A randomized pilot trial evaluating safety and immunogenicity of recMAGE-A3 + AS15 immunotherapeutic administered by intramuscular versus intradermal/subcutaneous routes

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Introduction
The recMAGE-A3 protein has been administered intramuscularly (IM) with immunostimulant AS15 as an experimental immunotherapeutic. AS15 contains 3-O-desacyl-4′-monophosphoryl lipid A (MPL), QS-21, CpG 7909 and liposome. This MAGE-A3/AS15 immunotherapeutic has not been studied for intradermal (ID) or subcutaneous (SC) use. A clinical trial (NCT01425749) was initiated to test the hypotheses that ID/SQ administration is safe and may induce CD4+ and CD8+ T cell responses to MAGE-A3.

Patients and methods
Twenty-five eligible patients with resected stage IIB-IV MAGE-A3+ melanoma were randomized to 2 arms, treated with MAGE-A3/AS15 Immunotherapeutic IM (Arm A, n = 13) or ID/SC (Arm B, n = 12). Adverse events (CTCAE 4) were recorded. Antibody (Ab) responses to MAGE-A3 protein were assessed by ELISA assay. T cell responses were assessed by flow cytometry after intracellular cytokine staining (ICS) for multifunctional CD4+ and CD8+ responses to overlapping MAGE-A3 peptides, assaying lymphocytes from peripheral blood (PBMC) and sentinel immunized node (SIN), after one in vitro stimulation.

Results
In both arms, the recMAGE-A3/AS15 immunotherapeutic was well-tolerated, with only one grade 3 treatment-related adverse event (hyperglycemia, Arm B), and no grade 4 or 5 events. Grade 2 injection site reactions were observed in 10 patients in Arm A and 7 in Arm B (P > 0.3). Ab responses were detected in all patients, most with high titers persisting at least 6 months, without difference between arms. Preliminary T cell data are that multifunctional (IFNg and TNFα) CD4+ T cell responses to MAGE-A3 were detected in 64% of patients (54% A; 75% B; Table 1). Multifunctional CD8+ T cell responses were evident in 20% of patients (8% A, 33% B). CD4+ responses were higher magnitude in SIN than in PBMC.

Conclusion
Safety profiles were comparable for ID/SC and IM administration of the MAGE-A3/AS15 immunotherapeutic, which induced high-titer Ab, multifunctional CD4+ Th1 responses, and CD8+ responses when administered by either route. Immune responses were more readily detected in the SIN than in PBMC. These pilot data

<table>
<thead>
<tr>
<th>Arm</th>
<th>% of CD4+ T cells (90% CI)</th>
<th>% of CD8+ T cells (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIN</td>
<td>31% (11, 58)</td>
<td>0% (0, 21)</td>
</tr>
<tr>
<td>PBMC</td>
<td>31% (11, 58)</td>
<td>8% (0, 32)</td>
</tr>
<tr>
<td>Either</td>
<td>54% (29, 78)</td>
<td>8% (0, 32)</td>
</tr>
<tr>
<td>SIN</td>
<td>64% (35, 86)</td>
<td>18% (7, 53)</td>
</tr>
<tr>
<td>PBMC</td>
<td>50% (25, 75)</td>
<td>25% (7, 53)</td>
</tr>
<tr>
<td>Either</td>
<td>75% (47, 93)</td>
<td>33% (12, 61)</td>
</tr>
<tr>
<td>Total</td>
<td>46% (28, 64)</td>
<td>16% (6, 33)</td>
</tr>
<tr>
<td>40%</td>
<td>64% (24, 58)</td>
<td>20% (8, 38)</td>
</tr>
<tr>
<td>64%</td>
<td>48% (46, 80)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 Multifunctional (IFNg and TNFα) T cell responses to MAGE-A3

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support further investigation of ID/SC immunization with antigen plus AS15 to support Th1 CD4+ responses and CD8+ responses. Production of Th1 cytokines IFNγ and TNFα suggests the induced CD4+ responses may support CD8+ T cells. Other forms of antigen (e.g.: long peptides) may further support induction of CD8+ T cell responses in combination with AS15.

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