Immunologic Therapy with Cadi-05 for the Treatment of Advanced Melanoma

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Background
- Cadi-05 is a heat-killed mycobacterial preparation with immunomodulatory properties.
- As a Toll-like receptor agonist, Cadi-05 has been postulated to have antineoplastic activity.

Purpose
- The primary objective of this study was to evaluate the safety and toxicity of Cadi-05 monotherapy in the treatment of advanced melanoma patients.

Experimental Design
- 12 patients with stage IV melanoma and measurable disease were treated with one, two, or three 8-week cycles of intradermal Cadi-05.
- Patient demographics are represented in Table 1 and clinical characteristics in Table 2.
- Patients who tolerated treatment without severe adverse events and did not progress were eligible to receive a maximum of three cycles.
- Clinical and translational endpoints were assessed at baseline and after each cycle.

Table 1. Demographics

<table>
<thead>
<tr>
<th>Demographic</th>
<th>No. of Patients</th>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>50</td>
<td>Median (range)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Sex</td>
<td>50</td>
<td>M</td>
<td>50</td>
<td>F</td>
</tr>
<tr>
<td>Weight</td>
<td>50</td>
<td>70-90 lbs</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 2. Clinical Characteristics

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>No. of Patients</th>
<th>Median (range)</th>
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</thead>
<tbody>
<tr>
<td>Prior Therapy</td>
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<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy/Targeted Therapy</td>
<td>50</td>
<td></td>
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<tr>
<td>Surgery</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Interferon</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Resection/debulking</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Gamma knife</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Amputation</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Other therapies</td>
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</tr>
</tbody>
</table>

Results
- Ten of 12 patients enrolled completed at least one cycle of treatment; two patients who failed to complete a single cycle did so because of complications related to disease progression.
- One patient experienced grade 3 toxicity related to treatment; no other patients had grade 3 or higher toxicity.
- There were no objective clinical responses.
- Mixed responses were observed in some patients with regression of one or more lung lesions despite progression elsewhere (Fig. 1).
- One patient developed vitiligo of the treated extremity (Fig. 2). Median follow-up was 6.5 months. Mean survival was 11.9 months (95% CI [5.8, 18.0]), and median survival was 6.7 months (95% CI [3.5, 10.0]).
- Prolonged survival was noted in patients who underwent prior high dose IL-2 treatment (20.7 months 95% CI [10.225, 31.082] versus 5.6 months 95% CI [3.90, 7.38], p = 0.03) (Fig. 3).
- Seven evaluable patients exhibited a decrease in CD4+FoxP3+ regulatory T cell frequency following one cycle of treatment (Fig. 4).

Conclusions
- Cadi-05 is well tolerated in patients with advanced melanoma, but no objective responses were observed in this small single-arm study.
- Cadi-05 appears to decrease regulatory T cell frequency and thus may have desirable immunologic effects as an adjuvant agent in the treatment of advanced melanoma.

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