Safety and Feasibility Results from a Phase 1/2 Clinical Trial of Rhenium (^{186}Re) Obisbemeda (^{186}RNL) in Recurrent Glioma: The ReSPECT-GBM Trial

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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.

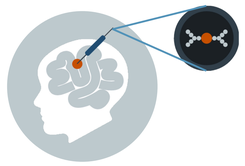
Traditionally, radiation exposure to adjacent normal brain tissue limits the use of External Beam Radiation Therapy (EBRT) to typical doses of ~30-50 Gray (Gy). As most glioma recurrences are within 2 cm of the resection margin, radiopharmaceuticals that can be delivered directly to the tumor and minimize 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 186RNL showed no test article-related pathologic changes at the highest administered amount (6 mCi).

For GBM, ^{186}RNL is administered via Convection Enhanced Delivery (**Fig. 1**).

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



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).

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**).

Phase / Cohort	Infused Volume (mL)	Total ^{186}RNL Activity Infused (mCi)	Concentration (mCi/mL)	Patients Treated
Phase 1 – 1	0.66	1.0	1.5	3
Phase 1 – 2	1.32	2.0	1.5	3
Phase 1 – 3	2.64	4.0	1.5	3
Phase 1 – 4	5.28	8.0	1.5	3
Phase 1 – 5	5.28	13.4	2.5	3
Phase 1 – 6a	8.80	22.3	2.5	3
Phase 1 – 6b	8.80	22.3	2.5	3
Phase 1 – 7	12.3	31.2	2.5	3
Phase 1 – 8	16.34	41.5	2.5	4/6
Phase 2	8.8	22.3	2.5	6/34

Table 1. ReSPECT-GBM Trial with dose escalation for Cohorts 1-8 and Phase 2 at the Cohort 6 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 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.

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.

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

The average tumor volume across 34 patients was 10.25 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 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 ^{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 **Figure 2**.

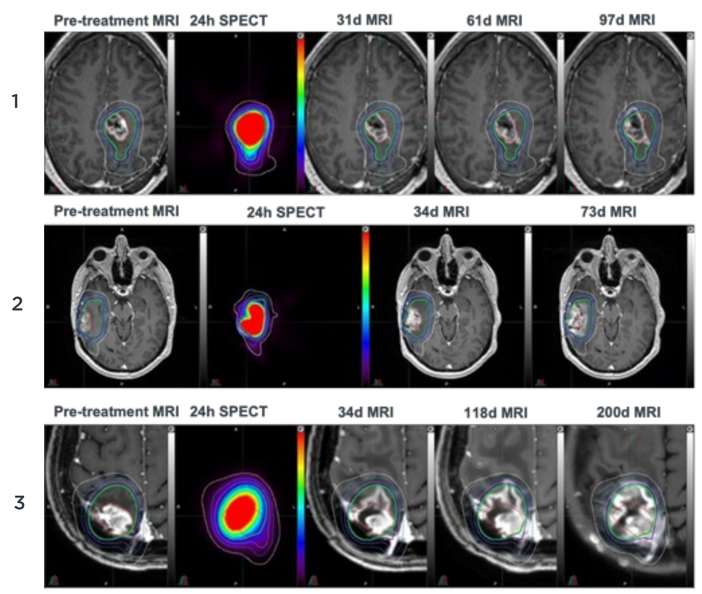


Figure 2. Pretreatment MRI, 24-hr post-treatment SPECT, and post-treatment MRI. (1) Phase 1 patient, Cohort 4. (2) Phase 1 patient, Cohort 5. (3) Phase 1 patient, Cohort 6. Overall survival ranged from 750-1200 days. One patient remains alive.

ABSORBED DOSE

28 patients in the Phase 1 received ^{186}RNL in doses ranging from 1.0 – 41.5mCi in volumes ranging from 0.6 – 16.3 mL. 6 patients in the Phase 2 received a dose of 22.3 mCi in a volume of 8.8 mL. The 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 (**Table 2**). The average absorbed dose to the tumor for five Phase 2 patients was 248 Gy (**Table 2**). 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 5 Phase 2 patients (100%). The average percent of treated tumor was 75%, with only 8/33 (24%) receiving <70% tumor coverage. Representative dosimetry analysis is shown in **Figure 3**.

Phase / Cohort	Average Absorbed Dose
Phase 1 – 1	199
Phase 1 – 2	122
Phase 1 – 3	233
Phase 1 – 4	171
Phase 1 – 5	423
Phase 1 – 6a	287
Phase 1 – 6b	462
Phase 1 – 7	308
Phase 1 – 8	198
Phase 2	248

Table 2. Average absorbed doses to the tumor per Phase/Cohort.

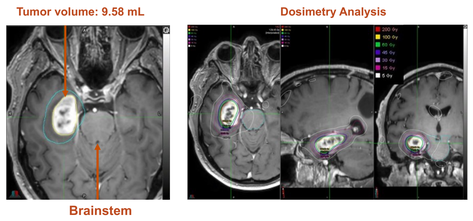


Figure 3. Phase 2 patient presented with rapidly progressing, deep brain rGBM, adjacent to the brainstem. 3 catheters, 8.8 mL infused volume, 22.3 mCi total injected radioactivity used per protocol. 186RNL tumor coverage at EOI was 94.6%. The mean tumor dose was 105 Gy. The patient was still alive at >100 days post treatment.

SAFETY

A single dose of ^{186}RNL was generally well-tolerated, with no dose limiting toxicities observed and minimal systemic radiation exposure across 28 Phase 1 patients/8 dose Cohorts and 6 Phase 2 patients. No patient had treatment-related adverse events (AEs) with outcome of death, and no patient withdrew due to AEs. The MTD was not reached.

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.

SURVIVAL

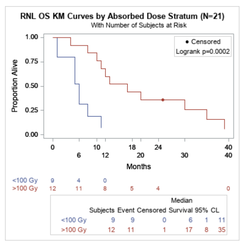


Figure 4. Overall Survival (OS) Kaplan-Meier by absorbed dose.

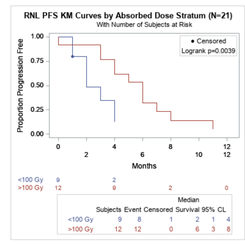


Figure 5. Progression Free Survival (PFS) Kaplan-Meier by absorbed dose.

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 (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.

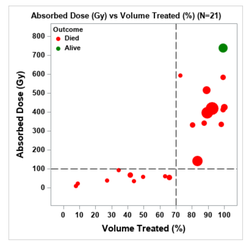


Figure 6. Absorbed dose to tumor by percent tumor volume treated.

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=21) was 11-months (95% CI 5 to 17-months) with 1 patient remaining alive 20-months after treatment.

When dichotomized by absorbed dose of 100Gy, a significant difference was observed with a median OS of 6-months (95% CI 1 to 11-months) for <100 Gy (n=9) and 17-months (95% CI 8-35-months) for ≥100 Gy (n=12) (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).

CONCLUSION

+ Results from Phase 1 (Cohorts 1-8) and 6 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 and Accelerated Failure Time 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. The MTD was not reached.
+ 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 more than 70% of 33 patients treated.
+ Phase 1 Cohort 8 and Phase 2 (tumor size ≤20 cm^3) studies are currently enrolling.

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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.