Understanding the Impact of Immunotherapy on Head and Neck Cancer

A Look at the Science, Practice, and Future of Multimodal Treatment

The American Society for Radiation Oncology (ASTRO) has reviewed and approved this symposium as appropriate for presentation as an Industry Satellite Symposium. The symposium constitutes the content and views of the provider and is not part of the official ASTRO Annual Meeting program.
Robert L. Ferris, MD, PhD, has a financial interest/relationship or affiliation in the form of:

Grant/Research Support from AstraZeneca/MedImmune; Bristol-Myers Squibb; Merck & Co., Inc.; and VentiRx Pharmaceuticals.

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Robert L. Ferris, MD, PhD, does intend to discuss either non-FDA-approved or investigational use for the following products/devices: several immune therapies currently in testing for various SCHNN populations, including durvalumab, nivolumab, pembrolizumab, lirilumab, epacadostat, and other immune-stimulating therapies.
Disclosures

Ezra Cohen, MD, FRCPSC, FASCO, has a financial interest/relationship or affiliation in the form of:

*Consultant for AstraZeneca; Bristol-Myers Squibb; Eisai Inc.; Human Longevity, Inc.; Merck & Co., Inc.; and Pfizer.*

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Quynh-Thu Le, MD, F ACM, FASTRO, has a financial interest/relationship or affiliation in the form of:

*Consultant for Bristol-Myers Squibb.*

*Grant/Research Support from Amgen Inc.; RedHill; and Varian Medical Systems, Inc.*

Quynh-Thu Le, MD, F ACM, FASTRO, does intend to discuss either non-FDA-approved or investigational use for the following products/devices: several immune therapies currently in testing for various SCHNN populations, including durvalumab, nivolumab, pembrolizumab, lirilumab, epacadostat, and other immune-stimulating therapies.
Welcome and Introduction

Immunotherapy and the Way Forward in SCCHN Management

Robert L. Ferris, MD, PhD
UPMC Hillman Cancer Center
Pittsburgh, Pennsylvania
The Evolution of Treatment in Head and Neck Cancer

Before 1900

- Surgery
- Radiation Therapy
- Chemotherapy
- Targeted Immunotherapy
<table>
<thead>
<tr>
<th>Approved</th>
<th>Name, Target (indications)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pembrolizumab, anti–PD-1 (recurrent or metastatic SCCHN with disease progression on or after platinum-containing CT)</td>
</tr>
<tr>
<td></td>
<td>Nivolumab, anti–PD-1 (recurrent/metastatic SCCHN following platinum-based tx)</td>
</tr>
<tr>
<td>First-line trials of nivolumab, pembrolizumab in recurrent/metastatic SCCHN underway</td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Durvalumab, anti–PD-L1</td>
</tr>
<tr>
<td></td>
<td>Ipilimumab, tremelimumab (anti-CTLA-4) being evaluated in combination studies</td>
</tr>
</tbody>
</table>

- **Beyond recurrent/metastatic disease:** multiple studies of checkpoint inhibitors in locally advanced SCCHN and adjuvant/neoadjuvant settings underway
The Promise of Immunotherapy:
The Kaplan-Meier Curve Tail

Chemotherapy
Genomically targeted therapy
Immune checkpoint therapy
Combination with genomically-targeted agent and immune checkpoint therapy

Tonight’s Agenda

1. An up-to-date look at the evidence for immunotherapy in HNC; from single-agent to combination studies (including immune combinations)

2. One patient’s therapeutic journey—including his experience of RT and immune checkpoint therapy via a clinical trial

3. Integrating immune checkpoint blockade with RT: evidence and practical issues to consider
Understanding the Rapid Emergence of Immunotherapy in SCCHN

From Major Trials to Novel Combinations

Ezra Cohen, MD, FRCPC, FASCO
UC San Diego
San Diego Center for Precision Immunotherapy
UC San Diego Moores Cancer Center
La Jolla, California
Mutational Load in SCCHN

PD-1/PD-L1 Pathway and Immune Resistance in HPV-Associated SCCHN

Assessing the HNC Immune Landscape

M2-Regulated Immune Response Signature is Associated With Outcome in Human Tumors

Anti–PD-1/PD-L1 Monotherapy: Reproducible Single-Agent Activity
KEYNOTE-012: Single-Agent Pembrolizumab in Recurrent/Metastatic SCCHN

KEYNOTE-012: Single-Agent Pembrolizumab in Recurrent/Metastatic SCCHN (Cont’d)¹

### Pembrolizumab for Platinum- and Cetuximab-Refractory HNC: Single-Arm, Phase 2 Study

<table>
<thead>
<tr>
<th>Response Evaluation</th>
<th>All Patients (N = 171)</th>
<th>HPV+ (n = 37)</th>
<th>HPV- (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% (95% CI)</td>
<td>No.</td>
</tr>
<tr>
<td>ORR</td>
<td>28</td>
<td>16 (11-23)</td>
<td>6</td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>1 (0-3)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>27</td>
<td>16 (11-22)</td>
<td>6</td>
</tr>
<tr>
<td>SD</td>
<td>33</td>
<td>19 (14-26)</td>
<td>6</td>
</tr>
<tr>
<td>PD</td>
<td>87</td>
<td>51 (43-59)</td>
<td>21</td>
</tr>
<tr>
<td>Nonevaluable</td>
<td>4</td>
<td>2 (1-6)</td>
<td>0</td>
</tr>
<tr>
<td>Data unavailable</td>
<td>19</td>
<td>11 (7-17)</td>
<td>4</td>
</tr>
</tbody>
</table>

Further Evidence: KEYNOTE-055 (Cont’d)¹

FDA-approved in 2016 for recurrent/metastatic SCCHN with disease progression on or after platinum-based tx

Updated safety and efficacy of durvalumab (MEDI4736), an anti–PD-L1 antibody, in patients from a head and neck squamous cell carcinoma (HNSCC) expansion cohort

N.H. Segal,1 S-H.I. Ou,2 A.S. Balmanoukian,3 E. Massarelli,4 J.R. Brahmer,5 J. Weiss,6 P. Schöffski,7 S.J. Antonia,8 C. Massard,9 D.P. Zandberg,10 C. Maher,1 J. Weis,11 X. Jin,12 M. Rebelatto,12 K. Steele,12 J. Antal,12 A. Gupta,12 A. Spreafico13

1Memorial Sloan Kettering Cancer Center, New York, NY, US; 2UC Irvine School of Medicine, Irvine, CA, US; 3The Angeles Clinic and Research Institute, Los Angeles, CA, US; 4The University of Texas MD Anderson Cancer Center, Houston, TX, US; 5The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, US; 6Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, US; 7University Hospitals Leuven, Leuven, BE; 8Department of Thoracic Oncology, Moffitt Cancer Center, Tampa, FL, US; 9Institut Gustave Roussy, Villejuif, FR; 10University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD, US; 11Georgia Regents University Cancer Center, Augusta, GA, US; 12MedImmune, Gaithersburg, MD, US; 13Princess Margaret Cancer Centre, Toronto, ON, CA

Change in Target Lesion Size From Baseline by PD-L1 Status

Patients With PD-L1–High Tumors

Patients With PD-L1–Low/Negative Tumors

- Subjects with confirmed CR/PR
- Other subjects
- New lesion

- Change From Baseline Target Lesion Size, %
- Time, mo

Data cutoff: 29 April, 2016

Anti–PD-1/PD-L1 Monotherapy: Phase 3 Trials
Key eligibility criteria
- R/M SCCHN of the oral cavity, oropharynx, larynx, or hypopharynx
- ECOG PS 0-1
- Not amenable to curative therapy
- Progression ≤6 mo of last dose of platinum-based therapy
- Documentation of p16 for HPV status
- No active CNS metastases
- Stratified by prior cetuximab treatment

Nivolumab
3 mg/kg IV every 2 wk

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

Primary endpoint
- OS

Other endpoints
- PFS
- ORR
- Safety
- DOR
- Biomarkers
- QoL

Randomized
360/360
2:1

CheckMate 141: Updated Overall Survival (Follow-Up: 11.4 Months)\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 240)</th>
<th>Investigator’s choice (n = 121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>7.7 (5.7-8.8)</td>
<td>5.1 (4.0-6.2)</td>
</tr>
<tr>
<td>HR (95% CI); (P)</td>
<td>0.71 (0.55-0.90); .0048</td>
<td></td>
</tr>
</tbody>
</table>

# CheckMate 141: Treatment-Related Adverse Events in ≥10% of Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab (n = 236)</th>
<th>Investigator’s Choice (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade n (%)</td>
<td>Grade 3/4 n (%)</td>
</tr>
<tr>
<td>Any^a</td>
<td>139 (58.9)</td>
<td>31 (13.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33 (14.0)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (8.5)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (6.8)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>12 (5.1)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>10 (4.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>3 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

^a One grade 5 event (hypercalcemia) in the nivolumab arm and one grade 5 event (lung infection) in the investigator’s choice arm were reported; a second death occurred in the nivolumab arm subsequent to grade 3 pneumonitis.

CheckMate 141: Treatment-Related Select Adverse Events\textsuperscript{1,a}

<table>
<thead>
<tr>
<th>Event</th>
<th>Nivolumab (n = 236)</th>
<th>Investigator’s Choice (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade n (%)</td>
<td>Grade 3/4 n (%)</td>
</tr>
<tr>
<td>Skin</td>
<td>37 (15.7)</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine</td>
<td>18 (7.6)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>16 (6.8)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic</td>
<td>5 (2.1)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>5 (2.1)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Hypersensitivity/Infusion reaction</td>
<td>3 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a} AEs with potential immunologic etiology that require frequent monitoring/intervention.

CheckMate 141: Overall Survival by PD-L1 Expression

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median OS, mo (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 88)</td>
<td>8.7 (5.7-9.1)</td>
<td>0.55 (0.36-0.83)</td>
</tr>
<tr>
<td>IC (n = 61)</td>
<td>4.6 (3.8-5.8)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median OS, mo (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 73)</td>
<td>5.7 (4.4-12.7)</td>
<td>0.89 (0.54-1.45)</td>
</tr>
<tr>
<td>IC (n = 38)</td>
<td>5.8 (4.0-9.8)</td>
<td></td>
</tr>
</tbody>
</table>

CheckMate 141: Overall Survival by p16 Status¹

### p16-Positive

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median OS, mo (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 50)</td>
<td>7.5 (3.0-NA)</td>
<td>0.73 (0.42-1.25)</td>
</tr>
<tr>
<td>IC (n = 36)</td>
<td>5.8 (3.8-9.5)</td>
<td>1.00 (0.56-1.79)</td>
</tr>
</tbody>
</table>

### p16-Negative

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median OS, mo (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 63)</td>
<td>9.1 (7.2-10.0)</td>
<td>0.56 (0.32-0.99)</td>
</tr>
<tr>
<td>IC (n = 29)</td>
<td>4.4 (3.0-9.8)</td>
<td>1.00 (0.56-1.79)</td>
</tr>
</tbody>
</table>

Key eligibility criteria

- SCC of the oral cavity, oropharynx, hypopharynx, or larynx
- PD after platinum-containing regimen for R/M SCCHN or recurrence or PD within 3-6 mo of multimodal therapy using platinum\(^a\)
- ECOG PS 0 or 1
- Known p16 status (oropharynx)\(^b\)
- Tissue sample\(^c\) for PD-L1 assessment\(^d\)

- **Stratification Factors:** ECOG PS (0 vs 1), p16 status\(^b\) (positive vs negative), PD-L1 TPS\(^d\) (≥50% vs <50%)

### Pembrolizumab
200 mg IV 1x/3 wk for 2 y

**Methotrexate** 40 mg/m\(^2\) weekly\(^e\) or
**Docetaxel** 75 mg/m\(^2\) 1x/3 wk or
**Cetuximab** 250 mg/m\(^2\) weekly\(^f\)

- Clinically stable patients with radiologic PD could continue treatment until imaging performed ≥4 wk later confirmed PD
- Crossover not permitted

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\(^a\) Limit of 2 prior therapies for R/M SCCHN. \(^b\) Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%.

\(^c\) Newly collected preferred. \(^d\) Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies).

TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. \(^e\) Could be increased to 60 mg/m\(^2\) weekly in the absence of toxicity. \(^f\) Following a loading dose of 400 mg/m\(^2\). 1. Cohen EE et al. ESMO 2017. Abstract LBA45_PR.
Disposition of Assigned Study Treatment¹

**Median Follow-Up**<sup>a</sup>: 7.3 mo (Range: 0.03-28.4)

<table>
<thead>
<tr>
<th>Pembrolizumab (n = 247)</th>
<th>Standard of Care (n = 248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>246 Treated</td>
<td>234 Treated (64 methotrexate, 99 docetaxel, 71 cetuximab)</td>
</tr>
<tr>
<td>22 ongoing</td>
<td>2 ongoing</td>
</tr>
<tr>
<td>1 completed</td>
<td>0 completed</td>
</tr>
<tr>
<td>223 discontinued</td>
<td>232 discontinued</td>
</tr>
<tr>
<td>185 PD&lt;sup&gt;b&lt;/sup&gt;</td>
<td>171 PD&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>27 AEs</td>
<td>37 AEs</td>
</tr>
<tr>
<td>9 consent withdrawal</td>
<td>13 consent withdrawal</td>
</tr>
<tr>
<td>1 physician decision</td>
<td>11 physician decision</td>
</tr>
<tr>
<td>1 CR</td>
<td>0 CR</td>
</tr>
</tbody>
</table>

¹ Defined as time from randomization to death or last known survival. <sup>b</sup> Includes clinical progression. Data cutoff date: May 15, 2017.

Overall Survival in ITT Population

<table>
<thead>
<tr>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab 179</td>
<td>0.81(^a) (0.66-0.99)</td>
<td>.0204(^b)</td>
</tr>
<tr>
<td>SOC 201</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. Initially reported data: HR 0.82 (95% CI, 0.67-1.01), \(P = .0316\). After the initial report, updated survival data were obtained for 4 patients.

\(^b\) One-sided \(P\) value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

Cohen EE et al. ESMO 2017. Abstract LBA45_PR.
Overall Survival by PD-L1 Expression

### PD-L1 CPS ≥1

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>137</td>
<td>0.75(^a)</td>
<td>0.0078(^b)</td>
</tr>
<tr>
<td>SOC</td>
<td>157</td>
<td>(0.59-0.95)</td>
<td></td>
</tr>
</tbody>
</table>

**Overall Survival, %**
- Pembro: 40.1% (26.7%)
- SOC: 46.6% (25.8%)

**Median (95% CI)**
- Pembro: 8.7 mo (6.9-11.4)
- SOC: 11.6 mo (8.3-19.5)

**Time, mo**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Time, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>196</td>
</tr>
<tr>
<td>SOC</td>
<td>191</td>
</tr>
</tbody>
</table>

\(^a\) Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. \(^b\) Nominal one-sided P value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

Overall Survival in Subgroups, ITT Population

Unstratified Cox proportional hazards model with treatment as a covariate. Data cutoff date: May 15, 2017.

Objective Response Rate
(RECIST v1.1 Blinded Independent Radiology Review)

**ITT**

$P = .0610^a$

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>14.6%</td>
</tr>
<tr>
<td>SOC</td>
<td>10.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>17.3%</td>
</tr>
<tr>
<td>SOC</td>
<td>9.9%</td>
</tr>
</tbody>
</table>

**PD-L1 CPS ≥1**

$P = .0171^a$

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>26.6%</td>
</tr>
<tr>
<td>SOC</td>
<td>9.2%</td>
</tr>
</tbody>
</table>

**PD-L1 TPS ≥50%**

$P = .0009^a$

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>26.6%</td>
</tr>
</tbody>
</table>

$^a$ Nominal one-sided $P$ value based on the Miettinen and Nurminen method stratified by the randomization stratification factors.

Time to and Duration of Response: ITT (RECIST v1.1 Blinded Independent Radiology Review)¹

- **Pembrolizumab (n = 26ᵃ)**
  - Median (range) time to response: 4.5 mo (1.9-13.8)
  - Medianᵇ (range) duration of response: 18.4 mo (2.7-18.4)
  - Response duration ≥6 moᵇ: 71.5%

- **SOC (n = 18ᵃ)**
  - Median (range) time to response: 2.2 mo (1.6-9.3)
  - Medianᵇ (range) duration of response: 5.0 mo (1.4+-14.4+)
  - Response duration ≥6 moᵇ: 47.1%

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ᵃ Patients with confirmed response only. ᵃ KM estimate. ᵇ Whichever occurred first. Data cutoff date: May 15, 2017.

# Subsequent Therapy

Patients may have received ≥1 subsequent therapy.

<table>
<thead>
<tr>
<th>Type, n (%)</th>
<th>Pembrolizumab N = 247</th>
<th>SOC N = 248</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any</strong></td>
<td>84 (34.0)</td>
<td>100 (40.3)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>70 (28.3)</td>
<td>76 (30.6)</td>
</tr>
<tr>
<td>EGFR inhibitor</td>
<td>20 (8.1)</td>
<td>19 (7.7)</td>
</tr>
<tr>
<td>Kinase inhibitor</td>
<td>4 (1.6)</td>
<td>8 (3.2)</td>
</tr>
<tr>
<td>Immune checkpoint inhibitor</td>
<td>11 (4.5)</td>
<td>31 (12.5)</td>
</tr>
<tr>
<td>Other immunotherapy</td>
<td>5 (2.0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
</tr>
</tbody>
</table>

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* Patients may have received ≥1 subsequent therapy.
Overall Survival: Effect of Subsequent Immune Checkpoint Inhibitors in the SOC Arm

Overall Survival: Censoring at Time of First Subsequent Immune Checkpoint Inhibitor

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>172</td>
<td>0.72a (0.59-0.89)</td>
<td>.0011b</td>
</tr>
<tr>
<td>SOC</td>
<td>187</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cox proportional hazards model with treatment as a single covariate. Nominal one-sided P value based on the unstratified log-rank test.

Immune-Mediated AEs\textsuperscript{1,a}

\textsuperscript{a} Immune-mediated AEs based on a list of terms specified by the sponsor and included regardless of attribution to study treatment or immune relatedness by the investigator; related terms included. Data cutoff date: May 15, 2017.

Immune Combinations in SCCHN: PD-1 Inhibitor + Anti-KIR\textsuperscript{1-4}

**Lirilumab**, a fully human IgG4 mAb that blocks inhibitory KIRs on NK cells and promotes NK-cell activation and tumor cell death\textsuperscript{1}

**Nivolumab**, a fully human IgG4 mAb that blocks PD-1 receptor inhibition of T cells, with demonstrated clinical benefit in advanced/metastatic cancers\textsuperscript{2}

- SCCHN tumors have high infiltration of NK cells and *KIR* gene expression, suggesting that KIR blockade with lirilumab may enhance antitumor activity of nivolumab in patients with SCCHN\textsuperscript{3}
- In preclinical models, addition of an anti-KIR mAb potentiates the efficacy of an anti-PD-1 mAb\textsuperscript{4}

• Of the 7 patients with a response, none were HPV+ oropharyngeal patients

\[ a \] 26 of 29 evaluable patients had a post-baseline assessment. \[ b \] Patient with a 37% reduction in target lesion classified as SD. \[ c \] Patient with a 100% reduction in target lesion classified as SD. \[ d \] Patient with a 30% reduction in target lesion classified as PD.

Effect of Lirilumab + Nivolumab on Target Lesions in Patients With SCCHN (n = 26)


- The median duration of response was not reached
## Anti-KIR (Lirilumab) Plus Nivolumab in SCCHN

### ORR With Nivolumab + Lirilumab (Phase 1/2) and Nivolumab Monotherapy (CheckMate141) in Evaluable Patients With SCCHN

<table>
<thead>
<tr>
<th></th>
<th>Lirilumab + Nivolumab (Phase 1/2)</th>
<th>Nivolumab (From Phase 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, n/N (%)</strong></td>
<td>7/29 (24.1)</td>
<td>32/240 (13.3)</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>3 (10.3)</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>4 (13.8)</td>
<td>26 (10.8)</td>
</tr>
</tbody>
</table>

- First report of efficacy with lirilumab + nivolumab in SCCHN
- Similar safety profile to that observed with nivolumab alone

---

*a Includes unconfirmed responses.
Tumors can evade immunosurveillance through a number of mechanisms including immune checkpoint inhibition of T-cell activation and upregulation of the IDO1 enzyme.

IDO1 is an IFNγ-induced, intracellular enzyme that catalyzes the first and rate-limiting step of tryptophan degradation in the kynurenine pathway.

Depletion of tryptophan and production of kynurenine and other metabolites shifts the local immune microenvironment to an immunosuppressive state.

Epacadostat is a potent and specific oral inhibitor of IDO1, inhibiting tryptophan metabolism and augmenting immunosurveillance in the tumor microenvironment.

Combining epacadostat with a checkpoint inhibitor may improve patient outcomes.

ECHO-202/KEYNOTE-037: Epacadostat + Pembrolizumab Study Design

**Phase 1b**

**Dose Escalation**
- Epacadostat 25 mg 2x/d + Pembrolizumab 2 mg/kg 1x/3 wk
- Epacadostat 50 mg 2x/d + Pembrolizumab 2 mg/kg 1x/3 wk
- Epacadostat 100 mg 2x/d + Pembrolizumab 2 mg/kg 1x/3 wk
- Epacadostat 300 mg 2x/d + Pembrolizumab 200 mg 1x/3 wk

**Safety Expansion**
- Epacadostat 25 mg 2x/d + Pembrolizumab 2 mg/kg 1x/3 wk
- Epacadostat 50 mg 2x/d + Pembrolizumab 200 mg 1x/3 wk
- Epacadostat 100 mg 2x/d + Pembrolizumab 200 mg 1x/3 wk
- Epacadostat 300 mg 2x/d + Pembrolizumab 200 mg 1x/3 wk

**Phase 2**

**Tumor Cohorts**
- DLBCL, NSCLC, UC, TNBC, SCCHN, OC, EC, RCC, CRC (MSI-high), GC, HCC

Epacadostat 100 mg 2x/d + Pembrolizumab 200 mg 1x/3 wk

---

### Epacadostat + Pembrolizumab Phase 1/2 Metastatic or Recurrent SCCHN

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Total (N = 38)</th>
<th>Number of Prior Lines of Treatment</th>
<th>PD-L1 Expression (CPS)(^a)</th>
<th>HPV Status(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1-2 (n = 31)</td>
<td>≥3 (n = 7)</td>
<td>HPV Associated (n = 13)</td>
</tr>
<tr>
<td>ORR (CR + PR)</td>
<td>13 (34)</td>
<td>12 (39)</td>
<td>1 (14)</td>
<td>6 (27)</td>
</tr>
<tr>
<td>CR</td>
<td>3 (8)</td>
<td>3 (10)</td>
<td>0</td>
<td>2 (9)</td>
</tr>
<tr>
<td>PR</td>
<td>10 (26)</td>
<td>9 (29)</td>
<td>1 (14)</td>
<td>4 (18)</td>
</tr>
<tr>
<td>SD</td>
<td>10 (26)</td>
<td>8 (26)</td>
<td>2 (29)</td>
<td>7 (32)</td>
</tr>
<tr>
<td>DCR (CR + PR + SD)</td>
<td>23 (61)</td>
<td>20 (65)</td>
<td>3 (43)</td>
<td>13 (59)</td>
</tr>
<tr>
<td>PD</td>
<td>11 (29)</td>
<td>8 (26)</td>
<td>3 (43)</td>
<td>7 (32)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>4 (11)</td>
<td>3 (10)</td>
<td>1 (14)</td>
<td>2 (9)</td>
</tr>
</tbody>
</table>

\(^a\) Of 9 patients with unknown PD-L1 expression, there were 1 CR, 3 PR, 2 SD, and 3 PD by RECIST v1.1.

\(^b\) 1 patient had unknown HPV status and was not evaluable for response by RECIST v1.1.

Percentage Change From Baseline in Target Lesions: Epacadostat + Pembrolizumab by Prior Treatment

Patients With 1-2 Prior Lines of Treatment: ORR = 39%, DCR = 65% by RECIST v1.1

Data shown for 32 of 38 evaluable pts with ≥1 post-baseline scan (including assessment of target lesions)

Overall response is PD (SD per target lesions, PD per new lesions).

Overall response is PR (CR per target lesions, non-CR/non-PD per non-target lesions).

Percentage Change From Baseline in Target Lesions: Epacadostat + Pembrolizumab by PD-L1 Expression

Responses Were Observed Regardless of PD-L1 Expression

Data shown for 32 of 38 evaluable pts with ≥1 post-baseline scan (including assessment of target lesions)

a Overall response is PD (SD per target lesions, PD per new lesions).
b Overall response is PR (CR per target lesions, non-CR/non-PD per non-target lesions.
Percentage Change From Baseline in Target Lesions: Epacadostat + Pembrolizumab by HPV Association

Responses Were Observed in Both HPV- and Non-HPV–Associated Disease

Data shown for 32 of 38 evaluable pts with ≥1 post-baseline scan (including assessment of target lesions)

- Overall response is PD (SD per target lesions, PD per new lesions).
- Overall response is PR (CR per target lesions, non-CR/non-PD per non-target lesions.

### AEs of Special Interest: Epacadostat + Pembrolizumab

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>All Grade (N = 38)</th>
<th>Grade 3/4 (N = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>3 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1 (3)</td>
<td>0</td>
</tr>
</tbody>
</table>

- AEs of special interest include AEs with an immune-related cause, regardless of attribution to study treatment by the investigator.

---

Emerging in Immunology: Targeting Intratumoral Suppression of Anti-Tumor T-Cell Responses

Durvalumab
- Tumor cells can express PD-L1, which binds to PD-1 on T cells and sends an inhibitory signal
- Durvalumab binds to PD-L1 and blocks the inhibitory signal

STAT3
- Broadly modulates immune system function
- Contributes to immunosuppressive tumor microenvironment
- Is inhibited in stromal and immune cells by AZD9150, an antisense oligonucleotide, with monotherapy activity in DLBCL

CXCR2
- Modulates marrow myeloid cell release
- Is specifically inhibited by AZD5069, enhancing anti–PD-L1 effects in preclinical tumor models

Combining STAT3 and anti–PD-L1 mechanisms enhances anti-tumor activity in a CT26 murine tumor model

SCoReS Study Design

**Part A: Phase 1 (Solid Tumors)**
- AZD9150 + durvalumab
- AZD5069 + durvalumab
- AZD9150 + durvalumab
- AZD5069 + durvalumab + tremelimumab

**Part B: Phase 1b/2 (R/M SCCHN)**
- B1: AZD9150 3 mg/kg + durvalumab 20 mg/kg (n = 20)
- B2: AZD5069 40 mg 2x/d + durvalumab 20 mg/kg (n = 20)
- B3: AZD9150 3 mg/kg + durvalumab 20 mg/kg (n = 20) + Additional pts (n = 15)
- B4: AZD5069 40 mg 2x/d + durvalumab 20 mg/kg (n = 20) + Additional pts (n = 15)
- B5: AZD9150a 3 mg/kg (n = 12)
- B6: AZD5069a 40 mg 2x/d (n = 12)

**Phase 1b/2**
- Phase 1b: dose, PK, safety in solid tumours
- Phase 2: RCT in second-line R/M-SCCHN patients

**Part B primary objectives**
- ORR

**Part B secondary objectives**
- Safety
- DCR
- DOR
- PFS
- OS
- PK/PD

---

*a Monotherapy arms allow addition of durvalumab on progression. 1. Cohen EE et al. ESMO 2017. Abstract 1135O.*
<table>
<thead>
<tr>
<th>Arm</th>
<th>Dosed and Evaluable</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>Response (%)</th>
<th>DCR, n/Total Evaluablea (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1: PD-L1 pretreated AZD9150 + durvalumab</td>
<td>18</td>
<td>1 CMRb</td>
<td>1</td>
<td>2 (11)</td>
<td>8/18 (44)</td>
</tr>
<tr>
<td>B3: PD-L1 naïve AZD9150 + durvalumab</td>
<td>28</td>
<td>3</td>
<td>5c</td>
<td>8 (29)</td>
<td>16/28 (57)</td>
</tr>
<tr>
<td>B5: PD-L1 naïve AZD9150 monotherapy</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

a Evaluable patients with first reassessment visit or met with an event prior to first reassessment visit. b CMR by PERCIST. c Includes 1 CR in target lesions. Data cutoff date: July 20, 2017; unvalidated data by best response.

Exposure and Best Response by Patient Over Time: AZD9150 + Durvalumab in Anti-PD-L1–Naïve Patients

Treatment Exposure by Patient Over Time

Best Change From Baseline Target Lesion Size (RECIST v1.1), by Patient

- Plots show 28 patients who were evaluable at data cut-off date 20 July 2017, unvalidated data by best response; each bar represents a subject in Arm B3; all RECIST CRs represented as -100% change

a A CR in target lesions. b Only baseline tumor measurement available.

Efficacy: AZD9150 + Durvalumab in Anti–PD-L1–Naïve Patients

Tumor Size Change (RECIST v1.1) vs Treatment Time

- Plot shows 28 patients who were evaluable at data cut-off date 20 July 2017, unvalidated data by best response; each bar represents a subject in Arm B3; all RECIST CRs represented as -100% change

### Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AZD9150 + durvalumab (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (n)</td>
<td>29 (3 CR, 5 PR&lt;sup&gt;a&lt;/sup&gt;)</td>
</tr>
<tr>
<td>DCR, % (n)</td>
<td>57 (3 CR, 5 PR&lt;sup&gt;a&lt;/sup&gt;, 8 SD)</td>
</tr>
</tbody>
</table>

<sup>a</sup> One patient had a CR in target lesions only. <sup>b</sup> Based on best response.

PD-L1 Staining vs Response in Anti–PD-L1–Naïve Patients Receiving AZD9150 + Durvalumab

**PD-L1 Tumor Expression**

- **PD-L1 Tumor Expression**

  ![](image)

<table>
<thead>
<tr>
<th>PD-L1–Positive Tumor Cells, %</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to &lt;1</td>
<td>0</td>
</tr>
<tr>
<td>1 to 25</td>
<td>2</td>
</tr>
<tr>
<td>26 to 50</td>
<td>4</td>
</tr>
<tr>
<td>51 to 75</td>
<td>6</td>
</tr>
<tr>
<td>76 to 100</td>
<td>4</td>
</tr>
</tbody>
</table>

**Tumor PD-L1 expression**

<table>
<thead>
<tr>
<th>Tumor PD-L1 expression</th>
<th>Patient n (%)</th>
<th>ORR n (%)</th>
<th>CRb n (%)</th>
<th>PR n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>28 (100)</td>
<td>8 (28.5)</td>
<td>3 (11)</td>
<td>5 (18)</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>11 (39)</td>
<td>3 (27)</td>
<td>0 (0)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>≥1%</td>
<td>17 (61)</td>
<td>5 (29)</td>
<td>3 (18)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>13 (46)</td>
<td>3 (23)</td>
<td>0 (0)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>≥10%</td>
<td>15 (54)</td>
<td>5 (33)</td>
<td>3 (20)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>≤25%</td>
<td>17 (61)</td>
<td>3 (18)</td>
<td>0 (0)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>&gt;25%</td>
<td>11 (39)</td>
<td>5 (45)</td>
<td>3 (27)</td>
<td>2 (18)</td>
</tr>
</tbody>
</table>

**Patient n (%):**

- **PD-L1 expression was determined by Ventana SP263 staining of fresh biopsies, except for 1 patient with progressive disease for whom archived tissue was used. Chart shows 28 patients who were evaluable at data cutoff date: July 20, 2017.**

**CRb n (%):**

- **One patient had a CR in target lesions only.**

1 Cohen EE et al. ESMO 2017. Abstract 1135O.
Reversible thrombocytopenia and transaminitis (previously associated with AZD9150 monotherapy) were managed with dose interruptions and reductions.

AZD9150/durvalumab treatment revealed no apparent unexpected or synergistic toxicities.

21 patients experienced a drug-related AE (9 grade 3/4).

One patient discontinued treatment because of a drug-related AE (grade 1 pneumonitis).

### Drug-Related AEs Observed in ≥5% of Patients Treated With AZD9150 + Durvalumab in the Anti–PD-L1–Naïve Arm B3 (n = 38)

<table>
<thead>
<tr>
<th>Drug-Related AE</th>
<th>All grades</th>
<th>Grade 3&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Grade 4&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n (%)</td>
<td>21 (55)</td>
<td>9 (24)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>ALT increase</td>
<td>5 (13)</td>
<td>2 (5)</td>
<td>0</td>
</tr>
<tr>
<td>AST increase</td>
<td>5 (13)</td>
<td>3 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count decrease</td>
<td>5 (13)</td>
<td>2 (5)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (13)</td>
<td>2 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> AEs were graded according to CTCAE version 4.03.

Combining Immunotherapies: Ongoing Major Studies
# Durvalumab (MEDI4736, Anti–PD-L1) Plus Anti–CTLA-4 Phase 2 Trials in SCCHN

<table>
<thead>
<tr>
<th>Regimen</th>
<th>PDL1 Status</th>
<th>Setting</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durvalumab mono</td>
<td>PD-L1+ N = 112</td>
<td>2L SCCHN post-platinum in R/M setting</td>
<td>Accelerated approval of the monotherapy in PD-L1+</td>
</tr>
<tr>
<td>Durvalumab + tremelimumab</td>
<td>PD-L1- n = 120</td>
<td>2L SCCHN post-platinum in R/M setting</td>
<td>Accelerated approval of the combination in PD-L1-</td>
</tr>
<tr>
<td>Durvalumab mono</td>
<td>PD-L1- n = 60</td>
<td></td>
<td>Establishes individual component contribution to combination in PD-L1-</td>
</tr>
<tr>
<td>Tremelimumab mono</td>
<td>PD-L1- n = 60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ESMO 2017**
- Durable responses: ORR 16.2%, more than half of responses ongoing at cut-off
- Median OS 7.1 months, with a 12-month survival rate of 33.6%

Phase 3 EAGLE Study: Durvalumab ± Tremelimumab in Previously-Treated R/M SCCHN

PD-L1+ or PD-L1-

Disease progression after tx with a platinum-containing regimen for R/M SCCHN or with recurrent/progressive disease <6 mo from multimodality therapy containing platinum N = 720

Stratification factors
- HPV status
- Smoking history
- PD-L1 status

1:1:1

R

Durvalumab + tremelimumab (N = 240)

Durvalumab monotherapy (N = 240)

SOC (N = 240)

Objective disease progression

Follow-up for OS

Subsequent tx

Objective disease progression

Co-primary endpoints: OS and PFS

KESTREL: First-Line Durvalumab ± Tremelimumumab vs Active Comparator in R/M SCCHN¹

- Phase 3, randomized, open-label study
- **Start Date:** October 2015
- **Primary endpoints:** PFS, OS (durvalumab + tremelimumab vs SOC)
- **Other endpoints:** ORR, PFS2, DOR, APF12, OS24, PFS (durvalumab vs SOC), OS (durvalumab vs SOC), PK, immunogenicity, and QoL

**Key Eligibility Criteria**
- No prior systemic chemotherapy for recurrent or metastatic disease
- No progression or recurrence ≤6 months since last platinum-based therapy
- Fresh or archival tumor biopsy

**Randomized (2:1:1)**
**Stratification factor:** PD-L1, HPV, and smoking status

**Durvalumab**

**Durvalumab + Tremelimumab**

**Active Comparator (cetuximab, 5-FU, cisplatin/carboplatin)**

---

KEYNOTE-048: First-Line Pembrolizumab vs Active Comparator With R/M SCCHN

- Phase 3, randomized, open-label, study in patients with R/M SCCHN without prior systemic chemotherapy
- **Start Date:** March 2015
- **Primary endpoints:** PFS
- **Other endpoints:** OS, PFS (by immune-related response), and ORR

Key Eligibility Criteria

- No prior systemic therapy in R/M setting, except if completed >6 months prior to locally advanced disease
- Available tumor biopsy for PD-L1 analysis
- Have results for HPV status for oropharyngeal cancer (OPC)

---

CheckMate 651: First-Line Nivolumab + Ipilimumumab vs EXTREME Regimen in R/M SCCHN

- Phase 3 randomized, open-label study
- **Start Date:** August 2016
- **Primary endpoints:** OS, PFS
- **Other endpoints:** ORR, time to deterioration, and PD-L1 expression as biomarker

**Key Eligibility Criteria**
- No prior systemic therapy for R/M disease except if chemotherapy was part of multimodal treatment ≤6 months prior to enrollment
- Tumor tissue required for HPV p16 (for OPC) and PD-L1 testing prior to randomization

**Randomized**
- **Nivolumab + Ipilimumab**
- **EXTREME** (cetuximab + cisplatin/carboplatin + 5-FU)

---

• Single agent anti–PD-L1 is active and effective in SCCHN
  – Approval granted in US for pembrolizumab and nivolumab
• Combinations targeting immunosuppressive tumor microenvironment appear promising
  – IDO, KIR, STAT3
• Many more combinations capitalizing on other mechanisms are moving forward
• Phase 3 trials in first-line recurrent/metastatic SCCHN completed or near completion with results expected in 12-18 months
Immunotherapy and Radiotherapy
Pursuing Synergistic Modalities in SCCHN

Quynh-Thu Le, MD, FACR, FASTRO
Stanford University
Stanford, California
PD-1 Expression Predicts Locoregional Relapse in HPV- Patients Treated With Surgery + PORT

Anti–PD-L1 Blockade Synergizes With Radiation

PD-1/PD-L1 Blockade Synergizes With Fractionated RT

RT + Anti–PD-1

RT + Anti–PD-L1

Survival, %

0 20 40 60 80 100
Time Since Tumor Implantation, d

No treatment
Anti–PD-L1 mAb 10 mg/kg
5 x 2 Gy RT
5 x 2 Gy RT + anti–PD-L1 mAb

a $P < .001$, log-rank (Mantel-Cox) test vs control mice.
b $P < .001$, log-rank (Mantel-Cox) test vs monotherapy.
c Significance when compared with control mice.
Directions for Immune Checkpoint Therapy in HNC

- First-line therapy in metastatic HNC
- Second-line therapy in NPC before moving to first-line
- Locoregionally advanced HNC
  - With CRT in definitive setting
  - With CRT in high-risk postoperative setting
  - With RT alone (replacing chemotherapy or cetuximab) in cisplatin-unfit or elderly patients
  - With RT alone (replacing chemotherapy or cetuximab) in good-risk patients
- With SBRT in recurrent/metastatic setting
- Other rare cancer in the head and neck
Clinical Trial Landscape of RT + Immunotherapy in Head and Neck Cancer

- 17 trials listed on clinicaltrials.gov: 2 completed, 10 recruiting, 5 planned
- 6 phase 1, 1 phase 1-2, 3 phase 2, 3 phase 2R, 3 phase 3

<table>
<thead>
<tr>
<th>ID</th>
<th>Phase</th>
<th>Setting</th>
<th>Setting</th>
<th>RT</th>
<th>N</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02684253</td>
<td>2R</td>
<td>Nivolumab +/- SBRT</td>
<td>Met</td>
<td>SBRT</td>
<td>40</td>
<td>–</td>
</tr>
<tr>
<td>NCT02707588</td>
<td>2R</td>
<td>Cetuximab + RT vs pembrolizumab + RT (unfit)</td>
<td>LA</td>
<td>RT</td>
<td>114</td>
<td>Concurrent</td>
</tr>
<tr>
<td>NCT02777385</td>
<td>2R</td>
<td>CRT + nivolumab (concurrent vs sequential)</td>
<td>LA</td>
<td>RT</td>
<td>44</td>
<td>Concurrent vs Sequential</td>
</tr>
<tr>
<td>NCT02952586</td>
<td>3R</td>
<td>CRT +/- avelumab</td>
<td>LA</td>
<td>RT</td>
<td>640</td>
<td>Concurrent</td>
</tr>
<tr>
<td>NCT02999087</td>
<td>3R</td>
<td>CRT vs cetuximab + avelumab + RT (fit)</td>
<td>LA</td>
<td>RT</td>
<td>688</td>
<td>Concurrent</td>
</tr>
<tr>
<td>NCT02777385</td>
<td>3R</td>
<td>CRT +/- pembrolizumab</td>
<td>LA</td>
<td>RT</td>
<td>780</td>
<td>Concurrent</td>
</tr>
</tbody>
</table>
**RTOG 3504: Phase 1 Schema**

Oropharynx cancer, p16+ by IHC with smoking status >10 pack-years stage T2N2b-N3 or T3-4N0-N3 OR ≤10 pack years stage T4N0-N3 or T2-3N2c-N3

---

**Step 1: Registration**

Oral cavity, larynx, and hypopharynx cancer patients proceed to Step 2 registration

Oropharynx cancer patients: p16 IHC to confirm eligibility required to proceed to Step 2 registration

---

**Arm 1** (n = 10-30)
- Nivolumab 240 mg every 14 days prior to IMRT, then 480 mg every 28 days x 7
- Cisplatin 40 mg/m² every 7 days x 7
- IMRT 70 Gy

**Arm 2** (n = 10-30)
- Nivolumab 240 mg every 14 days, then 360 mg day 1 of IMRT and every 21 days x 6, then 480 mg every 28 days x 7
- Cisplatin 100 mg/m² every 21 days x 3
- IMRT 70 Gy

**Arm 3** (n = 10-30)
- Nivolumab 240 mg every 14 days x 10 starting 14 days prior to IMRT, then 480 mg every 28 days x 7
- Cetuximab 400 mg/m² loading, then 250 mg/m² x 7
- IMRT 70 Gy

**Arm 4** (n = 10-30)
Either >70 y, Zubrod of 2, ≥3 grade neuropathy, ≥2 hearing loss, or CrCl <50 mL/min
- Nivolumab 240 mg every 14 days x 10 starting 14 days prior to IMRT, then 480 mg every 28 days x 7
- IMRT 70 Gy

---

*a Dose reduced to 80 mg in event of DLT per Section 5.1.1. b Feasibility of 7 months of adjuvant nivolumab will be determined in first 8 evaluable patients. 1. https://clinicaltrials.gov/ct2/show/NCT02764593. Accessed September 14, 2017.*
Multiple Planned Studies of Checkpoint Inhibitors in Locally Advanced SCCHN

**CRT backbone ±**

- Avelumab (Javelin Head & Neck 100)
- Nivolumab
- Pembrolizumab

And possibly more…
Adjuvant Cisplatin-IMRT and Pembrolizumab in High-Risk, HPV− SCCHN (HN003)¹

Phase 1 and Expansion-Cohort Study

Postoperative, high-risk PULA SCCHN
- Pathologically high-risk, stage III-IV oral cavity, hypopharynx, or larynx or p16− oropharynx
- + margin
- ECE
M0
Zubrod 0-1

Dose Level 3, Starting Dose (n = 12)
- Adjuvant CRT 6 weeks
- Maintenance 15 weeks
- Pembrolizumab⁴
- IMRT (60 Gy) + weekly cisplatin

LTFU: PFS

PI: Julie Bauman
CTEP Approved Design December 2015
Dose-finding cohort: 12; dose-expansion cohort: 20

Pembrolizumab⁴
*                  *                  *                  *                  *                  *                  *

IMRT (60 Gy) + weekly cisplatin

¹ Pembrolizumab 200 mg IV every 3 wk x 8 doses: wk -1 (loading dose), wk 3, 6, 9, 12, 15, 18, 21, 24.
Immune Therapy in Cisplatin-Unfit Patients

• Phase 2 feasibility of pembrolizumab + RT (UNC)¹

• PembroRad: RT + pembrolizumab vs RT + cetuximab in cisplatin-unfit patients² (GORTEC)

• NRG Oncology (HN004): RT + anti–PD-L1 vs RT + cetuximab in cisplatin-unfit patients

• Reach Trial: RT + avelumab + cetuximab vs RT + cetuximab (NCT02999087; GORTEC)

HN004: NRG Phase 2/3 Trial

Cisplatin unfit or Age ≥ 70 with poor performance status or co-morbidities (intermediate and high risk patients)

**Tumor biopsy PD-L1 assay**

- **Stage**
  - T1-3N02b
  - T4 or N2c-3

- **Age and PS**
  - ≥70, PS 0-1, no comorbidity
  - <70, PS 2, comorbidity

- **p16 and site**
  - p16+ OP/CUP
  - p16- OP/CUP
  - Lx, Hpx, Oc

**Randomize**

- Durvalumab 70 Gy IMRT
- Cetuximab 70 Gy IMRT

- **Durvalumab**
- **Cetuximab**

- **Primary end point: PFS**
- **N = 444 (phase 2-3 with phase 1 run in)**

Pembrolizumab + SBRT vs SBRT Alone for Locoregionally Recurrent or Second Primary HNC

Phase 2R KEYSTROKE Study (RTOG 3507)

Eligibility
- Prior RT (>30 Gy) overlap
- Disease limited to a single contiguous site
- No skin involvement
- <180 carotid involvement
- No distant metastatic disease

STRATIFY

Randomize

SBRT (40 Gy/5 fx) + Pembrolizumab (200mg 1x/3wk)

Adjuvant pembrolizumab (1x/3wk) up to 1 year

SBRT (40Gy/5fx) alone

Proceed to pembrolizumab at recurrence

• Primary end point: PFS (1 year)
• Accrual goal: N = 102
• Study is not yet open for participant recruitment

1. Slide courtesy of Quynh-Thu Le.
Randomized Trial of Consolidative Local vs Systemic Treatment Alone in Oligometastatic NSCLC

Patients with ≤3 metastases after front-line systemic therapy
Only 1 patient received surgery alone for local therapy

Step 1
- Enrollment

Frontline systemic therapy

Step 2
- Enrollment
- Non-PD

Physician choice for standard maintenance or surveillance

Consider LCT (surgery ± radiation to primary and metastases)

Local Consolidative Therapy

LCT (surgery ± radiation to primary and metastases)

Physician choice for standard maintenance or surveillance

Crossover allowed at progression

Surgery and RT allowed

Local Therapy Significantly Improved PFS\(^1\)

- One patient not evaluable (24 in each group)
- Median PFS times
  - No-LCT arm: 3.9 months (95% CI, 2.2-6.6)
  - LCT arm: 11.9 months (95% CI, 5.4-NA)

### Probability of Progression-Free Survival

<table>
<thead>
<tr>
<th>Time, y</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>LCT: 24</td>
</tr>
<tr>
<td></td>
<td>No LCT: 24</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Median OS not reached
Exploratory analysis showed that local therapy increased time to new site failure

RT + PD1-Pathway Targeting Therapy in Metastatic HNC

• **Trial testing RT fractionation**¹
  – Pembrolizumab + 8 Gy vs pembrolizumab + 20 Gy in recurrent/met HNC, RCC, NSCLC (Thomas Jefferson)

• **Trial testing RT abscopal effect**²
  – Nivolumab ± RT (27 Gy in 3 fractions to one lesion) in metastatic HNC (MSKCC)

Other Clinical Trials in Planning Stages

- Single vs combination immunotherapy + RT in good prognosis (replacing chemotherapy)

- PD-1 blockade with local therapy or SBRT in Merkel cell tumors

- PD-1 + CTLA-4 blockade with local therapy in mucosal melanoma
Immune-Related Adverse Events

**Hepatic**
- Autoimmune hepatitis\(^1,2\)
- ALT/AST increases\(^1,3\)

**Renal**
- Nephritis\(^1\)
- Renal failure\(^5\)

**Skin**
- Maculopapular rash\(^1\)
- Pruritus\(^1,3\)

**Endocrine**
- Hypophysitis\(^1,3\)
- Thyroiditis\(^1,2\)
- Type 1 diabetes\(^4\)

**Respiratory**
- Pneumonitis\(^1,2\)

**Gastrointestinal**
- Colitis/diarrhea\(^1,3\)

**Neuromuscular**
- Peripheral sensory neuropathy\(^1\)

---

<table>
<thead>
<tr>
<th>Eventa (n = 236)</th>
<th>Any Grade, n (%)</th>
<th>Grade 3/4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>37 (15.7)</td>
<td>0</td>
</tr>
<tr>
<td>Endocrine</td>
<td>18 (7.6)b</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>16 (6.8)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic</td>
<td>5 (2.1)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>5 (2.1)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Hypersensitivity/ infusion reaction</td>
<td>3 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

a AEs with potential immunologic etiology that require frequent monitoring/intervention.
b Similarly seen with other PD inhibitors (eg, pembrolizumab).

1. Ferris RL et al. ASCO 2016. Abstract 6009
irAEs: General Principles

- Often diagnosed by exclusion; other causes should be ruled out, but immunotherapy-related toxicity should always be included in the differential.
- Early recognition, evaluation, and treatment + patient education are essential for best outcomes.
- Depending on severity of the event, management may require corticosteroid or other immunosuppressive treatment and interruption or discontinuation of therapy.
- If appropriate immunosuppressive treatment is used, patients generally recover from the adverse event.
- The need for immunosuppressive therapy to manage AEs does not appear to impact the response to checkpoint blockade therapy.
General Algorithm for Managing irAEs

Grade 1
(Minimal or No Symptoms; Diagnostic Changes Only)

- Continue immunotherapy (or consider temporary delay)
- Symptomatic therapy

Grade 2
(Mild to Moderate Symptoms)

- Withhold immunotherapy
- Corticosteroids if symptoms do not resolve in 1 wk (prednisone 0.5-1 mg/kg/d or equivalent)
- Taper corticosteroids over ≥1 mo to reduce recurrence
- Re-dose if toxicity resolves to grade ≤1

Grade 3/4
(Severe/Life-Threatening Symptoms)

- Discontinue immunotherapy; hospitalization, multidisciplinary evaluation indicated
- High-dose corticosteroids (prednisone 1-2 mg/kg/d or equivalent)
- Taper high-dose corticosteroids over ≥1 mo until toxicity resolves to grade ≤1 (prednisone 1-2 mg/kg/d or equivalent)
- If no improvement or progression, consider additional immunosuppressant tx
- If >4 weeks of corticosteroids or other immunosuppressants needed, administer antimicrobial/antifungal prophylaxis to prevent opportunistic infections

Skin Toxicity$^{1,2}$

- Rash and pruritus ($\sim$15% any grade in HNC); focal maculopapular appearance on trunk, back, or extremities
- Severe skin adverse reactions are rare (<0.1%)
- Grade 1-2 ($\leq$30% BSA): antihistamine and topical steroid
- Consider dermatology referral, oral steroid, and biopsy if persists
- Grade 3-4 (>30% BSA): dermatology referral and IV steroids ($\sim$1 mg/kg prednisolone)
- Long taper ($\sim$4 wk) upon improvement
- Educate patients on importance of immunosuppression
- Unclear if PD-1 blockade will enhance in-field skin reaction with RT

Endocrinopathies

- In HNC, ~8% any grade with anti–PD-1 alone had endocrinopathy, most commonly hypothyroidism
- RT alone can lead to hypothyroidism in ~20%-60% of patients
- Factors associated with hypothyroidism risk include
  - Thyroid gland volume
  - Mean thyroid dose
  - Volume receiving dose >30, 40, 50 Gy or inverse volume spare
- Unclear if RT + immune therapy is additive or > additive effect on thyroid function—needs to be studied prospectively

### Unanswered Questions With Checkpoint Inhibitors in Combination With RT or RT + CT

<table>
<thead>
<tr>
<th>Category</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient selection</strong></td>
<td>• Which are the best biomarkers?</td>
</tr>
<tr>
<td></td>
<td>• Can we extrapolate data from metastatic setting to nonmetastatic setting?</td>
</tr>
<tr>
<td><strong>Radiation dose and fractionation</strong></td>
<td>• What is the optimal radiation dose and fractionation?</td>
</tr>
<tr>
<td><strong>When and how much IO?</strong></td>
<td>• Is concurrent better than adjuvant?</td>
</tr>
<tr>
<td></td>
<td>• If adjuvant is needed, how long?</td>
</tr>
<tr>
<td><strong>Radiation field</strong></td>
<td>• Will treating the nodes affect treatment outcomes?</td>
</tr>
<tr>
<td><strong>Single vs combination IO</strong></td>
<td>• Is combination better than single therapy</td>
</tr>
<tr>
<td></td>
<td>• What mediates treatment resistance</td>
</tr>
</tbody>
</table>
SABR and Fractionated RT Have Different Effects on the Tumor Microenvironment

Radiation Dose and Fractions: Preclinical Studies of RT + Immunomodulation Antibodies

<table>
<thead>
<tr>
<th>Year</th>
<th>Tumor Model(s)</th>
<th>Immunotherapy</th>
<th>RT</th>
<th>Admin. Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>B-cell lymphoma¹</td>
<td>Anti-CD40</td>
<td>TBI 0-8 Gy x 1f</td>
<td>Concomitant</td>
</tr>
<tr>
<td>2005</td>
<td>Breast²</td>
<td>Anti-CTLA-4</td>
<td>12 Gy x 2f</td>
<td>Post-radiation</td>
</tr>
<tr>
<td>2006</td>
<td>Lung, breast³</td>
<td>Anti-CD137</td>
<td>5 Gy x 1f; 10 Gy x 1f; 15 Gy x 1f</td>
<td>Post-radiation</td>
</tr>
<tr>
<td>2008</td>
<td>Lung⁴</td>
<td>Anti-OX40</td>
<td>20 Gy x 1f</td>
<td>Post-radiation</td>
</tr>
<tr>
<td>2009</td>
<td>Breast⁵</td>
<td>Anti-CTLA-4</td>
<td>20 Gy x 1f; 8 Gy x 3f; 6 Gy x 5f</td>
<td>Concomitant + post-radiation</td>
</tr>
<tr>
<td>2010</td>
<td>Intracranial glioma⁶</td>
<td>Anti-CD137</td>
<td>4 Gy x 2f</td>
<td>Post-radiation</td>
</tr>
<tr>
<td>2012</td>
<td>Breast⁷</td>
<td>Anti-CD40, anti-CD137, anti–PD-1</td>
<td>12 Gy x 1f; 4 Gy x 4f; 5 Gy x 4f</td>
<td>Post-radiation</td>
</tr>
<tr>
<td>2013</td>
<td>Intracranial glioma⁸</td>
<td>Anti–PD-1</td>
<td>10 Gy x 1f</td>
<td>Post-radiation</td>
</tr>
<tr>
<td>2014</td>
<td>Colon⁹</td>
<td>Anti-CTLA-4, iDC</td>
<td>10 Gy x 3f</td>
<td>Concomitant</td>
</tr>
<tr>
<td>2014</td>
<td>Breast, colon¹⁰</td>
<td>Anti–PD-L1</td>
<td>12 Gy x 1f</td>
<td>Post-radiation</td>
</tr>
<tr>
<td>2014</td>
<td>Melanoma, colorectal, breast¹¹</td>
<td>Anti–PD-L1</td>
<td>2 Gy x 5f</td>
<td>Concomitant + post-radiation</td>
</tr>
<tr>
<td>2015</td>
<td>Melanoma, breast¹²</td>
<td>Anti–PD-1</td>
<td>10 Gy x 1f</td>
<td>Concomitant</td>
</tr>
</tbody>
</table>

Abscopal Response in Patients With RT + Immune Therapy

Metastatic Melanoma
RT + Ipilimumab¹

Metastatic Solid Cancers
CRT + GM-CSF²
(35 Gy in 10 fractions)

Radiation Dose and Fractions: Preclinical Studies

Relationship Between Fractionated RT, T Cells, and Immune Therapy¹,²

Changes in Peripheral Blood Mononuclear Cells

- CD8+ (P = .09)
- CD8+ (P = .06)
- T-reg (P = .01)
- MDSC (P = .03)

Changes in T Cell Subsets

- T Cells With Anergic Phenotype

- CD4+ Teff
- CD4 Lag3+
- CD4 Tim3+
- CD4 PD-1+
- CD8 Teff
- CD8 Lag3+
- CD8 Tim3+
- CD8 PD-1+

P < .05

Increase
Decrease

RR to Anti-PD-1 by Absolute Lymphocyte Count, N = 167

- Spearman’s rho = -0.06
- P = .43

OS From Anti-PD-1 by Absolute Lymphocyte Count, N = 167

Baseline lymphocytes
<1 x 10⁹/L
≥1 x 10⁹/L

No. at Risk
<1 x 10⁹/L 48 35 25 20 13 9 6
≥1 x 10⁹/L 119 104 79 66 58 40 36

P = .31

Concurrent vs Adjuvant Immune Therapy for Fractionated RT


**Timing of RT + anti–PD-L1 mAb is important**

- **Concurrent RT:** Anti–PD-L1 mAb starting on day 1 of RT
- **Adjuvant RT:** Anti–PD-L1 mAb starting on day 5 of RT
- **Rechallenge of LTS mice:** Anti–PD-L1 mAb starting 7 days after the last dose of RT

![Graph](image)
Dosing Schedule Is Critical for Outcome With RT\textsuperscript{1}

...Using loading dose vs concurrent, sequential anti–PD-1 therapy

\textbf{RT}: 4 Gy x 5

\textbf{PD-1 Ab}: 3 mg/kg

No treatment (n = 8)

PD-1 Ab (n = 9)

RT alone (n = 9)

RT + PD-1 Ab concurrent (n = 9)

PD-1 Ab loading dose + RT (n = 8)

Sequential RT PD-1 Ab (n = 9)

Ideal Timing Maybe Dependent on the Type of Immune Checkpoint Therapy

Concurrent treatment resulted in better metastasis shrinkage than non-concurrent treatment.

Concurrent treatment resulted in better overall survival (OS) than non-concurrent treatment.

Anti–PD-1 resulted in better metastasis shrinkage than anti–CTLA-4.

Timing of Immune Checkpoint Therapy and RT in Human Melanoma Brain Metastases

UPCI 15-132: Sequential vs Concomitant Pembrolizumab + CRT

**PULA SCCHN**
Stage III-IVb intermediate-risk or high-risk oral cavity, oropharynx, hypopharynx, larynx, or unknown primary
ECOG 0-1

**Stratification**
HPV status (p16)
N0-2b vs N2c-3

**Tumor Biomarkers**
- Blood Biomarkers Arm 1
- Blood Biomarkers Arm 2

**Concurrent CRT 7 weeks**
- IMRT + weekly cisplatin

**Sequential 24 weeks**
- Pembrolizumab

- Window 1 week
- Pembrolizumab
- IMRT + weekly cisplatin

**Biopsy**

**Pis: Ferris and Bauman**
Accrual = 7/44

---

a Pembrolizumab 200 mg IV every 3 wk x 8 doses. b Cisplatin: 40 mg/m²/wk x 7 doses.
The Role of Draining Lymph Nodes on RT Response—Implications for Field Size\(^1\)

Draining LN Surgically Removed

- Unirradiated
- Unirradiated (ope.)
- Unirradiated (ope., DLN cut)
- Irradiated
- Irradiated (ope.)
- Irradiated (ope., DLN cut)

Genetically LN-Deficient Mice

- Unirradiated (Wt)
- Unirradiated (Aly/Aly)
- Irradiated (Wt)
- Irradiated (Aly/Aly)

\( a \) \( P < .05 \), two-tailed Student’s t test.

Systemic Immunity is Required for Effective Immune Therapy

Response Adapted Volume De-Escalation With Induction Chemotherapy

...Can this concept be tested with immune therapy?

2 Cycles of Cisplatin/Paclitaxel/Cetuximab TFHX + 75 Gy (1.5 Twice Daily)

12/13 were in field failure and 11/13 were in PTV75

RT + Combination Immune Therapy May Be Better Than RT + Single Immune Therapy

Increased PD-L1 expression in RT + CTLA-4–resistant melanoma cells

PD-L1 genetic down regulation or blockade with RT + CTLA-4 increased mouse survival in resistant tumors

AXL Mediates Resistance to RT + Immune Therapy

Conclusions

• **Immune checkpoint therapy, specifically PD-1 pathway blockade**
  – Improves survival in patients with metastatic SCCHN

• **Several questions remain**
  – Does adding immune therapy to RT ± CT improve survival in patients with nonmetastatic disease?
  – Can immune therapy replace CT in certain settings?
  – Are there unanticipated toxicities when combined with RT ± CT?
  – What are the optimal dose, fractionation, and field size in locally advanced HNC?
Symposium Summary and Audience Q&A
Please remember to complete and submit your Post-Test and Evaluation for CME/CE/CPE credit.

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