Safety and Feasibility of (^{186}Re) Obisbemeda (Rhenium-186 Nanoliposome, ^{186}RNL) in Recurrent Glioma: The ReSPECT™-GBM Phase 1/2 Trial

Norman LaFrance[1], Andrew Brenner[2], Ande Bao[3], Joel E. Michalek[2], William T. Phillips[2], John R. Floyd[2], Toral R. Patel[4], Jeffrey S. Weinberg[5], Melissa Moore[1], Marc Hedrick[1]

[1]Plus Therapeutics, Inc., [2]UT Health San Antonio, [3]Case Western Reserve University, School of Medicine, [4]UT Southwestern Medical Center, [5]UT MD Anderson Cancer Center

OVERVIEW AND STUDY DESIGN

Overview

- **Rhenium (^{186}Re) obisbemeda** (^{186}RNL), *a next generation radiotherapeutic*, is BMEDA-chelated ^{186}Re encapsulated in liposomal nanoparticles and administered via Convection Enhanced Delivery (CED) to brain tumors.
- ^{186}Re is a beta emitting therapeutic radionuclide with a 90-hour half-life, ~2 mm tissue path length, and optimal 137 keV γ-decay (~10% yield). This 186Re γ decay optimally allows real-time imaging of the in vivo drug distribution using standard nuclear medicine imaging methods (e.g., SPECT/CT).
- Durable, localized treatment with beta emitters has the potential to dramatically widen the therapeutic window, increase the delivered dose, avoid normal tissue exposure, and extend survival in patients with glioma. ^{186}Re has the optimal half-life and beta decay energy for this application.
- Radiation exposure to adjacent normal brain tissue limits the use of External Beam Radiation Therapy (EBRT) to typical doses of ~30-50 Gray (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.
- Molecularly targeted radiation therapy improves upon EBRT, but is reliant on receptor specificity, is delivered systemically, and few cross the blood brain barrier (BBB). These limitations can lead to off-target effects and inefficient tumor treatment.
- ^{186}RNL uses **Direct Targeted Delivery**, which deposits high doses of radiation non-systemically and locoregionally to achieve thorough tumor coverage and retention with high absorbed radiation doses.
- In preclinical models of glioma, ^{186}RNL 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 186RNL showed no test article-related pathologic changes at the highest administered amount (6 mCi).
- We report initial results of Phase 1 and Phase 2 trial of ^{186}RNL in 33 patients with recurrent glioma (ReSPECT-GBM).

Study Design

ReSPECT-GBM is an ongoing, first-in-human, open-label, Phase 1/2 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 ^{186}RNL in recurrent adult glioma (IND 116117).

CED Planning, Catheter Placement, and Drug Administration

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 Varioguide Stereotactic system. A single administration of ^{186}RNL was delivered by CED utilizing 1-5 catheters at a maximum flow rate of up to 20 µL/min per catheter.

Imaging and Dosimetry

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 ^{186}RNL infusion to assess the radiation absorbed dose to the tumor and other organs during the treatment. Serial blood samples and urine collections were also counted for activity. Dosimetry was performed using region of interest data and OLINDA dose calculation software.

Dose Escalation Scheme

Phase / Cohort	Infused Volume (mL)	Total ^{186}RNL Activity Infused (mCi)	Concentration (mCi/mL)	Average Absorbed Dose (Gy)
Phase 1 – 1	0.66	1.0	1.5	199
Phase 1 – 2	1.32	2.0	1.5	122
Phase 1 – 3	2.64	4.0	1.5	233
Phase 1 – 4	5.28	8.0	1.5	171
Phase 1 – 5	5.28	13.4	2.5	423
Phase 1 – 6a	8.80	22.3	2.5	287
Phase 1 – 6b	8.80	22.3	2.5	462
Phase 1 – 7	12.3	31.2	2.5	308
Phase 1 – 8	16.34	41.5	2.5	198
Phase 2	8.8	22.3	2.5	248

Cohort 6b utilized same volume and dose as Cohort 6a but with increase in maximum flow rate to 20 microliters/minute. Cohorts 1-7 have 3 patients per cohort. Cohort 8 is currently enrolling and Average Absorbed Dose (Gy) reported is for 4 patients. Phase 2 is current enrolling and Average Absorbed Dose (Gy) is for 5 patients.

Patients

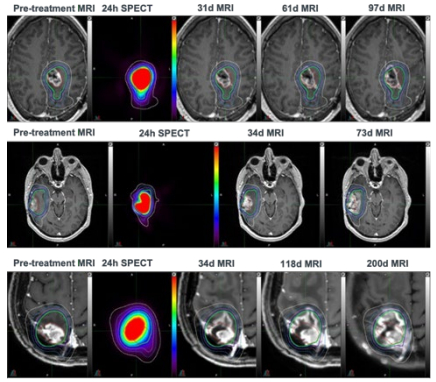
- Twenty-eight adult recurrent glioma patients in the Phase 1 study, across the 8 dosing Cohorts, were treated from 2015 to 2023; 18 were male and 10 were female. Five patients in Cohorts 1-4 received prior bevacizumab.
- Five adult recurrent glioma patients in the Phase 2 study were treated in 2023; 1 was female and 4 were male. All Phase 2 patients are limited to tumor sizes ≤20 cm^3, 1 recurrence, bevacizumab-naïve, and histologically confirmed glioblastoma.
- The average tumor volume across all 33 patients was 10.41 mL (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 mutational 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). 2 were methylated and 3 were unmethylated in Phase 2.

RESULTS

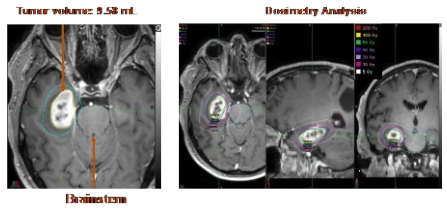
Summary

- Twenty-eight patients in the Phase 1 (8 cohorts) received ^{186}RNL in doses ranging from 1.0 – 41.5mCi in volumes ranging from 0.6 – 16.3 mL.
- Five patients in the Phase 2 received ^{186}RNL doses of 22.3 mCi in a volume of 8.8 mL.
- The maximum CED administration rate was 5-20 µl/min and 1-5 catheters were used per patient.
- Average absorbed dose to the tumor for all Phase 1 patients was 264 Gy (range: 8.9-740 Gy) while exposure outside the brain was negligible. Average absorbed dose to the tumor for all Phase 2 patients was 248 Gy.
- An average absorbed dose of >100 Gy was achieved in 5/12 (42%) patients in Phase 1, Cohorts 1-4.
- An average absorbed dose of >100 Gy was achieved in 13/16 (81%) patients in Phase 1, Cohorts 5-8.
- An average absorbed dose of >100 Gy was achieved in all Phase 2 patients (100%).
- Average percent of treated tumor was 75%, with only 8/33 (24%) <70% tumor coverage.

Case Studies



1: Recurrent glioma patients 1-3 pretreatment MRI, 24-hr post-treatment SPECT, and post-treatment MRIs. 1: Phase 1 patient, cohort 4. 2: Phase 1 patient, cohort 5. 3: Phase 1 patient, cohort 6. Overall survival ranged from 750-1200 days. One patient remains alive.



Phase 2 patient presented with rapidly progressing, deep brain rGBM, adjacent to the brainstem. Three catheters, 8.8 mL infused volume, 22.3 mCi total injected radioactivity used per protocol. ^{186}RNL tumor coverage at EOI was 94.6%. The mean tumor dose was 105 Gy. The patient was still alive at >100 days post treatment.

Figure 1: Absorbed Dose by Volume Treated

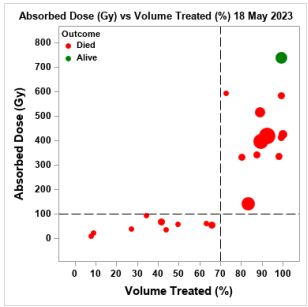
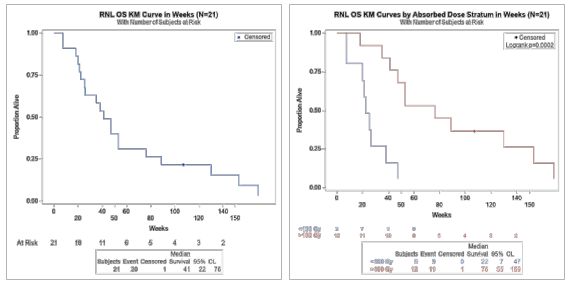


Figure 2: OS KM Curves in Weeks



Safety

- A single dose of ^{186}RNL was generally well-tolerated, with no dose limiting toxicities and minimal systemic radiation exposure across 28 Phase 1 patients/8 dose cohorts and 5 Phase 2 patients.
- No patient had treatment-related adverse events (AEs) with outcome of death, and no patient withdrew due to AEs.
- Most AEs were mild or moderate (Grade 1 or 2) in intensity and non-serious.
- The AEs with the highest incidence were fatigue (50.0%), muscular weakness and headache (33.3% each), and gait disturbance (27.8%); and were generally unrelated to treatment.
- Grade 3 AEs were leukocytosis, hyperglycemia, muscular weakness, seizure, brain edema, avascular necrosis of the shoulder (worsening), vasogenic cerebral edema, and pneumonia; and were generally unrelated to treatment.
- Serious AEs (SAEs) were reported for two patients in Cohort 2 (seizure and vasogenic cerebral edema), one patient each in Cohort 4 and Cohort 5 (both seizure), and two patients in Cohort 6 (pneumonia, avascular necrosis of the shoulder (worsening) and cerebral edema).
- No meaningful differences or patterns in the incidence of treatment emergent AEs across cohort groups were observed.

Figure 3a and b: PFS KM Curves in Weeks

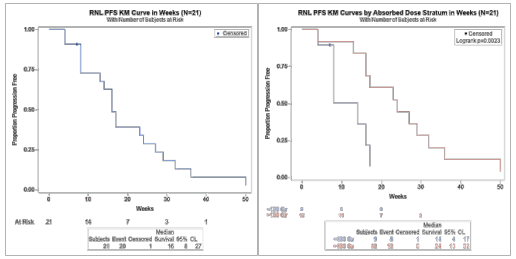


Figure Summaries

- Overall survival (OS) in terms of average absorbed dose to the tumor and tumor coverage measured by %TuV/TrV is reported for 21 patients (Cohort 1-6) treated with a single dose of ^{186}RNL.
- Of all 28 Phase 1 patients (Cohorts 1-8), four patients remain alive and 24 have died. Four Phase 2 patients (out of 5) are still alive.
- For the Phase 1 cohorts, dosing ranged from 1 mCi in 0.6mL to 41.5 mCi in 16.3ml. The MTD was not reached. There were no CED failures. No dose limiting toxicities were observed.
- Most common AEs were pre-existing GBM related signs and symptoms (e.g., weakness, fatigue, headache, seizure, scalp discomfort after CED) and >80% of AEs had the unrelated or unlikely attribution. For The Median absorbed radiation dose to the tumor (MARDT) was 308.4 Gy (8.9 Gyto 739.5 Gy).
- Patients were stratified by MARDT (<100 Gy, ≥100 Gy).
- In all patients (n=27), the median overall survival (OS) was 8 months (m), 95% CI 5 m to 13 m).
- In those receiving <100 Gy (N=10), the median OS was 5 m (95% CI 1 m to 11 m) and in those with ≥100 Gy (N=17) the median was 12 m (95% CI 5 m to 30m), p< 0.001).
- 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

CONCLUSIONS

- Results from Phase 1 (Cohorts 1-8) and 5 patients in Phase 2 of a single treatment of ^{186}RNL 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.
- ^{186}RNL delivered directly by CED provides up to 20 times the absorbed dose of radiation that can be administered by EBRT.
- A single dose of ^{186}RNL was generally well tolerated with no dose limiting toxicities and minimal systemic radiation exposure.
- SPECT/CT can accurately and reliably detect the tumor location and residual radioactivity of the ^{186}RNL during decay.
- Greater than 100 Gy absorbed dose to the tumor was observed in 70% of 33 patients treated.
- Cox hazards and Accelerated Failure Time modeling demonstrated increased absorbed radiation dose and percent tumor treated tumor volume correlates with improvement in OS.
- Phase 1 Cohort 8 and Phase 2 (RP2D, tumor size ≤20 cm3) are currently enrolling.

Contact Information: Dr. Andrew J. Brenner at BrennerA@uthscsa.edu; Dr. Norman LaFrance at nlafrance@plustherapeutics.com

To learn more about Rhenium (^{186}Re) Obisbemeda and the ReSPECT-GBM clinical trial, visit https://www.respect-trials.com/gbm/

Clinical Trial ID: 116117

ClinicalTrials.gov Identifier: NCT01906385

Disclosures: This study was supported by an NCI award 1R01CA235800, a pilot award from Mays Cancer Center P30CA054174, a Commercialization Award from CPRIT DP150021, and Plus Therapeutics. ^{186}RNL is an investigational treatment.