IMMUNOGENICITY AND CLINICAL EFFICACY OF A HI-8™ PRIMEBOOST THERAPEUTIC VACCINE IN STAGE III/IV MELANOMA PATIENTS IN A PHASE I/II TRIAL

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Hi-8™ MEL: Melanoma Therapeutic Vaccine

“Prime”
DNA vaccine

“Boost”
MVA viral vector

Melanoma Epitope String

HLA restriction:
A2 A2 A2 A1 A2 A1 A2

Epitope:
Tyros (1 – 9)
Melan-A Analogue (26 - 35)
MAGE-3 (168 – 176)
MAGE-3 (271 -279)
NY-ESO-1 (155-167)

Melan-A Analogue (26 - 35)
Tyros (369 – 377)
MAGE-1 (161 – 169)
Treatment Protocol

41 stage III/IV patients (UK and Germany) sequentially enrolled to 7 treatment groups

<table>
<thead>
<tr>
<th>Regimen</th>
<th>DDMM</th>
<th>DMM</th>
<th>MMMM</th>
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</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>8</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td><strong>DNA.Mel3 (i.m.)</strong></td>
<td>2mg</td>
<td>2mg</td>
<td>2mg</td>
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<tr>
<td><strong>MVA.Mel3 (i.d.)</strong></td>
<td>5x10^7</td>
<td>2x10^8</td>
<td>5x10^8</td>
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<tr>
<td></td>
<td>4mg</td>
<td>4mg</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>5x10^7</td>
<td>1x10^9</td>
<td>1x10^9</td>
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</tbody>
</table>

Vaccines administered 3 weeks apart

Additional MVA.Mel3 boosts given at weeks 16 and 24
Study Endpoints

- **Immunogenicity**
  - Melan-A epitope response by *ex vivo* Tetramer assay
  - All epitopes by *ex vivo* IFN-γ ELISPOT assay
  - Anti-MVA antibody by ELISA

- **Clinical response**
  - Tumour response (RECIST criteria)
  - Time-to-progression
  - Overall survival (to 12 months)

- **Safety and Tolerability**
Immune Response (Frequency)

Melan-A Specific CD8 Tetramer & ELISPOT Responders
Average Melan-A Tetramer Response

DDMM

DMM

MVA Only
Patient 047: Multi-Epitope Response

**Tetramer- Melan A**

- % Tet+/CD8+
- 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13

**ELISPOT- Melan A**

- SFC/million PBMC
- 0, 500, 1000, 1500

**ELISPOT- All Epitopes**

- SFC/million PBMC
- NC, Tyr-L, Tyr-Int, MAGE-3 (A1), MAGE-3 (A2), MAGE-1, NY-ESO-1

Assay Cut-off
Patient 033: Melan-A Response
Patient 033: CCR7 / CD45RA Phenotyping

CD45RA / CCR7 Phenotyping of Tet+ CD8+ T cells

% T cell subset

Week

SFC / million PBMC

% Tet+ CD8+ PBMC

memory
effmem
effector
naive

ELISPOT
Tetramer

Week
Tumour Responses

- 1 PR > 24 months
- 7 SD ≥ 6 months
- Tumour responses evident in subjects with all stages and sites of disease
- Tumour responses only seen following Hi-8™ PrimeBoost
- No tumour responses after MVA alone
- 87% of tumour responses were associated with immune response
Patient 033: Tumour Response

<table>
<thead>
<tr>
<th>Week</th>
<th>8</th>
<th>16</th>
<th>24</th>
<th>28</th>
<th>40</th>
<th>48</th>
<th>56</th>
<th>64</th>
<th>72</th>
<th>108</th>
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<tbody>
<tr>
<td>Δ LDsum</td>
<td>-15%</td>
<td>-25%</td>
<td>-30%</td>
<td>-30%</td>
<td>-37%</td>
<td>-37%</td>
<td>-48%</td>
<td>-52%</td>
<td>-48%</td>
<td>-51%</td>
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</tbody>
</table>

Baseline

Week 72

SFC/million PBMC

% Tet+ CD8+ PBMC

ELISPOT

Tetramer
Time-to-Progression: Immune Responders

Evaluation of survival distribution function showing the progression of patients over time. The graph demonstrates a statistically significant difference between immune responders and non-responders, with a p-value of 0.037. The evaluable per protocol population is 34, excluding the MVA alone treatment arm of 5 patients.

- **Hi-8™ MEL Responders (N=20)**
- **Hi-8™ MEL Non Responders (N=9)**

The graph indicates a higher survival rate for immune responders compared to non-responders, with the progression rate peaking at weeks 8 and 16.
Survival Analysis

- Median survival for stage III/IV tetramer responders was 86 weeks compared to 37 weeks for non-responders \((p<0.001)\).
- Median survival for stage IV tetramer responders was 82 weeks \((p<0.001)\).
Conclusions

• Immune response
  - 91% Melanoma-specific immune responders at highest dose
  - Multi-epitope responses in 3 subjects
  - Effector Memory response after treatment
  - Multiple MVA boosts effective

• Tumour responses associated with immune responses

• Immune responders → survival benefit

• Hi-8™ MEL to be evaluated in a Phase III clinical trial
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