Immunotherapy for the Treatment of Head and Neck Cancer

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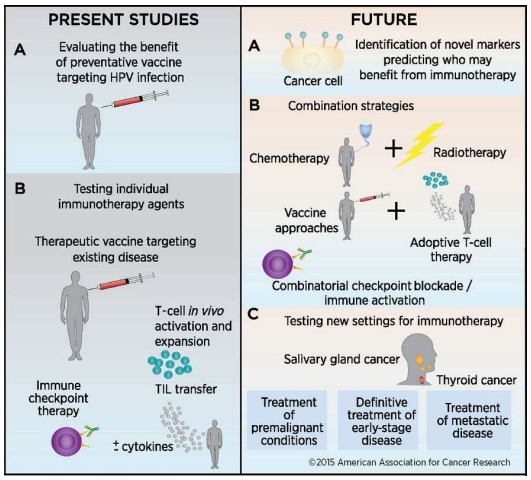
Disclosures

- Advisory board: Sanofi-Genzyme
- I will *not* be discussing non-FDA approved indications during my presentation.

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

Approved Checkpoint Inhibitors in Head and Neck Cancers

Drug	Approved	Indication	Dose
Pembrolizumab	2016	Recurrent/metastatic HNSCC, progression on/after chemotherapy	200 mg Q3W
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
Pembrolizumab	2019	Recurrent/metastatic HNSCC 1st line – PD-L1 CPS ≥ 1	200 mg Q3W
Pembrolizumab	2019	Recurrent locally advanced/metastatic squamous cell carcinoma of esophagus (PD-L1 CPS ≥ 10)	200 mg Q3W

KEYNOTE-012: Pembrolizumab in R/M HNSCC

Nonrandomized, Phase 1b Trial, Cohorts† B, B2

Patients
- R/M HNSCC
- Measurable disease (RECIST v1.1)
- ECOG PS 0-1
- PD-L1+ (initial cohort)
- PD-L1+ or PD-L1- (expansion cohort)

Initial Cohort
Pembrolizumab 10 mg/kg Q2W
N = 60

Expansion Cohort*
Pembrolizumab 200 mg IV Q3W
N = 132

Continue until:
- 24 months of treatment‡
- Disease progression
- Death
- Withdrawal of consent
- Investigator decision

Combined analyses of Initial and Expansion cohorts

Response assessment: Every 8 weeks until disease progression

Primary end points: ORR (RECIST v1.1, central imaging vendor review), safety

Secondary end points: ORR (investigator), PFS, OS, duration of response (DOR), ORR in HPV+ patients §

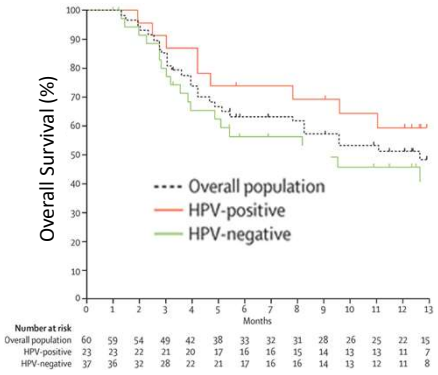
†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§ Initial cohort only.
*Median duration of disease not reached.

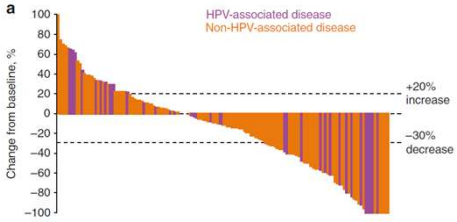
Seiwert, ASCO 2017.

KEYNOTE-012: Pembrolizumab in R/M HNSCC

Nonrandomized, Phase 1b Trial, Cohorts† B, B2

- ORR = 18%
  - CR = 4%
  - PR = 14%
- mOS = 8.0 months
- mPFS = 2.1 months





Seiwert, ASCO 2017.
Mehra, Br J Can 2018.

KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum/Cetuximab
Phase II Trial, Single Arm

Patients (n=171):
- R/M HNSCC
- Resistant to platinum and cetuximab*
- Measurable disease (RECIST v1.1)
- ECOG PS 0-1

→ **Pembrolizumab** 200 mg IV Q3W Fixed dose →

Continue until:
- 24 months of treatment
- PD
- Intolerable toxicity
- Investigator/ patient decision

→ **Safety and Survival Follow-up**

Response assessment: Imaging every 6 to 9 weeks (central radiology review)

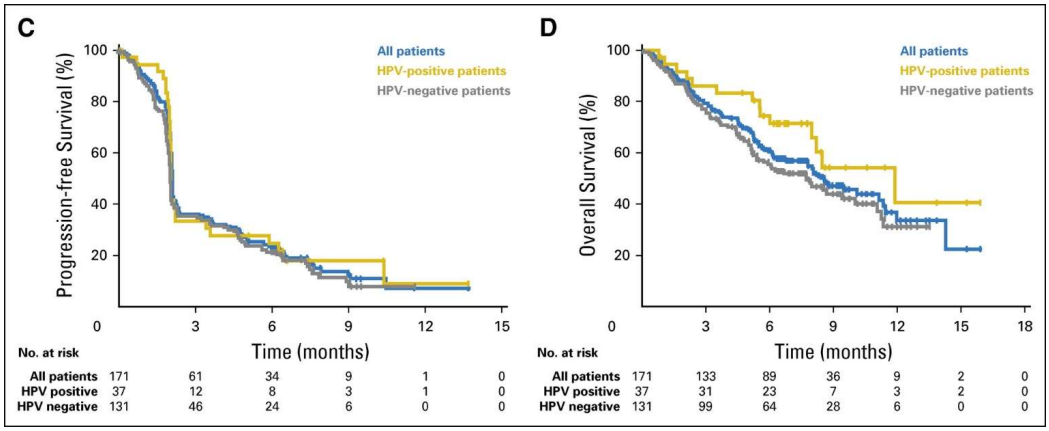
Primary end points: ORR (RECIST v1.1) by Response Evaluation Criteria in Solid Tumors and safety

Secondary end points: ORR (RECIST v1.1) in all dosed patients, ORR for HPV+, PD-L1+, DOR, PFS, OS

*75% of patients had ≥ 2 prior lines of therapy for metastatic disease

Bauml, J Clin Oncol 2017.

KEYNOTE-055: Pembrolizumab in R/M HNSCC after Progression on Platinum/Cetuximab
Phase II Trial, Single Arm



Bauml, J Clin Oncol 2017.

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

Phase III Randomized, Safety and Efficacy Trial

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

R 2:1

Nivolumab
3 mg/kg IV Q2W

Vs.

Investigator's Choice
- Methotrexate 40 mg/m² IV weekly
- Docetaxel 30 mg/m² IV weekly
- Cetuximab 400 mg/m² IV once, then 250 mg/m² weekly

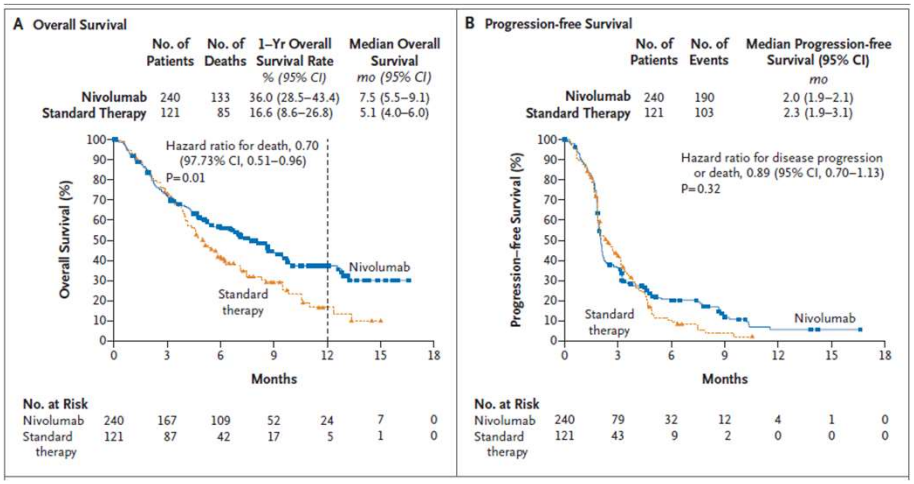
Primary endpoint
- OS

Other endpoints
- PFS
- ORR
- Safety
- DOR
- Biomarkers
- Quality of life

DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

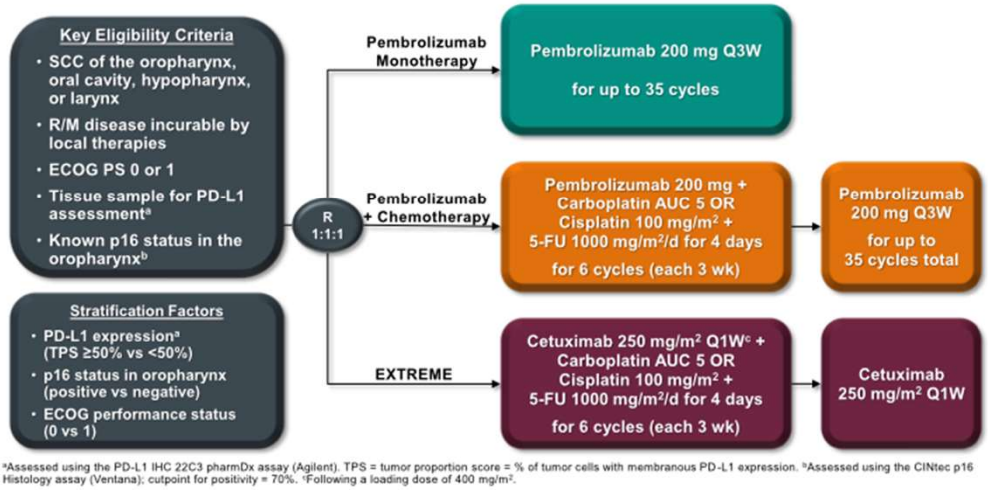
Ferris & Gillison, NEJM 2016.

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



Ferris & Gillison, NEJM 2016.

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

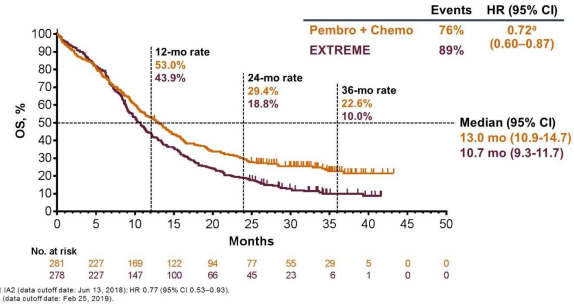


[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Rischin, ASCO 2019.

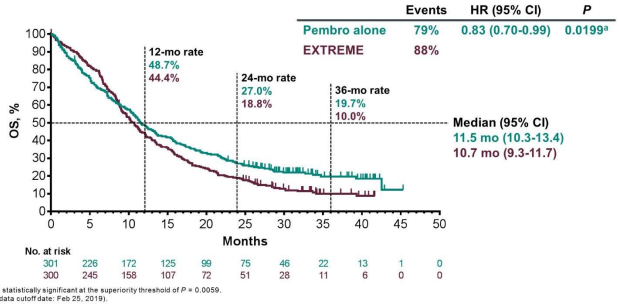
KEYNOTE-048: Pembrolizumab +/- Chemotherapy in newly diagnosed R/M HNSCC

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.

KEYNOTE-048 Final Analysis

	5FU/platin/cetuximab EXTREME regimen	5FU/platin/pembrolizumab	Pembrolizumab
CPS >= 20			
• Median OS	10.7 months	14.7 months	14.9 months
• Objective RR	36%	43%	23%
• Median response duration	4.2 months	7.1 months	22.6 months
CPS >=1			
• Median OS	10.3 months	13.6 months	12.3 months
• Objective RR	35%	36%	19%
• Median response duration	4.5 months	6.7 months	23.4 months
Total Population			
• Median OS	10.7 months	13.0 months	11.6 months (noninferior)
• Objective RR	36%	36%	17%
• Median response duration	4.5 months	6.7 months	22.6 months

Burtness, B. et al. Lancet 2019; 394:1915-1928.

Evaluating Biomarkers in HNSCC

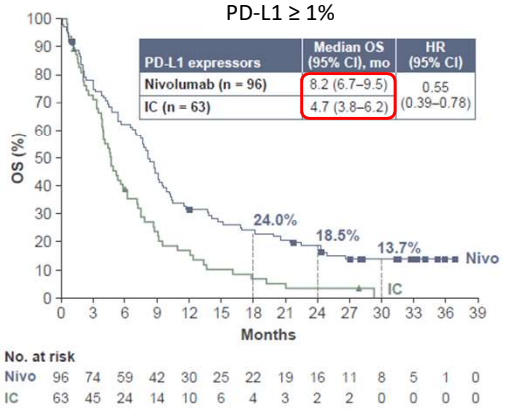
- Only indication that relies on PD-L1 expression:
  - pembrolizumab monotherapy in 1st line HNSCC: CPS ≥ 1 (KEYNOTE-048)
- All other approvals not dependent on PD-L1 expression
  - KEYNOTE-012/055: Response rates not significantly different on the basis of tumor PD-L1 staining
  - Checkmate 141: Most benefit seen in PD-L1 positive tumors
  - KEYNOTE-040: pembrolizumab vs investigator's choice chemotherapy – did not meet survival endpoints in total population but improved outcomes in PD-L1-expressors

Evaluating Biomarkers in HNSCC

CheckMate 141: 2 year update

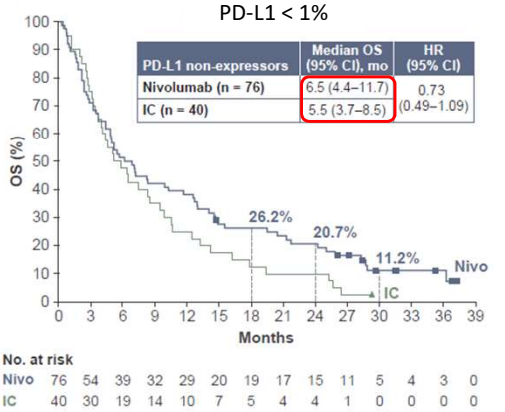
PD-L1 ≥ 1%

PD-L1 expressors	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 96)	8.2 (6.7–9.5)	0.55 (0.39–0.78)
IC (n = 63)	4.7 (3.8–6.2)	



PD-L1 < 1%

PD-L1 non-expressors	Median OS (95% CI), mo	HR (95% CI)
Nivolumab (n = 76)	6.5 (4.4–11.7)	0.73 (0.49–1.09)
IC (n = 40)	5.5 (3.7–8.5)	



Ferris, Oral Oncol 2018.

In development: KEYNOTE-137
T-VEC + pembrolizumab

- T-Vec 10^6 PFU/mL intratumoral injection followed by 10^8 PFU/mL Q3W
- Pembrolizumab 200 mg IV Q3W
- Eligibility:
  - R/M HNSCC not suitable for curative therapy
  - Progressed after platinum treatment
  - At least 1 injectable cutaneous, subcutaneous, or nodal tumor ≥ 10 mm in longest diameter
- ORR: 16.7%

Harrington, ASCO 2018.

In development: Checkpoint inhibitors + radiotherapy

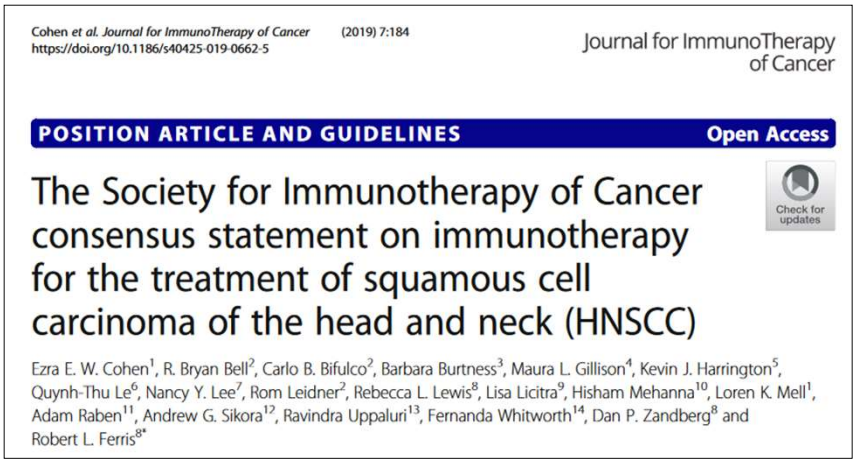
- NCT03247712: neoadjuvant nivolumab + SBRT
  - Decreased tumor size prior to surgery; high pathologic CR rate
- KEYNOTE-412: pembrolizumab + cisplatin + radiation
  - Safety confirmed
- REACH: avelumab + cetuximab + radiation
  - Safety confirmed

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 generally 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**

Check for updates

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

- 60 year old with squamous cell carcinoma of the left maxillary sinus with invasion into the left orbit
- Summer 2015, Orbital exenteration, partial maxillary sinus removal: SCC with perineural invasion, positive margins
- Fall 2015, adjuvant chemoradiation with cisplatin
- October 2017, recurrence s/p wide local excision of left orbit sinus tract, left anterior ethmoidectomy
- Early 2018, recurrence in left premaxillary region: poorly differentiated SCC with positive margins
- Mid 2019, recurrence left buccal space excision: muscle and perineural invasion
- Early 2020, recurrence in left mid face, cheek, left level 1b neck lymph nodes
- Mid 2020, PET/MRI scan: new uptake along left buccal space, left neck lymph nodes (1a, 2a, 5a), with new CONTRALATERAL lymph nodes

Case Study 1

When would you have discontinued additional surgical resection and moved on to systemic therapy?

a. At the time of the first recurrence (October 2017, ~24 months from original diagnosis)
b. At the time of the second recurrence (Early 2018, ~3-4 months from last recurrence)
c. At the time of the third recurrence (Mid 2019, ~14 months from last recurrence)
d. At the time of the fourth recurrence (Early 2020, ~9 months from last recurrence)

Case Study 1

- PD-L1 (22C3) CPS 55

When would you have discontinued additional surgical resection and moved on to systemic therapy?

a. At the time of the first recurrence (October 2017, ~24 months from original diagnosis)
b. At the time of the second recurrence (Early 2018, ~3-4 months from last recurrence)
c. At the time of the third recurrence (Mid 2019, ~14 months from last recurrence)
d. At the time of the fourth recurrence (Early 2020, ~9 months from last recurrence)

- Does knowing the PD-L1 expression level change your thinking?

Case Study 1

- I had the conversation about systemic therapy (immunotherapy, chemotherapy, or clinical trials) at the time of the second recurrence.
- Long discussions regarding quality of life, cosmetic look of his face, and ability to work
- Ultimately, the patient was the driver to decide when he was "ready" for systemic treatment
  - Transition of thinking from curative intent to palliative intent can be challenging, especially when there is sign of no metastatic disease
  - How much should the PD-L1 status play in the discussion?

Case Study 2

- 54 year old with a 1 year history of right neck swelling and voice changes.
- Presented to the ER with worsening neck swelling and drainage from the neck.
- Past medical history:
  - Significant anxiety disorder
  - Hypertension
- Physical examination: 90% airway obstruction at the level of the oropharynx (endoscopy)
- Underwent emergent tracheostomy and G tube placement.

Oropharyngeal carcinoma (metastatic)

- CT imaging noted widely metastatic disease:
  - right base of tongue (primary)
  - Multiple **hepatic** lesions, lytic **bone** lesions (T11, L1), **pulmonary** nodules.
- Liver biopsy: invasive squamous cell carcinoma, p16 positive
- PD-L1 (22C3) combined positive score (CPS): 70

What would be your first line of treatment?

a. Pembrolizumab monotherapy
b. Carboplatin/paclitaxel
c. 5FU/carboplatin/pembrolizumab
d. 5FU/carboplatin/cetuximab
e. Paclitaxel/cetuximab

Case Study 2

- Initially started on pembrolizumab monotherapy
  - Significant anxiety associated with blood draws, IV placement
- Received 4 cycles of pembrolizumab with repeat imaging (after 12 weeks of pembrolizumab)
- CT neck, CAP: New and enlarging hepatic lesions, the largest measuring 11.2 x 12.9 x 14.5 cm with a new occlusion in the branch of the right posterior portal vein. New enlarged retroperitoneal lymph nodes.

What would you do next?

a. Continue with pembrolizumab monotherapy
b. Add 5FU/carboplatin to the pembrolizumab
c. Switch to carboplatin/paclitaxel
d. Switch to 5FU/carboplatin/cetuximab
e. Enroll patient on an immunotherapy combination clinical trial

Case Study 2

- We talked about continuing with pembrolizumab alone given that he was asymptomatic.
  - We followed the protocol algorithm of KEYNOTE-048 (but technically were not on the clinical trial and didn't have central review)
- I added 5FU/carboplatin to the pembrolizumab
  - The new occlusion of the right posterior portal vein was what pushed me to add cytotoxic chemotherapy.
  - I wasn't quite ready to give up on pembrolizumab given his high PD-L1 CPS score
- Lingering questions:
  - Does pseudoprogression exist in head/neck cancers?
  - My patient was doing so well, surely I was hopeful for additional immunotherapy effect?
  - If I don't change regimens, would I miss an opportunity for alternate treatments?

Pseudoprogression

- Definition: Radiologic appearance of an increase in tumor burden with subsequent tumor regression or response.
  - Generally results from infiltration of inflammatory cells, edema, and necrosis generated by immunotherapy.
- Pseudoprogression is rare in HNSCC
  - KEYNOTE-012 (with HNSCC) had 1 out of 45 pt with a tumor flare followed by a complete response
  - CheckMate 141: 1.3% pts with nivolumab had growth in target lesions followed by subsequent response (no other specifics)

Lauber K and Dunn L. 2019 ASCO Educational Book, 352-363.

Pseudoprogression

- Patients who continue on checkpoint blockade therapy despite early radiologic signs of progression should be selected based on:
  - absence of clinical deterioration
  - presence of modest tumor growth
  - and the lack of alternative treatment options
- Weigh pros/cons of
  - What is the risk of aggressive true progression and clinical deterioration while waiting for imaging confirmation that will occur in 4-8 weeks?
  - Are there other available therapeutic options (standard or investigational)?
  - What is the potential for functional decline secondary to tumor growth?

Thank you!