Presenter Disclosure Information

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The following relationships exist related to this presentation:

Celldex, Inc. - Received Consulting Fees, Travel Support, and Licensing Fees
EGFRvIII Vaccine (CDX-110) alone and with Simultaneous Temodar in Patients with Newly-diagnosed, Resected, EGFRvIII+ GBM

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The Preston Robert Tisch Brain Tumor Center at Duke
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Durham, NC
Epidermal Growth Factor Receptor Mutation (EGFRvIII)

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-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

Diagram:
- Extracellular Domain
  - NH₂
  - 1 5 6 273
  - Deleted Segment
  - EGF Binding Domain
- Transmembrane Segment
- Intracellular Domain
  - COOH
  - 1 5 6 273
Donor 1 Donor 2 Donor 3

No peptide

EGFRvIII peptide 10 μg/ml

IFN-γ ELISPOT

<table>
<thead>
<tr>
<th></th>
<th>Donor 1</th>
<th>Donor 2</th>
<th>Donor 3</th>
</tr>
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<tbody>
<tr>
<td>vIII</td>
<td>+</td>
<td>-</td>
<td>+</td>
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</table>
% Specific Killing

E:T Ratios: 40:1, 20:1, 10:1, 5:1

HLA:
A2, A3
A2, -
A3, A68
A2, A1
A2, A68
A2, A69

U87 (HLA-A2, B44 DR11)
U87-EGFRvIII
PBMC + EGFRvIII + Effector T cells

3H- Thymidine Uptake (cpm)

PBMC
PBMC + Effector T cells
PBMC + EGFRvIII + Effector T cells

DR 8, 15
DR 13, -
DR 11, -
DR 16, 51
DR 11, 52

0 5000 10000 15000 20000 25000

1 2 3 4 5 6
ACTIVATE / ACT II Trial

**Leukapheresis**

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

**Immunologic Monitoring**

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

- **6000 cGy with Temozolomide**

**6000 cGy with Temozolomide**
# Patient Selection

**Inclusions**

- Newly-Diagnosed Glioblastoma Multiforme
- Karnofsky $\geq 80$
- Gross total resection (95% volumetric)
- No evidence of progression on MRI after XRT

**Exclusions**

- Hepatitis B serology positive
- Pregnancy
- Corticosteroids (above physiologic levels)
- Leptomeningeal disease
- Autoimmune disorder
- Immunosuppressive disease
- Severe intercurrent medical conditions
Temozolomide Induced Lymphopenia in Patients with GBM

Peripheral blood counts were monitored in patients with newly diagnosed GBM (n=10) prior to initiation of standard treatment and then monthly during administration of TMZ (50-75 mg/kg per day for six weeks during external beam radiotherapy followed by 28 day cycles of TMZ (150-200 mg/kg per day for five days). T cell counts are displayed as cells/ml of peripheral blood.

**Grade 2 lymphopenia** (blue dashed line above; Common Toxicity Criteria*; <800 lymphocytes/ ml of blood) was induced in all patients receiving TMZ, and **Grade 3 lymphopenia** (red dashed line above CTC; <500 lymphocytes/ml of blood) was induced in 7 out of 10 (70%) patients after the first cycle of TMZ.

Lymphocyte counts returned to normal levels after cessation of TMZ treatment.
### Adverse Events

**ACTIVATE**

(N=22)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Number of Patients</th>
<th>Severity</th>
<th>Relationship to Study</th>
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<tr>
<td>Neurology</td>
<td>2</td>
<td>2 (1)</td>
<td>1-probable 1-likely</td>
</tr>
<tr>
<td>Constitutional</td>
<td>2</td>
<td>1 (2)</td>
<td>1-possible 1-likely</td>
</tr>
<tr>
<td>GI</td>
<td>3</td>
<td>1 (3)</td>
<td>3-likely</td>
</tr>
<tr>
<td>Pain</td>
<td>2</td>
<td>2 (1)</td>
<td>2-likely</td>
</tr>
<tr>
<td>Dermatology/Skin</td>
<td>1</td>
<td>1 (1)</td>
<td>1-probable</td>
</tr>
<tr>
<td>Allergy</td>
<td>2</td>
<td>3 (1)</td>
<td>2-possible</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>Number of Patients</td>
<td>Severity</td>
<td>Relationship to Study</td>
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<td>--------------------</td>
<td>----------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Constitutional</td>
<td>3</td>
<td>1 (3)</td>
<td>1-possible 2-unlikely</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1</td>
<td>2 (1)</td>
<td>1-possible</td>
</tr>
<tr>
<td>Blood/Bone Marrow</td>
<td>1</td>
<td>3 (1)</td>
<td>1-possible</td>
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Anti-EGFRvIII IgG Response: ACT-II

12/12 have strong humoral response to immunizing peptide

* = last time point available for testing
Anti-EGFRvIII IgG responses are maintained or boosted with cycling Temodar treatment.
Serum Levels of Anti-EGFRvIII Antibodies in a Patient Receiving Monthly PEPvIII Vaccines

Anti-PEPvIII Binding (~ng/mL) vs. Weeks
Post CDX-110

U87 Cells  U87-EGFRvIII Cells

Pre  Post CDX-110

ACT II-1

ACT II-3

ACT II-10
Nearly-complete Response: GBM

Pre-Vaccination

Post-Vaccination
(15 Months)

Survival = 6.3 years!
Time To Progression for Patients Treated on the ACTIVATE and ACTII Peptide Immunotherapy Trial

- **ACTIVATE** Median TTP = 61.6 Weeks
- **ACTII** Median TTP = 72.2 Weeks

Historical Controls = 28.5 weeks

(P<0.0001 versus both ACTIVATE & ACTII)
Table IV. Data for RPA IV, Corrected for time to Randomization

<table>
<thead>
<tr>
<th>Patient Category</th>
<th>Median OS, wks</th>
<th>Actuarial 2-year OS</th>
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<tbody>
<tr>
<td>Vaccine Patients</td>
<td>113</td>
<td>60%</td>
</tr>
<tr>
<td>Patients treated with XRT/Temodar</td>
<td>63</td>
<td>0%</td>
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<tr>
<td>Patients treated with Older Regimens</td>
<td>54</td>
<td>11%</td>
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</table>
EGFRvIII-expressing Cells Eliminated by Vaccine

Pre-Vaccine Primary Tumor

Post Vaccine Recurrent Tumor

wtEGFR

EGFRvIII
EGFRvIII Expression Analysis of Stem Cells (CD133+) from Human Glioma 2159
Acknowledgements

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American Brain Tumor Association
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