Disclosures

_Honoraria_: Amgen, Astra Zeneca, BMS, Celgene, Eisai, Eli Lilly, Innate, Jounce, Merck/MSD, Merck/EMD-Serono
Presentation Outline

I. Background and Genetic Basis of HNSCC

II. New Treatments/ New Targets

1. Progress with Immunotherapy
2. HPV+ HNC
   1. De-escalation
3. Other novel targets
   1. Angiogenesis
   2. CDK4/6
   3. PI3K

III. Conclusions
I. HNC Disease Background

- Head and neck cancer (HNC) is 6<sup>th</sup> most common cancer worldwide; 60,000 new cases per year in the United States

- Human Papilloma Virus (HPV) is involved in the etiology of ~60-80% of Oropharyngeal HNC in the US

- HPV(-)/Tobacco-related HNC AND HPV(+) HNC are distinct clinical entities.
I. The HPV “Epidemic”
Recurrent / metastatic HNC

→ Large unmet need

• Salvage surgery (or XRT) for selected cases

• Systemic chemotherapy
  – **First Line:** EXTREME, Platinum Doublet
  – **Second Line:** Docetaxel, cetuximab, Methotrexate,...
  …and as of Aug 2016 – anti-PD-1 in the US

→ Highly symptomatic
→ Median survival ~10-12 months
I. HNC Tumor Heterogeneity

HNC is a diverse group of multiple “biologic entities”

- We have done “good” with HPV+ biology
  → distinct entity, but much known biology remains unaccounted for
- Breast Cancer or Lung Cancer are far ahead

Hayes/Seiwert – JCO 2015
Keck/Seiwert – CCR 2015
## Potentially Targetable Genetic Changes

<table>
<thead>
<tr>
<th>Gene</th>
<th>HPV(-) n=243</th>
<th>HPV(+) n=36</th>
</tr>
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<tbody>
<tr>
<td>EGFR</td>
<td>15%</td>
<td>6%</td>
</tr>
<tr>
<td>FGFR1</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>ERBB2</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>IGF1R</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>EPHA2</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>DDR2</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>FGFR2</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>FGFR3</td>
<td>2%</td>
<td>11%</td>
</tr>
<tr>
<td>MET</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>CCND1</td>
<td>31%</td>
<td>3%</td>
</tr>
<tr>
<td>MYC</td>
<td>14%</td>
<td>3%</td>
</tr>
<tr>
<td>HRAS</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>19%</td>
<td>36%</td>
</tr>
<tr>
<td>PTEN</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>NF1</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>TP53</td>
<td>84%</td>
<td>0%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>58%</td>
<td>3%</td>
</tr>
</tbody>
</table>

TCGA, Nature: Figure generated by Nikki Schultz / Tanguy Seiwert
II.1 Progress with Immunotherapy
1899: Coley’s Toxin

New York Times - July 29, 1908

ERYSIPelas GERMS AS CURE FOR CANCER

Dr. Coley’s Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases—Probably 150 Sure Cures.

Following news from St. Loui's that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York. It came out yester-
Fast forward to 2016: Coley’s Toxin meets PD-1 (?)
Simple Conclusion...
II. Tumor Shrinkage (KeyNote 12)

Analysis includes patients with measurable disease at baseline who received ≥1 pembrolizumab dose and had ≥1 post-baseline tumor assessment (n = 106)

Unconfirmed and confirmed RECIST v 1.1 responses by site radiology review

*2 oropharynx cancer patient are HPV unknown. Cancers outside the oropharynx are considered HPV negative by convention

Data cutoff date: March 23, 2015. OP = oropharyngeal primary

~50% experienced a decrease in target lesions

Seiwert TY Lancet Oncol 2016
II. Major Impact on Overall Survival

Seiwert TY Lancet Oncol 2016
II. Survival matters!

The Tail at the end of the curve

FDA Approves Pembrolizumab for Head and Neck Cancer

Subscribe

August 24, 2016 by NCI Staff

The Food and Drug Administration (FDA) approved pembrolizumab (Keytruda®) on August 5 for the treatment of some patients with an advanced form of head and neck cancer. The approval is for patients with recurrent or metastatic squamous cell carcinoma of the head and neck, as well as for pembrolizumab (Keytruda®) in combination with chemoradiotherapy for patients with locally advanced or recurrent head and neck squamous cell carcinoma who have not responded to prior platinum-containing chemotherapy.

Pembrolizumab is a humanized monoclonal antibody that targets the programmed death-1 (PD-1) receptor on T cells to prevent it from interacting with its ligand, programmed death-ligand 1 (PD-L1). When PD-L1 binds to PD-1, the immune system is suppressed. Pembrolizumab blocks this interaction, allowing T cells to attack cancer cells.

The approval is based on results from a phase 2 trial of 34 patients with recurrent or metastatic squamous cell carcinoma of the head and neck. Pembrolizumab was well tolerated, with 12 patients (35%) experiencing grade 3–4 adverse events, including fatigue, anemia, and rash. One patient developed a grade 3 rash, and 7% of patients discontinued pembrolizumab due to adverse events.

Overall, pembrolizumab demonstrated clinical benefit in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. Pembrolizumab is currently being studied in combination with other treatments for a variety of cancer types.

For more information, visit the FDA website.
Phase 3 CheckMate 141 Study Design

Nivolumab in R/M SCCHN After Platinum Therapy

Key Eligibility Criteria
- R/M SCCHN of the oral cavity, pharynx, or larynx
- Progression on or within 6 months of last dose of platinum-based therapy
- Irrespective of no. of prior lines of therapy
- Documentation of p16 to determine HPV status (oropharyngeal)
- Regardless of PD-L1 status

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

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

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

Ferris/Gillison
NEJM 2016
Overall Survival

Nivolumab in R/M SCCHN After Platinum Therapy

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mo (95% CI)</th>
<th>HR (97.73% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (n = 240)</td>
<td>7.5 (5.5, 9.1)</td>
<td>0.70 (0.51, 0.96)</td>
<td>0.0101</td>
</tr>
<tr>
<td>Investigator’s Choice (n = 121)</td>
<td>5.1 (4.0, 6.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1-year OS rate (95% CI)

- Nivolumab: 36.0% (28.5, 43.4)
- Investigator’s Choice: 16.6% (8.6, 26.8)

Response Rate only 13%, but major impact on Survival

Ferris/Gillison
NEJM 2016
FDA Approves Nivolumab for Head and Neck Cancer

The Food and Drug Administration (FDA) approved nivolumab (Opdivo®) on November 10 for the treatment of squamous cell cancer of the head and neck (SCCHN).

Nivolumab is already approved for the treatment of several other cancers. This new approval is for the use of nivolumab in patients with SCCHN that has progressed during chemotherapy with a platinum-based drug or that has recurred or metastasized after platinum-based chemotherapy.

Nivolumab is the second immunotherapy drug approved to treat SCCHN. In August of this year, the FDA approved pembrolizumab (Keytruda®) for patients with SCCHN whose disease has progressed during or after platinum-containing chemotherapy. Both nivolumab and pembrolizumab are immune checkpoint inhibitors, drugs that prevent tumor cells from blocking attack by the immune system. Cytotoxic T cells (red) attacking an oral squamous cancer cell (white). Immune checkpoint inhibitors like nivolumab prevent tumors from turning off T cells, allowing them to attack and kill the tumor cells. Credit: National Cancer Institute
A Overall Survival

Hazard ratio for death, 0.49 (95% CI, 0.38–0.64)
P<0.001

No. at Risk
Pembrolizumab combination
Placebo combination
410 377 347 278 163 71 18 0
206 183 149 104 59 25 8 0
Adjuvant/minimal residual disease Treatment:

PATHWay study

- High-risk for recurrence after surgery/TORS or RT/CRT
- Patients who recur on control arm get early access to Pembrolizumab
- Testing HYPOTHESIS that PD-1 blockade has most impact for minimal residual disease

Head & Neck Cancer Program

**Figure 1.** Progression-free Survival in the Intention-to-Treat Population.
“Adjuvant” Pathway Study

PCCC

TITLE: A randomized, double-blind Phase II study of pembrolizumab versus placebo in patients with head and neck cancers at high risk for recurrence or low-volume residual disease – the PATHWay Study.

Short Title: PATHWay – PembrolizumAb in the Treatment of Head and neck cancer With high risk (treatment for 1 year)
iPRIME study

- Salivary Gland Cancers
- Thyroid Cancers

→ Pembrolizumab + Docetaxel
Re-irradiation study
PD-1 Failure studies

OPEN:
• Pembrolizumab + Epacadostat (+chemotherapy boosters)

PENDING:
• R3 Hafnium Nanoparticle + RT + PD1
• Durvalumab – Tremelimumab - Carbo/Docetaxel
Biomarkers predictive of response to pembrolizumab in head and neck cancer (HNSCC)

Tanguy Y. Seiwert, MD¹; Robert Haddad, MD²; Joshua Bauml, MD³; Jared Weiss, MD⁴; David G. Pfister MD⁵; Shilpa Gupta, MD⁶; Ranee Mehra, MD⁷,⁸; Iris Gluck, MD⁹; Hyunseok Kang, MD¹⁰; Francis Worden, MD¹¹; J. Paul Eder, MD¹²; Makoto Tahara, MD¹³; Barbara Burtness, MD¹²; Stephen V. Liu, MD¹⁴; Andrea Webber, PhD¹⁵; Lingkang Huang, PhD¹⁵; Robin Mogg, PhD¹⁵; Razvan Cristescu, PhD¹⁵; Jonathan Cheng, MD¹⁵; Laura Q. M. Chow, MD¹⁶

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## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>Overall study cohort&lt;sup&gt;a&lt;/sup&gt; (N=363)</th>
<th>WES&lt;sup&gt;b&lt;/sup&gt; (N = 258)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>61 (20-90)</td>
<td>61 (25-90)</td>
</tr>
<tr>
<td>Male</td>
<td>297 (82)</td>
<td>208 (81)</td>
</tr>
<tr>
<td>ECOG status (1 &amp; 2)</td>
<td>258 (71)</td>
<td>178 (69)</td>
</tr>
<tr>
<td>Metastatic staging (M1)</td>
<td>321 (88)</td>
<td>231 (90)</td>
</tr>
<tr>
<td>Prior therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>37 (10)</td>
<td>25 (10)</td>
</tr>
<tr>
<td>1</td>
<td>80 (22)</td>
<td>49 (19)</td>
</tr>
<tr>
<td>2</td>
<td>113 (31)</td>
<td>93 (36)</td>
</tr>
<tr>
<td>≥3</td>
<td>133 (37)</td>
<td>91 (35)</td>
</tr>
<tr>
<td>HPV-positive p16 IHC</td>
<td>82 (23)</td>
<td>57 (22)</td>
</tr>
<tr>
<td>HPV-positive WES</td>
<td>–</td>
<td>79 (31)</td>
</tr>
</tbody>
</table>

- Patients with WES data had baseline characteristics similar to those in the overall population.

<sup>a</sup>Overall study cohort: KN-012 (n=192) + KN-055 (n=171); <sup>b</sup>Patients with WES data available: KN-012 (n=107) and KN-55 (n=151) cohorts.
PD-L1 and TMB Response Rates (BOR)

- Response rates were higher in those who had both high PD-L1 and TMB across all patients and in both HPV subgroups than those with low levels of both.

Dashed horizontal line is the clinically applicable TMB threshold (TMB ≥175 mutations per exome) using GEP and TMB data from the pan tumor cohort (Panda A, et al., JCO Precis Oncol. 2017). Dashed vertical line is PD-L1 CPS ≥1. PD-L1 CPS high (hi) and low (lo): ≥1 and 0; TMB hi and lo: ≥ and <175.
• PFS times were longer in patients with higher vs lower levels of PD-L1 CPS, GEP, and TMB
• Results were generally similar in HPV subgroups

PD-L1 CPS high (hi) and low (lo): ≥1 and 0. GEP hi and lo: ≥ and <0.318. TMB hi and lo: ≥ and <175. HR=hazard ratio associated with difference in PFS curve for hi vs lo cutoffs.
Multicolor IF

4x overview

<table>
<thead>
<tr>
<th></th>
<th>Number of Fields</th>
<th>HLADR%</th>
<th>IDO1%</th>
<th>HLADR+IDO+ in DR+</th>
<th>HLADR+IDO+CK+ in DR+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13</td>
<td>10%</td>
<td>19%</td>
<td>36%</td>
<td>14%</td>
</tr>
</tbody>
</table>
II.2 HPV+ HNC
DE-INTENSIFICATION / DE-ESCALATION IS A NEW STANDARD OF CARE
Approaches

1. Lower Radiation Dose
2. Replace Cisplatin with Cetuximab
3. Use Induction response or surgery/TORS to differentiate good and bad prognosis patients
4. Volume De-escalation (VD)
5. Various Combinations of the above – e.g. RAVD
<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Sponsor</th>
<th>Trial Details</th>
<th>Pre-Radiation Treatment</th>
<th>RT based treatment</th>
<th>De-escalation Element/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG 1308 [38]</td>
<td>Eastern Cooperative Oncology Group (ECOG-ACRIN)</td>
<td>PII, NR, AL</td>
<td>Induction chemotherapy</td>
<td>LR: Cetuximab + RT (54Gy)</td>
<td>1. Induction based risk stratification</td>
</tr>
<tr>
<td>NCT01084083</td>
<td></td>
<td></td>
<td></td>
<td>HR: Cetuximab + RT (69Gy)</td>
<td>2. Lower RT dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. Substitution of cisplatin with cetuximab (CRT)</td>
</tr>
<tr>
<td>RAVD Chicago Trial [75]</td>
<td>University of Chicago</td>
<td>PII, NR, AL</td>
<td>Induction chemotherapy</td>
<td>LR: Volume de-escalated CRT (PTV2 omission)</td>
<td>1. Induction based risk stratification</td>
</tr>
<tr>
<td>NCT01133678</td>
<td></td>
<td></td>
<td></td>
<td>HR: CRT</td>
<td>2. RAVD (Response adjusted volume de-escalation = PTV2 omission)</td>
</tr>
<tr>
<td>UNC 1120 [74]</td>
<td>University of North Carolina</td>
<td>PII, NR, AL</td>
<td>--</td>
<td>a) CRT with 60Gy, and lower dose cisplatin</td>
<td>1. Lower RT dose</td>
</tr>
<tr>
<td>NCT01530997</td>
<td></td>
<td></td>
<td></td>
<td>b) selective/confirmatory surgery</td>
<td>2. Lower Cisplatin dose (CRT)</td>
</tr>
<tr>
<td>OPTIMA</td>
<td>University of Chicago</td>
<td>PII, NR, AL</td>
<td>Induction chemotherapy</td>
<td>LR: RT alone 50Gy &amp; RAVD</td>
<td>1. Lower RT dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IR: 45Gy CRT &amp; RAVD</td>
<td>2. No Cisplatin/chemo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR: Regular CRT</td>
<td>3. RAVD</td>
</tr>
</tbody>
</table>
**OPTIMA = Oro-Pharynx Tumor Induction Response**

Stratified Therapy To Minimize Adverse Events

**Low Risk**
- \( \leq T3 & \leq N2B & \leq 10 \) PYH
- \( N = 28 \)

**High Risk**
- T4 or \( \geq N2C \) or \( > 10 \) PYH

**Induction Chemotherapy**
- 1) Carboplatin AUC=6, d1
- 2) Nab-paclitaxel 100 mg/m² d1/d18/d15

**Radiologic Assessment of Response**
- \( \geq 50\% \): Low-dose RT
  - PTV1: 50 Gy
  - \( pCR: 94.7\% \)
  - \( N = 20 \)
- 30-50\%: Low-dose CRT
  - PTV1: 45 Gy
  - PTV2: 30 Gy
  - \( pCR: 100\% \)
  - \( N = 6 \)
- < 30\%: Standard CRT
  - PTV1: 75 Gy
  - PTV2: 45 Gy
  - \( N = 2 \)
OPTIMA = Oro-Pharynx Tumor Induction Response Stratified Therapy To Minimize Adverse Events

Low Risk

≤T3 & ≤N2B & ≤10 PYH

Induction Chemotherapy x 3 Cycles

1) Carboplatin AUC=6, d1
2) Nab-paclitaxel 100 mg/m² d1/d18/d15

Radiologic Assessment of Response

≥ 50%

N = 24

Low-dose RT PTV1: 50 Gy

pCR: 86.4%

N = 34

High Risk

T4 or ≥N2C or >10 PYH

N = 24

Low-dose CRT PTV1: 45 Gy PTV2: 30 Gy

N = 9

Standard CRT PTV1: 75 Gy PTV2: 45 Gy

≥ 50%

< 50%

Melotek/Seiwert ASCO 2017
Results

**Overall Survival**

- 2-year OS: 100.0% (95% CI N/A)
- 2-year OS: 97.0% (95% CI 80.4% – 99.6%)

**Progression-Free Survival**

- 2-year PFS: 100.0% (95% CI N/A)
- 2-year PFS: 92.9% (95% CI 74.2% – 98.2%)
Key Points:
1) Risk stratified treatment – 45-50Gy
2) Better outcomes than published national series
3) Less toxicity → Avoid Radiation
KEO study

- Neo-Adjuvant Study
- Pembrolizumab + Epacadostat prior to curative intent surgery

Diagram:
- SCCHN patients, who are candidates for surgical therapy
  - Pembrolizumab 200mg q3 weeks up to 3 doses
    - Epacadostat 100mg BID po
  - Week 3-4: 1. CT, 2. Biopsy, 3. ctDNA
- Week 7-8: 1. CT, 2. Surgery, 3. ctDNA
- Week 8: Surgery
- 8 weeks: Time to surgery in responders
- ~4 weeks until SOC in non-responders
- Pathologic CR **
- Major pathologic Response **
- >10% residual tumor
- De-escalated adjuvant Tx
  - Per RadOnc Guidance
- SOC Adjuvant Therapy

Observations:
- a) 12 week PET
- b) Serial ctDNA

Adjuvant for 12 months:
- Pembrolizumab + Epacadostat

Standard of care - Curative Intent Therapy
- Surgery or CRT (+/- induction with carbo/docetaxel)
Targeted Therapies

- Infigratinib in FGFR – altered tumors
Conclusions

I. Multiple Novel Therapies are emerging for HNSCC

1. Immunotherapy is here to stay and changing our paradigm
   1. Combination approaches with IDO, STAT3, CTLA4 appear more active
   2. Integration into curative intent – adjuvant / concurrent

2. HPV(+) tumors – De-escalation is an emerging standard of care

3. Other targeted targets are being explored (PI3K, Anti-angiogenesis, CDK4/6)

4. Biomarkers will be essential to personalize HNSCC care

II. Lots of activity → SOC is literally shifting under our feet.
The University of Chicago Head and Neck Cancer Team

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