Pediatric Melanoma Treatment Update and Clinical Trial Participation

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Pediatric Melanoma Summit
September 13, 2014
Difficult to perform melanoma trials in pediatric patients due to very low patient numbers

Table 5.1: Incidence of Melanoma in Persons Younger Than 30 Years of Age, U.S., 1975-2000

<table>
<thead>
<tr>
<th>AGE AT DIAGNOSIS (YEARS)</th>
<th>&lt;5</th>
<th>5-9</th>
<th>10-14</th>
<th>15-19</th>
<th>20-24</th>
<th>25-29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average incidence per million, 1975-2000, SEER</td>
<td>0.7</td>
<td>0.9</td>
<td>2.8</td>
<td>14.0</td>
<td>38.9</td>
<td>69.4</td>
</tr>
<tr>
<td>Average annual % change in incidence, 1975-2000, SEER</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>0.87</td>
<td>1.23</td>
<td>0.58</td>
</tr>
<tr>
<td>Estimated incidence per million, year 2000, U.S.</td>
<td>na</td>
<td>na</td>
<td>4.0</td>
<td>15.5</td>
<td>44.4</td>
<td>73.8</td>
</tr>
<tr>
<td>Estimated number of persons diagnosed, year 2000, U.S.</td>
<td>13</td>
<td>19</td>
<td>81</td>
<td>314</td>
<td>841</td>
<td>1431</td>
</tr>
</tbody>
</table>
SEER Data

- Of the very low number of pediatric patients with melanoma, only about 15% need treatment beyond surgery.
Pediatric Melanoma Treatment

• Based on trials done in adults
• A few trials allow for patients under age 18 (usually to age 16)
• Very few trials in melanoma targeting pediatric patients
# 2009 AJCC Staging

<table>
<thead>
<tr>
<th>Classification</th>
<th>Thickness (mm)</th>
<th>Ulceration Status/Mitoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Tis</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
| T1             | ≤ 1.00         | a: Without ulceration and mitosis < 1/mm²  
|                |                | b: With ulceration or mitoses ≥ 1/mm²      |
| T2             | 1.01-2.00      | a: Without ulceration      |
|                |                | b: With ulceration         |
| T3             | 2.01-4.00      | a: Without ulceration      |
|                |                | b: With ulceration         |
| T4             | > 4.00         | a: Without ulceration      |
|                |                | b: With ulceration         |
## 2009 AJCC Staging

<table>
<thead>
<tr>
<th>N</th>
<th>No. of Metastatic Nodes</th>
<th>Nodal Metastatic Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>N1</td>
<td>1</td>
<td>a: Micrometastasis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: Macrometastasis†</td>
</tr>
<tr>
<td>N2</td>
<td>2-3</td>
<td>a: Micrometastasis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: Macrometastasis†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c: In transit metastases/satellites without metastatic nodes</td>
</tr>
<tr>
<td>N3</td>
<td>4+ metastatic nodes, or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>matted nodes, or in transit metastases/satellites with metastatic nodes</td>
<td></td>
</tr>
</tbody>
</table>
### 2009 AJCC Staging

<table>
<thead>
<tr>
<th>M</th>
<th>Site</th>
<th>Serum LDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
<td>NA</td>
</tr>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous, or nodal metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Any distant metastasis</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

*JCO 2009 27(36) 6199-6206*
<table>
<thead>
<tr>
<th>Clinical Staging</th>
<th>Pathologic Staging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T</strong></td>
<td><strong>N</strong></td>
</tr>
<tr>
<td>0</td>
<td>Tis</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
</tr>
<tr>
<td>IIA</td>
<td>T2b</td>
</tr>
<tr>
<td></td>
<td>T3a</td>
</tr>
<tr>
<td>IIB</td>
<td>T3b</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
</tr>
<tr>
<td>IIC</td>
<td>T4b</td>
</tr>
<tr>
<td>III</td>
<td>Any T</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
</tr>
</tbody>
</table>
2009 AJCC Staging

JCO 2009 27(36) 6199-6206
SEER Data

- Of the very low number of pediatric patients with melanoma, only about 15% need treatment beyond surgery.
Adult Trial – ECOG1684

- Established the use of interferon in treating melanoma
- Study done prior to lymph node mapping being used to stage melanoma
Adult Trial – ECOG1684

- CS1PS1 - >4 mm
- CS1PS2 – N1 regional lymph node metastasis detected at elective lymph node dissection with clinically inapparent regional lymph node metastasis
- CS2 PS2 - clinically apparent N1 regional lymph node involvement synchronous
- CS2R - regional lymph node recurrence
Adult Trial – ECOG1684

• Randomized to observation or interferon α-2b

• IFN treatment
  – 20 MU/m²/d IV 5 days per week for 4 weeks, then
  – 10 MU/m²/d SC three times weekly for 48 weeks

JCO 1996 14(1) 7-17
Adult Trial – ECOG1684

A

RFS all patients

OS all patients

Stratified Logrank (1-sided) P-value = .0023

Stratified Logrank (1-sided) P-value = .0237

Years

Years

Time Interval

Time Interval

Group

Group

0-2

0-2

2-4

2-4

4-6

4-6

6-8

6-8

8-10

8-10

OBS

OBS

IFN

IFN

87/137

58/137

12/49

21/78

2/37

9/56

1/23

1/33

1/4

1/7

(# events/# at risk)

(# events/# at risk)
Adult Trial – ECOG1684

**RFS CS1PS1 patients**

Logrank (1-sided) P-value = 0.1211

**RFS CS1PS2 patients**

Logrank (1-sided) P-value = 0.0686

**Years**

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Group</th>
<th>0-2</th>
<th>2-4</th>
<th>4-6</th>
<th>6-8</th>
<th>8-10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OBS</td>
<td>3/15</td>
<td>1/12</td>
<td>1/11</td>
<td>1/8</td>
<td>0/0</td>
</tr>
<tr>
<td></td>
<td>IFN</td>
<td>7/16</td>
<td>1/8</td>
<td>0/7</td>
<td>0/3</td>
<td>0/1</td>
</tr>
</tbody>
</table>

**Years**

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Group</th>
<th>0-2</th>
<th>2-4</th>
<th>4-6</th>
<th>6-8</th>
<th>8-10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OBS</td>
<td>7/14</td>
<td>3/7</td>
<td>0/4</td>
<td>0/1</td>
<td>1/1</td>
</tr>
<tr>
<td></td>
<td>IFN</td>
<td>8/20</td>
<td>2/12</td>
<td>1/9</td>
<td>0/7</td>
<td>0/3</td>
</tr>
</tbody>
</table>

(# events/# at risk)

JCO 1996 14(1) 7-17
Adult Trial – ECOG1684

A

RFS CS1PS2 patients

Logrank (1-sided) P-value = .0004

Years

Time Interval

Group 0-2 2-4 4-6 6-8 8-10

--- OBS 19/21 1/2 0/1 0/1 0/0

--- IFN 12/20 2/8 0/6 0/4 0/1

(# events/# at risk)

A

RFS CS1PS2 recurrent

Logrank P-value = .0477

Years

Time Interval

Group 0-2 2-4 4-6 6-8 8-10

--- OBS 58/87 7/28 1/21 0/13 0/3

--- IFN 48/87 7/38 2/30 0/21 0/9

(# events/# at risk)
# Adult Trial – ECOG1684

## Table 6. Toxic Events by Type and Degree

<table>
<thead>
<tr>
<th>Type</th>
<th>Grade (N = 143)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Constitutional*</td>
<td>18</td>
<td>53</td>
<td>64</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>37</td>
<td>57</td>
<td>34</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>30</td>
<td>39</td>
<td>20</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Neurologic</td>
<td>31</td>
<td>47</td>
<td>33</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Worst grade/patient</td>
<td>2</td>
<td>30</td>
<td>96</td>
<td>13</td>
<td>2</td>
</tr>
</tbody>
</table>

*Worst grade of any constitutional toxicity, including fever, chill, and flu-like symptoms: fatigue, malaise, diaphoresis.*
Pediatric Trials – MEL06

- Phase II in melanoma
- Objectives
  - Response of temozolomide/PEG-IFN in unresected stage III, metastatic or recurrent
  - Safety of temozolomide/PEG-IFN in resected IIIC, unresected III, metastatic or recurrent
  - Safety/feasibility of 48 wks PEG-IFN in IIC and resected IIIA and IIIB
Pediatric Trials – MEL06

- Secondary Objectives
  - Pharmacokinetics of IFN (+/- PEG) in pedi patients
  - Pharmacokinetics of temozolomide with PEG-IFN
  - Quality of Life
  - Utility of FDG PET/CT in high risk melanoma
  - Tissue/serum banking
Pediatric Trials – MEL06

**Eligibility**

- ≤21 years of age
- Melanoma IIC (T4b), III (LN mets) or IV (mets)
- Performance Status ≥50%
- Hematologic Function: ANC ≥ 1.0 x 10⁹/L, Platelet ≥ 75 x 10⁹/L, Hgb ≥ 8.0 (transfusion permitted)
- Hepatic: Bili ≤ 1.5xULN, SGPT ≤ 3xULN, Albumin ≥ 2g/dl
- Renal: Creatine appropriate for age
- Pancreatic: Amylase & lipase ≤ 1.5xULN
Pediatric Trials – MEL06

Eligibility

- Echo: SF≥28%
- Prior Therapy Statum A – None
- Prior Therapy Stratum B – fully recovered
  - Myelosuppressive – at least 2 weeks
  - Biologics – prior biologics ok, including IFN
  - XRT at least 3 weeks
  - Growth factors – at least 1 week
Pediatric Trials – MEL06

Treatment

• Statum A (resected IIC, IIIA and IIIB)
  – IFNα-2b 20MU/m2 IV 5d/wk x 4wk
  – PEGIFNα-2b 1mcg/kg subq weekly x 48wk

• Statum B (IIIC, IV, unresected III, recurrent)
  – Up to 7 courses
  – PEGIFNα-2b 0.5mcg/kg subq weekly x 8wk
  – Temozolomide 75 mg/m2/d PO for 6 weeks
  – B1 (measurable disease) – reassess for resectability after each course, postop treatment to complete 7 courses
Pediatric Trials – MEL06

• Activation date
  – St Jude 10/2007
  – MD Anderson 3/2009
• Study closed 12/2012
• Enrollment at time of closure – 29 patients
  – St. Jude:
    • Stratum A - 17 patients
    • Stratum B1 - 2 patients
    • Stratum B2 - 3 Patient
  – MD Anderson:
    • Stratum A - 6 patients
    • Statum B2 - 1 Patient
Ipilimumab

- Ipilimumab is a medicine that helps stimulate the immune system to fight against cancer cells.
- Ipilimumab is a recombinant human IgG1 immunoglobulin monoclonal antibody which binds to the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4).
- CTLA-4 is a down-regulator of T-cell activation pathways. Blocking CTLA-4 allows for enhanced T-cell activation and proliferation.
- In melanoma, ipilimumab may indirectly mediate T-cell immune responses against tumors.
Ipilimumab Mechanism

Activation is initiated by binding of B7 molecules on the APC to CD28 receptors on the T-cell.

Inhibition results from CTLA-4 expression on the T-cell surface where it competes with CD28 for binding to B7 on APCs.

Potentiation of T-cell proliferation achieved by CTLA-4 inhibition using ipilimumab, an anti-CTLA-4 monoclonal antibody.

MHC = major histocompatibility complex; APC = antigen presenting cell; TCR = T-cell receptor; CTLA-4 = cytotoxic T lymphocyte-4
Trials - Ipdilimumab

Figure 2: Kaplan-Meier estimate for overall survival, by treatment arm

Lancet Oncol 2010 11(1) 155-64
# Trials - Ipilimumab

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab 0-3 mg/kg (n=72)</th>
<th>Ipilimumab 3 mg/kg (n=71)</th>
<th>Ipilimumab 10 mg/kg (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall serious adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>35</td>
<td>38</td>
</tr>
<tr>
<td>Grade 5</td>
<td>15</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Drug-related</td>
<td>6</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Drug-related (grade 5)</td>
<td>0</td>
<td>0*</td>
<td>0</td>
</tr>
<tr>
<td><strong>Adverse events leading to discontinuation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Drug-related (any grade)</td>
<td>2</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Drug-related (grade 3-4)</td>
<td>2</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>
Pediatric Trials - Ipilimumab

- A phase II trial looking at ipilimumab in children.
- Advanced melanoma that cannot be removed with surgery.
- Ipilimumab is already FDA approved for use in treating adults with melanoma.
- Open at multiple sites in the United States and throughout the world.
Pediatric Trials - Ipilimumab

• Primary Outcome Measures:
  – Overall Survival Rate at 1-Year
  – Severe Immune-mediated Adverse Events (imARs) rate 1-Year

• Secondary Outcome Measures:
  – Disease Control Rate (DCR) at 1-Year
    • DC is defined as a best overall response of Complete Response (CR), Partial Response (PR), or Stable Disease (SD)
  – Progression-Free Survival (PFS) at 1-Year
  – Best Overall Response Rate (BORR) at 1-Year
Pediatric Trials - Ipilimumab

- **Inclusion Criteria:**
  - 12 < 18 years of age
  - Previously treated or untreated, unresectable Stage III or Stage IV malignant melanoma
  - Karnofsky Performance Status (KPS) or Lansky Score ≥ 50

- **Exclusion Criteria:**
  - Primary Ocular Melanoma
  - Prior therapy with a Cytotoxic T Lymphocyte Antigen 4 (CTLA-4) or Programmed death-1 (PD-1) antagonist, or Programmed cell death- ligand 1 (PD-L1) or CD137 agonists
  - Symptomatic brain metastases
  - History of autoimmune diseases
Pediatric Trials - Ipilimumab

- Ipilimumab
  - 3 mg/Kg solution by Intravenous (IV) once every 3 weeks for 4 doses, then
  - every 12 weeks until progression of disease or unacceptable toxicity
Pediatric Trials - Ipilimumab

- Diarrhea
- Nausea and vomiting
- Itching and/or rash
- Fatigue
- Colitis
- Immune related
  - GI/liver
  - Endocrine
  - Skin
Pediatric Trials - Ipilimumab

Recruitment – estimated 30 patients

• Started - November, 2012
• Planned End – July, 2017
Vemurafenib

- Vemurafenib is a type of biologic therapy called a BRAF inhibitor.
- BRAF is a protein that sends signals to cells telling them to divide and grow.
- Blocking BRAF may stop cancer cells growing.
- Certain changes in the BRAF gene cause a change in the BRAF protein that can increase the growth and spread of cancer cells.
Trials - Vemurafenib

Figure 3: Progression-free survival (randomised population; censored at crossover) for patients randomly assigned to vemurafenib or to dacarbazine (cutoff Feb 1, 2012)

Lancet Oncol 2014 15(3) 323-32
Figure 2: Overall survival (randomised population; censored at crossover) for patients randomly assigned to vemurafenib or to dacarbazine (cutoff Feb 1, 2012)
## Trials - Vemurafenib

<table>
<thead>
<tr>
<th></th>
<th>Dacarbazine (n=287)</th>
<th></th>
<th>Vemurafenib (n=337)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Grade 1-2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>8 (3%)</td>
<td>3 (1%)</td>
<td>..</td>
<td>169 (50%)</td>
<td>20 (6%)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (2%)</td>
<td>..</td>
<td>..</td>
<td>108 (32%)</td>
<td>30 (9%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>94 (33%)</td>
<td>6 (2%)</td>
<td>..</td>
<td>146 (43%)</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>13 (5%)</td>
<td>..</td>
<td>..</td>
<td>124 (37%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Increase in LFTs</td>
<td>16 (6%)</td>
<td>6 (2%)</td>
<td>..</td>
<td>83 (25%)</td>
<td>35 (10%)</td>
</tr>
<tr>
<td>Cutaneous squamous-cell carcinoma</td>
<td>..</td>
<td>2 (&lt;1%)</td>
<td>..</td>
<td>..</td>
<td>65 (19%)</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>..</td>
<td>2 (&lt;1%)</td>
<td>..</td>
<td>3 (&lt;1%)</td>
<td>34 (10%)</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>1 (&lt;1%)</td>
<td>..</td>
<td>..</td>
<td>94 (28%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>123 (43%)</td>
<td>5 (2%)</td>
<td>..</td>
<td>121 (36%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8 (3%)</td>
<td>17 (6%)</td>
<td>9 (3%)</td>
<td>1 (&lt;1%)</td>
<td>..</td>
</tr>
<tr>
<td>New primary melanoma</td>
<td>..</td>
<td>..</td>
<td>..</td>
<td>2 (&lt;1%)</td>
<td>6 (2%)</td>
</tr>
</tbody>
</table>

Data are number of patients (%). LFT = liver function test.

*Table 4: Summary of selected adverse events in treated patients (safety population)*
BRIM-P

- A phase I trial looking at vemurafenib (Zelboraf), also known as RO5185426, in children
- Advanced melanoma that cannot be removed with surgery.
- Vemurafenib is already FDA approved for use in treating adults with melanoma.
- Open at multiple sites in the United States and throughout the world.
The aims of this study are to find out

- The best dose of vemurafenib to give
- How well it works
- About the side effects
- What happens to vemurafenib in the body
- How quickly the body gets rid of it
BRIM-P

Eligibility Criteria

• Between 12 and 17 years old
• Stage 3C or 4 melanoma that cannot be removed with surgery
• Melanoma cells with the BRAF gene change
• Melanoma that can be measured by CT or MRI
• Are well enough to be up and about for at least half the day, performance status 60-100%
• Have fully recovered from any surgery
• Able to swallow tablets
• Willing to use reliable contraception during treatment and for 6 months afterwards if sexually active and there is any chance that you or your partner could become pregnant
BRIM-P

Exclusion Criteria

• Chemotherapy, biological therapy, biological therapy, radiotherapy or surgery in the last 2 weeks
• Melanoma that has spread to the brain or spinal cord and is causing you problems
• Still have any side effects from previous treatment
• Radiotherapy to your head, spine or the area between your hips (pelvis) in the last 3 months
• Prior treatment with vemurafenib
• Prior treatment with a BRAF Inhibitor or MEK inhibitor, unless it was sorafenib
This study is in two parts. Everyone taking part will take vemurafenib tablets daily.

People in the 1st part of the study will have the lowest dose of vemurafenib. If they don’t have any serious side effects, the next people will have a higher dose, and so on, until they find the best dose to give. This is called a dose escalation study.

In the 2nd part of the study everyone will have the best dose of vemurafenib found in the first part.

Vemurafenib tablets can be taken for as long as they are helping.
BRIM-P

Tests before treatment include

• Blood tests
• Physical examination
• Heart trace (ECG)
• Urine tests
• CT or MRI scan
• PET scan
• Skin examination
• Having a sample of tissue taken (biopsy)
Tests done often while on treatment include

- CT scans or MRI scans every 8 weeks for a year and then every 12 weeks until the cancer gets worse.
- PET scan after 8 weeks of treatment.
- After a participant stops taking vemurafenib they see the trial team 30 days later for a physical examination and blood tests. The trial team will then contact them every 3 months to see how they are.
The most common side effects of vemurafenib:

- Hair loss
- Feeling or being sick
- Tiredness (fatigue)
- Increased sensitivity to sun light
- Aching joints and muscle pain
- Rash
- Itchy skin
- Diarrhea
- Changes in your skin including skin tags or thickening of the skin
- Non harmful skin cancers, including squamous cell and basal cell cancers happen in about 25%
BRIM-P

Recruitment
• Started - December 22, 2011
• Planned End – April 30, 2015

Enrollment
• Recently enrolled 6th patient