Tumor-Specific Peptide Vaccination in Newly Diagnosed Patients with GBM

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Epidermal Growth Factor Receptor Mutation

Wild Type Amino Acid Sequence
LEU-GLU-GLU-LYS-LYS-VAL-CYS-...-PRO-ARG-ASN-TYR-VAL-VAL-THR-ASP-HIS

Wild Type cDNA Sequence
CTG-GAG-GAA-AAG-AAA-GTT-TGC-...-CCC-CGT-AAT-TAT-GTG-GTG-ACA-GAT-CAC

Variant III Amino Acid Sequence
LEU-GLU-GLU-LYS-GLY-ASN-TYR-VAL-VAL-THR-ASP-HIS

Variant III cDNA Sequence
CTG-GAG-GAA-AAG-AAA-GGT-AAT-TAT-GTG-GTG-ACA-GAT-CAC

PEP-3
Glioblastoma Multiforme (GBM)

- GBM is the most aggressive and common primary malignant brain tumor in adults characterized by diffuse infiltration of the brain parenchyma.

- Newly diagnosed GBM patients treated with radiation and temozolomide have a time to progression and median survival of 6.9 and 14 months respectively¹.

- The expression of epidermal growth factor receptor variant III (EGFRvIII) does not impact median survival (12.8 months)².

- EGFRvIII is expressed on 30-50% of GBM²,³.

³ Liu et al., Journal of Molecular Medicine, 83(11):917-926, 2005.
Patient Selection

**Inclusions**
- Newly Diagnosed Glioblastoma Multiforme
- Karnofsky $\geq 80$
- s/p gross total resection (95% volumetric)
- s/p XRT $\pm$ temozolomide
- No evidence of progression on MRI post XRT
- EGFRvIII expression

**Exclusions**
- Hepatitis B serology positive
- Pregnancy
- Corticosteroids (above physiologic levels)
- Leptomeningeal Disease
- Autoimmune Disorder
- Immunosuppressive Disease
- Severe Intercurrent medical conditions
ACTIVATE Trial

Leukapheresis

Saline + GM-CSF
(Every 2 weeks i.d.)

Randomize

PEPvIII-KLH + GM-CSF
(Every 2 weeks i.d.)

PEPvIII-KLH + GM-CSF
(Every 1 month i.d.)

Immunologic Monitoring

6000 cGy
## Toxicity

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reaction/Urticaria</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>Leukoencephalopathy with radiographic changes</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Surface Area (sq-cm) Skin Reaction**

**Days After Vaccine Injection**

**Vaccine Injection Reaction Area**
Immunological responses: Vaccination results in the induction of CD8+γ-IFN EGFRvIII T cells
Immunological Responses: Vaccination results in the induction of EGFRvIII-specific humoral responses

P < 0.0001

P = 0.00015

38%

P = 0.0008
### Immunological Responses: Delayed-type hypersensitivity reactions

<table>
<thead>
<tr>
<th></th>
<th>Pre-Vaccination</th>
<th>Post-Vaccination</th>
<th>3-Months</th>
<th>6-Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida</td>
<td>25%</td>
<td>50%</td>
<td>64%</td>
<td>75%</td>
</tr>
<tr>
<td>Trichophyton</td>
<td>10%</td>
<td>25%</td>
<td>29%</td>
<td>17%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>25%</td>
<td>70%</td>
<td>100%</td>
<td>58%</td>
</tr>
<tr>
<td>PEP-3</td>
<td>0%</td>
<td>0%</td>
<td>7%</td>
<td>15%</td>
</tr>
<tr>
<td>KLH</td>
<td>0%</td>
<td>35%</td>
<td>47%</td>
<td>62%</td>
</tr>
</tbody>
</table>

**Image:**
- KLH: Key Lever Hypersensitivity
- Candida: Positive Response
- Trichophyton: Positive Response
- Tetanus: Positive Response
- PEP-3: Negative Response
- KLH: Negative Response
## Demographic characteristics of patients with glioblastoma multiforme treated with the EGFRvIII peptide vaccination and the historical cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EGFRvIII vaccine group</th>
<th>Historical cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, N</td>
<td>23</td>
<td>39</td>
</tr>
<tr>
<td>Sex, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>16 (70)</td>
<td>21 (54)</td>
</tr>
<tr>
<td>F</td>
<td>7 (30)</td>
<td>18 (46)</td>
</tr>
<tr>
<td>Age, years, Median (range)</td>
<td>52 (29-73)</td>
<td>59 (31-82)</td>
</tr>
<tr>
<td>KPS score, Median (range)</td>
<td>91 (80-100)</td>
<td>90 (70-100)</td>
</tr>
<tr>
<td>EGFRvIII expression, N (%)</td>
<td>23 (100)</td>
<td>39 (100)</td>
</tr>
<tr>
<td>Radiation, N (%)</td>
<td>23 (100)</td>
<td>39 (100)</td>
</tr>
<tr>
<td>Extent of surgical resection, Median (range)</td>
<td>&gt;95 (95-100)</td>
<td>100 (95-100)</td>
</tr>
<tr>
<td>Temozolomide delivered concurrently with radiation, N (%)</td>
<td>22 (96)</td>
<td>17 (44)</td>
</tr>
</tbody>
</table>

*EGFR, epidermal growth factor receptor; vIII, vIII mutant; KPS, Karnofsky Performance Scale*
Time to progression of GBM patients receiving the EGFRvIII vaccine compared to a historical cohort

TTP in the vaccine group is **12.8 months**
TTP in the historical cohort is 7.1 months

\[ p = 0.0058 \]
Median Survival of GBM patients receiving the EGFRvIII vaccine compared to a historical cohort

MS in the vaccine group is >18 months
MS in the historical cohort is 13 months
EGFRvIII Vaccinated GBM Patient MRI

Presentation | Post-Operative | 6-months vaccination | 10-months Recurrence

[Images of brain MRI scans showing progression of treatment and recurrence]
EGFRvIII is not expressed at tumor recurrence n=6

Pre Vaccination

Post Vaccination

Magnification is 250X
EGFRvIII expression is maintained in a patient that was randomized to saline and recurred
CONCLUSIONS

- Toxicity is minimal
- CD8+ γ-IFN EGFRvIII-specific cytotoxic T cell responses are induced
- EGFRvIII humoral responses are induced
- Time to tumor progression is 12.1 months
- Median survival has not yet been reached but will exceed at least 18 months
- Treatment failure presumably is secondary to the loss of epidermal growth factor receptor variant III antigen
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