SCCHN – Systemic Therapy

Merrill Kies
Current Treatment Approaches

- Surgery
- Radiation therapy
- Chemotherapy
- Targeted therapy
- Immunotherapy

Local / Regional

Distant / MR
Basis for Immune therapy – Immune Escape

- Expression of PD-L1 on
  a) tumor cells &
  b) macrophages
  can suppress immune surveillance.

- In mouse models antibodies blocking PD-1 / PD-L1 interaction lead to tumor rejection

- Clinical prognosis correlates with presence of TILs and PD-L1 expression in multiple cancers.

Current Status

- Nivolumab (CheckMate 141) and Pembrolizumab (KEYNOTE-012) approved in 2016 for R/M HNSCC
- Ongoing trials: First-line recurrent disease, definitive with RT, neoadjuvant and adjuvant settings
- Single agents, combinations + chemotherapy, and biologics
CheckMate 141: Study Design

Randomized, global, phase III 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

Investigator’s Choice

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

Primary endpoint

- OS

Other endpoints

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

Ferris R et al, NEJM 2016
CheckMate 141: Overall Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, Months (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, 0.1)</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)

- 36.0% (28.5, 43.4)
- 16.6% (8.6, 26.8)
## CheckMate 141: Treatment Administration

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 240)</th>
<th>Investigators Rx (n = 121)</th>
<th>Total (n = 361)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pts receiving ≥ 1 dose, n (%)</strong></td>
<td>236 (98.3)</td>
<td>111 (91.7)</td>
<td>347 (96.1)</td>
</tr>
<tr>
<td><strong>Investigator’s therapy, n (%)</strong></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><strong>Median time on Rx, mo (95% CI)</strong></td>
<td>1.9 (1.6-2.3)</td>
<td>1.9 (1.6-2.0)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Median follow-up, mo (range)</strong></td>
<td>5.3 (0-16.8)</td>
<td>4.6 (0-15.2)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Number of deaths, n (%)</strong></td>
<td>133 (55.4)</td>
<td>87 (70.2)</td>
<td>218 (60.4)</td>
</tr>
<tr>
<td><strong>Ongoing treatments, n (%)</strong></td>
<td>41 (17.4)</td>
<td>3 (2.7)</td>
<td>44 (12.7)</td>
</tr>
</tbody>
</table>

Ferris R et al, NEJM 2016
Overall Survival by PD-L1 Expression

![Graph showing overall survival rates by PD-L1 expression levels.](image)

**PD-L1 Expression ≥1%**
- Nivolumab (n = 88): Median OS, Months (95% CI) = 8.7 (5.7-9.1) vs 4.6 (3.8-5.8) for Investigator’s Choice (n = 61)
- Hazard Ratio (HR): 0.55 (0.36-0.83)

**PD-L1 Expression <1%**
- Nivolumab (n = 73): Median OS, Months (95% CI) = 5.7 (4.4-12.7) vs 5.8 (4.0-9.8) for Investigator’s Choice (n = 38)
- Hazard Ratio (HR): 0.89 (0.5-1.45)

Ferris R et al, NEJM 2016
Overall Survival by p16 Status

**p16-Positive**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, Months (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>Investigator’s Choice (n = 29)</td>
<td>4.4 (3.0-9.8)</td>
<td></td>
</tr>
</tbody>
</table>

**p16-Negative**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, Months (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>Investigator’s Choice (n = 36)</td>
<td>5.8 (3.8-9.5)</td>
<td></td>
</tr>
</tbody>
</table>

Ferris R et al, NEJM 2016
# Treatment-Related Select AEs

<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>

Select AEs: AEs with potential immunologic etiology that requires monitoring/intervention

Ferris R et al, NEJM 2016
Immune-Related Adverse Events (IRAEs)

- Skin: Exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, vitiligo, alopecia
- Eyes: Uveitis, iritis
- Endocrine: Hypothyroidism, adrenal, insufficiency, hypophysitis
- Pulmonary: Pneumonitis, interstitial lung disease, acute interstitial pneumonitis
- Gastrointestinal: Colitis, enterocolitis, necrotizing colitis, gastrointestinal perforation
- Hepatic: Autoimmune hepatitis
- Renal: Autoimmune nephritis, renal failure
- Neurologic: Autoimmune neuropathy, demyelinating polyneuropathy, Guillain-Barre, myasthenia gravis

CheckMate 141: Nivolumab Beyond Progression

- Of the 236 nivolumab-treated patients, 139 (59%) progressed and of these patients, 57 (41%) were treated with nivolumab beyond RECIST-defined progression.
- Patients treated beyond progression received a median of 9 doses (range: 3, 33) of nivolumab.
- Of 57 patients treated beyond progression, 13 (23%) had a reduction in target lesion size and 14 (25%) had stable lesion size post-progression.
  - Of the 13 patients with reductions, 7 were p16 positive, 3 had PD-L1 expression ≥1%, and 4 had ≥20% tumor size increase at first progression.
  - Two patients had post-progression reduction in target lesions of >30%.
- Median OS was 12.7 months for patients treated beyond progression and 6.1 months for those not treated beyond progression.

Haddad R /abstr, Proc AACR 2017
KEYNOTE-012: Study Design

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

**Initial Cohort**
- Pembrolizumab 10 mg/kg Q2W
  \( N = 60 \)

**Expansion Cohort**
- Pembrolizumab 200 mg Q3W
  \( N = 132 \)

**Continue until:**
• 24 months of treatment<sup>b</sup>
• PD
• Intolerable toxicity

**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<sup>c</sup>

Chow LQ et al, JCO 2016
## Baseline Demographics and Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N = 132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>60 (25-84)</td>
</tr>
<tr>
<td>Male</td>
<td>110 (83)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>95 (72)</td>
</tr>
<tr>
<td>Asian</td>
<td>29 (22)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (6)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>38 (29)</td>
</tr>
<tr>
<td>1</td>
<td>94 (71)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Smoked</td>
<td>81 (61)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>51 (39)</td>
</tr>
<tr>
<td>HPV status</td>
<td></td>
</tr>
<tr>
<td>HPV-associated</td>
<td>28 (21)</td>
</tr>
<tr>
<td>Non-HPV associated</td>
<td>104 (79)</td>
</tr>
<tr>
<td>Sum of target lesions at baseline, median (range), mm</td>
<td>99 (16-664)</td>
</tr>
<tr>
<td>Primary location</td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>60 (45)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>17 (13)</td>
</tr>
<tr>
<td>Larynx</td>
<td>16 (12)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Nasal cavity</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Sinus</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Previous adjuvant and/or neoadjuvant therapy</td>
<td>53 (40)</td>
</tr>
<tr>
<td>Number of previous lines of therapy for recurrent of metastatic diseases</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24 (18)</td>
</tr>
<tr>
<td>1</td>
<td>33 (25)</td>
</tr>
<tr>
<td>2</td>
<td>27 (21)</td>
</tr>
<tr>
<td>3</td>
<td>20 (15)</td>
</tr>
<tr>
<td>4</td>
<td>15 (11)</td>
</tr>
<tr>
<td>≤5</td>
<td>13 (10)</td>
</tr>
</tbody>
</table>
KEYNOTE-012: Efficacy

Chow LQ et al, JCO 2016
### KEYNOTE-012: PDL-1, PFS and OS

<table>
<thead>
<tr>
<th>PD-L1 Status</th>
<th>Tumor and Immune Cells</th>
<th>Tumor Cells Only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonresponders, No.</td>
<td>Responders, No.</td>
</tr>
<tr>
<td>Negative (&lt; 1%)</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Positive (≥ 1%)</td>
<td>84</td>
<td>23</td>
</tr>
</tbody>
</table>

Chow LQ, et al, JCO 2016
## Studies with Checkpoint Inhibitors in R/M HNSCC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Ph</th>
<th>N</th>
<th>Eligibility</th>
<th>Treatment</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; EP</th>
<th>ORR</th>
<th>DOR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate-141&lt;sup&gt;1&lt;/sup&gt;</td>
<td>III (R)</td>
<td>361</td>
<td>Platinum refractory within 6m</td>
<td>Nivolumab SOC (MTX, Doc, Cet)</td>
<td>OS</td>
<td>13% 6%</td>
<td>-</td>
<td>2.0m 2.3m</td>
<td>7.5m 5.1m</td>
</tr>
<tr>
<td>KEYNOTE-055&lt;sup&gt;2&lt;/sup&gt;</td>
<td>II</td>
<td>171</td>
<td>Platinum and cetuximab refractory</td>
<td>Pembrolizumab</td>
<td>ORR</td>
<td>16%</td>
<td>8m</td>
<td>2.1m</td>
<td>8m</td>
</tr>
<tr>
<td>KEYNOTE-012&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Ib</td>
<td>132</td>
<td>Any N of prior lines</td>
<td>Pembrolizumab</td>
<td>Safety ORR</td>
<td>18%</td>
<td>NR</td>
<td>2.0m</td>
<td>8m</td>
</tr>
<tr>
<td>KEYNOTE-012&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Ib</td>
<td>60</td>
<td>PD-L1 positive (≥ 1%), any N of prior lines</td>
<td>Pembrolizumab</td>
<td>Safety ORR</td>
<td>18%</td>
<td>53w</td>
<td>2.0m</td>
<td>13m</td>
</tr>
</tbody>
</table>

Courtesy of Ferrarotto R.
KEYNOTE 040: Pembrolizumab vs Standard Treatment (methotrexate, docetaxel, or cetuximab) in R/M SCCHN

Randomized, open-label Phase III trial

- **Pembrolizumab**
  - 200 mg, intravenously (IV) q3w

- **Investigator’s Choice**
  - **Cetuximab**
    - Cetuximab 400 mg/m² then 250 mg/m² weekly
  - **or Methotrexate**
    - Methotrexate 40–60 mg/m² IV weekly
  - **or Docetaxel**
    - Docetaxel 75 mg/m² IV weekly q3w

- **Recurrent and/or metastatic SCCHN After failure of platinum**
- **N=600**
- **Primary endpoints**: PFS and OS
- **Secondary endpoints**: ORR, TTP
  - Safety: time to first grade 3/5

Accrual completed

KEYNOTE-048: Study Design

- Phase III, randomized, open-label, clinical trial of pembrolizumab in first-line treatment versus active comparator in patients with R/M HNSCC without prior systemic chemotherapy\(^1\)

### 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)

### Start Date: March 2015

### Primary Endpoint:
- PFS

### Other Endpoints:
- OS, PFS (by immune-related response), ORR

### Randomized

- Pembrolizumab
- Pembrolizumab + Platinum + 5FU
- Active Comparator (Cetuximab + Platinum + 5FU)

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HPV, human papillomavirus; ORR, overall response rate; PD-1, programmed cell death protein 1; PFS, progression-free survival; R/M, recurrent or metastatic.

Patients with R/M HNSCC, progressive disease at study entry, an ECOG PS of 0 or 1, and no prior anti-PD-1/PD-L1 exposure

- Most responses (all PRs) occurred in the first 16 weeks
- Among 7 responders, 6 had duration of response ≥12 months
- Median OS was 8.4 months for PD-L1 high and 8.9 for PD-L1 low/negative
- Treatment related grade 3-4 AEs were reported in 8% of patients; no grade 3-4 pneumonitis, no drug-related colitis of any grade

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab 10 mg/kg q 2 w</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients</td>
</tr>
<tr>
<td>ORR by RECIST, % (n/N)</td>
<td>11 (7/62)</td>
</tr>
<tr>
<td>DCR at 12 weeks, % (n/N)</td>
<td>29 (18/62)</td>
</tr>
</tbody>
</table>

DCR, disease control rate
**EAGLE: Study Design**

- **EAGLE:** Phase III, randomized, open-label study of efficacy and safety of durvalumab +/- tremelimumab versus standard of care in patients with R/M SCCHN after failure of platinum-based treatment. 

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### Key Eligibility Criteria
- PD-L1 +/- as determined by Ventana SP263 (cutoff: 25%)
- Failure of exactly one Pt-tx for recurrent/metastatic disease, or progression within 6 months of completing platinum-containing multimodality therapy with curative intent
- No prior exposure to immune-mediated therapy

### Start Date: September 2015

**Primary Endpoint:** OS

**Other Endpoints:** OS (PD-L1+), OS (PD-L1-), PFS, ORR, DOR, DCR, APF, safety and tolerability

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**APF, alive and progression-free; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; Pt-tx, platinum-based treatment**

KESTREL: Study Design

Phase III randomized, open-label efficacy and safety of durvalumab +/- tremelimumab versus active comparator in the treatment of first-line R/M HNSCC\(^1\)

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Iplilimumab and Nivolumab: Complementary Mechanism of Action
CheckMate 651: Study Design

Phase III randomized, open-label of nivolumab + ipilimumab compared to the EXTREME regimen as first-line treatment in patients with R/M HNSCC\(^1\)

**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 + 5FU

**Platinum Sensitive**
- Adopted from Mellman I, et al 2011.\(^2\)

**Start Date:** August 2016

**Primary Endpoints:** OS, PFS
**Other Endpoints:** ORR, time to deterioration, PD-L1 expression as biomarker

**CTLA-4, cytotoxic T-lymphocyte-associated protein 4**
JAVERLIN Head and Neck 100: Study Design

A randomized double-blind phase III study of avelumab in combination with standard of care (SOC) chemoradiotherapy (cisplatin plus definitive radiation therapy) versus SOC chemoradiotherapy in the front-line treatment of patients with locally advanced (LA) HNSCC

Inclusion criteria:
- LA SCC oral cavity, oropharynx, larynx, hypopharynx
- HPV-; stage II, Iva, Ivb
- HPV+: T4 or N2c (AJCC 7) or N3
- ECOG PS = 0 or 1
- No prior therapy

Primary Endpoint: PFS by investigator per modified RECIST v1.1

Stratification Factors
- T stage (<T4 vs T4)
- N stage (N0/N1/2b vs N2c/N3)
- HPV (+ vs -) as measured by p16 IHC
**Pembrolizumab with CRT**

**Study Design**

**Treatment Dose and Schedule**
- cisplatin 40 mg/m² weekly (6 planned doses)
- pembrolizumab 200 mg every 3 weeks (8 planned doses)
- radiation therapy at 2 Gy once daily for 35 fractions (total 70 Gy)

**Primary end points:**
- Safety - dose-limiting adverse events (AEs) and immune-related AEs (irAEs)
- Efficacy - complete response (CR) rate on imaging or salvage surgery at day 150

**Secondary end points:** PFS, OS, locoregional control, distant metastasis rate, quality-of-life (FACT H&N)

Presented by Steven F. Powell at the 2017 ASCO Annual Meeting
Immunotherapy with pembrolizumab in HPV-negative locally advanced, surgically resectable HNSCC

Pre-treatment biopsy and PBMCs → Neoadjuvant Pembrolizumab (1 dose) → Surgery (original margins) with biopsy and PBMCs

- ECE/margins → standard of care

+ ECE/margins → PO-ACRT → Maintenance pembrolizumab

NCT02296684

Presented By Ravindra Uppaluri at 2017 ASCO Annual Meeting
Immunobiology Related to ML and GEP

ML reflects tumor antigenicity

GEP reflects activated T-cells in tumor microenvironment

Presented By Robert Haddad at 2017 ASCO Annual Meeting
Adjuvant Studies in Locally Advanced HNSCC

Adjuvant (post-operative) studies also underway:

– University of Cincinnati: Pembrolizumab + RT or CRT depending on pathologic risk factors
– University of Chicago: Pembrolizumab vs placebo + CRT in high-risk patients
– UCSD: Pembrolizumab in patients with recurrent/resectable disease
Conclusions: Present Role of PD-1 Inhibitors in HNSCC

- Immunotherapy is an option for patients with R/M SCCHN
- Nivolumab and pembrolizumab have demonstrated benefit +/- PD-L1 expression and p16 status, but greater in patients expressing PD-L1
- Safety profile is favorable
Conclusions

- Nivolumab and pembrolizumab are now standard of care options for patients with R/M HNSCC after platinum-based therapy
  - Pseudoprogression is unusual
- PD-L1 expression is an imperfect biomarker for the efficacy of immune checkpoint inhibitors; benefit in both HPV+ and HPV-; gene signatures are under evaluation
- Single agents and combination regimens are in late stage development in first-line treatment of R/M SCCHN
- Combination with radiotherapy and with other multimodality approaches are being investigated in potentially curable disease
- Preclinical studies suggests further improved efficacy with combinations of immunotherapeutic approaches that target tumor microenvironment