ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Head and Neck Cancers

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Disclosures

- Consulting Fees: Merck, EMD Serono
- I will not be discussing non-FDA approved indications during my presentation.

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Case Study

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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

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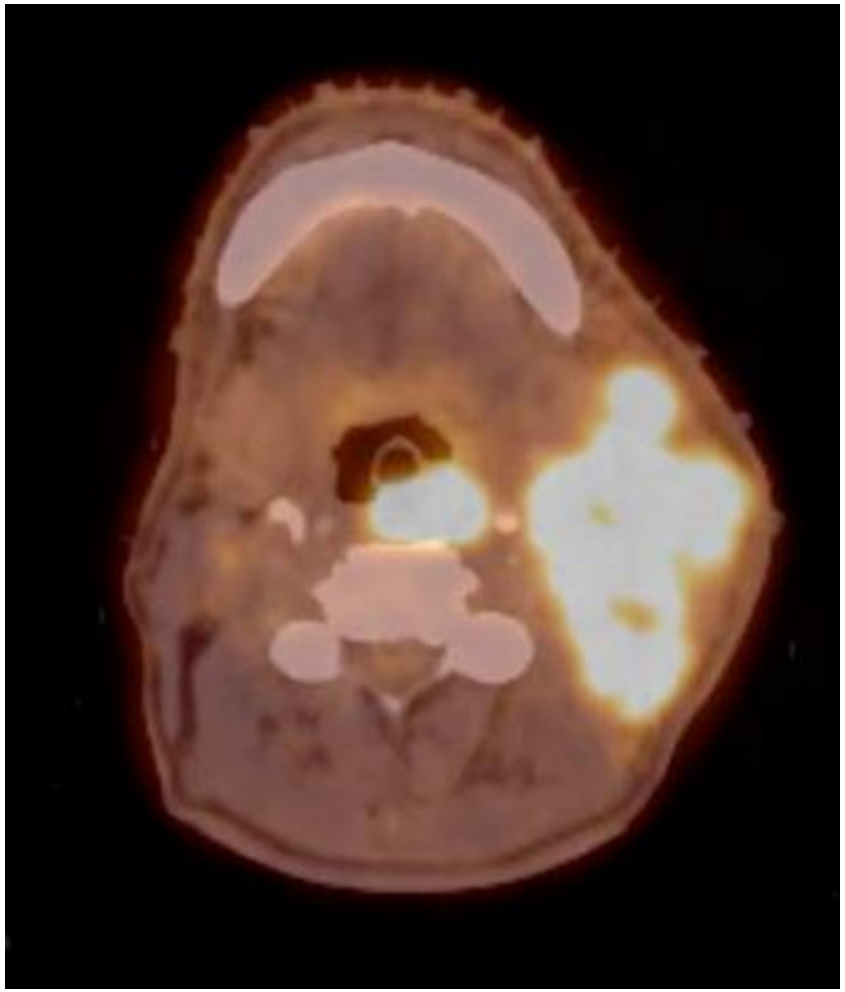
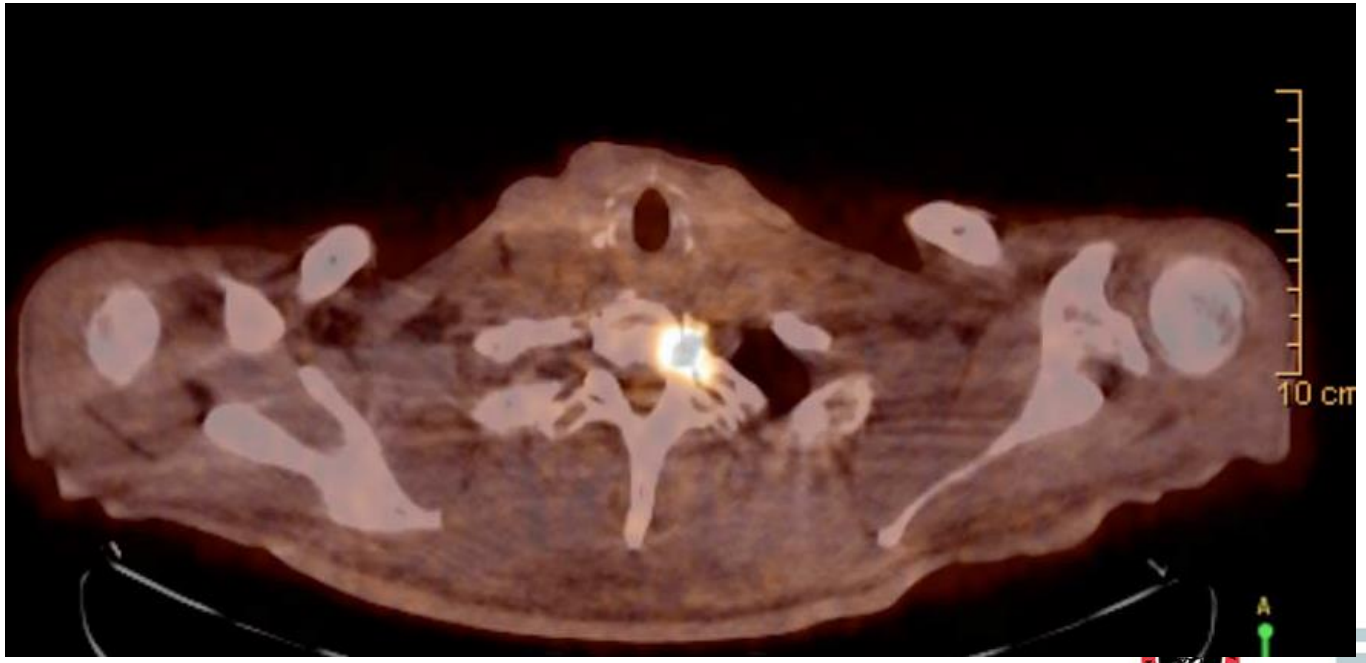
11/2014

- 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



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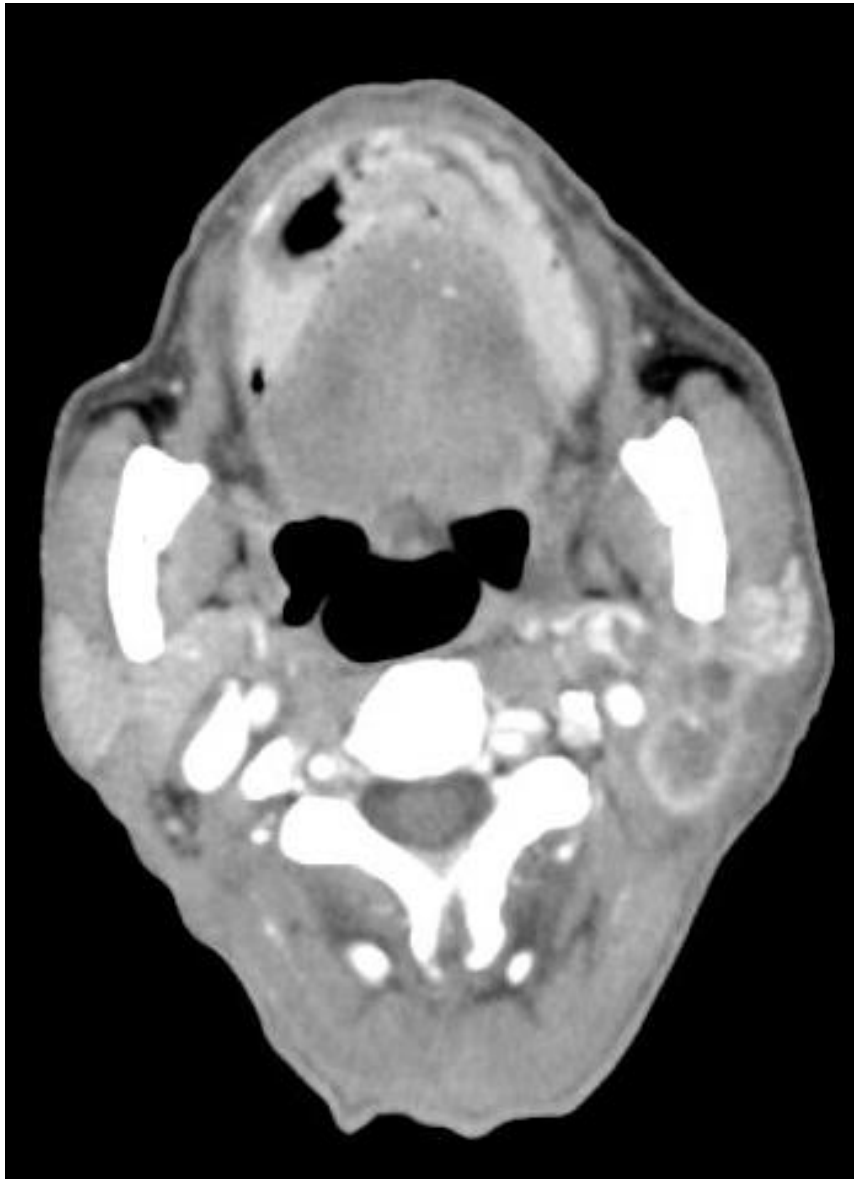
6/2015

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



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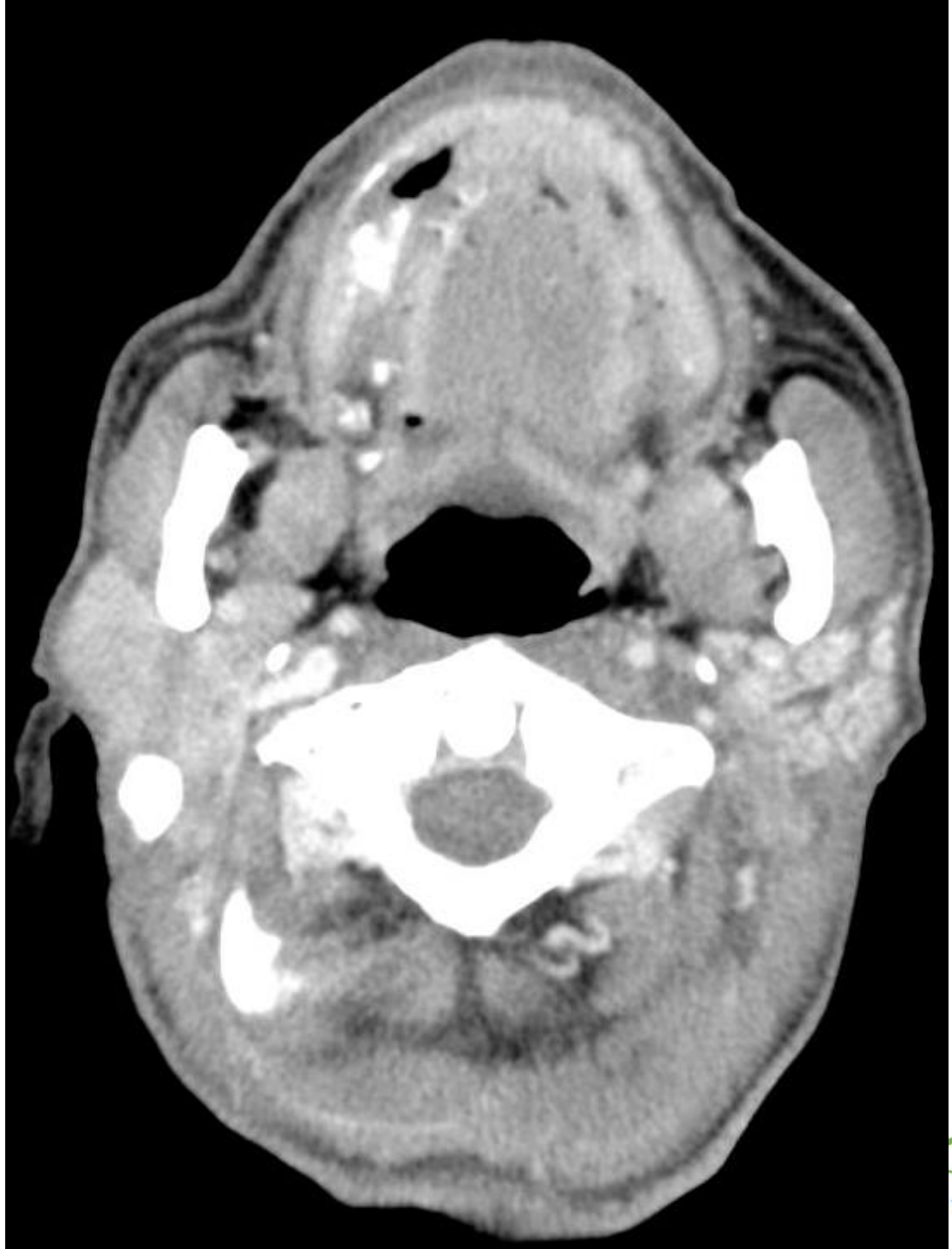
10/2015

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



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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

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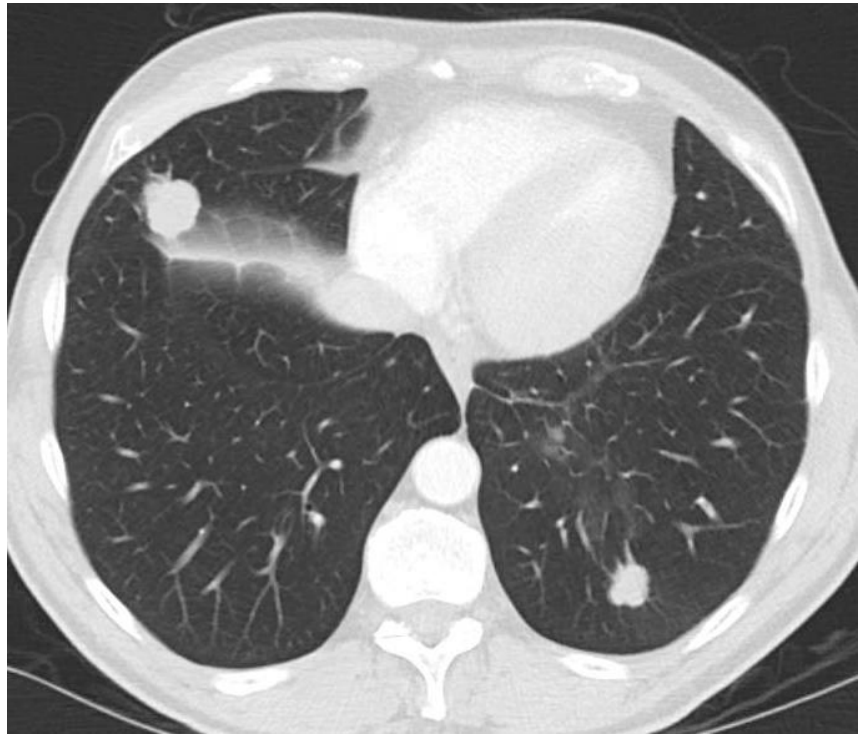
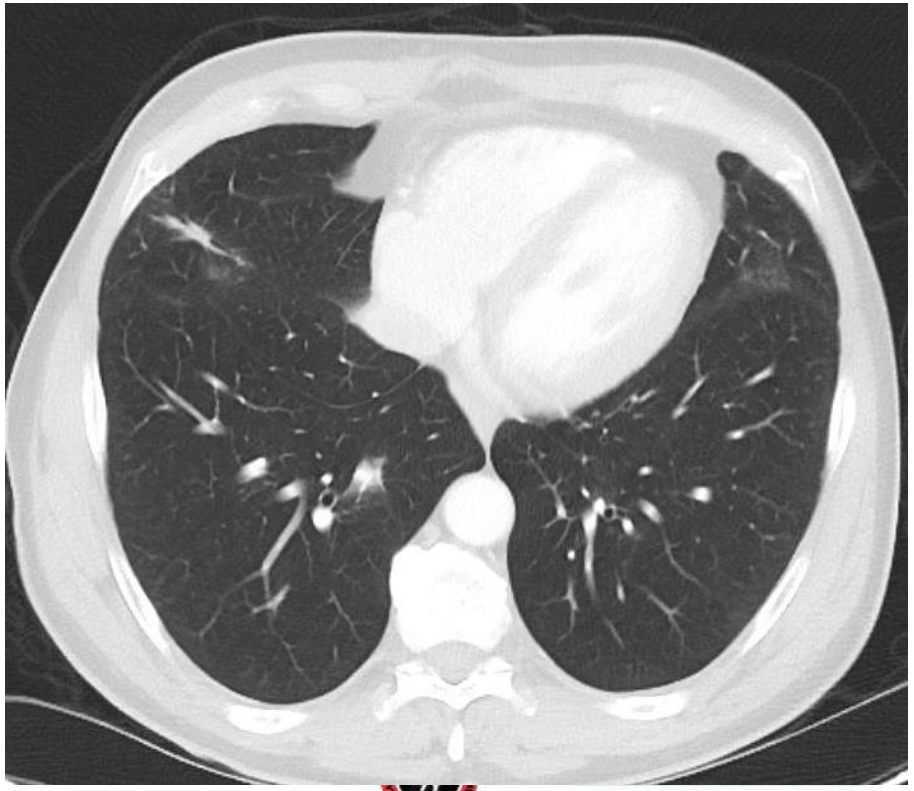
2/2015

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





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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 an enjoy an excellent response (ongoing) to pembrolizumab, 2.5 years on therapy

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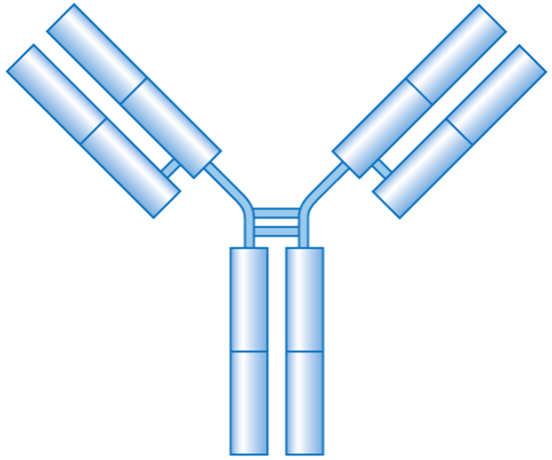
IO Agents approved and in development for HNC

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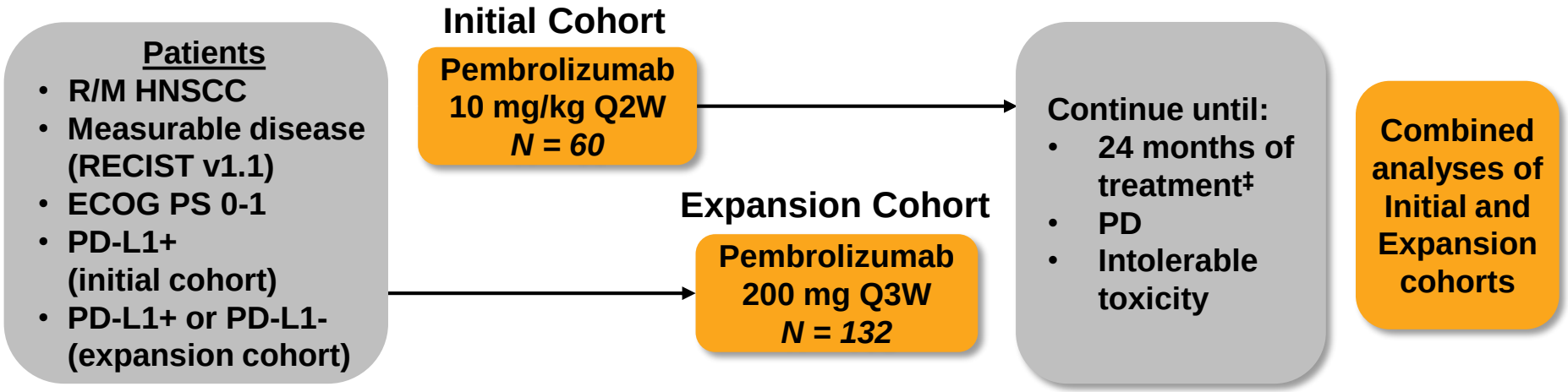
HNSCC Cohorts of Nonrandomized, Phase 1b, Multi-cohort KEYNOTE-012 Trial



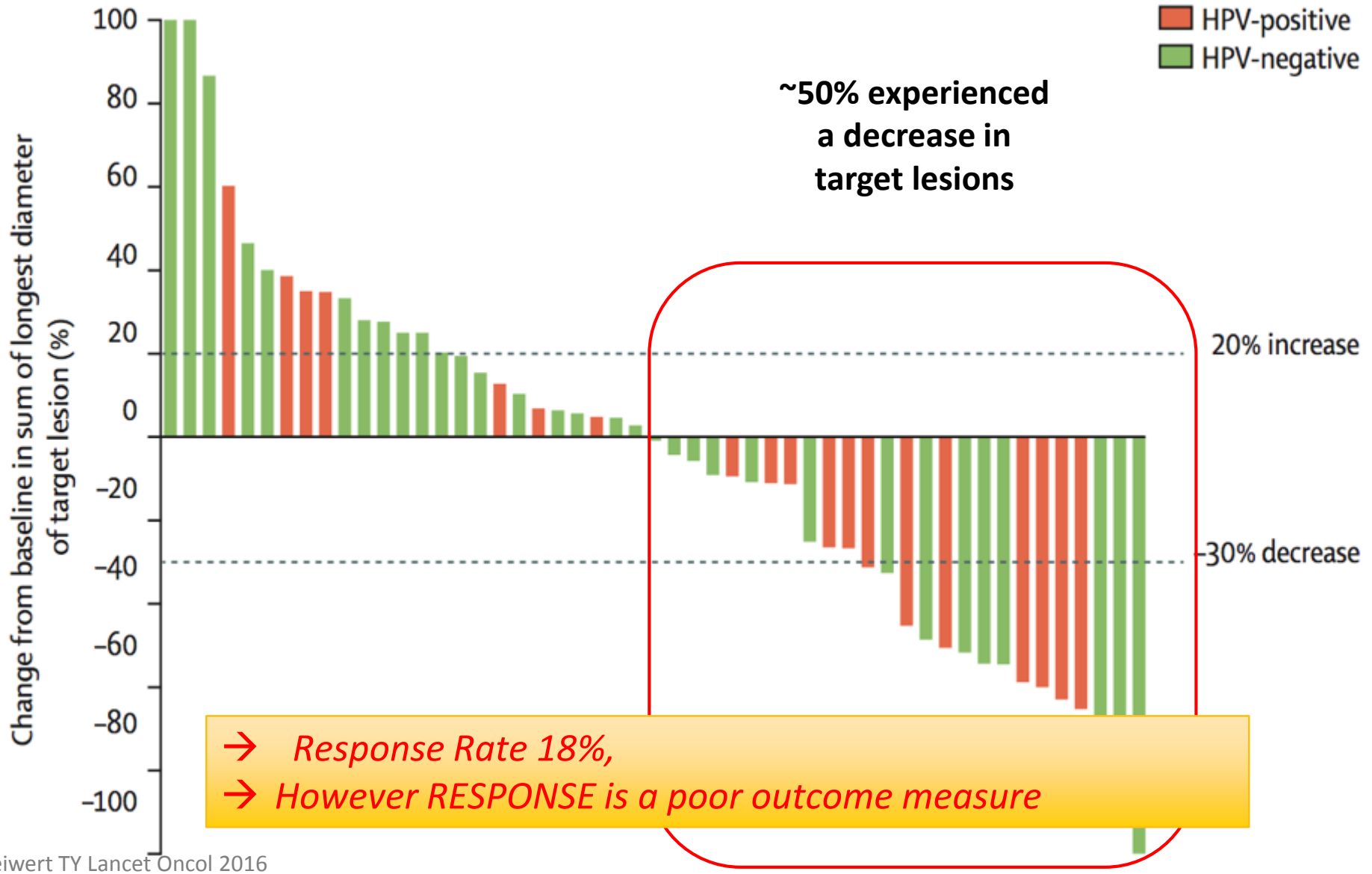
Response assessment: Every 8 weeks

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.

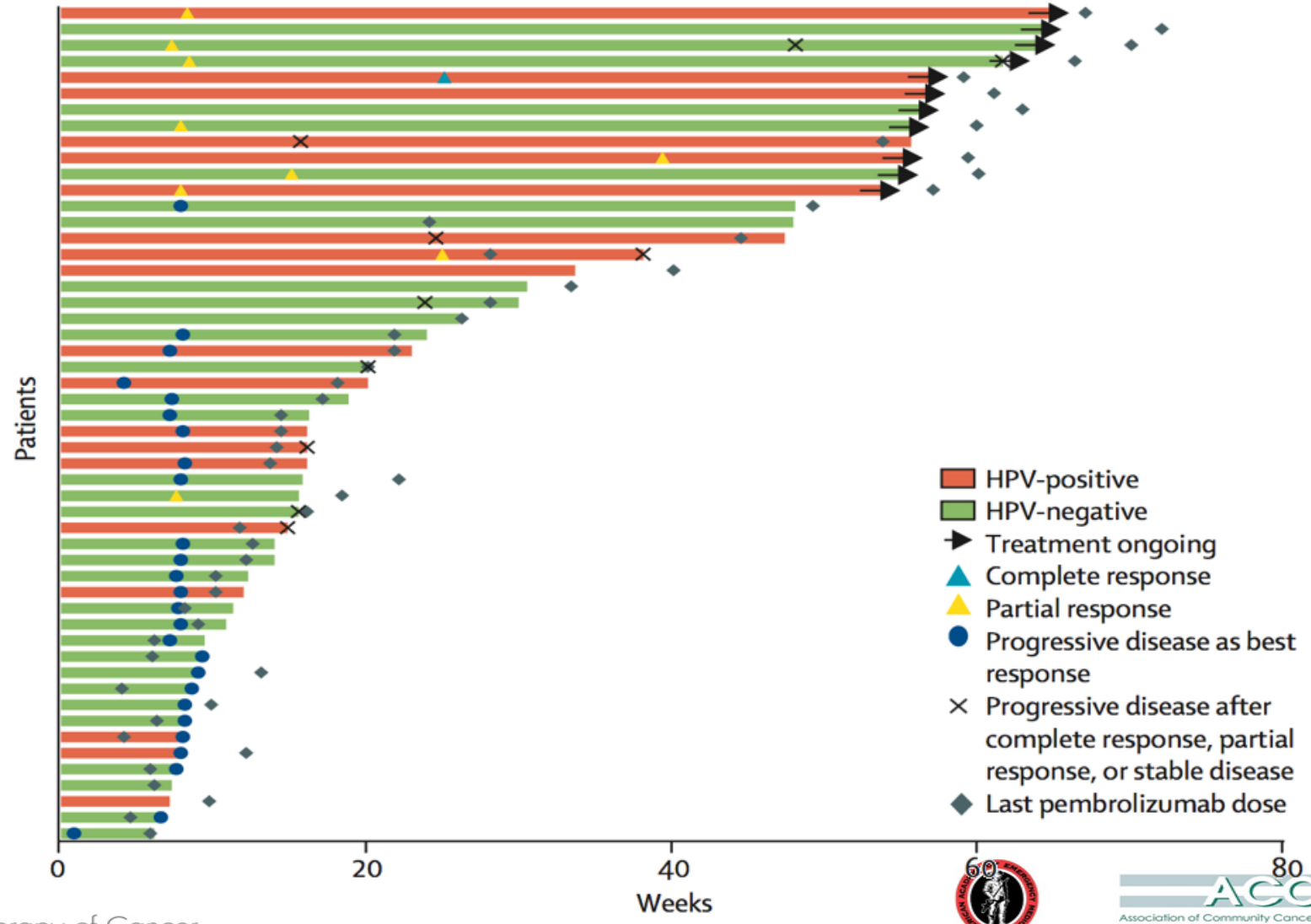
Tumor Shrinkage (KeyNote 12)



→ *Response Rate 18%,*
→ *However RESPONSE is a poor outcome measure*

Seiwert TY Lancet Oncol 2016

Durability (KeyNote 12)



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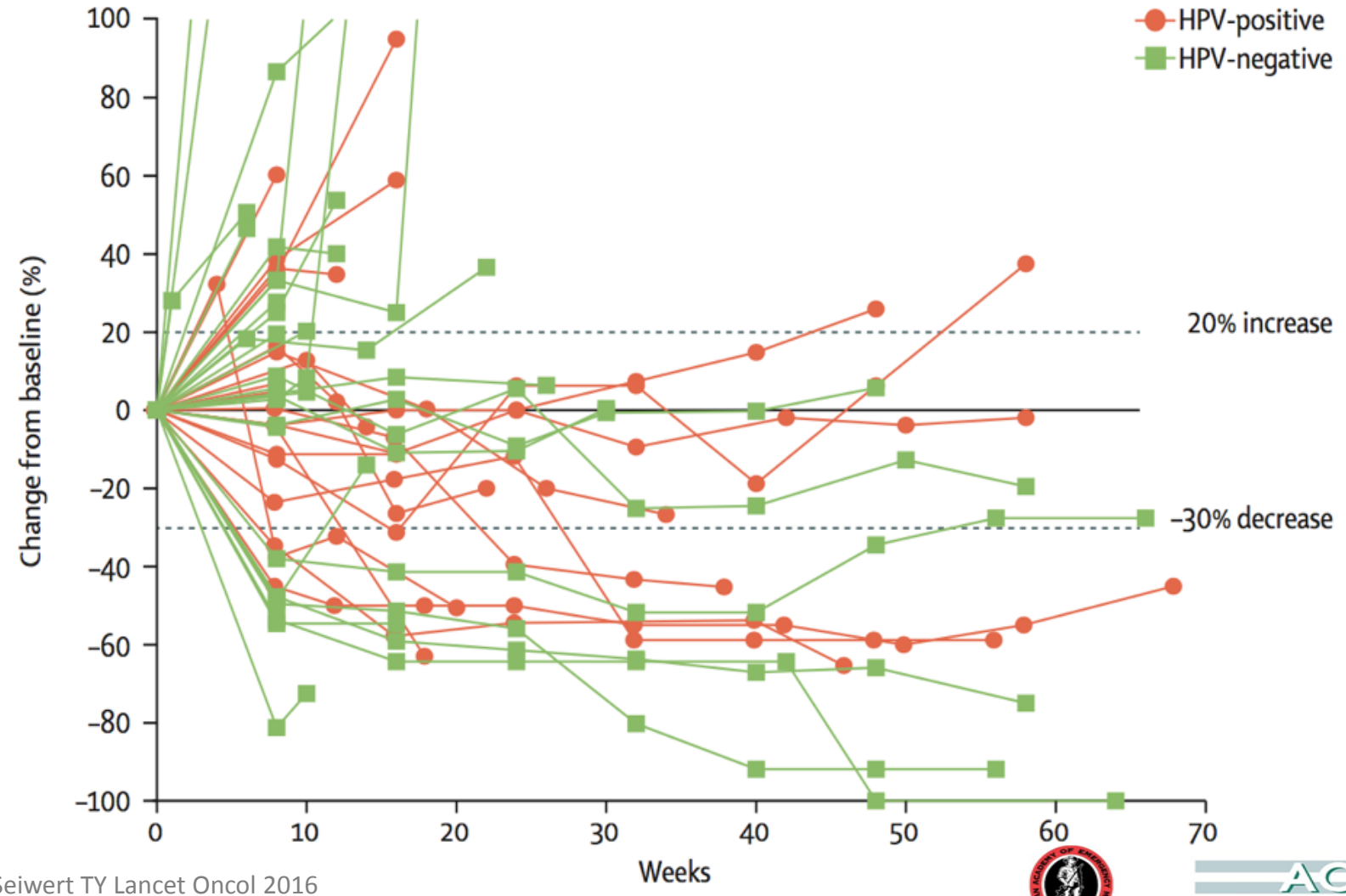
Most responses are early, *few delayed, BUT virtually no Pseudoprogression!*



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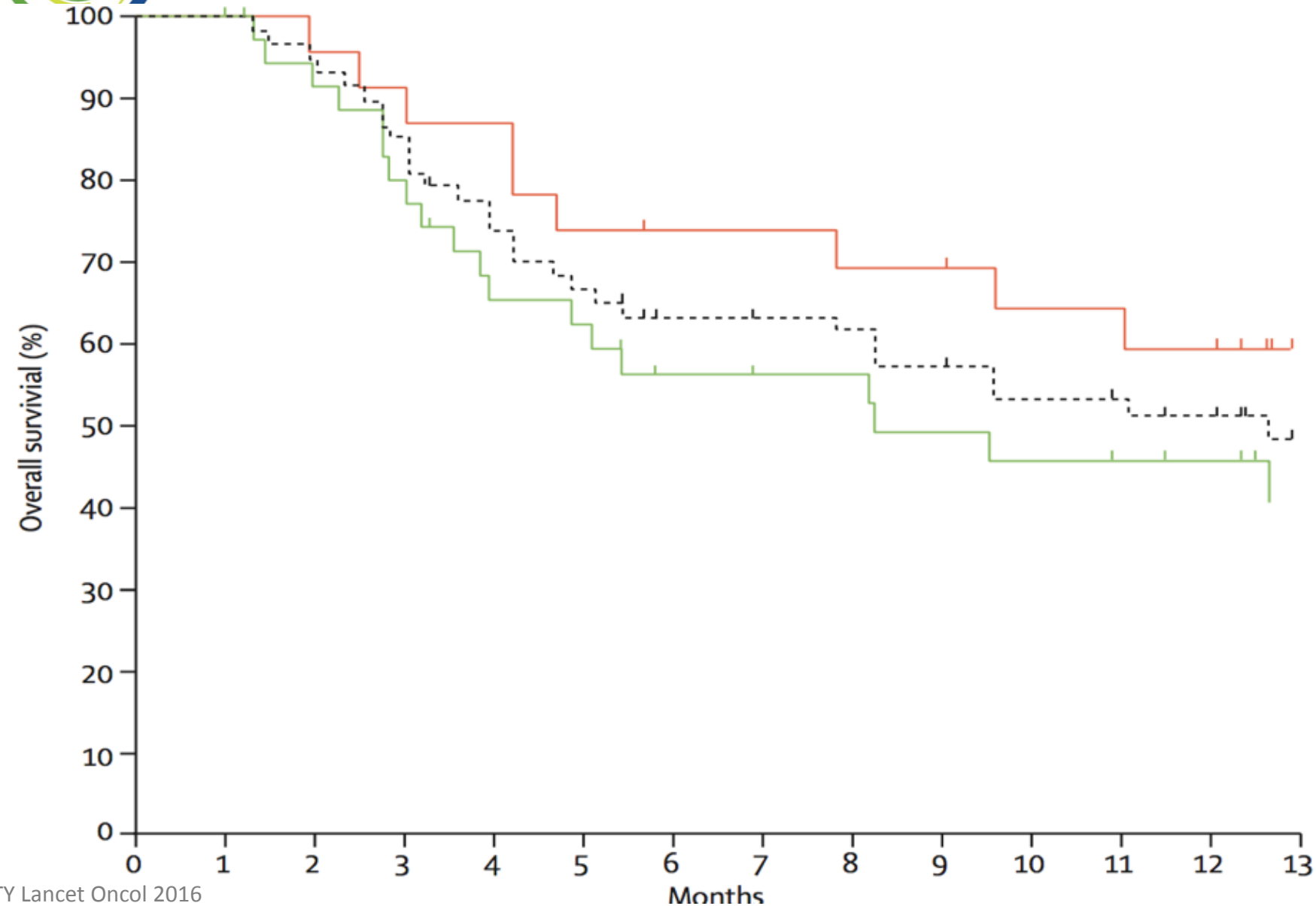
Major Impact on Overall Survival



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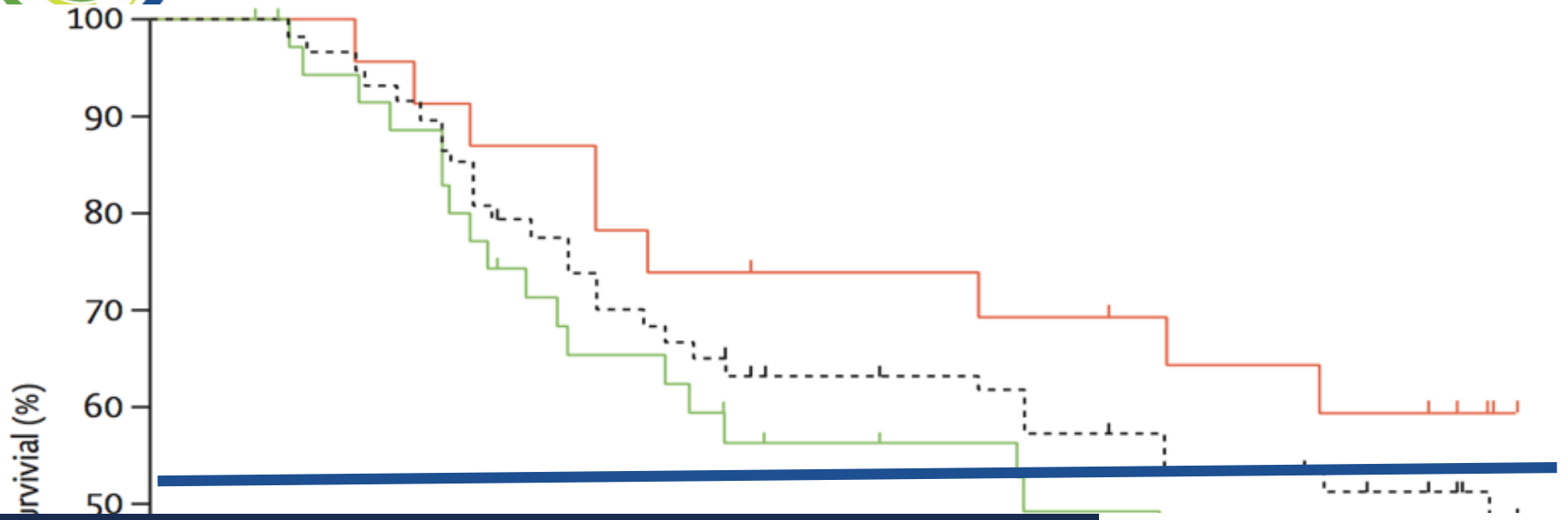
Major Impact on Overall Survival



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

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

KN55: N=171
- RR = 16%
- mOS = 8 months
- DOR: 8 months

Bauml*/Seiwert* et al

JCO 2017 in Press

FDA Approves Pembrolizumab for Head and Neck Cancer

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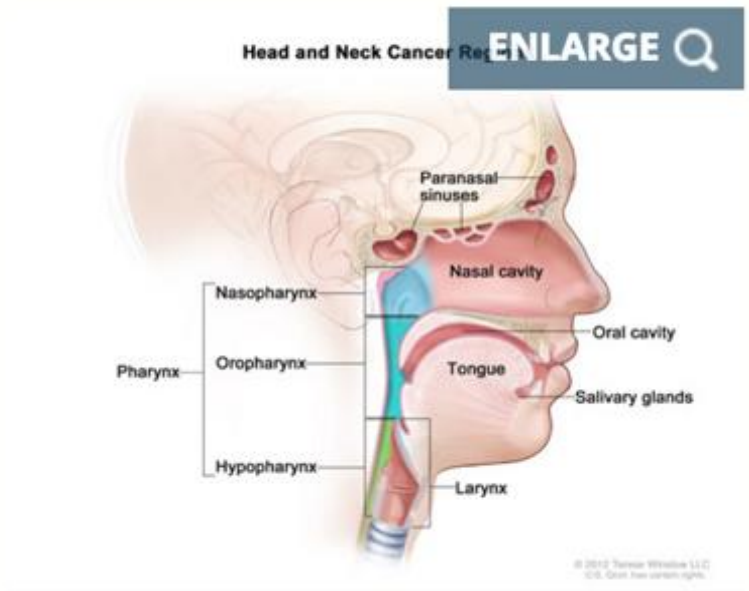
August 24, 2016 by NCI Staff

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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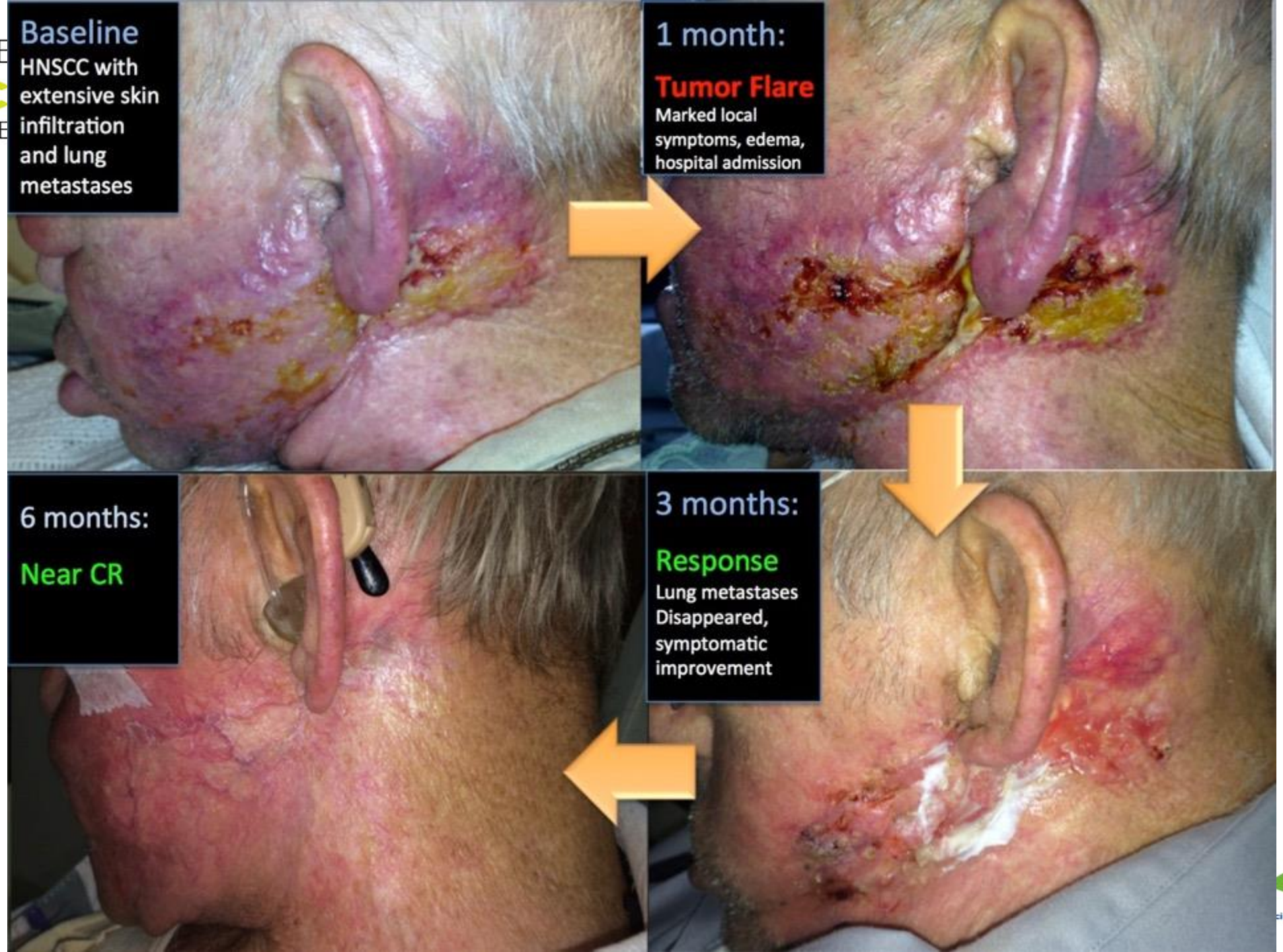

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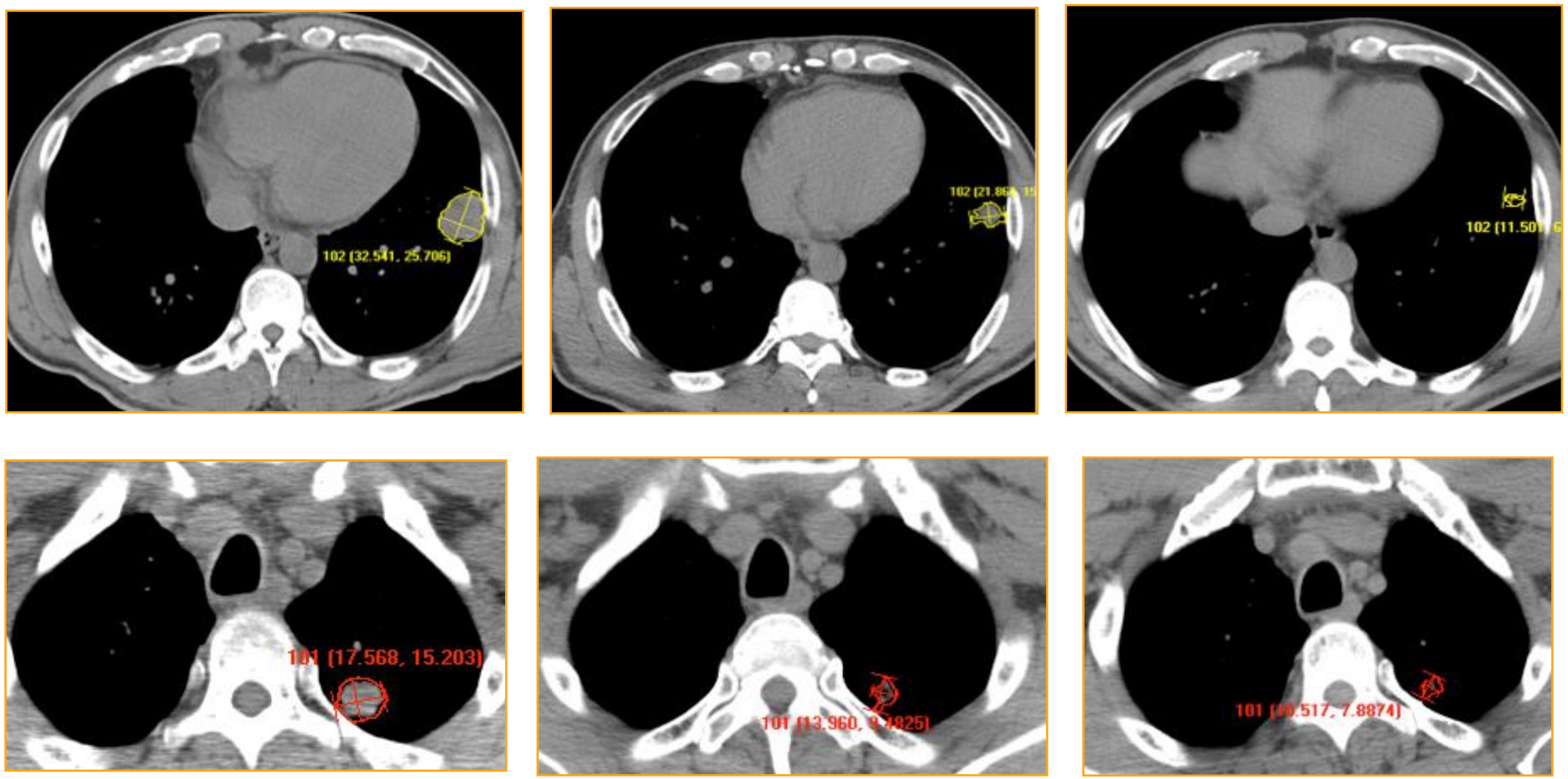
Patient Response *(central review)*

Baseline **Cycle 4 -28.3%** **Cycle 8 -56.1%**



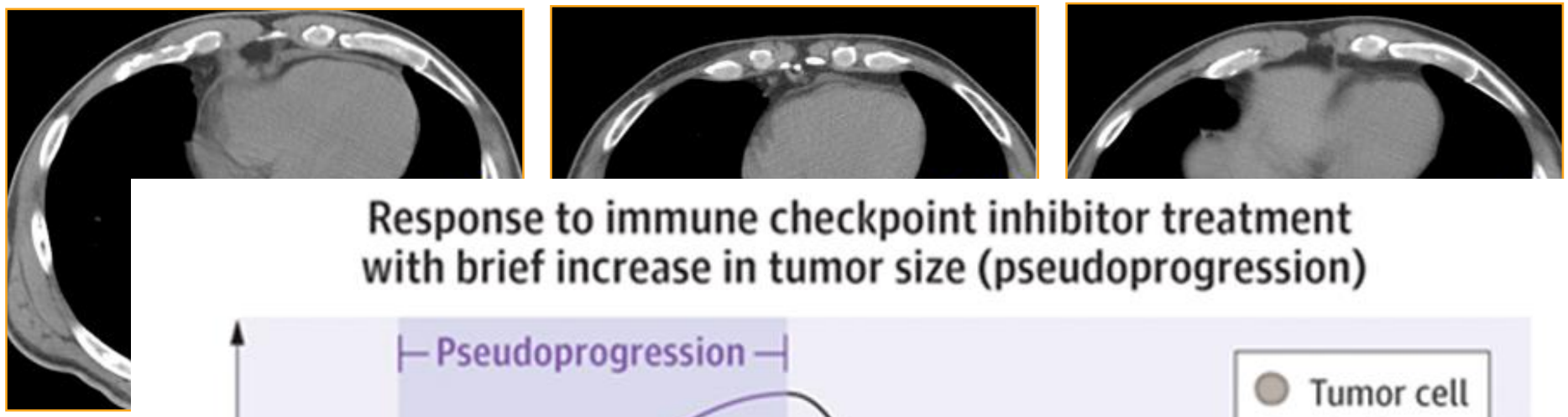
Wk 8 SD

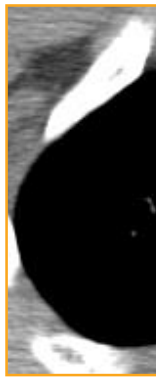
Wk 16 PR

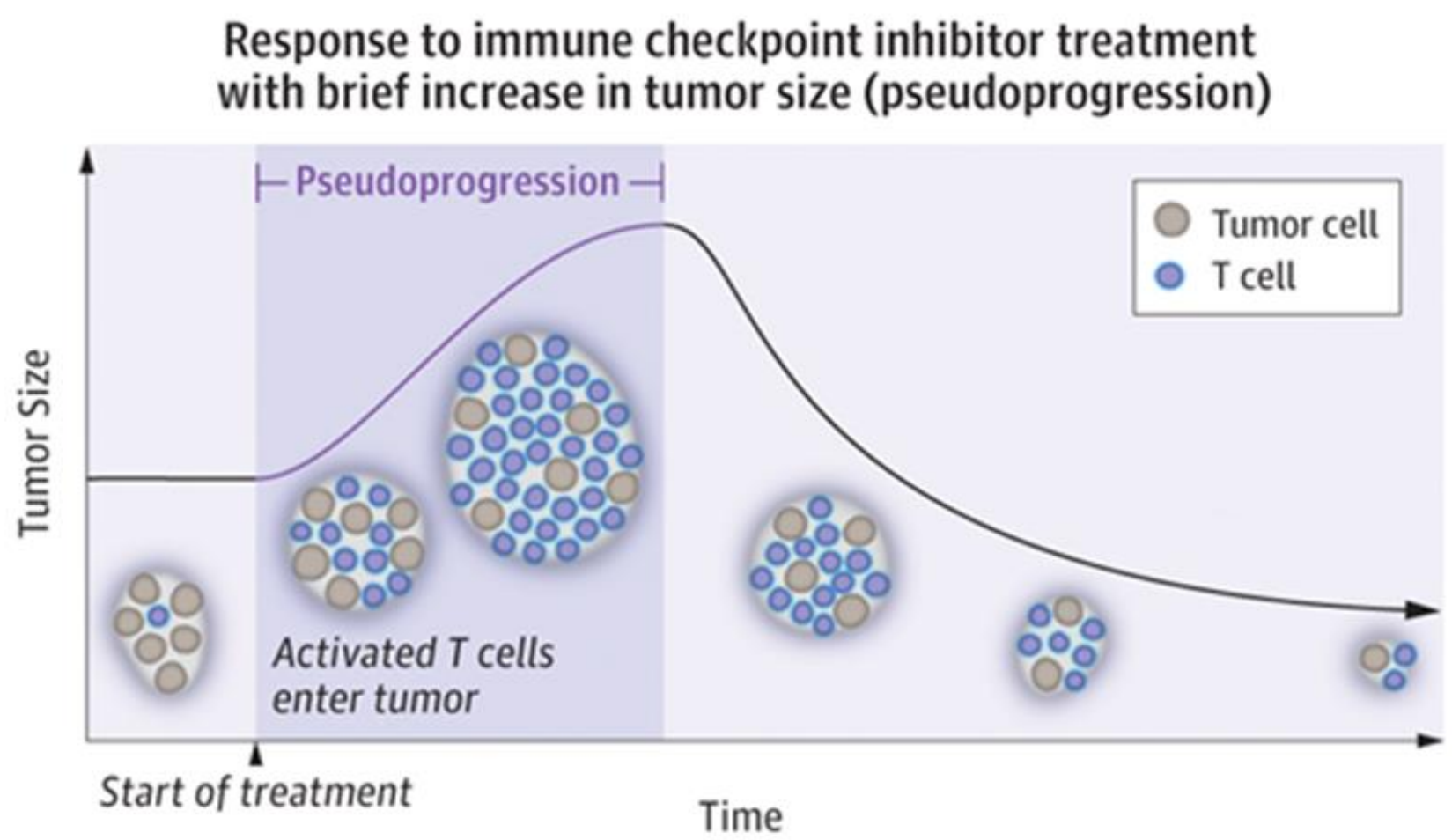
Images from: Tanguy Seiwert, MD

Patient Response *(central review)*

Baseline **Cycle 4 -28.3%** **Cycle 8 -56.1%**







Presented

Phase 3 CheckMate 141 Study Design

Nivolumab in R/M SCCHN After Platinum Therapy

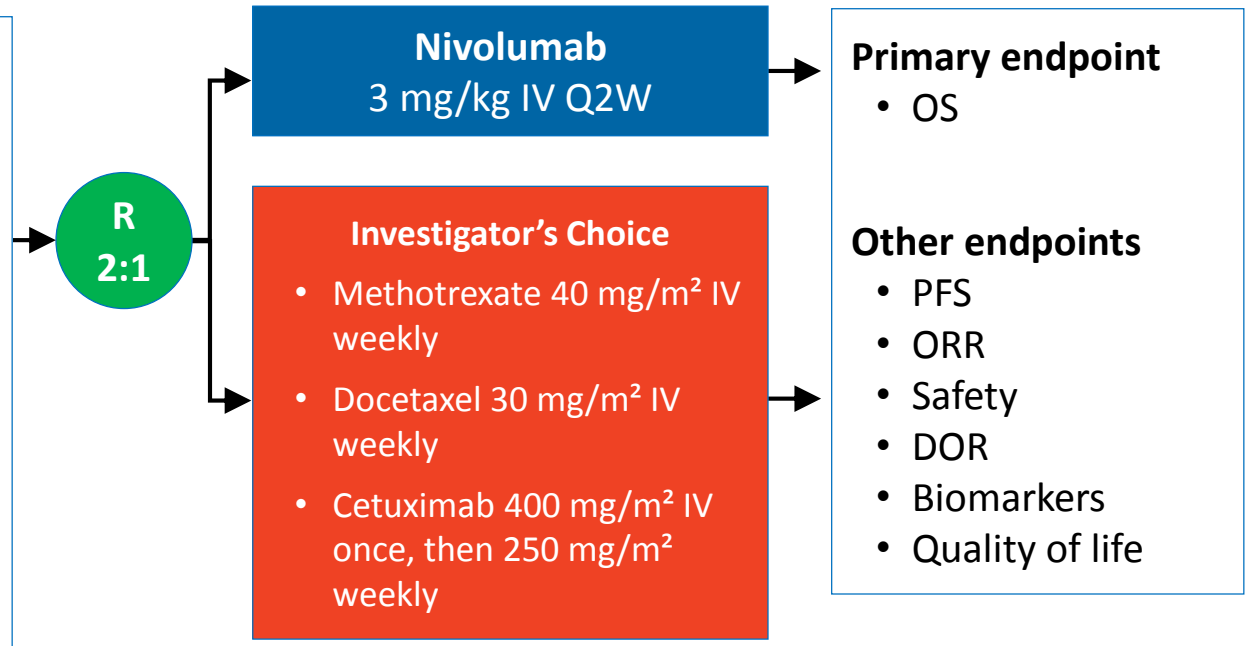
Randomized, global, phase 3 trial of the efficacy and safety of nivolumab vs investigator's choice in patients with R/M SCCHN

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.

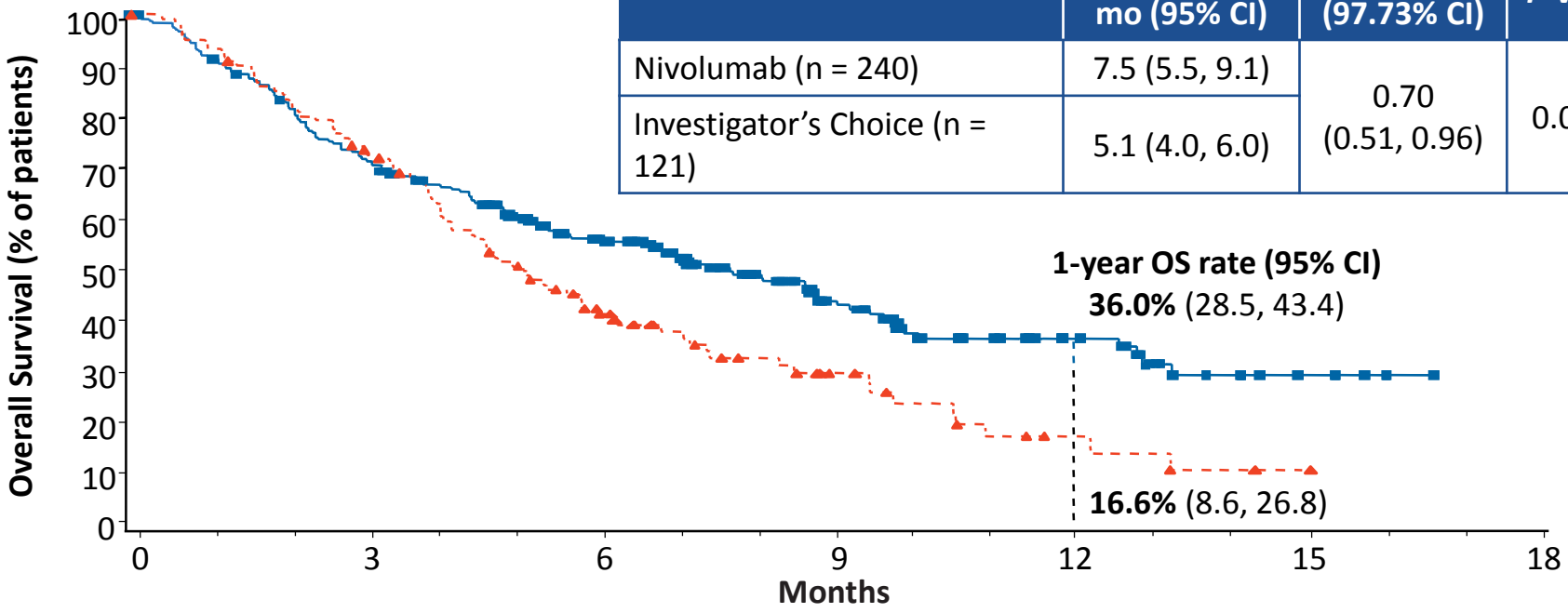
[a]Tissue required for testing

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

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FDA Approves Nivolumab for Head and Neck Cancer

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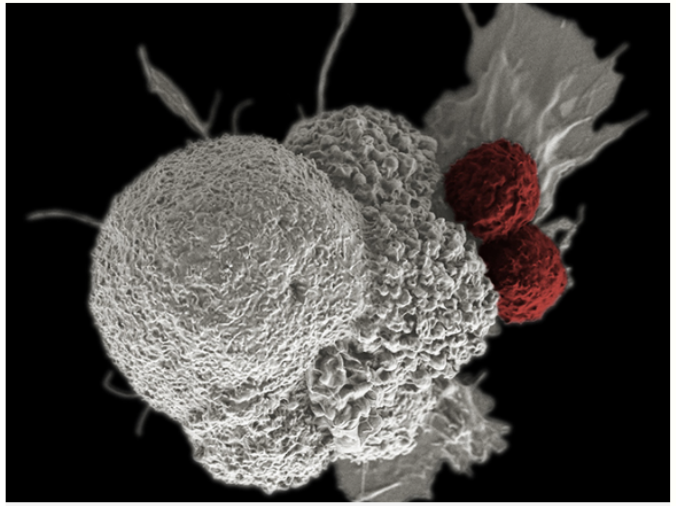
December 1, 2016, by NCI Staff

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

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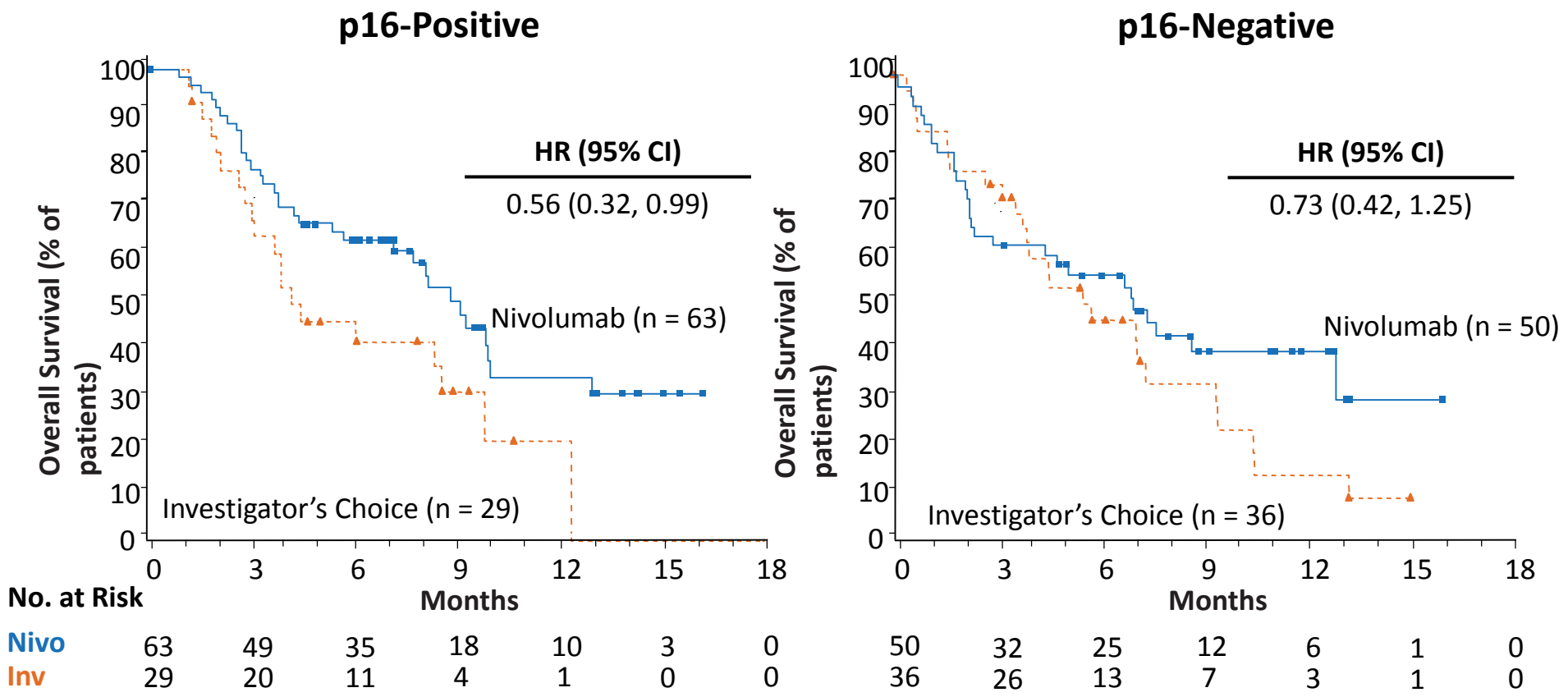
Overall Survival by p16 Status

Nivolumab in R/M SCCHN After Platinum Therapy



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KEYNOTE 40: *2nd Line PIII*

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

N=466

Key Eligibility Criteria

- Recurrent or metast
  cavity, orop
  lar

NEGATIVE

Methotrexate, or Docetaxel, or Cetuximab

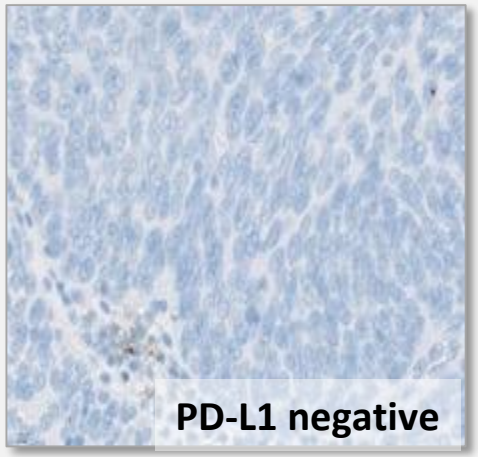
Start Date: November 2014
Estimated Study Completion Date: ~March 2017

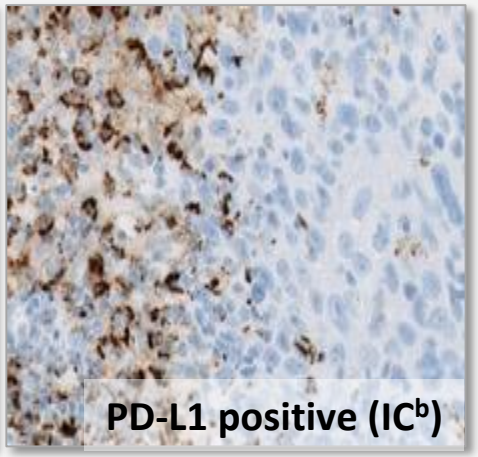
Primary Outcome Measure:

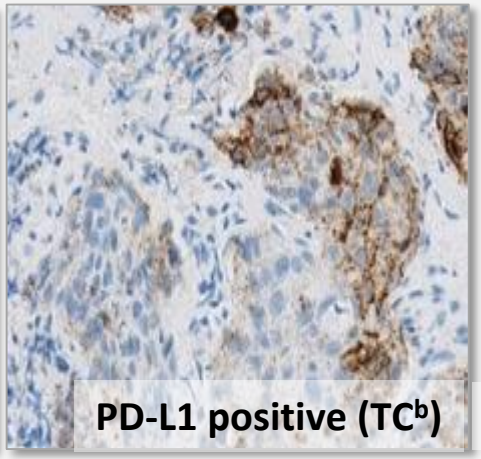
- OS and PFS* in all patients
- OS and PFS* in strong PD-L1+ patients

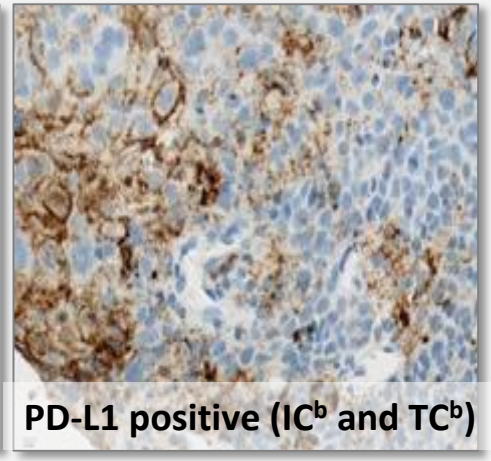
Inflamed tumor express PD-L1

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	
	≥5%	11.9	16.3	9.3	0.27
Immune Cells (IC)	≥1%	69.6	71.4	68.6	
	≥5%	32.6	38.8	29.1	0.26
Immune and/or Tumor Cells	≥1%	72.6	73.5	72.1	
	≥5%	40.0	49.0	34.9	0.14

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

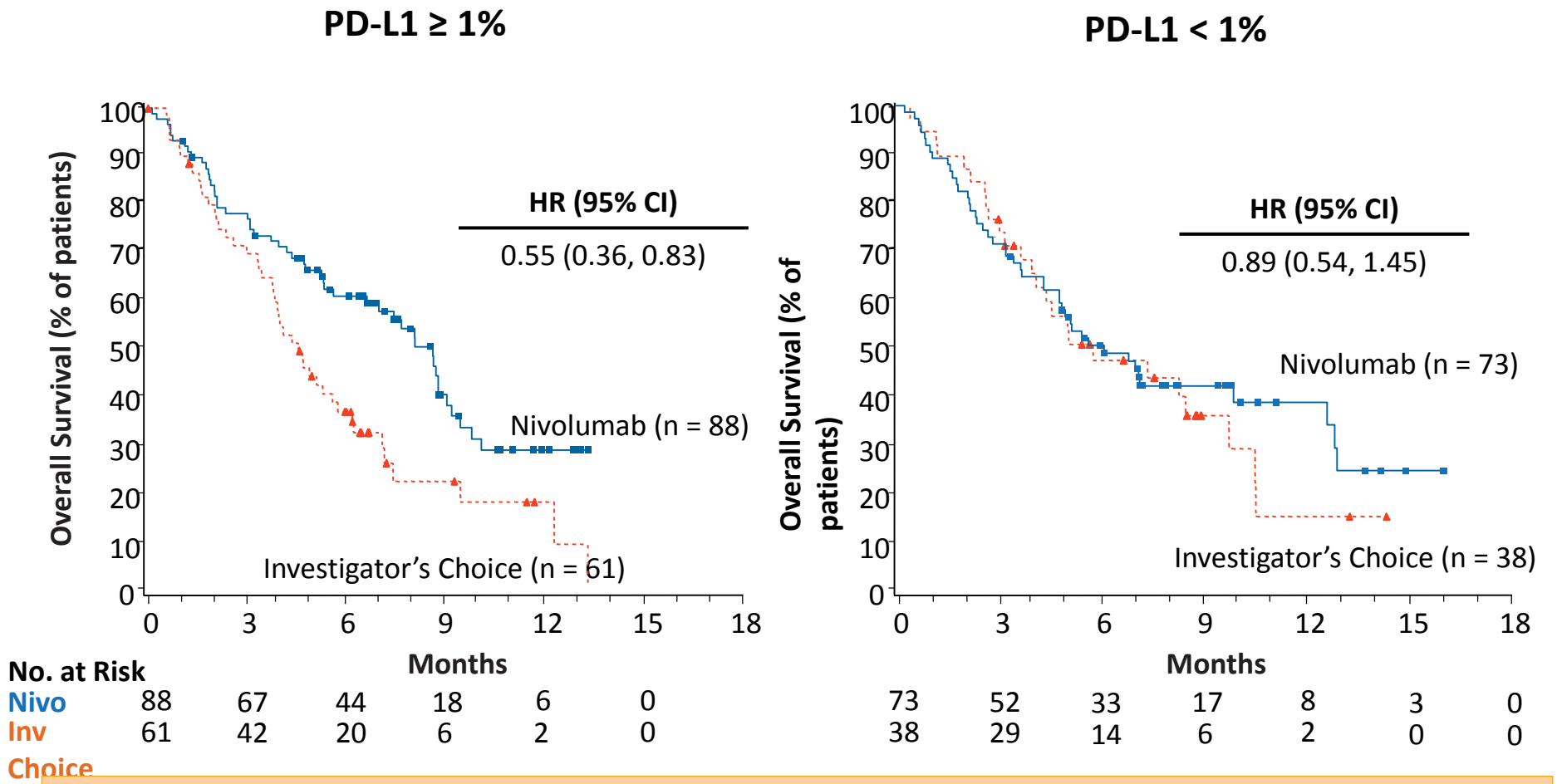
* Fisher's exact test

SP142 PD-L1 IHC
H. Koeppen, Y. Xiao, M. Kowanetz (Genentech)

[a] PD-L1 assessed by proprietary Genentech/Roche IHC assay
[b] IC – tumor infiltrating immune cells; TC – tumor cells

CM141: OS by PD-L1 Expression

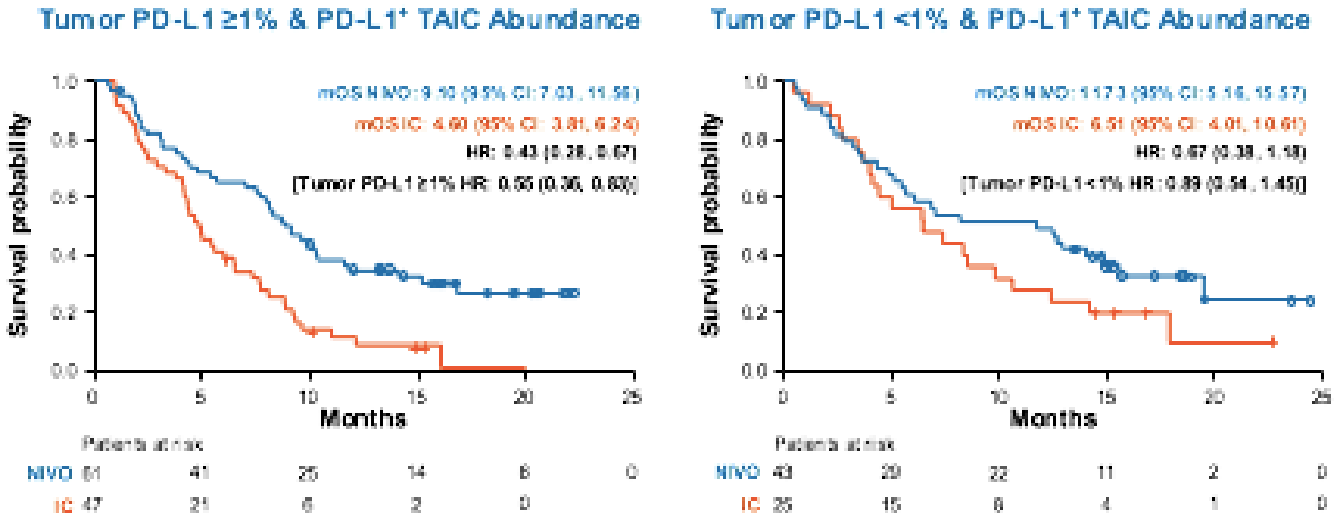
TPS 1% cutpoint



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

PD-L1 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



Ferris et al AACR 2017

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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

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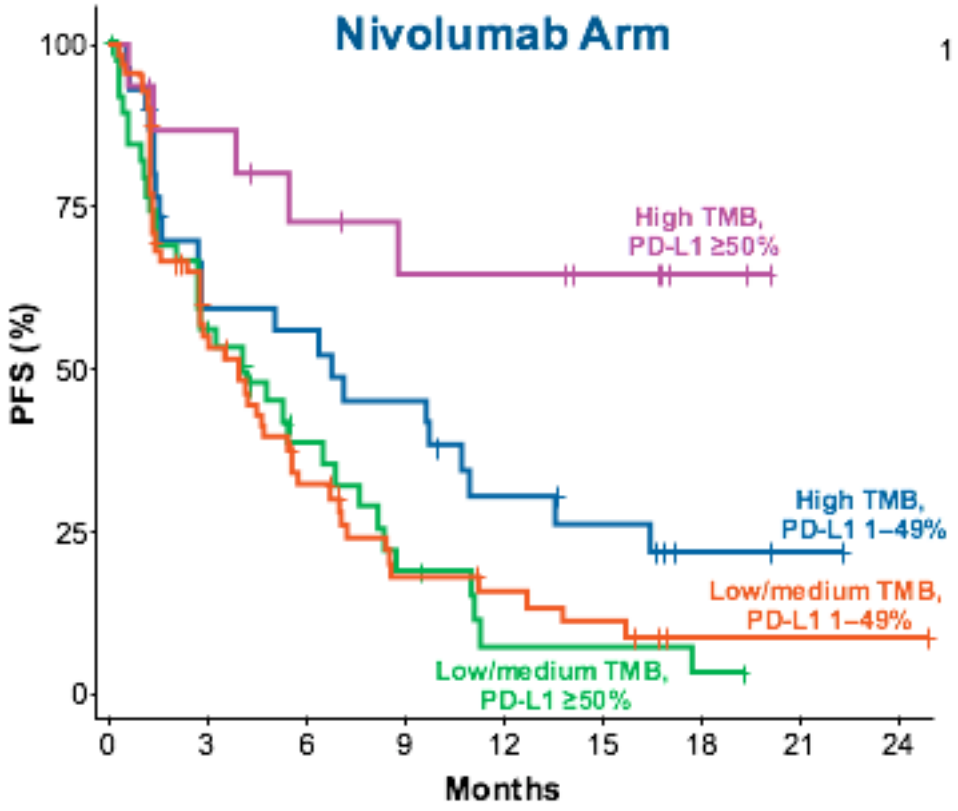
PD-L1 isn't Everything!



Peters et al AACR 2017

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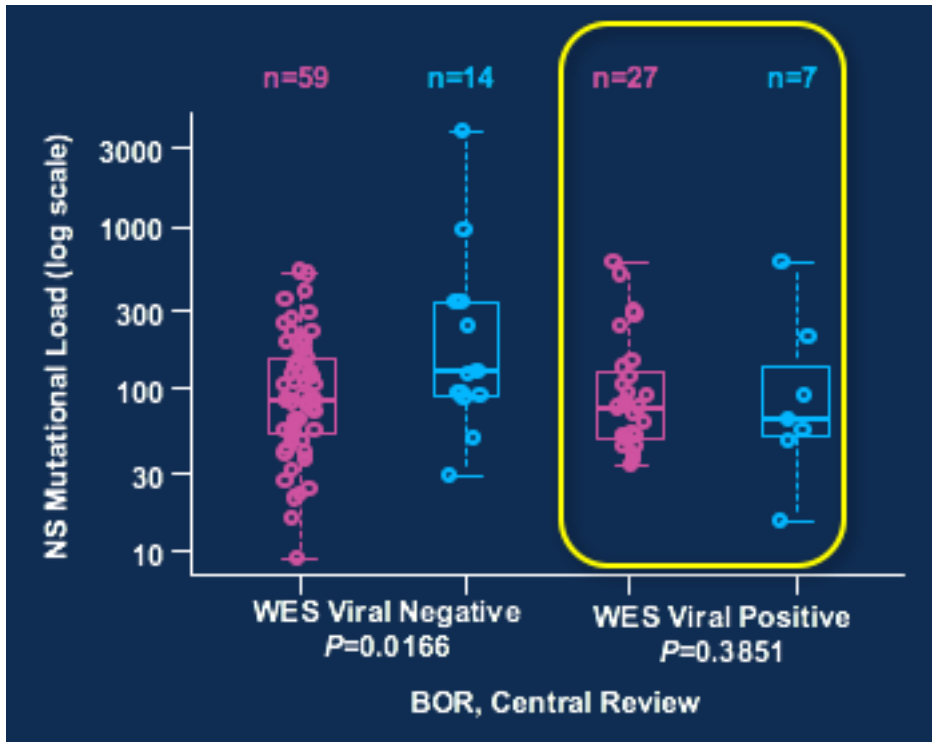
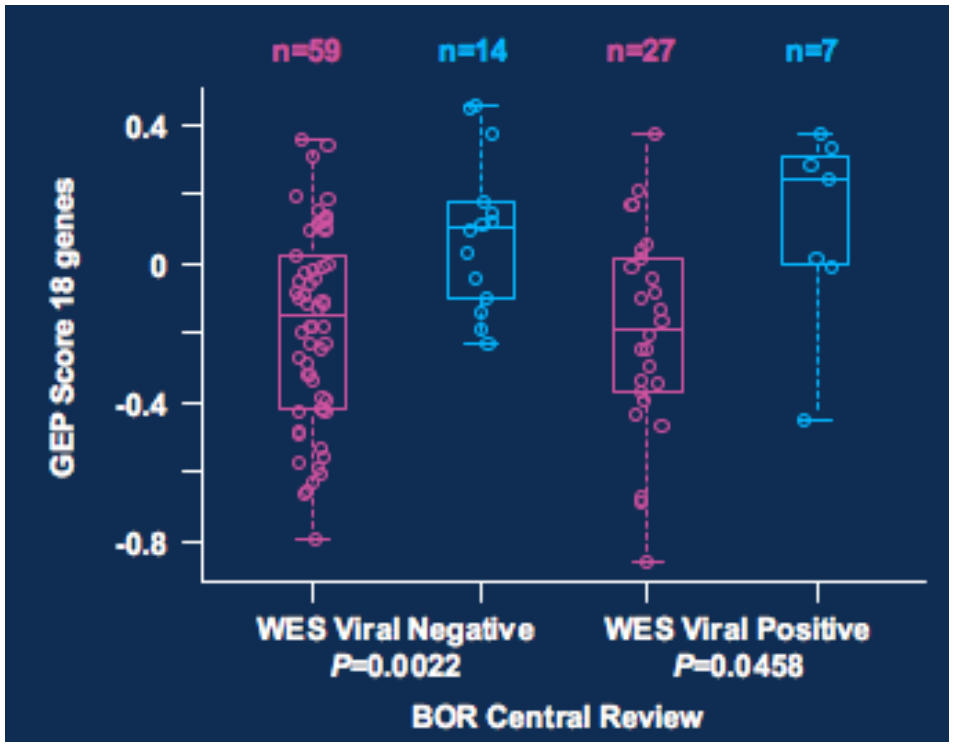
Various Biomarkers in HNC



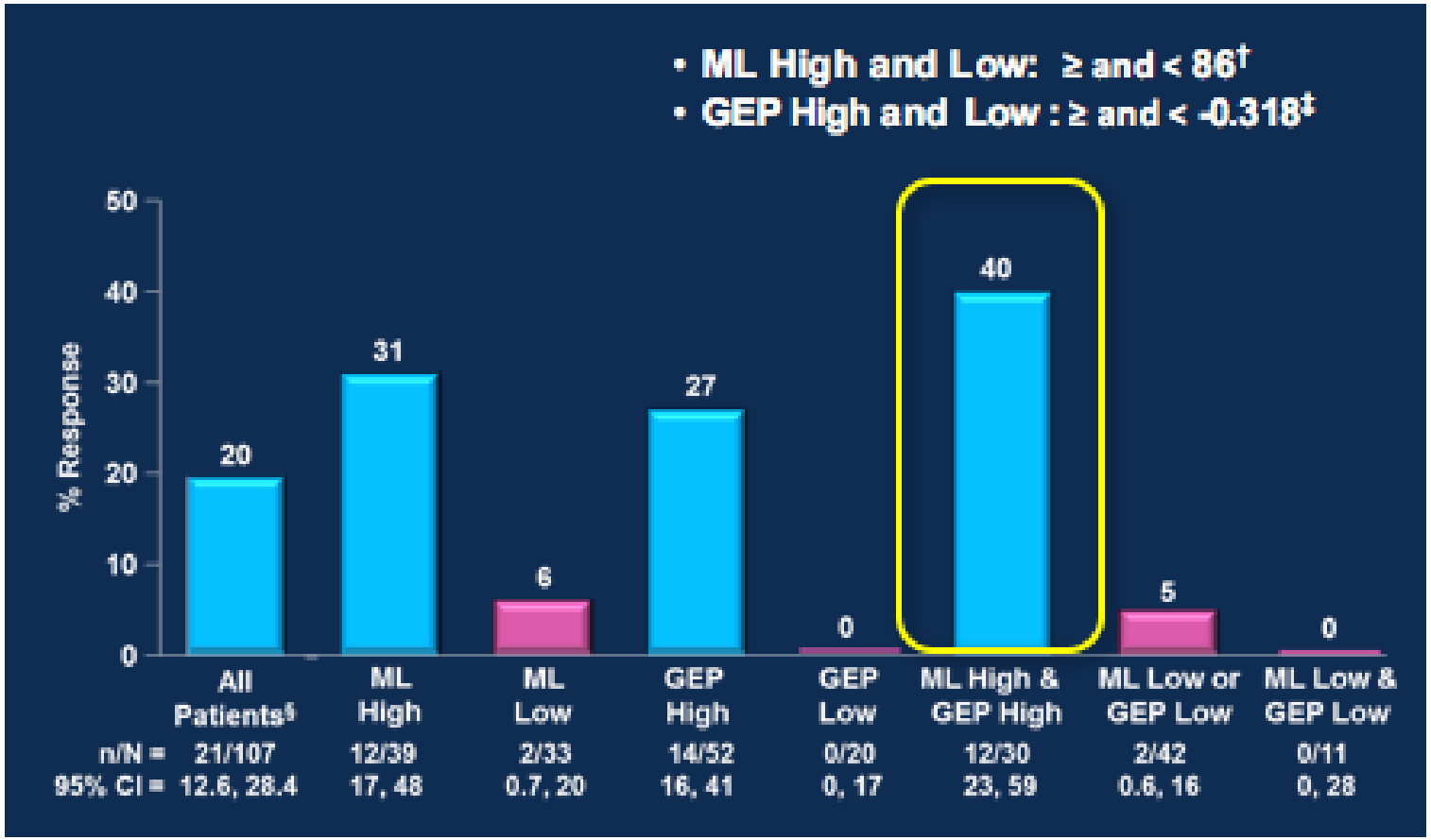


Haddad et al ASCO 2017

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

Combined GEP/ML



Haddad et al ASCO 2017

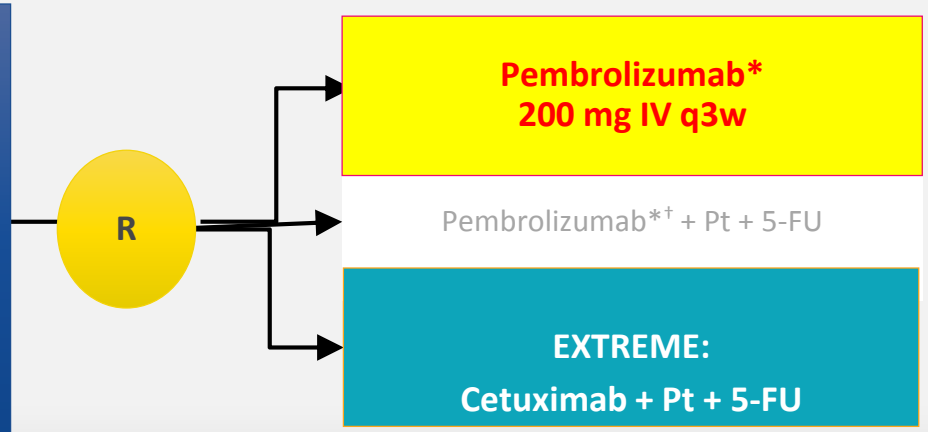
KEYNOTE 48: 1st Line - PIII

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

ADVANCES IN Cancer IMMUNOTHERAPY™

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.

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer