Webinar Agenda

3:00–3:05 p.m. EDT  Welcome, Introductions and Overview

3:05–3:40 p.m. EDT  Review of SITC Cancer Immunotherapy Guideline – Squamous Cell Carcinoma of the Head and Neck (HNSCC)

3:40–3:55 p.m. EDT  Question and Answer Session

3:55–4:00 p.m. EDT  Closing Remarks
To Submit a Question

Computer

Mobile Phone

Q: Has the webinar started?
A: Yes, thank you for joining today!
The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC)

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Webinar Faculty

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*University of California San Diego*

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*Stanford University*

Rom Leidner, MD  
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*Dana-Farber Cancer Center*
Squamous Cell Carcinoma of the Head and Neck (HNSCC)
FDA-approved Checkpoint Inhibitors in Head and Neck Cancer

2013
Pembrolizumab trials initiated

2014
Nivolumab trials initiated

2016
Pembrolizumab approved for 2nd line R/M HNSCC
Nivolumab approved for 2nd line R/M HNSCC

2018
Cemiplimab approved for metastatic or locally advanced cutaneous squamous cell carcinoma

2019
Pembrolizumab approved for 1st line R/M HNSCC (CPS ≥1)
Pembrolizumab + Chemotherapy approved for 1st line R/M HNSCC (all patients)

In Development
- Curative Therapies integrating IO with RT in the neoadjuvant, concurrent, and adjuvant settings
- Anti-PD-1 for R/M NPC in first- and second-line settings
- Anti-PD-1 in combination with other immunotherapies
Immune Checkpoint Inhibitor (ICI)-based trials leading to FDA approvals

First-Line: Phase III KEYNOTE-048 Study Design
Pembrolizumab or Pembrolizumab + Chemotherapy (platinum/fluorouracil) vs. EXTREME in R/M HNSCC

**Key Eligibility Criteria**
- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment
- Known p16 status in the oropharynx

**Stratification Factors**
- PD-L1 expression (TPS ≥50% vs <50%)
- p16 status in oropharynx (positive vs negative)
- ECOG performance status (0 vs 1)

**Pembrolizumab 200 mg Q3W for up to 35 cycles**

**Pembrolizumab + Chemotherapy**
- Pembrolizumab 200 mg + Carboplatin AUC 5 OR Cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for 6 cycles (each 3 wk)

**EXTREME**
- Pembrolizumab 200 mg Q3W for up to 35 cycles total
- Cetuximab 250 mg/m² Q1W + Carboplatin AUC 5 OR Cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for 6 cycles (each 3 wk)
- Cetuximab 250 mg/m² Q1W

---

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

Immune Checkpoint Inhibitor (ICI)-based trials leading to FDA approvals

First-Line: Phase III KEYNOTE-048 Trial
Overall Survival: P vs E, CPS ≥20 Population

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro alone</td>
<td>62%</td>
<td>0.61 (0.45-0.83)</td>
</tr>
<tr>
<td>EXTREME</td>
<td>78%</td>
<td></td>
</tr>
</tbody>
</table>

12-mo rate
56.9%
44.9%

24-mo rate
38.3%
22.1%

Median (95% CI)
14.9 mo (11.6-21.5)
10.7 mo (8.8-12.8)

No. at Risk

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>133</td>
<td>106</td>
<td>85</td>
<td>65</td>
<td>47</td>
<td>24</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>122</td>
<td>100</td>
<td>64</td>
<td>42</td>
<td>22</td>
<td>12</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Data cutoff date: Jun 13, 2018.
Immune Checkpoint Inhibitor (ICI)-based trials leading to FDA approvals

First-Line: Phase III KEYNOTE-048 Trial
Overall Survival: P vs E, CPS ≥1 Population

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro alone</td>
<td>69% 0.78 (0.64-0.96)</td>
<td>0.0086</td>
</tr>
<tr>
<td>EXTREME</td>
<td>81%</td>
<td></td>
</tr>
</tbody>
</table>

12-mo rate
51.0%
43.6%

24-mo rate
30.2%
18.6%

Median (95% CI)
12.3 mo (10.8-14.9)
10.3 mo (9.0-11.5)

Data cutoff date: Jun 13, 2018.

Immune Checkpoint Inhibitor (ICI)-based trials leading to FDA approvals

First-Line: Phase III KEYNOTE-048 Trial
Response Summary, P vs E

### CPS ≥20

<table>
<thead>
<tr>
<th>Confirmed Response, n (%)</th>
<th>Pembrolizumab N = 133</th>
<th>EXTREME N = 122</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>31 (23.3)</td>
<td>44 (36.1)</td>
</tr>
<tr>
<td>CR</td>
<td>10 (7.5)</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>PR</td>
<td>21 (15.8)</td>
<td>40 (32.6)</td>
</tr>
<tr>
<td>SD</td>
<td>40 (30.1)</td>
<td>42 (34.4)</td>
</tr>
<tr>
<td>PD</td>
<td>42 (31.6)</td>
<td>13 (10.7)</td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
<td>8 (6.0)</td>
<td>6 (4.9)</td>
</tr>
<tr>
<td>Not evaluable or assessed</td>
<td>12 (9.0)</td>
<td>17 (13.9)</td>
</tr>
</tbody>
</table>

### CPS ≥1

<table>
<thead>
<tr>
<th>Confirmed Response, n (%)</th>
<th>Pembrolizumab N = 257</th>
<th>EXTREME N = 255</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>48 (19.1)</td>
<td>89 (34.9)</td>
</tr>
<tr>
<td>CR</td>
<td>14 (5.4)</td>
<td>7 (2.7)</td>
</tr>
<tr>
<td>PR</td>
<td>35 (13.6)</td>
<td>82 (32.2)</td>
</tr>
<tr>
<td>SD</td>
<td>72 (28.0)</td>
<td>83 (32.5)</td>
</tr>
<tr>
<td>PD</td>
<td>100 (38.9)</td>
<td>34 (13.3)</td>
</tr>
<tr>
<td>Non-CR/non-PD</td>
<td>11 (4.3)</td>
<td>11 (4.3)</td>
</tr>
<tr>
<td>Not evaluable or assessed</td>
<td>25 (9.7)</td>
<td>38 (14.9)</td>
</tr>
</tbody>
</table>

**Duration of response, median (range)**

- **Pembrolizumab (P):** 20.9 mo (2.7 to 34.8+)
- **EXTREME:** 4.2 mo (1.2 to 22.3+)

P: Patients without measurable disease at baseline or who did not have CR or PD. CR: Complete Response. PR: Partial Response. SD: Stable Disease. PD: Progression Disease. CPS: Cancer Predisposition Score.

Immune Checkpoint Inhibitor (ICI)-based trials leading to FDA approvals

First-Line: Phase III KEYNOTE-048 Trial
Overall Survival, P+C vs. E, Total Population

Events | HR (95% CI)
--- | ---
Pembro + Chemo | 76% | 0.72\(^a\) (0.60–0.87)
EXTREME | 89% |  

12-mo rate | 53.0% | 43.9%
24-mo rate | 29.4% | 18.8%
36-mo rate | 22.6% | 10.0%

Median (95% CI)
13.0 mo (10.9–14.7)
10.7 mo (9.3–11.7)

\(^a\)At IA2 (data cutoff date: Jun 13, 2018): HR 0.77 (95% CI 0.53–0.93).
FA (data cutoff date: Feb 25, 2019).
ICI-based trials leading to FDA approvals

Second-Line: Phase I/II KEYNOTE-012 Trial
Single-Agent Pembrolizumab in R/M HNSCC

Seiwer TY et al. Lancet Oncology 2016
ICI-based trials leading to FDA approvals

Second-Line: Phase II KEYNOTE-055 Trial
Single-Agent Pembrolizumab in R/M HNSCC

FDA-approved in 2016 for recurrent/metastatic HNSCC with disease progression on or after platinum-based tx
ICI-based trials leading to FDA approvals

Second-Line: Phase III KEYNOTE-040 Trial
Pembrolizumab vs SOC (methotrexate, docetaxel or cetuximab) for R/M HNSCC with disease progression during or after platinum-based chemotherapy

Overall survival in the intention-to-treat population

Overall survival by PD-L1 expression

Lopes et al. ASCO 2018
ICI-based trials leading to FDA approvals

Second-Line: Phase III CheckMate141 Trial
Nivolumab vs. SOC (methotrexate, docetaxel or cetuximab) for R/M HNSCC with disease progression within 6 months of platinum-based chemotherapy

Overall Survival, Progression-free Survival, and Treatment Effect on Overall Survival According to Subgroup

ICI-based trials leading to FDA approvals

Phase I Study of Cemiplimab
Cemiplimab for patients with locally advanced or metastatic cutaneous squamous-cell carcinoma

**Table 2. Tumor Response to Cemiplimab, as Assessed by Independent Central Review.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Expansion Cohorts of the Phase 1 Study (N=26)</th>
<th>Metastatic-Disease Cohort of the Phase 2 Study (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Partial response</td>
<td>13 (50)</td>
<td>24 (41)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6 (23)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3 (12)</td>
<td>11 (19)</td>
</tr>
<tr>
<td>Could not be evaluated‡</td>
<td>3 (12)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>Nontarget lesions only§</td>
<td>1 (4)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Objective response — % (95% CI)</td>
<td>50 (30–70)</td>
<td>47 (34–61)</td>
</tr>
<tr>
<td>Durable disease control — % (95% CI)</td>
<td>65 (44–83)</td>
<td>61 (47–74)</td>
</tr>
<tr>
<td>Median observed time to response (range) — mo¶</td>
<td>2.3 (1.7–7.3)</td>
<td>1.9 (1.7–6.0)</td>
</tr>
</tbody>
</table>

* The expansion cohorts of the phase 1 study involved patients with metastatic or locally advanced cutaneous squamous-cell carcinoma. The metastatic-disease cohort of the phase 2 study involved patients with metastatic cutaneous squamous-cell carcinoma.

Migden, et al. NEJM, 2018
## Consensus Treatment Recommendations for patients with R/M HNSCC

### Key clinical immunotherapy recommendations for treatment of patients with HNSCC

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Summary recommendation</th>
</tr>
</thead>
</table>
| **How should immunotherapy with PD-1 inhibitors be integrated into the treatment of recurrent/metastatic HNSCC?** | **First-line:**  
- Pembrolizumab is indicated for treatment-naïve R/M HNSCC  
  - Pembrolizumab monotherapy may be used to treat patients with treatment naïve R/M HNSCC and PD-L1 CPS ≥1  
  - Pembrolizumab + Chemotherapy (platinum and fluorouracil (FU)) may be used to treat all patients with treatment naïve, biomarker-unspecified R/M HNSCC patients  
* Positivity for PD-L1 as ≥1 CPS by IHC staining |

Cohen et al. JITC 2019
Consensus Treatment Recommendations for patients with R/M HNSCC

First-Line

Diagnostic Workup
- Patient evaluated by multidisciplinary team
- Disease status/stage confirmed including histology/cytology and radiographic imaging
- Disease Status: Locoregional recurrence* and/or metastatic disease
- Patient is considered eligible for immunotherapy by treating physician

Patient Selection
- R/M HNSCC Systemic Therapy Naive Patients

Initial Therapy Treatment Recommendations
- Pembrolizumab monotherapy for PD-L1 expressing, or Pembrolizumab/Cisplatin/5-FU

1. Disease Progression on or after Pembrolizumab monotherapy

2. Refractory Patients
   - Clinical trial, or Platinum based chemotherapy

3. Refractory Patients
   - Clinical trial, **Immune Checkpoint Inhibitor monotherapy, or Non-platinum based chemotherapy

*Locoregional recurrence without salvage surgical or radiation option or declines local therapies

**Refer to Figure 2. Initial Therapy Treatment Recommendations: Immune Checkpoint Inhibitor monotherapy (nivolumab or pembrolizumab)
Consensus Treatment Recommendations for patients with R/M HNSCC Second-Line

**Diagnostic Workup**
- Patient evaluated by multidisciplinary team and is eligible for immunotherapy
- Disease status/stage confirmed including histology/cytology and radiographic imaging
- **Disease Status**: Locoregional recurrence* and/or metastatic disease
- Patient is considered eligible for immunotherapy by treating physician

**Patient Selection**

1. **Disease progression on or after prior platinum-based chemotherapy without receipt of immunotherapy?**
   - No
   - Yes

**Initial Therapy Treatment Recommendations**

- **Immune Checkpoint Inhibitor monotherapy** (Nivolumab or Pembrolizumab)
- Clinical Trial
- **Platinum-based chemotherapy** (e.g. EXTREME regimen, Doublet chemotherapy or single agent chemotherapy)
- **Disease Progression on or after Platinum-based chemotherapy?**
  - Yes
  - No

**Refractory Patients**

- Clinical trial
- Non-Platinum based chemotherapy
- Palliative care

*Locoregional recurrence without salvage surgical or radiation option or declines local therapies

**Disease Progression on or after Platinum-Based Therapy: Disease progression on or after platinum-based therapy including within 6 months of platinum-based CRT given in the locally advanced setting. Patients that receive but cannot tolerate platinum-based chemotherapy would also be included in this category.

HNSCC: head and neck squamous cell carcinoma
Pan-tumor genomic biomarkers for PD-1:
TMB and inflammatory biomarkers (T cell–inflamed GEP and PD-L1 expression) to jointly predict clinical response to pembrolizumab in patient samples

Analysis of PD-L1 Expression and Efficacy from anti-PD-1 Trials

Biomarker-defined responses to pembro monotherapy

Individual association of TMB or T cell–inflamed GEP with anti–PD-1 response across multiple patient cohorts
### Analysis of PD-L1 Expression and Efficacy from anti-PD-1 Trials

**Keynote-040: Pembrolizumab vs. SOC**

<table>
<thead>
<tr>
<th></th>
<th>CPS ≥1</th>
<th>CPS ≥20</th>
<th>TPS ≥50%</th>
<th>TPS &lt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS HR (95% CI)</td>
<td>1.28 (0.8, 2.07)</td>
<td>0.74 (0.58, 0.93)</td>
<td>0.53 (0.35, 0.81)</td>
<td>0.93 (0.73, 1.17)</td>
</tr>
<tr>
<td>OS (mos) Median (95% CI)</td>
<td>6.3 vs. 7.0</td>
<td>8.7 vs. 7.1</td>
<td>11.6 vs. 6.6</td>
<td>6.5 vs 7.1</td>
</tr>
</tbody>
</table>

Cohen, et al. The Lancet 10167(393), 2018

**CheckMate 141: Nivolumab vs. SOC**

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>&lt;1%</th>
<th>≥1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS HR (95% CI)</td>
<td>0.68 (0.54, 0.86)</td>
<td>0.73 (0.49, 1.09)</td>
<td>0.55 (0.36-0.83)</td>
</tr>
<tr>
<td>OS (mos) Median (95% CI)</td>
<td>7.7 (5.7, 8.8) vs. 5.1 (4.0, 6.2)</td>
<td>6.5 (4.4, 11.7) vs. 5.5 (3.7, 8.5)</td>
<td>8.2 (6.7, 9.5) vs. 4.7 (3.8, 6.2)</td>
</tr>
<tr>
<td>2-yr OS %</td>
<td>16.9% (12.4, 22.0) vs. 6.0% (2.7, 11.3)</td>
<td>20.7%</td>
<td>18.5%</td>
</tr>
<tr>
<td>PFS HR (95% CI)</td>
<td>0.89 (0.70-1.13)</td>
<td>1.13 (0.75, 1.71)</td>
<td>0.59 (0.41, 0.84)</td>
</tr>
<tr>
<td>PFS (mos) Median (95% CI)</td>
<td>2.0 (1.9, 2.1) vs. 2.3 (1.9, 3.1)</td>
<td>2.0 (1.9, 2.1) vs. 2.7 (2.0, 4.6)</td>
<td>2.1 (2.0, 3.5) vs. 2.0 (1.9, 3.1)</td>
</tr>
</tbody>
</table>

Ferris, et al. Oral Oncology 2018
Analysis of PD-L1 Expression and Efficacy from anti-PD-1 Trials

<table>
<thead>
<tr>
<th></th>
<th>Keynote-048: Pembrolizumab vs. EXTREME</th>
<th>Keynote-048: Pembrolizumab + Chemotherapy vs. EXTREME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ITT</td>
<td>CPS ≥1</td>
</tr>
<tr>
<td>OS HR (95% CI)</td>
<td>0.83, 95% CI 0.70-0.99</td>
<td>0.77 [95% CI 0.61-0.90]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.77 [95% CI 0.63-0.93]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.65, 95% CI 0.53-0.80</td>
</tr>
<tr>
<td>Median OS (mos) (95% CI)</td>
<td>11.5 vs. 10.7</td>
<td>12.3 vs 10.3</td>
</tr>
<tr>
<td></td>
<td>13.0 vs 10.7</td>
<td>13.6 vs 10.4</td>
</tr>
<tr>
<td>ORR %</td>
<td>16.9% vs 36%</td>
<td>19% vs 35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36% vs 36%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>42.9% vs 38.2%</td>
</tr>
<tr>
<td>PFS HR (95% CI)</td>
<td>1.34 (1.13-1.59)</td>
<td>1.16 [95% CI 0.96-1.39]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.92 [95% CI 0.77-1.10]</td>
</tr>
<tr>
<td></td>
<td>0.73 (0.55-0.97)</td>
<td></td>
</tr>
<tr>
<td>Median PFS (mos) (95% CI)</td>
<td>2.3 vs. 5.2</td>
<td>3.2 vs 5.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.9 vs 5.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.8 vs 5.2</td>
</tr>
</tbody>
</table>

Rischin, et al. J Clin Oncol 37, 2019 (suppl; abstr 6000)
Burtness, et al. Oncology Pro, ESMO 2018
# Consensus Treatment Recommendations for patients with R/M HNSCC

The role of biomarker testing

## Key clinical immunotherapy recommendations for treatment of patients with HNSCC

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Summary recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the role of biomarker testing in patients with HNSCC?</td>
<td>The subcommittee recommends against standard MSI testing</td>
</tr>
<tr>
<td></td>
<td>Positivity for PD-L1 is ≥1% TPS or ≥1 CPS by IHC staining</td>
</tr>
<tr>
<td></td>
<td>The best use of biomarker testing when treating patients with HNSCC with immunotherapy is by combined positive score (CPS)</td>
</tr>
</tbody>
</table>
Does human papillomavirus (HPV) influence the use of immunotherapy in HNSCC?

**HPV-related Data:**

- **Keynote-012**, **CheckMate 141**, **HAWK**

**Keynote-012 Long-term follow-up: Best percentage change from baseline in target lesions (n = 139)**

![Graph showing percentage change from baseline in target lesions](image)

**HAWK Exploratory analysis of OS by HPV status**

<table>
<thead>
<tr>
<th>HPV status</th>
<th>HPV positive (n = 34)</th>
<th>HPV negative (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med. OS (mos) (95% CI)</td>
<td>10.2 (7.2-16.3)</td>
<td>5.0 (3.4-8.4)</td>
</tr>
<tr>
<td>Survival at 12 months, % (95% CI)</td>
<td>44.5 (27.1-69.3)</td>
<td>28.2 (17.4-46.0)</td>
</tr>
</tbody>
</table>

**CheckMate 141: Outcomes by HPV status lesions (n = 139)**

<table>
<thead>
<tr>
<th>HPV status</th>
<th>HPV positive (n = 34)</th>
<th>HPV negative (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. CR/No. PD</td>
<td>34/30</td>
<td>23/19</td>
</tr>
<tr>
<td>No. PD</td>
<td>26/18</td>
<td>19/13</td>
</tr>
<tr>
<td>OS HR (95% CI)</td>
<td>0.60 (0.37, 0.97)</td>
<td>0.59 (0.38, 0.92)</td>
</tr>
<tr>
<td>OS (mos) Median (95% CI)</td>
<td>9.1 (6.5, 11.8) vs. 4.4 (3.0, 9.8)</td>
<td>7.7 (4.8, 13.0) vs. 6.5 (3.9, 8.7)</td>
</tr>
<tr>
<td>PFS HR (95% CI)</td>
<td>0.75 (0.46, 1.23)</td>
<td>1.01 (0.65, 1.56)</td>
</tr>
<tr>
<td>PFS (mos) Median (95% CI)</td>
<td>2.0 (1.9, 3.3) vs. 2.0 (1.6, 2.8)</td>
<td>2.1 (1.9, 3.1) vs. 3.3 (1.9, 4.0)</td>
</tr>
</tbody>
</table>

**Table:**

<table>
<thead>
<tr>
<th>HPV status</th>
<th>HPV positive</th>
<th>HPV negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>34</td>
<td>65</td>
</tr>
<tr>
<td>No.</td>
<td>30</td>
<td>65</td>
</tr>
<tr>
<td>No. CR/No. PD</td>
<td>34/30</td>
<td>23/19</td>
</tr>
<tr>
<td>No. PD</td>
<td>26/18</td>
<td>19/13</td>
</tr>
</tbody>
</table>


Zandberg, 2019. European Journal of Cancer; 107, 142-152

Ferris, et al. Radiation Oncology. 2018
Consensus Treatment Recommendations for patients with R/M HNSCC

Does human papillomavirus (HPV) influence the use of immunotherapy in HNSCC?

<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Summary Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>How does HPV status influence the use of immunotherapy in HNSCC?</td>
<td>HPV status (based on p16 overexpression) should be included in treatment planning, but should not influence the decision to treat patients with R/M HNSCC with SOC immunotherapy</td>
</tr>
</tbody>
</table>
Immune-related Adverse Events (irAEs)

- Encephalitis, aseptic meningitis
- Hypophysitis
- Uveitis
- Thyroiditis, hypothyroidism, hyperthyroidism
- Dry mouth, mucositis
- Pneumonitis
- Rash, vitiligo
- Thrombocytopenia, anemia
- Myocarditis
- Hepatitis
- Adrenal insufficiency
- Nephritis
- Vasculitis
- Arthralgia
- Neuropathy
- Pancreatitis, autoimmune diabetes
- Colitis
- Enteritis

Postow, et al. 2018. NEJM
Immune-related Adverse Events

CheckMate 141, Keynote-012, Keynote-040, Keynote-048
Pembrolizumab or Nivolumab vs SOC (methotrexate, docetaxel or cetuximab) for R/M HNSCC with disease progression during or after platinum-based chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab vs. SOC (CheckMate 141)</th>
<th>Pembrolizumab (Keynote-012)</th>
<th>Pembrolizumab vs. SOC (Keynote-040)</th>
<th>Pembrolizumab vs. SOC (Keynote-048)</th>
<th>Pembrolizumab or Pembrolizumab + Chemotherapy vs. SOC (Keynote-048)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related Grade 3-5 AEs</td>
<td>15.3 vs. 36.9%</td>
<td>17%</td>
<td>13% vs 36%</td>
<td>54.7 vs. 83.3%</td>
<td>85.1 vs. 83.3%</td>
</tr>
<tr>
<td>Primary AEs</td>
<td>Hypothyroidism</td>
<td>Alanine aminotransferase, aspartate aminotransferase elevations, hyponatremia</td>
<td>Hypothyroidism</td>
<td>Fatigue, Anemia, Constipation, Nausea, Diarrhea</td>
<td>Anemia, Nausea, Constipation, Fatigue, Neutropenia, Diarrhea, Thromboctyopenia</td>
</tr>
</tbody>
</table>

*Of note, while most irAEs appear to occur during immunotherapy, there is growing evidence to suggest the existence of post-immunotherapy irAEs, which occur months or years after treatment discontinuation. With an increasing number of neoadjuvant/adjuvant IO trials currently being conducted in the definitive/curative setting, it will be necessary to recognize this emerging clinical entity and perhaps adjust follow-up and reporting times.*
<table>
<thead>
<tr>
<th>Clinical Question</th>
<th>Summary recommendation</th>
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</table>
| **How should immune-related adverse events be recognized and managed in patients with HNSCC?** | • *For further detail into toxicity management strategies please refer to the NCCN Clinical Practice Guidelines in Oncology: Management of Immunotherapy-Related Toxicities (2019)*  
  • For an irAE < grade 3, continue ICIs for grade 1 events with the exception of some neurologic, hematologic or cardiac toxicities. For grade 2 events, stop IO therapy and provide closely monitored outpatient treatment, including consideration of oral steroids.  
  • For irAE development ≥ grade 3, halt treatment, admitting the patient to the hospital and administering steroids  
  • Routine monitoring of thyroid function, neck and airway through imaging, and AST/ALT levels  
  • In patients that develop hypothyroidism, continue immunotherapy, providing levothyroxine for management, and evaluating thyroid function in two-month intervals  
  • In the event of bulky disease leading to functional or organ compromise: halt immunotherapy  
  • Pneumonitis is not a greater concern in immunotherapy patients with HNSCC compared to other cancers |
Currently in development:

- Immune Checkpoint Inhibitor and Cytokine-related Adverse Events Guideline
- Immune Effector Cell-related Adverse Events Guideline
Clinical benefit, as measured by validated PRO measures, indicates that pts experienced improved QoL in addition to prolonged survival, higher response rate, and fewer high-grade toxicities relative to investigator's choice.

Differences between groups were significant and clinically meaningful at weeks 9 and 15 in favor of nivolumab for role functioning, social functioning, fatigue, dyspnoea, and appetite loss on the EORTC QLQ-C30 and pain and sensory problems on the EORTC QLQ-H&N35.

Nivo delayed time to deterioration of patient-reported quality-of-life outcomes and stabilized symptoms and functioning from baseline to weeks 9 and 15, whereas investigator's choice led to clinically meaningful deterioration.

* Scales range from 0 to 100 and were scored such that higher values indicated better functioning or lower symptom burden. A clinically meaningful score change was regarded as one of 10 points (dashed lines) or more.
Immunotherapies in Development

IMMUNOTHERAPY
WHAT TO EXPECT IN 2019

Combinations of immune checkpoint inhibitors with other treatments

New engineering approaches to CAR T therapies

Dealing with adverse events from immunotherapy

Development of personalized vaccines

Developing CAR T therapies for solid tumors

Graphic based on conversation with James P. Allison, MD; Courtesy of the American Association for Cancer Research.
## Ongoing Clinical Trials
Incorporation of immunotherapy within novel combination therapy strategies for HNSCC

### Treatment Setting

<table>
<thead>
<tr>
<th>Recurrent/Metastatic</th>
<th>Trial</th>
<th>Description</th>
<th>Objective</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>IO-IO: checkpoint + vaccine</td>
<td>(NCT02426892)</td>
<td>Phase 2. Nivolumab + ISA101 in patients with incurable oropharyngeal cancer.</td>
<td>To determine if nivolumab efficacy is amplified through treatment with ISA 101, a synthetic long-peptide HPV-16 vaccine inducing HPV-specific T cells, in patients with incurable HPV-16-positive cancer.</td>
<td>mPFS: 2.7 months (95% CI, 2.5-9.4 months) and mOS: 17.5 months (95% CI, 17.5 months to inest). Response was positively correlated with tumor cell PD-L1 positivity (≥1%).  36% ORR in patients with oropharyngeal cancer compared to 16% by nivolumab alone.</td>
</tr>
</tbody>
</table>
## Ongoing Clinical Trials
Incorporation of immunotherapy within novel combination therapy strategies for HNSCC

### Treatment Setting

<table>
<thead>
<tr>
<th>Definitive</th>
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</thead>
<tbody>
<tr>
<td><strong>IO- Chemotherapy and/or radiotherapy</strong></td>
<td><strong>RTOG-3504 (NCT02764593)</strong></td>
<td>Phase 2. Adding nivolumab to strd cetuximab-RT for pts with newly diagnosed interm/high-risk LA HNSCC.</td>
<td>Immunotherapy is added to enhance other conventional therapies such as surgery, CT and RT.</td>
</tr>
<tr>
<td><strong>GORTEC 2015-01 (NCT02707588)</strong></td>
<td>Phase 2. Pembrolizumab or cetuximab + RT in LA HNSCC patients.</td>
<td>Determine synergistic effects when combining ICI with RT vs. SOC cetuximab + RT.</td>
<td>Decrease in serious AEs in pembrolizumab arm (78% pts) vs. cetuximab arm (94% pts).</td>
</tr>
<tr>
<td><strong>GORTEC 2017-01 (REACH) (NCT02999087)</strong></td>
<td>Phase 3. Avelumab + cetuximab and RT vs. SOC in LA HNSCC.</td>
<td>Hypothesis: synergistic effect to occur upon combination of avelumab with cetuximab + RT.</td>
<td>Acceptable safety profile. Continuation approved by Data and Safety Monitoring Cmte.</td>
</tr>
<tr>
<td><strong>SH MISP203 (NCT02586207)</strong></td>
<td>Phase I. Pembrolizumab + chemoradiation (CRT; cisplatin) in LA HNSCC</td>
<td>Defining a role for pembrol in definitive therapy for LA-SCCHN; occurrence of CRT or pembro dose-limiting AEs and irAEs; CR rate on imaging or with salvage surgery at 100 days post-CRT completion.</td>
<td>21/27 pts completed all planned doses of pembro; 3 discont due to irAEs (G2 peripheral motor neuropathy, G3 AST elevation, G1 Lhermitte-like syndrome); 3 discont due to protocol. All pts completed full RT dose (70 Gy) without significant delay (&gt; 5 days). 23 pts received target dose of cisplatin (≥200 mg/m2).</td>
</tr>
</tbody>
</table>
### Consensus Treatment Recommendations for patients with R/M HNSCC

#### Summary

<table>
<thead>
<tr>
<th>Clinical Question</th>
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</tr>
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</table>
| **How should immunotherapy with PD-1 inhibitors be integrated into the treatment of recurrent/metastatic HNSCC?** | **First-line:**  
  - Pembrolizumab is indicated for treatment-naïve R/M HNSCC  
    - Pembrolizumab monotherapy may be used to treat patients with treatment naïve R/M HNSCC and PD-L1 CPS ≥1  
    - Pembrolizumab + Chemotherapy (platinum and fluorouracil (FU)) may be used to treat all patients with treatment naïve, biomarker-unspecified R/M HNSCC patients  
  
  *Positivity for PD-L1 as ≥1 CPS by IHC staining*  

**Second-line:**  
  - Pembrolizumab or nivolumab monotherapy should be used to treat patients with R/M HNSCC who are platinum-refractory, including those that progressed within six months of platinum-based chemotherapy  
  
  *Alternatively, if a clinical trial is available, this is the preferred option, especially if biomarker-based, hypothesis-driven*  

| **What is the role of biomarker testing in patients with HNSCC?** |  
|---------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| **•** The subcommittee recommends against standard MSI testing   |
| **•** Positivity for PD-L1 is ≥1% TPS or ≥1 CPS by IHC staining      |
| **•** The best use of biomarker testing when treating patients with HNSCC with immunotherapy is by combined positive score (CPS) |
### Clinical Question

How should treatment response be evaluated and managed in patients with advanced HNSCC?

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<tr>
<td></td>
<td>• If radiographic progression is observed early in treatment, and the patient is clinically stable, continue treatment until progression is confirmed on a second scan</td>
</tr>
<tr>
<td></td>
<td>• If disease progression on or after treatment with a PD-1 inhibitor: enrollment in a clinical trial, treat with palliative radiotherapy and/or chemotherapy (a taxane)</td>
</tr>
<tr>
<td></td>
<td>• Anatomical site of the tumor is an important consideration</td>
</tr>
<tr>
<td></td>
<td>• *potential for airway obstruction, surgical resection or RT to the site may alter the course of treatment</td>
</tr>
<tr>
<td></td>
<td>• The term “pseudoprogression” should be avoided in a setting of worsening symptoms</td>
</tr>
<tr>
<td></td>
<td>• Hyperprogression defined as “a rapid increase in tumor growth rate (minimum two-fold) compared to expected or prior growth rate”</td>
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**Consensus Treatment Recommendations for patients with R/M HNSCC**

**Summary**

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  • For irAE development ≥grade 3, halt treatment, admit patient to the hospital and administer steroids  
  • Routine monitoring of thyroid function, neck and airway through imaging, and AST/ALT levels  
  • In patients that develop hypothyroidism, continue immunotherapy, providing levothyroxine for management, and evaluating thyroid function in two-month intervals  
  • In the event of bulky disease leading to functional or organ compromise: halt immunotherapy  
  • Pneumonitis is not a greater concern in immunotherapy patients with HNSCC compared to other cancers |
| **Are there categories of patients with HNSCC who should not receive immunotherapy?** | • Do NOT automatically disqualify patient for anti-PD-1 immunotherapy based on: age, lung metastases, co-morbidities, auto-immune disease  
  • Patients with controlled diseases such as Hepatitis C or are HIV+ with normal CD4+ T cell counts and who are on antiretroviral therapy are generally suitable for ICI treatment |
Case Study 1: R/M HNSCC

Background:

• 52 y/o man who initially presented to our clinic in January 2017 with recurrent oral tongue SCC

• Oncology history:
  • January 2010: Presented with T1, N2b, underwent surgery including neck dissection
  • February 20 – April 7 2010: Underwent adjuvant CDDP/RT
  • August 2016: Relapse - Left tongue SCC
  • August 2016: Hemiglossectomy, lymph node dissection
  • November 2016: New neck mass, FNA confirmed SCC

• Pain left head, neck, tongue; Mild dysphagia for liquids and some solids; Speech slurred

• CT chest demonstrates pulmonary nodules and intracardiac mass
Case Study 1: R/M HNSCC
Case Study 1: R/M HNSCC
Case Study 1: R/M HNSCC

How would you manage this patient?
Case Study 2: Toxicity

**Background:** 49-Year-Old Male with Recurrent HPV-Mediated (p16+) Tongue Cancer

- 5 months post-treatment, chest x-ray and CT showed a suspicious lung nodule (images at right)

Biopsy: p16+ HPV+ SCC
His disease has recurred

- Received 4 doses of pembrolizumab at (200 mg q3 wk)

Developed dyspnea and cough
Case Study 2: Toxicity

What is the likely diagnosis?

A. pneumonia
B. pulmonary embolism
C. autoimmune pneumonitis
D. colitis
Conclusion/take-away:

- Autoimmune/inflammatory toxicities may occur at any point in IO therapy

- Early recognition and intervention, including stopping drug(s) and instituting anti-inflammatory agents is warranted

- Management of adverse events using steroids does not appear to decrease efficacy
Biopsy-Proven Pneumonitis is Highly Variable in Presentation
Management of Grade 3/4 Immune-Mediated Pneumonitis

NCCN Guidelines® Recommendations

- **Permanently discontinue immunotherapy**
- **Inpatient care**
- **Infectious workup:**
  - Consider that patient may be immunocompromised
  - Nasal swab for potential viral pathogens
  - Sputum culture, blood culture, and urine culture
- **Pulmonary and infectious disease consultation, consider PFTs**
- **Bronchoscopy with BAL to rule out infection and malignant lung infiltration**
- **Consider empiric antibiotics if infection has not yet been fully excluded**
- **Methylprednisolone** 1–2 mg/kg/day. Assess response within 48 hours and plan taper over ≥6 weeks
- **Consider adding any of the following if no improvement after 48 hours:**
  - **Infliximab** 5 mg/kg IV, a second dose may be repeated 14 days later at the discretion of the treating provider
  - **Mycophenolate mofetil** 1–1.5g BID then taper in consultation with pulmonary service
  - **Intravenous immunoglobulin (IVIG)**--Total dosing should be 2 g/kg, administered in divided doses per PI.

*Please see IMMUNO-A for important guidance on administering this agent.*
Management of Grade 3/4 Immune-Related Colitis

<table>
<thead>
<tr>
<th>NCCN Guidelines® Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3: Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity</td>
</tr>
<tr>
<td>Grade 4: Permanently discontinue immunotherapy agent responsible for toxicity</td>
</tr>
<tr>
<td>Consider inpatient care for provision of supportive care</td>
</tr>
<tr>
<td>- Intravenous (IV) methylprednisolone*§ (2 mg/kg/day)†</td>
</tr>
<tr>
<td>- No response in 2 days:</td>
</tr>
<tr>
<td>- Continue steroids, consider adding infliximab‡§</td>
</tr>
<tr>
<td>- If infliximab-refractory, consider vedolizumab§</td>
</tr>
</tbody>
</table>

*Convert to prednisone when appropriate.
†Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
‡Duration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers is not clearly defined, but is usually a single dose. Repeat endoscopy may be helpful, but optional for the guidance of treatment. (See Principles of Immunosuppression regarding TB testing.)
§Please see IMMUNO-A for important guidance on administering this agent.
Immune-Related Colitis

Ulceration in Descending Colon

Focal Active Colitis

Alterations in Crypt Epithelium

Question and Answer Session
Submit Your Questions

Computer

Mobile Phone

Q: Has the webinar started?
A: Yes, thank you for joining today!
SITC Cancer Immunotherapy Guidelines (CIG) are a collection of consensus statements developed by experts in the treatment of specific types of cancer. Each consensus statement provides key indicators to help practicing oncologists determine when and how to best use immunotherapy to treat their patients. These systematically developed recommendations promote enhanced clinical decisions concerning patient selection, toxicity management, clinical endpoints, and the sequencing or combination of therapies.

**Current Guideline**

Published July 15, 2019 in *Journal for Immunotherapy of Cancer (JITC)* as "The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of squamous cell carcinoma of the head and neck (HNSCC)."

**Webinar**

SITC Cancer Immunotherapy Guidelines – Squamous Cell Carcinoma of the Head and Neck (HNSCC)

WEBINAR

July 24, 2019, from 3-4 p.m. EDT – Register Now

This FREE CME-, CNE-, CPE-certified webinar is for healthcare providers who treat cancer patients, including oncologists, physicians, disease specialists, registered nurses, nurse practitioners, pharmacists and physician assistants to learn about the recommendations from the published guideline on immunotherapy for the treatment of head and neck cancers.

This free webinar will feature discussion of:
Continuing Education Credits are offered for Physicians, PA’s, NP’s, RN’s and Pharmacists.

You will receive an email following the webinar with instructions on how to claim credit.

Questions and comments: connectED@sitcancer.org

Thank you for attending the SITC Cancer Immunotherapy Guidelines- HNSCC Webinar!

Jointly provided by Postgraduate Institute for Medicine and the Society for Immunotherapy of Cancer

This webinar is supported, in part, by independent medical education grant funding from Amgen and AstraZeneca Pharmaceuticals LP