Advanced Cutaneous Squamous Cell Carcinoma: Immuno-Oncology and the Evolving Landscape of Multidisciplinary Care

Presented by:
The Angeles Clinic & Research Institute & ACCC
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Speakers

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Santa Monica, CA

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Santa Monica, CA
Importance of Multidisciplinary Care

- Emerging multidisciplinary care models across the country.
- Association of Community Cancer Centers education program on *Multidisciplinary Advanced Cutaneous Squamous Cell Carcinoma Care*.

Publication available in print and online!
Mark Faries Disclosures

• Advisory Board:
  • Novartis, Array Biopharma, Pulse Bioscience, Castle Bioscience, Bristol Myers Squibb, Sanofi
OBJECTIVES

To know:

1. Current data regarding the epidemiology of cutaneous squamous cell carcinoma (cSCC)

2. Potential preventative strategies for skin cancer, including cSCC

3. What modern, multidisciplinary options are available for local and regional treatment of cSCC

4. What systemic therapy options are available for treatment of advanced or metastatic cSCC

5. The precautions and potential toxicities of immunology therapies in cSCC
Cutaneous Squamous Cell Carcinoma

- Epidemiology
- Diagnosis / Prognosis
- Primary Treatment
  - Surgery / Mohs’
- Staging
  - SLN
  - Imaging
- Follow up
cSCC: Epidemiology

• Data are not great: Not captured in registries
• Second most common cancer
• Incidence approaching that of Basal Cell Carcinoma
    ➢ Increase of 263%
• Karia et al estimated (in USA, 2012)
  • 5604 - 12,572 with cSCC developed nodal metastases
  • 3932 - 8791 deaths from cSCC (1.5-4% mortality rate?)

cSCC: Risk Factors

- Male > Female (3:1), Hx of sun exposure, Actinic Keratoses, Immunosuppression, Fitzpatrick Type 1, CLL
- Arsenic, tar, +/- HPV (periungual, anogenital), Smoking?
- Genetic:
  - xeroderma pigmentosum, Ferguson-Smith Syndrome, oculocutaneous albinism, epidermodysplasia verruciformis.
  - MC1R
- Drugs: BRAF monotherapy, Vismodegib
- Older age: Australia <40 yo: 7/100K, >70 yo: 2972/100K
- Prior SCC - 40% new cSCC at 5-years after first
  - 82% new cSCC at 5 years after >1 cSCC

cSCC: Risk Factors

- TCGA
- Mutations of melanoma TP53, RAS, CDKN2A
cSCC: Risk Factors: Transplant

- Keratinocyte carcinomas are the most common cancers among white solid organ transplant patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Location</th>
<th>Kidney</th>
<th>Liver</th>
<th>Heart</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapman 2013⁶²</td>
<td>KC</td>
<td>Finland</td>
<td>39·2 (29·3–51·4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sweden</td>
<td>57·7 (51·0–65·1)</td>
<td>34·0 (17·0–60·6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>U.K.</td>
<td>16·6 (15·9–17·3)</td>
<td>6·6 (5·8–7·5)</td>
<td>18·5 (16·9–20·3)</td>
<td>16·1 (13·1–19·6)</td>
</tr>
<tr>
<td>Jensen 2010⁶⁵</td>
<td>cSCC</td>
<td>Denmark</td>
<td>81 (68–96)</td>
<td>60 (27–113)</td>
<td>113 (74–166)</td>
<td>65 (28–128)</td>
</tr>
<tr>
<td>Jensen 2010⁶⁵</td>
<td>BCC</td>
<td>Denmark</td>
<td>6·9 (5·8–8·1)</td>
<td>4·6 (2·1–8·7)</td>
<td>5·6 (3·1–9·5)</td>
<td>4·1 (1·7–8·5)</td>
</tr>
<tr>
<td>Krynnitz 2013³</td>
<td>cSCC</td>
<td>Sweden</td>
<td>53 (46–61)</td>
<td>15 (7·2–28)</td>
<td>67 (46–94)³</td>
<td></td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–9 years</td>
<td></td>
<td></td>
<td>92 (83–102)</td>
<td>40 (25–61)</td>
<td>218 (174–269)³</td>
<td></td>
</tr>
<tr>
<td>10–19 years</td>
<td></td>
<td></td>
<td>165 (154–177)</td>
<td>51 (31–80)</td>
<td>357 (297–425)³</td>
<td></td>
</tr>
<tr>
<td>≥ 20 years</td>
<td></td>
<td></td>
<td>206 (187–226)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krynnitz 2013³</td>
<td>cSCC</td>
<td>Sweden</td>
<td>121 (116–127)</td>
<td>32 (24–42)</td>
<td>198 (174–224)³</td>
<td></td>
</tr>
</tbody>
</table>

KTR, kidney transplant recipient; LTR, liver transplant recipient; HTR, heart transplant recipient; LuTR, lung transplant recipient. ³Heart and lung transplant recipients.
Chemoprevention:
Vitamin B3: nicotinamide
May enhance DNA repair by preventing UVR-induced adenosine triphosphate depletion

*Difluormethylornithine: decreases polyamine synthesis*

**NSAIDS**

Field Therapy: 5-fluorouracil, diclofenac, PDT
cSCC: Prevention

Chemoprevention:
Vitamin B3: nicotinamide
May enhance DNA repair by preventing UVR-induced adenosine triphosphate depletion

Difluormethylornithine: decreases polyamine synthesis

NSAIDS

Field Therapy: 5-fluoruracil, diclofenac, PDT

SUN PROTECTION

Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial
A Green, G Williams, R Neale, V Hart, D Leslie, P Parsons, GC Marks, P Gaffney, D Battistutta, C Frost, C Lang, A Russell

The Lancet 1999

The New England Journal of Medicine
A Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention

<table>
<thead>
<tr>
<th>Skin cancer</th>
<th>Participants</th>
<th>Tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily sunscreen</td>
<td>No daily sunscreen</td>
</tr>
<tr>
<td>Basal-cell carcinoma</td>
<td>65</td>
<td>63</td>
</tr>
<tr>
<td>Number</td>
<td>2588</td>
<td>2509</td>
</tr>
<tr>
<td>Incidence per 100 000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate ratio (95% CI)</td>
<td>1.03</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>(0.73–1.46)</td>
<td></td>
</tr>
</tbody>
</table>

| Squamous-cell carcinoma| 22           | 25       | 28            | 46              |
| Number                 | 876          | 996      | 1115          | 1832            |
| Incidence per 100 000  |              |          |               |                 |
| Rate ratio (95% CI)    | 0.88         | 1.00     | 0.61          | 1.00            |
|                        | (0.50–1.56)  |          | (0.46–1.81)   |                 |
cSCC Staging: AJCC 8 vs. BWH

High-risk features:
- Diameter ≥2 cm
- Poorly differentiated
- Perineural invasion ≥0.1mm
- Tumor invasion beyond subcutaneous fat

(Bone invasion automatic T3)

Table I. American Joint Committee on Cancer (AJCC) cutaneous SCC staging system for tumors of the head and neck skin 8th edition

<table>
<thead>
<tr>
<th>Stage</th>
<th>T category</th>
<th>T criteria</th>
<th>N category</th>
<th>N criteria for pathologic N</th>
<th>M category</th>
<th>M criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>Primary tumor cannot be identified</td>
<td>NR</td>
<td>Regional lymph nodes cannot be assessed</td>
<td>M0</td>
<td>No distant metastasis</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Carcinoma in situ</td>
<td>N0</td>
<td>No regional lymph node metastasis</td>
<td>M1</td>
<td>Distant metastasis</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor ≤2 cm in greatest dimension</td>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt;2 cm but ≤4 cm in greatest dimension</td>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node &gt;3 cm in greatest dimension and ENE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;4 cm or clinical diameter ≥2 cm, minor bone erosion or perineural invasion or deep invasion</td>
<td>N2a</td>
<td>Metastasis in single ipsilateral or contralateral node &gt;3 cm in greatest dimension and ENE, or in a single ipsilateral node &gt;3 cm but not &gt;6 cm in greatest dimension and ENE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumor with gross cervical bone marrow, skull base invasion, and/or skull base or brain involvement</td>
<td>N2b</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none &gt;6 cm in greatest dimension and ENE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumor with skull base invasion and/or skull base or brain involvement</td>
<td>N3</td>
<td>Metastasis in a lymph node &gt;6 cm in greatest dimension and ENE, or in a single ipsilateral node &gt;3 cm in greatest dimension and ENE, or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor with skull base invasion</td>
<td>N3a</td>
<td>Metastasis in a lymph node &gt;6 cm in greatest dimension and ENE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor with skull base invasion and/or skull base or brain involvement</td>
<td>N3b</td>
<td>Metastasis in a single ipsilateral node &gt;2 cm in greatest dimension and ENE, or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4c</td>
<td>Tumor with skull base invasion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table II. Brigham and Women’s Hospital tumor staging system

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of high-risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>0</td>
</tr>
<tr>
<td>T2a</td>
<td>1</td>
</tr>
<tr>
<td>T2b</td>
<td>2–3</td>
</tr>
<tr>
<td>T3</td>
<td>≥4</td>
</tr>
</tbody>
</table>

SKT Que, FO Zwald, CD Schmults. Cutaneous squamous cell carcinoma Incidence, risk factors, diagnosis, and staging JAAD 2018
cSCC: Prognostic factors

**Location:** Area L (trunk/extremities)  
Area M (cheek, forehead, scalp, neck, shin)  
Area H (“mask”, genitalia, hands/feet)

**Size:** Diameter: L ≥20mm, M ≥ 10 mm, H any  
Depth (subcut or >6mm)

**Histology:**  
Low: Keratoacanthoma, verrucous carcinoma  
High: desmoplastic, adenosquamous,  
cSCC associated w/ scarring process (e.g. burn)

**Borders**  
Recurrent lesion  
Growth rate  
Neurologic symptoms

---

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk Factor</th>
<th>No of Studies</th>
<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>Breslaw thickness ≥2 mm</td>
<td>1</td>
<td>9.64 (1.30-71.52)</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td>Invasion beyond subcutaneous fat</td>
<td>3</td>
<td>7.61 (4.17-13.83)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Breslaw thickness &gt;6 mm</td>
<td>1</td>
<td>7.13 (3.94-16.72)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>PNI</td>
<td>6</td>
<td>4.30 (2.80-6.69)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Diameter &gt;20 mm</td>
<td>5</td>
<td>3.22 (1.91-5.45)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Temple</td>
<td>1</td>
<td>3.20 (1.12-9.56)</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td>Poor differentiation</td>
<td>11</td>
<td>2.66 (1.72-4.14)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Immunosuppression</td>
<td>6</td>
<td>1.51 (0.81-2.81)</td>
<td>.20</td>
</tr>
<tr>
<td></td>
<td>Lip</td>
<td>4</td>
<td>1.28 (0.41-3.97)</td>
<td>.67</td>
</tr>
<tr>
<td></td>
<td>Ear</td>
<td>6</td>
<td>1.28 (0.56-2.90)</td>
<td>.56</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Invasion beyond subcutaneous fat</td>
<td>5</td>
<td>11.21 (3.59-34.97)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Breslaw thickness ≥2 mm</td>
<td>3</td>
<td>10.76 (2.55-45.31)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Breslaw thickness &gt;6 mm</td>
<td>2</td>
<td>6.93 (4.02-11.94)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Diameter &gt;20 mm</td>
<td>6</td>
<td>6.15 (3.56-10.65)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Poor differentiation</td>
<td>10</td>
<td>4.08 (2.30-7.19)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>PNI</td>
<td>13</td>
<td>2.95 (2.31-3.75)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Temple</td>
<td>7</td>
<td>2.62 (1.72-4.63)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Ear</td>
<td>13</td>
<td>2.33 (1.07-5.23)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td></td>
<td>Immunosuppression</td>
<td>15</td>
<td>2.18 (1.54-3.17)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

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**Disease-specific death**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>No of Studies</th>
<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasion beyond subcutaneous fat</td>
<td>1</td>
<td>19.10 (5.30-62.85)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Poor differentiation</td>
<td>4</td>
<td>3.65 (1.76-8.12)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Ear</td>
<td>2</td>
<td>4.67 (1.28-17.12)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>1</td>
<td>0.25 (0.05-1.38)</td>
<td>.30</td>
</tr>
</tbody>
</table>

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SKT Que, FO Zwald, CD Schmults. Cutaneous squamous cell carcinoma Incidence, risk factors, diagnosis, and staging JAAD 2018
cSCC: Mohs’ vs. Excision Pathology
cSCC: Pathology
“Breadloaf”
cSCC: Pathology
CCPDM
Primary Treatment (NCCN)

Suspicious lesion for skin cancer

H&P
- Complete skin exam
- Regional LN exam
- Biopsy
- Inclusion of deep reticular dermis if indicated
  Imaging as indicated for suspicion of extensive disease

->
cSCC confirmed

Local

Low risk

High risk

Clinically or radiographically concerning regional LN

Or

Distant metastases

Hamid

Primary Treatment: Low Risk (NCCN)

Low Risk

- Curretage and electrodesiccation
  - Excluding terminal hair bearing areas such as scalp, pubic, axillary regions, beard area in men

  Or

- Standard excision with 4-6 mm clinical margin and post-operative margin assessment

  Or

- Radiation therapy for non-surgical candidates

Positive margin

- Mohs’ or resection with CCPDMA
  or
  - Re-excision if feasible
  or
  - RT for non-surg candidates

Negative margin
Sentinel Lymph Node
# Nodal staging of high-risk cutaneous squamous cell carcinoma

M Fox, M Brown, N Golda, D Goldberg, C Miller, M Pugliano-Mauro, C Schmults, T Shin, T Stasko, YG Xu, K Nehal, High Risk SCC Workgroup, Dermatol Surg Section of Assoc Prof Derm

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Tumor site</th>
<th>SLN + (14.5%)</th>
<th>False - (5.1%)</th>
<th>Other:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navarrete-Dechent</td>
<td>2015</td>
<td>System review</td>
<td>Various</td>
<td>13.9% (32/231)</td>
<td>4.6% (10/215)</td>
<td>(24%)</td>
</tr>
<tr>
<td>Gore</td>
<td>2016</td>
<td>Prospective</td>
<td>cSCC</td>
<td>14% (8/57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krediet</td>
<td>2015</td>
<td>Case series</td>
<td>Head / neck, legs, trunk</td>
<td>11.7% (2/17)</td>
<td>35.2% (6/17)</td>
<td></td>
</tr>
<tr>
<td>Schmitt</td>
<td>2014</td>
<td>System review</td>
<td>Various</td>
<td>12.3%</td>
<td></td>
<td>BWH T2b/T3: 34.7% (8/23)</td>
</tr>
<tr>
<td>Ahmed</td>
<td>2014</td>
<td>System review</td>
<td>Various</td>
<td>13%</td>
<td></td>
<td>100%/NPV 92.5%</td>
</tr>
<tr>
<td>Fukushima</td>
<td>2014</td>
<td>Prosp case series</td>
<td>Head/neck, extrem, trunk, genitalia</td>
<td>7.4% (4/54)</td>
<td></td>
<td>T2 and above: 12.9%</td>
</tr>
<tr>
<td>Takahashi</td>
<td>2014</td>
<td>Case series</td>
<td>Head/neck, extrem, trunk, genitalia</td>
<td>23.1% (6/26)</td>
<td>0/26</td>
<td></td>
</tr>
<tr>
<td>Kwon</td>
<td>2011</td>
<td>Case series</td>
<td>Head, extremities, perineum</td>
<td>0% (0/6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rastrelli</td>
<td>2010</td>
<td>Case series</td>
<td>Head and neck, extrem, trunk</td>
<td>5% (1/20)</td>
<td>2/20</td>
<td></td>
</tr>
<tr>
<td>Renzi</td>
<td>2007</td>
<td>Prosp case series</td>
<td>Not specified</td>
<td>4.5% (1/22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resendiz-Colosia</td>
<td>2007</td>
<td>Prosp case series</td>
<td>Head and neck, extrem, trunk</td>
<td>20% (4/20)</td>
<td>0/20</td>
<td></td>
</tr>
<tr>
<td>Ross</td>
<td>2006</td>
<td>System review</td>
<td>Various</td>
<td>21%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Cecchi</td>
<td>2006</td>
<td>Case series</td>
<td>Head, extremities</td>
<td>16.6% (1/6)</td>
<td>0/6</td>
<td></td>
</tr>
<tr>
<td>Hatta</td>
<td>2005</td>
<td>Prosp case series</td>
<td>Lower extremity</td>
<td>0% (0/4)</td>
<td>0/4</td>
<td></td>
</tr>
<tr>
<td>Nouri</td>
<td>2004</td>
<td>Prosp case series</td>
<td>Head and neck</td>
<td>12% (1/8)</td>
<td>0/8</td>
<td></td>
</tr>
<tr>
<td>Eastman</td>
<td>2004</td>
<td>Prosp case series</td>
<td>Extremities</td>
<td>80% (4/5)</td>
<td>0/5</td>
<td></td>
</tr>
<tr>
<td>Wagner</td>
<td>2004</td>
<td>Prosp case series</td>
<td>Head and neck, extrem, perineum, vulva</td>
<td>29.4% (5/17)</td>
<td>1/17</td>
<td></td>
</tr>
<tr>
<td>Reschly</td>
<td>2003</td>
<td>Prosp case series</td>
<td>Head and neck, extrem, trunk</td>
<td>44.4% (4/9)</td>
<td>0/9</td>
<td></td>
</tr>
<tr>
<td>Michl</td>
<td>2003</td>
<td>Case series</td>
<td>Head/neck, trunk, extrem, genitalia</td>
<td>18.1% (2/11)</td>
<td>0/11</td>
<td></td>
</tr>
<tr>
<td>Altinyollar</td>
<td>2002</td>
<td>Prosp case series</td>
<td>Lower lip</td>
<td>16.6% (3/18)</td>
<td>0/18</td>
<td></td>
</tr>
</tbody>
</table>
Sentinel Lymph Node in cSCC

High-risk cutaneous squamous cell carcinoma and the emerging role of sentinel lymph node biopsy: A literature review

C Navarrete-Dechent, MJ Veness, N Droppelmann, P Uribe


Ave SLN +: Depth 10.7mm
Diam. 4.6 cm

Survival:
(Takahashi et al, Eur J Surg Oncol 2014)
3-yr OS SLN− 100%
SLN+ 20.8%

<table>
<thead>
<tr>
<th>Table 1. Summary of high-risk features and clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factors</strong></td>
</tr>
<tr>
<td>Size: &gt;2 cm</td>
</tr>
<tr>
<td>Depth: Breslow &gt;2-4 mm or Clark IV, V</td>
</tr>
<tr>
<td>Recurrent tumor</td>
</tr>
<tr>
<td>Poorly differentiated in histology</td>
</tr>
<tr>
<td>Perineural invasion</td>
</tr>
<tr>
<td>Site: Lip</td>
</tr>
<tr>
<td>External ear</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
</tr>
<tr>
<td>Histologic subtype (mainly desmoplastic)</td>
</tr>
<tr>
<td>Incomplete excision</td>
</tr>
<tr>
<td>De novo cSCC**</td>
</tr>
<tr>
<td>Immunosuppression:</td>
</tr>
<tr>
<td>Solid organ transplantation</td>
</tr>
<tr>
<td>CLL</td>
</tr>
</tbody>
</table>

---


---

**Sentinel Lymph Node in cSCC**

**Staging for Cutaneous Squamous Cell Carcinoma as a Predictor of Sentinel Lymph Node Biopsy Results**  
Meta-analysis of AJCC and a Proposed Alternative System  
AR Schmitt, JD Brewer, JS Bordeaux, CL Baum  
*JAMA Dermatology* January 2014 Volume 150, Number 1

**Risk Factors:**  
- ≥2 cm diameter,  
- Poor Differentiation  
- Perineural invasion  
- invasion beyond subcut fat (except bone which =T3)

**Table 2. Alternative Tumor Staging System for cSCC**

<table>
<thead>
<tr>
<th>Primary Tumor</th>
<th>Criteriaa</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>In situ squamous cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>0 Risk factors</td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>1 Risk factor</td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>2-3 Risk factors</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>4 Risk factors or bone invasion</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4. SLN+ by T Stage in Patients With Nonanogenital cSCC in 2 Staging Systems**

<table>
<thead>
<tr>
<th>T Stage</th>
<th>No. of SLN+ Tumors/Total No. of Tumors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJCC staging systema</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>0/9</td>
</tr>
<tr>
<td>T2</td>
<td>13/116 (11.2)</td>
</tr>
<tr>
<td>T3</td>
<td>0/0</td>
</tr>
<tr>
<td>T4</td>
<td>3/5 (60.0)</td>
</tr>
<tr>
<td>Alternative staging systemb</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>Not included</td>
</tr>
<tr>
<td>T1</td>
<td>0/9</td>
</tr>
<tr>
<td>T2a</td>
<td>6/85 (7.1)</td>
</tr>
<tr>
<td>T2b</td>
<td>5/17 (29.4)</td>
</tr>
<tr>
<td>T3</td>
<td>3/6 (50.0)</td>
</tr>
</tbody>
</table>
Sentinel Lymph Node in cSCC

• Rationale?
  • Therapy: Guide for CLND or XRT
    • Essentially no data

• NCCN
  • No specific recommendation:
    • “In certain high-risk lesions, consider sentinel lymph node mapping, although benefit of and indication for this technique has yet to be proven.”
Regional Nodes

- **Single ≤ 3 cm**
  - Selective neck dissection
  - One positive ≤ 3 cm, no ECE → RT or obs

- **Single > 3 cm or multiple ipsilateral**
  - Comprehensive neck dissection
  - One positive > 3 cm or multiple positive, no ECE → RT

- **Bilateral**
  - Bilateral neck dissection
  - Any node with ECE → RT +/- clinical trial systemic

- **Parotid involvement**
  - Superficial parotidectomy and neck dissection
  - Incompletely excised nodal disease → RT +/- systemic
Unresectable or Metastatic cSCC

Suspicious lesion for skin cancer → H&P
- Complete skin exam
- Regional LN exam
- Biopsy
- Inclusion of deep reticular dermis if indicated
  Imaging as indicated for suspicion of extensive disease

→ cSCC confirmed →

Local
- Low risk
- High risk

Clinically or radiographically concerning regional LN

Or

Distant metastases → Hamid
Lifestyles of the Rich and Squamous: Recent cSCC Data

Omid Hamid MD
Chief, Translational Research/Immuno-Oncology
Director, Experimental Therapeutics Cedars Sinai Foundation
@OmidHamidMD  •  ohamid@theangelesclinic.org
Disclosures

• The more conflicts of interest for the speaker, the more balanced the talk . . . . .

Hauschild 2015

• Pfizer
• Rinat
• Genentech
• Roche
• BMS
• Merck
• Merck Serano
• Immunocore
• Medimmune
• Tesaro

• Astra Zeneca
• Novartis
• Celldex
• Incyte
• Esai
• Eli Lilly
• Cytomx
• Curis
• Aduro
• Regeneron
General Facts About Cutaneous SCC

- 2nd most frequent NMSC (after BCC) – 20% of all cutaneous malignancies
- Incidence rate increases have been recorded (50-200%) in last 30 years
- The majority occur on the head and neck (80-90%)
- Usually develops from precursor lesions (actinic keratosis), but also de novo
- > 90% of cases have excellent prognosis
- 700,000 new cases
- 2000 deaths per year
- Most cSCCs are curable with surgery or radiation
• 5% metastasize
  • treated typically with platinum-based chemotherapy and EGFR inhibitors
  • Overall response rates (ORR) of only 10-20%
  • No current treatments have been shown to improve survival

• Risk factors:
  - UV radiation, immunosuppression

• Lifetime risk:
  - Men: 9%-14%; Women: 4%-9%

• Risk of nodal metastases: 2%-5.8%

• Disease-specific death rate: 1.5%

• Lifetime risk: M-9-14%. W- 4-9%

Locally Advanced and Metastatic SCC

- **Radiotherapy**
- **Cisplatin-based chemotherapy**
  - No established standard regimen
  - short-lived remissions (average duration: 3 months) up to 60%
  - toxic

- **Mutation-driven targeted therapies**: ⇝ *EGFR/pan-HER inhibitors*
  - Cetuximab: 28% RR, 69% DCR
  - Panitumumab: 31% RR, 68% DCR
  - Dacomitinib (pan-HER inhibitor): 28% RR, 86% DCR

- **Immunotherapies**
  - Change of immunosuppression in OTRs – toward mTOR inhibitors
  - PD-1 antibodies

---

The prevalence of somatic mutations across human cancer types.
Correlation Between Tumor Mutational Burden and Objective Response Rate with Anti–PD-1 or Anti–PD-L1 Therapy in 27 Tumor Types
Rationale for PD-1 Inhibition in CSCC

- Higher mutation burden than any tumor type in The Cancer Genome Atlas (TCGA)\(^1\)
- Mutation burden exceeded by that of BCC\(^2\)

> Immunosuppression is a well-described risk factor for CSCC, especially in solid organ transplant patients\(^3\)
> PD-L1 expression has been associated with high-risk disease\(^4\)
> In the phase I dose escalation study of cemiplimab (REGN2810), a **durable radiologic complete response** to cemiplimab was achieved in a CSCC patient\(^5,6\)
PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma


ABSTRACT

BACKGROUND
No systemic therapies have been approved for the treatment of advanced cutaneous squamous-cell carcinoma. This cancer may be responsive to immune therapy, because the mutation burden of the tumor is high and the disease risk is strongly associated with immunosuppression. In the dose-escalation portion of the phase 1 study of cemiplimab, a deep and durable response was observed in a patient with metastatic cutaneous squamous-cell carcinoma.
Binds to PD-1 and Blocks its Interaction with PD-L1 and PD-L2

- Binds to PD-1 and blocks its interaction with PD-L1 and PD-L2.
- Releases PD-1 pathway–mediated inhibition of the immune response, including the anti-tumor immune response.
- In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.
Co-primary objectives:
- To characterize the safety and tolerability of IV cemiplimab, 3 mg/kg Q2W
- To evaluate the efficacy of cemiplimab by measuring ORR

Papadopoulos KP. REGN2810, A Human Anti-PD-1 Monoclonal Antibody, for Patients with Unresectable Locally Advanced or Metastatic Cutaneous Squamous Cell Carcinoma (CSCC): Initial Safety and Efficacy. Presented at the 2017 Annual Meeting of the American Society of Clinical Oncology; 2017 Jun 2-6; Chicago, IL.
PD1 antibodies in SCC patients

Borradori et al., Br J Dermatol, 2016. 175: 1382–1386
CSCC EXPANSION COHORTS WERE OPENED IN THE PHASE 1 STUDY OF REGN2810
CSCC EXPANSION COHORTS WERE OPENED IN THE PHASE 1 STUDY OF REGN2810
Cemiplimab is Active Across All PD-L1 Strata in CSCC (Tumor PD-L1 Expression by Immunohistochemistry; Dako 22C3 Clone)

91% (10/11) of evaluated tumors were positive (≥1%) for tumor expression of PD-L1 by IHC

<table>
<thead>
<tr>
<th>Tumor PD-L1</th>
<th>Total</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
<th>ORR†</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50%</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>20% (1/5)</td>
</tr>
<tr>
<td>≥1–49%</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>60% (3/5)</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No apparent association between PD-L1 IHC results and objective responses

Papadopoulos KP. REGN2810, A Human Anti-PD-1 Monoclonal Antibody, for Patients with Unresectable Locally Advanced or Metastatic Cutaneous Squamous Cell Carcinoma (CSCC): Initial Safety and Efficacy. Presented at the 2017 Annual Meeting of the American Society of Clinical Oncology; 2017 Jun 2-6; Chicago, IL.
### Defined Population per Study Design

<table>
<thead>
<tr>
<th>Metastatic cSCC&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Locally advanced cSCC&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nodal metastasis</td>
<td>• Locally advanced cSCC patients who were not candidates for curative surgery or curative radiation</td>
</tr>
<tr>
<td>• Distant metastasis</td>
<td></td>
</tr>
</tbody>
</table>

**Recurrence**
- cSCC that has recurred in the same location after 2 or more surgical procedures and curative resection is deemed unlikely

**Location of disease**
- cSCC in anatomically challenging locations for which surgery may result in severe disfigurement or dysfunction (eg, removal of all or part of a facial structure, such as nose, ear, or eye; or requirement for limb amputation)

**Invasive disease**
- cSCC with significant local invasion that precludes complete resection

**Other**
- Other conditions deemed to be contraindicating for surgery

---

Not a candidate for curative surgery:

Factors to consider<sup>a</sup>

---

Cemiplimab for Advanced cSCC

• Phase I
  • Response in 13 of 26 patients
  • RR: 50% (95% CI, 30 to 70)

• Phase II
  • Response in 28 of 59 patients
  • RR: 47% (95% CI, 34 to 61)
  • Median follow-up: 7.9 months
  • Response duration > 6 months in 57%
  • 82% continued response on treatment

## 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>
Tumor Response to Cemiplimab Among Patients in the Phase 2 Study Who Had Metastatic Cutaneous Squamous-Cell Carcinoma

Examples of Reductions in Visible CSCC Lesions Following Treatment with Cemiplimab

- Upper left: 85-year-old man with supraclavicular lesion who had received prior RT.
- Upper right: 66-year-old man with anterior chest wall lesions who had received prior cisplatin.
- Lower left: 83-year-old man with multiple prior surgeries for CSCC.

* The patient in panel A is an 85-year-old man with supraclavicular lesion who had received prior radiotherapy. The patient in panel B is an 83-year-old man with multiple prior surgeries for CSCC. The patient in panel C is a 86-year-old man with anterior chest wall CSCC lesions who had received prior cisplatin.

Data cut-off date: October 27, 2017
Target Lesion Percent Change from Baseline Among Responders (N=49)\textsuperscript{1}

- Each line represents the individual percent change in target lesions from baseline among the 49 responders who reached a complete or partial response.\textsuperscript{1}
- For a patient to be assessed as at least a partial response (PR), for target lesion evaluation, there had to be at least 30% reduction in the sum of target lesion diameters by RECIST 1.1 and at least 50% reduction by WHO.\textsuperscript{1}
- Patients with new lesions or unequivocal progression of non-target lesions were characterized as non-responders.\textsuperscript{1}
- At the time of data cutoff, among the responders included in the figure, 4 patients had disease progression—at 7.3, 8.2, 9.1, and 9.2 months of study, respectively—and 6 patients had their response duration censored for the following reasons: withdrawal of consent (2), not evaluable for last response assessment (2), tumor resection (1), and AEs resulting in study discontinuation (1) at 2.8, 3.7, 14.7, 9.1, 4.6, and 9.2 months, respectively.\textsuperscript{1}

Median duration of follow-up for all patients included in the efficacy analysis was 8.1 months for metastatic CSCC, 10.2 months for locally advanced CSCC, and 8.9 months for combined CSCC (N=108).\textsuperscript{2}
Progression-free Survival among Patients in the Phase 2 Study Who Had Metastatic Cutaneous Squamous-Cell Carcinoma
Cemiplimab Phase II Study: Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic-Disease Cohort of the Phase 2 Study (N=59)</td>
<td>no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>59 (100)</td>
<td>25 (42)</td>
</tr>
<tr>
<td>Serous</td>
<td>21 (36)</td>
<td>17 (29)</td>
</tr>
<tr>
<td>Led to discontinuation of treatment</td>
<td>4 (7)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Associated with an outcome of death</td>
<td>3 (5)</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occurred in ≥5 patients</td>
<td>no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16 (27)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14 (24)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>9 (15)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Rash</td>
<td>9 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>8 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>8 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>6 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>6 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (8)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>5 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Increased alanine aminotransferase</td>
<td>5 (8)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>5 (8)</td>
<td>0</td>
</tr>
</tbody>
</table>

Pembrolizumab for Recurrent/Metastatic Cutaneous Squamous Cell Carcinoma: Efficacy and Safety Results From the Phase 2 KEYNOTE-629 Study

J.-J. Grob¹; R. Gonzalez Mendoza²; N. Basset-Seguin³; O. Vornicova⁴; J. Schachter⁵; A. Joshi⁶; N. Meyer⁷; F. Grange⁸; J. M. Piulats⁹; J. R. Bauman¹⁰; P. Zhang¹¹; B. Gumuscu¹¹; R. F. Swaby¹¹; B. G. M. Hughes¹²,¹³

¹AIX-Marseille University, Marseille, France; ²Centro Estatal de Cancerologíade Chihuahua, Chihuahua, Mexico; ³Hôpital Saint-Louis, Paris, France; ⁴Rambam Health Care Campus, Haifa, Israel; ⁵Sheba Medical Center at Tel Hashomer, Ramat Gan, Israel; ⁶Townsville Cancer Centre, Townsville, Queensland, Australia; ⁷IUCT–Oncopole, Toulouse, France; ⁸CHU Reims–Hôpital Robert Debre, Reims, France; ⁹Hospital Duran i Reinals ICO de Hospitalet, Barcelona, Spain; ¹⁰Fox Chase Cancer Center, Philadelphia, PA, USA; ¹¹Merck & Co., Inc., Kenilworth, NJ, USA; ¹²Royal Brisbane and Women’s Hospital, Herston, Queensland, Australia; ¹³University of Queensland, Brisbane, Queensland, Australia
Best Percentage Change From Baseline in Target Lesion in the R/M Cohort

44 patients (57.9%) patients had ≥30% reduction

Database cutoff date: April 8, 2019.
Response Duration and PFS and OS in the R/M Cohort

- Grob ESMO 2019

<table>
<thead>
<tr>
<th>Response</th>
<th>Duration</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c PFS</td>
<td>6.9 months (95% CI, 3.1-8.5)</td>
<td>6-month rate: 50.4%</td>
<td></td>
</tr>
<tr>
<td>c OS</td>
<td>NR (95% CI, 10.7-NR)</td>
<td>6-month rate: 79.0%</td>
<td></td>
</tr>
<tr>
<td>12-month rate: 32.4%</td>
<td>12-month rate: 60.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BOR, best overall response; CR, complete response; NR, not reached; PR, partial response; SD, stable disease. Database cutoff date: April 8, 2019. Response was based on blinded independent central review per RECIST v1.1; confirmed responses are shown. *Discontinued or ongoing refers to status in relation to study treatment. †This patient achieved a best overall response of CR. ‡Per Kaplan-Meier estimate.
NEOAdjuvant Approach
Immune Modulatory Receptors

Turning up The Activating

Blocking the Inhibiting

Durable Response of Metastatic Squamous Cell Carcinoma of the Skin to Ipilimumab Immunotherapy.

- A 72-year-old male patient was receiving second-line chemotherapy for metastatic squamous cell carcinoma of the skin (SCCS) when he was diagnosed with concurrent metastatic melanoma (BRAF mutant).
- Chemotherapy was ceased and he was treated with 4 cycles of ipilimumab immunotherapy. The patient experienced clinical benefit and durable remission in both malignancies and remains free of cancer progression 8 months after the last cycle of ipilimumab.
- Response of SCCS to ipilimumab has not been previously described, pembrolizumab efficacy confirm the critical role of the immune system in SCCS pathogenesis and suggest further exploration of checkpoint immunotherapy for the treatment of this disease.
Genomic profiling of squamous malignancies across anatomic sites. 2017 #11512

• HPV driven SCC have similar genomic profiles regardless of site origin, and have a significantly lower median TMB than HPV negative SCC.
• Site independent genomic predictors of therapy response.
• Sites of origin were head and neck (HNSCC, \( n = 1300 \)), cervical (cSCC; \( n = 318 \)), anal (aSCC, \( n = 248 \)), esophageal (\( n = 242 \)), lung (lSCC, \( n = 2386 \)), and cutaneous (sSCC, \( n = 289 \)) SCC cases.
• TMB of all SCC cases was significantly different (\( p < 10^{-12} \)) when stratified by HPV status.
• In sSCC, the most common GA were in \( TP53 \) (85.5%), \( CDKN2A \) (54.3%), and \( TERT \) (44.0%), and mean TMB was 59.5 with HPV in 3.1% of cases.
# Post Transplant Skin Cancer

- 36-fold higher incidence in OTRs (SCC:BCC = 4:1)
- Aggressive biological behavior; poor outcomes
- Incidence rates (cases per 100,000 person-years)

<table>
<thead>
<tr>
<th>Post Transplant Skin Cancer</th>
<th>OTR</th>
<th>US population</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMSC</td>
<td>1,436</td>
<td>449</td>
</tr>
<tr>
<td>SCC</td>
<td>1,355</td>
<td>38</td>
</tr>
<tr>
<td>MM</td>
<td>125</td>
<td>18</td>
</tr>
<tr>
<td>MCC</td>
<td>3.3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Complete pathologic response of metastatic cutaneous squamous cell carcinoma and allograft rejection after treatment with combination immune checkpoint blockade

David M. Miller, MD, PhD,1,2 Beverly E. Faulkner-Jones, MD, PhD,3
James R. Stone, MD, PhD,4 and Reed E. Drews, MD5
Boston, Massachusetts
Pembrolizumab for Metastatic CSCC in Organ-Transplant Patient

- Sept 2014 – started off-label pembrolizumab
- Nov 2014 – irreversible organ rejection: dense T-cell infiltrate with PD-L1 expression
- 85% reduction in metastatic tumor burden
- Pembro continued with dialysis

Explanted renal allograft

- PD-L1 expression on endothelial cells and infiltrating immune cells
- Infiltrating T-cells express PD-1
- Immune cells are CD8+
Safe and effective administration of T-VEC in a patient with heart transplantation and recurrent locally advanced melanoma

Gustavo Schvartsman¹, Kristen Perez², Jill E. Flynn³, Jeffrey N. Myers³ and Hussein Tawbi²,4*

Abstract

Background: Immunotherapy plays a key role in the treatment of metastatic melanoma. Patients with autoimmune conditions and/or on immunosuppressive therapy due to orthotopic transplants, however, are systematically excluded from clinical trials. Talimogene laherparepvec (T-VEC) is the first oncolytic virus to be approved by the FDA for cancer therapy. To our knowledge, this is the first report of T-VEC being administered in the setting of an organ transplant recipient.

Case presentation: Here we present the case of a patient with recurrent locally advanced cutaneous melanoma receiving salvage T-VEC therapy in the setting of orthotopic heart transplantation. After 5 cycles of therapy, no evidence of graft rejection has been observed to date, and the patient achieved a complete remission, and is currently off therapy.

Conclusion: This case advocates for further investigation on the safety and efficacy of immunotherapeutic approaches, such as T-VEC, in solid organ transplant recipients.

Keywords: Cancer, Melanoma, Immunotherapy, Allotransplant, Rejection, T-VEC
• History of hepatitis B status post liver transplant (1993)
• Multiple basal cell carcinomas, squamous cell carcinoma
• Neuroendocrine carcinoma and Merkel cell carcinoma
• Has received ---- for metastatic squamous cell carcinoma.
Raising the bar ……

Chemotherapy

Immunotherapy

Radiotherapy

Targeted therapy

Combination approaches
Cetuximab in mSCC

August 2010

December 2010
An open-label, non-randomized, multi-arm, phase II trial evaluating pembrolizumab combined with cetuximab in patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): Results of the interim safety analysis #6037

- This is the first trial to combine pembrolizumab with cetuximab to evaluate anti-tumor synergy. As this specific drug combination has not been previously tested, an interim safety analysis was completed per protocol.

- pembrolizumab at a fixed dose of 200mg IV on day 1 with cetuximab 400mg/m2 loading dose followed by 250mg/m2 weekly (21-day cycle).

- **Results:** Of the 10 patients included in the analysis, median age 58y (range 47-79y), M: F 5:5. 8 pts had mucosal (6 oral cavity, 1 oropharynx, 1 nasopharynx) and 2 had cutaneous HNSCC primaries.

- 65 adverse events (AEs) were reported in 9 pts; G1: 39, G2: 15, ≥G3: 11. Of the 11 ≥G3 AEs, only 1 was treatment-related (see Table). There were no treatment-related deaths or dose-limiting toxicities (DLTs).

- 3 pts discontinued treatment, none of which were due to toxicity (2 had disease progression, 1 withdrew from study).

- Pembrolizumab combined with cetuximab has a very tolerable safety profile, with no DLTs. Efficacy analysis of this combination will be performed.
Initial Efficacy of Anti-Lymphocyte Activation Gene-3 (anti-LAG-3; BMS-986016) in Combination With Nivolumab in Patients With Melanoma Previously Treated With Anti–PD-1/PD-L1 Therapy

Dose Escalation N = 8 (advanced solid tumors) → Relatlimab (80 mg) + Nivolumab (240 mg) IV Q2W

Dose Expansion N = 262

Study Endpoints (dose expansion)
- **Co-Primary:** Preliminary efficacy and safety/tolerability
- **Other:** Immunogenicity, QTc, PK, PD, biomarkers

Efficacy: Melanoma progressed during prior I-O; n = 68

Safety: All patients

### Safety of Relatlimab 80 mg + Nivolumab 240 mg Q2W

|                      | All Patients
|----------------------|----------------
|                      | N = 279
| Any TRAE§            | 157 (56) 27 (10)
| TRAEs in ≥ 2% of patients |
| Fatigue              | 33 (11) 0
| Pruritus              | 19 (7.0) 0
| Diarrhea              | 18 (6.7) 3 (1.1)
| Anorexia              | 17 (6.1) 0
| Infusion-related reaction | 15 (5.5) 0
| Any serious TRAE§     | 18 (6.7) 12 (4.4)
| Serious TRAEs in ≥ 1 patient |
| Colitis               | 4 (1.5) 3 (1.1)
| Pneumonitis           | 2 (0.7) 2 (0.7)
| Myocarditis§          | 2 (0.7) 0
| Pyrexia               | 2 (0.7) 0
| Any TRAE leading to discontinuation§ | 11 (4.1) 6 (3.5)

- The safety profile of the melanoma prior PD-(L)1 cohort was similar to that of the overall population
- No treatment-related deaths were reported

### Depth and Duration of Response by LAG-3 and PD-L1 Expression

- **Responses were more likely in patients with LAG-3 expression ≥ 1%**
- **PD-L1 expression did not appear to enrich for response**

**Presented by Paolo A. Ascierto at ASCO 2018**
**Phase 1b Study Schema**

- T-VEC intralesional
  - Up to 4 mL per treatment
  - 1st dose 10⁶ PFU/mL
  - Then 10⁷ PFU/mL Q2W

- Pembrolizumab 200mg IV Q2W

- N=21
  - Unresectable stage III or IV melanoma
  - Treatment naive
  - Injectable lesions
  - No clinically active brain mets
  - No active herpetic skin lesions or prior complications from herpetic infection

**Treatment until whichever occurs first:**
- Progressive disease (PD) per irRC
- Intolerance
- All injectable tumors disappeared (T-VEC only)
- 2 Years

**MASTERKEY-265 (pembro+T-Vec)**

**Best Change in Tumor Burden**

- N=16

Includes all patients who received at least 1 dose of talimogene laherparepvec or pembrolizumab.

Include patients who had at least 2 assessments with bi-dimensional measurements.
# Current Approaches to Squamous Cell Carcinoma Skin

<table>
<thead>
<tr>
<th>ClinicalTrials.Gov</th>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02268747 Efficacy and Safety of Dacomitinib in the Treatment of Skin Squamous Cell Cancer</td>
<td>II</td>
<td>Pan-HER inhibitor, Coexpression of EGFR, HER2 and HER3</td>
</tr>
<tr>
<td>NCT00423397 Gefitinib and PEG-Interferon Alfa-2a in Treating Patients With Unresectable or Metastatic Skin Cancer</td>
<td>I/II</td>
<td>Immuno/Immuno Combination</td>
</tr>
<tr>
<td>NCT02978625 Talimogene Laherparepvec and Nivolumab in Treating Patients With Refractory Lymphomas or Advanced or Refractory Non-melanoma Skin Cancers</td>
<td>II</td>
<td>Immuno/Immuno Combination, Local Oncolytic and Systemic Immunotherapy</td>
</tr>
<tr>
<td>NCT02218164 Capecitabine or 5-FU With Pegylated Interferon Alpha-2b in Unresectable/Metastatic Cutaneous Squamous Cell Carcinoma</td>
<td>II</td>
<td>Chemo/Immuno Combination</td>
</tr>
<tr>
<td>NCT03291002 Study of Intratumoral CV8102 in cMEL, cSCC, hnSCC, and ACC</td>
<td>I</td>
<td>Intratumoral Therapy</td>
</tr>
<tr>
<td>NCT03108131 Cobimetinib and Atezolizumab in Advanced Rare Tumors</td>
<td>II</td>
<td>Targeted Immuno Combination</td>
</tr>
</tbody>
</table>
## Factors Predictive of Recurrence / Death

<table>
<thead>
<tr>
<th></th>
<th>Nodal Metastases</th>
<th>Disease-Specific Death</th>
<th>Overall Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter ≥2 cm</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Poor differentiation</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Invasion beyond fat</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Ear/temple location</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anogenital location</td>
<td></td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Perineural invasion</td>
<td></td>
<td></td>
<td>✔</td>
</tr>
</tbody>
</table>

3.7% risk of metastases; 2.1% DSD

Adjuvant trials

Figure 1: Study Schematic for Part 1 the Study (blinded for primary analysis)

- Surgery, with high risk features on surgical pathology report
- Patient Information Cards (optional)
- Completion of Post-Op RT
- Randomize 1:1
  - Informed Consent and Screening
  - 350 mg Cemiplimab Q3W IV X 48 weeks
    - Primary Endpoint: disease-free survival
  - Placebo Q3W IV X 48 weeks
The Where, the When, and the How of Immune Monitoring for Cancer Immunotherapies in the Era of Checkpoint Inhibition

Priti S. Hegde, Vaios Karanikas, and Stefan Evers

Trial design considerations for combination therapies. A, a commonly employed trial design for interrogation of drug mechanism of action employs multiple biopsies (Bx) from the same individual with the combining partner (CP) alone or the combination of CP with checkpoint inhibitors (CPI).

B, tumor immune modulation is a dynamic process. Trial designs that incorporate sequential biopsies keeping the time between biopsies constant for each agent enable comparison of the impact of each combining partner on tumor immune microenvironment.
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Importance of Multidisciplinary Collaboration

NCCN Guidelines

Dermatologist:
Diagnosis and topical/field therapy

Pathologist: Biopsy, staging
Radiologist: Rule out metastases, help surgeon assess operability

Surgeon:
Assess if tumor is operable

Patient with metastatic cSCC receives appropriate treatment for their condition

Medical oncologist or dermatoncologist:
Identify patients for whom systemic therapy is the best approach

Radiation oncologist:
Assess if radiation is an appropriate treatment approach

Conclusion

• Dramatic advances have been made in the molecular understanding of cSCC
• Early data suggest rapid and (possibly) durable responses to anti-PD-1 therapy in advanced cSCC
• This sets the stage for investigation into combination therapy
• Identifying biomarkers of response is key
• Work to do
• Clinical trials, clinical trials, clinical trials …..
This lecture will be made available as an on-demand webinar.

For more information about this project:

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