Safety and feasibility results from a Phase 1/2 clinical trial of rhenium (186Re) obisbemeda (186ReRNL) in recurrent glioma: The ReSPECT-GBM trial

Andrew Brenner1, John Floyd1, Ande Bao1, William T. Phillips2, Joel E. Michalek2, Michael Vousden3, Toral Patel4, Jeffrey S. Weinberg5, Marc Hedrick6, Melissa Moore7, Norman LaFrance8

1 Ut Health San Antonio, 2 Case Western Reserve University, 3 Ut Southwestern Medical Center, 4 MD Anderson, 5 Plus Therapeutics

INTRODUCTION

Rhenium (186Re) obisbemeda (186ReRNL), a next generation radiopharmaceutical, is BMEDA-chelated 186Re encapsulated in liposomal nanoparticles. 186Re is a beta-emitting therapeutic radionuclide with a 90-hour half-life, ~2 mm tissue path length, and optimal 137 keV y-decay that allows real-time imaging of in vivo drug distribution by SPECT/CT.

Traditionally, radiation exposure to adjacent normal brain tissue limits the use of External Beam Radiation Therapy (EBRT) to typical doses of ~30-50 Gy (Gy). As most glioma recurrences are within 2 cm of the resection margin, radiopharmaceuticals that can be delivered directly to the tumor and minimize adjacent exposure to healthy tissues are attractive treatment alternatives. Moleularly targeted radiation therapy improves EBRT, but is reliant on receptor specificity, is delivered systemically, and lacks the barrier effect of the BBB. These limitations can lead to off-target effects and inefficient tumor treatment. Durable, localized treatment with beta emitters, like 186Re, has the potential to dramatically widen the therapeutic window, increase the delivered dose, avoid normal tissue exposure, and extend survival in patients with glioma. 186Re uses Direct Targeted Delivery, which deposits high doses of radiation non-systematically and locoregionally to achieve thorough tumor coverage and retention with high absorbed radiation doses.

In preclinical models of glioma, 186ReRNL eradicated transplanted tumor cells when >100 Gy of radiation was delivered, with no evidence of neurologic compromise or other safety and toxicity markers. Furthermore, a study in beagles to assess toxicity of an intracranial, single dose administration of 186ReRNL showed no test article-related pathologic changes at the highest administered amount (6 mCi).

For GBM, 186ReRNL is administered via Convection Enhanced Delivery (Fig. 1).

STUDY DESIGN

ReSPECT-GBM is an ongoing, first-in-human, open-label, Phase I/2 study investigating dose escalation and other delivery parameters (i.e., number of catheters (1-5), infusion rates, drug volumes, and drug concentrations) to determine the maximum tolerated dose (MTD), maximum feasible dose (MFD), safety, and efficacy of 186ReRNL in recurrent adult glioma (NID 16117).

The primary objective of the Phase 1 study was to determine a maximum tolerated dose (MTD)/maximum feasible dose (MFD) utilizing a modified 3+3 Fibonacci design, followed by a Phase 2 at the recommended Phase 2 dose (RP2D) (Table 1).

<table>
<thead>
<tr>
<th>Phase / Cohort</th>
<th>infused Volume (mL)</th>
<th>Total 186Re Activity infused (mCi)</th>
<th>Concentration (mCi/mL)</th>
<th>Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 - 1</td>
<td>0.66</td>
<td>1.0</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>Phase 1 - 2</td>
<td>1.22</td>
<td>2.0</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>Phase 1 - 3</td>
<td>2.64</td>
<td>4.0</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>Phase 1 - 4</td>
<td>5.28</td>
<td>8.0</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>Phase 1 - 5</td>
<td>8.80</td>
<td>13.4</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>Phase 1 - 6a</td>
<td>8.80</td>
<td>13.4</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>Phase 1 - 6b</td>
<td>8.80</td>
<td>13.4</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>Phase 1 - 7</td>
<td>16.34</td>
<td>26.8</td>
<td>2.5</td>
<td>4/6</td>
</tr>
<tr>
<td>Phase 1 - 8</td>
<td>22.3</td>
<td>37.2</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>Phase 1 - 9</td>
<td>22.3</td>
<td>37.2</td>
<td>2.5</td>
<td>5</td>
</tr>
<tr>
<td>Overall survival ranged from 750-1000 days. One patient remains alive.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. ReSPECT-GBM Trial with dose escalation for Cohorts 1-8 and Phase 2 at the Cohort 9 dose. Cohorts 1-7 are complete. Cohort 8 is still enrolling concurrently with the Phase 2.

Brainlab iPlan Flow software was used to plan BrainLab Flexible Catheter (SmartFlow) placement in the tumor while avoiding white matter tracts and CSF spaces (e.g., fissures, sulci, cisterns, ventricles, and resection cavities). Frameless image-guided catheter placement was achieved with Brainlab Variglide Stereotactic system.

Patients were given supersaturated potassium iodide (SSKI) prior to treatment. A single administration of 186ReRNL, was delivered by CED utilizing 1 catheters at a maximum flow rate of up to 20 UL/min/catheter.

Serial 1-minute dynamic planar imaging was performed during the time of the infusion. SPECT/CT imaging and serial whole-body planar imaging scans were performed at end of infusion (EOI) and at 1-, 3-, 5-, and 8-days after 186ReRNL infusion to assess the radiation absorbed dose to the tumor and other organs during the treatment. Serial blood samples and urine collections were also accounted for activity. Dosimetry was performed using region of interest data and OLINDA dose calculation software.

PATIENTS

28 adult recurrent glioma patients in the Phase 1 study, across 8 dosing Cohorts, were treated from 2015 to 2023. 18 were male and 10 were female. Five patients in Cohorts 1-4 received prior bevacizumab. 4

6 adult recurrent glioma patients in the Phase 2 study were treated. 1 was female and 5 were male. All 2 Phase 3 patients were limited to tumor sizes ≤20 cm³, 1 recurrence, bevacizumab-naive, and historically confirmed glioblastoma.

The average tumor volume across 34 patients was 10.25 cm³ (range 0.88-33.00). For the Phase 1 patients, the pathologic grade was Grade IV glioma in 26 patients and Grade III in 2 patients. All Phase 2 patients were Grade IV (inclusion criteria). For those genotyped in Phase 1, IDH mutation status was WT in 20 patients and mutated in 2 patients (4 patients were pending at time of poster). All Phase 2 were WT. For those genotyped in Phase 1, MGMT status was methylated in 5 patients and unmethylated in 16 patients (4 patients were pending analysis). 2 were methylated and 3 were unmethylated (1 patient pending analysis) in Phase 2.

IMAGING

Planar and tomographic (SPECT/CT) images were collected from all subjects using a dual-detector SPECT/CT camera. A sealed 186Re radioactivity vial with known 186Re radioactivity (~5% of injected radioactivity) was positioned next to each subject’s head and well inside the image field of view at each time of image acquisition for in vivo radioactivity quantification. Representative SPECT/CT images are shown in Figure 2.

SURVIVAL

Overall survival (OS) in terms of average absorbed dose to the tumor and tumor coverage measured by %N/TVW, is reported for 21 patients (Cohort 1-6) treated with a single dose of 186ReRNL (Figs. 4, 5, 6).

Of all 28 Phase 1 patients (Cohorts 1-8), 4 patients remain alive and 24 have died. 5 Phase 2 patients (out of 6) are still alive.

For the Median Absorbed Radiation Dose to the tumor (MARDT) was 308.4 Gy (8.9 Gy to 739.5 Gy). Patients were stratified by MARDT (<100 Gy; ≥100 Gy).

Median overall survival (mOS) across Cohorts 1 to 6 (n=27) was 11-months (95% CI 5 to 17-months) with 1 patient remaining alive 20-months after treatment.

When dichotomized by absorbed dose of 100 Gy: a significant difference was observed with a median OS of 6-months (95% CI 1 to 10-months) for <100 Gy (n=19) and 17-months (95% CI 8-35-months) for ≥100 Gy (n=12) (p=0.001). For all 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).

CONCLUSION

+ Results from Phase 1 (Cohorts 1-8) and 6 patients in Phase 2 of a single treatment of 186ReRNL by CED for patients with recurrent glioma showed that OS is significantly associated with absorbed dose and percent treated tumor volume based on Cox Proportional Hazards modeling and Accelerated Failure Time Modeling.

+ 186ReRNL delivered directly by CED provides up to 20 times the absorbed dose of radiation that can be administered by EBRT.

+ A single dose of 186ReRNL was generally well tolerated with no dose limiting toxicities and minimal systemic radiation exposure. The MTD was not reached.

+ SPECT/CT can accurately and reliably detect the tumor location and residual radioactivity of the 186ReRNL during decay.

+ Greater than 100 Gy absorbed dose to the tumor was observed in more than 70% of 33 patients treated.

+ Phase 1 Cohort 8 and Phase 2 (tumor size ≤20 cm³) studies are currently enrolling.