Power and precision in cancer radiotherapeutics

The Society of Nuclear Medicine and Molecular Imaging
June 28, 2023
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PLUS Direct Targeted Drug Delivery Strategies for CNS Cancers

Overcomes the primary ‘barrier’ to CNS drug development

**Blood-Brain-Barrier (BBB)**

CNS Drug Delivery Limitations
+ Network of closely spaced cells for CNS protection
+ Prevents >98% of systemically delivered drugs from reaching a therapeutic concentration in the brain

**Brain Parenchyma**

Convection-Enhanced Delivery (CED)
+ FDA-approved and utilized for 20+ years
+ Bypasses BBB
+ ‘Biological fracking’: Controlled pressure and flow rate provides optimal drug delivery to region of interest
+ Standard technology found in any hospital with neurosurgery

**Cerebrospinal Fluid**

Ommaya Reservoir
+ FDA-approved and utilized for 60+ years
+ Bypasses BBB
+ Small reservoir is placed under the scalp and allows drug to be directly delivered to the ventricle
+ Allows multi-drug dosing and CSF sampling
+ Commonly placed in LM patients
Visualization and Monitoring of CED in Real-Time via $\gamma$ emission

ReSPECT Trial Patient, use of up to 5 catheters feasible
PLUS Uses Isotopic Rhenium for CNS Indications

Ideal radioisotope for CNS tumors

+ Two clinically relevant isotopes, Rhenium-186 & Rhenium-188
+ ‘Goldilocks’ energy profile between Yttrium-90 & Lutetium-177
+ Dual energy: $\beta$ is tumoricidal & $\gamma$ for imaging
+ Rhenium/BMEDA chemistry is ideal for nanoliposome loading
+ Lacks affinity for bone & thyroid
+ Rapid clearance
+ High radiation density & optimal half-life
+ Mature, redundant supply chain

<table>
<thead>
<tr>
<th></th>
<th>Rhenium-186</th>
<th>Rhenium-188</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average path length</td>
<td>~ 2 mm</td>
<td>~ 4 mm</td>
</tr>
<tr>
<td>Radiation half life</td>
<td>3.8 days</td>
<td>17 hours</td>
</tr>
<tr>
<td>Manufacture</td>
<td>Reactor</td>
<td>Generator</td>
</tr>
</tbody>
</table>

+ Technetium (Tc) is adjacent in the periodic table to Rhenium (Re) and have similar properties
+ Tc is used in 40 million diagnostic procedures per year (80% of all nuclear medicine procedures globally)
PLUS’ Lead Drug Rhenium Re\(^{186}\) Obisbemeda Prolongs Radiation in the Brain & CSF

Complementary technologies drive efficacy & safety profile

**Rhenium Re\(^{186}\) Obisbemeda**

**Rhenium-186 Radionuclide**

*Emits tumor destroying radiation over short distances while sparing healthy tissue*

**BMEDA Small Molecule**

*Chelates to Rhenium & is loaded into a NanoLiposome where it is irreversibly trapped*

**100 nm NanoLiposome**

*Carries BMEDA-Rhenium to target tumor & improves retention*

**Tumor Retention**

- 186Re-NanoLiposomes
- 186Re-BMEDA
- 186Re-Perrenate

**Improved Drug Distribution Coverage**

Preclinical Evidence for Rhenium Re\textsuperscript{186} Obisbemedea Use in CNS Cancers

**Nanoliposome Enhances Tumor Dispersion & Response**

- **Tumor Retention**
  - Graph showing % Injected Activity over time (hours) with different Rhenium Re\textsuperscript{186} treatments.

- **Tumor Response**
  - Graph showing Tumor Volume (cm\textsuperscript{3}) over time (days) with different Rhenium Re\textsuperscript{186} treatments.

**Glioblastoma Intracranial Xenograft Model**

- **Clear Separation in Rat Survival at a Radiation Dose of 100 Gray**
  - Graph showing survival over days from inoculation with different radiation doses.

- **\textsuperscript{186}Re Treated Tumors Progressively Disappear Over Time**
  - Graph showing tumor response with different treatments.

**Leptomeningeal Metastases Wistar Rat Model**

- **Radioactivity Visualized at 48 Hours; Mean Absorbed Radiation Dose of 1,094 Gy**
  - Graph showing clearly visible radioactivity.

- **Statistically Significant Difference in Overall Survival with \textsuperscript{186}RNL-Treated Animals Outliving the Controls**
  - Graph showing survival comparison with different treatments.

ReSPECT-GBM Trial for Recurrent Glioblastoma

3 case studies from ReSPECT-GBM Phase 1 Trial
(OS between 750 & 1200 days, 2 alive)
ReSPECT-GBM Trial for Recurrent Glioblastoma

Phase 1 Safety Profile (n=27 patients)

<table>
<thead>
<tr>
<th>Serious Adverse Event Possibly Related to Study Drug</th>
<th>Grade 1 Mild</th>
<th>Grade 2 Moderate</th>
<th>Grade 3 Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased platelet count</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

+ No catheterization complications
+ The majority of adverse events are Grade 1 or 2 in severity & unrelated to study drug
+ Minimal systemic radiation exposure observed
**ReSPECT-GBM Trial for Recurrent Glioblastoma**

Phase 1 efficacy data through RP2D determination (n=21 patients)

<table>
<thead>
<tr>
<th>Dose Escalation Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Very poor prognostic group of recurrent GBM patients</td>
</tr>
<tr>
<td>+ 6 dose escalation cohorts, range:</td>
</tr>
<tr>
<td>+ Volume: 0.66 to 8.8 mL</td>
</tr>
<tr>
<td>+ Dose: 1.0 to 22.3 mCi</td>
</tr>
<tr>
<td>+ RP2D: 22.3 mCi/8.8 mL</td>
</tr>
<tr>
<td>+ No treatment failures</td>
</tr>
<tr>
<td>+ 1-4 catheters used</td>
</tr>
<tr>
<td>+ Increased tumor coverage &amp; dose at higher dose cohorts</td>
</tr>
<tr>
<td>+ Publication pending</td>
</tr>
</tbody>
</table>

**Patient Response: Dose vs. Tumor Coverage**

Accelerated Failure Time (AFT) Model: Parametric model complements the Cox Proportional Hazards Model

100 Gy threshold based on preclinical observations
ReSPECT-GBM Trial for Recurrent Glioblastoma

Phase 1 efficacy data through RP2D determination (n=21 patients)
ReSPECT-GBM Trial for Recurrent Glioblastoma

Phase 1 efficacy data through RP2D determination (n=21 patients)

**Overall Survival**

- **RNL OS KM Curve in Weeks (N=21)**
  - With Number of Subjects at Risk

- **RNL OS KM Curves by Absorbed Dose Stratum in Weeks (N=21)**
  - With Number of Subjects at Risk

*Proportion Alive vs. Weeks*
# ReSPECT-GBM Trial for Recurrent Glioblastoma

Phase 1 efficacy data through RP2D determination (n=21 patients)

<table>
<thead>
<tr>
<th>Dose Response by Quartile</th>
<th>Hazard Ratio Model (Cox)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Dose Response by Quartile" /></td>
<td><img src="image" alt="Hazard Ratio Model" /></td>
<td>+ Increased absorbed radiation dose (p=0.003) and percent tumor volume treated (p=0.002) correlates with improvement in overall survival</td>
</tr>
<tr>
<td><img src="image" alt="Dose Response by Quartile" /></td>
<td></td>
<td>+ Median OS in patients receiving &gt; 100 Gy of absorbed dose was 76 weeks vs. 22 weeks if &lt; 100 Gy (p=0.0002) compared to standard of care of 32.1 weeks in recent meta-analysis*</td>
</tr>
<tr>
<td><img src="image" alt="Dose Response by Quartile" /></td>
<td></td>
<td>+ Up to 20 times the absorbed dose of EBRT delivered</td>
</tr>
<tr>
<td><img src="image" alt="Dose Response by Quartile" /></td>
<td></td>
<td>+ Therapeutic absorbed radiation dose (&gt;100 Gy) was reliably achieved in &gt;80% of patients treated in high dose cohorts</td>
</tr>
</tbody>
</table>

*For each 100 Gy increase of Total Dose in Distribution Volume, the risk of death decreases by 45.6% (p=0.003)

*For each 10% increase in the Ratio of Treated to Total Tumor Volume, the risk of death decreases by 66.9% (p=0.002)

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## Comparative Survival Data

### ReSPECT-GBM vs. ‘Best’ Real World Data

<table>
<thead>
<tr>
<th>Trial or Data Source</th>
<th>Number Patients</th>
<th>Median Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis*- Bevucizamab</td>
<td>~700</td>
<td>32.1 weeks (7 months)</td>
</tr>
<tr>
<td>MEDS- Bevacizumab</td>
<td>163</td>
<td>7.9 months</td>
</tr>
<tr>
<td>MEDS- CED</td>
<td>636</td>
<td>8.4 Months</td>
</tr>
</tbody>
</table>

### ReSPECT-GBM Phase 1 Dose Escalation

<table>
<thead>
<tr>
<th>Dose Range</th>
<th>Number Patients</th>
<th>Median Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>21</td>
<td>41 weeks (11 months)</td>
</tr>
<tr>
<td>&lt;100Gy</td>
<td>9</td>
<td>22 weeks (6 months)</td>
</tr>
<tr>
<td>&gt;100Gy</td>
<td>11</td>
<td>76 weeks (17 months)</td>
</tr>
</tbody>
</table>

*Neuro-Oncology, Volume 22, Issue 5, May 2020, Pages 705–717  

Medidata Enterprise Data Store (MEDS)
ReSPECT-GBM for Recurrent Glioblastoma

Phase 2 Case Study: Patient 02-004 – Imaging and Dosimetry

+ Rapidly progressing, deep brain rGBM, adjacent to the brainstem
+ 3 catheters used
+ 8.8 mL infused volume, 22.3 mCi total injected radioactivity
+ $^{186}$RO tumor coverage at EOI: 94.6%
+ Mean tumor dose: 105 Gy
+ Patient alive at >100 days post treatment
ReSPECT-GBM for Recurrent Glioblastoma

Phase 2 Case Study: Patient 02-004 – Pre/Post Treatment MRI & SPECT

Pre-treatment MRI

Post-treatment radiation distribution @ 24 hours

T1 FLAIR contrast MRI

T2 MRI

1 Month

1.5 Months

3 Months
ReSPECT-GBM Phase 1 Trial Clinical Update

+ A single dose of rhenium (186Re) obisbemedea was generally safe and well-tolerated, with no dose-limiting toxicities and minimal systemic radiation exposure.

+ In 21 patient phase 1- efficacy signals observed in a prognostically unfavorable patient population.

+ Median OS in all 21 patients (including those receiving very limited radiation doses in early cohorts, 5 Bev treated patients, etc.) was 11 months or 38% increase in survival vs. standard of care of ~8 months in rGBM.

+ Median OS in patients receiving > 100 Gy of absorbed dose (therapeutic) was 76 weeks (17 mos) vs. 22 weeks (6 mos) if < 100 Gy (p=0.0002).

+ Increased absorbed radiation dose and percent tumor volume treated best correlates with improvement in overall survival:
  + For each 100 Gy increase of Total Dose in Distribution Volume, the risk of death decreases by 45.6% (p=0.003).
  + For each 10% increase in the Ratio of Treated to Total Tumor Volume, the risk of death decreases by 66.9% (p=0.002).
For more information on how to become involved with this trial, please contact:

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