Phase I Clinical Trial of Intratumoral Reovirus (REOLYSIN) Infusion for Treatment of Recurrent Malignant Gliomas
Disclosures

NIH (NINDS and NCI), Neurovir, Medigene AG, and Oncolytics Biotech, Inc. have all provided funding for my time and role as PI for these trials.

NIH (NINDS and NCI) fund laboratory for the study of oncolytic viruses.

Catherex, Inc: Consultant, Co-founder, stockholder

All viruses in this talk are investigational agents.
Clinical research efforts utilizing oncolytic viruses for malignant glioma

- **HSV-1 mutants**
  - Most well studied—6 trials
  - U.S.: G207
  - Britain: 1716
  - Additional mutants

- **Adenovirus**
  - Onyx-015 completed by NABTT
  - Delta-24-RGD

- **Measles**
  - MV-CEA

- **Reovirus**
  - REOLYSIN™: 1st trial in Canada completed, follow-up study at UAB/multiple institutions just completed
Genome characterization defines human glioblastoma and core pathways.
Reovirus as an Oncolytic Virus

• RNA virus
• Advantages:
  – No genetic engineering required
    • Nonfunctional PKR pathway in glioma cells allows replication of virus
  – Not known to cause encephalitis
  – Smaller than HSV (70-80 nm)
  – Potentially replicates to higher titers
Reovirus as an Oncolytic Virus

- 12 patients with recurrent malignant glioma
  - 9 GBM
  - 2 AA
  - 1 anaplastic oligoastrocytoma
  - First to third recurrence
- Treated by stereotactic inoculation at three sites within tumor
- Dose escalation study
  - $1 \times 10^7$ TCID$_{50}$ (n=3)
  - $1 \times 10^8$ TCID$_{50}$ (n=6)
  - $1 \times 10^9$ TCID$_{50}$ (n=3)

Molecular Therapy 16:627-632, 2008
Goals of U.S. Phase I Infusion Trial

• Determine DLT and MTD of reovirus infusion

• Anti-tumoral effect of reovirus infusion

• Response rate of targeted lesions
Why Infusion?

- Convection enhanced delivery
  - Advantages
  - Limitations
  - Replicating v. static agents
  - Proof of true convection with Reovirus not yet established
    - May be limited by viral size, adhesion
Phase I Study of REOLYSIN Infusion in Recurrent Malignant Glioma

- UAB, OSU and Cedars-Sinai
- Patients underwent stereotactic biopsy, then catheter implantation
  - Dose escalation 3 x 3 design
    - Initial dose level $1 \times 10^8 \text{TCID}_{50}$
    - Increased by 0.5 log increments
    - Highest cohort at $1 \times 10^{10} \text{TCID}_{50}$
Method of Infusion

- 72 hour infusions at 400 microliters total dose per hour, 9.6 mL/day
- Pump Reloading  
  - Stability
- Catheter Tip Location
- Catheter number-  
  - Initially 1-2, later 3-4
- Evaluated: Baseline, discharge, 4, 8, 12, 16, 24 weeks
## Toxicity

<table>
<thead>
<tr>
<th>Total Adverse Events</th>
<th>132</th>
</tr>
</thead>
<tbody>
<tr>
<td>serious</td>
<td>13 (9.8%)</td>
</tr>
<tr>
<td>severe</td>
<td>8 (6.1%)</td>
</tr>
</tbody>
</table>

### Related to Virus

- Not likely related: 106 (83.5%)
- Possibly: 21 (16.5%)
- Probably: 0

### Outcome

- Fatal: 0

- **No DLTs**

### Serious AEs

- Somnolence
- UTI x3
- Post-op Pain
- Abnormal Gait
- Decreased Mental Activity
- Flashing Light Scintillation
- Expressive Aphasia
- Hyperglycemia
- Abnormal EKG
- Partial Seizures
- Seizure

### Severe AEs

- Tonic Clonic Seizure
- Seizure
- Mental Status Change
- Dizziness
- Lethargy
- Abnormal Gait
- Memory Loss
- Difficulty Walking
Progression and Survival by Cohort

<table>
<thead>
<tr>
<th>Dose</th>
<th>Median Time to Progression (Days)</th>
<th>Mean Time to Progression (Days)</th>
<th>Median Survival (Days)</th>
<th>Mean Survival* (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1 \times 10^8$</td>
<td>unavailable</td>
<td>43 ± 15</td>
<td>140 (97 – 157)</td>
<td>131 ± 31</td>
</tr>
<tr>
<td>$3 \times 10^8$</td>
<td>74 (35 – 89)</td>
<td>66 ± 28</td>
<td>134 (105 – 989)</td>
<td>409 ± 502</td>
</tr>
<tr>
<td>$1 \times 10^9$</td>
<td>unavailable</td>
<td>56</td>
<td>232 (107 - 234)</td>
<td>191 ± 73</td>
</tr>
<tr>
<td>$3 \times 10^9$</td>
<td>66 (29 – 68)</td>
<td>54 ± 21</td>
<td>153 (126 - 227)</td>
<td>169 ± 52</td>
</tr>
<tr>
<td>$1 \times 10^{10}$</td>
<td>unavailable</td>
<td>unavailable</td>
<td>135 (122 – 365)*</td>
<td>207 ± 137</td>
</tr>
</tbody>
</table>
24 Week response to one-time REOLYSIN infusion
Immediate pre-treatment MRI
Pathology: recurrent GBM

12 month post-treatment MRI
Status post-REOLYSIN infusion
No additional therapies
Conclusions

• Tolerability of Reovirus Infusion
  – No DLTs in either study
  – Limited adverse event profile

• Efficacy of Reovirus infusion
  – Three patients with stable disease
  – One patient with partial response
  – Additional long-term survivor classified as progression, today might have been classified as pseudoprogression
Reovirus-Future Plans

• 250 patients have been treated in various protocols for a variety of indications in U.S./Canada/UK to date

• Planning:
  • IV protocol now planned – trying to develop method for multiple dosing regimens using oncolytic viruses
  • Multicenter study as primary therapy in conjunction with temozolomide
  • Pilot study to determine whether effective levels of virus actually reach tumor
    – Improved results with combination therapy
    – Preclinical work in glioma suggests that there may be a treatment advantage in malignant glioma for combination treatments

• Antitumor immune response may be improved earlier in disease course. Follow-up trial would be planned in upfront group, whether IV or direct inoculation
A Phase 1 Study of M032 (NSC 733972), a Genetically Engineered HSV-1 Expressing IL-12, in Patients with Recurrent/Progressive Glioblastoma Multiforme, Anaplastic Astrocytoma, or Gliosarcoma
Clinical Study of M032

• M032—oncolytic HSV-1 that expresses human IL-12
  – IL-12 produces antitumor effect through stimulation of IFN-γ pathways and a $T_H^1$ (memory) response
  – also antiangiogenic
  – Preclinical studies support improved responses over other cytokine and non-expressing oHSV
• Potentially to begin enrollment this year
A Phase 1 Study of C134, a Genetically Engineered HSV-1
the PKR evasion gene IRS-1, in Patients with Recurrent/Progressive Glioblastoma Multiforme, Anaplastic Astrocytoma, or Gliosarcoma
Can a PKR evasion gene from Human Cytomegalovirus (HCMV) selectively complement a Δγ₁34.5 virus?

**Hypothesis**

Transfer of a PKR-evasion gene (TRS1 or IRS1) from an evolutionarily distant herpes virus will complement one function of the γ₁34.5 gene (wild-type viral protein synthesis) without restoring another function (wild-type neurovirulence).
The Future-Oncolytic Viral therapy guided by TCGA Genomic Glioblastoma Subtype

<table>
<thead>
<tr>
<th>Gene</th>
<th>Proneural (n = 37)</th>
<th>Neural (n = 19)</th>
<th>Classical (n = 22)</th>
<th>Mesenchymal (n = 38)</th>
<th>Total No. of Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>20 (54%)</td>
<td>4 (21%)</td>
<td>0 (0%)</td>
<td>12 (32%)</td>
<td>36</td>
</tr>
<tr>
<td>PTEN</td>
<td>6 (16%)</td>
<td>4 (21%)</td>
<td>5 (23%)</td>
<td>12 (32%)</td>
<td>27</td>
</tr>
<tr>
<td>NF1</td>
<td>2 (5%)</td>
<td>3 (16%)</td>
<td>1 (5%)</td>
<td>14 (37%)</td>
<td>20</td>
</tr>
<tr>
<td>EGFR</td>
<td>6 (16%)</td>
<td>5 (26%)</td>
<td>7 (32%)</td>
<td>2 (5%)</td>
<td>20</td>
</tr>
<tr>
<td>IDH1</td>
<td>11 (30%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>12</td>
</tr>
<tr>
<td>PIK3R1</td>
<td>7 (19%)</td>
<td>2 (11%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>10</td>
</tr>
<tr>
<td>RB1</td>
<td>1 (3%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
<td>5 (13%)</td>
<td>7</td>
</tr>
<tr>
<td>ERBB2</td>
<td>2 (5%)</td>
<td>3 (16%)</td>
<td>1 (5%)</td>
<td>1 (3%)</td>
<td>7</td>
</tr>
<tr>
<td>EGFRvIII</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>5 (23%)</td>
<td>1 (3%)</td>
<td>7</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>3 (8%)</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>1 (3%)</td>
<td>6</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>4 (11%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4</td>
</tr>
</tbody>
</table>
Conclusion

• Oncolytic Reovirus and HSV-1 appear safe for administration in patients with malignant glioma at doses tested to date

• An important subset of patients with recurrent malignant glioma appear to exhibit responses to treatment, both radiographically and in terms of long-term survival

• Administration with adjuvant agents such as radiation and chemotherapy and/or foreign gene expression is likely to improve antitumor effects

• Upfront studies must be conducted

• Data from early clinical trials will be critical to optimizing design of future studies by providing data on viral distribution and time course of infection, role of immune response, impact of tumor genotype, role of adjuvant therapy, defining pseudoprogression, etc.
Moving the field of Oncolytic Viral therapy for glioma patients forward

• Data from early clinical trials will be critical to optimizing design of future studies by providing data on viral distribution and time course of infection, role of immune response, impact of tumor genotype, role of adjuvant therapy, defining pseudoprogression, etc.

• Major questions remain:
  • How best to administer and distribute the virus?
  • How to develop multiple dosing regimens?
  • How should tumor genotype be used to guide therapy?
  • How should patient immune status guide therapy?
  • How prevalent is pseudoprogression?
  • What drug/viral combinations should be explored?
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