Rhenium (^{186}Re) Obisbemeda (^{186}RNL) in Recurrent Glioblastoma via Convection Enhanced Delivery: A Report on Phase 2

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INTRODUCTION

Rhenium (^{186}Re) obisbemeda (^{186}RNL), a next generation radiotherapeutic, is BMEDA-chelated ^{186}Re encapsulated in liposomal nanoparticles. ^{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 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 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.

Durable, localized treatment with beta emitters, like ^{186}Re, 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}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 ^{186}RNL showed no test article-related pathologic changes at the highest administered amount (6 mCi). For GBM, ^{186}RNL is administered via Convection Enhanced Delivery (CED) (**Figure 1**).

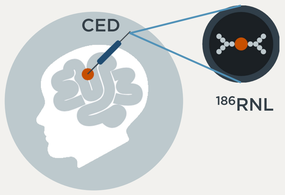

Figure 1. ^{186}RNL is BMEDA-chelated ^{186}Re encapsulated in nanoliposomes. For the treatment of GBM, it is directly delivered to the tumor by Convection Enhanced Delivery (CED).

STUDY DESIGN AND PROCEDURES

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).

The **primary objective of the Phase 2 study** is to assess overall survival (OS) following ^{186}RNL administration. The dosing variables are listed in **Table 1**.

Infused Volume (mL)	Total ^{186}RNL Activity Infused (mCi)	Concentration (mCi/mL)	Status
8.80	22.3	2.5	Enrolling

Table 1. ReSPECT-GBM Trial with dose escalation for Phase 2. A Phase 1 dose escalation trial is running concurrently (Abstract 1567248).

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.

Patients were given supersaturated potassium iodide (SSKI) prior to treatment. A single administration of ^{186}RNL was delivered by CED utilizing 1-5 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 ^{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. Progression was determined by Radiographic Assessment in Neuro-Oncology (RANO) criteria following standard treatment.

In the Phase 1 study, cohorts 1-7 are complete. Cohort 8 is enrolling concurrently with the Phase 2 study. Data presented here includes 15 patients: six from Phase 1, cohort 6 and nine from Phase 2. Data is pooled for analysis among these 15 patients due receiving the same dosing variables (8.80 mL, 22.3 mCi, 2.5 mCi/mL).

PATIENTS

15 adult recurrent glioblastoma patients were enrolled across two study sites: UT Heath San Antonio (7) and UT Southwestern Medical Center (8) between October 2020 and September 2023. Eligible participants were at least 18 years of age, were able to provide written consent, had histologically confirmed recurrent glioblastoma (1 recurrence), were bevacizumab-naïve, and had an enhancing tumor volume within the treatment field volume. All but two patients had tumor volumes equal to or less than 20 mL.

40% were female and 93.3% were white and non-Hispanic. The median age of patients was 60 years at time of informed consent (range 41-79).

All 15 patients were WT for IDH mutational status. MGMT status was methylated in 8 patients and unmethylated in 7 patients.

IMAGING

Planar and tomographic (SPECT/CT) images were collected from all subjects using a dual-detector SPECT/CT camera. A sealed ^{186}Re radioactivity vial with known ^{186}Re 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 **Figures 2 and 3**.

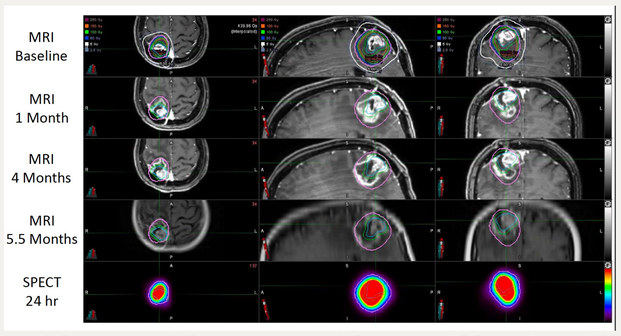

Figure 2. Pretreatment MRI, post treatment MRIs (1, 4, and 5.5 months), and SPECT (24-hours post treatment). Patient is still alive at time of reporting, with OS of 938 days.

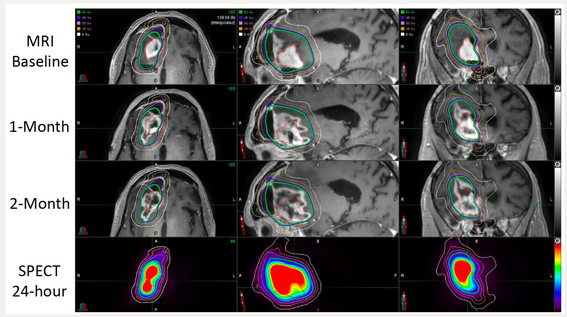

Figure 3. Pretreatment MRI, post treatment MRIs (1 and 2 months), and SPECT (24-hours post treatment). Patient is still alive at time of reporting, with OS of 273 days.

ABSORBED DOSE, PERCENT TUMOR COVERAGE, AND VOLUME OF DISTRIBUTION

The mean volume of distribution was 97.23 mL. Median tumor size was 5 mL.
All 15 patients received 22.3 mCi of ^{186}RNL in 8.8 mL. The average absorbed dose to the tumor was 309.14 Gy (range 62.60-739.5 Gy) (**Table 2**). An average absorbed dose of greater than or equal to 100 Gy was achieved in all but two patients.

The average percent of treated tumor (at 120 hours) across all 15 patients was was 87.2%, with 13/15 patients receiving greater than or equal 70% tumor volume coverage.

Patient ID	Tumor Volume (mL)	Percent of Tumor Volume Treated	Average Absorbed Dose to the Tumor (Gy)
01-019	5.20	34.4%	93.20
01-020	1.00	100.0%	424.60
01-021	22.76	63.2%	62.60
01-024	5.00	100.0%	123.10
01-026	11.00	100.0%	215.70
01-027	1.20	100.0%	338.7
01-028	3.8	100.0%	194.6
02-001	22.00	87.5%	342.70
02-002	3.50	99.4%	739.50
02-003	2.40	77.4%	584.20
02-004	8.90	87.7%	105.20
02-006	9.90	70.8%	353.20
02-009	0.90	99.1%	440.80
02-013	4.90	94.1%	353.8
02-014	17.5	94.7%	265.2

Table 2. Average Absorbed dose to the tumor and Percent Tumor Coverage per patient.

SAFETY

A single dose of ^{186}RNL was **generally safe and well-tolerated**, with no dose limiting toxicities observed and minimal systemic radiation exposure across 15 patients. No patient had treatment-related adverse events (AEs) with outcome of death, and no patient withdrew due to AEs.

Most AEs were mild (Grade 1, 66.35%) or moderate (Grade 2, 25%) The AEs with the highest incidence (>5%) were headache (12.5%) and fatigue (5.77%). Only 7 severe adverse events (SAEs) were reported, and of these, only one was possibly related to study drug (cerebral edema, grade 3) which was also attributed to a rapid corticosteroid taper and resolved.

Mean normalized organ absorbed radiation doses were highest in the liver, spleen, and urinary bladder wall as expected. Because of its smaller size, the spleen is anticipated to be the critical organ for dosimetry calculations; the absorbed dose was well within acceptable absorbed doses for these organs. No other organs showed clinically significant uptake of ^{186}RNL, besides the brain, which included the absorbed dose to the tumor.

SURVIVAL

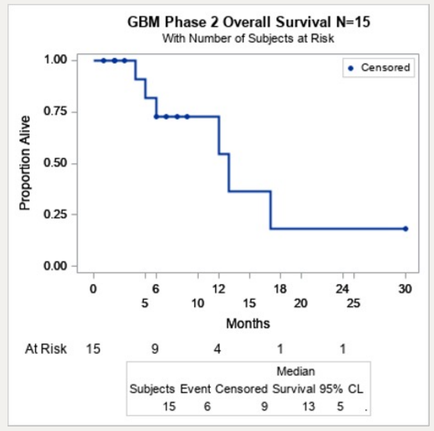

Figure 4a. Overall Survival (OS) Kaplan-Meier.

Median overall survival (mOS) was **13 months** (95% CI 5 months-NA) (**Figure 4a**). This is consistent with Phase 1 (Cohorts 1-6) data previously reported that showed a mOS of 17 months (95% CI 8-35 months) for >100 Gy (n=12). Nine patients were alive and censored at the time of analysis.

Median progression free survival (mPFS) was **11 months** (95% CI 6-11 months) (**Figure 4b**). This is consistent with Phase 1 (Cohorts 1-6) data previously reported that showed a mPFS of 6 months for ≥100 Gy (95% CI 3-8 months). Nine patients were alive and censored at the time of analysis.

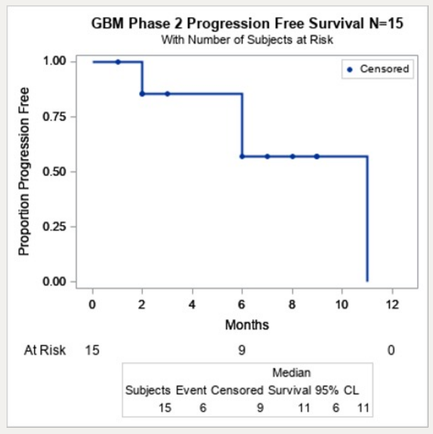

Figure 4b. Progression free survival (PFS) Kaplan-Meier.

CONCLUSION

- The mOS in 15 patients was 13 months (95% CI 5 months) and the mPFS was 11 months (95% CI 6-11 months) with 9 alive and censored patients, tracking consistently with Phase 1 data previously presented.
- Critically, this is a significant improvement over the ~8-month mOS for bevacizumab, the only approved treatment for recurrent GBM.
- Greater than 100 Gy absorbed dose to the tumor and 70% percent tumor volume coverage was observed in 86% of patients treated.
- A single dose of ^{186}RNL was safe and well tolerated.
- No dose limiting toxicities were found.
- Minimal systemic radiation exposure was reported.
- ^{186}RNL delivered directly by CED provides up to 20 times the absorbed dose of radiation that can be administered by EBRT.
- SPECT/CT can accurately and reliably detect the tumor location and be used to quantify the absorbed dose to the tumor and organs.
- Phase 2 is currently enrolling.

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CLINICAL TRIAL ID: 116117
CLINICALTRIALS.GOV IDENTIFIER: NCT01906385

TO LEARN MORE ABOUT RHENIUM (^{186}RE) OBISBEMEDA AND THE RESPECT-GBM CLINICAL TRIAL, VISIT: HTTPS://WWW.RESPECT-TRIALS.COM/ENROLLMENT/

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.