ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Head and Neck Cancers

Anupam Desai, MD

Beth Israel Deaconess Medical Center

Harvard Medical School

American Academy of Emergency Medicine

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

Disclosures

- I have no relevant disclosures
- I will be discussing non-FDA approved indications during my presentation.

Association of Community Cancer Centers
Society for Immunotherapy of Cancer

Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

Pt WS

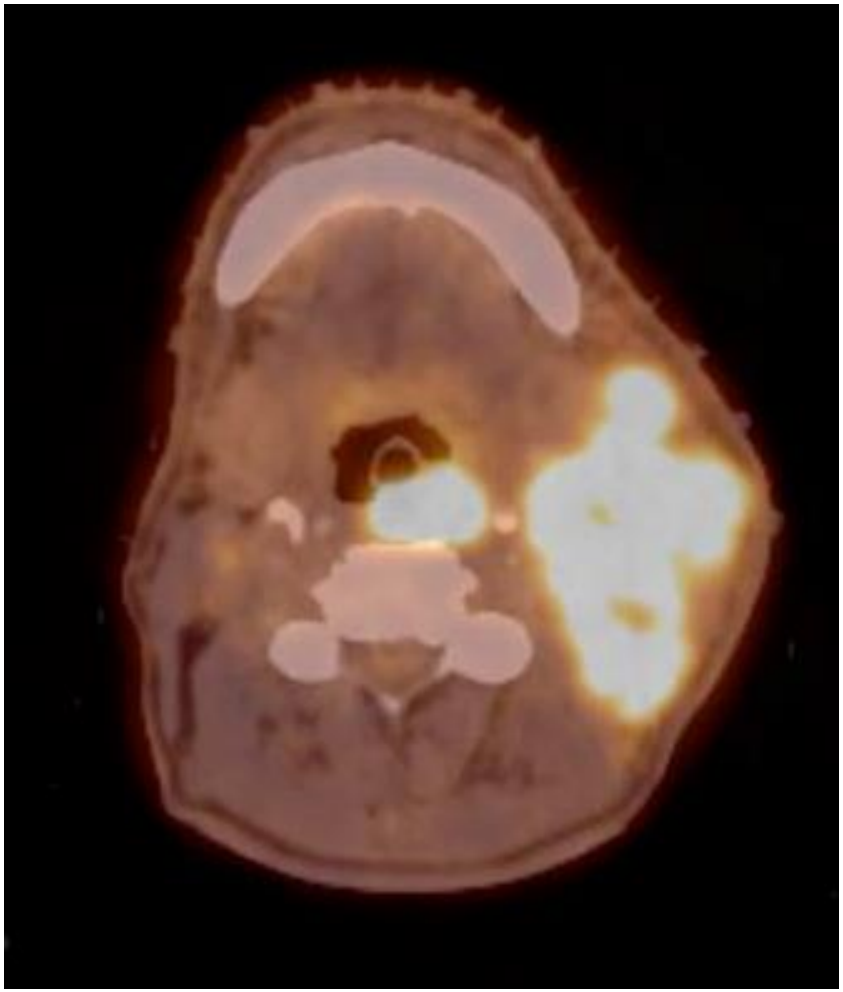
- 78 yo M with a history of CAD, HTN, HLD
- Presents with painful L sided neck mass
- Lost 30 lbs due to anorexia

Association of Community Cancer Centers

Society for Immunotherapy of Cancer

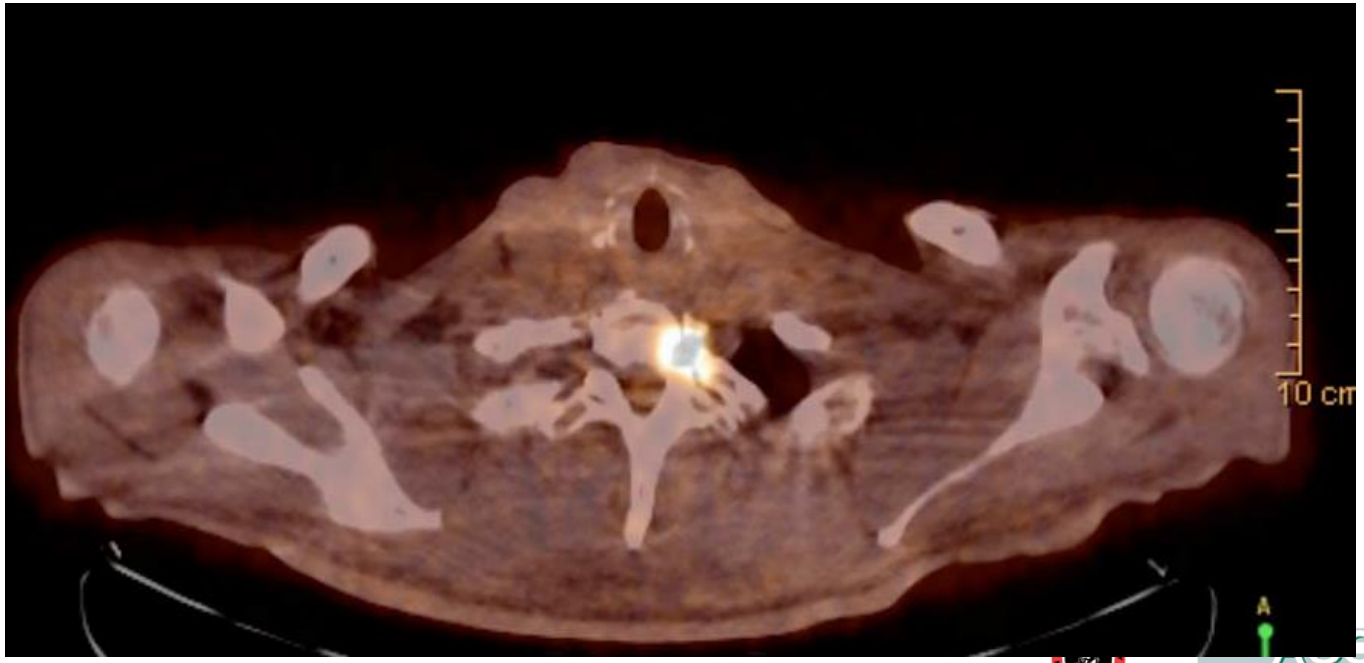
11/2014

- 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



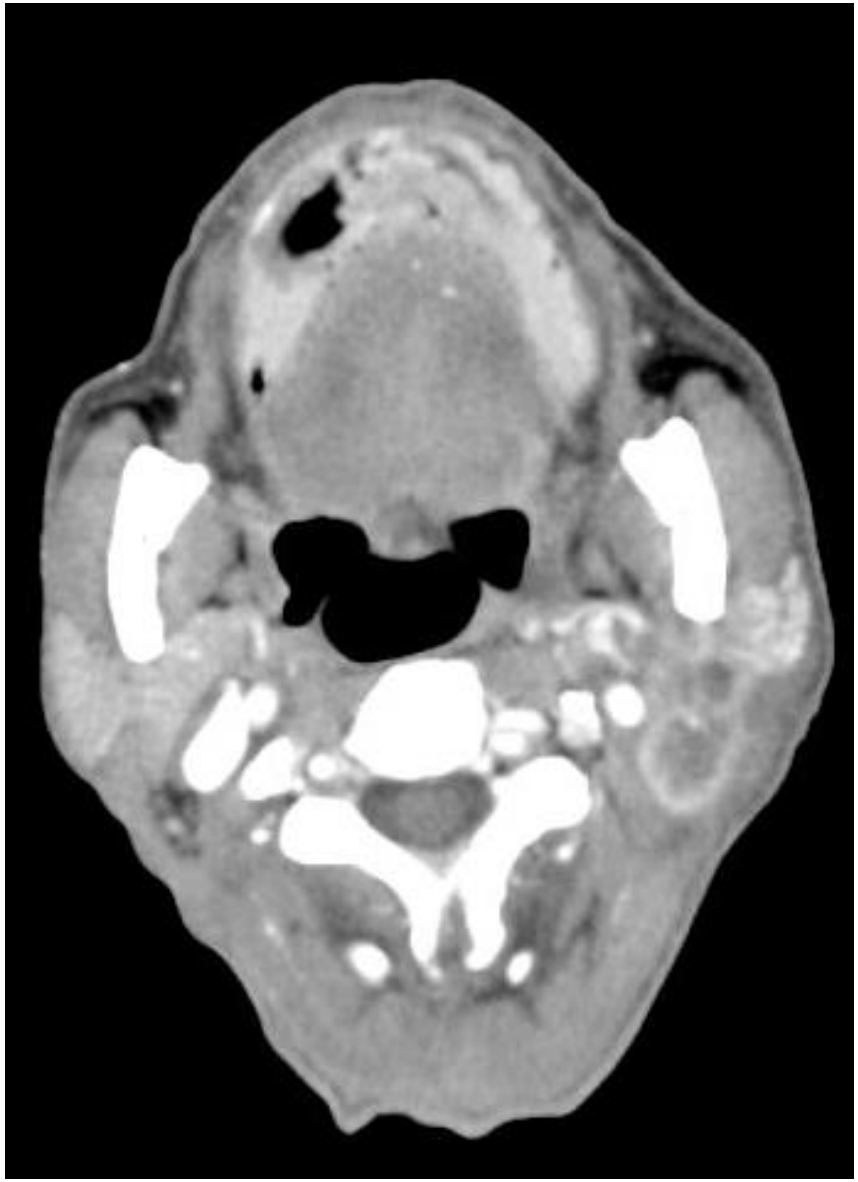
1/2015

- 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

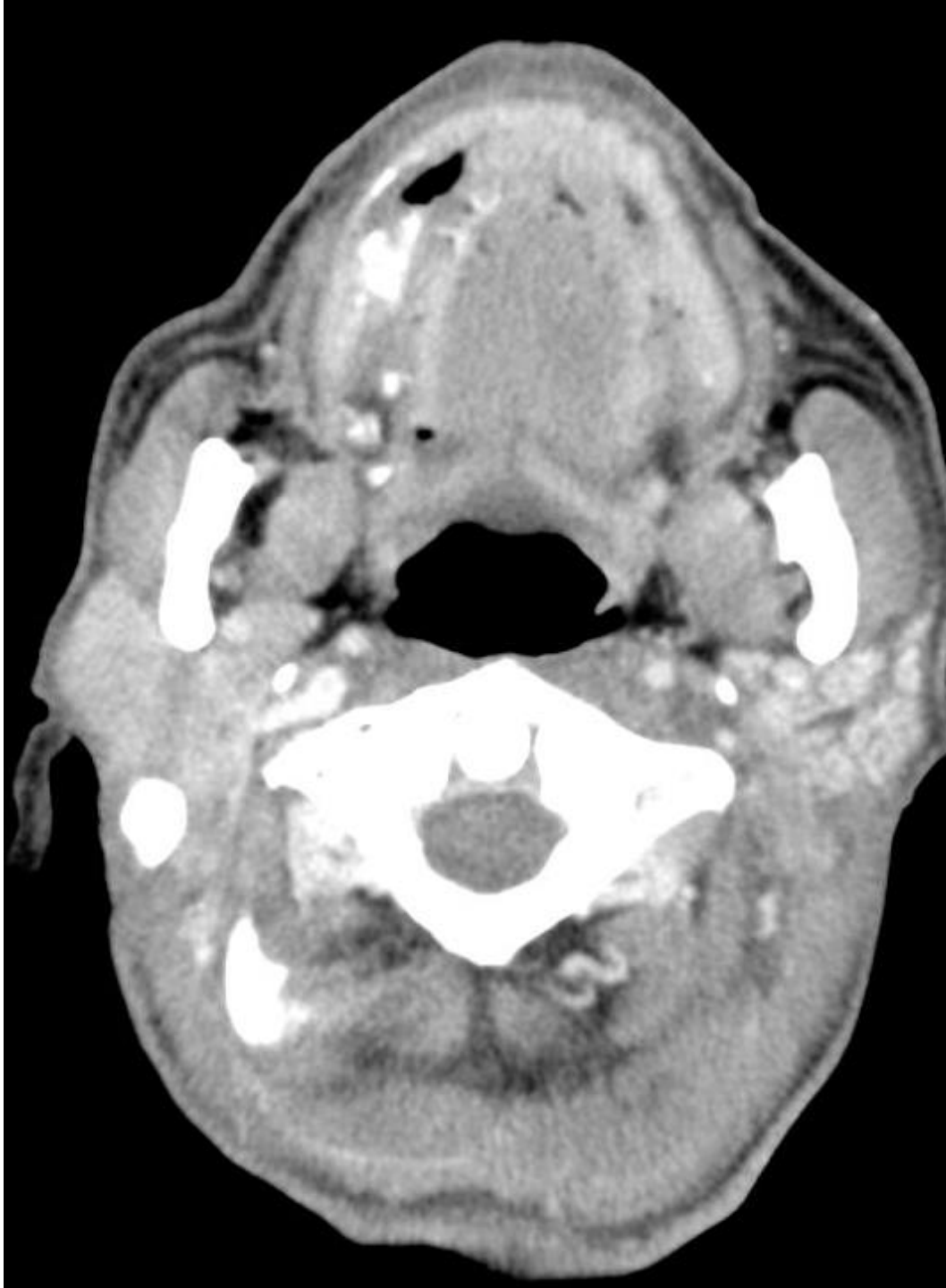


Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

10/2015

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



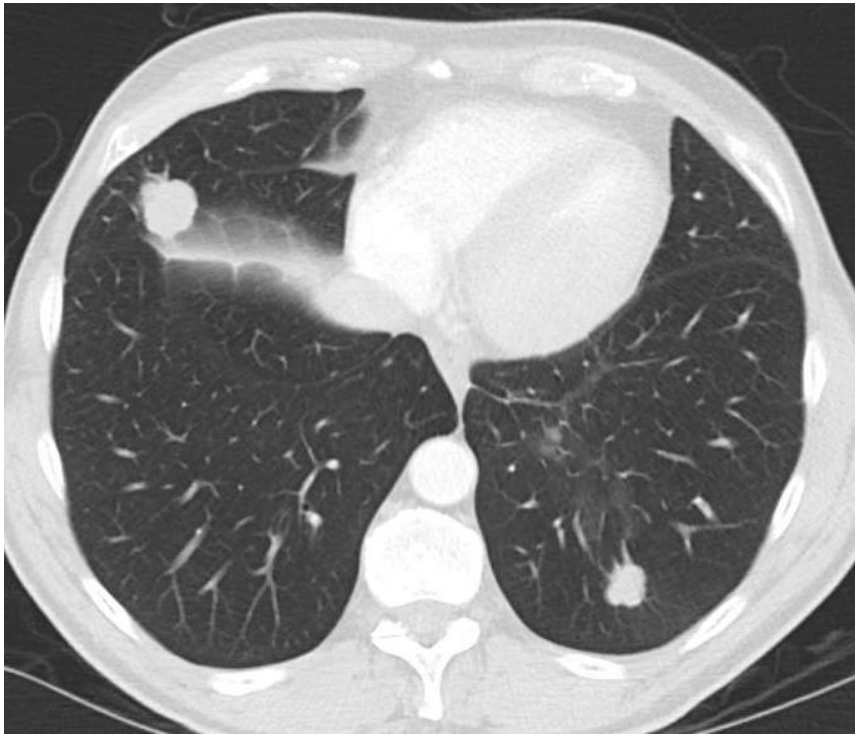
Pt SG

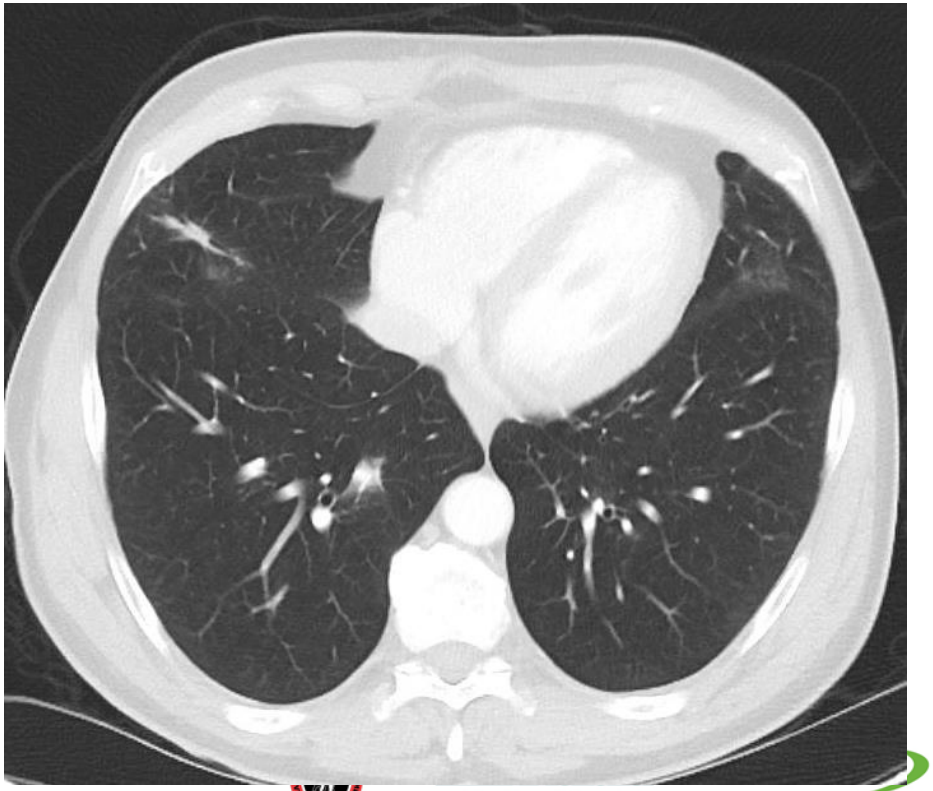
- Initially presented with a large mass in the R oropharynx
  - Underwent carboplatin/paclitaxel/cetuximab induction
  - Concurrent Chemoradiotherapy with high dose cisplatin
- 3 months after CRT, presented with multiple pulmonary nodules
- Cetuximab in metastatic setting

Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

2/2015

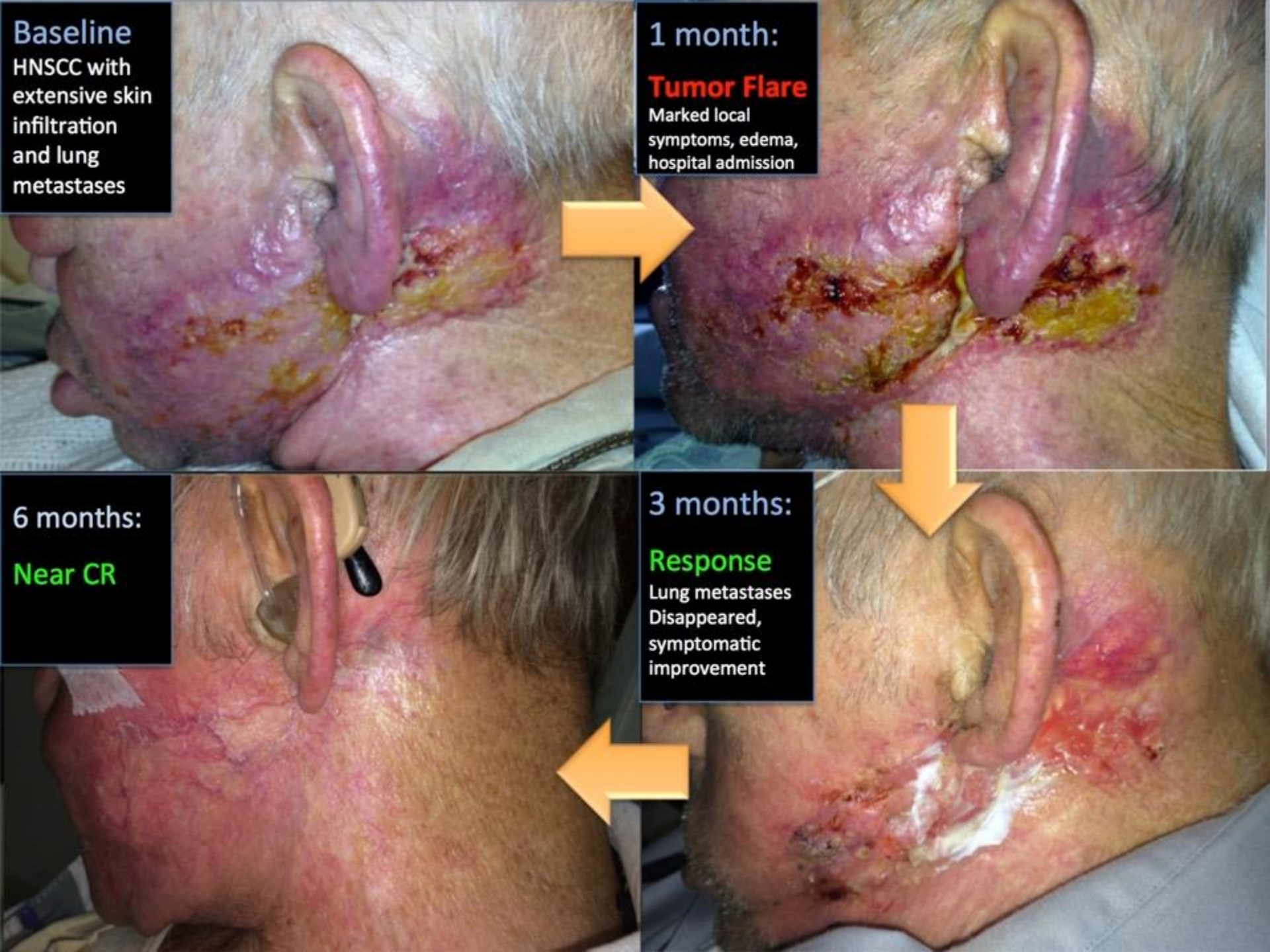
- Started on pembrolizumab
  - Enrolled in KEYNOTE 055
- Experienced a near CR





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

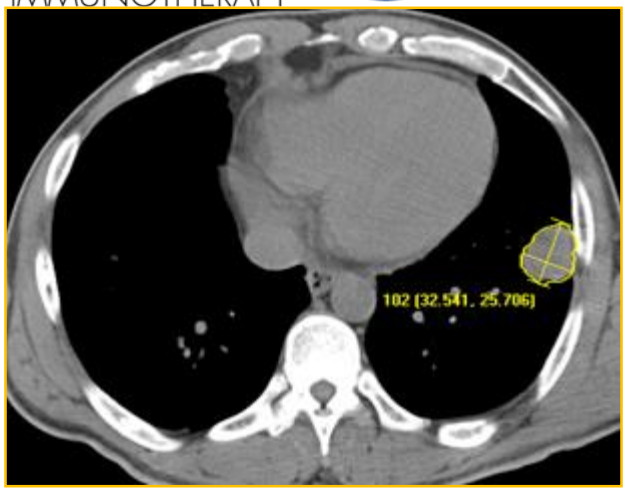

Baseline
HNSCC with extensive skin infiltration and lung metastases
1 month:
Tumor Flare
Marked local symptoms, edema, hospital admission
3 months:
Response
Lung metastases Disappeared, symptomatic improvement
6 months:
Near CR

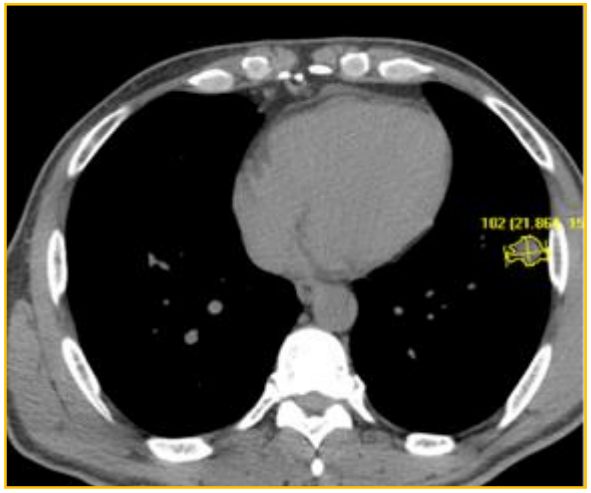
Society for Immunotherapy of Cancer

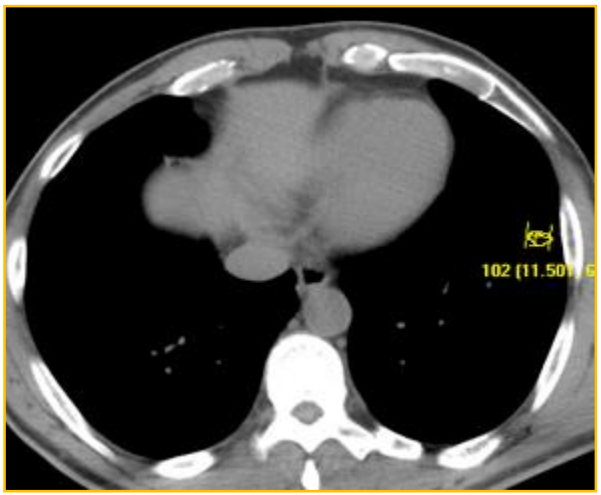
ADVANCES IN Cancer IMMUNOTHERAPY™

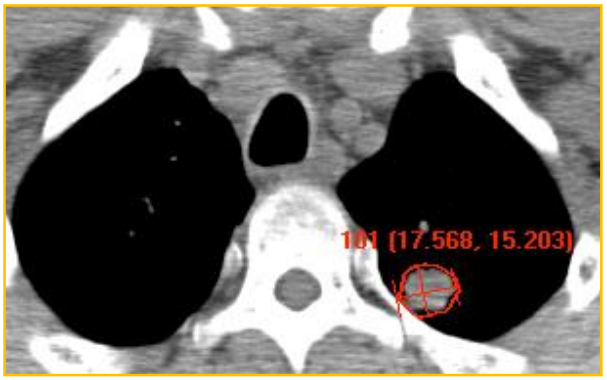
Patient Response *(central review)*

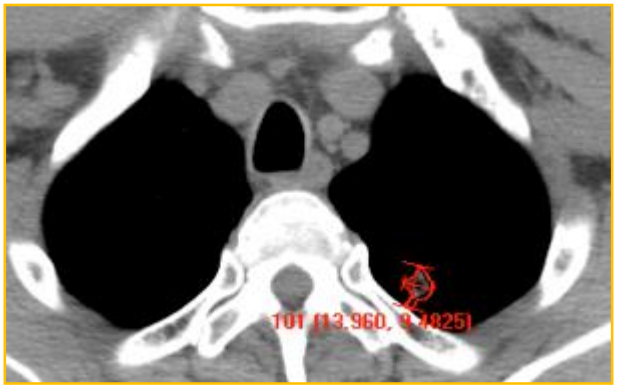
Baseline **Cycle 4 -28.3%** **Cycle 8 -56.1%**



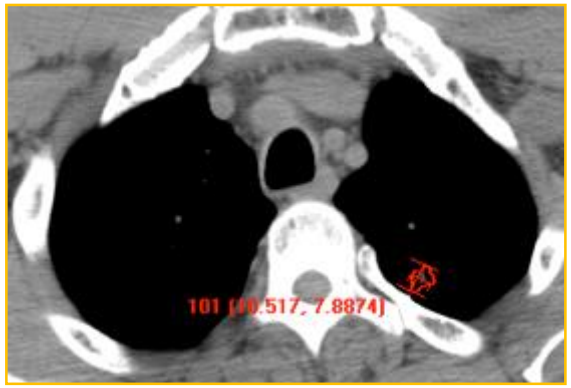








Wk 8 SD



Wk 16 PR

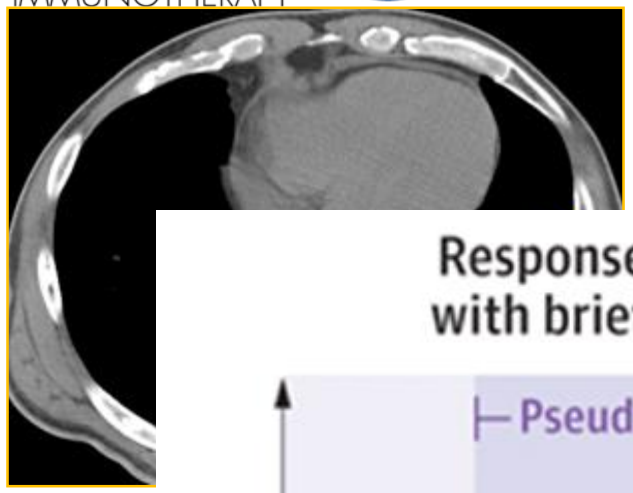
Images from: Tanguy Seiwert, MD

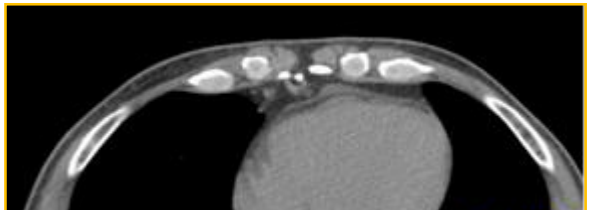
ACCC Association of Community Cancer Centers

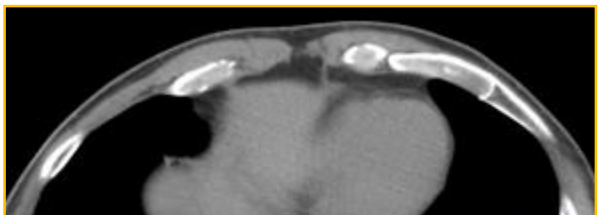
Society for Immunotherapy of Cancer

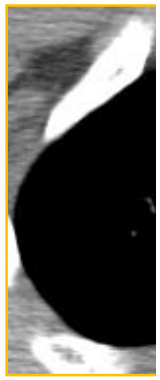
Patient Response *(central review)*

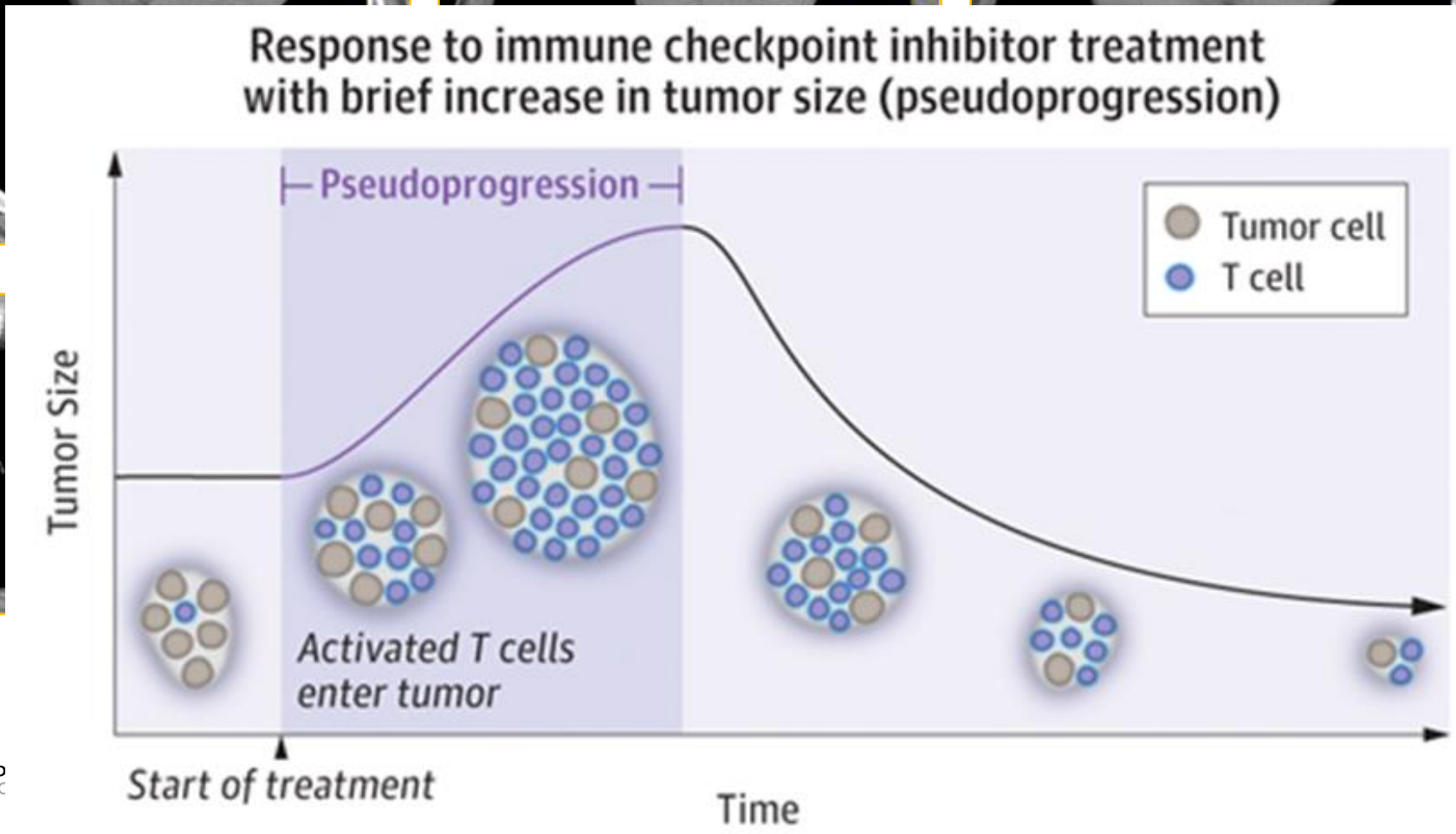
Baseline **Cycle 4 -28.3%** **Cycle 8 -56.1%**







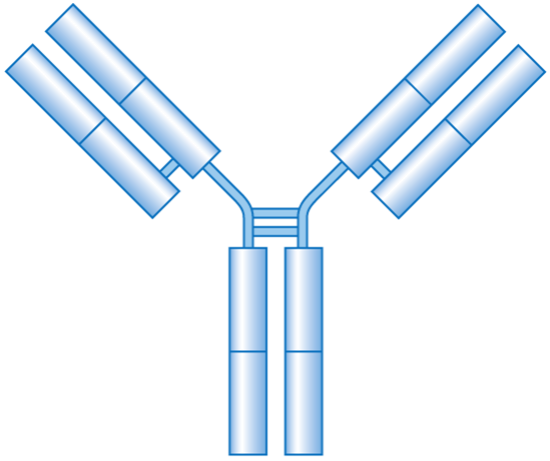




ADVANCES IN Cancer IMMUNOTHERAPY™

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

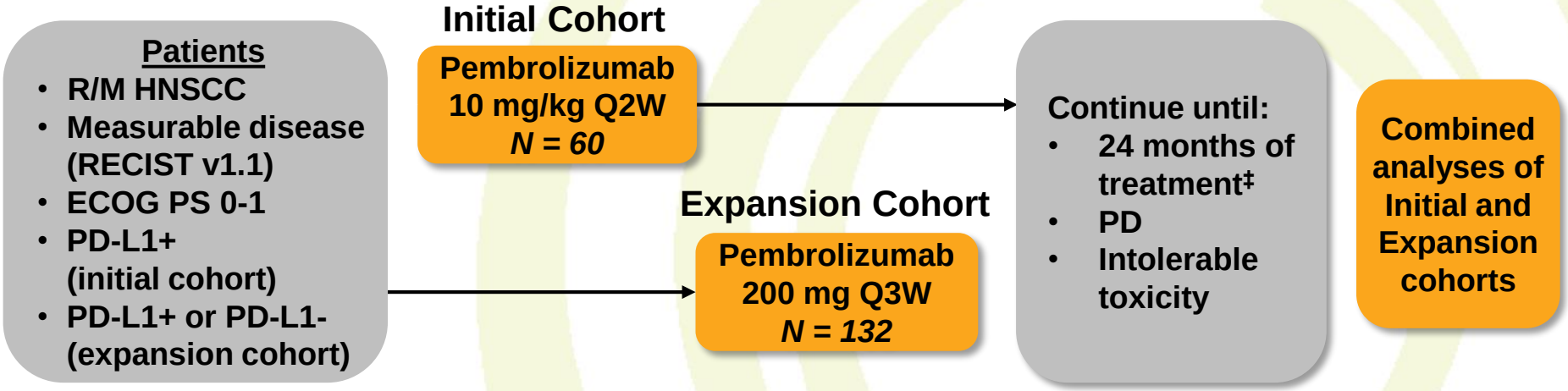
4. **Other PD-1/PD-L1 agents in development:**
   - PD-L1 agents – Atezolizumab (bladder, NSCLC approval), Avelumab
   - PD-1 agents: R2810, PRD001, Tesaro

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

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

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



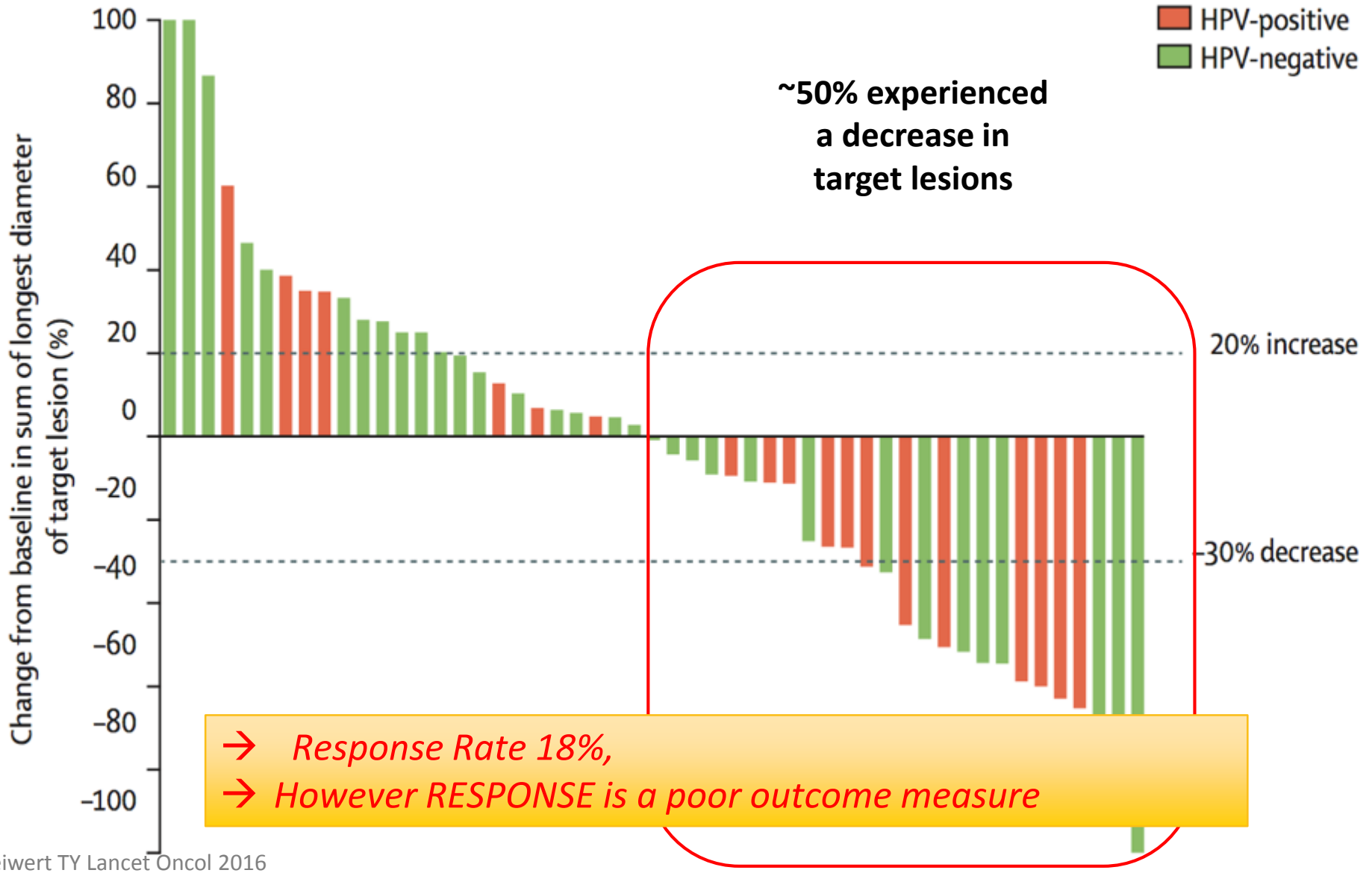
Response assessment: Every 8 weeks

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-012)

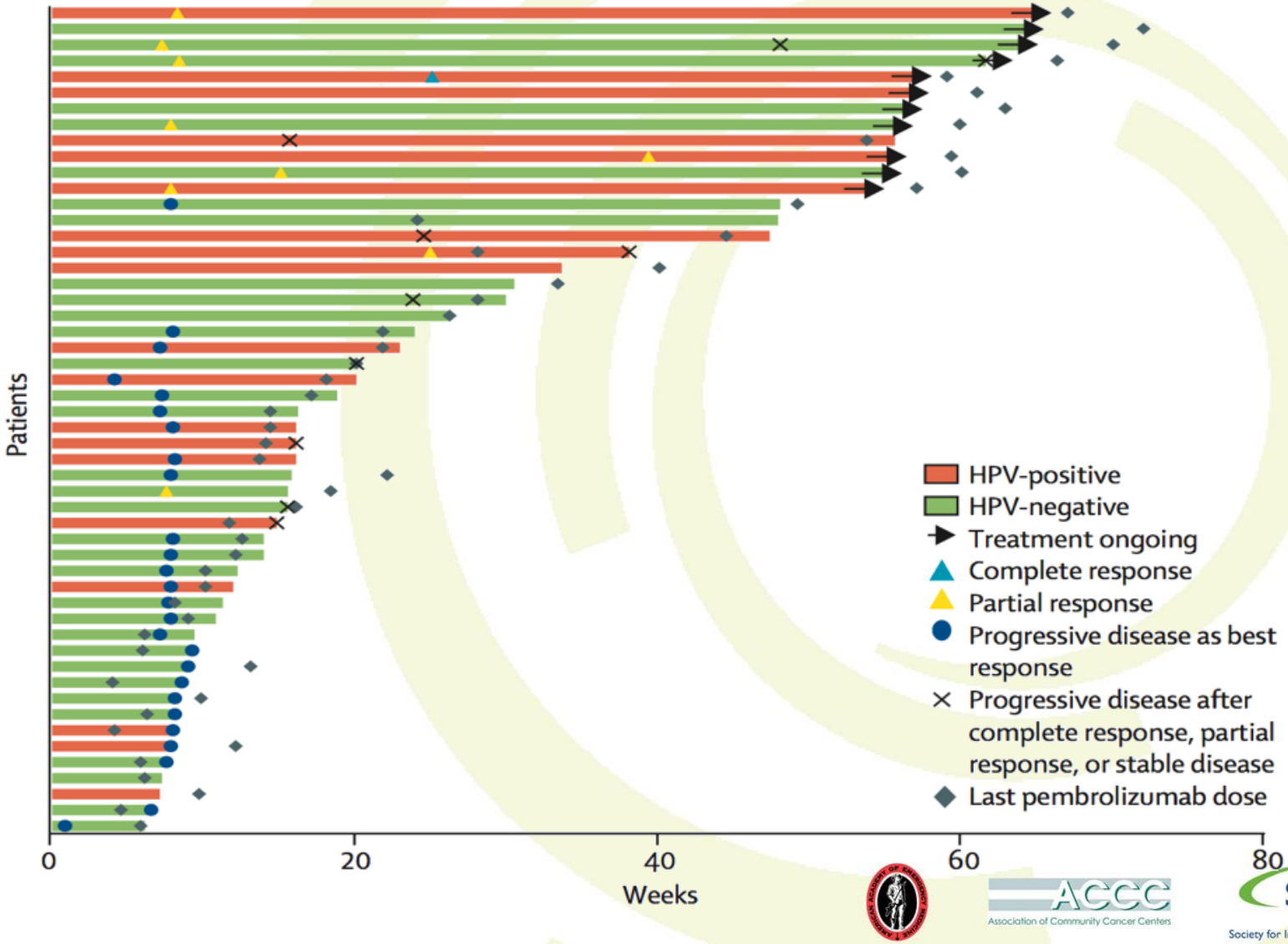


→ *Response Rate 18%,*

→ *However RESPONSE is a poor outcome measure*

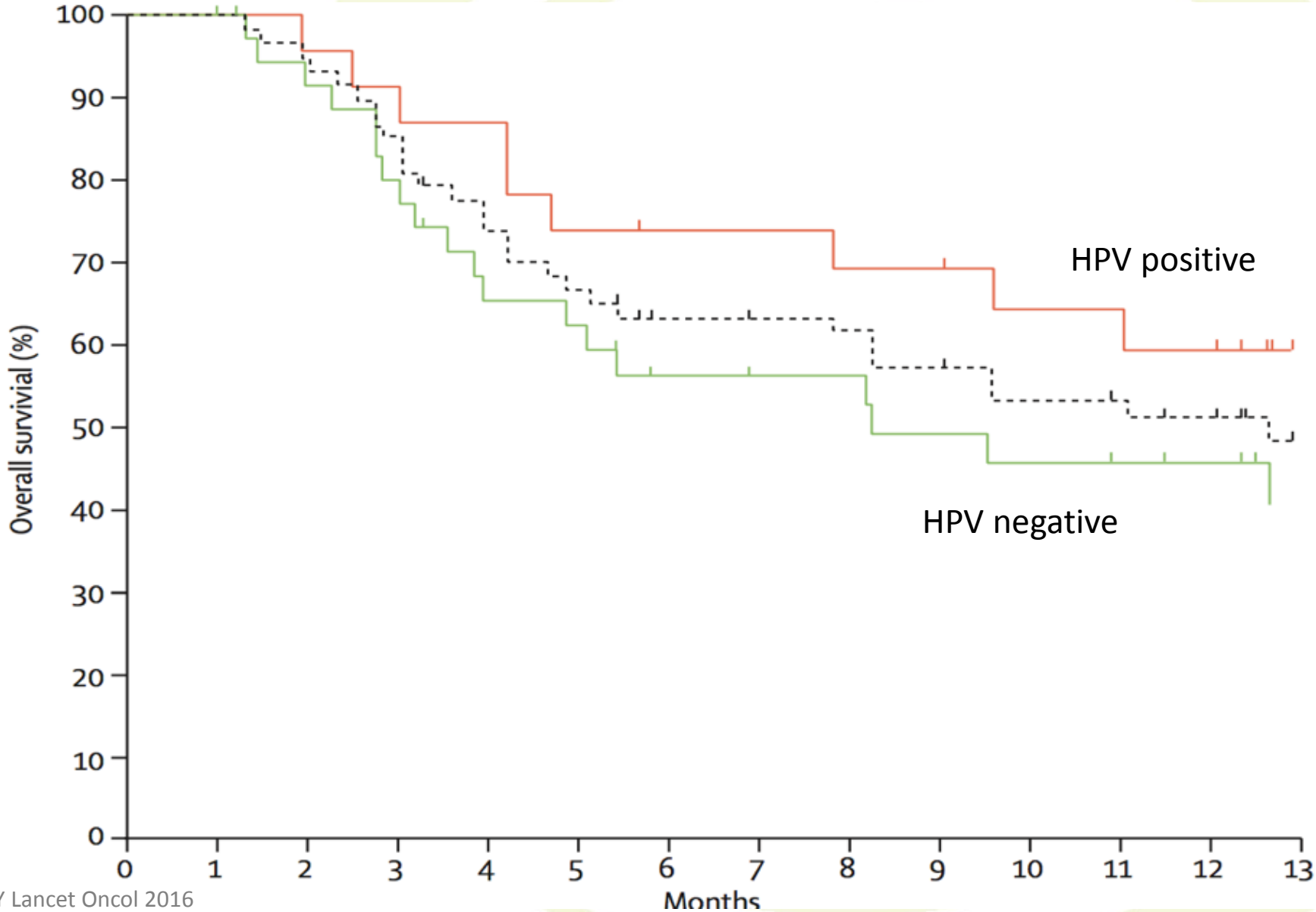
Seiwert TY Lancet Oncol 2016

Durability (KEYNOTE-012)



Seiwert TY Lancet Oncol 2016

HPV Impact on OS in KEYNOTE-012



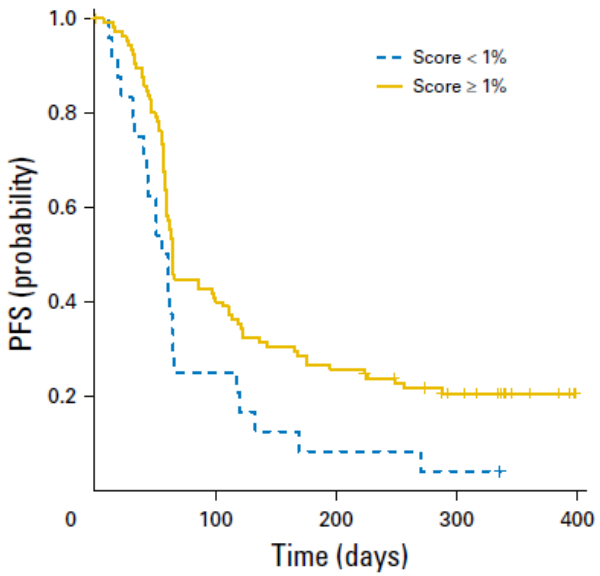
Seiwert TY Lancet Oncol 2016

PDL1 in expansion cohort KEYNOTE-012

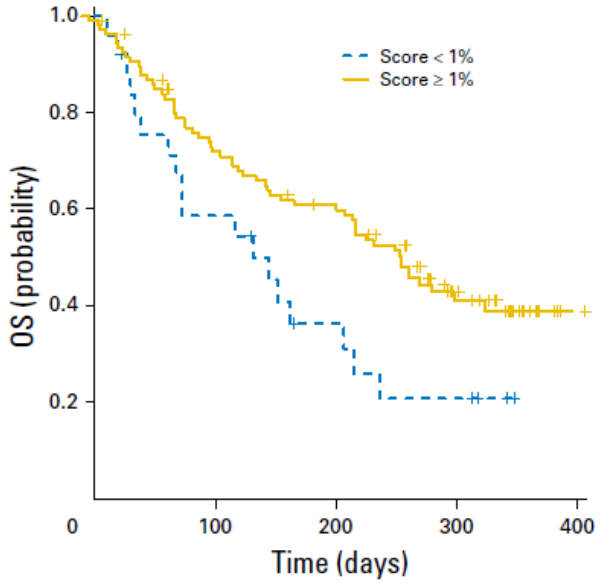
A

PD-L1 Status	Tumor and Immune Cells			Tumor Cells Only		
	Nonresponders, No.	Responders, No.	Response, % (95% CI)	Nonresponders, No.	Responders, No.	Response, % (95% CI)
Negative (< 1%)	24	1	4 (0.1 to 20)	36	7	16 (7 to 31)
Positive (≥ 1%)	84	23	22 (14 to 31)	72	17	19 (12 to 29)

B

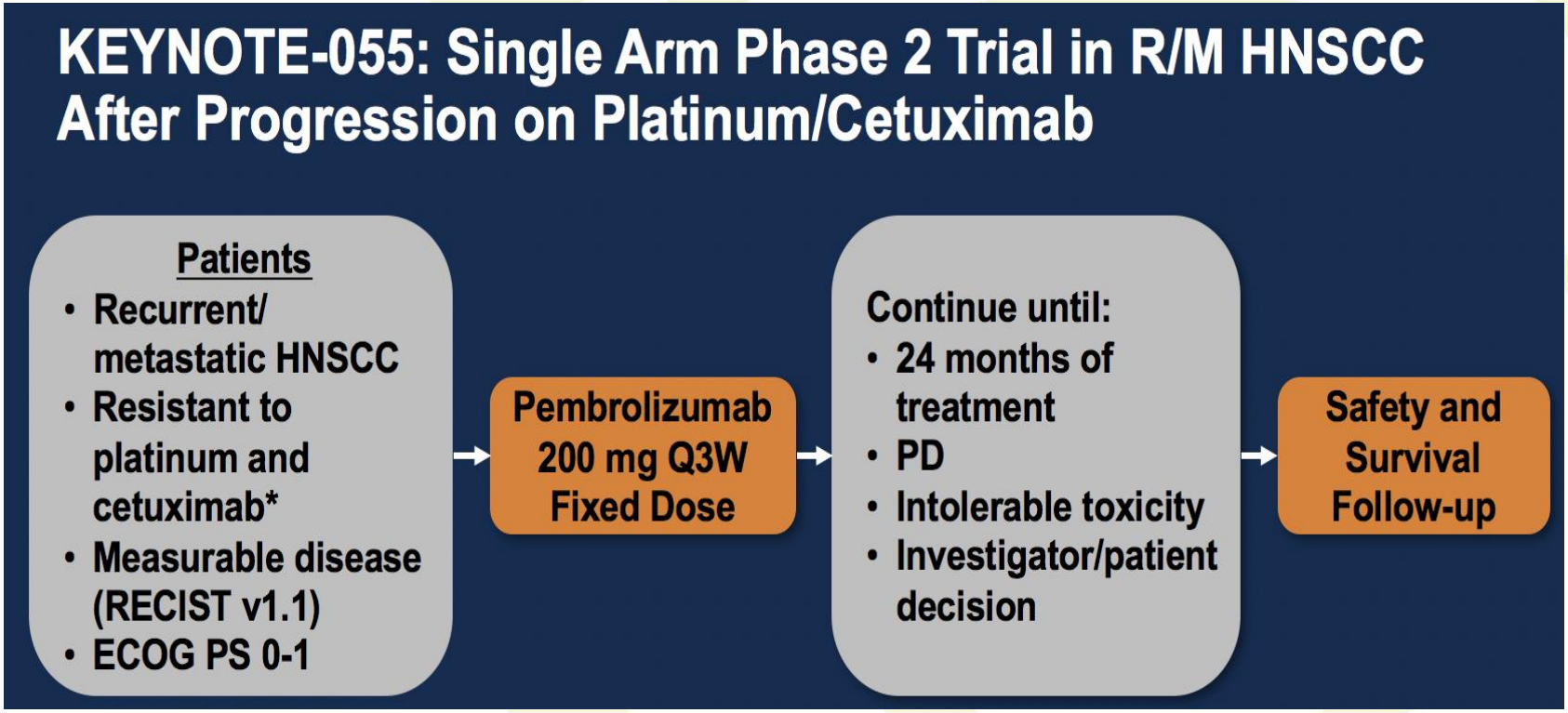


C



Chow et al JCO 2016

KEYNOTE-055



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

Bauml et al JCO 2017

KEYNOTE-055 PD-L1 status

Table 4. Antitumor Activity on the Basis of PD-L1 Expression Status

	CPS ≥ 1% (n = 140)		CPS < 1% (n = 26)		CPS ≥ 50% (n = 48)		CPS < 50% (n = 118)	
Response Evaluation	No.	% (95% CI)*	No.	% (95% CI)*	No.	% (95% CI)*	No.	% (95% CI)*
Overall response rate	25	18 (12 to 25)	3	12 (2 to 30)	13	27 (15 to 42)	15	13 (7 to 20)
Complete response	1	1 (0 to 4)	0	0 (0 to 13)	1	2 (0 to 11)	0	0 (0 to 3)
Partial response	24	17 (11 to 24)	3	12 (2 to 30)	12	25 (14 to 40)	15	13 (7 to 20)
Stable disease	23	16 (11 to 24)	7	27 (12 to 48)	7	15 (6 to 28)	23	20 (13 to 28)
Progressive disease	73	52 (44 to 61)	13	50 (30 to 70)	18	38 (24 to 53)	68	58 (48 to 67)
Nonevaluable	2	1 (0 to 5)	2	8 (1 to 25)	0	0 (0 to 7)	4	3 (1 to 9)
Data unavailable	17	12 (7 to 19)	1	4 (0 to 20)	10	21 (11 to 35)	8	7 (3 to 13)

NOTE. Confirmed responses per Response Evaluation Criteria in Solid Tumors, version 1.1, per central imaging vendor review.
Abbreviations: CPS, combined positive score; PD-L1, programmed death ligand 1.
*On the basis of binomial exact confidence interval method.

PD-L1 positive patients had a slightly improved response rate (18%) compared to PD-L1 negative (12%), but PD-L1 status did not discriminate well enough to exclude any patients from therapy

Bauml et al JCO 2017

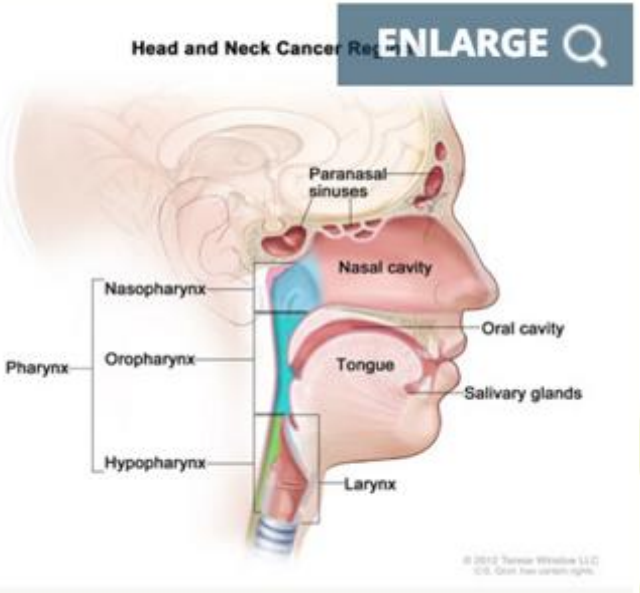
ADVANCES IN Cancer IMMUNOTHERAPY™

FDA Approves Pembrolizumab for Head and Neck Cancer

Subscribe

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.



ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

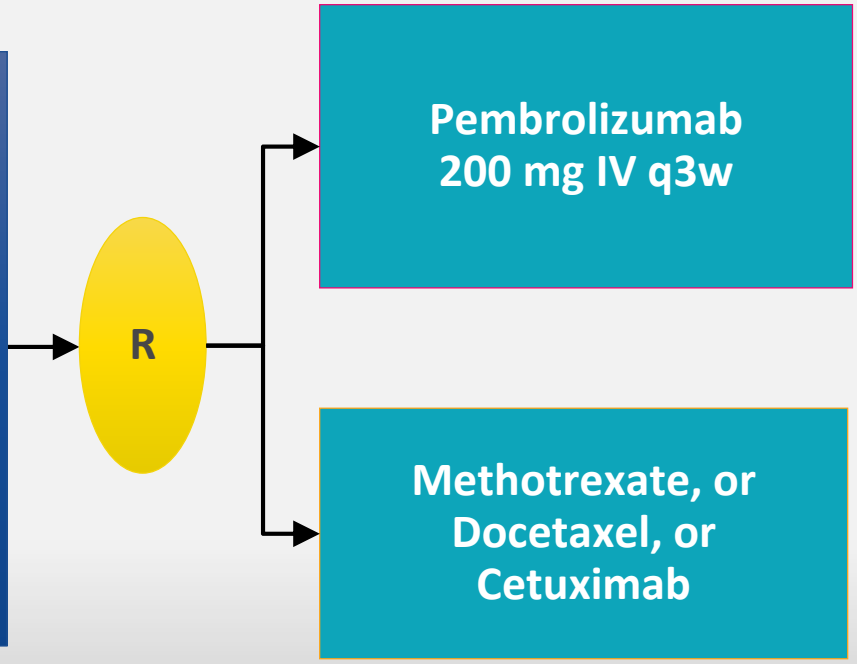
KEYNOTE-040: *Phase III*

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

N=495

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

KEYNOTE-040: *Phase III*

- Abstract presented at ESMO 2017
- At median followup of 7.3 months, mOS 8.4 months vs 7.1 months (HR 0.81),did not meet specified endpoint
- Minimal difference in PD-L1+ (>1%): 8.7 vs 7.1
- Overall more tolerable toxicity profile compared to chemotherapy, so still represents a good treatment option

ADVANCES IN Cancer IMMUNOTHERAPY™

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

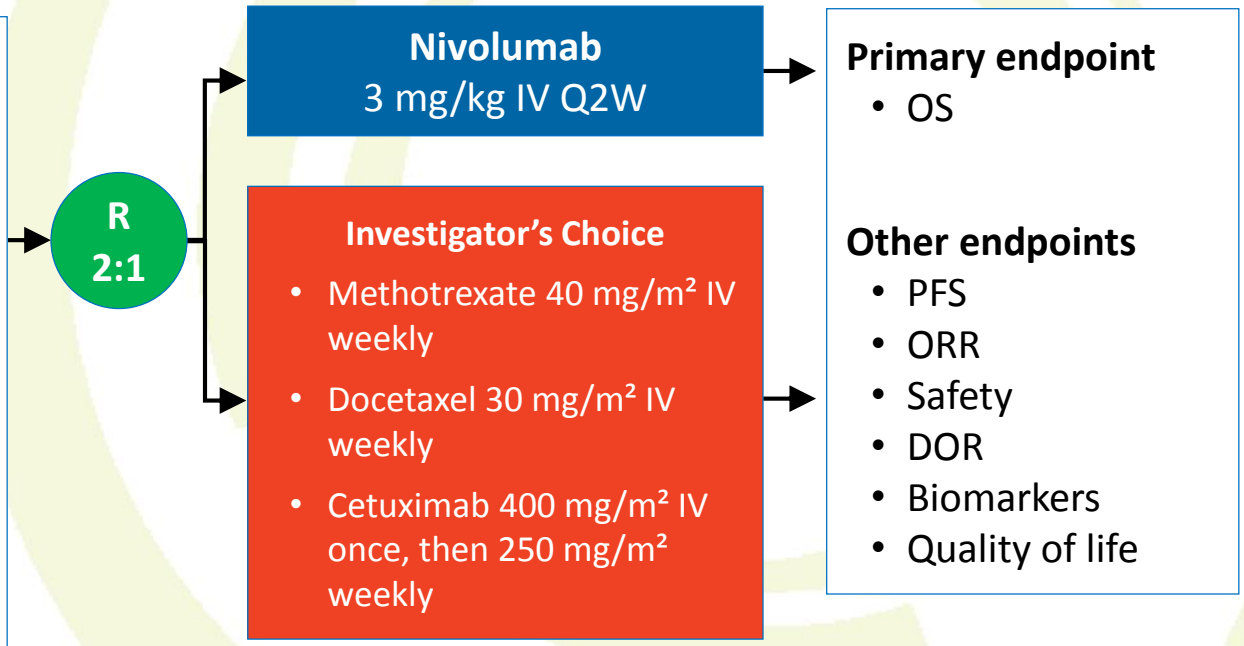
Key Eligibility Criteria

- 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.

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

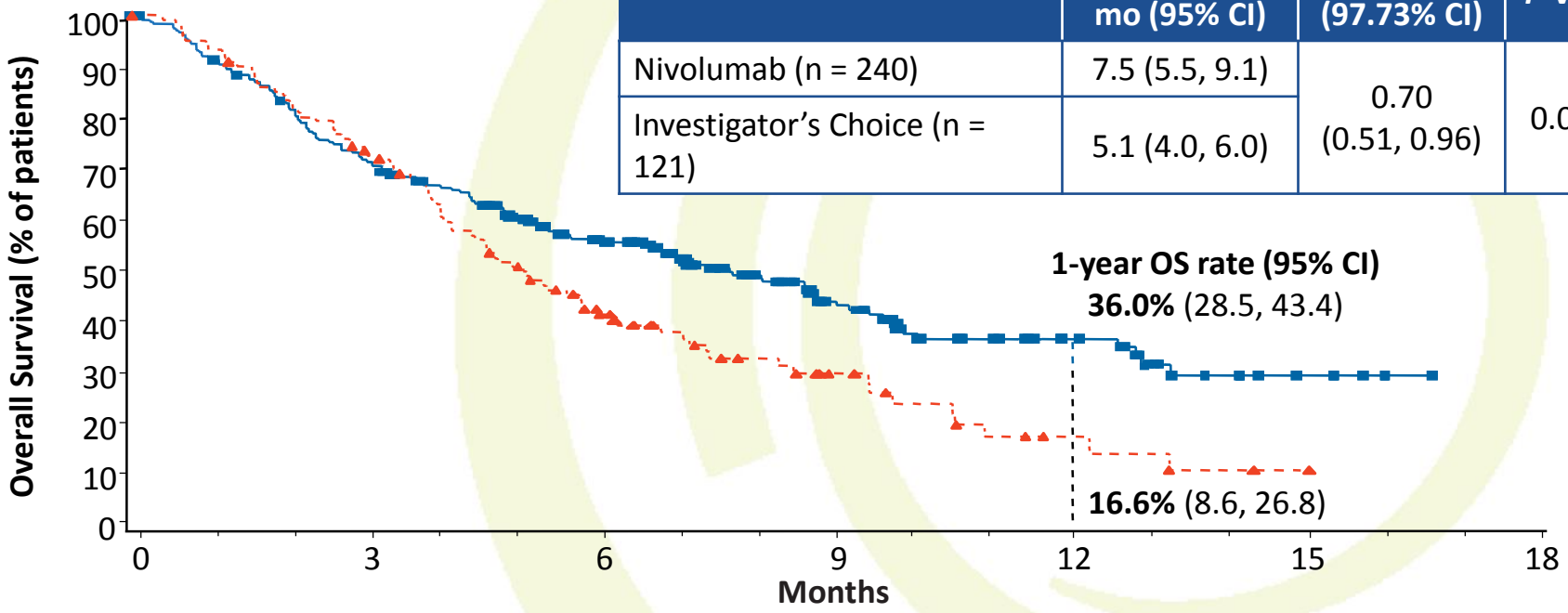
Ferris/Gillison NEJM 2016

ADVANCES IN Cancer IMMUNOTHERAPY™

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***

ACCC Association of Community Cancer Centers

sitc Society for Immunotherapy of Cancer

Ferris/Gillison NEJM 2016

ADVANCES IN Cancer IMMUNOTHERAPY™

FDA Approves Nivolumab for Head and Neck Cancer

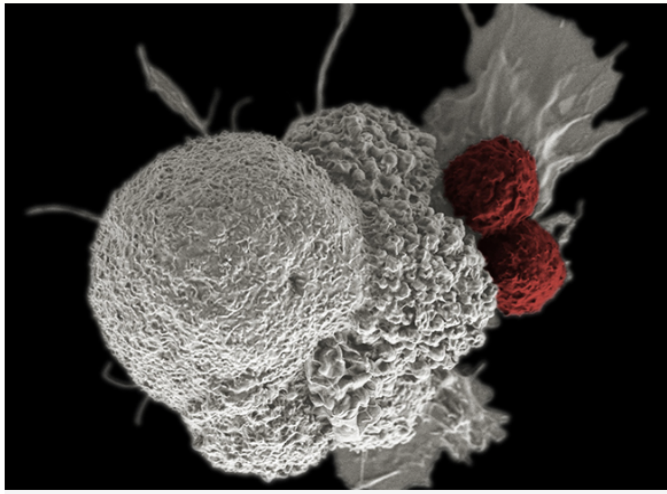
Subscribe

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.

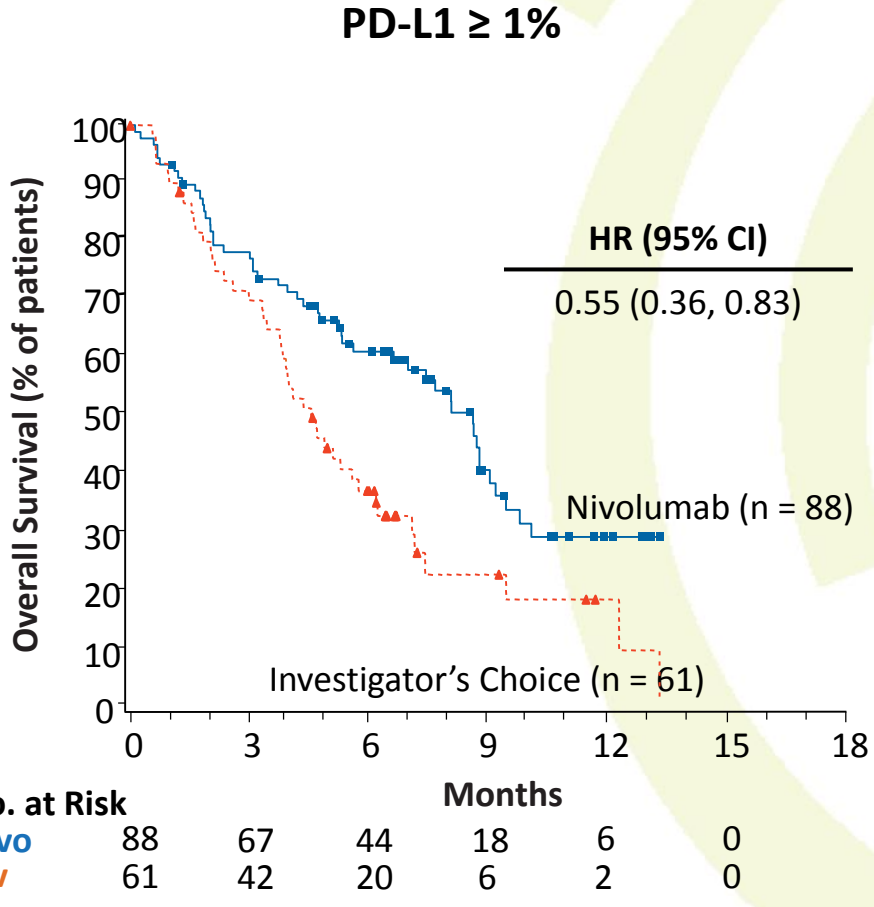


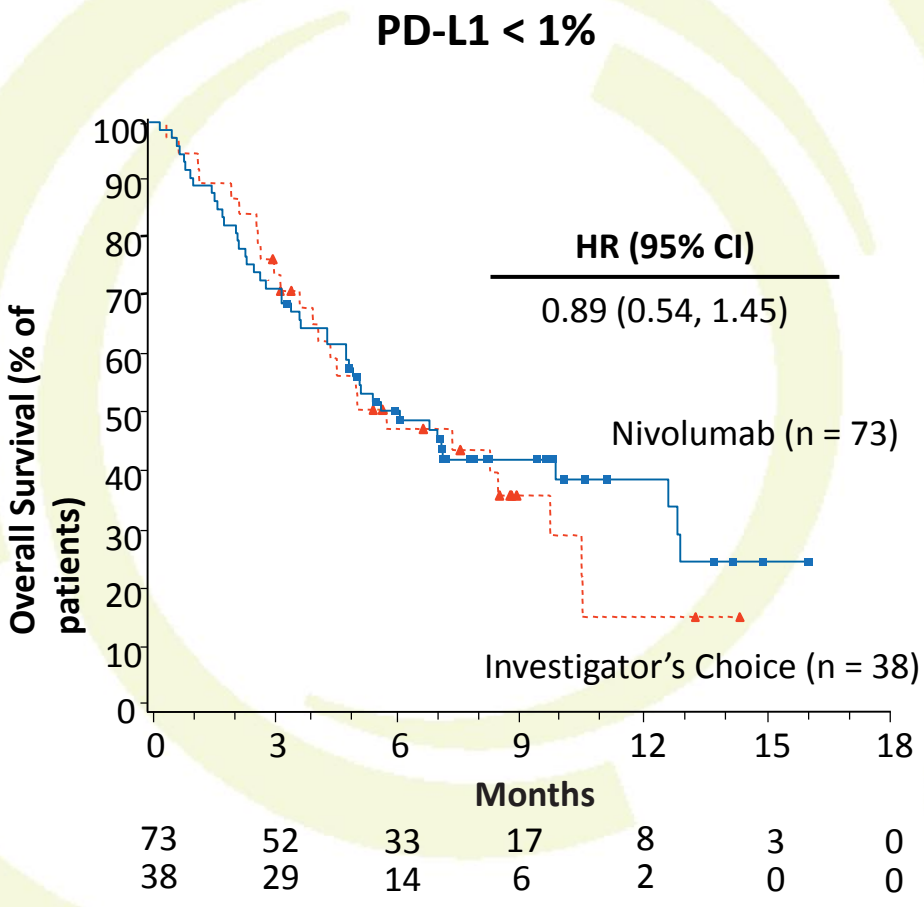
Cytotoxic T cells (red) attacking an oral squamous cancer cell (white). Immune checkpoint inhibitors like nivolumab prevent tumors from turning off T cells, allowing them to attack and kill the tumor cells.

Credit: National Cancer Institute

CM141: OS by PD-L1 Expression

TPS 1% cutpoint





ADVANCES IN Cancer IMMUNOTHERAPY™

Biomarkers in Head and Neck Cancer

- Current FDA approval of pembrolizumab and nivolumab is NOT contingent upon PD-L1 IHC
  - In KEYNOTE-012 and KEYNOTE-055 response rates were not significantly different on the basis of tumor PD-L1 staining
  - In CHECKMATE-141 most benefit was seen in PD-L1 positive tumors

Future Directions

- First line metastatic:
  - Pembrolizumab vs EXTREME regimen (cis/5-FU/cetux)
  - Ipilimumab/nivolumab vs EXTREME
  - Durvalumab +/- tremelimumab vs EXTREME

- Upfront with definitive chemoradiation:
  - Pembrolizumab
  - Avelumab

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