Immunological correlates of long-term survival in melanoma patients

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(SITC, N. Bethesda, 051111)
Presenter Disclosure Information

Graham Pawelec

The following relationships exist related to this presentation:

No Relationships to Disclose
Detection of antigen-reactive T-cells

- PBMC/PBL collected from stage IV melanoma patients, cryopreserved
- Day 0: Stimulate cells in vitro with selected candidate target antigens (overlapping peptides, PepMix)
- Day 4: IL-2 added to cultures
- Day 12: Restimulate with CFSE-stained autologous PBMCs/PBLs as APC, and PepMixes in the presence of Brefeldin A
Assay readout: intracellular cytokine staining (ICS)

Response defined as Pro-inflammatory: IFN-γ, TNF, IL-2, IL-17
Anti-inflammatory: IL-4, IL-10

e. g. NY-ESO-1
Pilot RNA vaccination trial (Garbe & Weide, Dermatology, Tübingen)

<table>
<thead>
<tr>
<th>Pat. ID</th>
<th>Stage at start</th>
<th>Survival (month)</th>
<th>NY-ESO-1</th>
<th>Survivin</th>
<th>MAGE-A3</th>
<th>Melan-A</th>
<th>NY-ESO-1 Expression</th>
<th>Pre Vacc response</th>
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</thead>
<tbody>
<tr>
<td>#10</td>
<td>IV M1c</td>
<td>5</td>
<td>pro</td>
<td>pro</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>#14</td>
<td>IIIc</td>
<td>5</td>
<td></td>
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<tr>
<td>#9</td>
<td>IIIb</td>
<td>8</td>
<td></td>
<td>pro</td>
<td></td>
<td>x</td>
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<tr>
<td>#3</td>
<td>IIIb</td>
<td>10</td>
<td></td>
<td>anti</td>
<td>pro</td>
<td>x</td>
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<td>#12</td>
<td>IV M1c</td>
<td>17</td>
<td>pro</td>
<td>pro</td>
<td>pro</td>
<td>pro</td>
<td></td>
<td></td>
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<tr>
<td>#2</td>
<td>IV M1a</td>
<td>19</td>
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<td>pro</td>
<td></td>
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<td></td>
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<td>#4</td>
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<td></td>
<td>pro</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>#11</td>
<td>IV M1c</td>
<td>23</td>
<td></td>
<td>pro</td>
<td>pro</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#7</td>
<td>IV M1c</td>
<td>24</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>#1</td>
<td>IV M1a</td>
<td>&gt;25</td>
<td></td>
<td>pro</td>
<td>pro</td>
<td>pro</td>
<td>x</td>
<td></td>
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<tr>
<td>#6</td>
<td>IV M1c</td>
<td>&gt;31</td>
<td></td>
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<tr>
<td>#5</td>
<td>IV M1a</td>
<td>&gt;32</td>
<td>pro + anti</td>
<td>pro + anti</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
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### Pilot trial, ipilimumab, (Garbe & Weide, Dermatology, Tübingen)

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>sex</th>
<th>CMV</th>
<th>Substage at onset</th>
<th>NY-ESO-1</th>
<th>Melan-A</th>
<th>MAGE-A3</th>
<th>Survivin</th>
<th>Survival in stage IV</th>
<th>Response</th>
<th>CTLA4</th>
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<tbody>
<tr>
<td>GFI</td>
<td>53</td>
<td>f</td>
<td>neg</td>
<td>M1c</td>
<td>pro</td>
<td></td>
<td></td>
<td></td>
<td>&gt; 7 years (NED)</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>UST</td>
<td>41</td>
<td>m</td>
<td>pos</td>
<td>M1c</td>
<td>pro</td>
<td></td>
<td></td>
<td></td>
<td>&gt; 3 years (NED)</td>
<td>MR</td>
<td>(finally tumorfree after surgery, chemotherapy)</td>
</tr>
<tr>
<td>HKR</td>
<td>63</td>
<td>f</td>
<td>neg</td>
<td>M1c</td>
<td>pro</td>
<td>pro</td>
<td></td>
<td></td>
<td>&gt; 5 years (NED)</td>
<td>SD</td>
<td>(finally tumorfree after surgery)</td>
</tr>
<tr>
<td>WHA</td>
<td>66</td>
<td>m</td>
<td>pos</td>
<td>M1c</td>
<td>pro + anti</td>
<td>pro</td>
<td></td>
<td></td>
<td>&gt; 3 years (NED)</td>
<td>CR</td>
<td></td>
</tr>
<tr>
<td>HSE</td>
<td>70</td>
<td>m</td>
<td>neg</td>
<td>M1c</td>
<td>pro + anti</td>
<td></td>
<td></td>
<td></td>
<td>&gt; 3 years (NED)</td>
<td>MR</td>
<td>(finally tumorfree after surgery)</td>
</tr>
</tbody>
</table>
Long-term survivors: Retrospective - Good Clinical outcome

Diagnosis: Stage IV, M1c
< any treatment >
>24 months

Usual patients:
Diagnosis: Stage IV, any substage
< any treatment >

No control for the LTS, more the mean situation in melanoma patients
Percentages of patients with TAA-specific T-cells in each group

L = Long-term survivors n=15
C = Control patients n=48 for NY-ESO and MAGE-A3, 35 for Melan-A and 30 for Survivin

Fraction of patients with T-cells against >1 TAA:

- NY-ESO: p=0.01
- Melan-A: p=0.0001
- MAGE-A3: p=0.2
- Survivin: p=0.17

(Zelba, 2010)
maybe you should delete this slide. the control patients are actually the prospective samples. so we see the same (but with more patients) on slide 10 and 12! you can show the right graph...

Henning, 5/1/2011
### Summary retrospective and prospective analyses

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Male</th>
<th>NY-ESO-1</th>
<th>Melan A</th>
<th>MAGE A3</th>
<th>Survivin</th>
<th>Influenza</th>
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</thead>
<tbody>
<tr>
<td><strong>Retrospective Long term survivors</strong></td>
<td>n=26</td>
<td>57</td>
<td>64%</td>
<td>62%</td>
<td>48%</td>
<td>68%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Prospective good (&gt;18 months survival)</strong></td>
<td>n=19</td>
<td>50</td>
<td>57%</td>
<td>63%</td>
<td>47%</td>
<td>69%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>Prospective middle (6-18 months survival)</strong></td>
<td>n=24</td>
<td>58</td>
<td>79%</td>
<td>38%</td>
<td>26%</td>
<td>63%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>Prospective bad (&lt;6 months survival)</strong></td>
<td>n=23</td>
<td>49</td>
<td>67%</td>
<td>13%</td>
<td>17%</td>
<td>42%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*(Zelba 2011)*
Significant association between survival of unresectable stage IV patients and the presence of T cells responding to NY-ESO-1 or Melan-A peptides
But no significant association between survival of unresectable stage IV patients and the presence of T cells responding to MAGE-A3 or survivin
Survival of patients possessing T cells responding to NY-ESO-1 and/or Melan-A

A

Melan-A or NY-ESO-1

Cum. survival probability

Follow up (years)

Specific T cells present (n=47)
Specific T cells absent (n=30)

p < 0.001
Survival according to type of response

NY-ESO-1

- Pro-inflammatory only
- Both pro- and anti-inflammatory

p=0.5768
Survival according to type of response

Pro-inflammatory only

Both pro- and anti-inflammatory

p=0.0463
Preponderance of CD4 and CD8 responses to NY-ESO-1 and Melan-A differs
Only CD8 cell reactivity to Melan-A correlates with survival

\[ p = 0.0249 \]
Both CD4 and CD8 reactivity to NY-ESO-1 correlate equally well with survival.
Conclusions

Prospective studies show that an unopposed pro-inflammatory CD4 or CD8 T cell response to NY-ESO-1 is associated with long-term survival in stage IV melanoma.

Only CD8 T cell responses to Melan-A are associated with extended survival.

No associations with survival are seen for any responses to MAGE-A3 or survivin.
Acknowledgements

Center for Medical Research
Waldhornlestr. 22
Derendingen

Center for Medical Research
Evelyna Derhovanessian
Valeria Pellicano
Lilly Oettinger
Karin Hähnel
Graziella Rubino
Iftikhar Alam Khan
Chris Shipp
David Goldeck
Nicole Janssen

Funding: EU, DFG

University of Nijmegen
Jolanda de Vries

University of Siena
Michele Maio

University of Essen
Dirk Schadendorf

University of Michigan
Allison Aiello
Sandro Galea

University of Surrey
Hardev Pandha

University of Tübingen
Claus Garbe
Benjamin Weide

Leuven University
Hans Wildiers

University of Copenhagen
Per thor Straten

University Hospital Sofia
Elissaveta Naumova