Update on Non-Melanoma Skin Cancer

William Sharfman, MD, FACP
Associate Professor of Oncology and Dermatology
Johns Hopkins University School of Medicine
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Non-Melanoma Skin Cancer

- Basal Cell Carcinoma
- Squamous Cell Carcinoma
- Merkel Cell Carcinoma
Incidence of Skin Cancer in the United States

• Skin cancer is the most commonly diagnosed cancer in the United States
  – BCC - > 1 million cases per year\textsuperscript{1}
  – Squamous cell carcinoma -  250,000
  – Melanoma – 70,000

Basal Cell Carcinoma (cont)

Photo courtesy of Dr. Sharfman.
Genetic Conditions Associated With Basal Cell Carcinoma

- Gorlin syndrome (NBCCS)
- Bazex syndrome
- Rombo syndrome
- Xeroderma pigmentosum
- Unilateral basal cell nevus syndrome

NBCCS = nevoid basal cell carcinoma syndrome.
Gorlin Syndrome (NBCCS)

- Multiple BCCs (few to 1000s)
- Patients are exceedingly sensitive to ionizing radiation
- Bone cysts—odontogenic keratocysts of the jaw
- Multiple skeletal abnormalities
- Calcification of the falx cerebri
- Dysmorphic features—broad nasal root
- Plantar and palmar pits
- Medulloblastoma
- Meningioma
- Borderline intelligence
- Defects in PTCH1 gene on chromosome 9

Lo Muzio L. Orphanet J Rare Dis. 2008;3:32.
The Hedgehog (Hh) Signaling Pathway as a Therapeutic Target for Advanced or Metastatic Basal Cell Carcinoma
Hh Signaling Pathway

- Hh ligands (sonic, indian, desert) bind the transmembrane receptor PTCH1
- In the absence of ligand, PTCH1 represses activity of the transmembrane receptor SMO
- Binding of ligand to PTCH1 releases its inhibition of SMO and activates downstream Hh signaling through the activity of GLI proteins

SMO = Smoothened; GLI = glioma-associated oncogene homolog.
The Hh Signaling Pathway and Basal Cell Carcinoma

- Hh signaling regulates events during early embryogenesis, as well as the morphogenesis of specific organs and tissues, but is subsequently silenced in adult tissue
- Cancer cells can reactivate Hh signaling, resulting in tumorigenesis
- There is evidence for aberrant activation of Hh signaling in BCC
  - Gorlin syndrome is caused by germline mutations in \textit{PTCH1}\textsuperscript{1}
  - \textit{PTCH1} (loss-of-function) or \textit{SMO} (gain-of-function) mutations are present in 90% of spontaneously arising BCCs\textsuperscript{2}

Inhibition of the Hh Pathway in Advanced Basal Cell Carcinoma

- A Phase 1 trial of the oral agent vismodegib
- 33 patients with metastatic (n = 18) or locally advanced (n = 15) BCC
- 18 patients had objective response: 2 CR, 16 PR, 11 SD, 4 PD
- Median duration of response was 8.8 months
- Response rate in patients with locally advanced tumors was 60%
- Recommended Phase 2 dose was 150 mg daily
- Common side effects: fatigue, muscle spasm, hyponatremia and dysgeusia

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.
EVIRANCE BCC/SHH4476g Trial: Vismodegib for Treatment of Advanced or Metastatic Basal Cell Carcinoma

• A Phase 2 multicenter, international, nonrandomized trial of vismodegib
• 104 patients with metastatic (n = 33) or locally advanced (n = 63) BCC
• No control group: patients were given 150 mg vismodegib once daily until disease progression, unacceptable toxic effects, or discontinuation of the study
• Primary endpoint: independently assessed objective response rate

Inclusion Criteria

- Tumor size ≥10mm in diameter
- Locally invasive BC extending into underlying tissue, cartilage, bone, or nerve
- Tumor is in a location where surgery or radiation would result in significant disfigurement or loss of function
- Expected morbidity or deformity if surgery or radiation were to be performed
- Curative resection unlikely or contraindicated
- Recurrence in the same location after ≥2 surgical procedures
- Metastasis to the regional lymph nodes, lung, liver, bone

### Primary and Secondary Efficacy Endpoints Following Treatment With Vismodegib

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metastatic BCC (N = 33)</th>
<th>Locally Advanced BCC (N = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Independent review</td>
<td>Site investigators</td>
</tr>
<tr>
<td>Objective response — no. (%)</td>
<td>10 (30)</td>
<td>15 (45)</td>
</tr>
<tr>
<td>95% CI</td>
<td>16-48</td>
<td>28-62</td>
</tr>
<tr>
<td>P value</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stable disease — no. (%)</td>
<td>21 (64)</td>
<td>15 (45)</td>
</tr>
<tr>
<td>Progressive disease — no. (%)</td>
<td>1 (3)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Data missing or could not be evaluated — no. (%)</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Median duration of response — months</td>
<td>7.6</td>
<td>12.9</td>
</tr>
<tr>
<td>Median progression-free survival, based on independent review — months</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>Duration of treatment — months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>10.0</td>
<td>9.7</td>
</tr>
<tr>
<td>Range</td>
<td>0.7-16.4</td>
<td>1.1-18.7</td>
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<tr>
<td>Patients still receiving treatment — no./total no. (%)</td>
<td>19/33 (58)</td>
<td>32/71 (45)</td>
</tr>
</tbody>
</table>

Maximum Tumor Shrinkage Following Treatment With Vismodegib

**Commonly Reported Adverse Events**

<table>
<thead>
<tr>
<th>Event*</th>
<th>Any Grade</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3 or 4</th>
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</thead>
<tbody>
<tr>
<td>Muscle spasms</td>
<td>68</td>
<td>48</td>
<td>16</td>
<td>4</td>
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<tr>
<td>Alopecia</td>
<td>63</td>
<td>49</td>
<td>14</td>
<td>0</td>
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<tr>
<td>Dysgeusia</td>
<td>51</td>
<td>28</td>
<td>23</td>
<td>0</td>
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<tr>
<td>Decrease in weight</td>
<td>46</td>
<td>27</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36</td>
<td>27</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>29</td>
<td>21</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Decrease in appetite</td>
<td>23</td>
<td>14</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>16</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

*These adverse events occurred in at least 20% of all patients and were coded with the use of the Medical Dictionary for Regulatory Activities (MedDRA), version 13.1. The highest grade of event is reported for each patient.

Vismodegib in Patients With Gorlin Syndrome

• Phase 2 trial investigating the use of vismodegib in patients with Gorlin syndrome

• Patients with Gorlin syndrome randomized to receive either placebo (n = 15) or 150 mg vismodegib (n = 26) for 18 months

• Primary endpoint: reduction in the incidence of new BCCs that were eligible for surgical resection

Reduced Number of New Basal Cell Carcinomas Following Treatment With Vismodegib vs Placebo

- Common adverse events associated with vismodegib include grade 1/2 dysgeusia, muscle cramps, hair loss, and weight loss

SEB = surgically-eligible BCCs.

Future Directions in the Treatment of Basal Cell Carcinoma

• Targeting GLI1
  – GANT61

• Vitamin D3
• Arsenic Trioxide
• Itroconazole

• Other Hh pathway inhibitors: clozapine, chlorpromazine, haloperidol

Weiss G. Cancer. 2012 Apr 17 [Epub ahead of print].
Skin Squamous Cell Carcinoma
Phase II Study of Cetuximab as First-Line Single-Drug Therapy in Patients with Unresectable Squamous Cell Carcinoma of the Skin. Maubec et al. JCO Sept 2011

- N=36
- Weekly Cetuximab at Standard Dosing
- DCR = 69%
- OR in 10 patients
Representative examples of patients showing response to cetuximab.

Maubec E et al. JCO 2011;29:3419-3426
Kaplan-Meier plot of (A) overall survival and (B) progression-free survival in the intention-to-treat population and per-protocol population.

Maubec E et al. JCO 2011;29:3419-3426
Merkel Cell Carcinoma
Fig. 2. (A) Schematic of MCV genome.
Survivin is a Therapeutic Target Merkel Cell Carcinoma. Reety Arora et al. Sci Transl Med 4, 133ra56(2012)
PD-L1 Expression in the Merkel Cell Carcinoma Microenvironment: Association of Inflammation, Merkel Cell Polyomavirus, and Overall Survival.