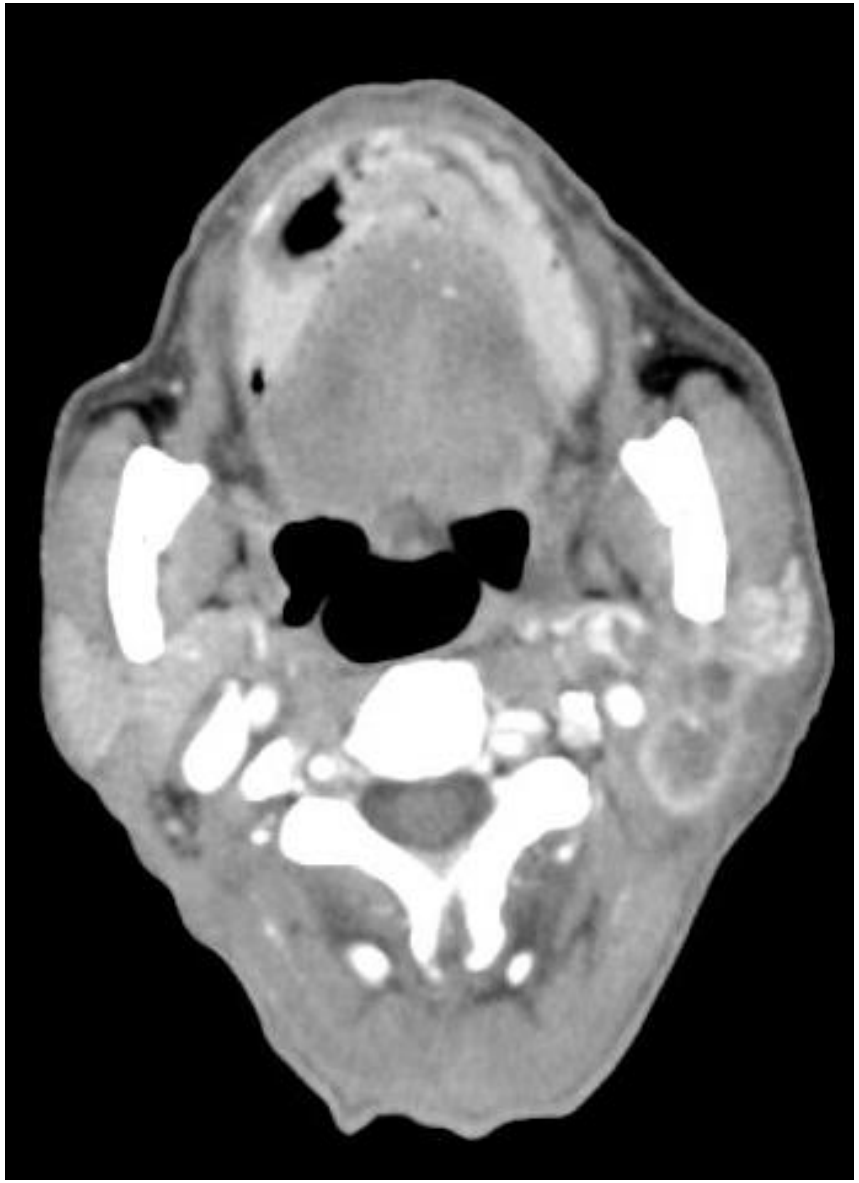
6/2015

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



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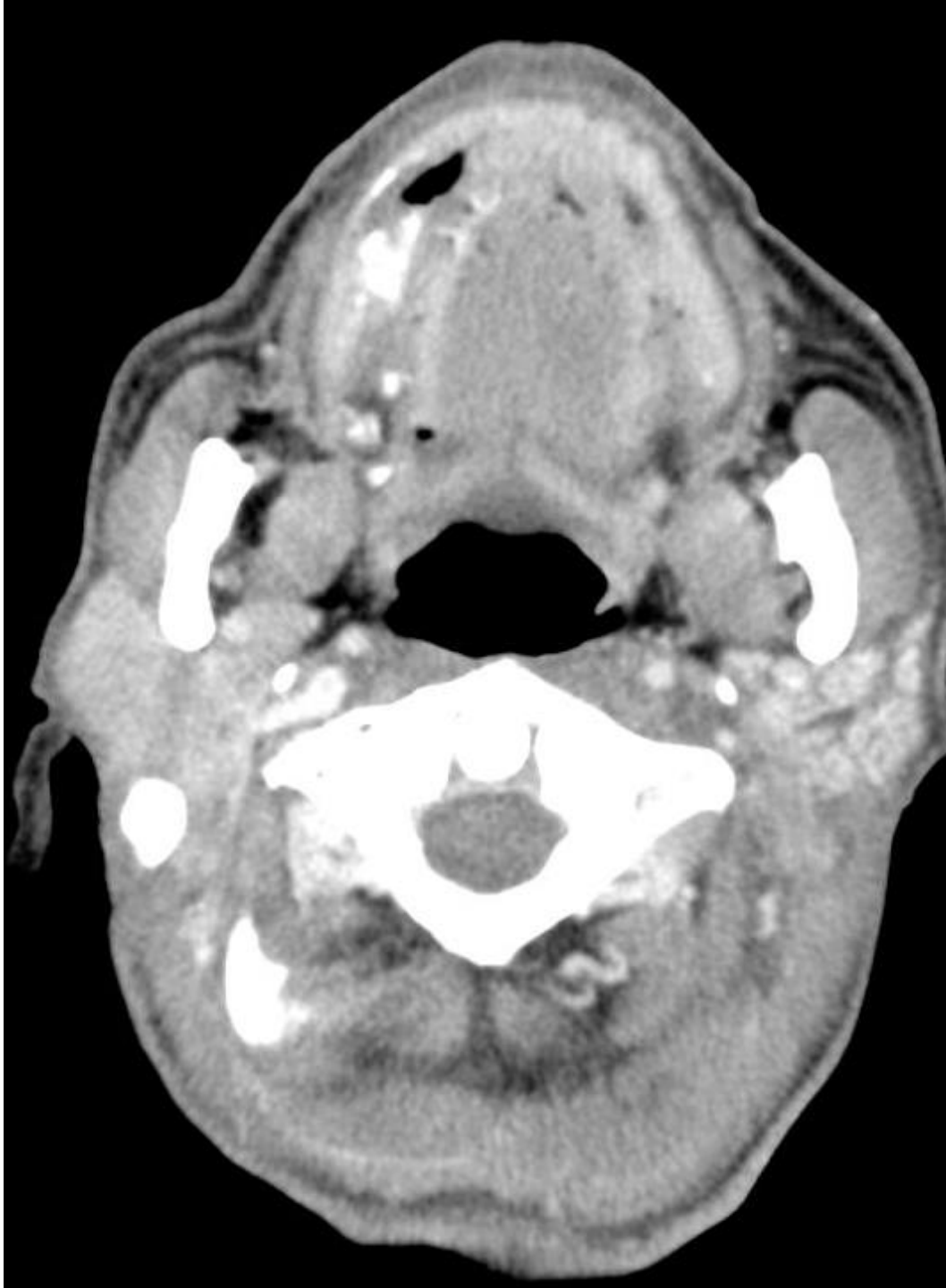
10/2015

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



Pt SG

- 65 yo, prior smoker (10ppy)
- 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

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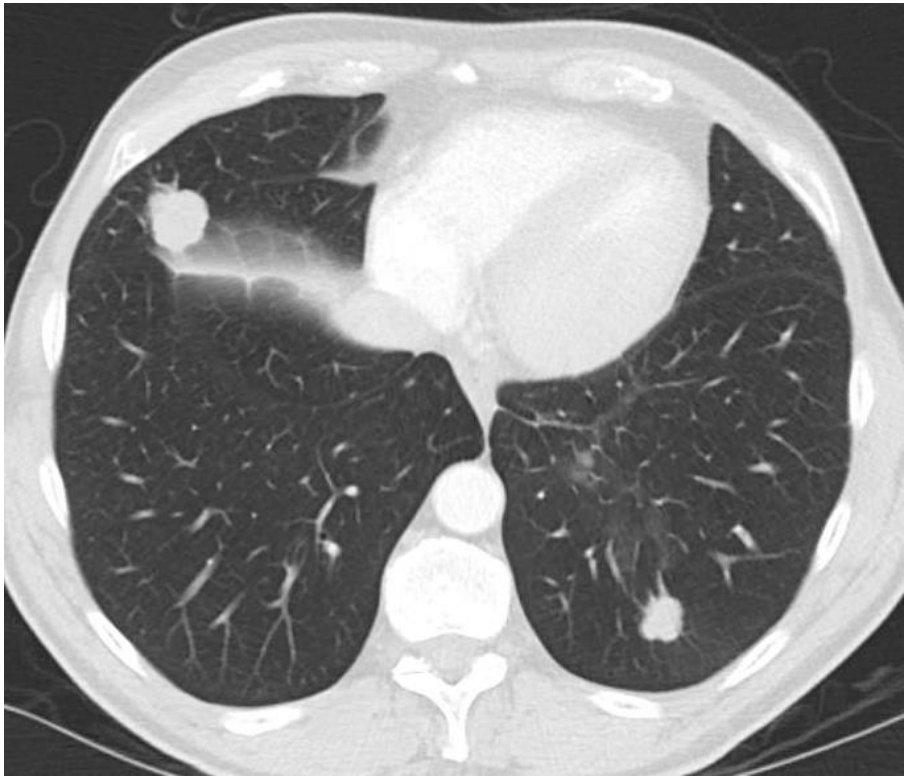
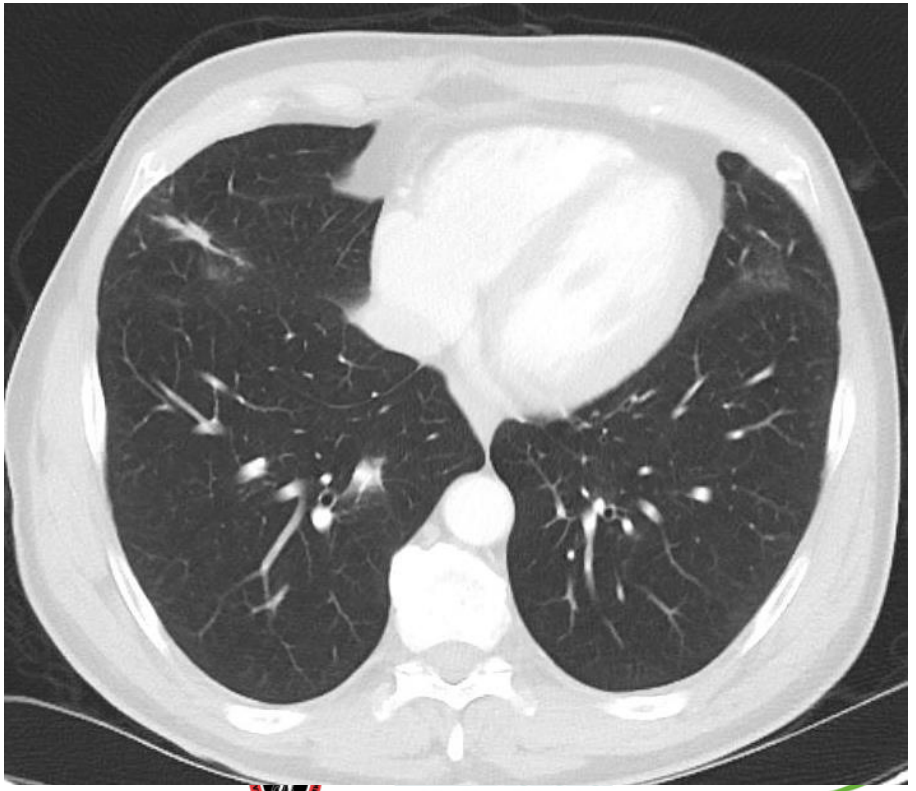
2/2015

- 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

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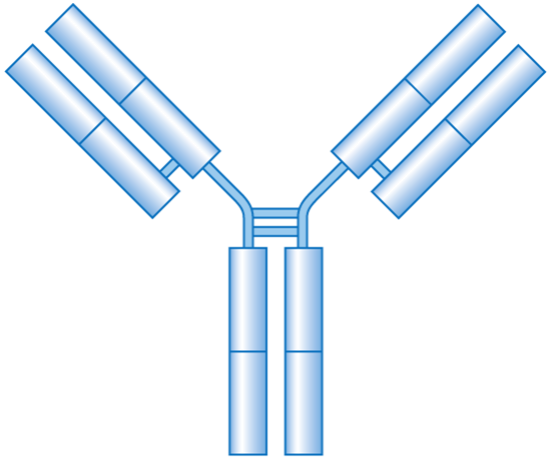
IO Agents approved and in development for HNC

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. **Durvalumab**
   - IgG1
   - Humanized
   - High Affinity for PD-L1 (K_D ~ 29 pM)
   - In Development for Head and Neck Cancer, Lung Cancer, others

4. **Other PD-1/PD-L1 agents in development:**
   - PD-L1 agents – Atezolizumab (bladder, NSCLC approval), Avelumab
   - PD-1 agents: R2810, PRD001, Tesaro

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

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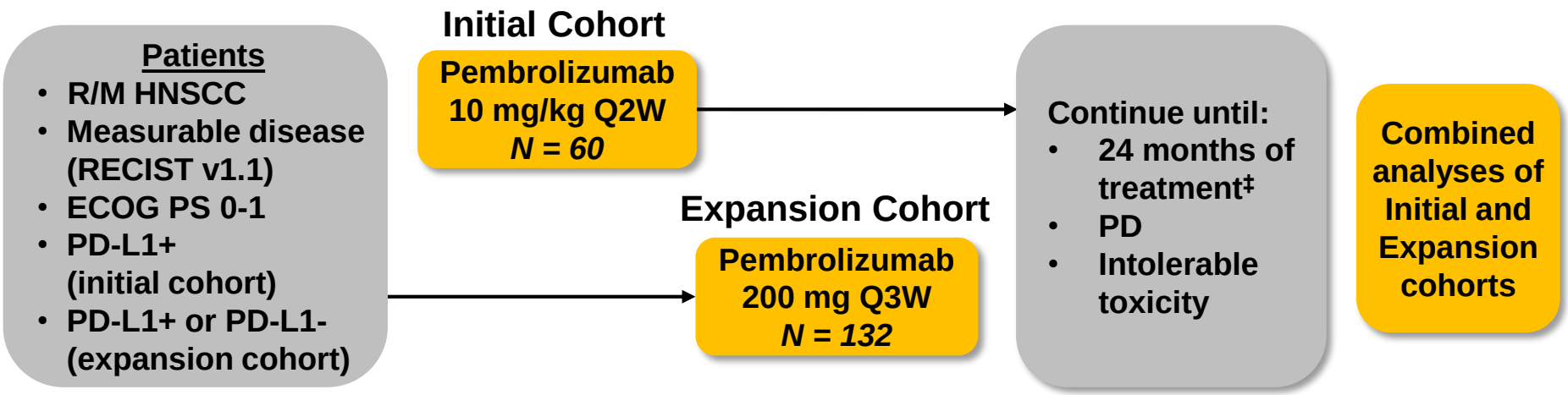
HNSCC Cohort of Phase 1b KEYNOTE-012



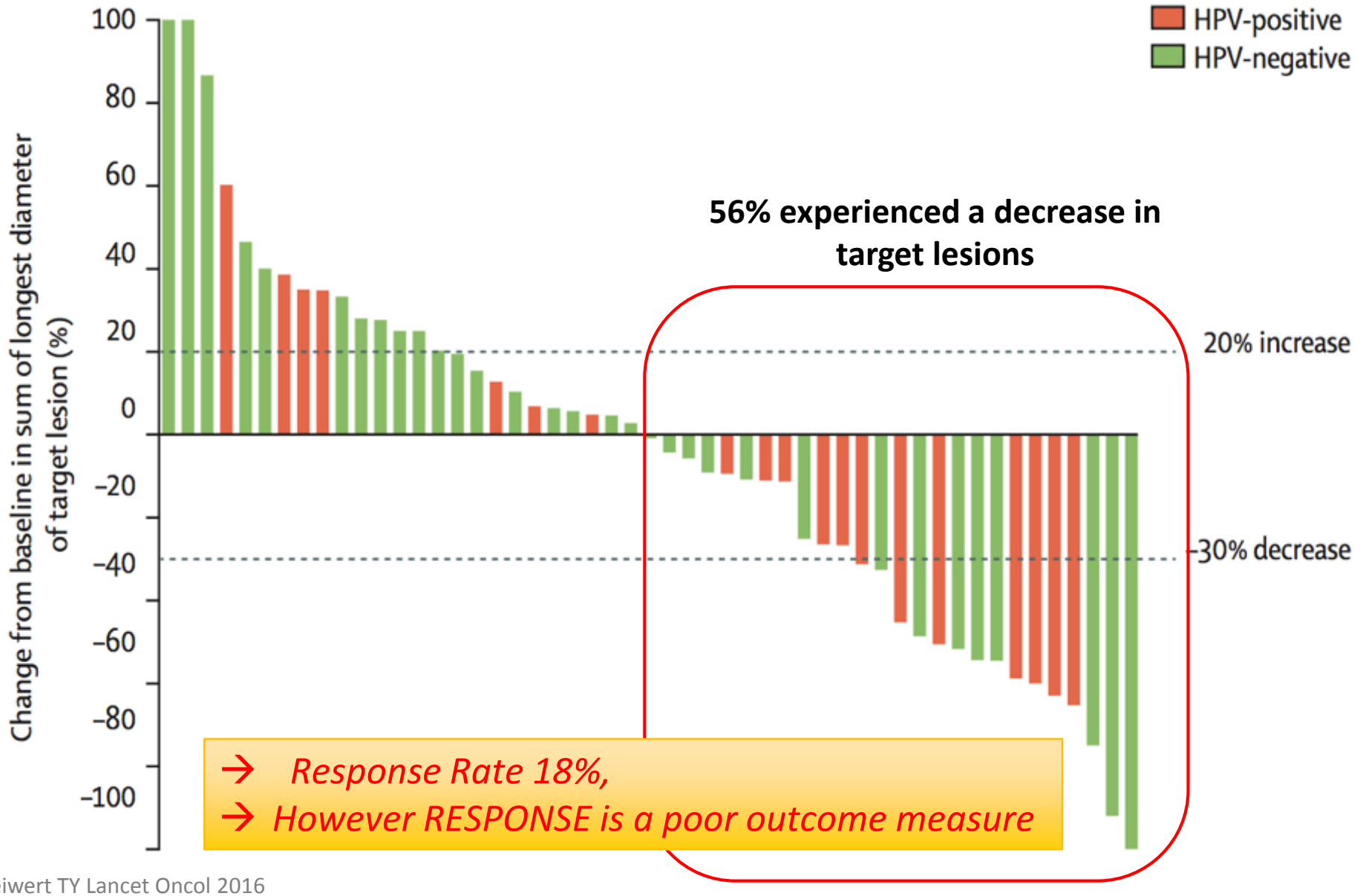
Response assessment: Every 8 weeks

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)

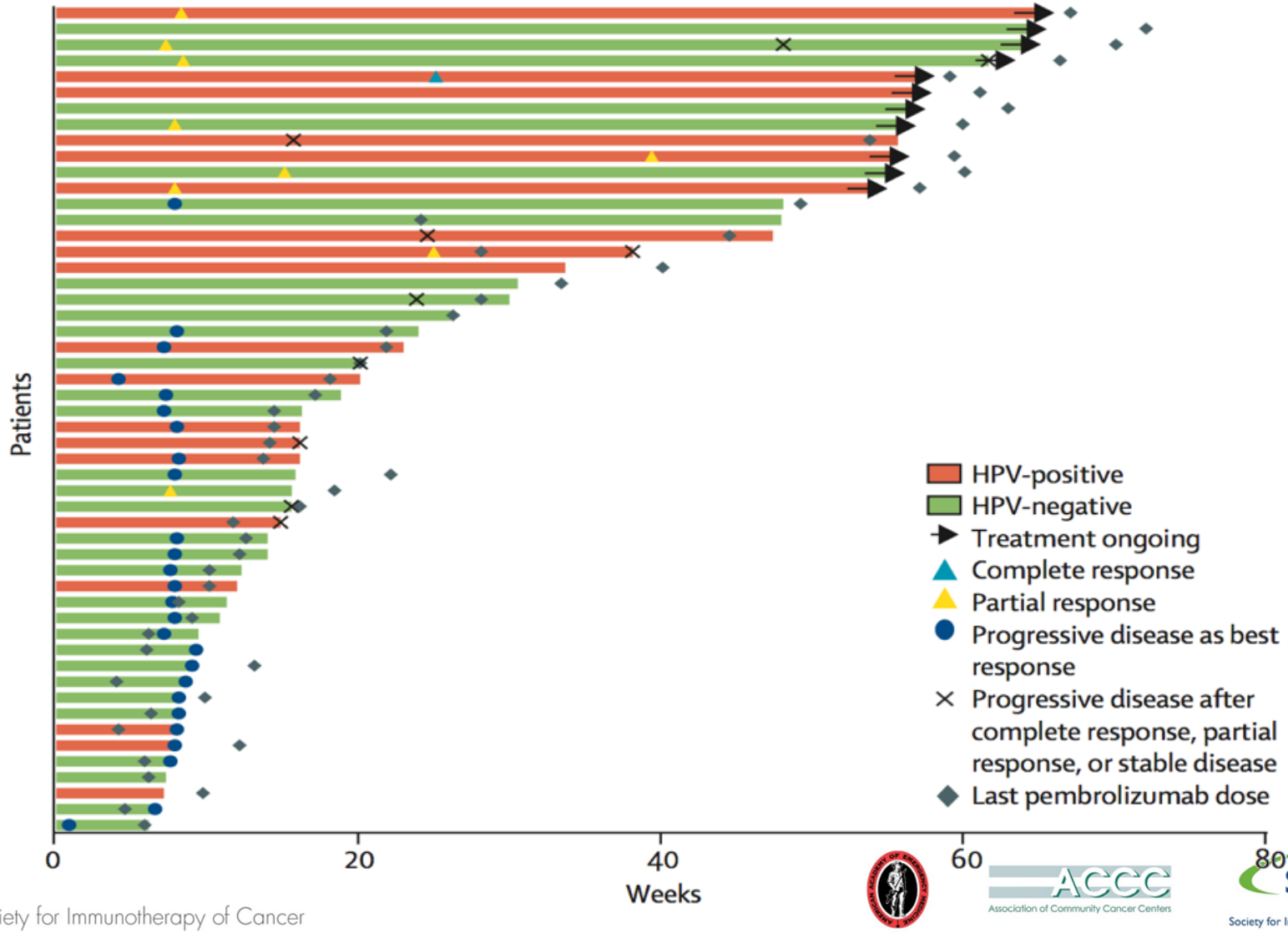


→ *Response Rate 18%,*

→ *However RESPONSE is a poor outcome measure*

Seiwert TY Lancet Oncol 2016

Durability (KEYNOTE 12)



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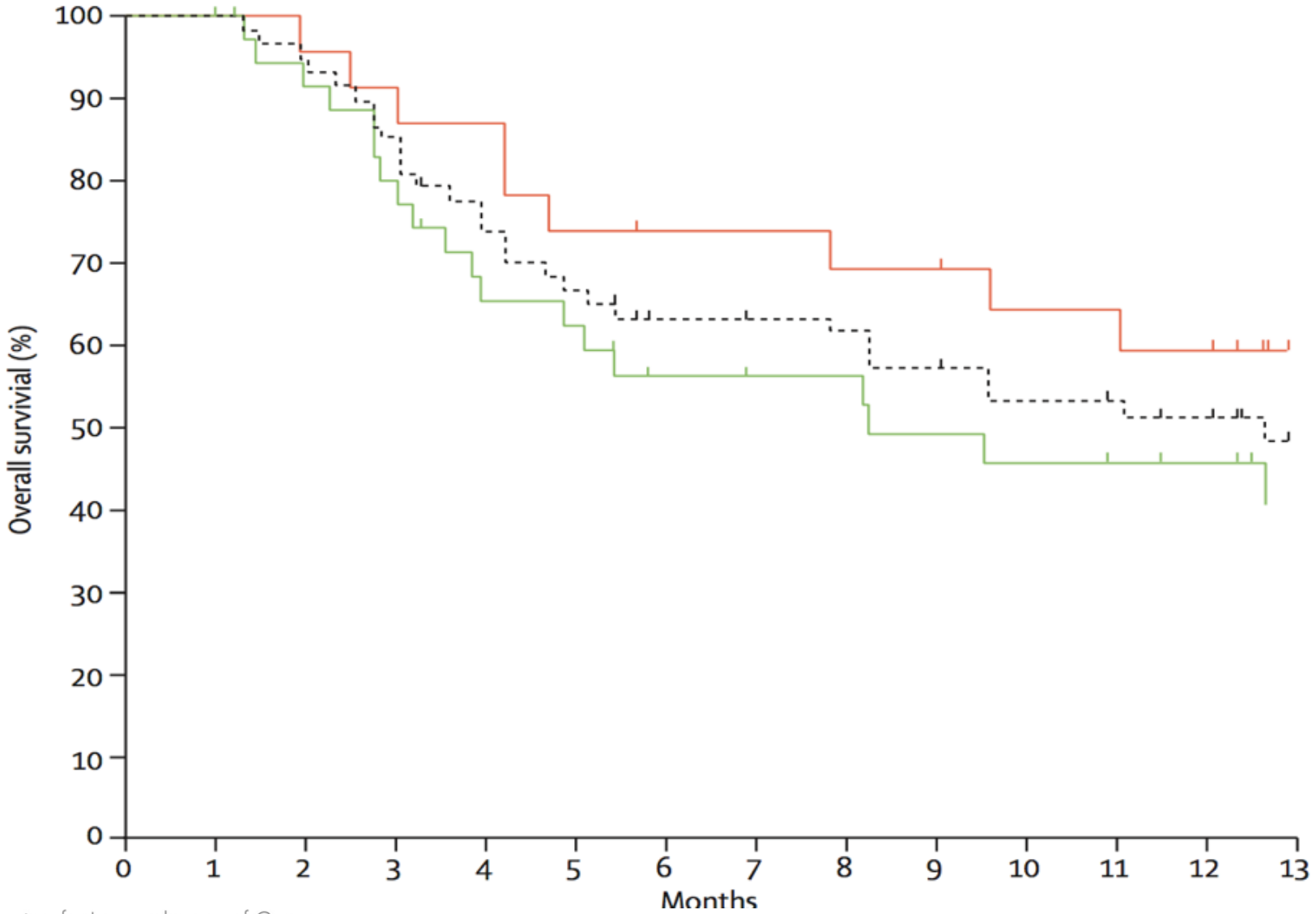
Overall Survival



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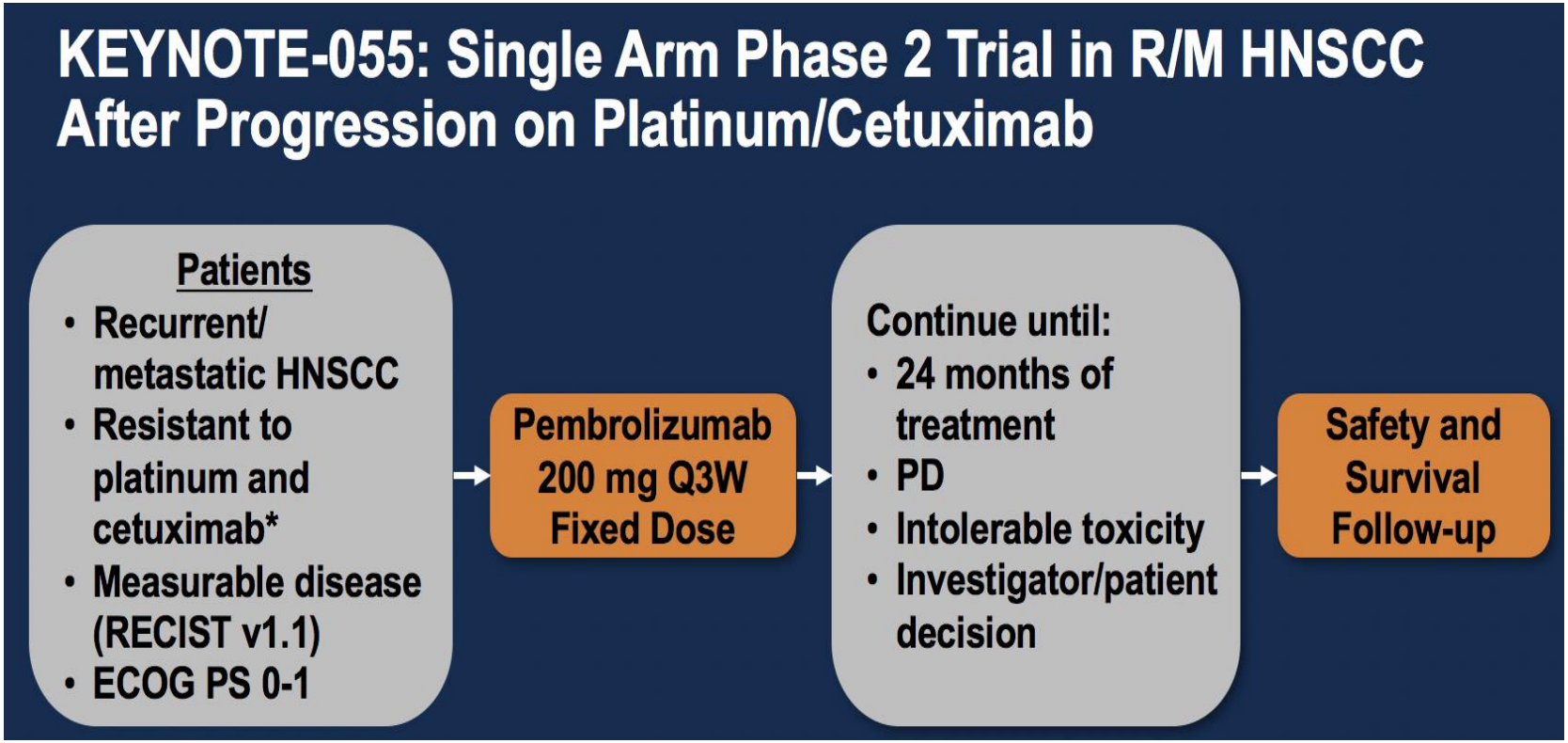
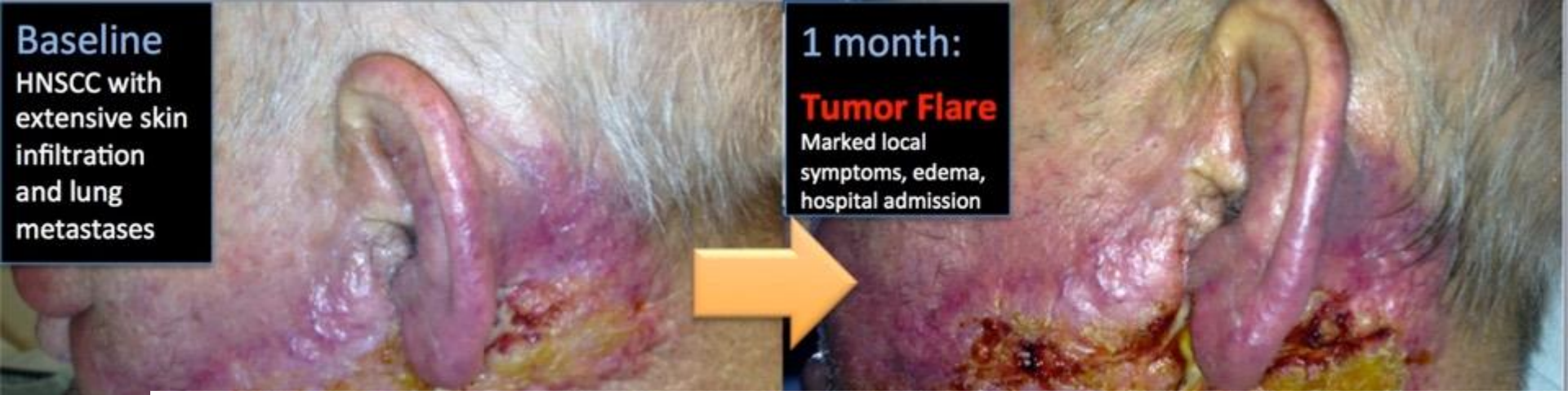
KEYNOTE-055

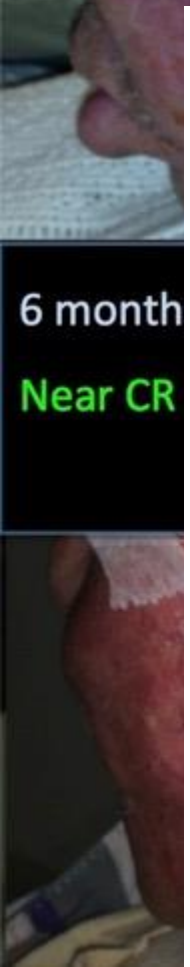


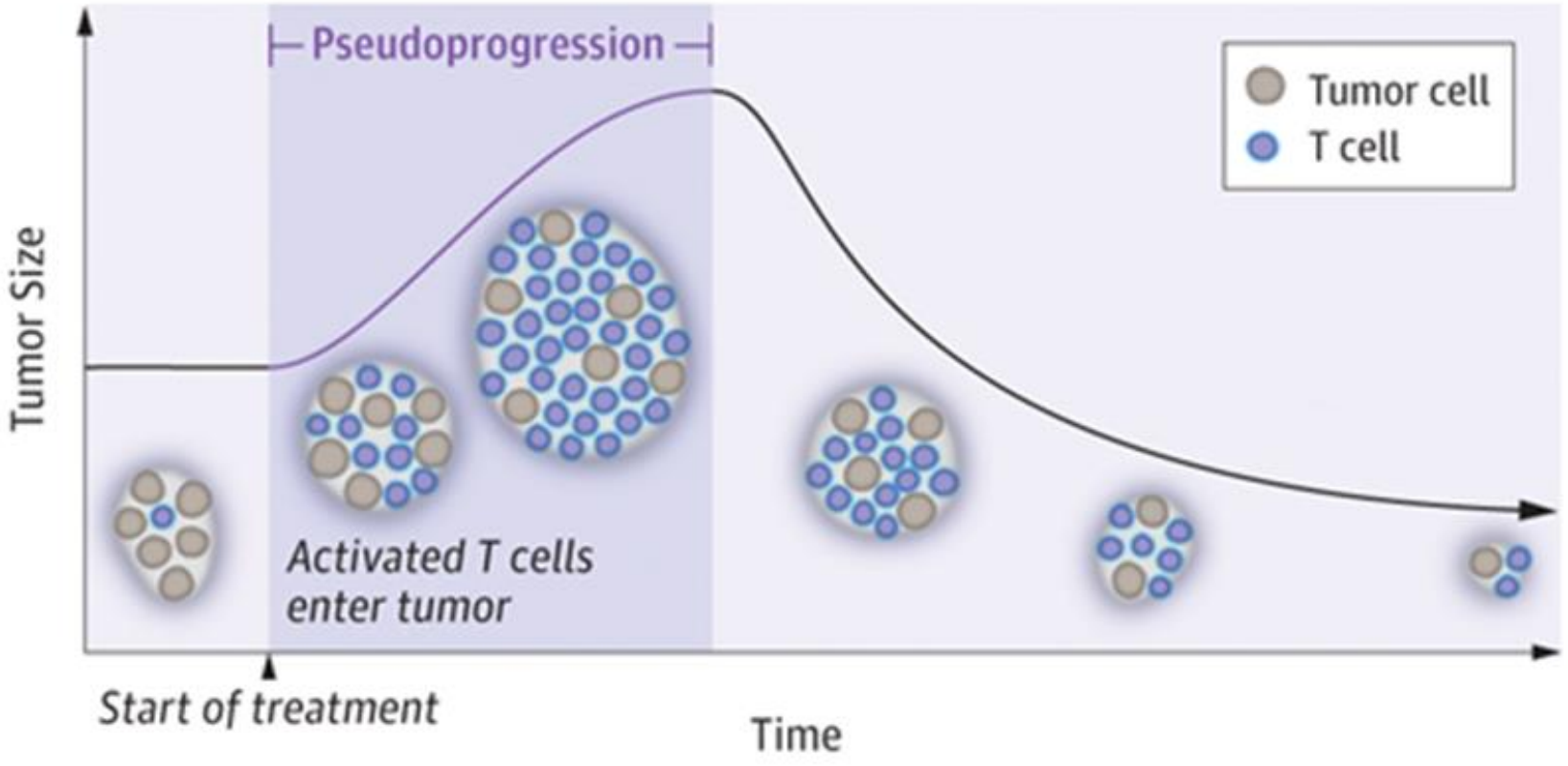
N=171

- ORR = 16%
- mOS = 8 months
- mDOR= 8 months

Bauml, JCO 2017


Baseline
HNSCC with extensive skin infiltration and lung metastases
1 month:
Tumor Flare
Marked local symptoms, edema, hospital admission


6 month
Near CR


Response to immune checkpoint inhibitor treatment with brief increase in tumor size (pseudoprogression)
Pseudoprogression
Tumor cell
T cell
Tumor Size
Activated T cells enter tumor
Start of treatment
Time

FDA Approves Pembrolizumab for Head and Neck Cancer

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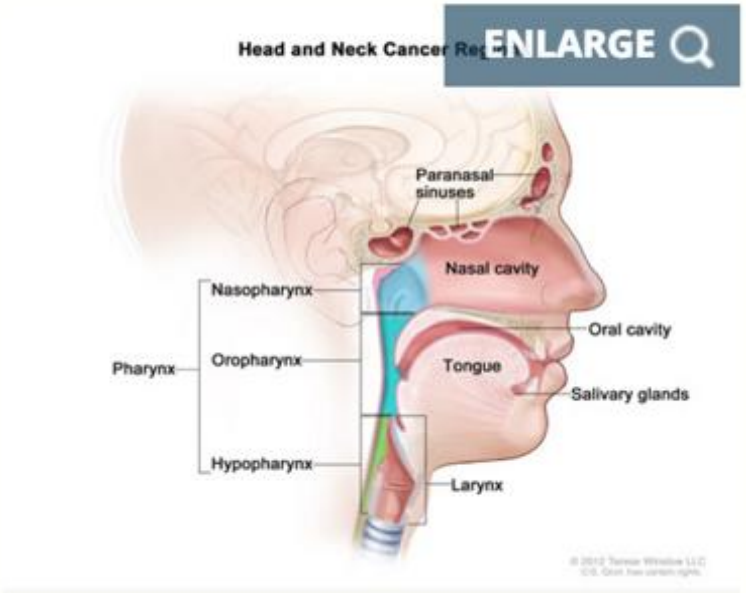
August 24, 2016 by NCI Staff

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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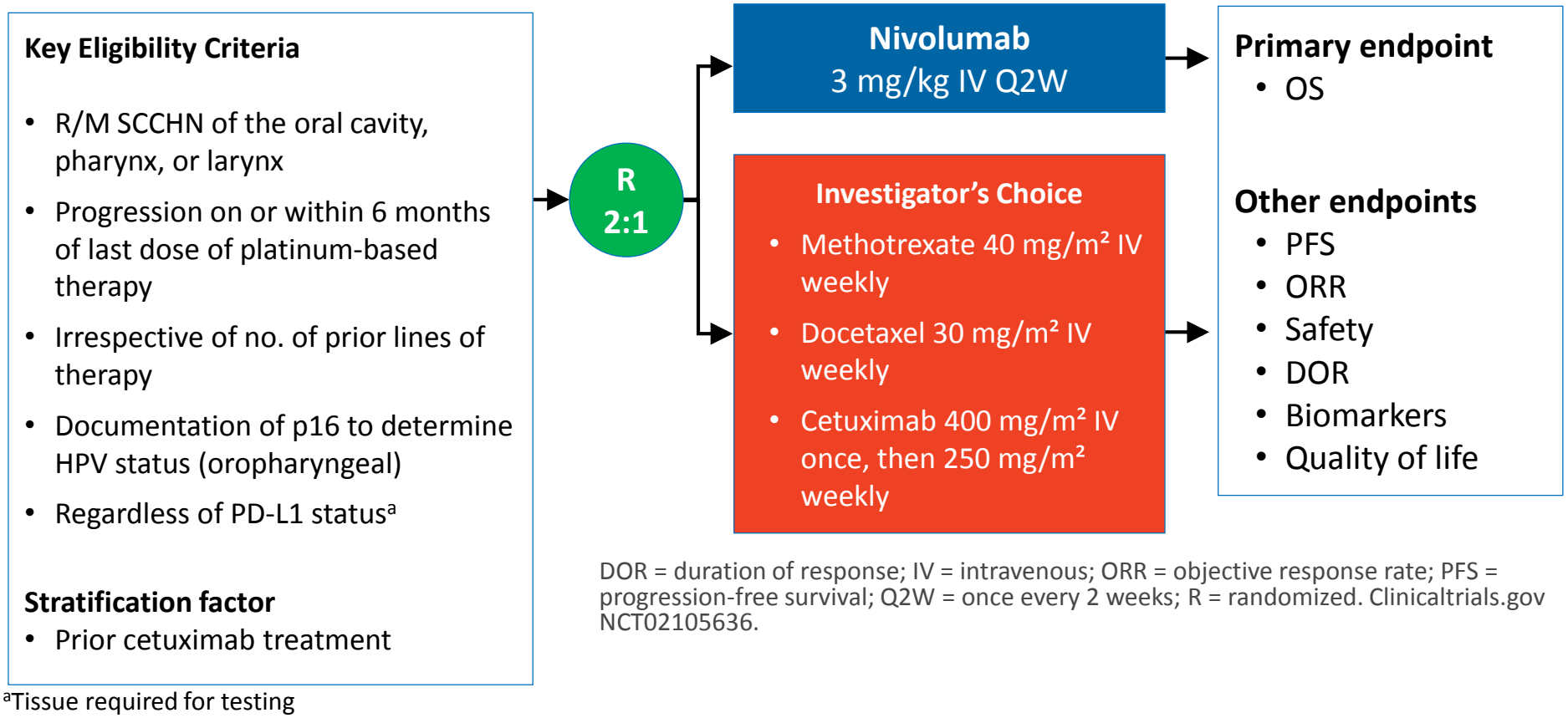
Phase 3 CheckMate 141

Nivolumab in R/M HNSCC 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



[a]Tissue required for testing

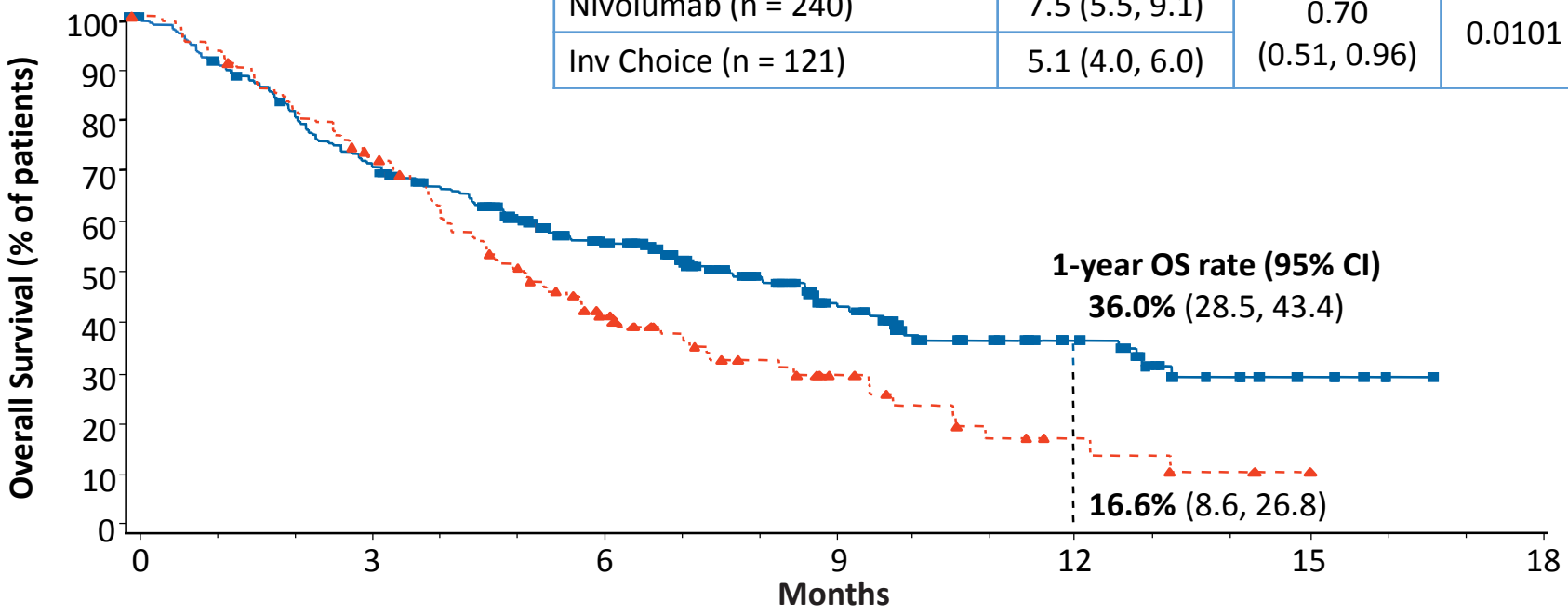
DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

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
Inv Choice (n = 121)	5.1 (4.0, 6.0)		



No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Inv 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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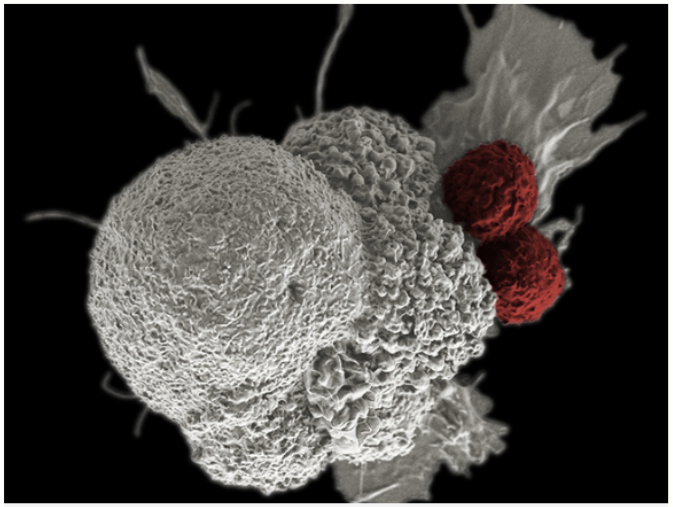
December 1, 2016, by NCI Staff

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.

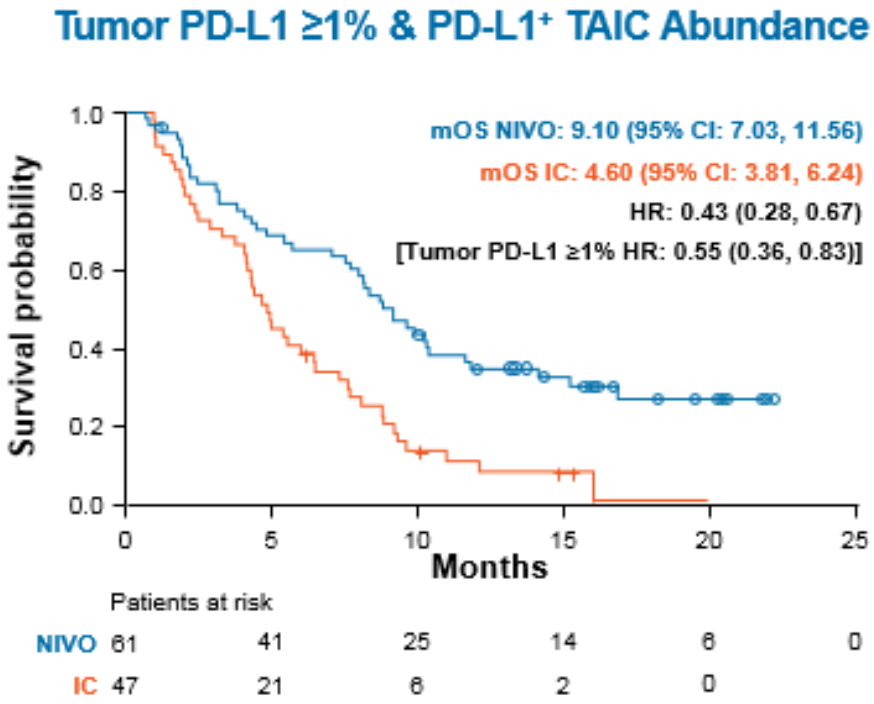
Credit: National Cancer Institute

Biomarkers in HNSCC

- 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

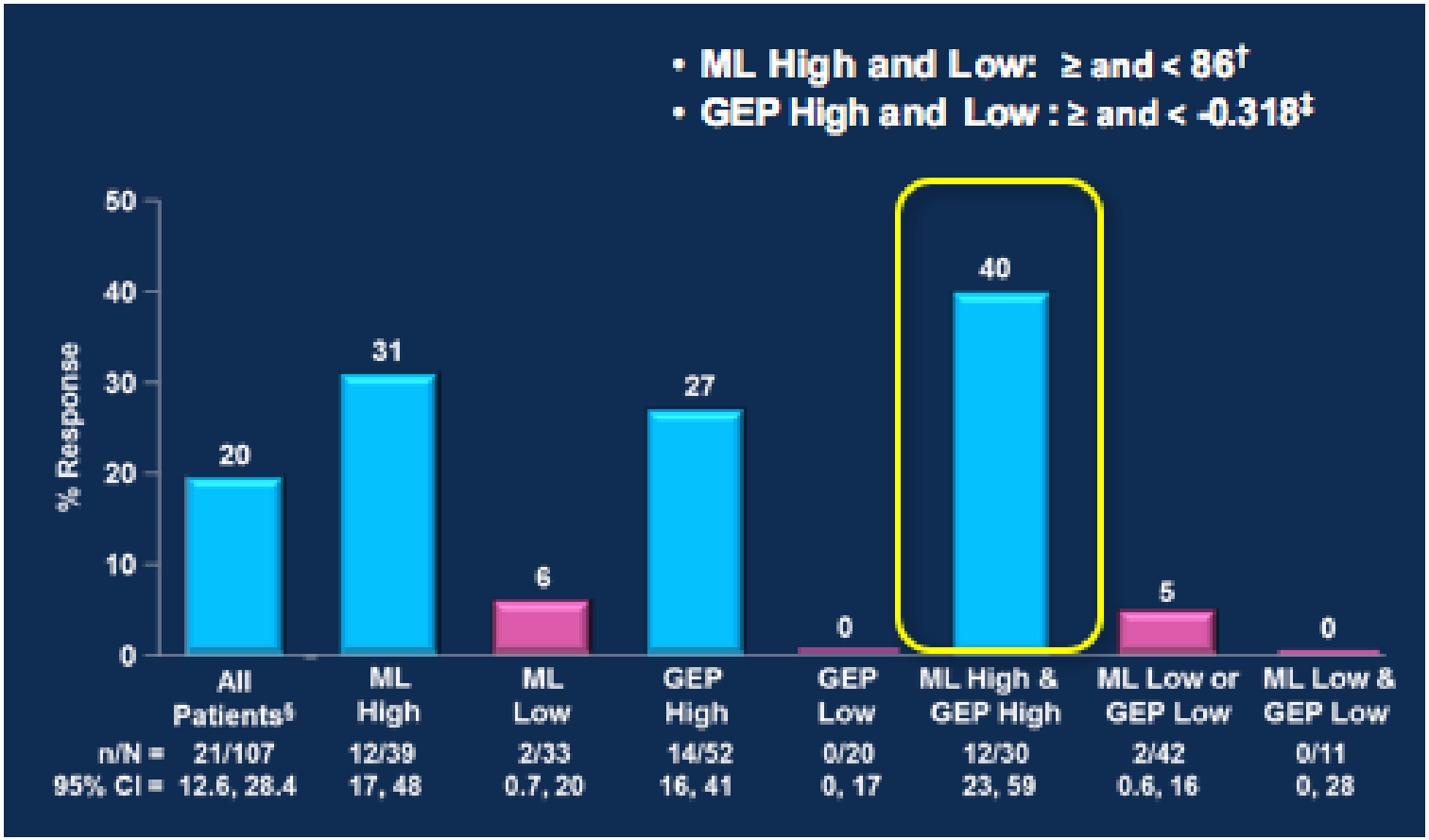
PD-L1 Staining: Think Outside the Tumor?

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



Ferris et al AACR 2017

Other biomarkers: GEP/ML



Haddad et al ASCO 2017

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 *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