Advances in Collaborative Practice for Patients With Head and Neck Cancers

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Learning Objectives

• Demonstrate increased understanding of the mechanisms of tumor immune escape and their role in cancer disease progression as well as the mechanisms of action of immunotherapy used in the treatment of head and neck squamous cell carcinoma (HNSCC)

• Monitor for and manage adverse effects of immune checkpoint inhibitor therapy and EGFR-directed therapy in the treatment of patients with recurrent or metastatic HNSCC
Financial Disclosure

- Dr. Haddad has received research support and acted as a consultant for AstraZeneca, Bristol-Myers Squibb, Celgene, Eisai, Merck, and Pfizer.
- Mr. Glass has nothing to disclose.
Head and Neck Cancer

• Introduction: Epidemiology, Clinical Features, Prevention, Treatment Modalities
• Concurrent Chemoradiotherapy
• Sequential Chemoradiotherapy
• Adjuvant Chemoradiotherapy
• Palliative Therapy: Targeted therapy and Immunotherapy
Head and Neck Cancer Primary Disease Sites

Oral cavity
Pharynx
Larynx
Nasal cavity
Paranasal sinuses
Epidemiology

- 48,000 new cases per year in US.
- Median age of diagnosis: ~60 years
- Male > female
- Strongly associated with tobacco and alcohol
- Epstein-Barr virus risk factor for nasopharynx cancers
- Human papillomavirus increasingly appreciated as a risk factor
Human Papillomavirus (HPV)

- Circular 8 kB dsDNA Genomes
- Only One Coding Strand
- Infect Epithelial Cells
  - ~ 200 HPV types
  - ~ 30 Mucosal HPVs
- Low-Risk: Genital Warts
- High-Risk: Lesions That Progress to Cancer

HPV-Associated Cancers
- > 99% of Cervical Carcinoma
- ~ 90% Anal Carcinomas
- ~ 40% Vulvar and Vaginal Carcinomas
- ~ 60% of Oropharynx Cancers

HPV GENOME INTEGRATION

Frequent Event During Malignant Progression
Terminates Viral Life Cycle
Expression of E6 and E7 Is Retained

HPV E6/E7 Oncoproteins
- Small, Non-Enzymatic Proteins
  - (~ 150aa E6; ~ 100aa E7)
- Associate With and Functionally Modify Host Cellular Protein Complexes
Human Papillomavirus (HPV)-Positive Head and Neck Cancer

- HPV 16 is the viral subtype in the vast majority of patients
- Half of oropharynx cancers will have HPV 16 DNA
- Often occurs in nonsmokers, nondrinkers
- Median age younger than HPV-negative patients; incidence increasing
- Men and women at more similar risk.
- Associated with ↑ number of sexual partners and high-risk sexual practices
- Favorable prognosis

HPV Testing in Tumors

- In situ hybridization
- p16 immunohistochemistry
- PCR
Rising Incidence of HPV-Associated Cancers

Survival Outcomes by HPV Status in Oropharyngeal Cancer in RTOG 0129

Ang et al NEJM 2010
RTOG 0129 Phase III Trial: Concomitant CRT With Standard vs. Accelerated Fractionation RT in Advanced SCCHN

Stage III/IV (T2, N2–3, M0, or T3–4, any N, M0) SCCHN

- Oral cavity, oropharynx, hypopharynx, larynx
- No prior RT to head and neck except radioactive iodine therapy
- No prior surgery to primary tumor or nodes except for diagnostic biopsy

Expected N = 720

<table>
<thead>
<tr>
<th>CRT</th>
<th>RTOG 0129</th>
<th>US NIH, 2010c.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT</td>
<td>RANDBLIND</td>
<td></td>
</tr>
<tr>
<td>CRT</td>
<td>Cisplatin (IV on D1, 22)</td>
<td>Standard fractionation RT (5 d/wk for 7 wks)</td>
</tr>
<tr>
<td>CRT</td>
<td>Cisplatin (IV on D1, 22)</td>
<td>Accelerated fractionation RT (5 d/wk for 3.5 wks; then twice daily, 5 d/wk for 2.5 wks)</td>
</tr>
</tbody>
</table>
### 3-Year Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HPV Positive (%)</th>
<th>HPV Negative (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>82.4</td>
<td>57.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PFS</td>
<td>73.7</td>
<td>43.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Locoregional failure</td>
<td>13.6</td>
<td>35.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>8.7</td>
<td>14.6</td>
<td>0.23</td>
</tr>
</tbody>
</table>

\[HR=0.38 \text{ (95\% CI: 0.26-0.55); } P<0.001\]

\[HR=0.40 \text{ (95\% CI: 0.29-0.557); } P<0.001\]
Two Distinct HNSCC Entities

<table>
<thead>
<tr>
<th></th>
<th>HPV positive</th>
<th>HPV negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomic site</td>
<td>Tonsil / Base of Tongue</td>
<td>All sites</td>
</tr>
<tr>
<td>Histology</td>
<td>Basaloid</td>
<td>Keratinized</td>
</tr>
<tr>
<td>Age</td>
<td>Younger</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>3:1 men</td>
<td>3:1 men</td>
</tr>
<tr>
<td>SE status</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Sexual behavior</td>
<td>ETOH/tobacco</td>
</tr>
<tr>
<td>Cofactors</td>
<td>Marijuana / Immune suppression</td>
<td>ETOH/tobacco</td>
</tr>
<tr>
<td>Incidence</td>
<td>Rising</td>
<td>Declining</td>
</tr>
<tr>
<td>Survival</td>
<td>Improved</td>
<td>Worse</td>
</tr>
</tbody>
</table>

There is a major change in the etiology of head and neck cancer, the incidence of OPC rapidly increasing mostly North America and Europe.
Head and Neck Cancer: Clinical Features

- Squamous cell cancer or variant
- Locoregional character
- M1 uncommon at presentation
- Medical comorbidity
- Second primary cancers: “field cancerization,” “condemned mucosa”
Lymphatic Drainage

Each anatomic site has a predilection for spreading to different lymph node level.

I: Oral cavity
II/III/IV: Larynx/pharynx
II/V: Nasopharynx
V: Scalp
III/IV/V: Thyroid
IV/V: Below the clavicles
Screening/Prevention

- United States Preventive Services Task Force: no definitive recommendations with regard to screening for head and neck cancers
- Direct inspection and palpation of oral cavity during dental examinations most commonly applied screening procedure
- Counsel regarding tobacco and alcohol use
- Human papillomavirus vaccine – not standard practice for prevention of head and neck cancer
- No proven standard chemopreventive agent

Evaluation and Staging

- Clinical exam of the head and neck
- Endoscopy
  - Fiberoptic flexible laryngopharyngoscopy
  - Exam under anesthesia: laryngoscopy, esophagscopy, bronchoscopy
- Biopsy
  - Fine needle aspiration of a neck node
  - Punch/core biopsy
  - Excisional biopsy
- Computed axial tomography/magnetic resonance imaging of primary site and neck
- Chest imaging
- Positron emission tomography
- Tumor-node-metastasis system applied
## Treatment Approach

<table>
<thead>
<tr>
<th>Disease Extent</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_1N_{0-1}$ or $T_2N_0$</td>
<td>Surgery or RT</td>
</tr>
<tr>
<td>$T_2N_1$ or $T_{3-4}$ or $N_{2-3}$</td>
<td>Combined modality</td>
</tr>
</tbody>
</table>
| Recurrent or $M_1$             | Surgery and/or RT
                                | Combined modality
                                | Chemotherapy                   |

Surgical Therapy: General Principles

• Oncologically adequate resection: Clear surgical margins
• Comprehensive vs selective neck dissection
• Factors suggesting disease unresectable for cure:
  • Massive skull base infiltration
  • Involvement of prevertebral fascia
  • Invasion of the cervical vertebrae or brachial plexus
  • Encasement of the carotid artery
  • Skin infiltration
  • Rapid local or regional recurrence after surgery
Toxicities of Radiation Therapy

- Mucositis/edema → dysphagia → feeding tube
- Xerostomia and loss of taste
- Hypothyroidism
- Lhermitte’s syndrome
- Long-term induration and fibrosis
- Osteoradionecrosis of the jaw
- Cervical myelopathy
Concurrent Chemoradiotherapy
# The Debate Over Therapeutic Sequence: MACH-NC Findings

<table>
<thead>
<tr>
<th>Design (No. of Studies/No. of Subjects)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Chemotherapy Effect (P-value)</th>
<th>Absolute Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant(^1) (8/1854)</td>
<td>0.98 (0.85-1.19)</td>
<td>0.74</td>
<td>1% 1%</td>
</tr>
<tr>
<td>Neoadjuvant(^1) (31/5269)</td>
<td>0.95 (0.88-1.01)</td>
<td>0.10</td>
<td>2% 2%</td>
</tr>
<tr>
<td>Concurrent(^1) (26/3727)</td>
<td>0.81 (0.76-0.88)</td>
<td>&lt; 0.0001</td>
<td>7% 8%</td>
</tr>
<tr>
<td>Total(^1) (65/10,850)</td>
<td>0.90 (0.85-0.94)</td>
<td>&lt; 0.0001</td>
<td>4% 4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of Trials</th>
<th>No. of Subjects</th>
<th>Difference at 5 Years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF induction(^2)</td>
<td>15</td>
<td>2487</td>
<td>5%</td>
</tr>
</tbody>
</table>

MACH-NC: Meta-Analysis of Chemotherapy in Head and Neck Cancer; PF=cisplatin + fluorouracil

Concurrent Therapy: Standard of Care

- Cisplatin 100 mg/m² days 1, 22, and 43 of RT
- RT standard fractionation, 70 Gy over 7 weeks (2-Gy fractions)
- Potential approaches to improve on CRT:
  - Addition of induction chemotherapy
  - Accelerated fractionation of RT
Phase III Trial: Cetuximab + RT for SCC

Advanced SCC
• Stage III/IV
• N = 424

Randomize

RT*
+Cetuximab (400 mg/m^2, then 250 mg/m^2/wk)

RT* alone

*Choice of:
• Once-daily RT: 70 Gy in 35 fractions
• Twice-daily RT: 72.0-76.8 Gy in 60-64 fractions
• Concomitant boost: 72 Gy in 42 fractions

<table>
<thead>
<tr>
<th>Grade 3-5 Toxicity</th>
<th>RT Alone (N = 212)</th>
<th>RT + Cetuximab (N = 208)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>52%</td>
<td>56%</td>
<td>.44</td>
</tr>
<tr>
<td>Acneiform Rash</td>
<td>1%</td>
<td>17%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Infusion Reaction</td>
<td>0%</td>
<td>3%</td>
<td>.01</td>
</tr>
<tr>
<td>Anemia</td>
<td>6%</td>
<td>1%</td>
<td>.006</td>
</tr>
</tbody>
</table>

Bonner JA, et al.  
**2006;354(6):567-578.*
Phase III: Cetuximab + RT for SCC Results

Locoregional Control
- 47% vs 34% at 3 years
- \( P < .01 \) at 3 years

OS
- 55% vs 45% at 3 years
- \( P = .05 \) at 3 years

Sequential Chemoradiotherapy
TAX 324: Sequential Combined Modality Therapy
TPF vs PF Followed by Chemoradiotherapy

TPF: Docetaxel 75_{D1} + Cisplatin 100_{D1} + 5-FU 1000_{CI-D1-4} Q 3 weeks x3
PF: Cisplatin 100_{D1} + 5-FU 1000_{CI-D1-5} Q 3 weeks x 3

## Patient Characteristics: TPF vs PF

### Intent-to-Treat Population

<table>
<thead>
<tr>
<th></th>
<th>TPF (N = 255)</th>
<th>PF (N = 246)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), y</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>55 (38-82)</td>
<td>56 (33-80)</td>
</tr>
<tr>
<td></td>
<td>13%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Male, % of pts</strong></td>
<td>84%</td>
<td>83%</td>
</tr>
<tr>
<td><strong>PS (WHO), % of pts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>56%</td>
<td>51%</td>
</tr>
<tr>
<td>1</td>
<td>44%</td>
<td>48%</td>
</tr>
<tr>
<td><strong>Primary tumor site, % of pts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>52%</td>
<td>53%</td>
</tr>
<tr>
<td>Larynx</td>
<td>18%</td>
<td>17%</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>13%</td>
<td>15%</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>17%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Clinical stage, % of pts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>16%</td>
<td>19%</td>
</tr>
<tr>
<td>IV</td>
<td>84%</td>
<td>81%</td>
</tr>
<tr>
<td><strong>Reason for inoperability, % of pts</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Technical unresectability</td>
<td>36%</td>
<td>34%</td>
</tr>
<tr>
<td>Low surgical curability</td>
<td>31%</td>
<td>30%</td>
</tr>
<tr>
<td>Organ preservation</td>
<td>33%</td>
<td>35%</td>
</tr>
</tbody>
</table>

TPF significantly improves survival and PFS compared with PF in an ICT regimen followed by CRT.

### TAX 324 Phase III Trial: Docetaxel/Cisplatin/5-FU vs Cisplatin/5-FU Sequential Therapy in Advanced SCCHN: Toxicity

<table>
<thead>
<tr>
<th>Grade 3/4 Toxicity</th>
<th>TPF</th>
<th>PF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomatitis</td>
<td>21%</td>
<td>27%</td>
</tr>
<tr>
<td>Nausea</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>83%</td>
<td>56%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>Neutropenic infection</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>37%</td>
<td>38%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>23%</td>
<td>24%</td>
</tr>
<tr>
<td>Mouth, nose dryness</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Rash/itch</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

During ICT
N = 251 TPF, 243 PF

During CRT
N = 203 TPF, 184 PF

## Taxane + PF Phase III Trials

<table>
<thead>
<tr>
<th></th>
<th>Vermorken (2007)(^1)</th>
<th>Hitt (2005)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>PF</td>
<td>PF</td>
</tr>
<tr>
<td>Subjects</td>
<td>181</td>
<td>193</td>
</tr>
<tr>
<td>Med PFS*</td>
<td>8.2 mo</td>
<td>12 mo</td>
</tr>
<tr>
<td>Med OS*</td>
<td>14.5 mo</td>
<td>37 mo</td>
</tr>
<tr>
<td>RR*</td>
<td>54%</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo</td>
<td>DPF</td>
<td>PaPF</td>
</tr>
<tr>
<td>Subjects</td>
<td>177</td>
<td>189</td>
</tr>
<tr>
<td>Med PFS*</td>
<td>11.0 mo</td>
<td>20 mo</td>
</tr>
<tr>
<td>Med OS*</td>
<td>18.8 mo</td>
<td>43 mo</td>
</tr>
<tr>
<td>RR*</td>
<td>68%</td>
<td>80%</td>
</tr>
</tbody>
</table>


* \(P < 0.05\) for all outcomes except \(P = 0.06\) for OS in Hitt study
Conclusions

- Overall survival advantage > 3 years with TPF sequential therapy
  - 40.5 month improvement in median overall survival at 3 years
  - 30% reduction in the risk of mortality ($P = .0058$)
    - Consistent with prior phase III trial (TAX 323)
- Patients received a median of 3 cycles of induction chemotherapy in the TPF and PF arms.
- In the TPF arm, 81% of patients went on to receive CRT.
- Grade 3/4 treatment-emergent adverse events:
  - Less stomatitis, thrombocytopenia, and lethargy in the TPF arm
  - More neutropenia and febrile neutropenia (any grade) in the TPF arm
Clinical Scenarios to Consider Induction Therapy

- Potential distant metastasis
- Delay in radiation simulation
- Impending local issue (e.g., airway)
- Markedly advanced disease (e.g., bulky, N2c, N2b, N3, low neck, dermal infiltration)
- Organ preservation strategy in patients with markedly advanced disease
Neck Dissection (ND) After Chemoradiotherapy

• Indicated for gross residual disease
• Not indicated for pretreatment N1 disease that has achieved clinical complete response
• For pretreatment N2-3 disease, opinions vary:
  • When pretreatment neck disease is N2-3, some centers recommend routine ND regardless of response to chemoradiotherapy.
  • However, others will observe if a clinical complete response on PET scan 12 weeks post-therapy is achieved with chemoradiotherapy.

Survivorship/Follow-Up

- Assess for recurrence/2nd primary/premalignant lesions
  - 1st year: Q 1-3 mo
  - 2nd year: Q 2-4 mo
  - 3rd–5th year: Q 4-6 mo
  - > 5 years: Q 6-12 mo
- TSH q 6-12 months if neck irradiated
- Chest imaging as indicated
- Speech/swallowing evaluation/rehabilitation as indicated
- Counsel regarding tobacco and alcohol use
- Integrate general medical care
- Once felt disease free, imaging of primary and neck not routinely indicated unless suspicious signs or symptoms

## Treatment Approach

<table>
<thead>
<tr>
<th>Disease Extent</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_1N_{0-1}$ or $T_2N_0$</td>
<td>Surgery or RT</td>
</tr>
<tr>
<td>$T_2N_1$ or $T_{3-4}$ or $N_{2-3}$</td>
<td>Combined modality</td>
</tr>
<tr>
<td>Recurrent or $M_1$</td>
<td>Surgery and/or RT, Combined modality, Chemotherapy</td>
</tr>
</tbody>
</table>
Palliative Chemotherapy
Palliative Chemotherapy

• Treatment for recurrent disease without surgical or radiotherapy option

• 1st-line therapy
  • Historically platinum-based doublet
  • Overall RR 30-40%
  • Median survival 6-9 months regardless of treatment
  • Randomized controlled trials fail to demonstrate clear improvement in OS compared to RX with single agents

• Active agents: cisplatin, carboplatin, 5-FU, taxanes, methotrexate, cetuximab, ifosfamide, gemcitabine (for nasopharynx cancer), and others

EXTREME: Study Design

5-FU 1000 mg/m² d1-4 with
Cisplatin 100 mg/m² d1 or
Carboplatin AUC 5 d1

6 cycles maximum

No treatment → POD or toxicity

5-FU 1000 mg/m² d1-4 with
Cisplatin 100 mg/m² d1 or
Carboplatin AUC 5 d1
plus
Cetuximab 250 mg/m²/week*
q 3 weeks

Cetuximab → POD or toxicity

N = 442

*Loading dose of 400 mg/m² on week 1

EXTREME: First-Line Platinum/5-FU ± Cetuximab in Recurrent/Metastatic SCC: Survival

Survival Time (months)

Patients at Risk:
Platinum/5-FU  220
Cetuximab + Platinum/5-FU  222

Survival Probability

RR
Platinum/5-FU  18%
Cetuximab + Platinum/5-FU  35%

HR (95% CI)=0.797 (0.644-0.986)
Strat. log-rank test: 0.0362

OS

## EXTREME: Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>C225 + Platinum + FU</th>
<th>Platinum + 5-FU</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 222</td>
<td>10.1 months</td>
<td>N = 220</td>
<td>7.4 months</td>
<td>0.80</td>
</tr>
</tbody>
</table>

**Conclusion:** Addition of cetuximab to standard first-line platinum-based chemotherapy improves overall survival.

Phase II Trial: Cetuximab Monotherapy in Platinum-Refractory Recurrent/Metastatic SCC

Platinum-refractory SCC
- Stage III/IV recurrent and/or metastatic SCC not suitable for local therapy
- Documented PD within 30 days of cisplatin- or carboplatin-based chemotherapy (≥ 2 and ≤ 6 cycles)
- Tumor tissue available for IHC of EGFR expression
- No nasopharyngeal carcinoma
- No nonplatinum chemotherapy or RT within past 3 week
- No prior/concomitant surgery within 30 days of enrollment

N = 103

Cetuximab
(400 mg/m² then by 250 mg/m²/wk)
≥ 6 wks

CR, PR, or SD
Continue cetuximab until PD

Optional: cisplatin or carboplatin + cetuximab

N = 53

Immunotherapy and Head and Neck Cancer
Checkpoint Inhibitors in Oncology

- Checkpoint inhibitors have had a major impact on the treatment of multiple cancer types within the past 6 years\textsuperscript{1-4}
- Checkpoint inhibitors are being evaluated for a wide array of tumor types* 

* Not an exhaustive list of tumor types under investigation.

SCCHN Is an Immunosuppressive Tumor

Immune modulation occurs on multiple levels within the SCCHN microenvironment[1,2]

Immune suppression in SCCHN[1,2]

- **CD8+ T cells**: reduced counts; display defects such as low responsiveness to cytokines and reduced proliferative ability
- **CD4+ T cells**: Th2 phenotype favored
- **TAMs**: secrete immunosuppressive molecules, impair CD8+ cells, promote Treg production
- **Soluble factors**: cytokine profile includes immunosuppressive molecules such as TGF-β, VEGF, IL-6 and IL-10, as well as apoptosis-promoting factors that induce T-cell death
- **Tregs**: secrete immunosuppressive molecules and induce T-cell and DC dysfunction
- **NK cells**: activity is impaired
- **DCs**: tumors prevent maturation of DCs, promoting T-cell dysfunction and promoting Treg production

Adapted from: www.cancer.gov/cancertopics/factsheet/Sites-Types/head-and-neck.3
Overview of Checkpoint Inhibitor Trials

Clinical research with I-O therapies highlight a potential role for PD-L1 as a biomarker in SCCHN, alongside the importance of HPV status.

### Correlation between HPV status and PD-L1 expression by tumor cells

<table>
<thead>
<tr>
<th></th>
<th>HPV+ (n=32)</th>
<th>HPV- (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 (high)</td>
<td>20 (62.5%)</td>
<td>13 (40.6%)</td>
</tr>
<tr>
<td>PD-L1 (low)</td>
<td>12 (37.5%)</td>
<td>19 (59.4%)</td>
</tr>
</tbody>
</table>

HPV, human papillomavirus; I-O, immuno-oncology; PD-L1, programmed death ligand-1; R/M, recurrent or metastatic; SCCHN, squamous cell carcinoma of the head and neck.

Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): Pooled analyses after long-term follow-up in KEYNOTE-012 (ASCO 2016)

Ranee Mehra,1 Tanguy Y. Seiwert,2 Amit Mahipal,3 Jared Weiss,4 Raanan Berger,5 J. Paul Eder,6 Barbara Burtness,6 Makoto Tahara,7 Bhumsuk Keam,8 Dung T. Le,9 Kei Muro,10 Ravit Geva,11 Hyun Cheol Chung,12 Chia-Chi Lin,13 Amy Meister,14 Kumudu Pathiraja,14 Jonathan Cheng,14 Laura Q. Chow,15 Robert Haddad16

1Fox Chase Cancer Center, Philadelphia, PA; 2University of Chicago, Chicago, IL; 3H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; 4Lineberger Comprehensive Cancer Center at the University of North Carolina, Chapel Hill, NC; 5Sheba Medical Center, Tel Hashomer, Israel; 6Yale Cancer Center, New Haven, CT; 7National Cancer Center Hospital East, Chiba, Japan; 8Seoul National University Hospital, Seoul, Republic of Korea; 9Johns Hopkins University, Baltimore, MD; 10Aichi Cancer Center Hospital, Nagoya, Japan; 11Sourasky Medical Center, Tel Aviv, Israel; 12Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; 13National Taiwan University Hospital, Taipei, Taiwan; 14Merck & Co., Inc., Kenilworth, NJ; 15University of Washington, Seattle, WA; 16Dana-Farber Cancer Institute, Boston, MA
HNSCC Cohorts of Nonrandomized, Phase 1b, Multi-cohort KEYNOTE-012 Trial

Initial Cohort

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

Pembrolizumab
10 mg/kg Q2W
N = 60

Continue until:
• 24 months of treatment‡
• PD
• Intolerable toxicity

Expansion Cohort

Pembrolizumab
200 mg Q3W
N = 132

Combined analyses of Initial and Expansion cohorts

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.
## Baseline Demographics All HNSCC Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 192†</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>60 (20−84)</td>
</tr>
<tr>
<td>Male</td>
<td>159 (83)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>57 (30)</td>
</tr>
<tr>
<td>1</td>
<td>135 (70)</td>
</tr>
<tr>
<td>Metastatic stage M1</td>
<td>165 (86)</td>
</tr>
<tr>
<td>HPV status‡</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>45 (23)</td>
</tr>
<tr>
<td>Negative</td>
<td>147 (77)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 192†</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Prior lines of systemic therapy§</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>47 (24)</td>
</tr>
<tr>
<td>2</td>
<td>56 (29)</td>
</tr>
<tr>
<td>≥3</td>
<td>86 (45)</td>
</tr>
<tr>
<td>Prior platinum therapy</td>
<td>174 (91)</td>
</tr>
<tr>
<td>Prior platinum and cetuximab therapy</td>
<td>110 (57)</td>
</tr>
</tbody>
</table>

Data cutoff date: Apr 26, 2016. †Includes patients who received ≥1 dose of pembrolizumab in the initial or expansion cohort. ‡HPV status was determined by the local institution. Cancers outside the oropharynx, identified from primary diagnosis/prior radiation/prior surgery, were considered HPV negative. §3 patients received 0 systemic therapies.
<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Total N = 192</th>
<th>HPV+ n = 45</th>
<th>HPV− n = 147</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>ORR</td>
<td>34</td>
<td>18</td>
<td>13–24</td>
</tr>
<tr>
<td>CR</td>
<td>8</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>PR</td>
<td>26</td>
<td>14</td>
<td>–</td>
</tr>
<tr>
<td>SD</td>
<td>33</td>
<td>17</td>
<td>–</td>
</tr>
<tr>
<td>PD</td>
<td>93</td>
<td>48</td>
<td>–</td>
</tr>
<tr>
<td>NA§</td>
<td>32</td>
<td>17</td>
<td>–</td>
</tr>
</tbody>
</table>

Data cutoff date: Apr 26, 2016. Response assessed per RECIST v1.1 (central imaging vendor review, all patients as treated). Only confirmed responses are included.

†Includes patients who received ≥1 dose of pembrolizumab in the initial or expansion cohort.

‡HPV status was determined by the local institution. Cancers outside the oropharynx, identified from primary diagnosis/prior radiation/prior surgery, were considered HPV negative.

§No assessment because patient did not have central imaging review data or images were not evaluable.
Progression-Free Survival and Overall Survival

Data cutoff date: Apr 26, 2016.

†RECIST v1.1 by central imaging vendor review.
Summary and Conclusions

• Pembrolizumab had robust, durable antitumor activity in heavily pretreated patients with R/M HNSCC (median 9 months of follow-up)
  • Promising ORR
    • Overall = 18%; Pts with prior platinum = 17%; Pts with prior platinum and cetuximab = 15%
  • Durable responses
    • Median response duration not reached
    • 65% of responders remain in response
    • 85% of responses lasted ≥6 months and 71% lasted ≥12 months
  • Encouraging survival
    • 6-month OS, 58%; 12-month OS, 38%

• Pembrolizumab was well tolerated
  • 6% discontinued due to a treatment-related AE
  • No treatment-related deaths
CheckMate 141 Study Design

Randomized, global, phase 3 trial of the efficacy and safety of nivolumab versus investigator’s choice in patients with R/M SCCHN

Key Eligibility Criteria
- R/M SCCHN of the oral cavity, pharynx, or larynx
- Not amenable to curative therapy
- Progression on or within 6 months of last dose of platinum-based therapy
- ECOG PS 0–1
- Documentation of p16 to determine HPV status
- No active CNS metastases

Stratification factor
- Prior cetuximab treatment

Nivolumab
3 mg/kg IV q2w

Primary endpoint
- OS

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

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

Ferris et al: NEJM 2016
### Demographics (1)

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 240) n (%)</th>
<th>Investigator’s Choice (n = 121) n (%)</th>
<th>Total (N = 361) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (years)</strong></td>
<td>59.0</td>
<td>61.0</td>
<td>60.0</td>
</tr>
<tr>
<td>&lt; 65</td>
<td>172 (71.7)</td>
<td>76 (62.8)</td>
<td>248 (68.7)</td>
</tr>
<tr>
<td>≥ 65</td>
<td>68 (28.3)</td>
<td>45 (37.2)</td>
<td>113 (31.3)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>197 (82.1)</td>
<td>103 (85.1)</td>
<td>300 (83.1)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>196 (81.7)</td>
<td>104 (86.0)</td>
<td>300 (83.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>29 (12.1)</td>
<td>14 (11.6)</td>
<td>43 (11.9)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (6.3)</td>
<td>3 (2.5)</td>
<td>18 (5.0)</td>
</tr>
<tr>
<td><strong>Smoking/tobacco use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/former</td>
<td>191 (79.6)</td>
<td>85 (70.2)</td>
<td>276 (76.5)</td>
</tr>
<tr>
<td>Never</td>
<td>39 (16.3)</td>
<td>31 (25.6)</td>
<td>70 (19.4)</td>
</tr>
</tbody>
</table>
## Demographics (2)

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 240)</th>
<th>Investigator’s choice (n = 121)</th>
<th>Total (N = 361)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>49 (20.4)</td>
<td>23 (19.0)</td>
<td>72 (19.9)</td>
</tr>
<tr>
<td>1</td>
<td>189 (78.8)</td>
<td>94 (77.7)</td>
<td>283 (78.4)</td>
</tr>
<tr>
<td>≥ 2</td>
<td>1 (0.4)</td>
<td>3 (2.5)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Not reported</td>
<td>1 (0.4)</td>
<td>1 (0.8)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td><strong>Number of prior lines of systemic cancer therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>105 (43.8)</td>
<td>58 (47.9)</td>
<td>163 (45.2)</td>
</tr>
<tr>
<td>2</td>
<td>81 (33.8)</td>
<td>45 (37.2)</td>
<td>126 (34.9)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>54 (22.5)</td>
<td>18 (14.9)</td>
<td>72 (19.9)</td>
</tr>
<tr>
<td><strong>Site of primary tumor</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>108 (45.0)</td>
<td>67 (55.4)</td>
<td>175 (48.5)</td>
</tr>
<tr>
<td>Pharynx</td>
<td>92 (38.3)</td>
<td>36 (29.8)</td>
<td>128 (35.5)</td>
</tr>
<tr>
<td>Larynx</td>
<td>34 (14.2)</td>
<td>15 (12.4)</td>
<td>49 (13.6)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (2.5)</td>
<td>3 (2.5)</td>
<td>9 (2.5)</td>
</tr>
</tbody>
</table>
## Treatment Administration

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 240)</th>
<th>Investigator’s choice (n = 121)</th>
<th>Total (N = 361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients receiving ≥ 1 dose, n (%)</td>
<td>236 (98.3)</td>
<td>111 (91.7)</td>
<td>347 (96.1)</td>
</tr>
<tr>
<td>Investigator’s choice therapy, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>–</td>
<td>46 (38.0)</td>
<td>–</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>–</td>
<td>52 (43.0)</td>
<td>–</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>–</td>
<td>13 (10.7)</td>
<td>–</td>
</tr>
<tr>
<td>Median time on therapy, mo (95% CI)</td>
<td>1.9 (1.6–2.3)</td>
<td>1.9 (1.6–2.0)</td>
<td>–</td>
</tr>
<tr>
<td>Median duration of follow-up, mo (range)</td>
<td>5.3 (0–16.8)</td>
<td>4.6 (0–15.2)</td>
<td>–</td>
</tr>
<tr>
<td>Number of deaths, n (%)</td>
<td>133 (55.4)</td>
<td>85 (70.2)</td>
<td>218 (60.4)</td>
</tr>
<tr>
<td>Ongoing treatment, n (%)</td>
<td>41 (17.4)</td>
<td>3 (2.7)</td>
<td>44 (12.7)</td>
</tr>
</tbody>
</table>
Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>HR (97.73% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 240)</td>
<td>7.5 (5.5–9.1)</td>
<td>0.70           (0.51–0.96)</td>
<td>.0101</td>
</tr>
<tr>
<td>Investigator’s choice (n = 121)</td>
<td>5.1 (4.0–6.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1-year OS rate (95% CI)
- Nivolumab: 36.0% (28.5–43.4)
- Investigator’s choice: 16.6% (8.6–26.8)

No. at Risk
- Nivolumab: 240 167 109 52 24 7 0
- Investigator’s Choice: 121 87 42 17 5 1 0
EORTC QLQ-C30 Functional Domains
CheckMate 141: Nivolumab vs IC in R/M SCCHN After Platinum Therapy

- Nivolumab-treated patients experienced stable PROs.
- Investigator’s choice–treated patients had statistically significant and clinically meaningful worsening in physical, role, and social functioning compared with nivolumab.
EORTC QLQ-C30 Functional Domains by PD-L1 Status CheckMate 141: Nivolumab vs IC in R/M SCCHN After Platinum Therapy

Differences in functional domains were numerically greater for patients with PD-L1 expression ≥1% compared with patients with PD-L1 expression <1%, but were not statistically significant.
EORTC QLQ-C30 Symptom Burden
CheckMate 141: Nivolumab vs IC in R/M SCCHN After Platinum Therapy

• Nivolumab-treated patients experienced stable PROs
• Investigator’s choice–treated patients had statistically significant and clinically meaningful worsening of symptoms compared with nivolumab
Conclusions: PD-1 Inhibitors in SCCHN

- Nivolumab is the first agent to demonstrate a significant improvement in survival in patients with SCCHN who progress after platinum-based therapy in a randomized, phase III comparative trial.
- Pembrolizumab has shown robust, durable antitumor activity in heavily pretreated patients with R/M HNSCC.
- Nivolumab and pembrolizumab demonstrated a benefit in the overall study population, regardless of PD-L1 expression or p16 status.
- Safety profile for both agents is favorable and consistent with prior studies.
- Nivolumab and pembrolizumab represents a new standard of care option for patients with R/M SCCHN after platinum-based therapy.
Conclusions: Treatment of SCCHN in 2016

• Multiple options available
  • Concurrent chemoRT
  • Sequential therapy: TPF is the standard induction regimen
  • Targeted therapy: Cetuximab/RT
  • PD-1 inhibitors: Clear activity shown in platinum-resistant disease

• Patient selection is important
  • Stage, patient characteristics, PS, and primary site

• HPV-related oropharynx disease is a major public health problem
  • HPV-positive and HPV-negative disease are distinct entities
    • Pts with HPV-positive disease demonstrate improved responses to therapy and better survival
    • De-intensification is a relevant and important research question
Monitoring and Managing Side Effects of Immunotherapy

Jason Glass, ACNP-BC
Dana-Farber Cancer Institute
Collaborative Practice at Dana-Farber

- Head and neck oncology team
  - Medical oncology
  - Radiation oncology
  - Head and neck surgeon
  - NP or PA
  - Program nurse

- Treatment support team
  - Primary nurse
  - Nutritionist
  - Speech and language pathologist
  - Social worker

- Collaborative support team
  - Pain & palliative care
  - Dermatology
  - Oral medicine
  - Psychiatry
Immunotherapy for Head and Neck Cancer
Starting on Immunotherapy

• Repeat medical history screening for autoimmune disorders, or conditions requiring immunosuppression

• Labs
  • Baseline thyroid function: start thyroid replacement as necessary
  • Baseline liver function
  • Baseline creatinine

• If applicable, discuss reproductive concerns
Side Effects

• Common reactions
  • Fatigue
  • Pruritus
  • Diarrhea
  • Decreased appetite
  • Rash
  • Dyspnea
  • Constipation
  • Nausea

• Rare reactions
  • Infusion-related reactions
  • Neurological effects

• Immune-mediated responses (-itis)
  • Pneumonitis
  • Dermatitis
  • Colitis
  • Hepatitis
  • Endocrinopathies
    • Hypophysitis
    • Hypo- and hyperthyroid
    • Adrenal insufficiency
    • Type 1 diabetes mellitus

• Nephritis
Side Effects: Pneumonitis

- Inflammation of the lung tissue
  - New or worsening cough
  - Shortness of breath
  - Tightness in the chest
  - Chest pain
  - Fatigue
Side Effects: Pneumonitis

- Differential diagnoses
  - Pneumonia
  - Pulmonary embolus

- Workup
  - CT chest
  - Consider pulmonary and infectious disease consults

- Management
  - Grade 1: Consider holding treatment
  - Grade 2: Hold treatment, start corticosteroids. If no improvement or worsening after 2 weeks, treat as Grade 3-4
  - Grade 3-4: Permanently discontinue treatment, admit, start corticosteroids, consider non-steroidal immunosuppression.

Side Effects: Dermatitis

• Rash
• Itchy skin
• Blisters
• Ulcers in the mouth or other mucous membranes

Photo courtesy Jason Glass
Side Effects: Dermatitis

Reducing the risk

- Start early with gentle moisturizers
- Minimize sun exposure
- Avoid tight-fitting or abrasive clothing
- Avoid scratching or scrubbing the skin

Side Effects: Dermatitis

Management

- Grade 1-2: Continue treatment, start antihistamines and topical steroids
- Grade 3: Hold treatment, refer to dermatology, start oral steroids
- Grade 4: Stop treatment, refer to dermatology, start oral steroids
Side Effects: Colitis

Inflammation of the colon
- Diarrhea/increased frequency of bowel movements
- Blood in the stool or dark, tarry, sticky stools
- Severe abdominal pain or tenderness
Side Effects: Colitis/GI Reactions

Management

• Early treatment of GI symptoms leads to a more rapid response
• Be sure to rule out bacterial, viral, or parasitic infections

Side Effects: Colitis/GI Reactions

Management

• Grade 1: Continue treatment and treat symptoms
• Grade 2: Hold treatment until improvement to Grade 0-1. Treat symptoms (Imodium, lomotil). If symptoms last > 5 days start corticosteroids. If colitis recurs, permanently stop treatment.
• Grade 3: Hold treatment until improvement to Grade 0-1. Treat symptoms (Imodium, lomotil). Start corticosteroids. Consider endoscopy.
• Grade 4: Permanently discontinue immunotherapy, high-dose steroids, consider endoscopy.
Side Effects: Hepatitis

Inflammation of the liver

- Elevation of LFTs
- Elevation of Tbili or jaundice
- Nausea/vomiting
- Right sided abdominal pain
- Drowsiness
- Dark urine
- Easy bruising/bleeding
- Loss of appetite
Side Effects: Hepatitis

- **Management**
  - Grade 1: continue treatment and monitor LFTs
  - Grade 2: Hold treatment, monitor LFTs every 3 days, start corticosteroids
  - Grade 3-4: Permanently discontinue immunotherapy, high-dose steroids, refer to gastroenterology
Side Effects: Endocrinopathies

Signs and symptoms

- Unusual or persistent headaches
- Fatigue
- Unexplained weight changes
- Dizziness or fainting
- Mood and behavior changes
- Hair loss
- Feeling cold
- Constipation
- Voice gets deeper
- Increased thirst
- Urinary frequency
Side Effects: Thyroid

- **Hypothyroid**
  - (Pembrolizumab) Median time to onset 3.4 months
  - Monitor and treat with thyroid hormone replacement as clinically necessary
  - Consider endocrinology consult

- **Hyperthyroid**
  - (Pembrolizumab) Median time to onset 1.4 months
  - Consider endocrinology consult
  - Manage with thionamides and beta-blockers as necessary
  - Withhold or discontinue immunotherapy for Grade 3-4 hyperthyroidism
Side Effects: Nephritis

Inflammation of the kidneys
- Increase in serum creatinine
- Decreased urination
- Blood in the urine
- Swelling in the ankles
- Loss of appetite
Side Effects: Nephritis

Management

• Grade 1: Continue treatment and monitor weekly
• Grade 2-3: Hold treatment, start steroids, monitor creatinine every 2-3 days. If worsening or no improvement increase steroids and permanently discontinue treatment. Consider renal biopsy.
• Grade 4: Stop treatment, monitor creatinine daily, start steroids, nephrology consult, consider renal biopsy
Infusion Reactions (<1%)

- Monitor for:
  - Rigors
  - Chills
  - Wheezing
  - Pruritus
  - Flushing
  - Rash
  - Hypotension
  - Hypoxemia
  - Fever

- For mild reactions administer steroids and slow the infusion rate

- Discontinue treatment for more severe infusion reactions
Neurological Reactions

• Rare, often non-specific
  • Neuropathy
  • Seizure
  • Oculomotor and facial nerve paresis
  • Guillian-Barré Syndrome
  • Radiculitis
  • Dysgeusia

• Management
  • Consider holding treatment based on severity
  • Rule out disease progression
  • Refer to neurology
Other Adverse Events

- **Musculoskeletal**
  - Polymyalgia rheumatica, myositis, and arthritis

- **Cardiac**
  - Myocarditis, pericardial effusion, arrhythmia, A-fib

- **Ocular**
  - Iritis, uveitis, conjunctivitis, dry eyes, blurred vision

- “Anti-PD-1 antibodies can affect any organ system and thus, all symptoms have to be considered as potentially anti-PD-1 associated.”

Side Effects of Immunotherapy

• In general these drugs are well tolerated, but have their own unique toxicities that can be life threatening.
• Early identification and close monitoring are key to managing these events.
• The mainstay of immune-related side effects is steroids with a long and slow taper.
• Multidisciplinary management of events includes medical oncology, dermatology, endocrinology, pulmonary, GI, nephrology, neurology and others.

HEAD AND NECK CANCER

PAMELA HALLQUIST VIALE, RN, MS, CNS, ANP: Our next session is entitled Advances in Collaborative Practice for Patients with Head and Neck Cancers. Please join me in welcoming Dr. Robert Haddad and Mr. Jason Glass of the Dana-Farber Cancer Center.

DR. HADDAD: I’m a medical oncologist. It’s a pleasure to come in and talk to you this morning with Jason Glass, one of our nurse practitioners. Jason and I work together in the head and neck clinic at the Farber. And we’re going to review some of the recent advances in the treatment of head and neck cancer and also review some of the recent advances with immunotherapy in particular, and Jason’s going to go over how we manage some of the side effects of the drugs we currently use in the clinic. We’ve had some recent approvals in head and neck cancer in immunotherapy. These are the objectives of our lecture today, and these are my disclosures.

I’m going to start with a quick introduction. Many of you who deal with head and neck cancer, we are seeing a change in the epidemiology of this disease in the United States and Western Europe; whereas, a lot of the patients we see today have head and neck cancer that’s related to an infection with a virus, the HPV virus. HPV infection is now the number one cause of head and neck cancer in the U.S. It’s really changing how we think of head and neck cancer. When I did my training 15 years ago, almost every patient we saw with head and neck cancer used to be a heavy smoker, heavy drinker. Right now, a lot of the patients we see are nonsmokers, they don’t drink alcohol heavily, and they have head and neck cancer because of HPV. We’re going to talk about that a
little bit. We’re going to talk about how we treat head and neck cancer with concurrent chemoradiation with induction chemotherapy and adjuvant chemo, and then talk at the end about immunotherapy and the role of immunotherapy in head and neck cancer.

When we talk about head and neck cancer, we’re talking about these sites. This is multiple locations, oral cavity, which is where the oral tongue is, oropharynx where the tonsils are, larynx, hypopharynx, nasopharynx. I like to show this slide to make the point that head and neck cancer initial treatment depends on the primary site. When you’re dealing with tumors in the oral cavity, so the anterior location tumors, the oral tongue, the floor of mouth, cheeks, lips, those tumors are treated with surgery first. When you’re dealing with posterior location tumors, oropharynx, tonsil, tongue-base, larynx, hypopharynx, those tumors are treated nonsurgically to achieve organ preservation with chemotherapy and radiation. The primary location is key in how you treat the patient with your first therapy; is it surgery, is it concurrent chemoradiation?

Close to 50,000 new cases of head and neck cancer per year worldwide, close to half a million new cases every year. Median is age is 60. This cancer affects men more than women. It’s linked to alcohol and tobacco. It’s linked to the EBC virus, the Epstein-Barr virus, for the nasopharynx primary, and as I mentioned, is linked to the HPV virus for the oropharynx.

Let’s talk about HPV. Obviously, many of you know HPV is the main cause of cervical cancer in women, the main cause of anal cancer in men and women, and now is the number one cause of oropharynx cancer in men and women; men more than women. Remember, there are a lot of types of HPV. We put a number on them, 6,
11, 16, 18, 31, 33. The high-risk ones -- 16/18 in particular -- are the ones that are the main cause of oropharynx cancer.

As mentioned before, the number one case of oropharynx cancer now, this is typically nonsmokers, nondrinkers, this is your typical 45, 50-year-old man that walks into your clinic with a neck node and has an oropharynx primary. This is a typical profile of the head and neck cancer patient we see today. We see probably two or three patients a week now with this entity of HPV-related oropharynx cancer. Remember, HPV is a sexually transmitted virus, and it causes a number of cancers. There is a vaccine for HPV, which is used for cervical cancer, anal cancer. The role of the vaccine in neck cancer prevention is not known yet, but we expect that if we got to a point in this country where we start vaccinating everybody, we will see less head and neck cancer. Obviously, the vaccination rate for HPV in the U.S. continues to be very low, so we need to do a better job with that.

The reason we check for HPV, the main reason we check for it today, is because those patients, the HPV group, they have a much more favorable prognosis compared to the non-HPV. If you have to get this cancer, it’s better to get it because of the HPV than because of smoking. The cure rate is much higher in the HPV cohorts compared to the smoking cohort. It’s around 80% to 90% cure rates for HPV head and neck cancer compared to 50% to 60% for the non-HPV ones.

How do you check for HPV? You check for HPV on the biopsy specimen. Your pathologist is supposed to be checking for HPV on the oropharynx samples, and it can be done with in situ hybridization, can be done with p16 IHC or PCR; any of those would be fine. Most people do p16 immunohistochemistry. At Dana-Farber, checking for
HPV status is a standard of care for all the oropharynx cancers, and that’s how it should be everywhere. It is accepted and highly recommended as a standard of care test for the oropharynx cases. You don’t have to check HPV status for larynx, hypopharynx, or for the oral cavity, but you should check for HPV status for all your oropharynx cases.

We are seeing a decrease in smoking-related cancers in the U.S. At the same time, we are seeing an increase in the HPV-related cancers, as you can see from this slide here. Some people like to use the word epidemics. I don’t necessarily like this word, but what I would say is that by 2020, there will be more head and neck cancer linked to HPV in the U.S. than cervical cancer. These are the numbers currently, and this is a major problem we’re seeing in our clinics.

When I mentioned that these patients do better, this information has been generated from a large number of trials. I’m showing you one example here. This is called the RTOG 0129. This was a study comparing chemoradiation with one or two fractions of radiation per day. The intent of this trial was to look at whether it’s better to give one fraction of radiation per day or two fractions. But this important study was published in the *New England Journal of Medicine* from the HPV angle. The authors found that there was no difference between once a day or twice a day radiation, and they elected to focus on the HPV question instead.

And what you see on this curve here, and you don’t have to be a statistician to see the difference between the HPV group on top in yellow and the non-HPV group, the HPV negative. The difference in survival, 82% versus 57%. If you’re HPV-positive with oropharynx cancer, you’re going to do very well with treatment. Obviously, we have to talk about the side effects, how many side effects of chemo,
radiation, but the outcome of these patients is excellent. These patients do very well with appropriate therapy.

One of the important questions in head and neck cancer in this decade and going forward -- a word you’re going to hear often -- is de-intensification. Because these patients do so well, an area of research currently in our field is can we de-intensify therapy, meaning can we give these patients less radiation, can we give them less chemotherapy or no chemotherapy and maintain this high cure rate? As many of you who might have dealt with head and neck cancer know, these patients get very sick with treatment. They have acute intermediate and many long-term side effects from radiation, from chemo, so there’s obviously a lot of interest in trying to decrease the morbidity of the treatment, to decrease the side effects. And one of the questions in this day and age is whether we can de-intensify therapy, whether we can give less treatment for these patients, because these are two different diseases, HPV positive and HPV negative, and I’ll show you the differences between these two.

Next, let’s talk about clinical features of head and neck cancer. We’re going to move away from HPV now. Most of the patients have squamous cell carcinoma, most of the patients will have lymph node metastasis. That’s usually why these patients go to the doctor, they have a lump in the neck; that’s the initial presentation of these patients. Distant metastatic disease is not common on presentation. Many of these patients have other comorbidities, especially the smokers, they have lung disease and other disease that you have to account for in the treatment. And many of the patients, especially the smokers, have also a high risk of second primaries, and that’s something we have to account for.
Lymphatic drainage. When you hear the word neck dissection, what does that mean? This means you’re moving the lymph node of the neck. There are five levels of nodes in the neck. Level I is the submandibular level; II, upper jugular; middle jugular is III; IV is lower jugular; and V is posterior. When you hear “modified radical neck dissection,” this means the surgeon is removing all these levels, I, II, III, IV, and V. When you hear the words “selective neck dissection,” this means you’re removing levels I, II, and III only, or II, III, and IV only -- selective modified radical.

Screening prevention. There’s not a really a good screening or prevention for head and neck cancer today. I spoke about HPV. That’s an area that’s important, but in the next decade or two or three, we will find out if HPV vaccination will decrease the rate of head and neck cancer. We don’t have that information. I expect that the answer would be yes. If we vaccinate every boy and girl before they’re sexually active, between the ages of 9 and 26, the earlier the better; if you vaccinate everybody, I would expect you’d see less head and neck cancer. We’re not there yet. What we tell our patients is the most important screening you can do is to make sure when you go to your dentist, get a full head and neck exam, and for any lesions, to be referred early on for a biopsy. Remember, your dentist and your dental hygienist are uniquely positioned to find these types of lesions early.

How do we assess these patients? We assess them in the operating room with a biopsy, we put patients to sleep, do an endoscopy, do a biopsy, we use imaging extensively. PET scans are very helpful in head and neck cancer. We do a PET scan on every patient before treatment and after treatment; also, sectional imaging, MRI, and CT scan.
How do we treat head and neck cancer? Early-stage disease, stage I and stage II, it's typically treated with a unimodality approach. One modality, either surgery or radiation. Most of the patients we see will have stage III or stage IV, and for those patients you need a multimodality approach that will combine chemotherapy, radiation, and sometimes surgery. For surgery -- very important -- head and neck cancer is treated by a head and neck surgeon, someone who does this for a living. And the reason I say that, because one of the most important features of treating head and neck cancer surgically is to achieve a negative margin. The ability to clear the margin and get a negative margin has a big effect on survival. We strongly advise patients with head and neck cancer, when they need surgery, for it to be performed in an academic center with a lot of experience, because these surgeries are very complex, they often require reconstruction, and this is not often available in smaller centers.

Radiation therapy is a mainstay of treatment of head and neck cancer. Almost every patient with head and neck cancer -- because most of the people we see have stage III or stage IV -- most of the patients we see will require radiation. You have a list here of the radiation therapy side effects. Radiation is quite toxic for our patients. One point I would make, the hypothyroid, because it's often overlooked, 30% of patients with head and neck cancer become hypothyroid, because your thyroid gland is in the radiation field. Checking a TSH on these patients on a regular basis is key.

Concurrent chemoradiotherapy is a standard approach for head and neck cancer. This means combining chemotherapy and radiation together. Meta-analysis of head and neck cancer, looking at 10,000 patients confirms when you add chemotherapy to radiation you improve outcome, and this is level 1 evidence standard of care today,
as you can see here from the P values, very significant. Also, induction chemotherapy with platinum 5-FU improved survival, as you can see, from 15 trials looking at 2,500 patients.

The standard of care for head and neck cancer is cisplatin, 100 milligrams per meter square every 3 weeks during radiation. It is very important in head and neck cancer to use cisplatin as the standard drug, not to use other agents. It’s the most effective agent. And for those patients who are not candidates for cisplatin, there are alternatives, such as weekly carboplatin or paclitaxel or weekly cetuximab. But for the fit patients in good performance status, the most effective drug is cisplatin. Cetuximab is also FDA approved. This is an EGFR inhibitor. It’s FDA approved for head and neck cancer based on this trial that compared radiation alone to radiation with cetuximab, and it showed that when you add cetuximab to radiation, you did better than radiation alone. And this led to the FDA approval in 2006 in combination with radiation. But, as I mentioned in the slide before that, we continue to favor cisplatin as the standard of care, and we reserve this option for patients who are not candidates for chemotherapy.

What about sequential chemoradiotherapy, also known as induction chemotherapy? This means giving chemo before radiation. This study shows the FDA-approved regimen for induction chemotherapy in the U.S. and in Europe. It’s known as the TPF, docetaxel, cisplatin, and 5-FU. This study compares TPF to PF, followed by concurrent chemoradiation. Five hundred patients enrolled in this trial, and these are the patients’ characteristics. These are young patients in their 50s, they had good performance status, and they were mostly stage IV locally advanced, nonmetastatic. This study showed than when you add docetaxel to PF, creating the TPF regimen, you
did better than with PF, improved survival, improved progression-free survival, leading to FDA approval of this regimen in 2007. When you use TPF when you use induction chemotherapy, this is the standard induction chemotherapy regimen.

These are the side effects of the regimen listed here. You have more neutropenia, you have more febrile neutropenia with TPF. You could use growth factors for those patients. The rate of febrile neutropenia is around 12%. You have more mucositis/dermatitis with the PF because the dose is higher.

These are the other studies that also show that TPF is better than PF. This is currently the standard of care for when you use induction chemotherapy. And these are the conclusions of the study that led to the approval of TPF in the U.S.

These are some of the scenarios that we use to consider induction chemotherapy. Remember, I said earlier that concurrent chemoradiation is the standard of care. These are some select situations where we would use induction chemotherapy, where we would use chemotherapy before radiation, patients with multiple nodes, patients with possibly metastatic disease, patients in need of immediate therapy who are symptomatic that you think might need a trach or a PEG. You start them on chemo within a few days, they start responding, you can avoid the trach and a PEG. These are some situations where, in our practice, we would consider induction chemotherapy for head and neck cancer patients.

The question of a neck dissection would often come up after treatment. This refers to removing the lymph nodes from the neck. The parent rule is that if your patient has a complete response to treatment, you do not need to do a neck dissection anymore. And the way you make that decision, you make it with imaging with a PET
scan around 3 months after treatment. Typical course is, you do a PET scan before treatment, you do your concurrent chemoradiation, 3 months later you do a PET scan. If that PET scan is clear, you don’t need to do a neck dissection.

This is how we follow these patients, and we touched on those, primarily imaging at 3 months, check a TSH, speech and swallow follow-up, nutrition, dental follow-up. These are standard follow-up procedures for head and neck cancer patients.

What about metastatic disease? Metastatic disease in head and neck cancer is seeing some changes, because now we have one drug that is approved, pembrolizumab, as of August of this year, and another drug that’s currently being reviewed by the FDA, nivolumab. We are now seeing a role of immunotherapy in head and neck cancer.

Let’s talk about chemotherapy in the palliative setting. Everything I’ve been talking about so far is in the curative setting. Now we’re going to talk about the palliative setting. This is a regimen that’s also FDA approved in the U.S., known as the extreme regimen. This is platinum 5-FU and cetuximab versus platinum 5-FU in the first-line metastatic setting. These are patients who have seen radiation or chemotherapy, have progressed, and now they are being treated in the first-line setting. This study showed an improvement in survival in 3 months between TP plus cetuximab versus TP. The triplet did better than the doublet, leading to the FDA approval of this regimen for first-line treatment of metastatic disease. This is level 1 evidence of standard of care, and these are the numbers: 10.1 months for three drugs versus 7.4 months for two drugs.
Monotherapy cetuximab also plays a role, though minimal today. This is the single-agent cetuximab, then platinum with refractory disease, showing a response rate of 12%, and that can be used in some patients if they have not seen cetuximab earlier.

Now what about immunotherapy in head and neck cancer? This is obviously now common in many solid tumors, and now it’s found its way into head and neck cancer. One drug already approved, a second on the way. You probably heard a lot during this conference about immunotherapy. It’s being used in lung cancer, in kidney cancer, Hodgkin’s, melanoma. A lot of uses of immunotherapy, and now head and neck cancer data that’s solid. There’s obviously a lot of rationale to use immunotherapy in head and neck cancer just like we see in other solid tumors. I’ll show you a long list of immune cell mediation in head and neck cancer listed here that’s justified testing immunotherapy in head and neck cancer.

In platinum-refractory head and neck cancer is where we have the indication today that I’m going to share with you shortly. The current studies are looking at the platinum-sensitive patients, or the first-line setting, and also, we are starting to incorporate these agents in the up-front setting with radiation and chemotherapy. We started in the platinum-refractory, now we are moving into first-line and also into definitive settings. This is the KEYNOTE-012 study that led to the FDA approval of pembrolizumab in August of this year. This is a phase I/II study that essentially looked at pembrolizumab as a single agent in patients that are heavily pretreated with chemotherapy. It’s a large study, 192 patients. As you can see here, most patients have seen either two or three lines of therapy. The response rate of single-agent
pembrolizumab in this study is 18%. It was a little bit higher in the HPV-positive group compared to the HPV-negative group. And this data led to the FDA approval in August. These are the overall survival and progression survival of this agent. This is now an option for our patients who have progressed on chemotherapy, to go on single-agent immunotherapy. These are the conclusions of the KEYNOTE-012 study.

The other study that also is now published 2 weeks ago in the *New England Journal of Medicine* is CheckMate 141, nivolumab versus investigator choice. This is a phase III study, 2:1 randomization between nivolumab or investigator choice, with a primary endpoint of overall survival. This is the first phase III study with immunotherapy in head and neck cancer. These are the patients’ characteristics listed here: 200 patients on nivolumab, 121 patients on the investigator choice. Many of these patients have seen a number of prior therapies, as I showed you before, also in the pembrolizumab study. These are the data of the study. The study was stopped early because there was a clear improvement in survival with the nivolumab, so the DSMB recommended stopping the study. When the study was analyzed, the number of deaths were 70% on the investigator choice versus 55% on nivolumab, clearly in favor of nivolumab in this indication.

This is the top-line data: 5.1 months with investigator choice versus 7.5 months with nivolumab. These are the survival data with this phase III study. This is the first phase III study to show an improvement in survival with nivolumab compared to chemotherapy. And as I mentioned, this drug is currently being reviewed by the FDA for a head and neck cancer indication.
This study also had quality of life data as shown here. Again, being a phase III study, there was a significant assessment of PROs -- patient reported outcomes. When we look at the role functioning of the patient, social functioning, physical functioning, on many scales what we’ve seen is a stabilization with nivolumab of the quality of life parameters versus a deterioration in the quality of life in the chemotherapy arms. This study essentially has an overall survival advantage, but also we have PRO data. This was presented 2 weeks ago in the Presidential Symposium in Copenhagen in the ESMO meeting, showing this data of not only the survival benefit but also the PRO data with nivolumab. What we are showing is a number of quality of life assessments that were done in this study. Here you’re looking at appetite loss, you’re looking at dyspnea, you’re looking at fatigue.

The PD-1 inhibitors in squamous cell carcinoma of the head and neck, nivolumab is the first one to show a significant improvement in survival compared to chemotherapy. Pembrolizumab, as I showed you, also showed a robust antitumor response of 18%, leading to FDA approval. Both of these agents have shown benefits, regardless of the PD-L1 status, but I would make the statement that the PD-L1-positive patients appear to benefit more compared to the PD-L1-negative patients.

Safety for these agents is consistent with what’s seen in prior indications. And Jason’s going to go over the side effects and how we manage the toxicity of these agents since they have become now a standard of care for our patients in 2016 and going forward. These agents represent a new standard of care for patients with platinum-resistant or platinum-refractory head and neck cancer, and as I mentioned,
now being taken into the first-line setting and into the definitive setting in combination with radiation therapy.

My last slide, treatment of head and neck cancer in 2016 and beyond. We have multiple options available to our patients: concurrent chemoradiotherapy, sequential chemoradiotherapy with a TPF regimen, and PD-1 inhibitors now are a standard approach for patients with platinum-resistant disease. Patient selection is important. Remember, we said site is important, oral cavity versus non-oral cavity. We spoke extensively about HPV and the role of HPV in head and neck cancer and how it has changed, how we think of head and neck cancer, and how it has completely changed the epidemiology of this disease in the U.S. and in Western Europe.

Thank you very much. Jason.

MR. GLASS: Good morning. My name’s Jason Glass. I’m the nurse practitioner in the head and neck oncology department at Dana-Farber where I work directly with Robert Haddad and also with one of the other docs at our group. He took you through a whole course of immunotherapy and treatments for head and neck cancer. Today I’m going to talk more about the collaborative practice that we have at Dana-Farber with the advanced practitioners and the medical oncologists, and then also on how we manage the side effects of these treatments.

I wanted to go through how our team is set up at Dana-Farber. When patients are registered at Dana-Farber and they’re coming in to be evaluated by us, they’re automatically assigned a medical oncologist, a radiation oncologist, a head and neck surgeon, one of the advanced practitioners, either me the nurse practitioner, or there’s a physician assistant in our group, and they’re also assigned a program nurse,
and then we evaluate the patient, sort of set the plan in motion of what’s going to go on for them, and then once they start treatment, then we start adding in other support folks that are part of the head and neck group. They get assigned a primary nurse when they’re getting their chemotherapy, a nutritionist, a speech language pathologist, and a social worker. And as things go along, and as Dr. Haddad had mentioned, a lot of our treatments can be very rough on the patient, we also have a lot of other things that we can bring into bear. We have a pain and palliative care group that’s on the same floor as us that we can bring in. One of the things that we’re even trialing right now is one day a week we have a pain and palliative care specialist in our clinic, so if something comes up that’s particularly challenging, we can just pull them right in at the moment. We have a dermatologist on the floor that we use, particularly for things like cetuximab or even for taxane toxicities. We have oral medicine and we also have psychiatry, because a lot of these patients can certainly struggle with a lot of different issues as they’re going through treatments.

It sounds like a lot of cooks in the kitchen, and sometimes it can feel a little overwhelming, there’s so many people around, but one of the things that’s really amazing with our group is how seamless this works and how well it can pull people in at a moment’s notice. One of the things I wanted to highlight, a common problem that I’ll have: I’ll come in one day, I’ll be seeing a patient to assess them for their chemotherapy that day, and they’ll come in complaining of a chronic nose bleed over the last couple of days, which is something that happens fairly often while they’re getting their radiation. And so, it sounds like a simple thing, and maybe it is, maybe we just need to put some pressure on it for a few minutes, apply some ice, and we’re done with it, but in other
cases, the patient might require packing, they might require cauterization because this is an ongoing issue. I might have to worry, is this actually a sign of disease progression if this is a nasopharynx cancer. What I’m able to do while I’m seeing that patient, I can walk right into the work room, I can talk to the surgeon or to the advanced practitioner that works with that surgeon. You can usually get something going right there in the room without having to bring them around. That’s improving the outcome for the patient, it’s speeding things up, it’s keeping them from delaying their treatment, it’s keeping people out of the emergency room for an intractable nose bleed. It does work really well for us.

In particular, I also wanted to just discuss how Dr. Haddad and I tend to work together. Typically, we’ll meet patients at the same time, and on the day that they’re starting treatment, we’ll usually do simultaneous visits, so that I can spend a few minutes after they’ve consented and everything’s ready to go to make sure the patient has a good feel for what’s going to go on for that day and review what that whole 6-hour day is going to look like. During the course of treatment, we may see patients at the same time, we may alternate visits, depending on how they’re doing. Oftentimes, my main role is to make sure that they are staying safe, that they are managing their symptoms as well as can be, and most importantly, that they’re staying on track with treatment. It’s critical for these patients, that they don’t have deviations in their radiation plan, and if they’re getting sick from their treatment, that could happen. I spend a lot of my time throughout the week catching up with people, seeing them two times a week, three times a week, to make sure that they’re getting the support that they need to get through treatment.
Since that talks a little bit about the side effects of treatment, why don’t we move on with that. As Dr. Haddad said, most of what I’m going to be talking about is in regards to immunotherapies, mainly focusing on pembrolizumab because that’s the drug that’s been approved, but this also applies to nivolumab. We can think of these as class effects, so in the future, if there are other drugs that are -- other immunotherapy that becomes available for head and neck cancer, a lot of this likely will apply to it as well.

The one thing to remember is, as Dr. Haddad said, these drugs right now are reserved for the palliative setting. All of these patients are coming in to you, for the most part, having already been extensively treated. So we have to remember that, because they’re going to be starting off usually with certain deficits that are typical for head and neck cancer patients, dry mouth, potentially thyroid dysfunction, dysphasia, chronic pain in the mouth and in the throat. Part of preparing the patient to start on immunotherapy is recognizing these deficits and being able to try and predict what’s likely to be exacerbated by treatment.

As our patient’s starting on immunotherapy for head and neck cancer, we want to -- same as with any other medication -- we want to take a good history from them again, go over everything, make sure we understand what’s going on with this patient. This way, we can minimize the risk of complications. And we want to get some baseline tests so that we have something to measure against. We want to, in this case, we want to be looking for any type of autoimmune disorders, such as Crohn’s disease, ulcerative colitis, lupus, or for other conditions that require immunosuppression, such as
an organ transplant. Patients with this type of a background are at risk for life-threatening flares if they were to go ahead with immunotherapy.

For blood work, we’re looking at getting baseline thyroid, liver, and creatinine. These tests should be repeated periodically throughout treatment and again after treatment is over. We do want to particularly focus on the thyroid. As Dr. Haddad said, about 30% of these patients are already at risk for thyroid dysfunction, or maybe starting off with thyroid dysfunction. This is something that can creep up as a result of their immunotherapy.

Also, we want to remember that immunotherapy is believed to cause fetal harm. Patients with reproductive capability should be counseled on contraceptive use. Women are recommended to discontinue breast feeding during treatment. The guidelines were a little bit different for pembrolizumab than for nivolumab. What I saw was 3 months after the discontinuation of therapy for pembro and 4 months for nivolumab.

Discussing the potential side effects of the patient beforehand allows them to be part of the conversation and allows them to let you know as things are going on. One thing to note is that both nivolumab and pembrolizumab have patient-specific materials listing side effects. The one for pembrolizumab is specific for head and neck patients. There is not one for nivolumab right now since it hasn’t been approved, but the basics of both of them are pretty much the same.

The most common side effects that we see, we have fatigue, pruritus, diarrhea, decreased appetite, rash, dyspnea, constipation, and nausea. Those are more common reactions that we’re seeing on this, but then we have our more serious, these
immune mediator responses, and these are our itises, pneumonitis, dermatitis, colitis, hepatitis, our endocrinopathies, and nephritis. And then there’s our rare reactions, these are the infusion-related reactions, which is very uncommon, and also neurologic side effects. And we'll talk about some other very rare reactions that could happen as we get towards the end.

As was already mentioned, patients tend to tolerate these drugs very well, and the rate of serious side effects is pretty low, but your patients do need to be monitored very closely to make sure that we're doing okay.

I wanted to start off talking about the immune-mediated inflammatory response, because these are the ones that really get in the way of treatment, these are the ones that are going to cause you to delay or even permanently stop treatment for the patient. I am starting with pneumonitis, not because it’s the most common one, but because I personally find it to be the most complicated one to deal with. There’s so many possibilities of what can be going on when the patient comes to you with a new or worsening cough, shortness of breath, or tightness in the chest, chest pain, or fatigue. We have to remember with these head and neck patients that they’re at high risk for aspiration, so we can be talking about an infection. These patients might be having tracheal compression, which could be causing breathing issues. These are patients with active cancer, so we’re also dealing with a higher risk of blood clots, and they might also have already had treatment to the lungs or they might have lung mass that could be causing new symptoms. When we’re evaluating the patient with respiratory issues, we want to start off with our differential diagnoses and looking at could they have a pneumonia, could they have a pulmonary embolism, but you want to keep pneumonitis
in mind with them. Fortunately, the work-up for all this is going to be basically the same. You’re going to be getting a CT of the chest, you want to consider getting a pulmonary or an infectious disease work-up if this is proving to be a very complicated patient. And the way that we’re going to be doing the management for this is at grade 1 -- and this is really your incidental finding -- you send the patient in for restaging scans, it says that they have pneumonitis, but they’re not complaining about any of these things. You can consider holding treatment, but in many cases for grade 1, you are able to continue to treat them. It’s at the grade 2, that’s when you’re holding treatment and you’re going to be starting steroids, and you’re going to be hearing me repeat this over and over again, steroids, steroids, steroids. I think every slide after this has steroids.

If there’s no improvement after about 2 weeks, you’re going to be treating this as a grade 3 to 4, which is when you’re going to be stopping treatment at that point, starting higher-dose steroids, you’re most likely going to be admitting the patient, and then you want to be considering nonsteroidal immunosuppression at that point.

Dermatitis. This occurs in about 30% of patients. It’s often mild in severity. I have to say, it certainly feels like I’m seeing this more than 30%, but these are the official numbers. And these can be anything from a mild rash to itchy skin, they can be developing blisters, or they could also develop ulcerations in the mouth and other mucus membranes.

Chemo dermatitis is minimizing that risk. You want to reduce the risk a bit and start early with gentle moisturizers. This is very similar to our teaching for cetuximab. We want to minimize sun exposure, we want to avoid tight-fitting or abrasive clothing, and avoid scrubbing or scratching the skin. One thing that comes up typically
with these patients is that some of them, people who progress very quickly after their primary treatment, they’re also still going to be having some radiation effects, and so they may already be coming into this with impaired skin. We also do see patients that have tumors that are very close to the surface or already with dermal invasion, and so you may see skin issues developing very quickly that might be malignant rather than treatment-related, and that requires its own teasing out and managing appropriately.

The management for grade 1 and 2, you are able to continue treatment for these patients. These are typically smaller contained rashes that aren’t having a significant effect on their quality of life, other than some discomfort. You’re going to be starting antihistamines and usually topical steroids. And I’ve set up -- in our EMR -- I have a list of go-to medications that I can pull up my dermatology side effects and then click off which steroids I’m starting, because we’re abusing those so often. It’s at grade 3 and grade 4, that’s where you’re starting to have problems, and this is not something that comes up too often, but this is when you’re holding treatment at grade 3. You’re going to get your dermatology referral, because they’re going to need a lot of other medications to deal with this, and then you’re starting your oral steroids at that point. And at grade 4, you’re looking at stopping treatment for them. It’s rare, but there have been severe skin reactions that have developed on immunotherapy, such as bullous pemphigoid and exfoliative dermatitis. So if things are getting worse, you want to be paying attention to this.

Colitis. This is another common one that we’re seeing. Patients will complain about diarrhea or increased frequency of bowel movements. There could be blood in the stool or dark and tarry sticky stools. Also, severe abdominal pain or
abdominal tenderness. And this is one of the ones that we hear a lot, people talking about the stomach not feeling right or some stomach pain. Key for this is early treatment is going to lead to a more rapid response. And you want to make sure that you’re ruling out the bacterial viral and parasitic infections when you’re dealing with GI issues for these patients.

With Grade 1, we’re going to be continuing treatment and we’re going to be starting them on things like Lomotil or Imodium for diarrhea. If they’re having cramping, you’ll be thinking of things like Bentyl. When we’re moving into grade 2, which is when they’re starting to get into the more serious four to six stools a day, require IV fluids throughout the week, abdominal pain, blood in the stool, that’s when you’re holding treatment. If the symptoms are lasting more than 5 days after stopping treatment, you’re going to be adding steroids in again at that point. At grade 3, you want to hold it until the patient improves back to a grade 0 or grade 1. You’re going to be treating the symptoms, steroids. And you want to consider an endoscopy at that point. And grade 4 is when you’re stopping treatment. They’re getting high-dose steroids; you’re getting a GI referral at that point.

Hepatitis. Inflammation of the liver, there can be an elevation in the LFTs, elevation in the bilirubin or in the jaundice, nausea, vomiting, right-sided abdominal pain, drowsiness, dark urine, easy bruising, easy bleeding, loss of appetite. Remember, these are patients that are palliative, so you also need to rule out an obstruction. You want to make sure you’re looking for all the possible causes if you’re see changes. In liver function tests, also consider alcohol use, Tylenol, statins, or other medications that patients are on. Recently, when I was seeing this, we ended up taking a patient off the
statins, not because we thought that was the cause, but because their LFTs got so high that we wanted to make sure we were minimizing all the insults to the liver at that point. Grade 1, continue treatment, monitor their LFTs, make sure things aren’t getting worse. Grade 1 is when you’re holding, you’re monitoring their LFTs every 3 days, you’re starting your steroids. Grade 3 to 4 is when you’re stopping treatment, you’re doing high-dose steroids, getting them to gastroenterology.

Just as an aside. I have one patient that’s on nivolumab as an off-label treatment for a larynx cancer who’s got hepatitis C among many comorbidities; the patient has a little bit of everything. Not only is his cancer responding exceptionally well to the nivolumab, but also his LFTs and his bilirubin have completely normalized. So who knows what’s going to go on in the future for other disease?

For endocrinopathies, we’re looking at unusual persistent headaches, fatigue, unexplained weight changes, dizziness, fainting, mood and behavioral changes, hair loss, feeling cold, constipation, voice getting deeper, voice changing, increased thirst, urinary frequency, the thyroid, the pituitary, the adrenal glands, and the pancreas can all be affected by immunotherapy.

For the next slides, I’m just going to focus mainly on thyroid, because that’s the most common one. The other endocrinopathies are fairly rare, and we simply don’t have enough time to go into all of them in detail. With our thyroid we’re talking about hypothyroid, which our patients are already at risk for. One thing that I noted for pembrolizumab, the median time for onset of hypothyroidism was 3.4 months. We want to monitor and treat with thyroid hormone replacement as clinically necessary, and we want to consider an endocrinology consult if things are not getting under control. For our
hyperthyroid patients, for pembrolizumab the median time to onset was 1.4 months. For this one, you’re looking more at endocrinology consult a little bit sooner. Most of us are a little less confident in dealing with this, but we’re going to be managing the same way you would for any type of hyperthyroidism with thionamides, beta blockers, and you want to withhold or discontinue immunotherapy for a grade 3 or 4 hyperthyroidism. That’s really the main difference there. For hypothyroidism, you typically will not have to stop treatment; you can manage them through that. For hyperthyroidism, you do reach a point where you need to stop.

Nephritis is inflammation in the kidneys, increase in serum creatinine, decreased urination, blood in the urine, swelling in the ankles, loss of appetite. Management: grade 1, try and manage them through this, see if you can support them with fluids and getting them back on track again. For grades 2 and 3, you’re going to be holding treatment, starting steroids, monitor the creatinine every 2 to 3 days. If it’s worsening, or if it’s not getting better, you want to increase the steroids and look at permanently stopping treatment. Grade 4, you’re going to be monitoring creatinine daily, you’re on steroids, getting an endocrinology consult, you want to consider getting a renal biopsy.

Those are our major problems that we see. These are the bigger problems that usually lead to people stopping treatment. Those are the more serious ones. We do have a couple of rare [ones], but as we notice we’re using this more, you’re going to see these things. I wanted to talk a little bit about infusion reactions. This typically presents as any type of infusion reaction, rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. For mild reactions, you want to do steroids, just as
you would for any other infusion reaction. It does say that you can try slowing down the infusio
rate and see how that goes, but for more serious ones, you want to discontinue treatment. I’m not going to get up here and say that I haven’t seen this happen yet, because I don’t want my pager going off in Boston while I’m down here talking, but this is a pretty uncommon reaction that we would see. Also, very rare would be neurologic reactions. Not only are these rare, they’re often very nonspecific and can be very difficult to tease out. Head and neck cancers do not often metastasize to the brain or the CNS, but it’s not impossible. We can be looking at issues like neuropathy. These patients are on platinums and taxanes, so we could be having neuropathy for a lot of reasons. Issues with seizures, ocular motor and facial nerve paresis; we can see this oftentimes with disease progression, so it can be very difficult to figure out what’s going on. Guillain-Barré syndrome has been reported, radiculitis. You want to consider holding treatment based on the severity of it, you want to rule out disease progression, and you want to make a referral to neurology, because this is going to be very challenging to tease out.

Other adverse events. I wanted to start with this piece that I found in one of the papers I was reading for this. Anti-PD-1 antibodies can affect any organ system, and thus, all systems have to be considered as anti-PD-1 associated. There are reports of musculoskeletal issues, of cardiac issues, of ocular issues. I had one patient that ended up coming in and was complaining about pain in her eye, and when we looked, the eye was getting notably red, swollen, with a lot of changes in it, and we were wondering were we seeing ocular affects related to her immunotherapy. It turned out in
her case it was disease progression invading into the eye. So you need to really be looking at this and how the patient is progressing.

To wrap things up, as Dr. Haddad said, in general, these drugs are well tolerated. They have their own unique toxicities that can be life-threatening. Early identification and close monitoring are key to managing these events. I think I could have probably wrapped up 90% of what I talked about today with just steroids. That is the mainstay. Remember, when you’re doing the steroids in these cases, it’s a long, slow taper. There is no rush to get these patients off. You need to make sure that these toxicities have really improved and gotten back to a point where things are manageable again.

And multidisciplinary management of events. This includes medical oncology, dermatology, endocrinology, pulmonary, GI, nephrology, neurology, social work, speech and language pathology, many others. These head and neck patients are very challenging, and putting them on immunotherapy does not make that any easier.

Thank you.

DR. HADDAD: We’re going to open this with questions. If anyone has any questions? Yeah, go ahead.

FEMALE: Do you restart the nivolumab if they are on steroids, a low dose, or do they have to be completely off?

DR. HADDAD: The question is whether you start nivolumab as the patient is being tapered off. In general, you would want to taper the patient off the steroids before you restart immunotherapy. Obviously, every situation’s going to be different. In our situation, head and neck cancer, as we mentioned, we’re treating patients with
platinum-refractory disease, so quality of life is going to play a big role in how we’re doing things. Our approach right now, we’re going to taper the patient off the steroid before we restart immunotherapy on them.

FEMALE: Are there any recommendations for pathological PD-L1 testing?

Right now we’re doing all the HPV testing. So what about the PD-L1?

DR. HADDAD: A great question. Right now, the label of pembrolizumab does not call for you to check for PD-L1 status, so you don’t have to do that. As I mentioned, in CheckMate 141, when you look at the survival data between PD-L1, more than 1%, or less than 1%, the patients who are more than 1% appear to benefit most from these agents. My personal opinion is there’s going to be a role in the future for PD-L1 testing. At this stage today, in November of 2016, we don’t have to check for PD-L1 status.

FEMALE: This is really a great review on some of the acute side effects of immunotherapy. I’m wondering if you have any insight for survivorship for patients for late in long-term effects related to that treatment, outside of the endocrinopathies that you may see with hypothyroid and things to that effect?

MR. GLASS: The question was management for survivorship for late effects on immunotherapy. This is something we’re going to figure that out as we get there. For head and neck cancer specifically, we just started using these. I’m watching one patient that’s coming off trial now after successfully completing it, and we’re waiting to see when things like how long does it take for the fatigue that he’s experienced to actually go away, or does it go away? Things like hypothyroidism, I don’t think that we’re
generally expecting that that’s going to improve. You’re going to continue to manage that just as you would for any hypothyroidism for the rest of the patient’s life.

DR. HADDAD: I want to add one thing here. This is a very good question, because obviously right now, we are using these agents in the palliative setting where survival is very limited, but as we move these agents into the up-front setting into a curative setting, your question becomes even more relevant, because if now we are using these agents in patients who are going to live for a long time, we don’t have the data on the long-term effects of these agents 2, 3, 4, 5 years down the road. There’s more data on melanoma patients because there’s more use of melanoma and it’s been around for a longer time. But this question becomes more relevant as we start to move these agents into a curative setting. We don’t have a lot of that information right now.

FEMALE: In regards to surgery and the oropharynx and tonsillar cancer, it’s common to see patients come in and have their tonsils removed. You were talking about how surgery -- generally, you’re going to do chemotherapy first. Can you speak to that?

DR. HADDAD: The question is about surgery on the tonsil, which in the United States and Europe, you have currently robotic surgery as one available way of treating oropharynx cancer. For the oropharynx, specifically for the tonsil, you can treat patients with surgery first with a tonsillectomy and a negative margin and a neck dissection. And based on the pathology report, then you can decide if you’re going to use radiation or chemoradiation. TORS, transoral robotic surgery, is an FDA-approved method in treating oropharynx cancer, for those patients who are treated with robotic surgery first. And there’s actually a phase III study with the HPV patient looking at
TORS and then putting patients into low-risk and high-risk groups. If the patient has surgery first, then the decision becomes about radiation or chemoradiation based on margins and based on pathological features. For the oropharynx, this also would be an acceptable way of treating the tonsils.

FEMALE: Can you talk a little bit about the decision making around a feeding tube, your perspective: early, late, when?

MR. GLASS: Up until about 2 years ago in our practice, pretty much everyone that came in did receive a feeding tube. We were maybe a little different than the rest of the country in that. But we felt justified in it because optimizing hydration and optimizing nutrition throughout this improves the quality of life for the patient and also accelerates their recovery afterwards. We are so aggressive with our speech language pathologist, that we felt that we didn’t get any sort of negative by allowing them to have a backup on that. We have since changed and we’re doing it much less now. We’re being a little more selective in terms of who we choose that with. You know, we do have a couple of guidelines in terms of patients that we’ll say, “Absolutely, they’re going to need one.” A lot of that comes from our radiation colleagues, depending on how large the radiation field is going to be and how much damage we think is going to happen to the tongue and to the throat. Also, patients that have other comorbidities, particularly, our diabetic patients, are much more likely to require a feeding tube so that we can manage them properly. Most of these patients won’t need to start off immediately with a feeding tube. You have a little bit of time to see how things go and how they’re tolerating their treatment, but you have to be very careful just to make sure things don’t rapidly fall apart, and that also, when you’re looking at a patient that’s lost five pounds in 1 week.
and five pounds the next week, and now you’re coming in and they’re already behind the curve. Personally, as someone that deals with side effects, I’m a big proponent of the feeding tube. I understand the patients’ desire to avoid that, and I am willing to work with them on it, but I do feel that for the most part, it is easier for the patient to get through treatment with a feeding tube than without.

DR. HADDAD: I would add to this that right now, we probably would say around 30% of patients can do this treatment without needing a feeding tube, and we are moving away from requiring this for every patient. As I mentioned, a lot of patients we see now are young and healthy and fit, HPV positive, so they have a lot of reserve and they can go through this without a PEG. But if you’re dealing with a patient who’s already going into the treatment having lost weight, an elderly patient, then put in the tube up front so you can avoid treatment interruption.

FEMALE: You had spoken about it needs to be a slow taper off of the steroids, but when you’re treating with nivolumab every 2 weeks, how long of a delay before you start worrying about further progression of the disease?

DR. HADDAD: That’s not a set rule on this. I mean the typical patient would require the steroid tapered over 4 to 6 weeks, which for the patients were are talking about today, this would be an acceptable delay. And again, many of these drugs are in the system, and for those patients who are responding, they’re going to continue to respond as you’re tapering the steroids. I’m not too worried about progression as you taper the steroids now. When you start moving into a different setting and to a more curative setting, that could be a different discussion, but for now, because of some of the life-threatening toxicities of these agents, it is recommended that you get the patient
into a grade 1 at baseline before you restart immunotherapy. I would point out that in this week’s *New England Journal of Medicine*, there is a report of two deaths from cardiac effects of these drugs. It’s a case report about two patients from Vanderbilt who died from myocarditis from these drugs. So we are learning more and more about these drugs, and we have to be a little bit careful as we get them into general practice.

FEMALE: Can you talk a little bit about your experience with any patients who have had organ transplant receiving immunotherapy?

DR. HADDAD: Question about organ transplant and immunotherapy. And that’s not really very well studied, because most of the patients we have, have been treated on clinical trials, and by definition, an entry criteria for these patients is not to be on steroids to enter the trials. And patients you’re talking, transplant patients, are typically on steroids, so there’s not a lot of data right now about what to do with these patients and whether immunotherapy plays a role in someone who’s immunosuppressed with steroids or organ transplant patients, heart transplant, or kidney transplant. I expect in the future, we’re going to have studies specifically directed at those patients to study the effects of immunotherapy. At this stage today, we don’t have a lot of information on those patients, as we just have not treated patients on steroids with these drugs.

FEMALE: I have two questions. First of all, of the patients who have HPV, how many of them, approximately, get HPV-related head and neck cancers? And secondly, with the feeding tube, has there been a study to show if patients are handling the treatment better because of supportive care because of the feeding tube compared to those who didn’t get the feeding tube?
DR. HADDAD: For those individuals who have HPV infection, how many get HPV cancer? It’s extremely small. Remember, with HPV infection, the vast majority of individuals who get HPV infection will never have a problem, and it’s the minority, way more than 1%, who will develop cancer. We don’t know why that happens. If you test 100 people for HPV, many have HPV infection, and the vast majority don’t know about it and will never have a problem from it.

MR. GLASS: There probably has been a study of that. I’m not aware of it. I’m going by my own anecdotal data of how often patients end up seeing me and the frequency of supportive treatment that they’re needing in terms of extra hydrations throughout the week and weight loss.

DR. HADDAD: There is data that patients who swallow during treatment have a much better functional outcome. That’s the idea behind trying to avoid the feeding tube, because for many patients when they have a feeding tube, they try to avoid swallowing, and you want to push patients to swallow, even if they have a feeding tube. The key point: there’s a lot of data about better functional outcome in those patients who continue to swallow during treatment and not just rely on a feeding tube. For our patients, even when we have a PEG, we are still pushing them to eat by mouth for as long as they can. And that’s the key, that we have data on better functional outcome, not a better survivor outcome.

MR. GLASS: We always stress the tube is meant to be a backup in all cases; it’s not meant to be your primary nutrition.

(End.)