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ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Head and Neck Cancer

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

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Disclosures

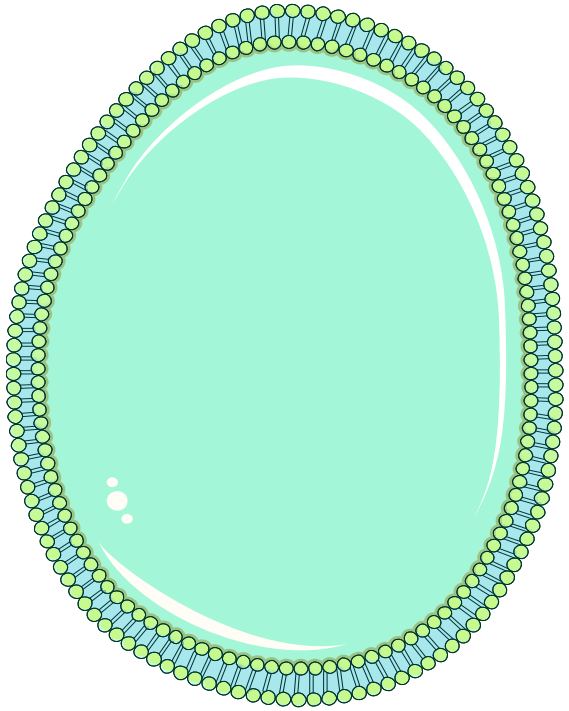
- No relevant financial relationships to disclose
- I will be discussing non-FDA approved indications during my presentation (clinical trials).

Outline

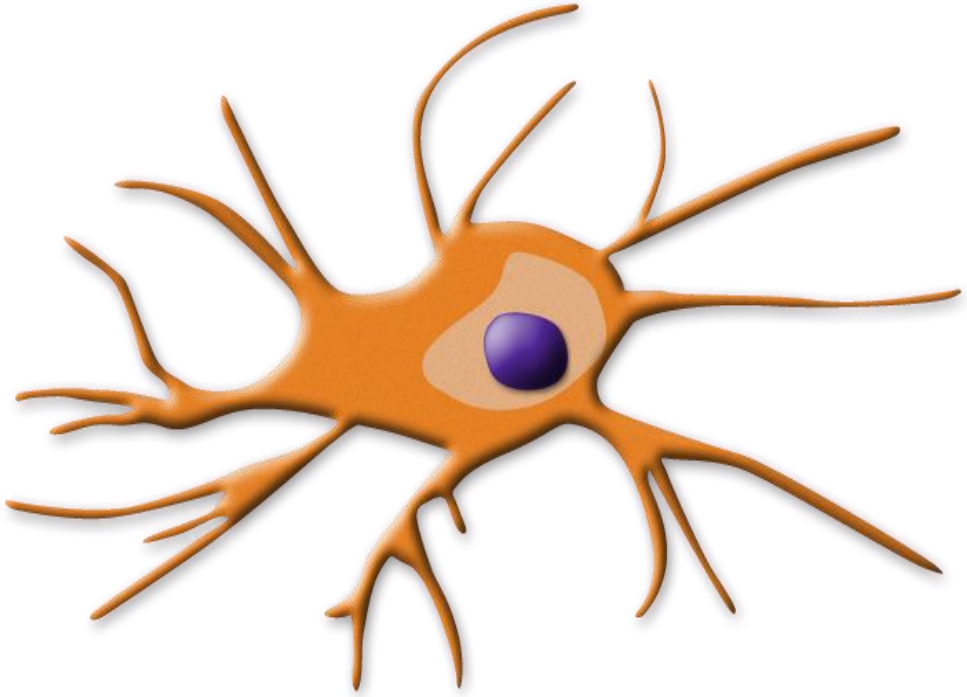
- Immunobiology of Head and Neck Cancer
- Anti-PD1 Immunotherapy in Head and Neck Cancer
- Biomarkers for Immunotherapy
- Future Directions
- Case Studies

The Cast of Characters:
Adaptive Immunity

HNSCC Tumor Cell



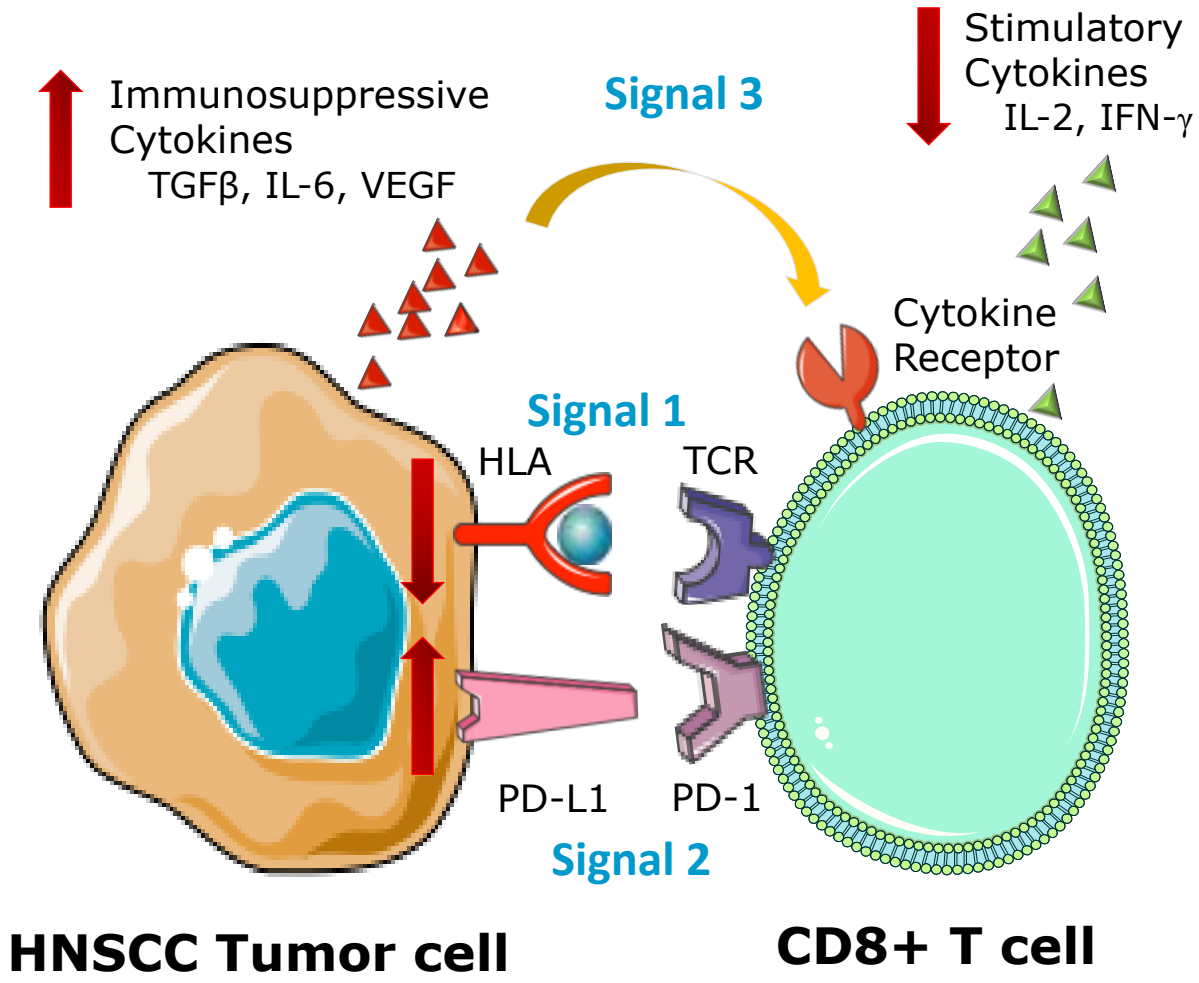
CD8+ T Cell



Antigen Presenting Cell

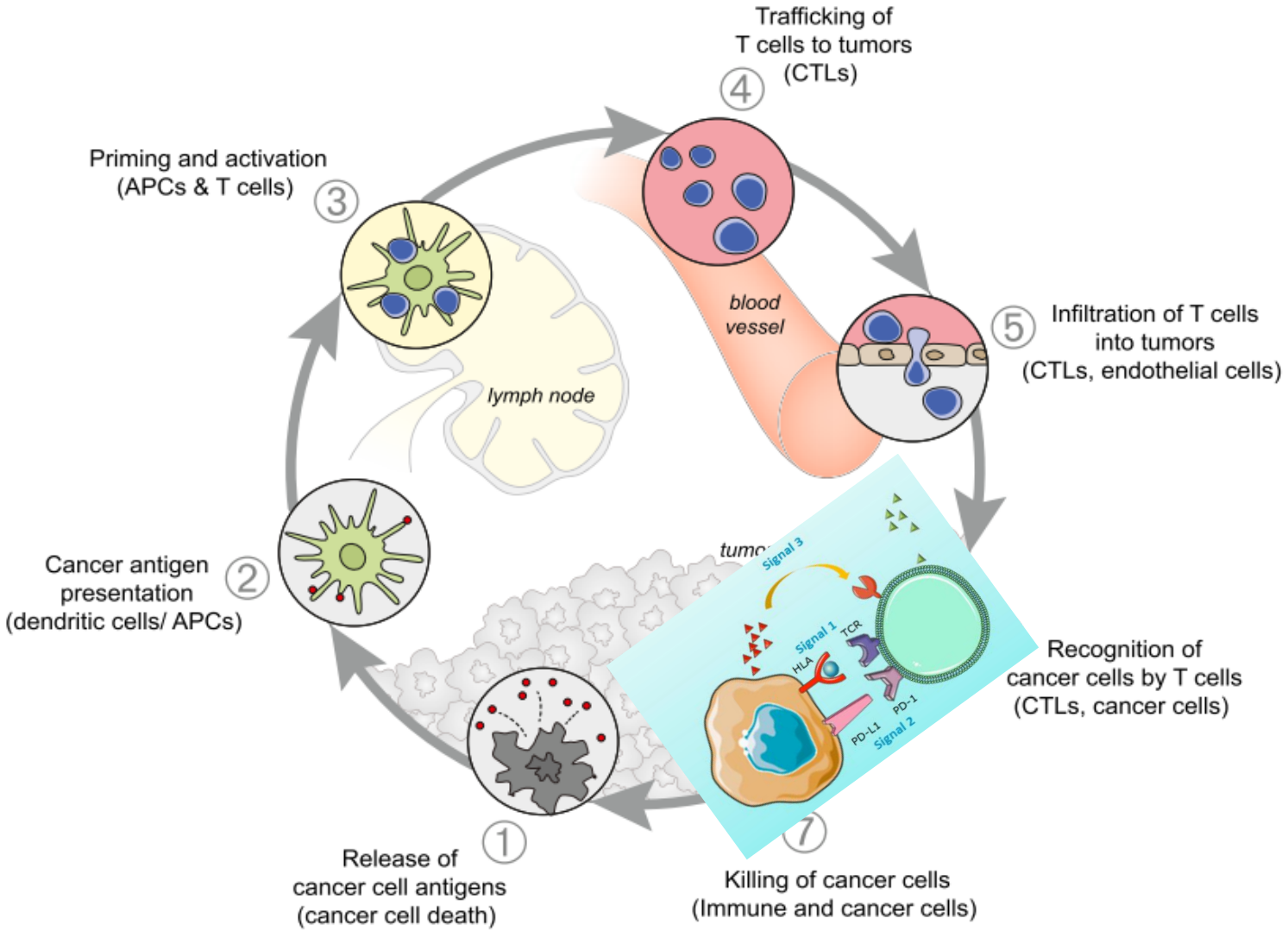
HNSCC suppresses adaptive immunity

- **Signal 1:** Reduced antigen processing and presentation
- **Signal 2:** Anergic T cells
  - ↑ Co-inhibitory receptors: CTLA-4, PD-1
  - ↓ Co-stimulatory receptors: CD137, OX40
- **Signal 3:** Tumor-permissive cytokine profile



Adapted from Robert Ferris, MD, PhD

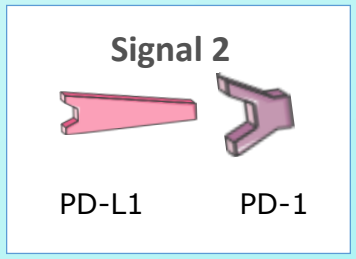
The Cancer-Immunity Cycle

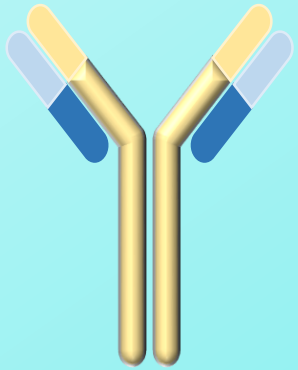


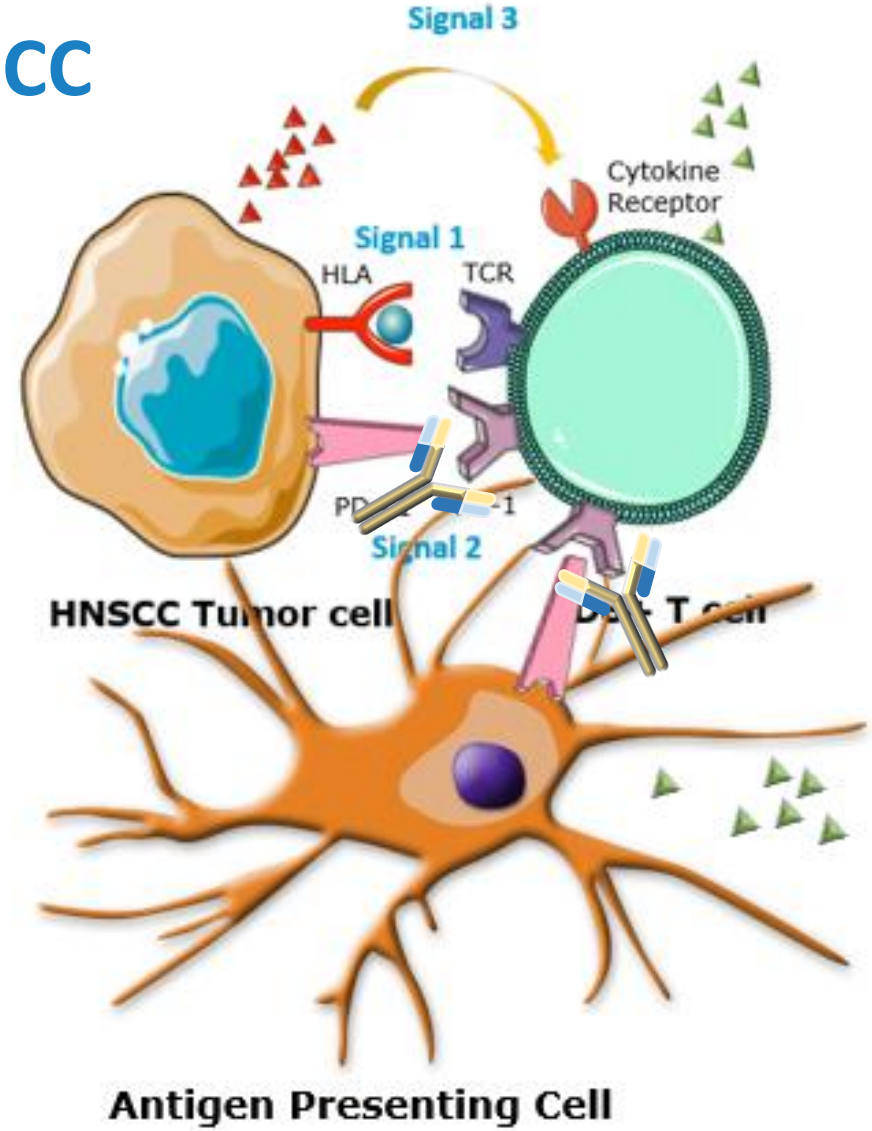
Chen DS and Mellman I.
Cell Press 2013.

Targeting Signal 2 in Recurrent/Metastatic HNSCC

- **2016:** FDA Approval of two anti-PD1 mAb in R/M HNSCC
  - Nivolumab
  - Pembrolizumab
- High-Affinity, IgG4, humanized mAbs against PD1





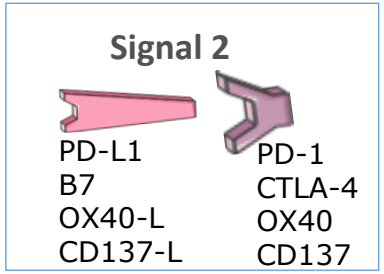


Approved checkpoint inhibitors in head and neck cancers

Drug	Approved	Indication	Dose
Pembrolizumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	200 mg Q3W or 400 mg Q6W
Nivolumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	240 mg Q2W or 480 mg Q4W
Cemiplimab-rwlc	2018	Metastatic cutaneous squamous cell carcinoma, not candidate for curative therapies (any site)	350 mg Q3W
Pembrolizumab + platinum + fluorouracil	2019	Recurrent/metastatic HNSCC 1st line – all patients	200 mg Q3W or 400 mg Q6W
Pembrolizumab	2019	Recurrent/metastatic HNSCC 1st line – PD-L1 CPS ≥ 1	200 mg Q3W or 400 mg Q6W

CheckMate 141: Nivolumab vs Investigator's Choice in R/M HNSCC after Platinum Therapy

*Targeting **Signal 2** in R/M disease*



Randomized Phase III
N=361
2014-2015
Eligibility:
- R/M HNSCC
- Platinum-refractory
- ECOG 0-1

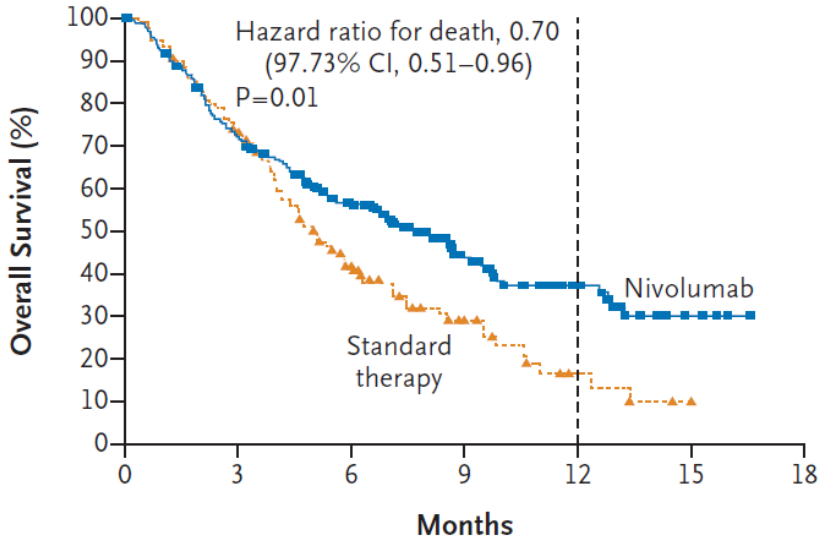
2:1

Nivolumab 3 mg/kg q 2 weeks

Investigator's Choice: Methotrexate, Docetaxel, or Cetuximab

A Overall Survival

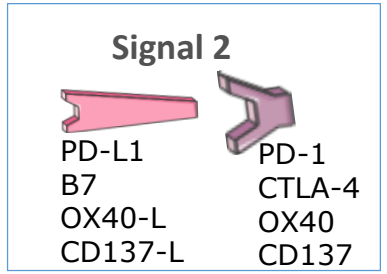
	No. of Patients	No. of Deaths	1–Yr Overall Survival Rate % (95% CI)	Median Overall Survival mo (95% CI)
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard Therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Standard therapy	121	87	42	17	5	1	0

KEYNOTE-040: Pembrolizumab vs Investigator's Choice in R/M HNSCC after Platinum Therapy

*Targeting **Signal 2** in R/M disease*



Randomized Phase III, N=495

Eligibility:

- R/M HNSCC
- Platinum-refractory
- ECOG 0-1

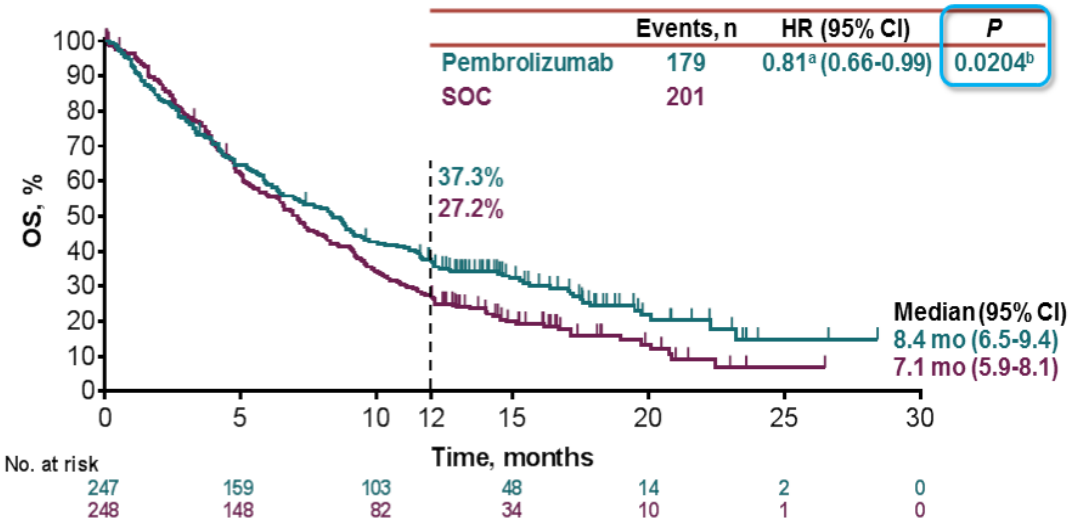
1:1

Pembrolizumab 200 mg IV q3 weeks

Investigator's Choice: Methotrexate, Docetaxel, or Cetuximab

E Cohen_ESMO 2017

Overall Survival in ITT Population



ox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. Initially reported data: HR 0.82 (95% CI, 7-1.01), *P* = 0.0316. After the initial report, updated survival data were obtained for 4 patients. [b]One-sided *P* value based on the log-rank test stratified by the ndomization stratification factors. Data cutoff date: May 15, 2017.

MADRID 2017 ESMO congress

Response Rate and Progression-Free Survival

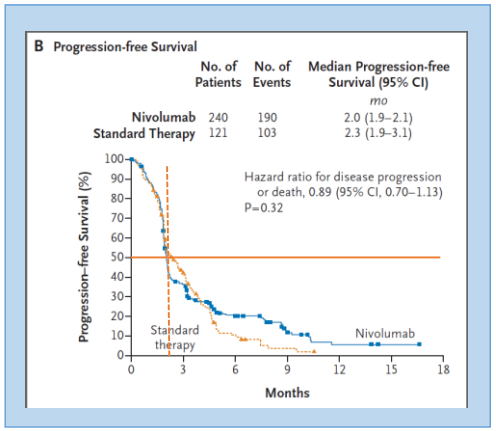
ORR

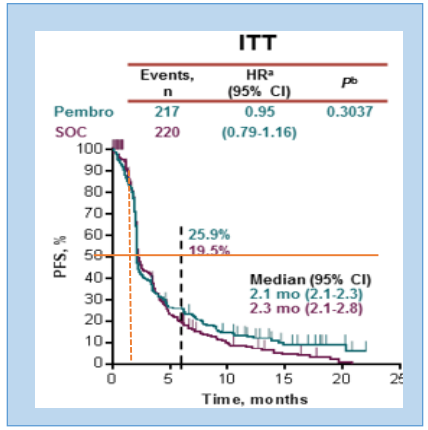
Best overall response	Nivolumab Total N = 240	Pembro Total N = 247	IC Nivo Total N=121	IC Pembro Total N=248
	n (%)	n (%)	n (%)	n (%)
ORR	**32 (13.3)**	**36 (14.6)**	**7 (5.8)**	**25 (10.1)**
CR	6 (2.5)	4 (1.6)	1 (0.9)	1 (0.04)
PR	26 (10.8)	32 (13)	6 (4.9)	24 (10)

Best overall response	Cetuximab-Cisplatin Total N = 96
	n (%)
ORR	**10 (10)**
CR	0 (0)
PR	10 (10)

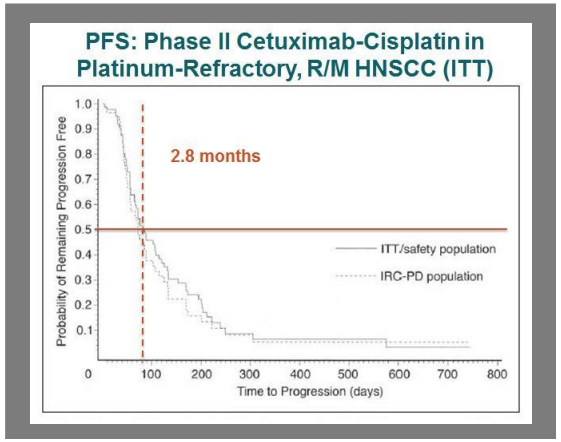
Best overall response	Cetuximab Total N = 103
	n (%)
ORR	**13 (13)**
CR	0 (0)
PR	13 (13)

PFS

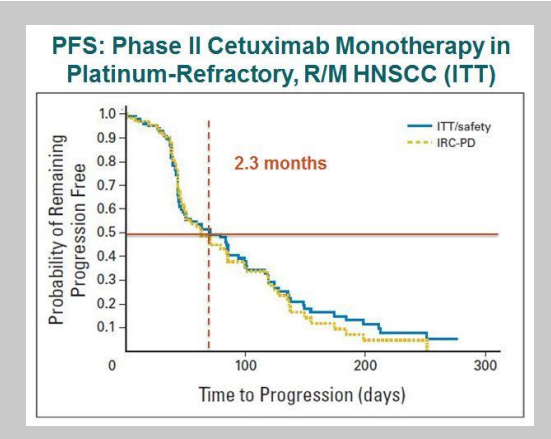




Ferris RL et al. NEJM 2016;375:1856-67.
Cohen EE et al. ESMO 2017.

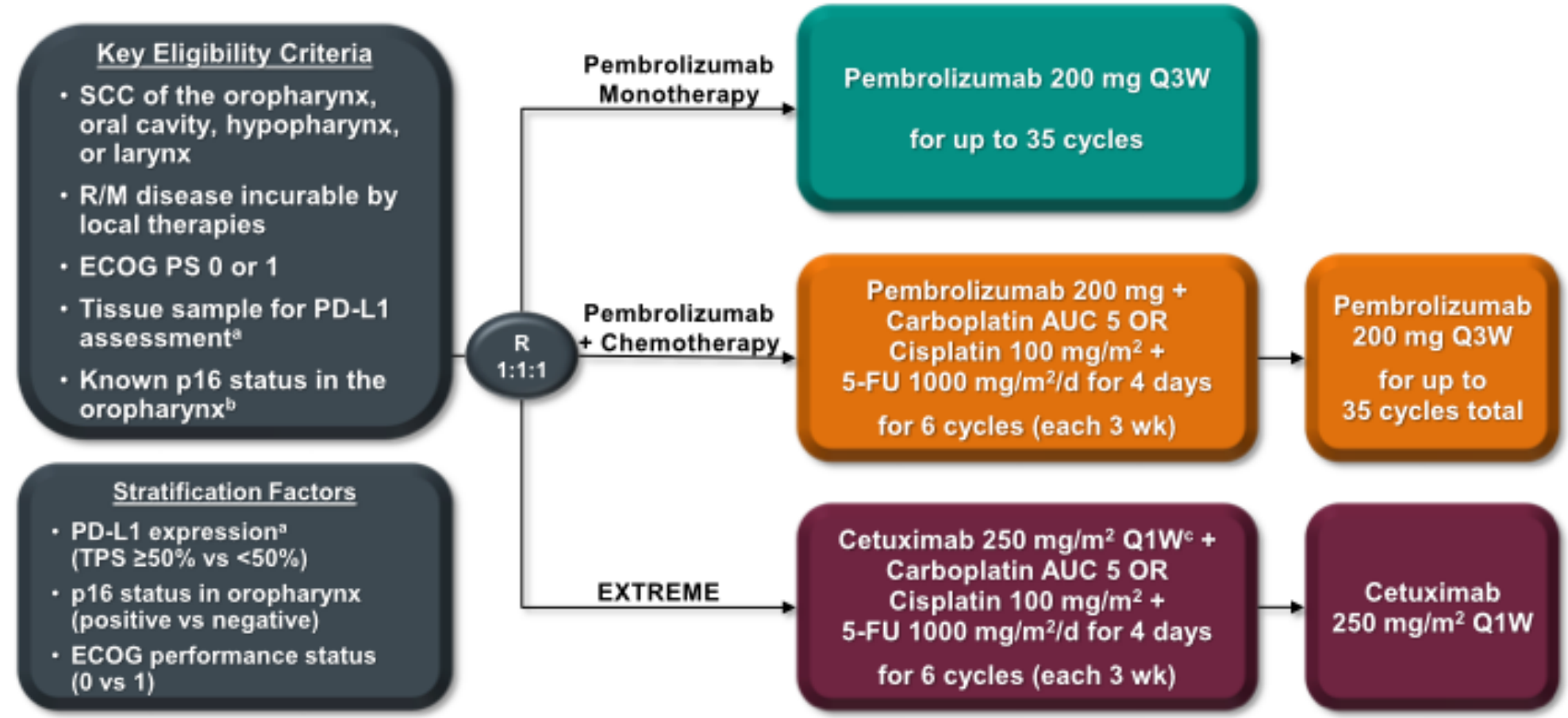


Baselga J. et al. *J Clin Oncol* 2005;23:5568-77.



Vermorken JB. et al. *J Clin Oncol* 2007; 25:2171-2177.

KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

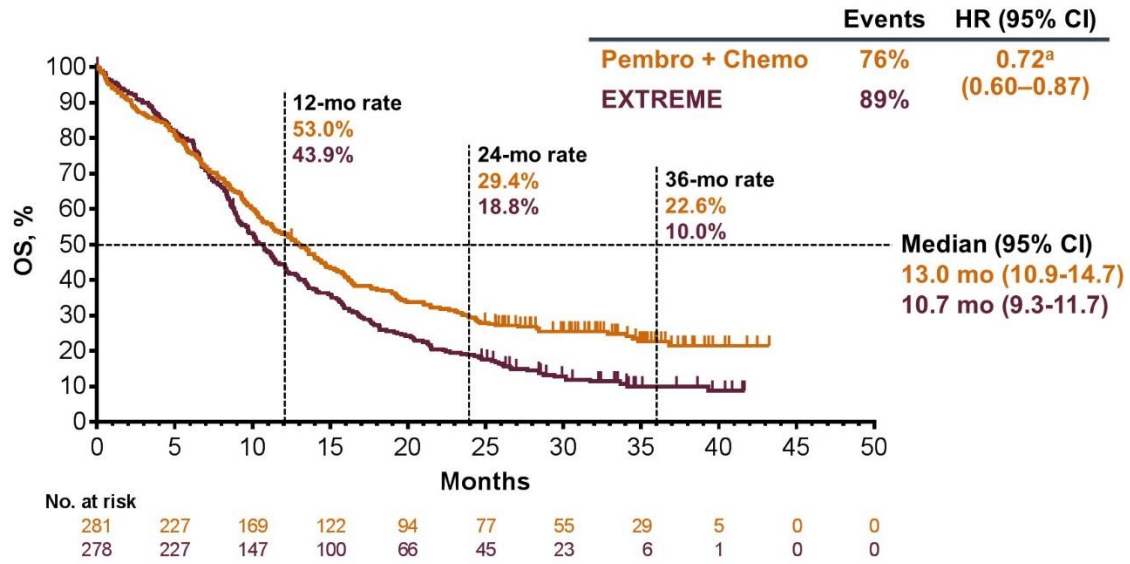


[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Rischin, ASCO 2019.

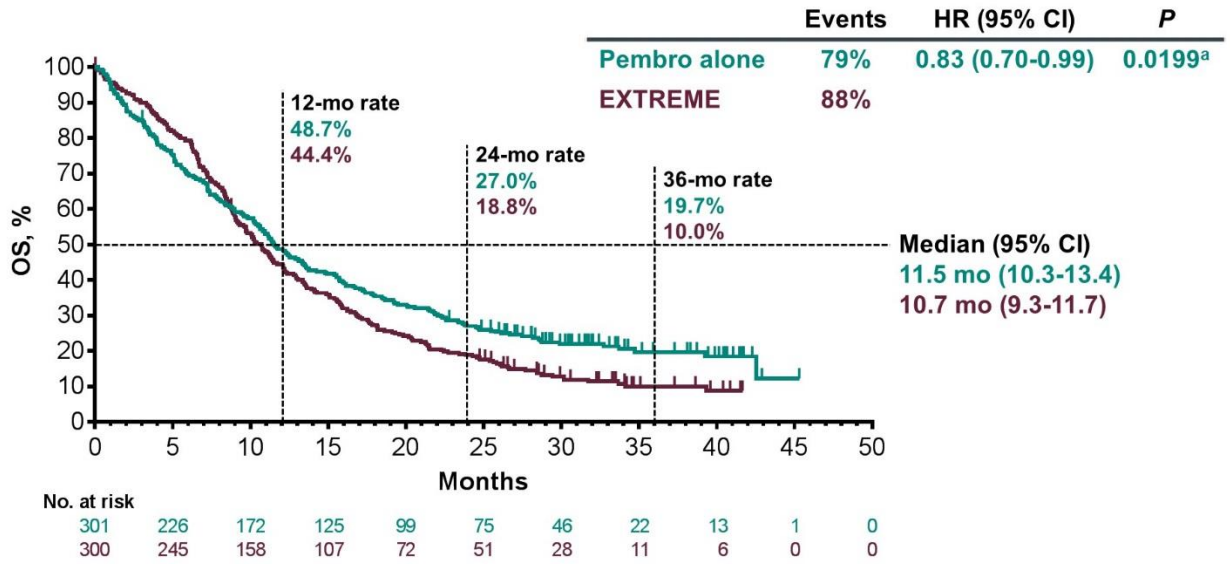
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

OS, P+C vs E, Total Population



[a]At IA2 (data cutoff date: Jun 13, 2018): HR 0.77 (95% CI 0.53–0.93).
FA (data cutoff date: Feb 25, 2019).

OS, P vs E, Total Population



[a]Not statistically significant at the superiority threshold of $P = 0.0059$.
FA (data cutoff date: Feb 25, 2019).

Rischin, ASCO 2019.

KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

Summary of Overall Survival

Population	IA2[1] HR (95% CI)	FA HR (95% CI)
Pembrolizumab monotherapy vs EXTREME		
PD-L1 CPS ≥20	0.61 (0.45–0.83); *P* = 0.0007[a]	0.58 (0.44–0.78)[c]
PD-L1 CPS ≥1	0.78 (0.64–0.96); *P* = 0.0086[a]	0.74 (0.61–0.90)[c]
Total	0.85 (0.71–1.03)[b]	0.83 (0.70–0.99); *P* = 0.0199[d]
Pembrolizumab + chemotherapy vs EXTREME		
PD-L1 CPS ≥20	—	0.60 (0.45–0.82); *P* = 0.0004[a]
PD-L1 CPS ≥1	—	0.65 (0.53–0.80); *P* < 0.0001[a]
Total	0.77 (0.63–0.93); *P* = 0.0034[a,b]	0.72 (0.60–0.87)[c]

[a]Superiority demonstrated. [b]Noninferiority demonstrated (boundary of 1.2). [c]No statistical testing performed. [d]Superiority not demonstrated.

1. Burtness B et al. *Ann Oncol* 2018;29(suppl 8):LBA8_PR.

Rischin, ASCO 2019.

Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

Key Eligibility Criteria
- Advanced cutaneous squamous-cell carcinoma (any site)
- Not eligible for surgery
- ECOG 0-1
- ≥1 assessable lesion

→

Cemiplimab
3 mg/kg IV Q2W

→

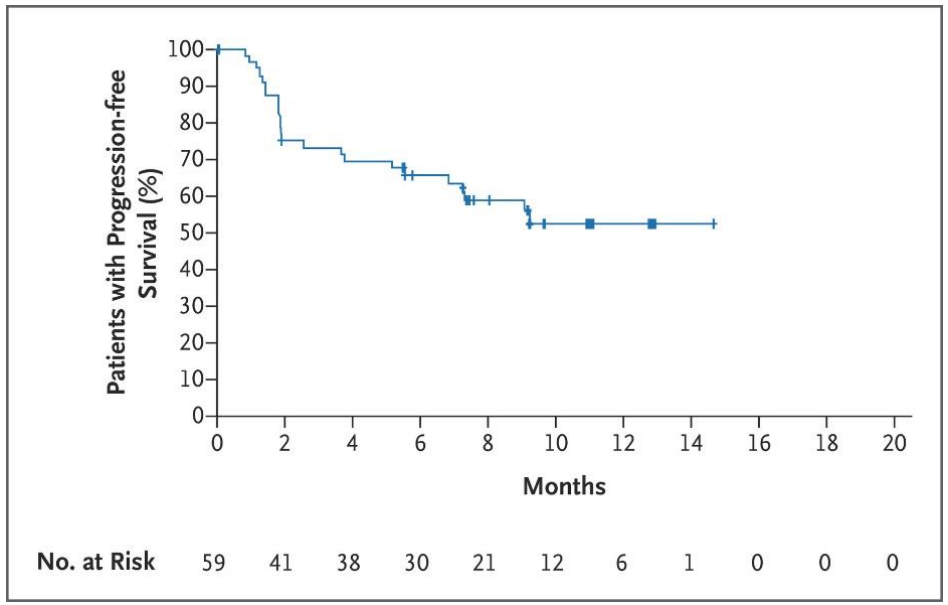
Primary endpoint
- Response rate

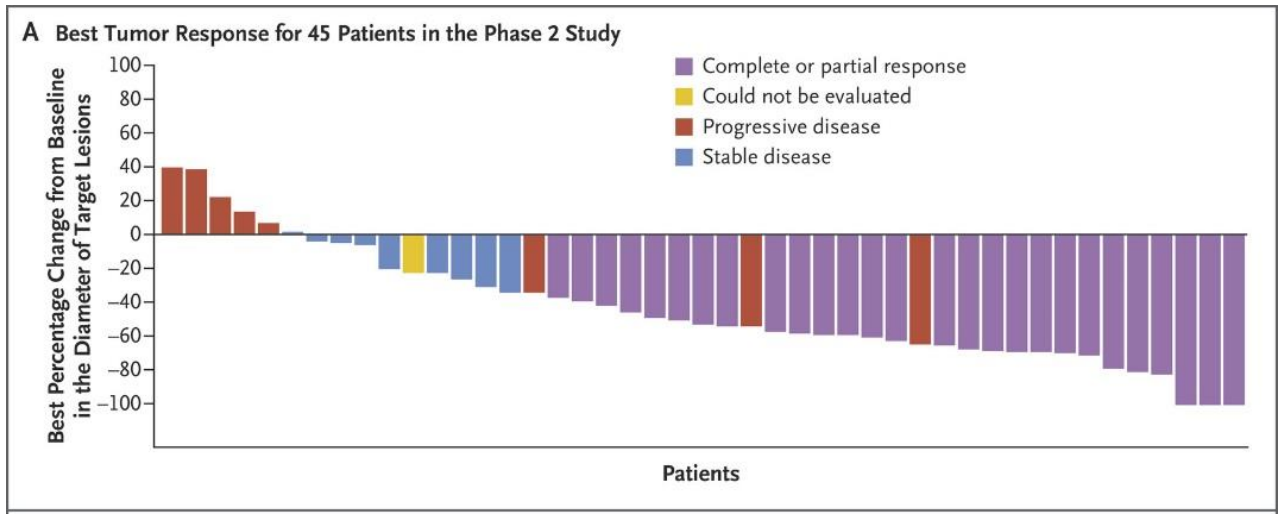
Other endpoints
- Duration of response
- PFS
- OS
- Side effects
- Durable disease control

Migden, NEJM 2018.

Cemiplimab in advanced/metastatic cutaneous squamous-cell carcinoma

- Cemiplimab 3 mg/kg Q2W
- 47% response rate in metastatic patients
- 60% of locally advanced had objective response



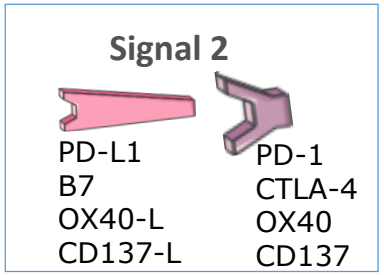


Migden, NEJM 2018.

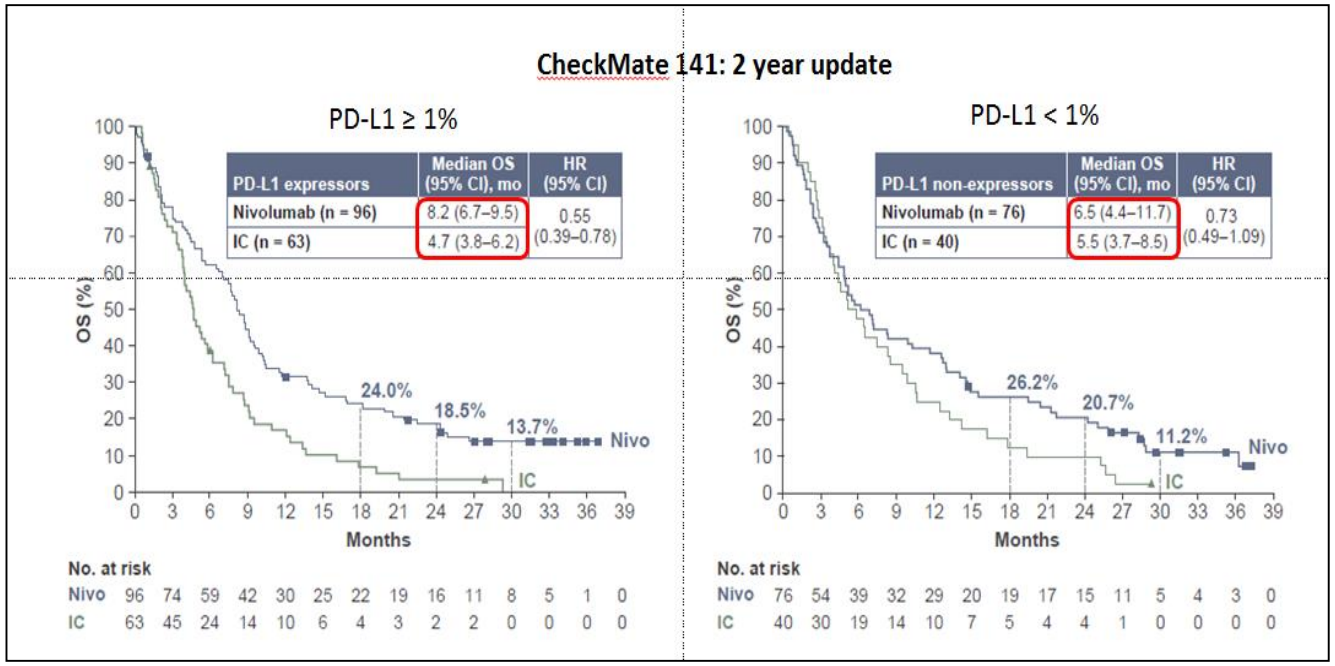
Evaluating Biomarkers in HNSCC

- Only indication that relies on PD-L1 expression: pembrolizumab monotherapy in 1st line HNSCC – CPS ≥ 1 (KEYNOTE-048)
- All other approvals not dependent on PD-L1 expression

The Impact of PD-L1 on Survival

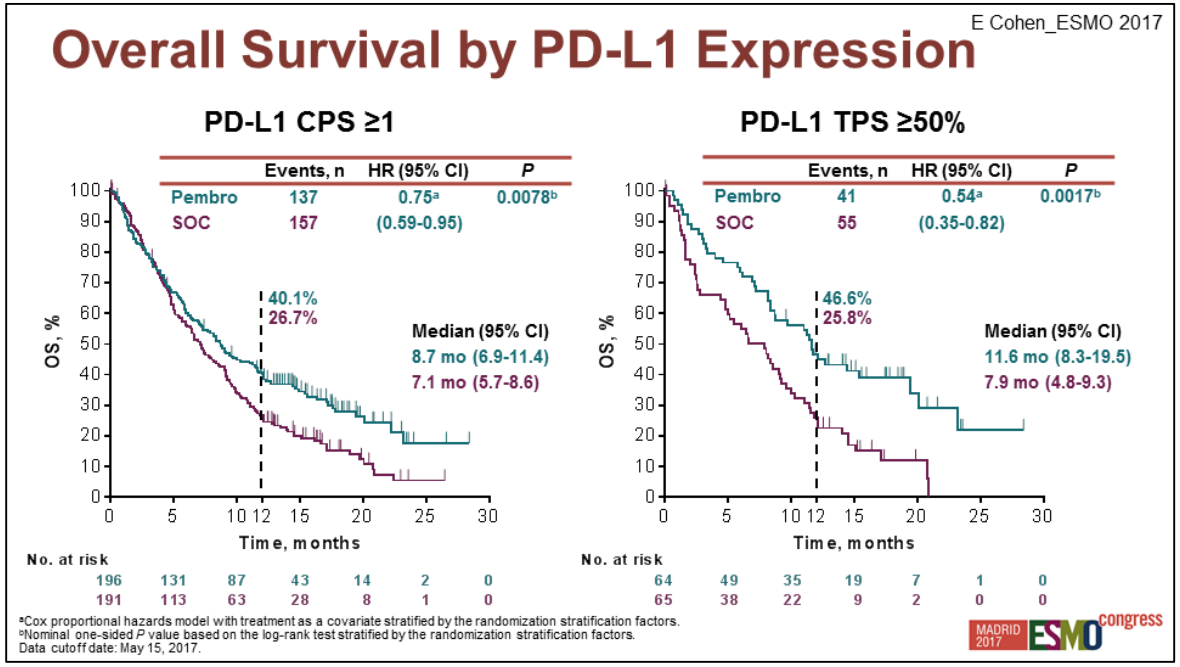


CHECKMATE-141



Ferris RL et al. NEJM 2016;375:1856-67.
Ferris RL et al. Oral Oncol 2018.

KEYNOTE-040



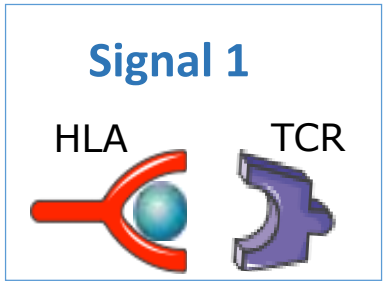
Cohen EE et al. ESMO 2017.

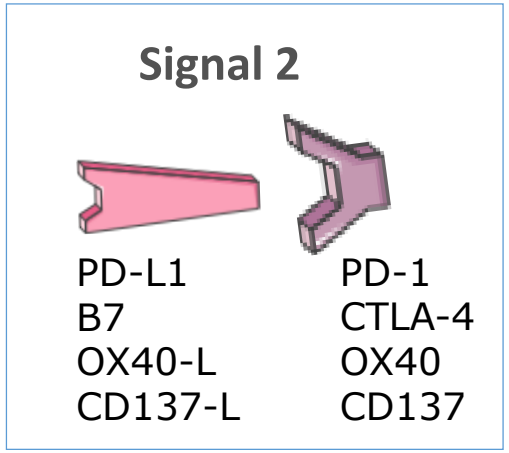
Future Directions: Combination Therapy
PD-1 mAb Plus…

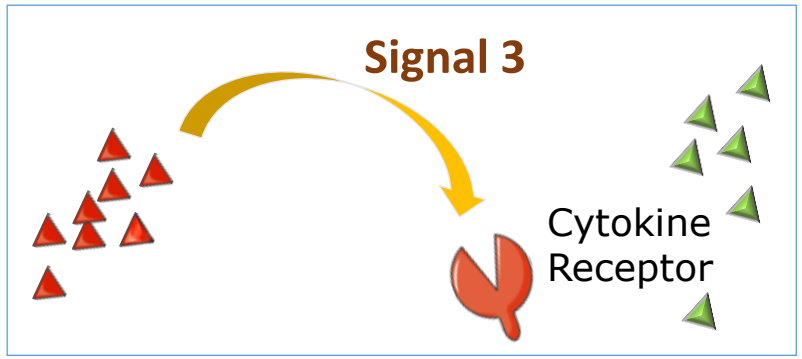
Signal 1	Candidate Agents
Immunogenic cell death	• Radiation • Cisplatin
APM upregulation	• IFN-γ • Cetuximab • TLR agonists • IL-12

Signal 2	Candidate Agents
Checkpoint Antagonism	• CTLA-4 • LAG-3 • IDO-1
Costimulatory Receptor Agonism	• OX-40 • CD137 • CD40

Signal 3	Candidate Agents
Inhibit suppressive cytokines	• VEGF(R), IL-6(R), TGF-β • JAK/STATi
Increase stimulatory cytokines	• IFN-γ • IL-12 • TLR agonists

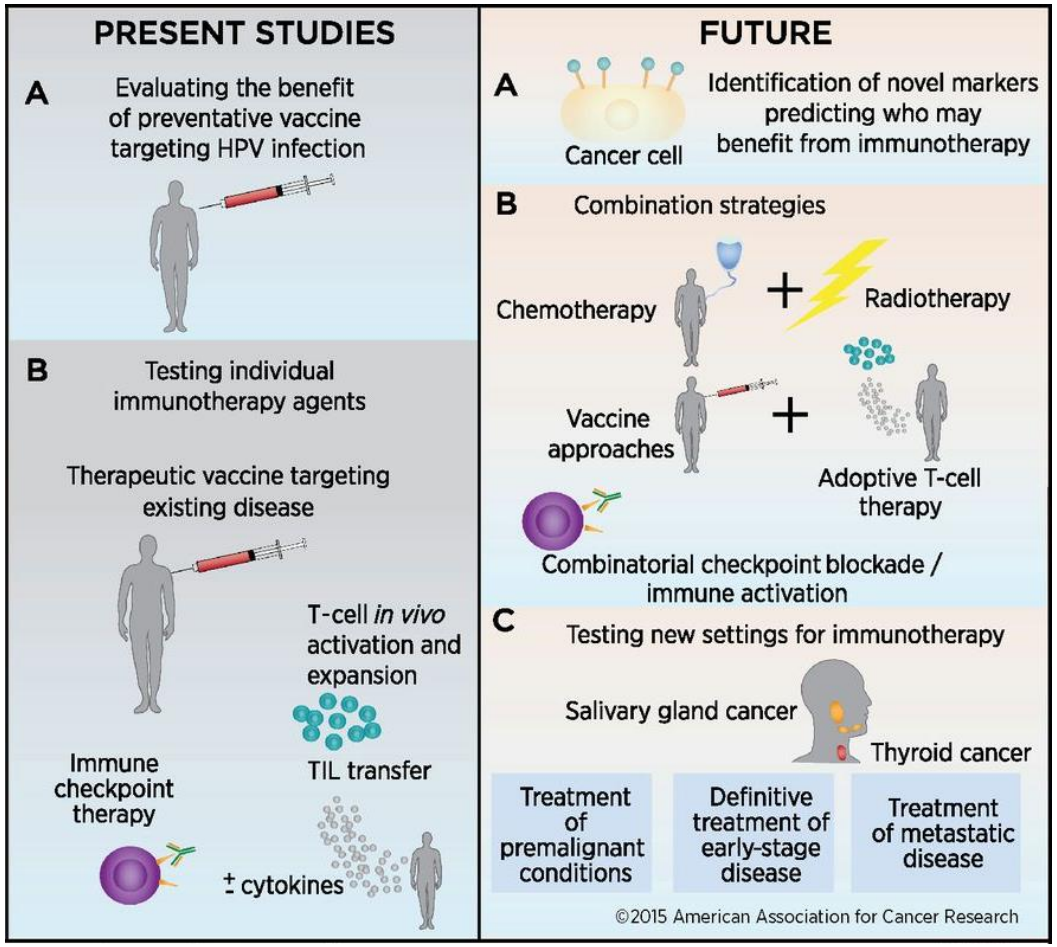






Immunotherapy for the Treatment of Head and Neck Cancers

- Immuno-Oncology (I-O) developments in treatment of head and neck cancers
  - Expression of immunologic markers to guide treatment
  - Preventive vaccination against virally mediated cancers
  - Therapeutic vaccines for established cancers
  - CAR-T and cell-mediated therapies
  - Combinations with immunotherapies



Schoenfeld, Cancer Immunol Res, 2015

In development:
T-VEC + pembrolizumab (KEYNOTE-137)

- T-VEC: Genetically modified, herpes simplex virus type 1–based oncolytic immunotherapy
  - Direct tumor cell lysis (immunogenic cell death)
  - Stimulation of immune microenvironment
- T-VEC 10^6 PFU/mL intratumoral injection followed by 10^8 PFU/mL Q3W PLUS pembrolizumab 200 mg IV Q3W
- Eligibility:
  - Platinum-refractory R/M HNSCC not suitable for curative therapy
  - At least 1 injectable cutaneous, subcutaneous, or nodal tumor ≥ 10 mm
- ORR: 16.7%

Harrington, ASCO 2018.

In development: Checkpoint inhibitors + radiation therapy

- KEYNOTE-412: Chemoradiation + pembrolizumab vs placebo in locally advanced, definitive setting
  - Safety confirmed
- REACH: Chemoradiation +/- avelumab vs. chemoradiation (platinum-eligible) or cetuximab-radiation +/- avelumab (platinum-ineligible) in locally advanced, definitive setting
  - Safety confirmed
- NRG HN003: Adjuvant pembrolizumab + chemoradiation in high risk post-operative setting
  - Phase I study, safety confirmed
- RTOG 1216: Phase III RCT of chemoradiation vs. docetaxel-cetuximab-radiation vs. chemoradiation plus atezolizumab

Leidner, AACR 2019.
Siu, AACR 2018.
Tao, ASCO 2018.

Conclusions

- Cytotoxic chemotherapy achieves limited survival with unfavorable side effects.
- Checkpoint inhibitors that target the PD-1 axis, nivolumab and pembrolizumab, are approved in platinum-refractory/exposed recurrent/metastatic HNSCC.
- Nivolumab and pembrolizumab are in general better tolerated than cytotoxic chemotherapy.
- Ongoing areas of research include: combinations of immunotherapy with radiation and/or other drugs, development of predictive biomarkers and approaches to overcoming resistance.

Resources

Cohen *et al. Journal for ImmunoTherapy of Cancer* (2019) 7:184
https://doi.org/10.1186/s40425-019-0662-5

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

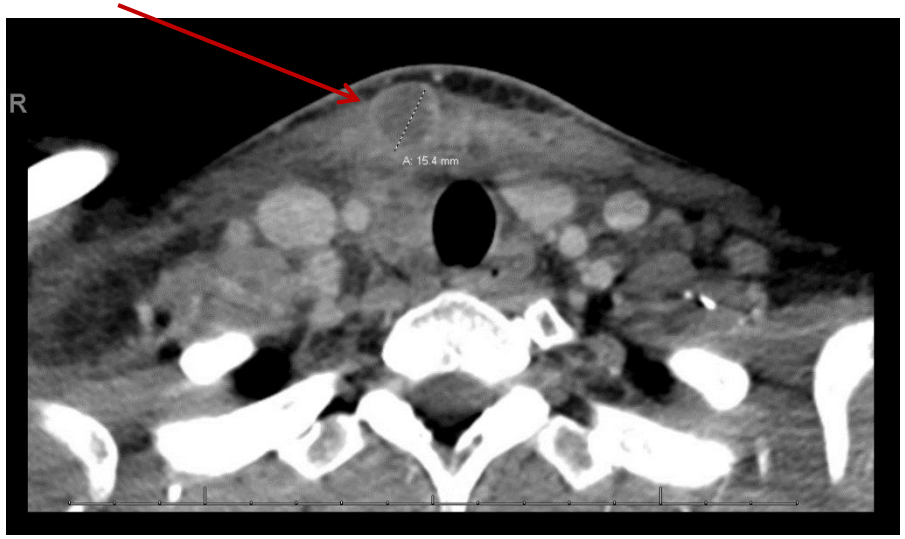
The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC)

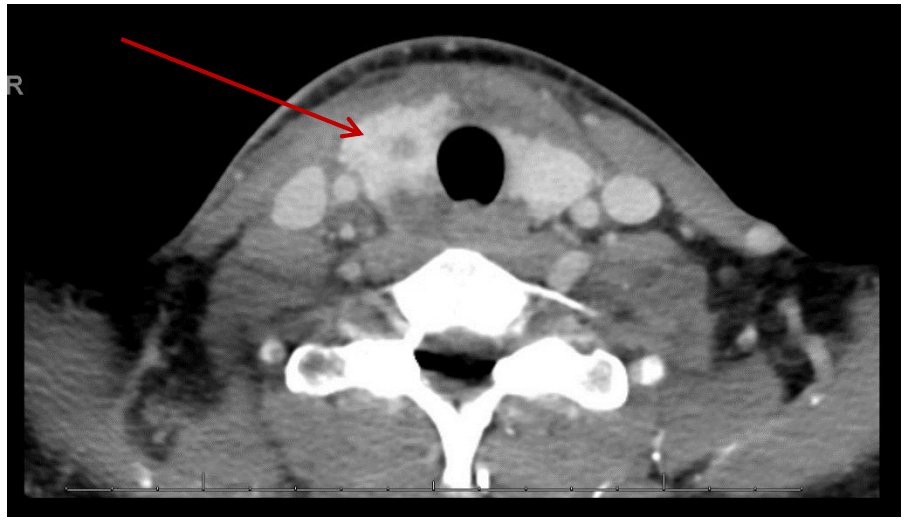
Ezra E. W. Cohen[1], R. Bryan Bell[2], Carlo B. Bifulco[2], Barbara Burtness[3], Maura L. Gillison[4], Kevin J. Harrington[5], Quynh-Thu Le[6], Nancy Y. Lee[7], Rom Leidner[2], Rebecca L. Lewis[8], Lisa Licitra[9], Hisham Mehanna[10], Loren K. Mell[1], Adam Raben[11], Andrew G. Sikora[12], Ravindra Uppaluri[13], Fernanda Whitworth[14], Dan P. Zandberg[8] and Robert L. Ferris[8*]

Case Studies

Case Study 1

- 36 yo non-smoking female completed adjuvant cisplatin-RT for T2N2b SCC of the oral tongue one month ago. She complains of right jaw pain and neck tightness. On exam, radiation mucositis and dermatitis have healed. She has grade 2 lymphedema, new right neck adenopathy, right supraclavicular SC nodule, and enlarged thyroid.
- CT scan demonstrates multifocal recurrence in the right floor of mouth, bilateral neck, thyroid, and mediastinum, which is pathologically documented by excisional biopsy.





Case Study 1

- What would you do next?
    a. Salvage surgery
    b. PD-L1 testing by CPS before selecting treatment
    c. Start anti-PD1 monoclonal antibody without further testing
    d. Start cetuximab monotherapy
    e. Brain MRI

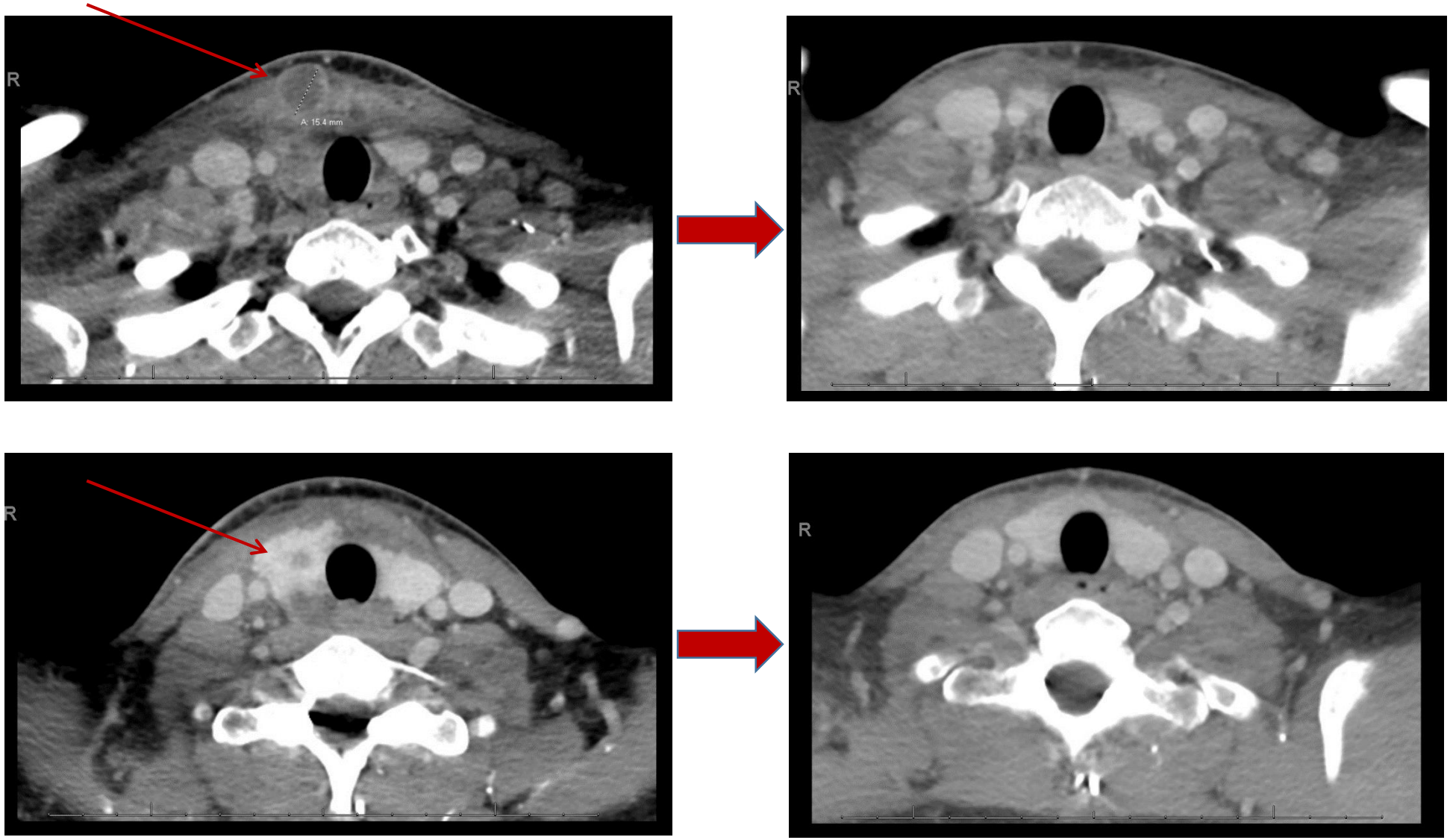
Case Study 1

- What would you do next?
    a. Salvage surgery
    b. PD-L1 testing by CPS before selecting treatment
    c. Start anti-PD1 monoclonal antibody without further testing
    d. Start cetuximab monotherapy
    e. Brain MRI

IN DEVELOPMENT: Personalized Cancer Vaccine

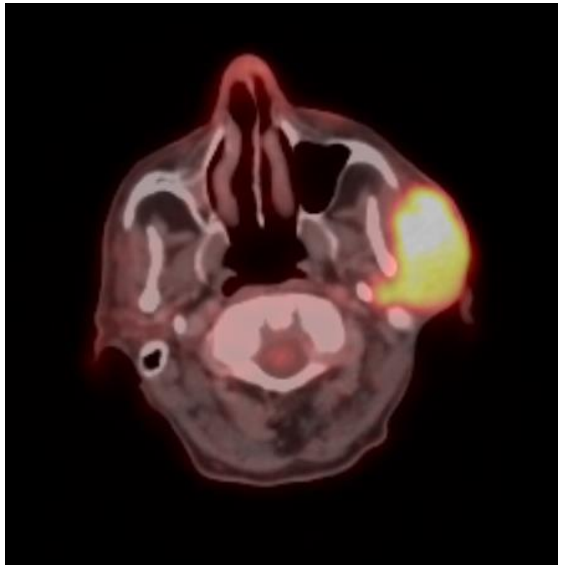
Safety, Tolerability, and Immunogenicity of mRNA-4157 in Combination With Pembrolizumab in Subjects With Unresectable Solid Tumors (NCT03313778)

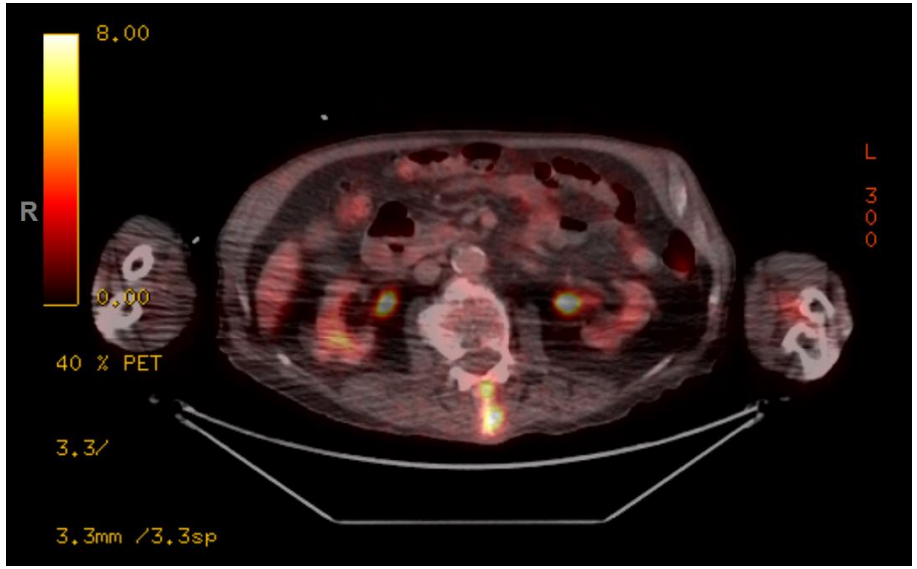
- Clinical trial: pembrolizumab plus personalized mRNA vaccine
- Tumor DNA was sequenced
- Vaccine derived from the mutations within her tumor administered starting week 7 of pembrolizumab



Case Study 2

- 89 year old Caucasian male noted a growing left skin temple lesion in early 2017. Due to recent bereavement, he did not seek medical attention for several months, at which time the lesion was grapefruit sized and hemorrhagic. A biopsy demonstrates basaloid squamous cell carcinoma. PET/CT staging indicates multiple metastases to the skeleton, pathologically proven with an L2 spinous process biopsy.





Case Study 1

- What would you do next?
    a. Palliative radiation therapy to the primary tumor mass
    b. PD-L1 testing by CPS
    c. Start anti-PD1 monoclonal antibody without further testing
    d. Start cetuximab monotherapy
    e. Both a. and c.

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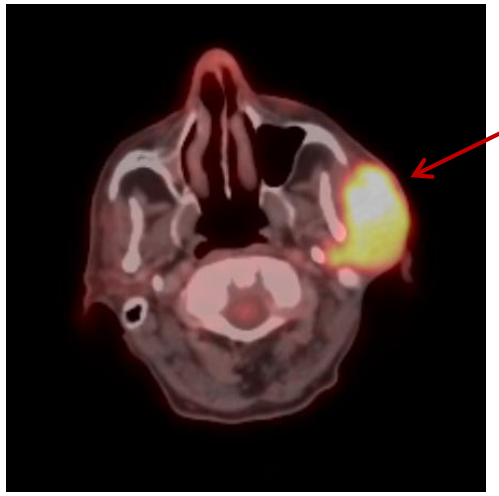
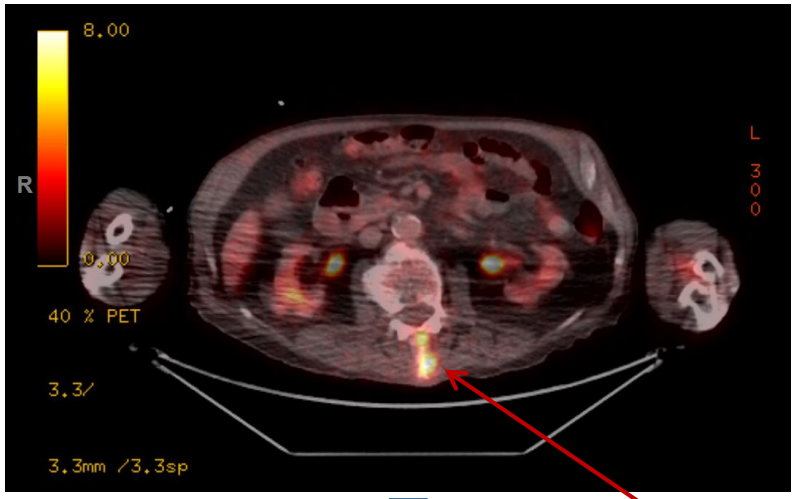
Case Study 2

- Palliative RT to hemorrhagic mass (5 fractions)
- Nivolumab monotherapy 240 mg q2 wks
- Near complete response evident after 2 weeks
- CR at all sites by 1 year, no AI toxicity
- Treatment holiday after 2 years, remains in CR





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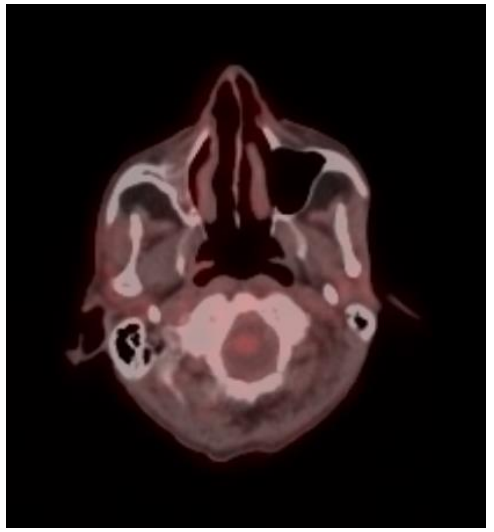

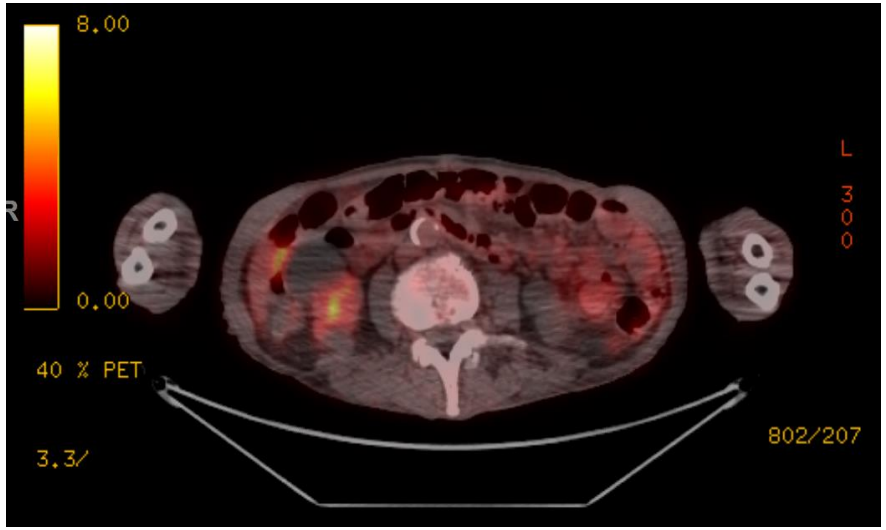

11/5/2018