Threshold of Credibility: A New Approach to Product Development for Metastatic Melanoma Therapy

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The Challenge

- Metastatic melanoma is a disease with an invariably fatal outcome in the absence of effective treatment. Only two therapies have been licensed by the FDA: dacarbazine and IL-2. To foster development of new therapeutics for metastatic melanoma, we have reviewed the data submitted for licensure with the intention of suggesting efficient models for pre-trial planning and trial design and to create model pathways for product development.
Patients in Clinical Trials that supported approval of IL-2 for melanoma

<table>
<thead>
<tr>
<th>Trial number</th>
<th>0524</th>
<th>0097</th>
<th>0053</th>
<th>0094</th>
<th>0063</th>
<th>70002</th>
<th>0170</th>
<th>29106</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number in study</td>
<td>28</td>
<td>84</td>
<td>32</td>
<td>3</td>
<td>9</td>
<td>45</td>
<td>64</td>
<td>5</td>
<td>270</td>
</tr>
<tr>
<td># CR</td>
<td>2</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td># PR</td>
<td>2</td>
<td>8</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>CR in % (95% CI)</td>
<td>7 (0.8–23.5)</td>
<td>7 (2.7–14.9)</td>
<td>6.4 (0.8–20.8)</td>
<td>0 (0–70.8)</td>
<td>0 (0–33.6)</td>
<td>11 (2.6–17.3)</td>
<td>2 (0.06–11.7)</td>
<td>20 (0.06–11.8)</td>
<td>6 (3.9–9.8)</td>
</tr>
<tr>
<td>PR in % (95% CI)</td>
<td>7 (0.8–23.5)</td>
<td>10 (4.2–17.9)</td>
<td>9.6 (2–25)</td>
<td>0 (0–70.8)</td>
<td>11 (0.3–48.3)</td>
<td>13 (3.5–19.3)</td>
<td>8 (3.7–24)</td>
<td>20 (3.7–24.1)</td>
<td>10 (6.7–13.7)</td>
</tr>
<tr>
<td>OR in % (95% CI)</td>
<td>14</td>
<td>17</td>
<td>16</td>
<td>0</td>
<td>11</td>
<td>17</td>
<td>13</td>
<td>40</td>
<td>16 (12–20.1)</td>
</tr>
</tbody>
</table>
The Observation

- Both empiric evidence and statistical analysis of pivotal trials leading to oncology product approvals have shown that, to obtain licensure, the intended clinical effect should be achieved in a minimum of 20-30 experimental subjects. We term this number the threshold of credibility.
The Concept

- The design and size of studies required to establish the threshold of credibility depend upon the endpoint selected and the activity of the regimen. To demonstrate clinical benefit, a sponsor should plan to show that at least 20-30 subjects in the same treatment arm of a clinical trial achieve a clinically meaningful endpoint.
95% Confidence Limits for 25 Patients with Clinical Effect

Value (%) vs. # of Patients
Hypothetical Staged Analyses of a Confirmatory Efficacy Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Analysis 1</th>
<th>Analysis 2</th>
<th>Analysis 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation</td>
<td>Response Rate</td>
<td>Progression</td>
<td>Overall Survival</td>
</tr>
</tbody>
</table>
Melanoma Proposal

- Resolution of cutaneous lesions could be considered clinical benefit
- Progression free survival and overall survival could be sequential endpoints in the same study
General Development Schema

Development of Specific Bioassay

Dose exploration for toxicity and biological effect. Expand cohort at effective biological dose to 20 patients

Efficacy exploratory studies in selected populations

Confirmatory efficacy study or studies with 25 patients in the same study at a single dose and on the same treatment regimen showing the same clinical effect
The Possibility

- Rapid development leading to a “go or no go” decision and recognition of potential based on accepted methodologies will not only conserve resources and reduce ambiguity, but also will provide a credible response to the urgency required by the current state of treatment for metastatic melanoma and the needs of melanoma patients and their care providers.
The Result

- Use of an integrated development plan and a threshold approach to trial design could shorten development time and conserve resources in addressing the urgent need for new therapies.