ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Head and Neck Cancers

Robert F. Taylor, MD

Aurora Health Care

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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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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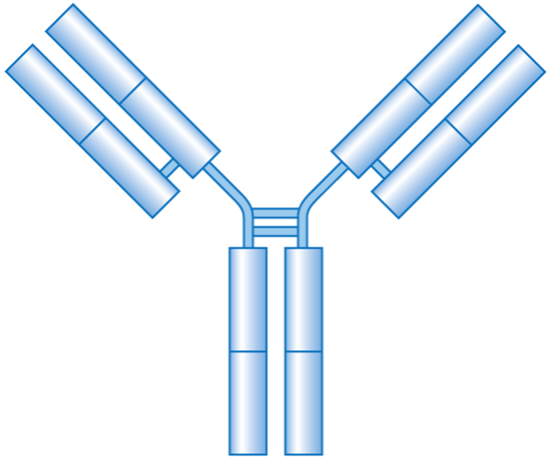
IO Agents approved and in development for HNC

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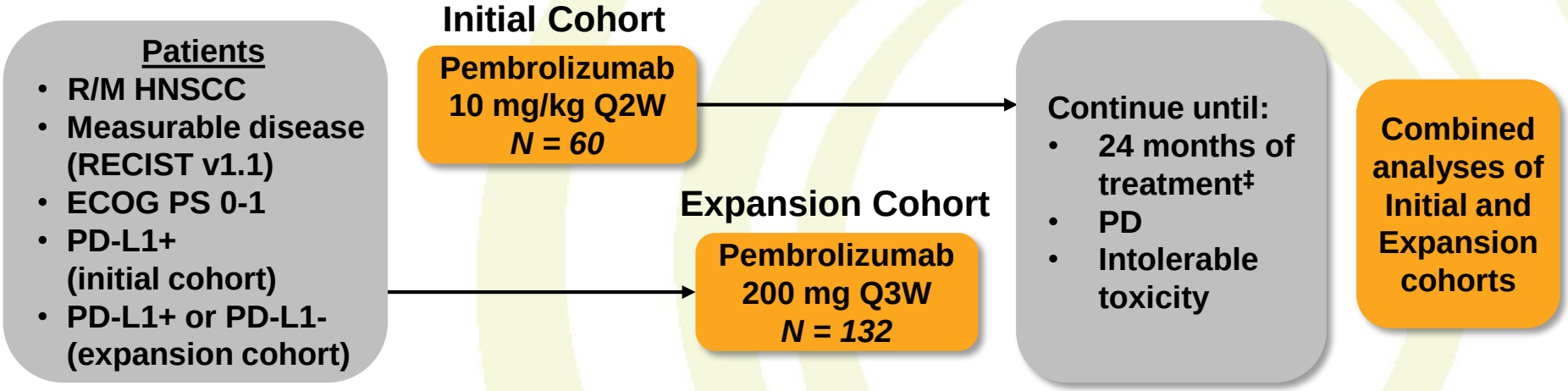
HNSCC Cohorts of Nonrandomized, Phase 1b, Multi-cohort KEYNOTE-012 Trial



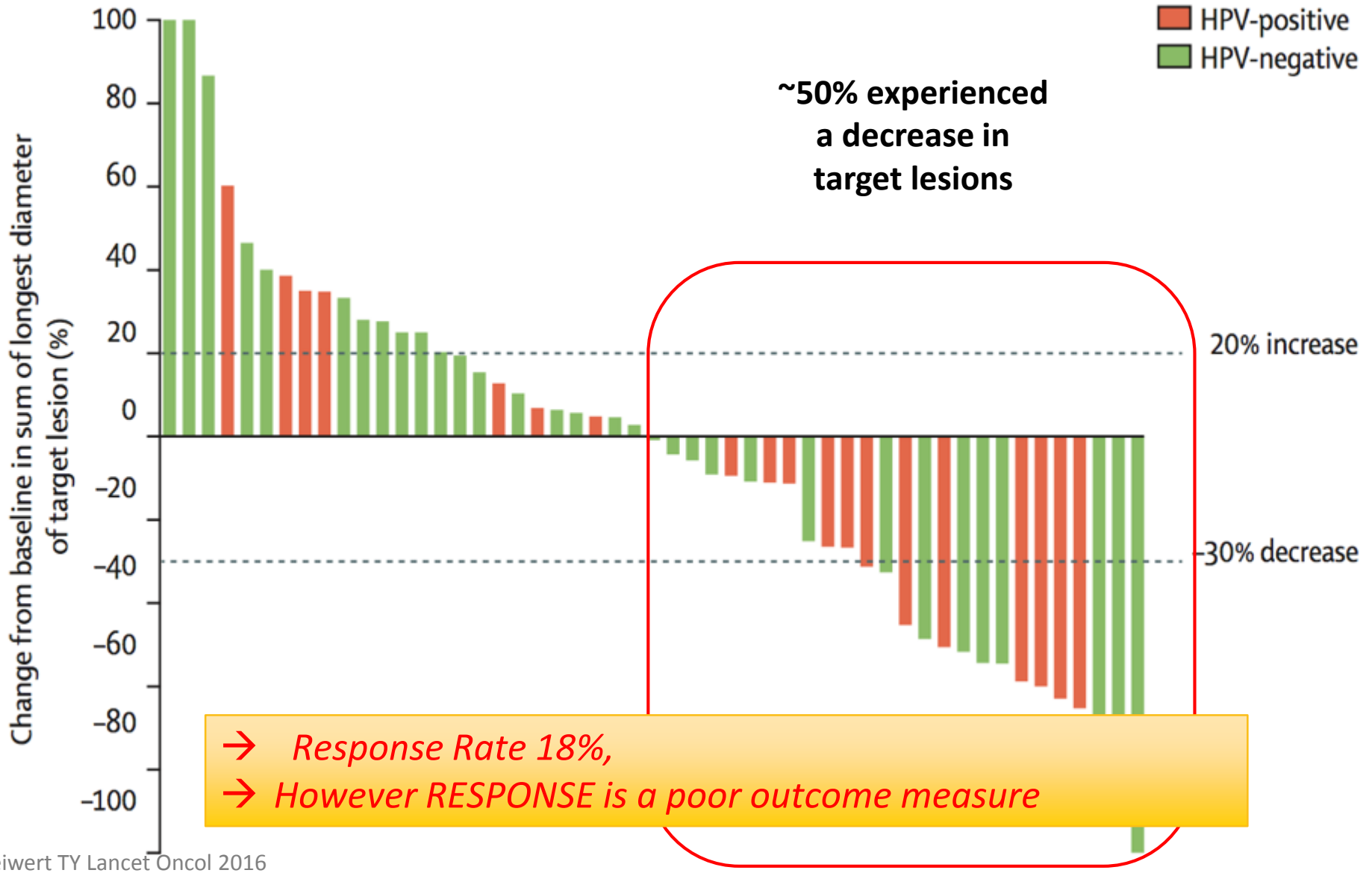
Response assessment: Every 8 weeks

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)

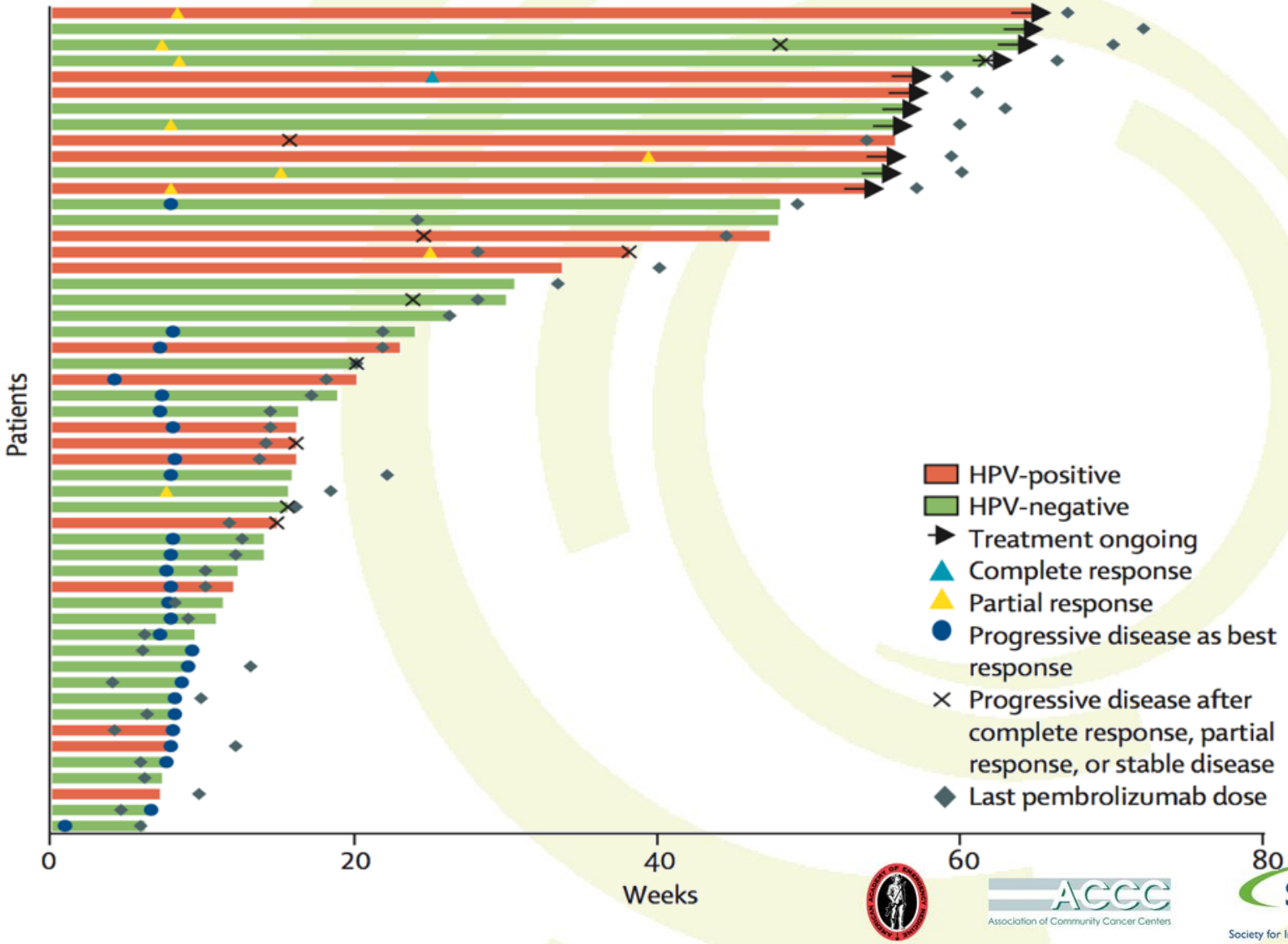


→ *Response Rate 18%,*

→ *However RESPONSE is a poor outcome measure*

Seiwert TY Lancet Oncol 2016

Durability (KeyNote 12)



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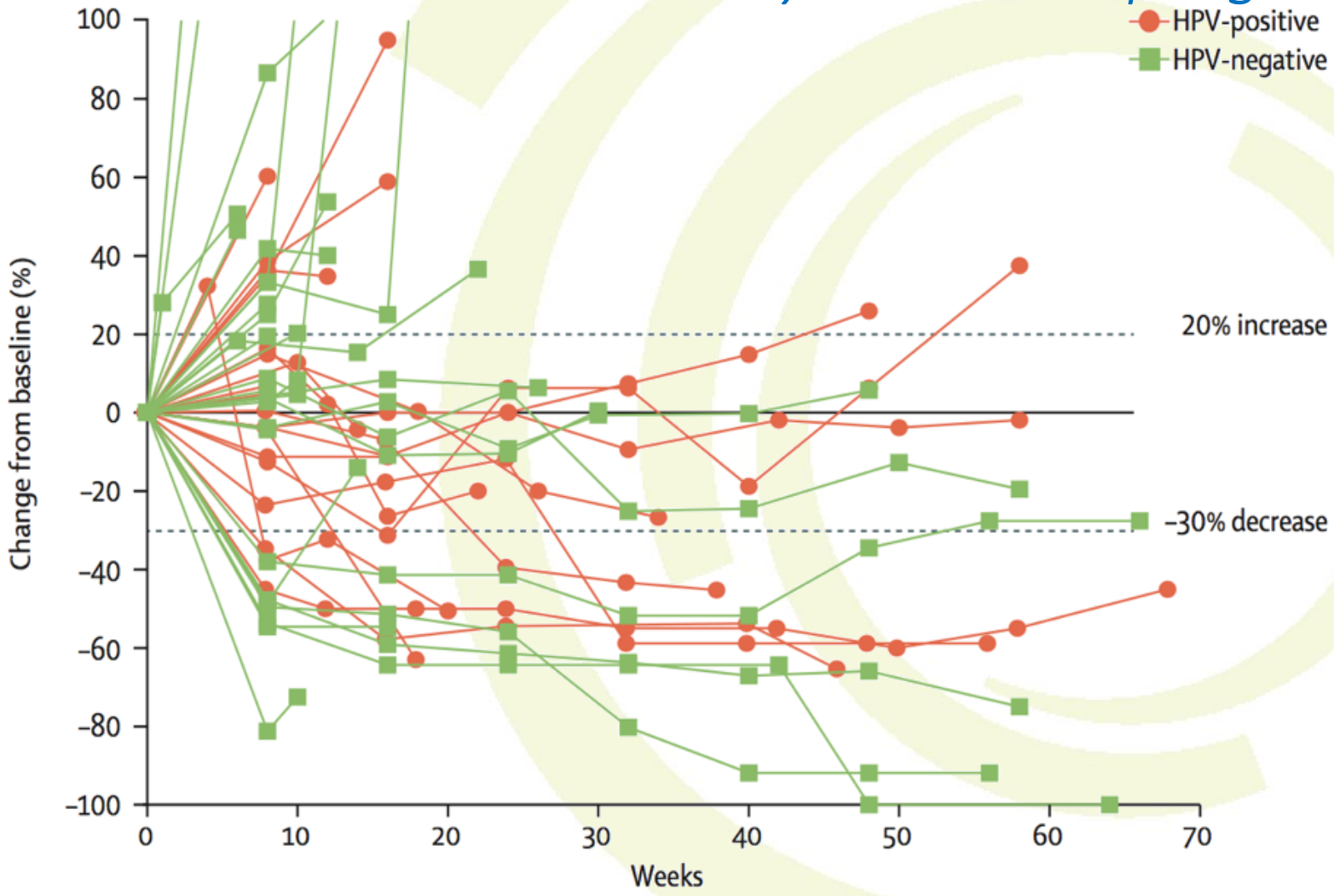
Most responses are early, *few delayed, BUT virtually no Pseudoprogression!*



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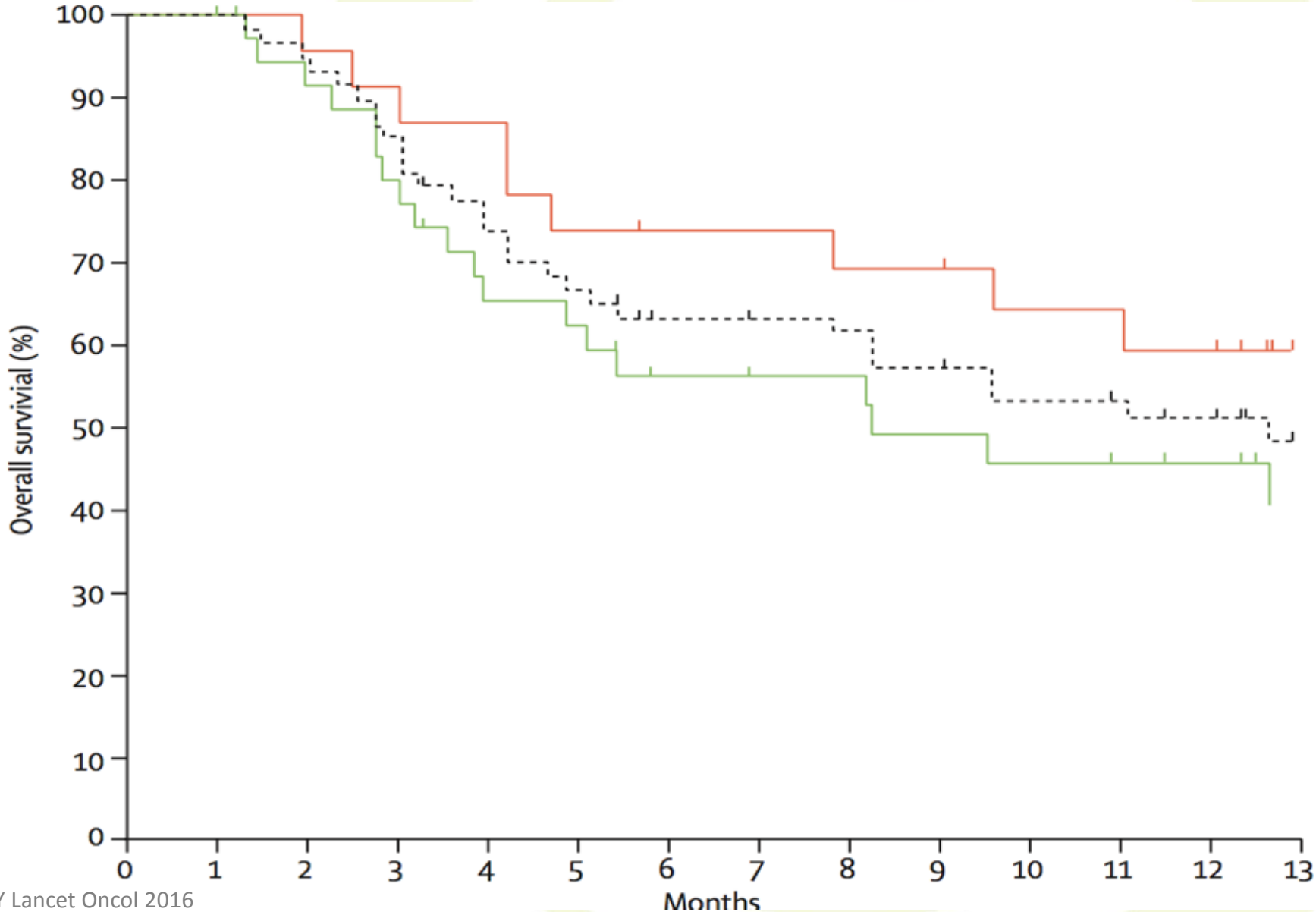
Major Impact on Overall Survival



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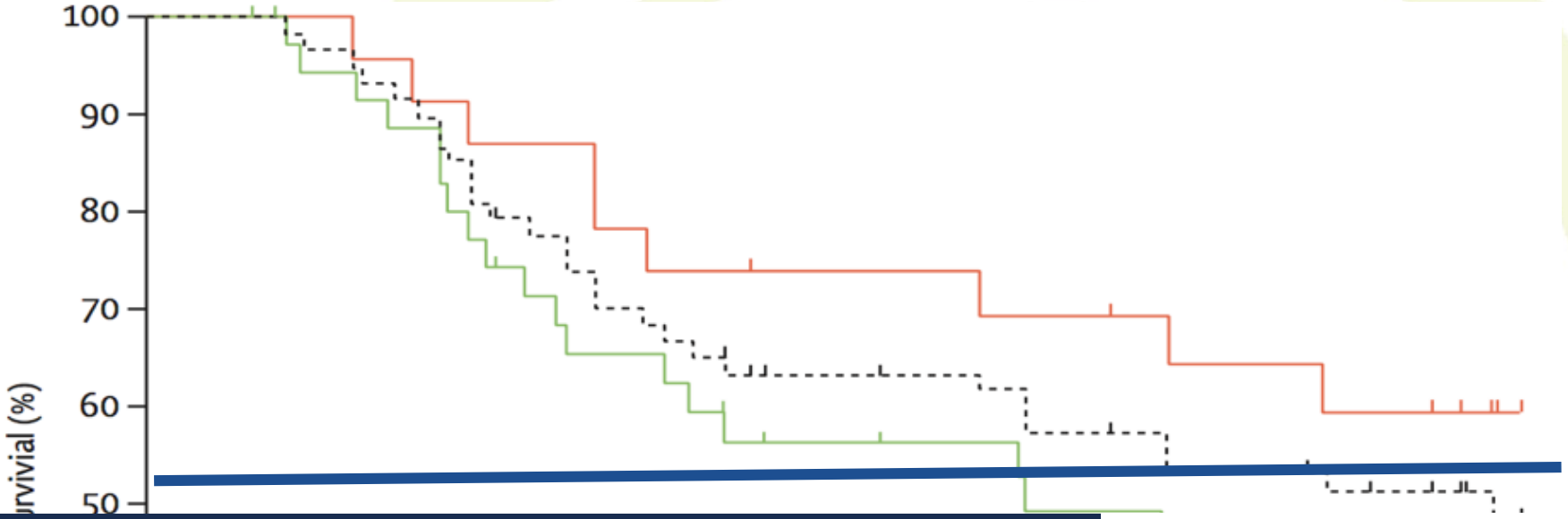
Major Impact on Overall Survival



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

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FDA Approves Pembrolizumab for Head and Neck Cancer

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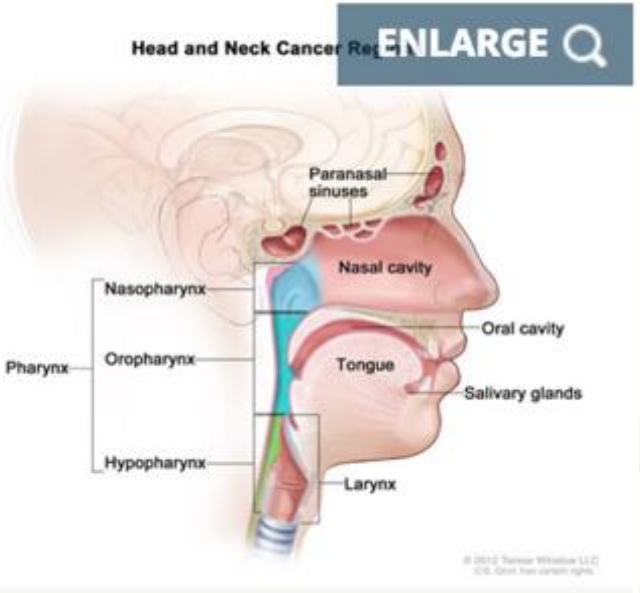
August 24, 2016 by NCI Staff

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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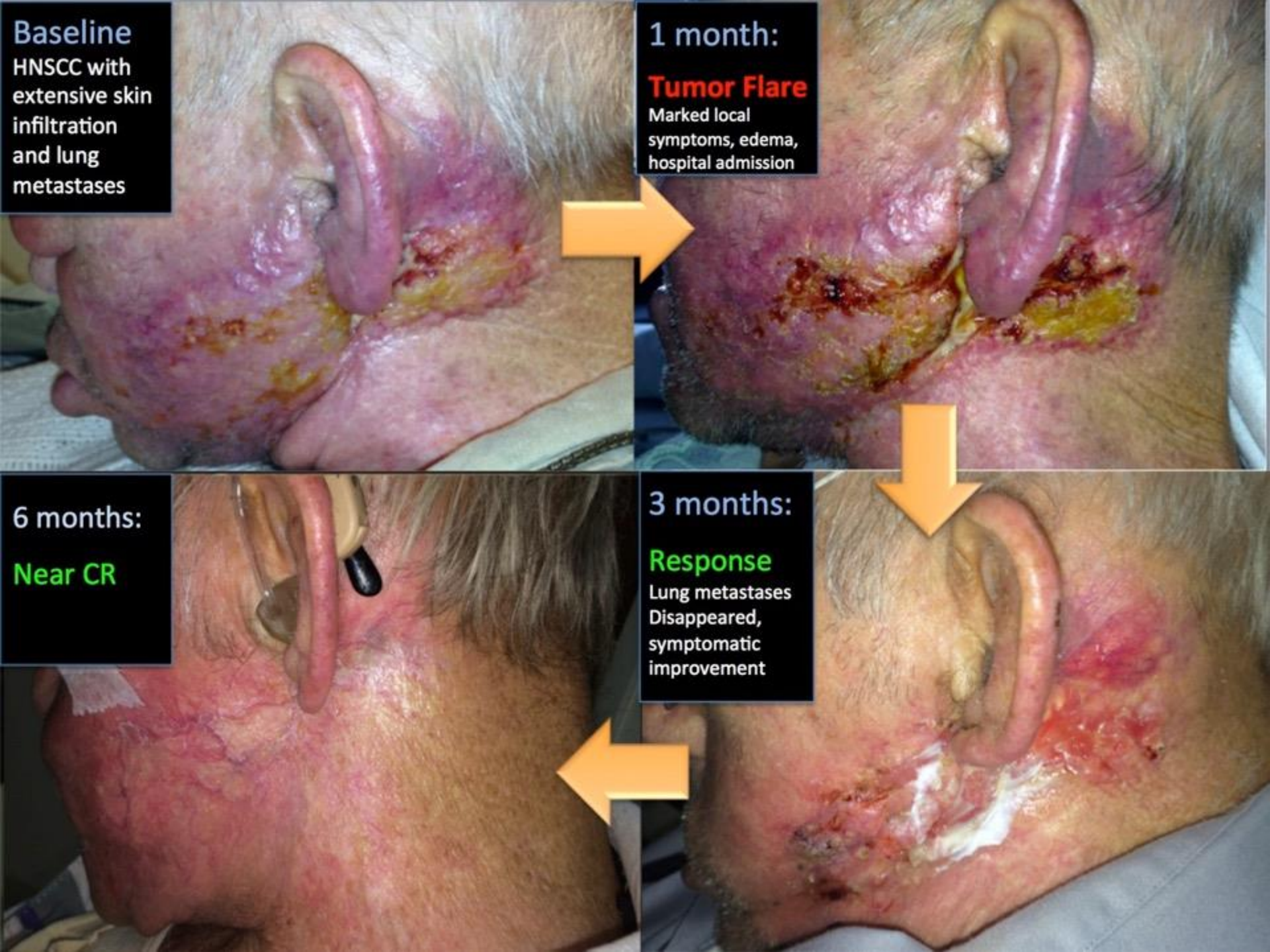
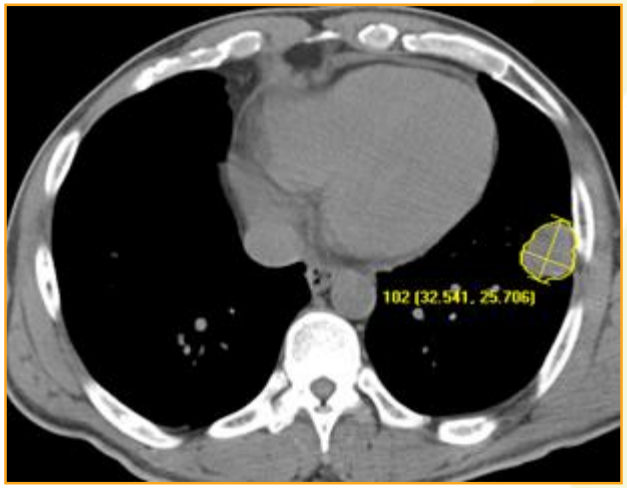
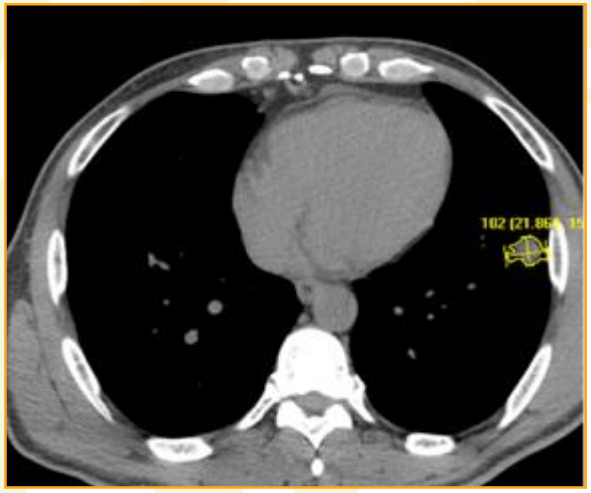
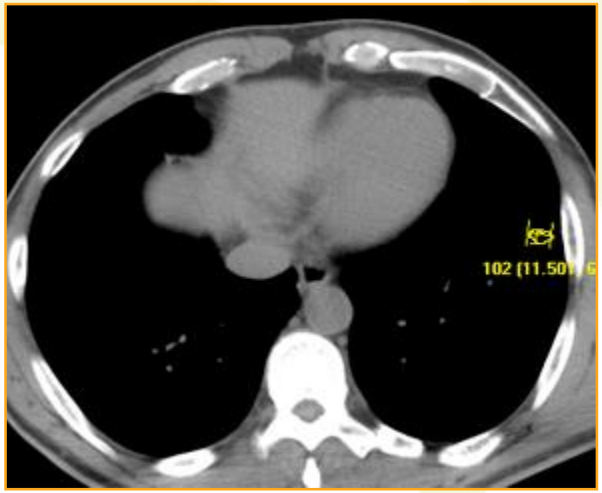

Baseline
HNSCC with extensive skin infiltration and lung metastases
1 month:
Tumor Flare
Marked local symptoms, edema, hospital admission
3 months:
Response
Lung metastases Disappeared, symptomatic improvement
6 months:
Near CR

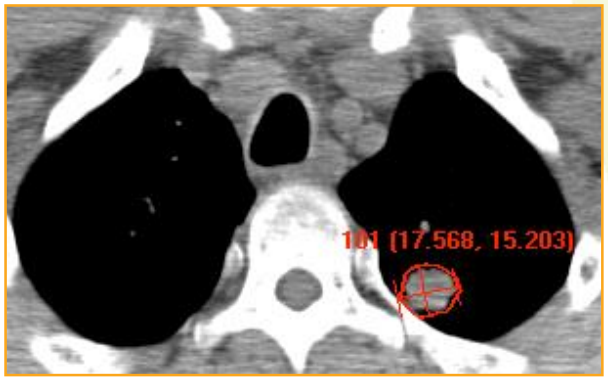
Patient Response *(central review)*

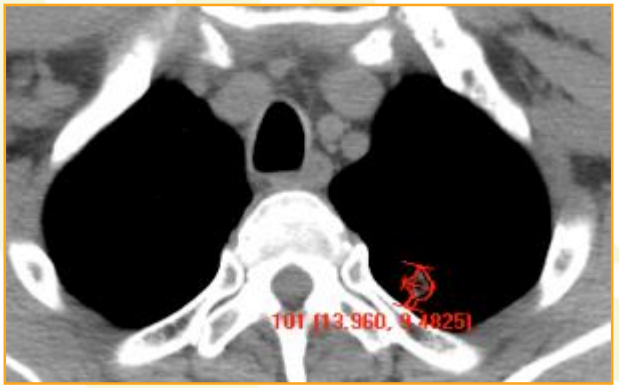
Baseline **Cycle 4 -28.3%** **Cycle 8 -56.1%**



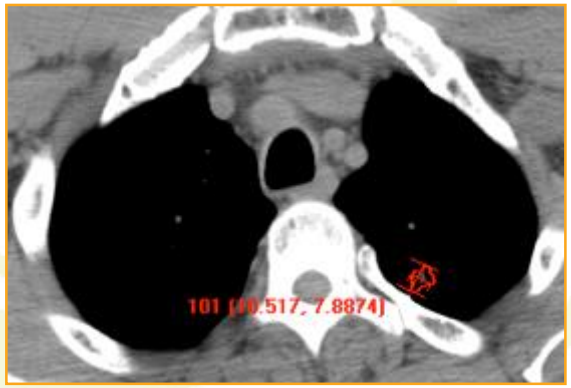








Wk 8 SD

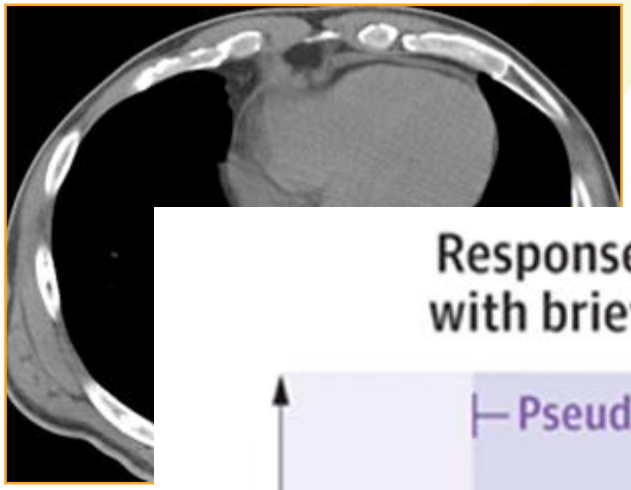


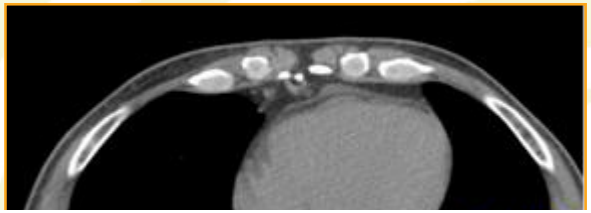
Wk 16 PR

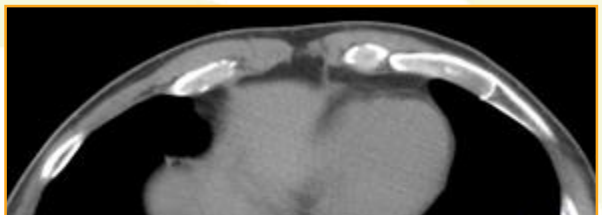
Images from: Tanguy Seiwert, MD

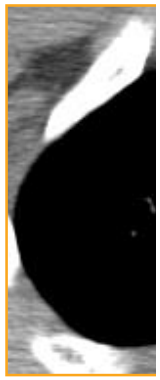
Patient Response *(central review)*

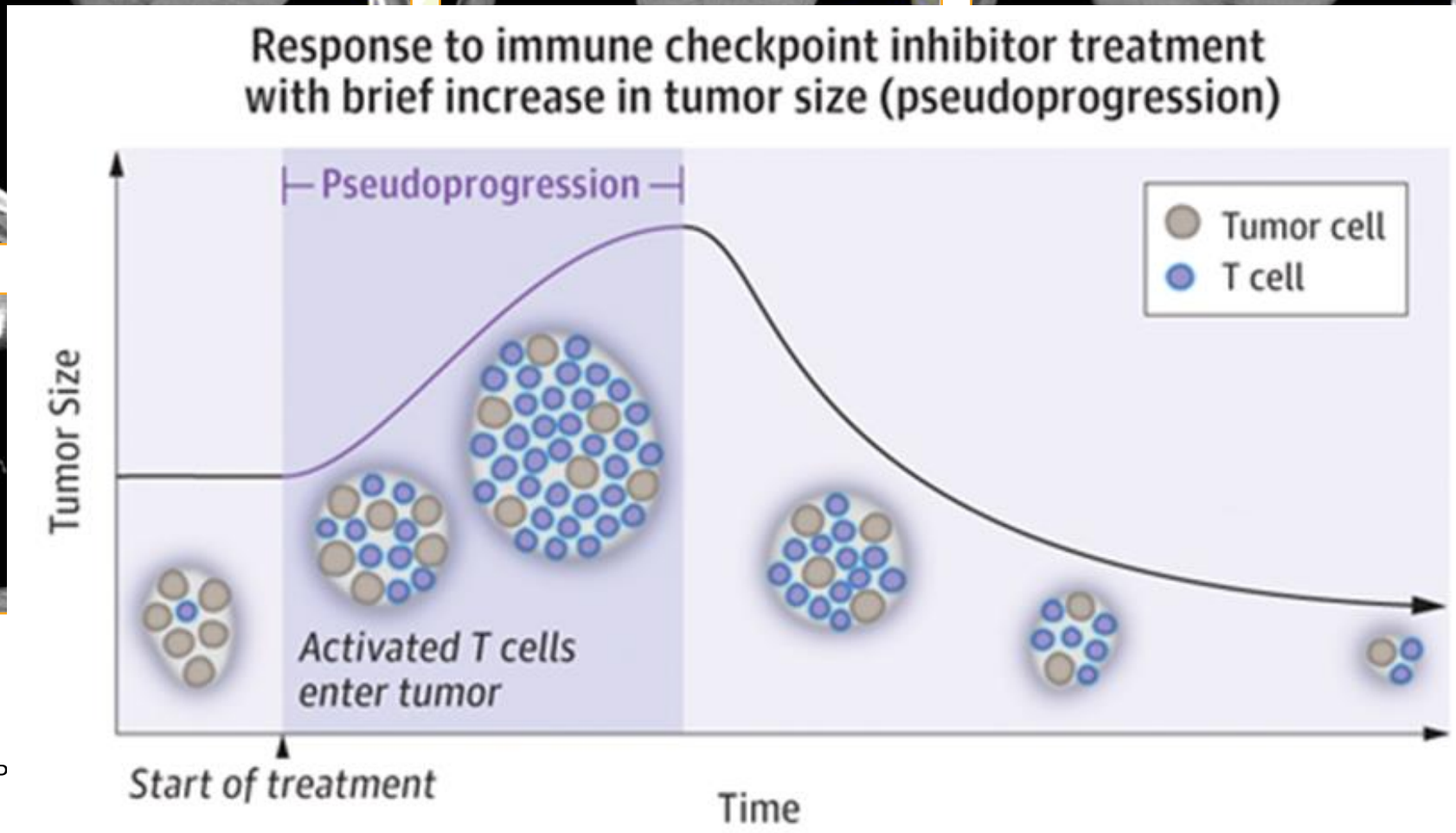
Baseline **Cycle 4 -28.3%** **Cycle 8 -56.1%**











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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

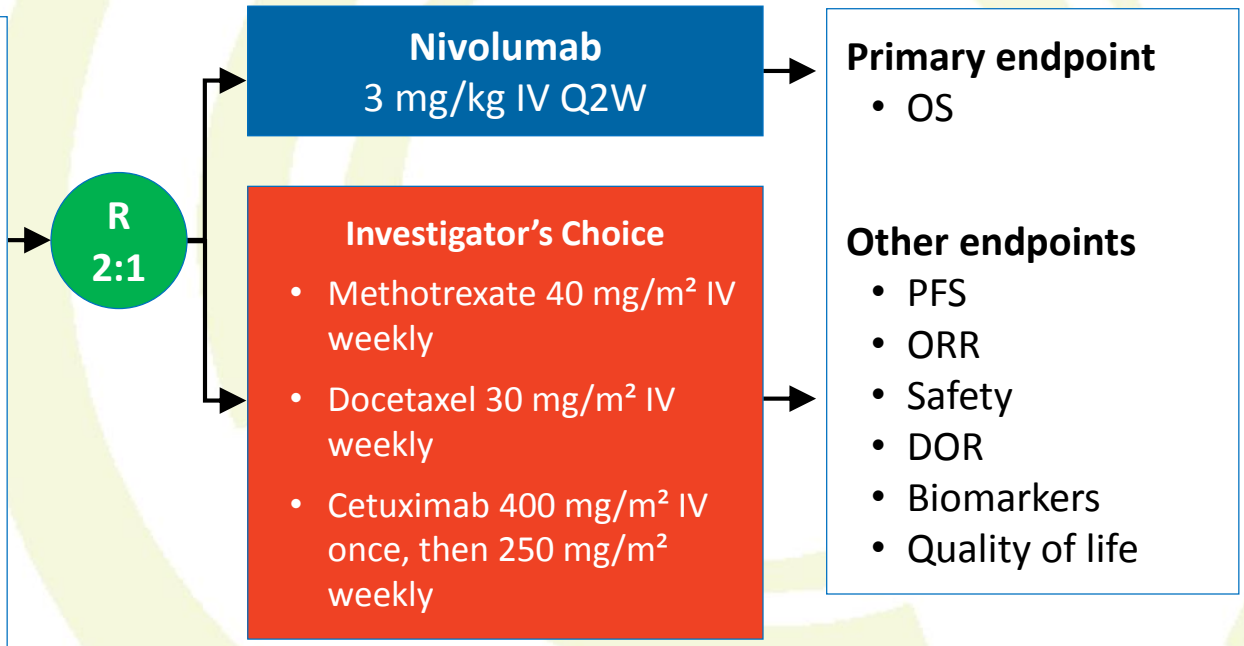
Key Eligibility Criteria

- 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.

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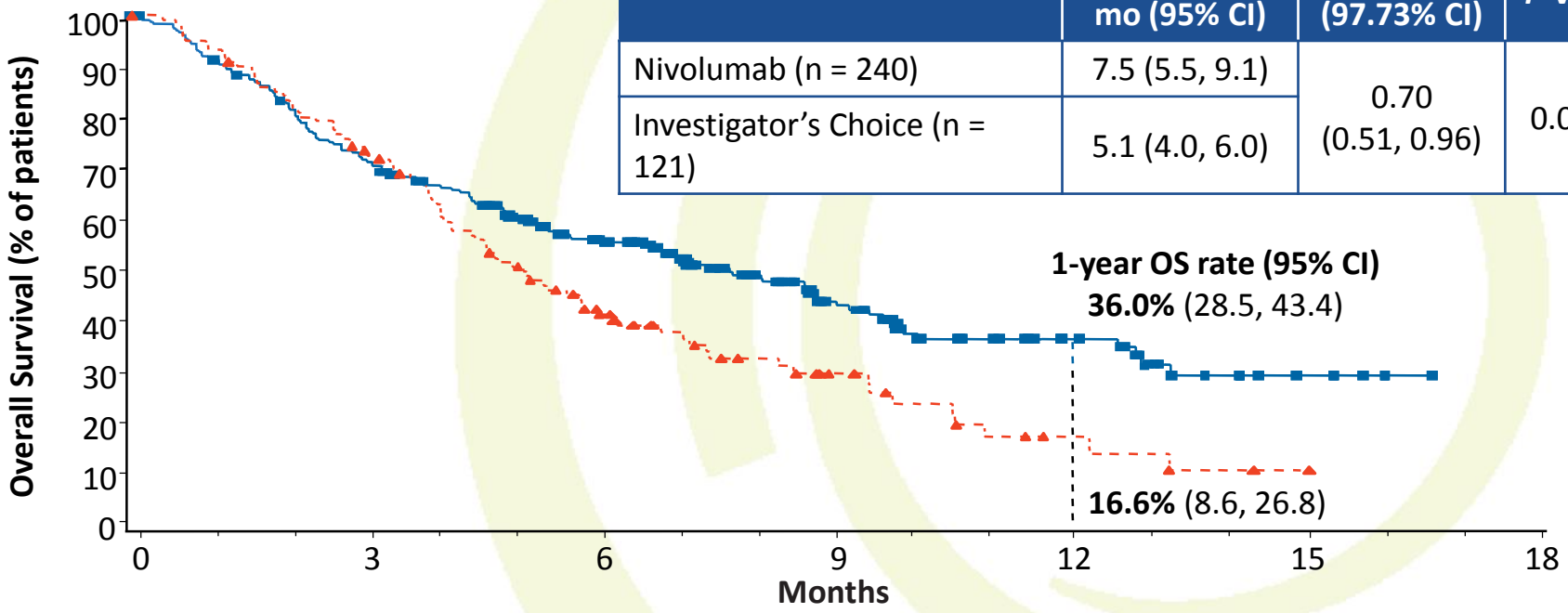
Overall Survival

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***

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FDA Approves Nivolumab for Head and Neck Cancer

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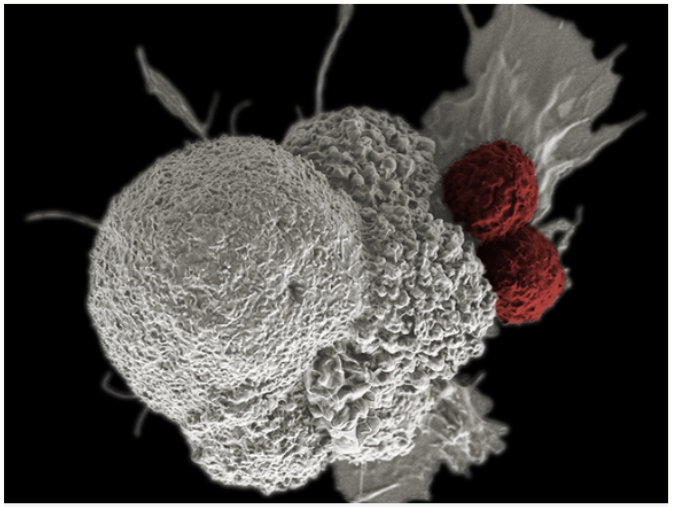
December 1, 2016, by NCI Staff

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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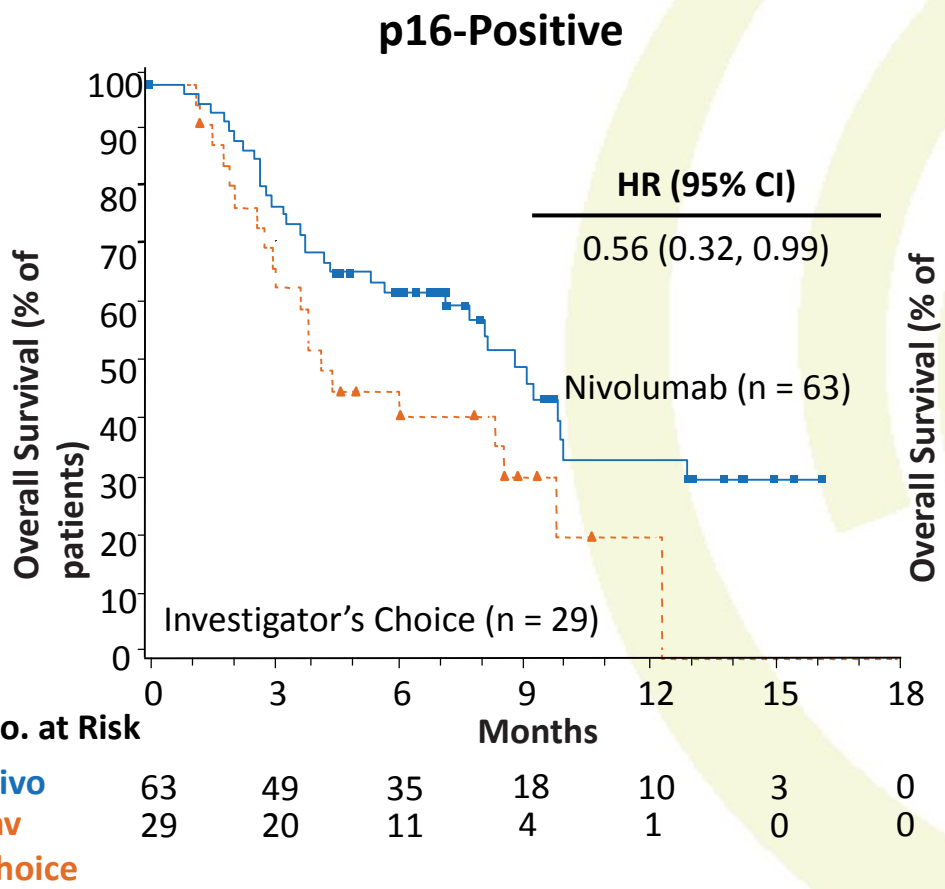
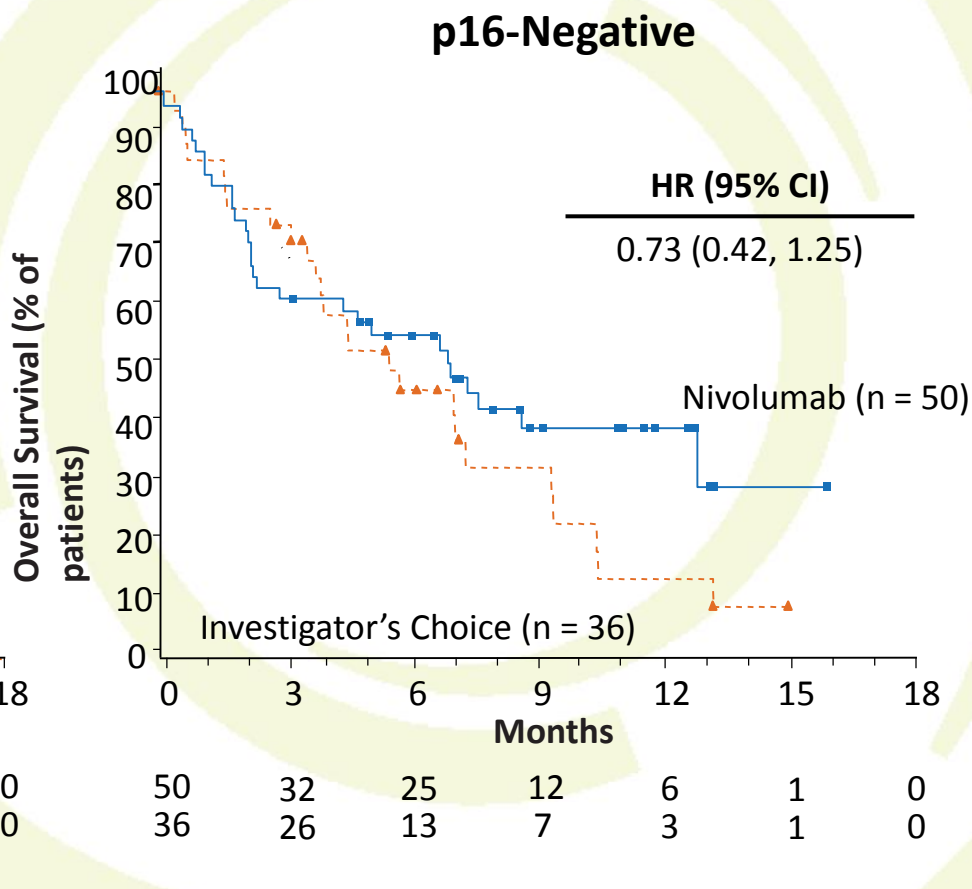
Overall Survival by p16 Status

Nivolumab in R/M SCCHN After Platinum Therapy





No. at Risk							
Nivo	63	49	35	18	10	3	0
Inv	29	20	11	4	1	0	0
Choice							

	50	32	25	12	6	1	0
	36	26	13	7	3	1	0

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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

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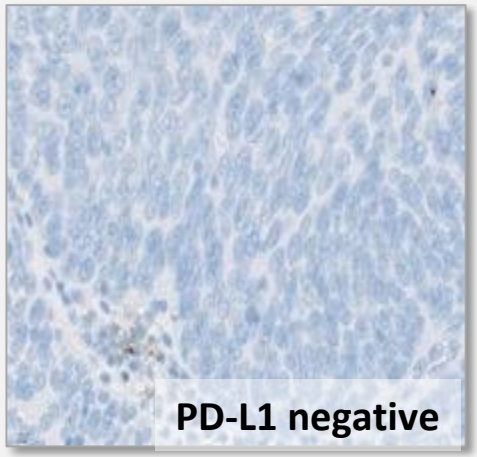
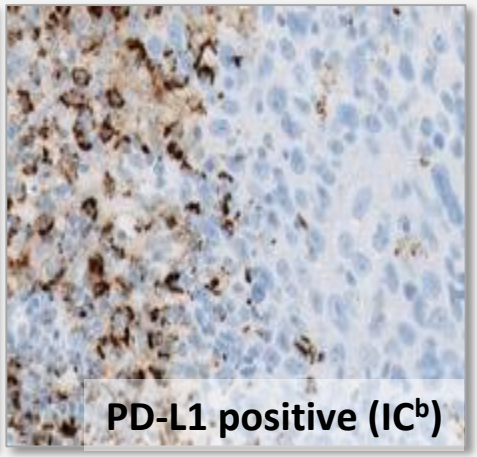
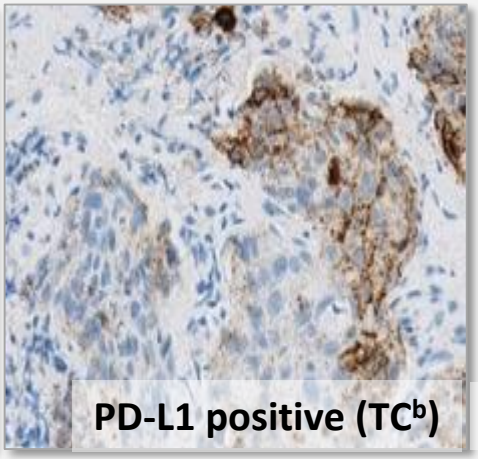
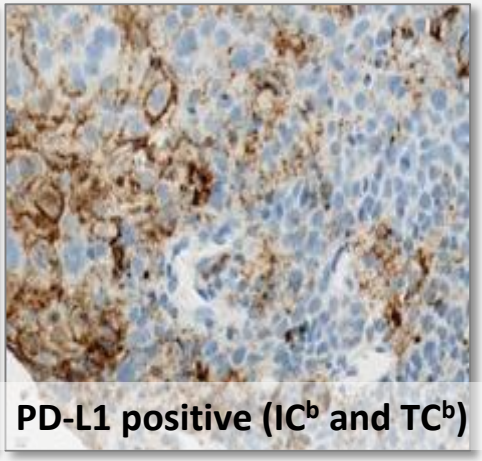
Inflamed tumor express PD-L1

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.

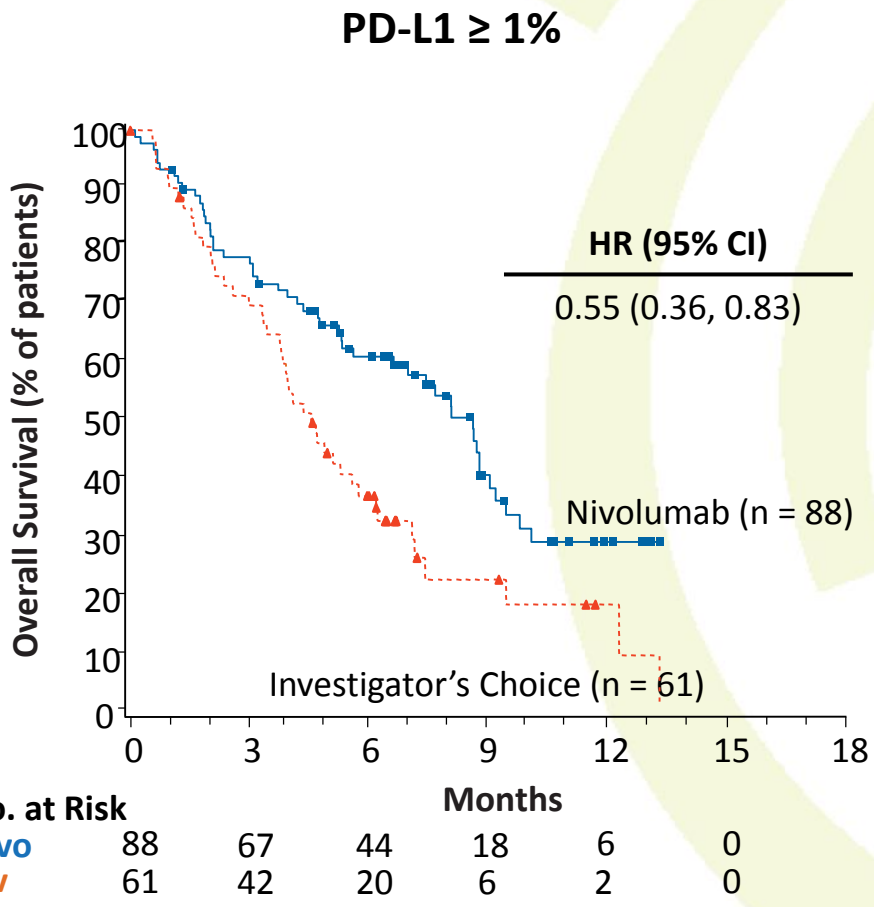
* Fisher's exact test

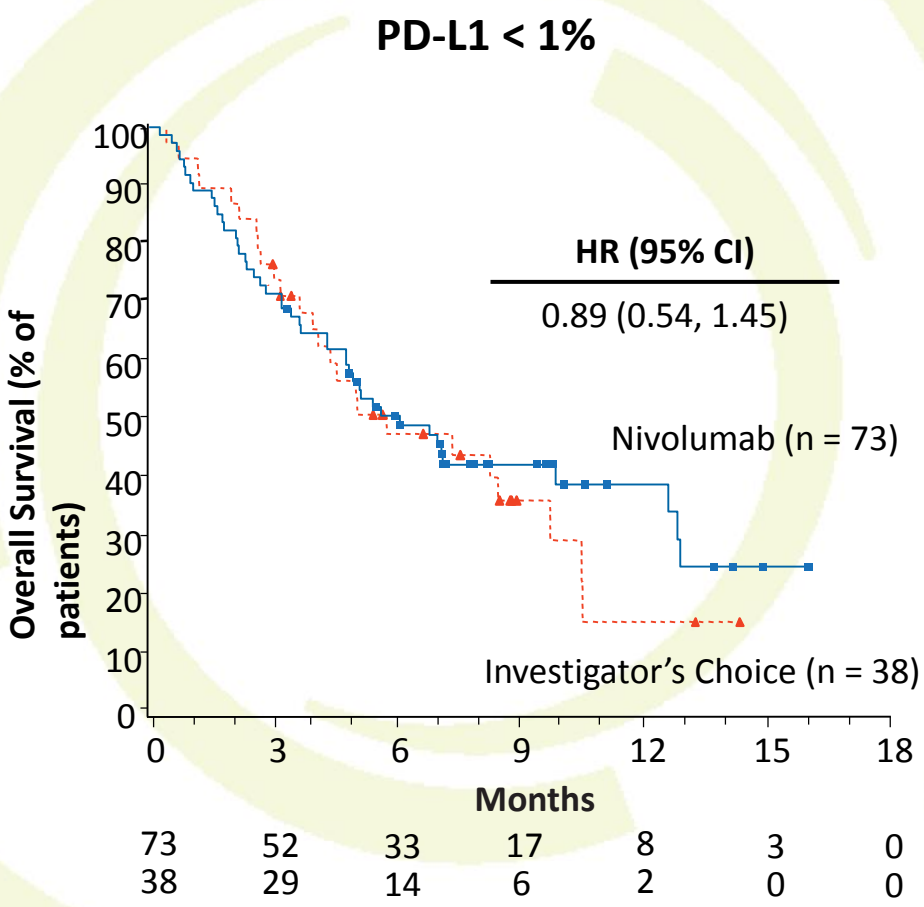
[a] PD-L1 assessed by proprietary Genentech/Roche IHC assay

[b] IC – tumor infiltrating immune cells; TC – tumor cells

CM141: OS by PD-L1 Expression

TPS 1% cutpoint



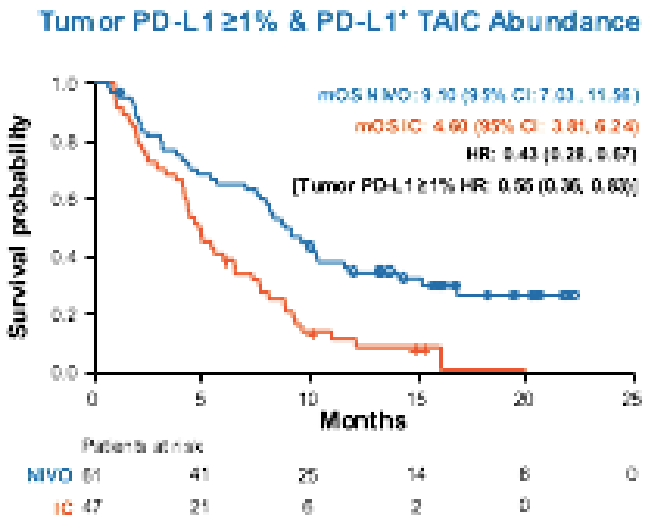


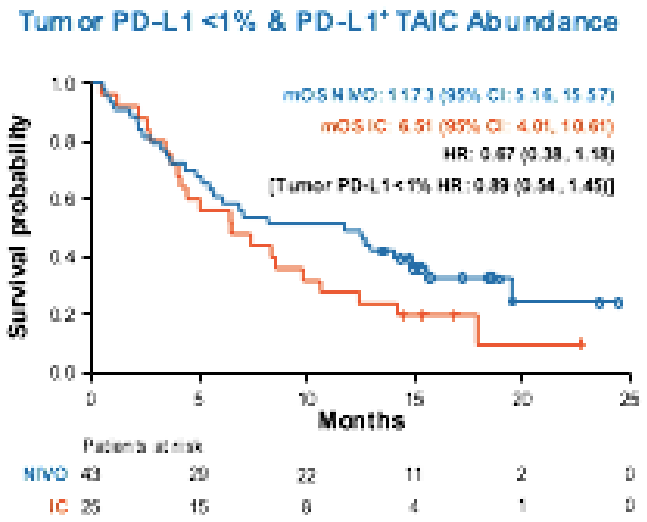
Similar data with *Pembrolizumab and Durvalumab*,

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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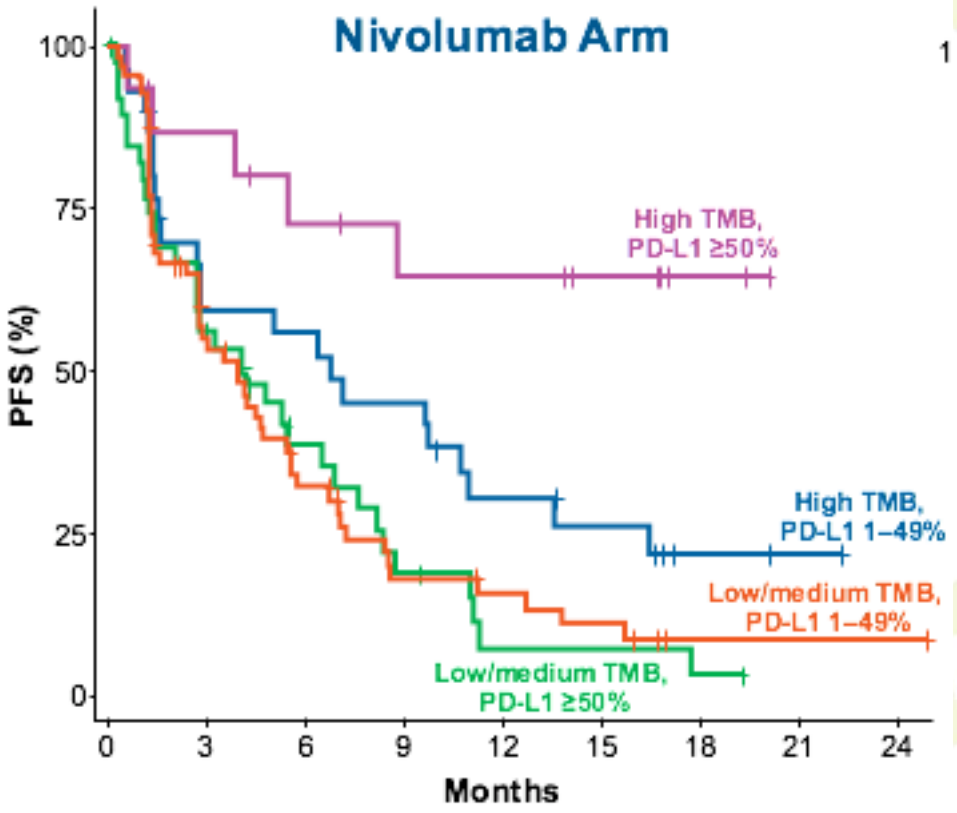
PD-L1 isn't Everything!



Peters et al AACR 2017

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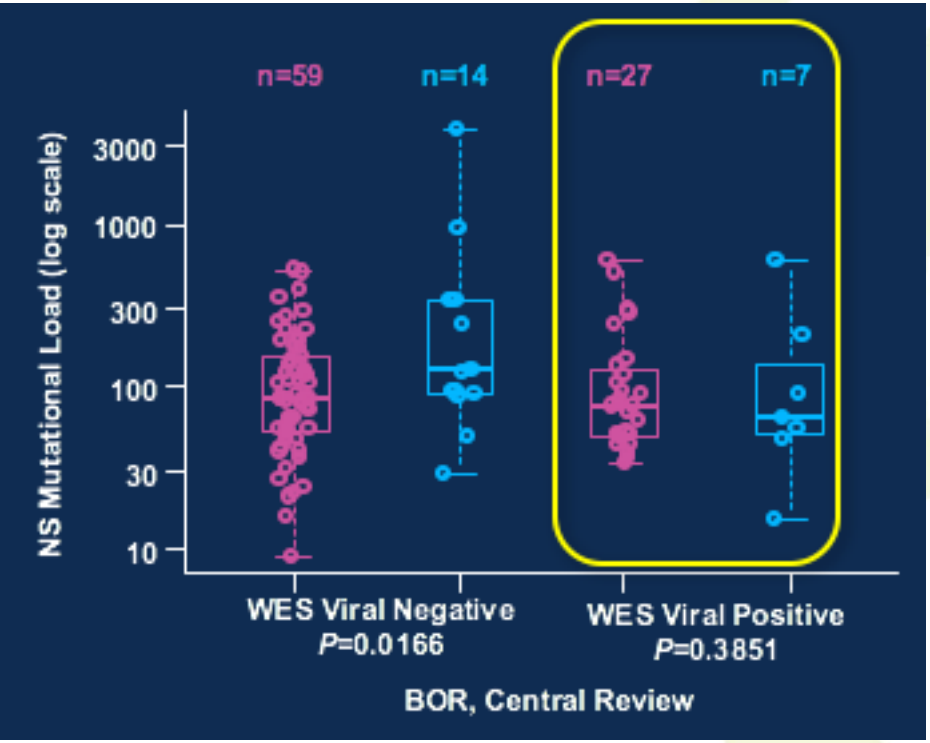
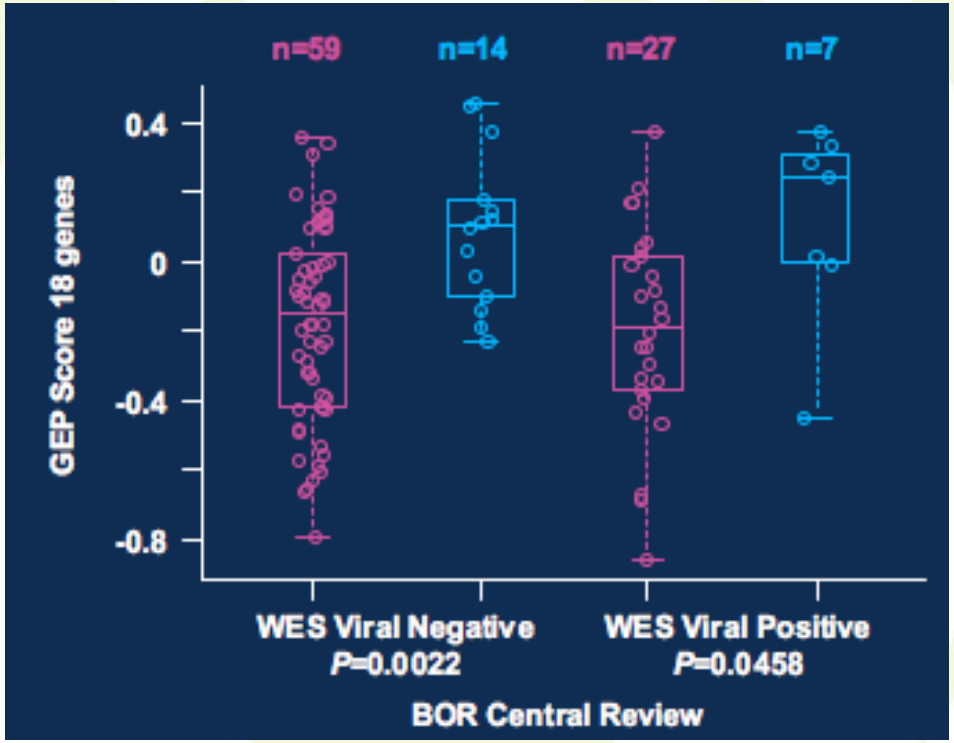
Various Biomarkers in HNC





Not PR or CR
PR or CR

Haddad et al ASCO 2017

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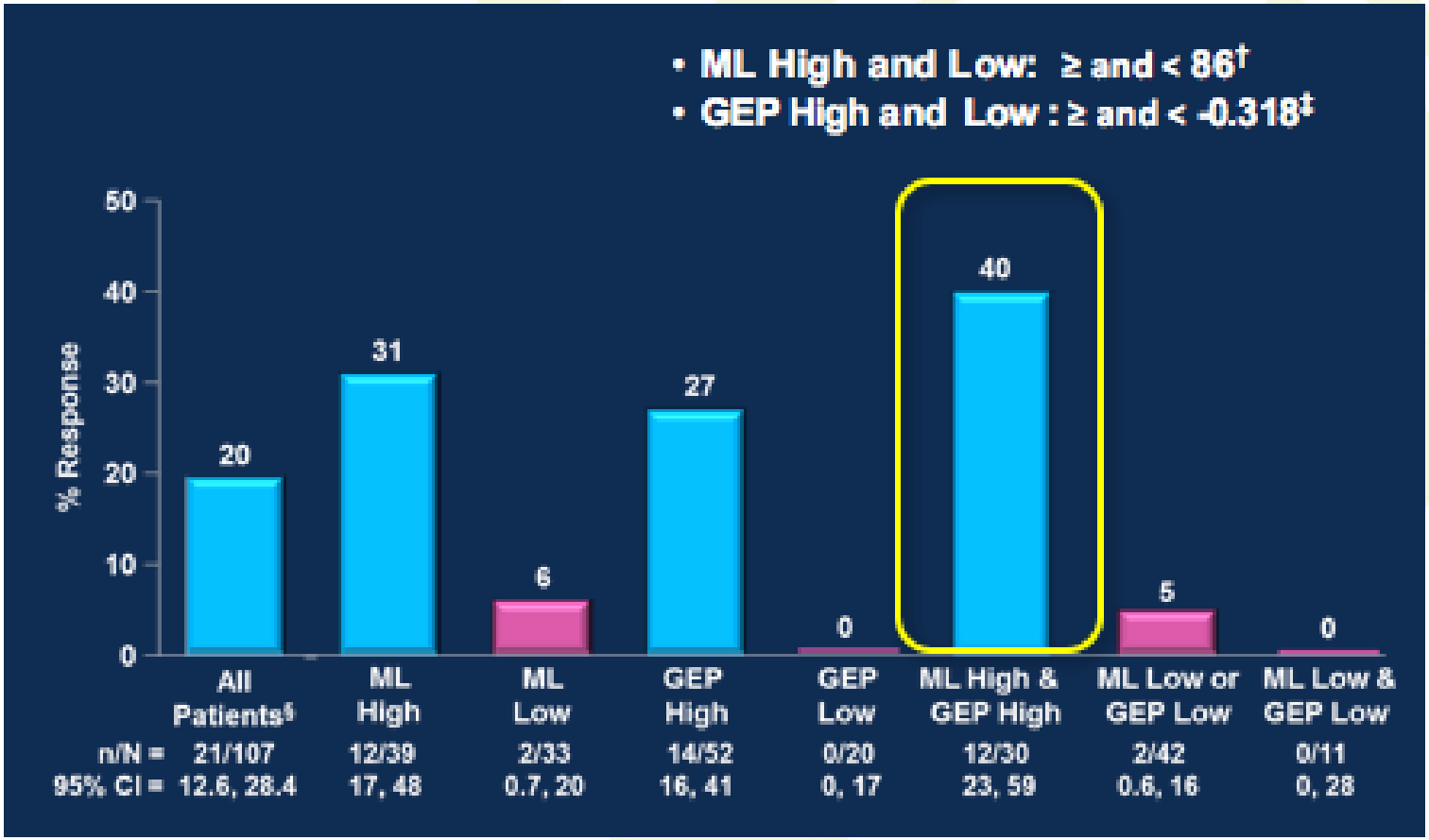
Combined GEP/ML



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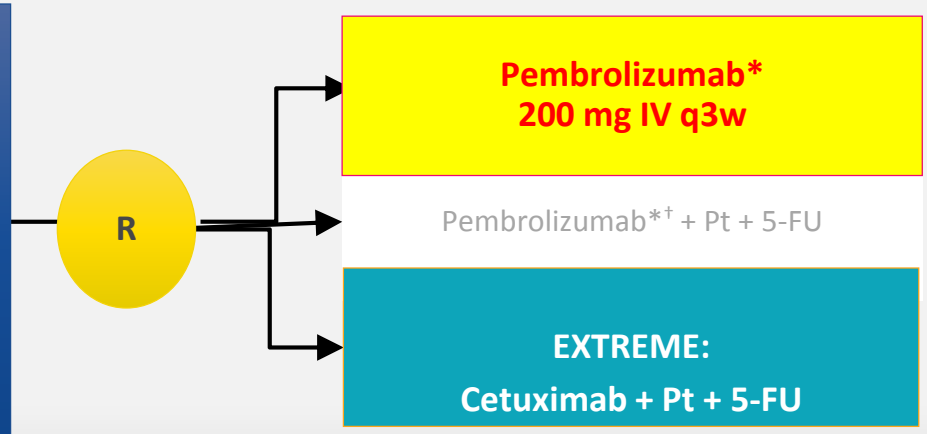
KEYNOTE 48: 1st Line - PIII

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

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Case #1

- 57 yo male with T4N2cM0 squamous cell carcinoma of the hypopharynx, P16 negative. Previous heavy smoker but currently not smoking or drinking. Underwent concurrent chemo/radiation with Cisplatin and 7000 cGy IMRT.
- Re assessed following completion of chemo/RT with CT scan and had residual adenopathy at 8 weeks. Subsequent neck dissection showed residual disease in 1 node. All others negative
- Restaging 6 months later demonstrated multiple 1 cm nodules in both lungs. Biopsy: squamous cell carcinoma, P16 negative. Treated with EXTREME regimen with progressive disease.
- Subsequently started on Pembrolizumab with 50% reduction in all nodules. Continues to receive treatment.

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

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Case #2

- 74 yo Laotian woman with hx of tongue pain for several months. No regular medical care. Ultimately saw a dentist who felt a mass in her tongue and possible nodes in neck. Referred to ENT. Biopsy of tongue base showed squamous cell carcinoma, P16 positive. PET scan showed mass at base of tongue and bilateral neck nodes.

- Pt offered surgery but refused. Was treated with definitive chemo/RT with resolution of pain and regression of nodes. She refused additional treatment.

- Re-assessment 6 months later demonstrated cervical adenopathy but no distant mets. She agreed to neck dissection at that time. Had 3/17 positive nodes for P16 positive squamous cell carcinoma

- Refused additional chemotherapy. Developed additional contralateral nodal disease 3 months later which was painful. Started on Nivolumab at that time. Remains in stable PR

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

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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.