JADPRO CE Regional Lectures

Clinical Advances and Case Studies in Immune Checkpoint Inhibitors in Oncology

Head and Neck Cancer

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Faculty Financial Disclosures

- Ms. Hoffner has received consulting fees/honoraria from Abbott, Array BioPharma, and Merck.
- Ms. Zitella has served on the advisory board for Array Biopharma and has equity interests/stock options in Kite Pharma.
- Dr. Lewis has nothing to disclose.

Planning Committee Financial Disclosures

- Moshe C. Ornstein, MD, MA, Cleveland Clinic Taussig Cancer Institute (Reviewer) has served as a consultant for Pfizer and Eisai.
- Dorothy Caputo, MA, BSN, RN (Lead Nurse Planner) has nothing to disclose.
- Annenberg Center for Health Sciences at Eisenhower
  - John Bayliss, VP, Business Development, spouse is an employee of Amgen, Inc.; Charles Willis, Director, Continuing Education, consults for Pfizer Inc.; all other staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.
- Alana Brody, Lynn Rubin, and Patti McLafferty (Harborside Medical Education) have nothing to disclose.
- Sandy Leatherman, Annamarie Luccarelli, and Jessica Tamasi (APSHO) have nothing to disclose.
- Claudine Kiffer and Annie Yueh (Harborside) have nothing to disclose.

This activity is supported by educational grants provided by AstraZeneca and Bristol-Myers Squibb.

Learning Objectives

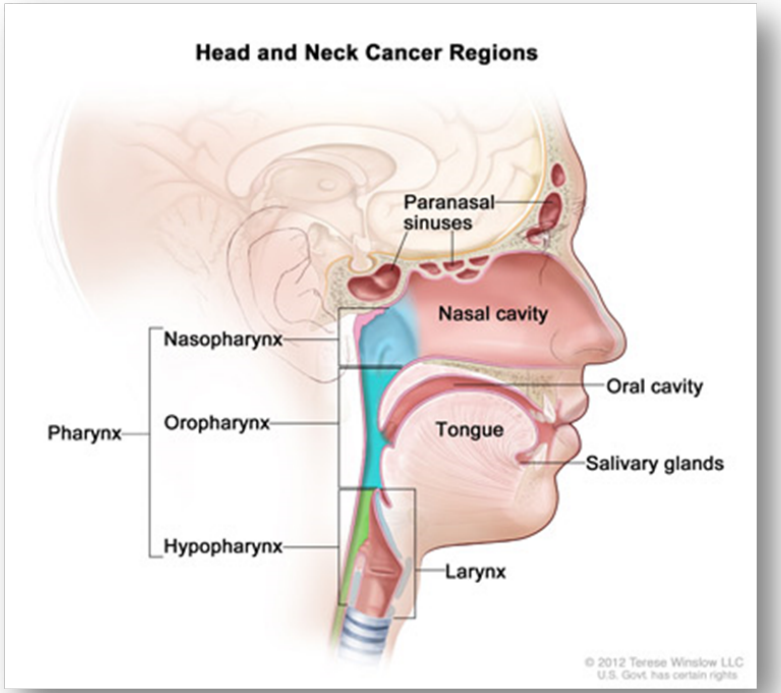
- Differentiate between early and late adverse effects associated with immunotherapeutic agents.
- Recognize the differences between immunotherapeutic agents and chemotherapeutic agents: mechanisms of action, adverse effects, and toxicity management.
- Summarize data on currently available immunotherapeutic agents as they relate to durable treatment responses.
- Explain the utility of biomarker testing in selecting patients for immunotherapy and in predicting clinical outcomes.

Goals

- Summarize data on currently available immunotherapeutic agents for recurrent/metastatic head and neck squamous cell carcinoma.
- Identify appropriate management of immune-related hypophysitis

Head and Neck Squamous Cell Cancer (HNSCC)

- Approximately 3% of all cancers in the United States
- 1.6% of all cancer deaths
- 49,670 estimated new cases in 2017



National Cancer Institute, Cancer Stat Facts: Oral Cavity and Pharynx Cancer, https://seer.cancer.gov/statfacts/html/oralcav.html. Ling, D. C., Bakkenist, C. J., Ferris, R. L., & Clump, D. A. (2018). Role of Immunotherapy in Head and Neck Cancer. Seminars in Radiation Oncology, 28(1), 12–16. https://doi.org/10.1016/J.SEMRADONC.2017.08.009 Photo Credit: National Cancer Institute, https://www.cancer.gov/PublishedContent/Images/images/cancer-types/head-neck/headandneck-diagram.__v60036464.jpg.

Head and Neck Squamous Cell Cancer (cont.)

Three common clinical presentations

- Stage I/II
- Stage III/IV (M_0)
  - Resectable
  - Unresectable
  - Organ preservation
- Stage IV (M_1), recurrent

Survival for recurrent or metastatic HNSCC is dismal

- 5-year survival rate for metastatic disease: 19%
- Patients with recurrent or metastatic HNSCC who progress after platinum-based chemotherapy: survival of < 6 months
- Incidence rising approximately 0.6% each year for the past 10 years

National Cancer Institute, Cancer Stat Facts: Oral Cavity and Pharynx Cancer, https://seer.cancer.gov/statfacts/html/oralcav.html. Ling, D. C., Bakkenist, C. J., Ferris, R. L., & Clump, D. A. (2018). Role of Immunotherapy in Head and Neck Cancer. Seminars in Radiation Oncology, 28(1), 12–16. https://doi.org/10.1016/J.SEMRADONC.2017.08.009

Standard of Care for 1st line R/M HNSCC: EXTREME: Platinum/5-FU/Cetuximab

- Platinum/5-FU/cetuximab x 6 cycles, followed by cetuximab maintenance until PD
  - Cisplatin at 100 mg/m^2 IV or carboplatin AUC 5 on day 1
  - 5-FU at 1,000 mg/m^2/day x 4 days q3wk
  - Cetuximab 400 mg/m^2 (initial dose)IV followed by 250 mg/m2 weekly administered ≥ 1 h prior to chemotherapy
- Median overall survival: 10 months

5-FU = 5-fluorouracil; HNSCC = head and neck squamous cell carcinoma; PD = progressive disease; R/M = recurrent/metastatic; AUC = area under the curve.

Vermorken JB, et al. N Engl J Med. 2008;359:1116-1127. ClinicalTrials.gov. NCT00122460.

Immune System Dysfunction Plays A Role In HNSCC

- Epidermal growth factor receptor (EGFR) is overexpressed in 80%–90% of HNSCC
  - Associated with tumor cell proliferation and worse survival outcomes
  - Cetuximab, an anti-EGFR monoclonal antibody causes tumor lysis via antibody-dependent cellular cytotoxicity and interacts with antigen-presenting cells to promote the opsonization of tumor for phagocytosis and antigen processing which elicits a tumor antigen-specific cytotoxic CD8+ T-cell response
- PD-L1 is overexpressed in > 50%–60% of HNSCC
  - More common in human papilloma virus (HPV)–positive than HPV-negative tumors
- Tumor-infiltrating lymphocytes and CD4 T helper 1 cells activate interferon-mediated signaling which induces expression of PD-L1 on cells in the tumor environment, which protects tumor cells from tumor-directed immunity

HNSCC = head and neck squamous cell carcinoma

Ling, D. C., Bakkenist, C. J., Ferris, R. L., & Clump, D. A. (2018). Seminars in Radiation Oncology, 28(1), 12–16. Chow LQM et al. (2016). Journal of Clinical Oncology, 34(32), 3838–3845. https://doi.org/10.1200/JCO.2016.68.1478

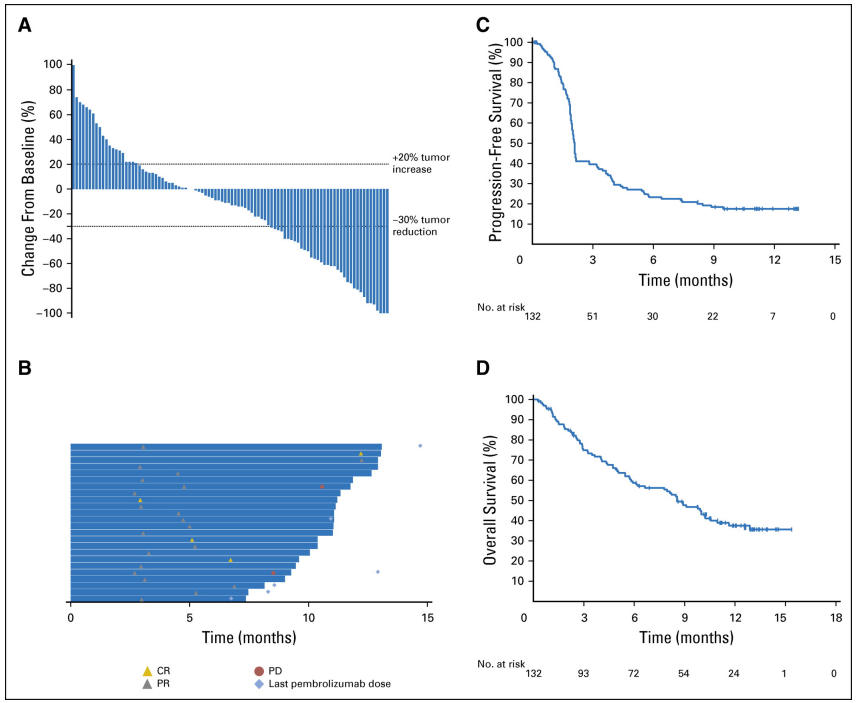
Approved Immunotherapy

- Pembrolizumab granted accelerated approval 8/5/2016 for HNSCC after progression beyond platinum-containing chemotherapy
  - Based on data from KEYNOTE-012
  - Confirmation study KEYNOTE-040 did not meet primary endpoint (OS)
- FDA approved nivolumab 11/10/16 for the same indication as pembrolizumab
  - Based on data from CheckMate-141

HNSCC = head and neck squamous cell carcinoma; FDA = U.S. Food and Drug Administration.

KEYNOTE-012: Phase 1 Trial Pembrolizumab for R/M HNSCC

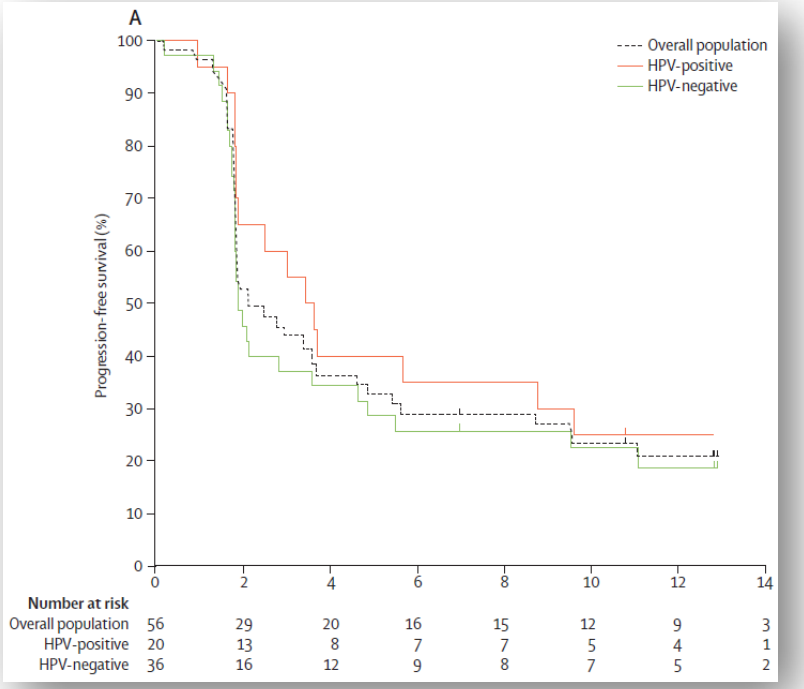
- Initial cohort: PD-L1+ > 1%
- Expansion cohort: any PD-L1 status
- Treated with pembrolizumab 10 mg/kg every 2 weeks
- 18% overall response in all patients
  - 32% overall response in HPV+ patients
  - 14% overall response in HPV- patients
- Response correlated with PD-L1 expression
  - 22% in PD-L1 positive
  - 4% PD-L1 negative

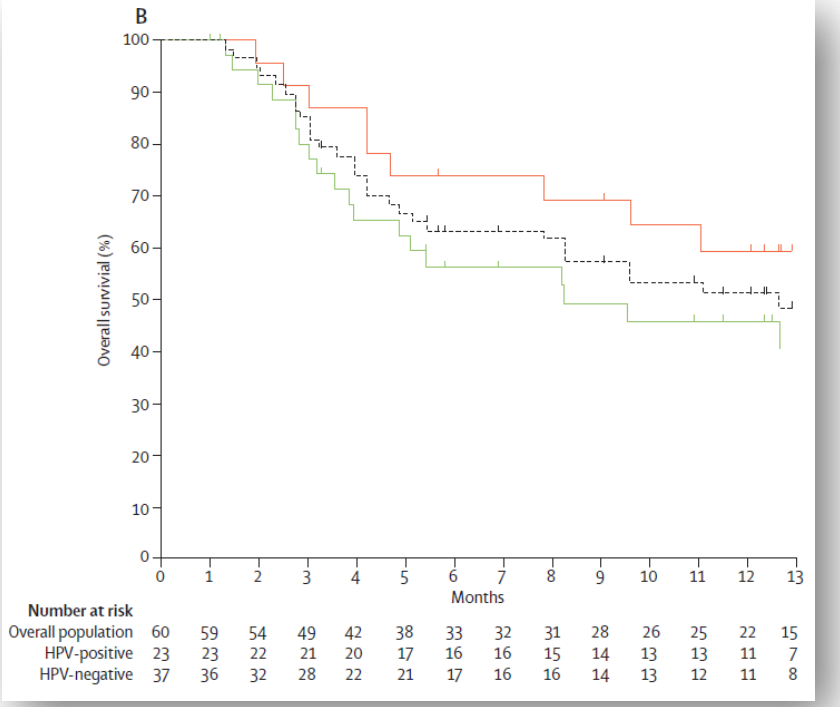


HNSCC = head and neck squamous cell carcinoma; R/M = recurrent/metastatic

Seiwert TY, et al. *Lancet Oncol* 2016;17:956-65 Chow LQM et al. Journal of Clinical Oncology 2016 34, no. 32, 3838-3845.
DOI: 10.1200/JCO.2016.68.1478

KEYNOTE-012: HPV-Positive Tumors Associated With Improved Overall Survival

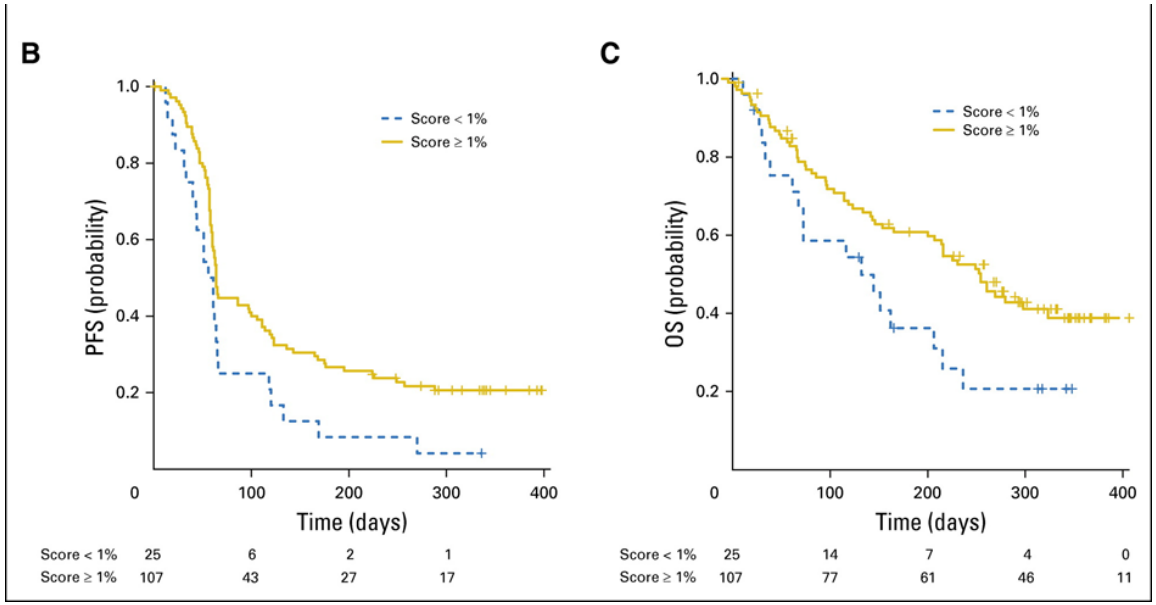




Seiwert TY, et al. *Lancet Oncol* 2016;17:956-65.

KEYNOTE-012:

Higher Response Rate With Greater PD-L1 Expression



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)

Seiwert TY, et al. *Lancet Oncol* 2016;17:956-65.

KEYNOTE-040: Phase III Trial Pembrolizumab vs. SOC Chemo for Second-Line R/M HNSCC

R/M HNSCC after platinum-based therapy (N = 495)

Pembrolizumab 200 mg IV q3w (n = 247)

Investigator's choice (SOC): (n = 248)

- Methotrexate 40 mg/m^2 weekly (in absence of toxicity could increase to 60 mg/m^2)
- Docetaxel 75 mg/m^2 q3w
- Cetuximab loading dose of 400 mg/m^2 followed by 250 mg/m^2 weekly

Response					
	mOS	**CR**	**PR**	**SD**	**mDOR**
Pembro (n=247)	8.4 mo (NS)	9%	32%	31%	18.4 mo
SOC chemo (n=248)	7.1 mo	1%	25%	45%	5 mo

Did not meet endpoint for overall OS. However, subset of patients with high PD-L1 expression did have significantly improved OS with pembrolizumab.

CR = complete response; HNSCC = head and neck squamous cell carcinoma; mDOR = median duration of response; mOS = median overall survival; NS = not significant; PD = progressive disease; PR= partial response; R/M = recurrent/metastatic; SD = stable disease; SOC = standard of care.

KEYNOTE-040: Pembrolizumab Significantly Improved Survival in Patients With High PD-L1 Expression

	PD-L1 ≥ 1%		PD-L1 > 50%	
	Pembrolizumab	SOC Chemo	Pembrolizumab	SOC Chemo
Median Overall Survival	8.7 mo	7.1 mo	11.6 mo	7.9 mo

SOC = standard of care.

CheckMate 141: Phase III Nivolumab Vs. Chemotherapy for Second-Line R/M HNSCC

R/M HNSCC after platinum-based therapy (N = 361)

Nivolumab 3 mg/kg IV Q2W (n = 240)

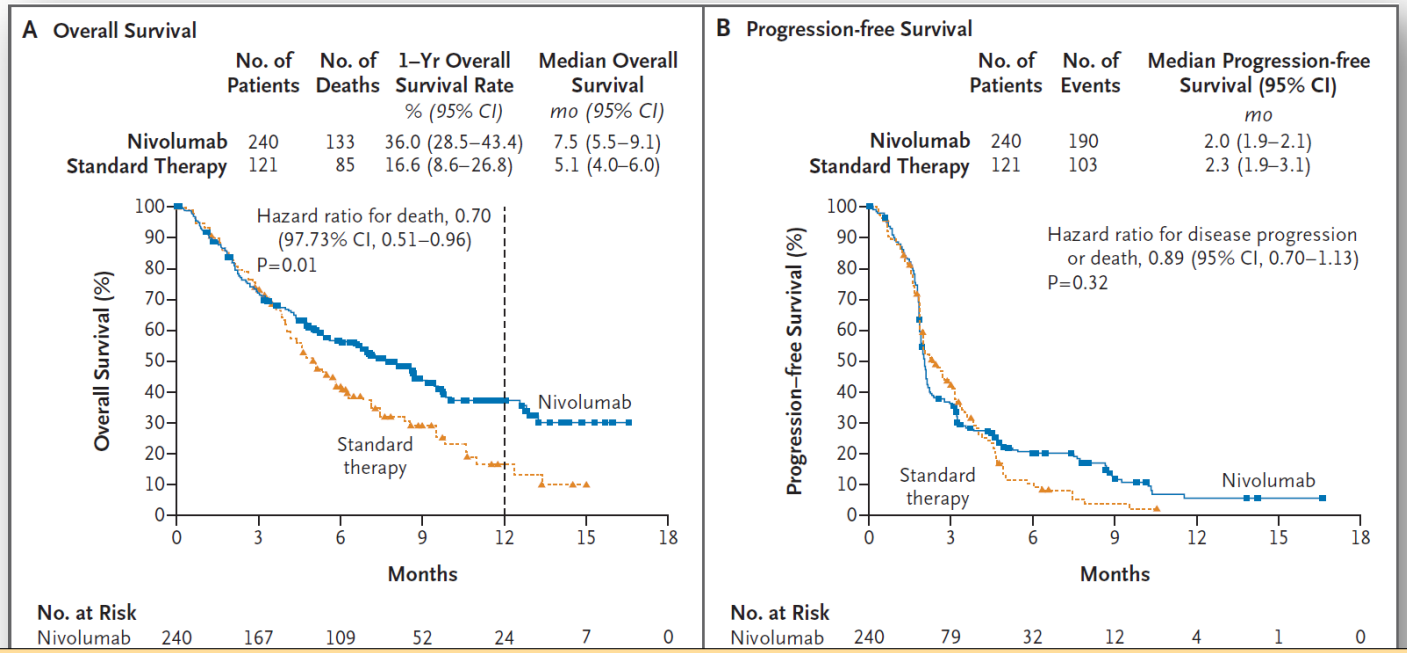
Investigator's choice (SOC): (n = 121)
- Methotrexate 40 mg/m^2 QW
- Docetaxel 30 mg/m^2 QW
- Cetuximab loading dose of 400 mg/m^2 followed by 250 mg/m^2 weekly

	ORR	18-mo OS	mOS	mDOR	Grade 3–4 AE
Nivolumab (n = 240)	13%	22%	7.7 mo	10 mo	13%
SOC chemo (n = 121)	6%	8%	5.1 mo	4 mo	35%

AE= adverse event; HNSCC= head and neck squamous cell carcinoma; mDOR=median duration of response; mOS=median overall survival; ORR= objective response rate; OS= overall survival; R/M= recurrent/metastatic; SOC=Standard of care

Ferris RL, et al. *N Engl J Med* 2016;375-1856-67; Gillison, M. L., et al. (2017). *Journal of Clinical Oncology*, *35*(15_suppl), 6019. https://doi.org/10.1200/JCO.2017.35.15_suppl.6019

CheckMate 141



Median OS: 7.5 months in nivolumab group vs. 5.1 months in SOC group
1-year OS: nearly doubled in nivolumab group---36% versus 17% (SOC)

Ferris RL, et al. *N Engl J Med* 2016;375-1856-67.

CheckMate 141--Sub-Analysis of Patients that received Nivolumab Vs Chemo for 1st Line R/M HNSCC

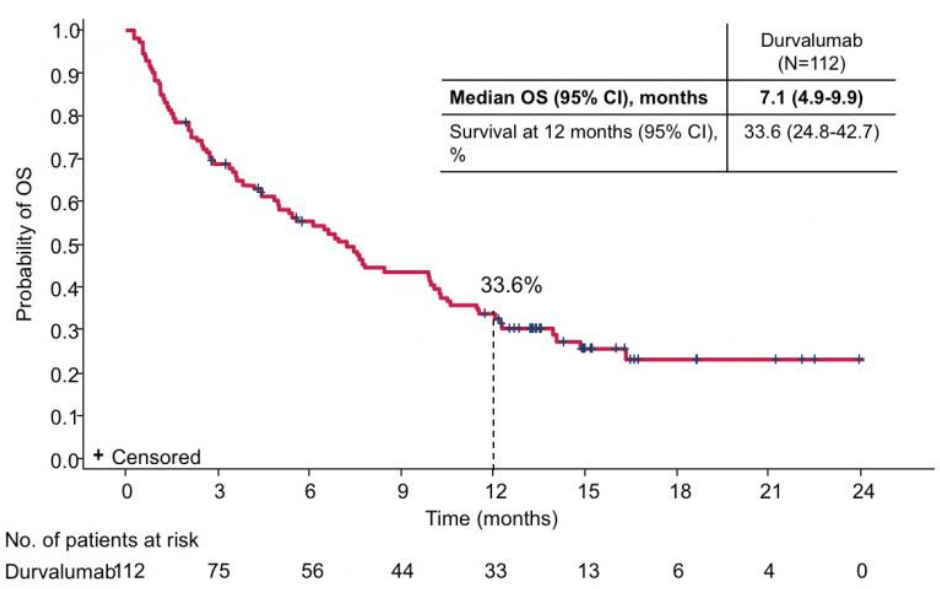
Response			
	mOS	**1-year OS**	**ORR**
Nivolumab (n = 52)	7.7 mo	40%	19%
SOC chemo (n = 26)	3.3 mo	15%	12%

HNSCC = head and neck squamous cell carcinoma;; mOS = median overall survival; ORR= objective response rate; OS= overall survival; R/M= recurrent/metastatic; SOC = standard of care

Gillison, M. L., et al. (2017). *Journal of Clinical Oncology*, *35*(15_suppl), 6019. https://doi.org/10.1200/JCO.2017.35.15_suppl.6019

HAWK: Phase II Trial Durvalumab for Second-Line R/M HNSCC

- Immunotherapy-naive adult patients with high PD-L1 expression, who had progression or recurrence during or after 1 platinum-based regimen for R/M HNSCC (n = 112)
- Durvalumab at 10 mg/kg IV for up to 12 months or until PD, the initiation of another anticancer therapy, consent withdrawal, or unacceptable toxicity occurred



HNSCC = head and neck squamous cell carcinoma; PD = progressive disease; R/M= recurrent/metastatic

Zandberg D, et al. Durvalumab for recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): preliminary results from a single-arm, phase 2 study. ESMO 2017 Abstract

Selected Ongoing Clinical Trials

- KESTREL (NCT02551159): Phase III comparing durvalumab with or without tremelimumab with EXTREME chemotherapy (carboplatin or cisplatin + 5-FU + cetuximab) for first-line treatment of R/M HNSCC
- EAGLE (NCT02369874): Phase III comparing durvalumab; tremelimumab plus durvalumab; or chemotherapy (cetuximab, taxane, methotrexate, or fluoropyrimidine) for second-line therapy in platinum-resistant R/M HNSCC
- CheckMate 651 (NCT02741570): Phase III comparing nivolumab and ipilimumab vs. EXTREME chemotherapy (Cetuximab + Cisplatin/Carboplatin + Fluorouracil) for first-line therapy of R/M HNSCC
- CheckMate 714 (NCT02823574): Phase II randomized trial comparing nivolumab/ipilimumab with nivolumab for first-line treatment of R/M HNSCC

HNSCC= head and neck squamous cell carcinoma; R/M= recurrent/metastatic

Case Study

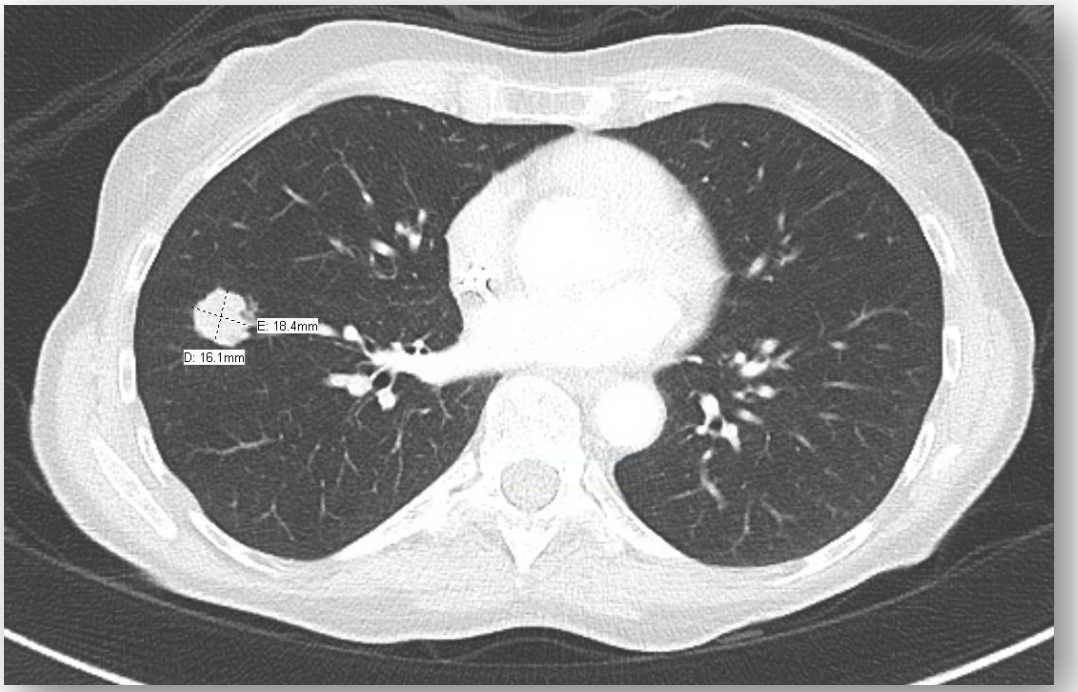
DC is a 65-year-old female with stage IVa (T2N2bM0) squamous cell carcinoma of the right tonsil, HPV/P16+

Oncology History:

- Right pharyngectomy and right lymph node dissection followed by adjuvant chemoradiation (RT and weekly cisplatin)
- One year later, developed pulmonary metastases, treated with EXTREME (5-FU, carboplatin, and cetuximab) for 6 cycles followed by cetuximab maintenance for 11 weeks until PD with worsening pulmonary metastases
- For second-line treatment of R/M HNSCC, started pembrolizumab at 200 mg IV over 30 minutes every 3 weeks
- DC tolerated therapy well through the first 3 cycles, except for mild joint pains controlled with prednisone at 10 mg/d

PD = progressive disease; RT = radiation therapy; 5-FU = 5-fluorouracil

Case Study (cont.)



Right lung nodule prior to initiation of pembrolizumab

Image courtesy Brianna Hoffner, University of Colorado.

Case Study (cont.)

DC presents for Cycle 4 pembrolizumab and looks unwell. She reports headaches, dizziness, and fatigue.

What is the most common presentation of hypophysitis?

A. Central adrenal insufficiency
B. Central hypothyroidism
C. Diabetes insipidus
D. Hypogonadism
E. Unsure

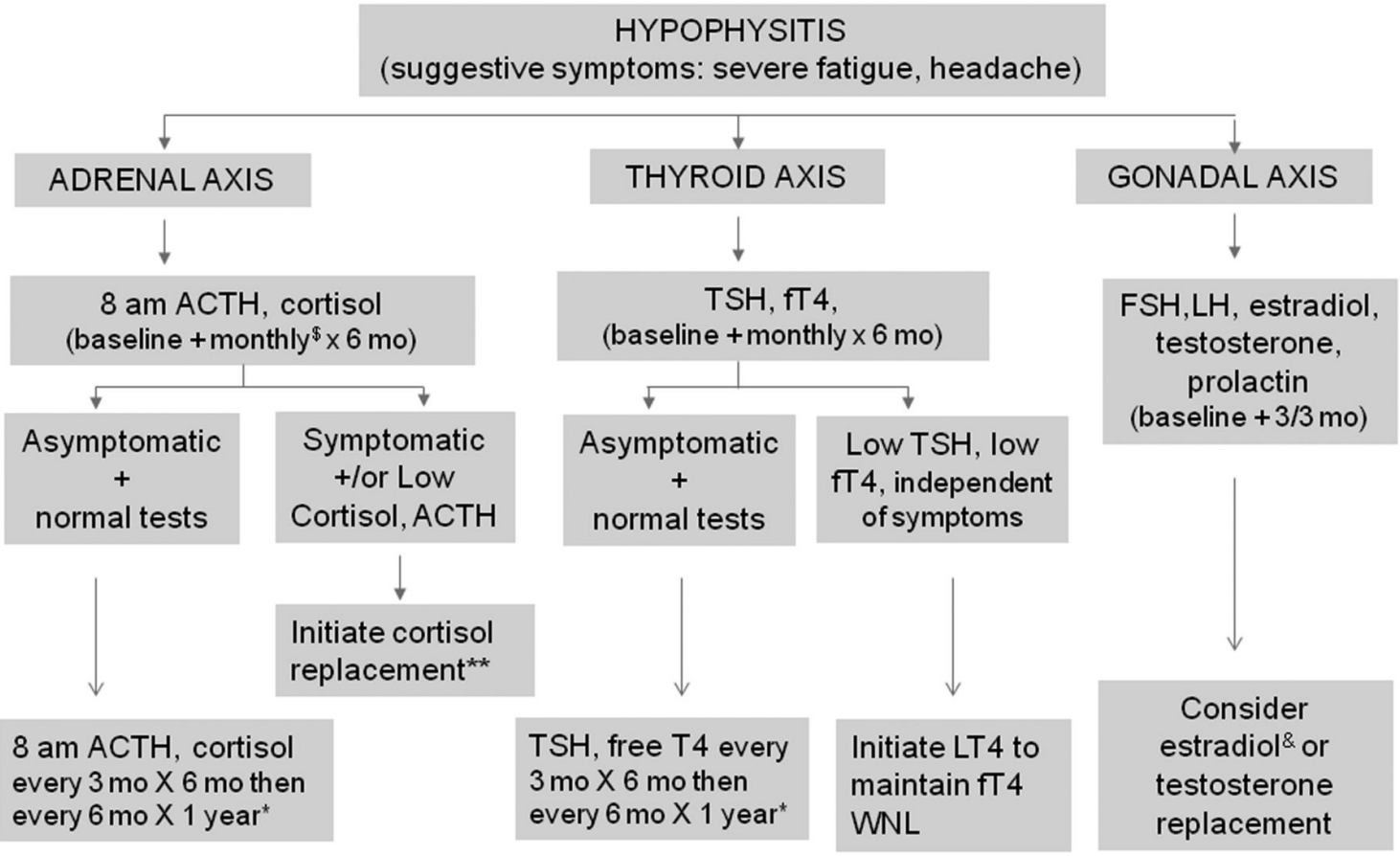
Hypophysitis: Inflammation of the Pituitary Gland

Results in deficiency of all or some of the pituitary hormones

- Most common presentation of hypophysitis
  - Central adrenal insufficiency
- Symptoms of hypophysitis
  - Headache, fatigue, muscle weakness
  - Constipation
  - Cognitive difficulties (related to thyrotropin axis)
  - Erectile dysfunction/amenorrhea (gonadotropin axis, LH/FSH)
  - Orthostatic hypotension, hypoglycemia/hyponatremia (corticotrophin deficiency, ACTH)
- Workup
  - Evaluation of pituitary gland hormones (ACTH, TSH, FSH, LH, AM cortisol)
  - Electrolytes
  - MRI brain with contrast (pituitary cuts)
- Diagnosis
  - Low ACTH with low cortisol
  - Low or normal TSH with low free T4
  - Hypernatremia and volume depletion with diabetes insipidus
  - Low testosterone or estradiol with low LH and FSH

ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; LH= luteinizing hormone; MRI = magnetic resonance imaging; TSH= thyroid-stimulating hormone.

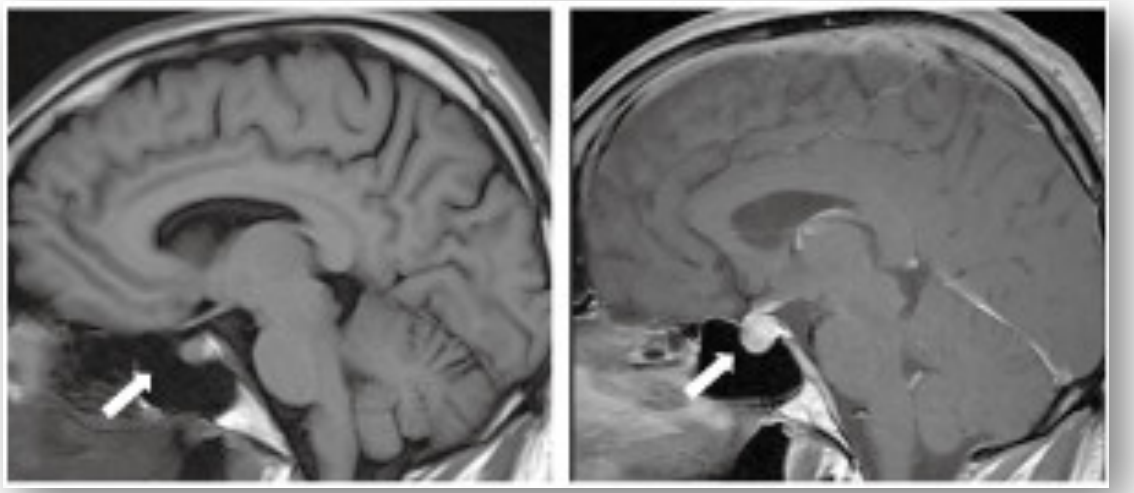
Michot JM, et al. *Eur J Cancer* 2016;54:139-48; Byun DJ, et al. *Nat Rev Endocrinol* 2017;13:195-207; Brahmer, J. R., et al. (2018). Journal of Clinical Oncology, JCO.2017.77.638. https://doi.org/10.1200/JCO.2017.77.6385



ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; TSH = thyroid-stimulating hormone

Case Study (cont.)

	ACTH (pg/mL)	TSH (ml/UL)	T4 (ng/dL)
Pre	30	1.3	1.1
Post	4	0.39	0.3
Reference	10–50	0.5–5.5	0.89–1.76



Pre-treatment MRI

MRI prior to cycle 4

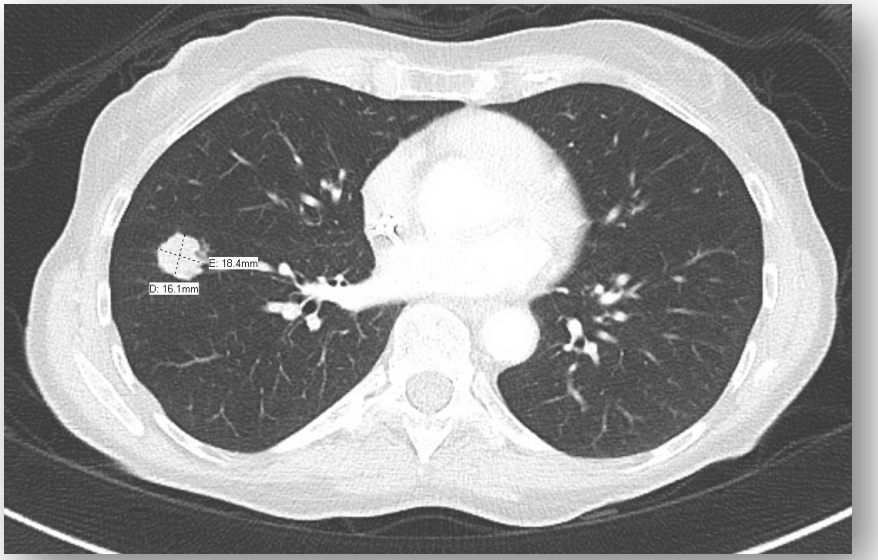
MRI = magnetic resonance imaging; ACTH = alpha melanocyte-stimulating hormone; TSH = thyroid-stimulating hormone.

Image courtesy Brianna Hoffner, University of Colorado.

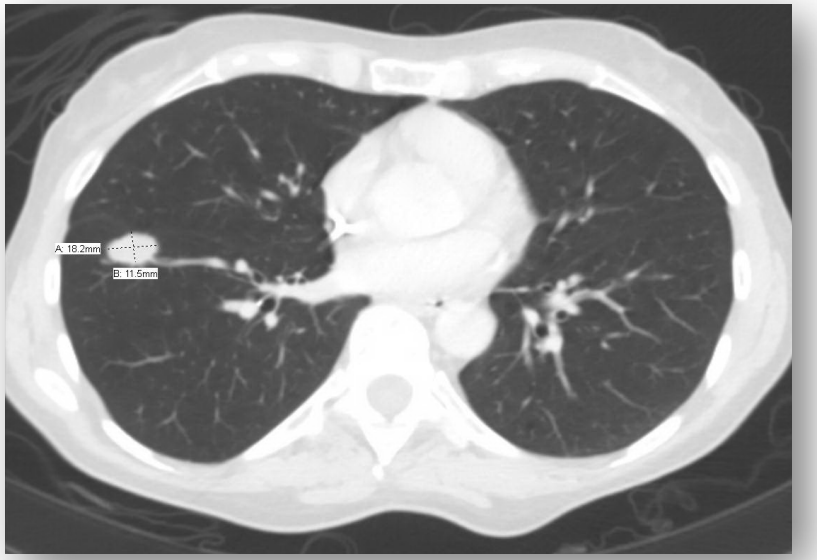
Case Study (cont.)

- Autoimmune hypophysitis with central adrenal insufficiency and central hypothyroidism
  - Prednisone at 1mg/kg daily, taper over four weeks
  - Hydrocortisone 20 mg every morning, 10 mg every evening
  - Levothyroxine 75 µg orally daily
  - Referral to endocrinologist
  - Educate patient on need for stress dosing steroids and a medical alert bracelet.
- OK to continue pembrolizumab after symptoms resolve on hormone replacement therapy

Case Study: Tumor Reduction after 7 cycles of Pembrolizumab



Baseline



After 7 cycles of pembrolizumab

Images courtesy Brianna Hoffner, University of Colorado.

Case Study (cont.)

DC presents for Cycle 4 pembrolizumab and looks unwell. She reports headaches, dizziness, and fatigue.

What is the most common presentation of hypophysitis?

A. Central adrenal insufficiency
B. Central hypothyroidism
C. Diabetes insipidus
D. Hypogonadism
E. Unsure

Summary

- Immune checkpoint inhibitors are the new standard of care for 2nd line treatment of R/M HNSCC after platinum-based therapy
- Higher response rates and improved survival seen in HPV-positive tumors and tumors with high PD-L1 expression
- Ongoing trials are comparing immune checkpoint inhibitors with EXTREME (SOC chemo) in the 1st line setting for R/M HNSCC