Tumor-Specific Peptide Vaccination in Newly Diagnosed Patients with GBM

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Epidermal Growth Factor Receptor Mutation

Deleted Segment

EGF Binding Domain

Transmembrane Segment

Intracellular Domain

Extracellular Domain

Wild Type Amino Acid Sequence

1
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 cDNA Sequence

CTG-GAG-GAA-AAG-AAA-GGT-AAT-TAT-GTG-GTG-ACA-GAT-CAC

Variant III Amino Acid Sequence

LEU-GLU-GLU-LYS-GLY-ASN-TYR-VAL-VAL-THR-ASP-HIS

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 respectively\(^1\)

- 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 GBM\(^2,3\)

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\(^3\) 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

Randomize

Saline + 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>

![Image of vaccine injection reaction area](image)

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

![Graph of Vaccine Injection Reaction Area](graph)

**Days After Vaccine Injection**

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage of Responding T Cells</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstimulated</td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>PEP-1</td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>Tetanus</td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>*PEP-3</td>
<td>71%</td>
<td>0.002</td>
</tr>
<tr>
<td>*KLH</td>
<td>64%</td>
<td>0.008</td>
</tr>
</tbody>
</table>
Immunological Responses: Vaccination results in the induction of EGFRvIII-specific humoral responses.
## 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>

- **KLH** is applied to the skin before **Candida** to induce an immunological response.
- **MDA4** is used as a control in the experiment.
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>

*aEGFR, 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**

$p=0.0058$

GBM, EGFRvIII+, GTR, s/p XRT
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 MRI scans showing different stages of the patient's condition]
EGFRvIII is not expressed at tumor recurrence $n=6$
EGFRvIII expression is maintained in a patient that was randomized to saline and recurred.
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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