Update Report of the ReSPECT Trials: Treatment of Recurrent Glioblastoma and Leptomeningeal Metastases with Rhenium (^{186}Re) Obisbemeda

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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. Durable, localized treatment with beta emitters, like ^{186}Re, has the potential to dramatically widen the therapeutic window, increase the delivered dose, and avoid normal tissue exposure. ^{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, localized absorbed radiation doses.

ReSPECT-GBM: 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. In preclinical models of glioma, ^{186}RNL delivered directly to the tumor eradicated transplanted tumor cells with absorbed dose of >100 Gy, 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 rGBM, ^{186}RNL is administered via Convection Enhanced Delivery (CED) (**Figure 1**).

ReSPECT-LM: Leptomeningeal metastasis (LM) is a devastating cancer of the CSF and membranes surrounding the brain and spinal cord, diagnosed in approximately 5-15% of all cancer patients. Typical treatment strategies include optimal systemic therapy for the primary disease, as well as neuroaxis-directed therapy, which may include intrathecal chemotherapy or radiotherapy. EBRT is given over multiple fractions to limit toxicity including myelopathy and marrow suppression given the dose to the brain, spinal cord, and surrounding tissues. With treatment, median overall survival is 2-6 months; without treatment, 4-6 weeks. For LM, ^{186}RNL is infused via Ommaya reservoir (intraventricular catheter) (**Figure 1**).

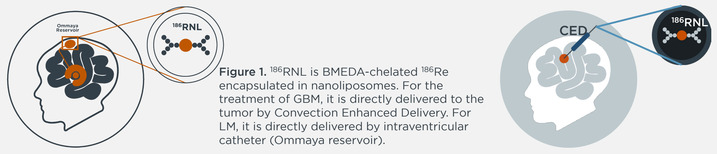

Figure 1. ^{186}RNL is BMEDA-chelated ^{186}Re encapsulated in nanoliposomes. For the treatment of GBM, it is directly delivered to the tumor by Convection Enhanced Delivery. For LM, it is directly delivered by intraventricular catheter (Ommaya reservoir).

ReSPECT-GBM PHASE 1/2

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** is to determine an **MTD/MFD** utilizing a modified 3+3 Fibonacci design. The **primary objective of the Phase 2 study** is to assess overall survival (OS) following ^{186}RNL administration. **Table 1** provides the administered dose, volume, and concentration over the dosing cohorts, with the recommended phase 2 dose (RP2D) derived from Cohort 6's parameters.

Cohort	Infused Volume (mL)	Total ^{186}RNL Activity Infused (mCi)	Concentration (mCi/mL)	
1	0.66	1.0	1.5	
2	1.32	2.0	1.5	
3	2.64	4.0	1.5	
4	5.28	8.0	1.5	
5	5.28	13.4	2.5	
6	8.80	22.3	2.5	RP2D
7	12.3	31.2	2.5	
8	16.34	41.5	2.5	

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

Methods: Brainlab iPlan Flow software was used to plan BrainLab Flexible Catheter placement in the tumor while avoiding white matter tracts and CSF spaces. 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.

Patients: 28 Phase 1 patients and 9 Phase 2 patients were enrolled across three study sites: UT Heath San Antonio (25), UT Southwestern Medical Center (13), and MD Anderson (1). Eligible participants are at least 18 years of age, able to provide written consent, have histologically confirmed recurrent WHO Grade 3 or 4 glioma, and an enhancing tumor volume within the treatment field volume in the respective cohort. Phase 2 patients are further restricted to histologically confirmed recurrent glioblastoma (1 recurrence), bevacizumab-naïve, with tumors ≤20cm^3. For the Phase 1, 26 had Grade 4 glioma. For those genotyped, IDH mutational status was WT in 21 and MGMT status was methylated in 7. For Phase 2, all were IDH WT and MGMT was methylated in 8.

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**.

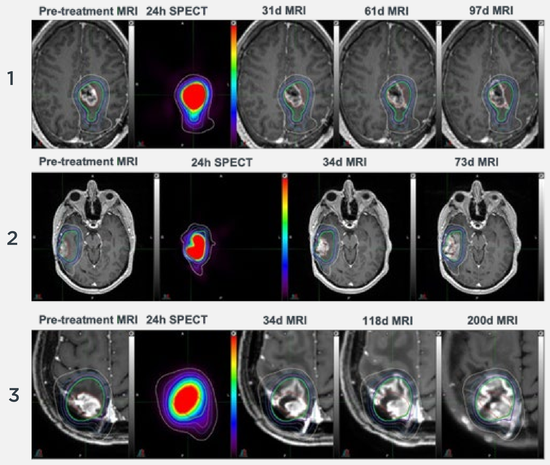

Figure 2. Pretreatment MRI, 24-hr post-treatment SPECT, and post-treatment MRI. (1) Phase 1 patient, Cohort 4. (2) Phase 1 patient, cohort 5. (3) Phase 1 patient, Cohort 6. Overall survival ranged from 750-1200 days.

Absorbed Dose, Percent Tumor Coverage, and Volume of Distribution: Early cohorts in the Phase 1 explored safety across all variables, with one catheter used and ^{186}RNL volumes not exceeding 3 mL (Cohorts 1-3); further cohorts (4-8) expanded these parameters. The mean volume of distribution (mVd) across all cohorts was 70.59 mL and generally increased over each cohort. Tumor size generally increased over cohorts; notably, each patient in Cohort 8 had tumor sizes of greater than or equal to 20 mL. 28 Phase 1 patients received ^{186}RNL in doses ranging from 1.0 – 41.5 mCi in volumes ranging from 0.60 – 16.34 mL. The average absorbed dose to the tumor for all Phase 1 patients was 264 Gy (range: 8.9-739.5 Gy). An average absorbed dose of ≥100 Gy was achieved in 18/28 (64.3%) of patients. The average percent of treated tumor (at 120 hours) across all 28 patients was was 69.7%, with 17/28 patients receiving ≥70% tumor coverage. For the Phase 2 patients, including the 6 patients from Cohort 6 with the same dosing parameters (n=15 total), the mean volume of distribution was 97.23 mL. Median tumor size was 5 mL. The average absorbed dose to the tumor was 309.14 Gy (range 62.60-739.5 Gy). An average absorbed dose of ≥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 ≥70% tumor volume coverage.

Safety: A single dose of ^{186}RNL was generally well-tolerated, with no dose limiting toxicities observed and minimal systemic radiation exposure. No patient had treatment-related adverse events (AEs) with outcome of death, and no patient withdrew due to AEs. There were no DLTs and the MTD was not reached in the Phase 1 dose escalation study. For the Phase 1, most adverse events (AEs) were mild (Grade 1, 66.67%) or moderate (Grade 2, 25.71). The AEs with the highest incidence were headache (6.67%), fatigue (5.24%), muscular weakness (4.29%), seizure (4.29%), and gait disturbance (3.33%). Only 8.1% severe adverse events (17) were reported, and of these, only two were possibly related to study drug (cerebral edema, grade 3 and decreased platelet count, grade 2). Both were resolved with treatment. No meaningful differences or patterns in the incidence of treatment emergent AEs across cohort groups were observed. Likewise, for the Phase 2, 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, but well within acceptable absorbed doses for these organs.

Phase 2 Survival: The median overall survival (mOS) was **13 months** (95% CI 5 months-NA) (**Figure 3a**). 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. The median progression free survival (mPFS) was **11 months** (95% CI 6-11 months) (**Figure 3b**). 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.

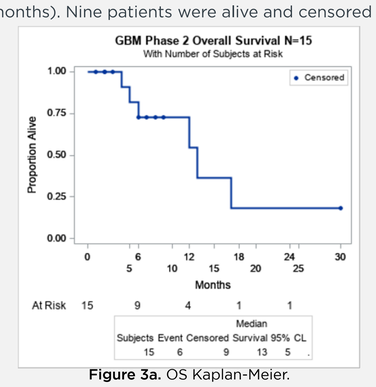

Figure 3a. OS Kaplan-Meier.

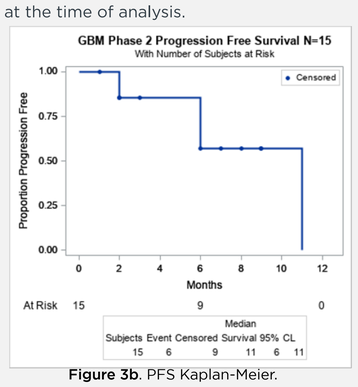

Figure 3b. PFS Kaplan-Meier.

Summary:

+ Rhenium (^{186}Re) Obisbemeda continues to demonstrate a favorable safety profile, despite delivering up to 20x the dose of radiation (up to 740 Gy) that is typically delivered by EBRT for rGBM patients (up to 35 Gy).
+ mOS in 15 patients from the Phase 2 study is 13 months vs. ~8 months for standard of care (bevacizumab)[1]; mPFS is 11 months, compared to bevacizumab at 3-4 months[1]
+ Phase 2 is currently enrolling

[1]Cloughesy et. al, Neuro Oncol. 2020 May 15;22(5):705-717. doi: 10.1093/neuonc/noz232.

ReSPECT-LM

Study Design: ReSPECT-LM is a multi-center, sequential cohort, open-label, dose-escalation, Phase 1 clinical trial to evaluate the safety and tolerability of a single dose of ^{186}RNL given by the intraventricular route (Ommaya reservoir) in adult patients with LM from any primary cancer. The **primary objective of the Phase 1 study** is to determine a maximum tolerated dose (MTD)/maximum feasible dose (MFD) over 7 cohorts utilizing a modified 3+3 Fibonacci design (**Table 2**).

Cohort	Infused Volume (mL)	Total ^{186}RNL Activity (mCi)	Concentration (mCi/mL)	Increase	Status
1	5	6.6	1.32	N/A	Complete
2	5	13.2	2.64	100%	Complete
3	5	26.4	5.28	100%	Complete
4	5	44.10	8.82	67%	Complete
5	5	66.14	13.23	50%	Enrolling
6	5	87.97	17.59	33%	Pending
7	5	109.96	21.99	25%	Pending

Table 2. ReSPECT-LM dose escalation schema for Cohorts 1-7. Cohort 5 is currently enrolling.

Patients are at least 18 years of age, have proven and documented LM (EANO-ESMO Clinical Practice Guidelines Type 1 and 2, except for 2D), Karnofsky performance status of 60-100, and standard organ function. Patients with any prior radiation dose to the spinal cord or whole brain radiation therapy are excluded from the study. Because 10-70% of subjects with LM have some sort of CSF flow abnormality, all study participants require a diagnostic CSF flow study using ^{111}In-DTPA prior to ^{186}RNL infusion. Patients are given supersaturated potassium iodide (SSKI) prior to treatment. ^{186}RNL is delivered intraventricularly through an Ommaya reservoir (5 mL, 1mL/min infusion). Whole Body Planar is completed at end of infusion (EOI) and 3.5-, 24-, 48-, and 168-hours post-infusion. SPECT/CT imaging is completed 45-minutes and 24-hours after EOI. Samples of the CSF are drawn via the Ommaya reservoir at various intervals to monitor radioactivity, estimate absorbed dose, and perform pharmacodynamic studies, such as determination of DNA damage markers, tumor cell count, and standard of care cytology analysis. Urine samples are collected at 0-24-hour and 24-48-hour intervals for radioactivity measurements. Likewise, blood samples are collected after ^{186}RNL infusion at various timepoints to estimate the absorbed dose to red marrow. Study subjects are routinely assessed by MRI (standard of care) until disease progression according to RANO criteria.

Patients: 16 patients were treated with ^{186}RNL over 4 cohorts. Patients were treated over three study sites: UT Heath San Antonio (7 patients), UT Southwestern (8 patients), and Northwestern (1 patient). Patients of all primary tumors are included in the Phase 1 study. The majority of the patients had breast cancer as their primary tumor.

CSF Tumor Cell (CSF-TC) Analysis: The CNSide assay was used for CSF tumor cell enumeration. CSF was removed via the Ommaya reservoir at various time points and tumor cells were captured using a biotinylated 10-antibody capture cocktail and immobilized in a streptavidin coated microfluidic channel. Cancer cells were identified with various Immunocytochemistry markers (e.g., Cytokeratin, CD45) and cells were quantified via digital analysis of the microfluidic channels. Tumor cells were defined as DAPI positive, CD45 negative, Cytokeratin positive or negative, and Streptavidin positive. **Figure 4** provides the percent change of tumor cell counts to predose at 24-hours, 48-hours, 28-days, and 56-days post infusion for patients with reported data. **Table 3** provides average percent change per Cohort (1-3).

Cohort	Number of evaluable subjects	Dose (mCi)	Average Percent Change in CSF-TC number at Day 28 compared to Baseline
1	3	6.6	- 65%
2	3	13.2	- 6%
3	1	26.4	- 81%

Table 4. Average percent change of CSF tumor cells by Cohort.

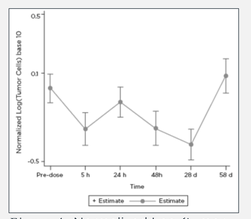

Figure 4. Normalized Log (tumor cells) by time.

Safety: To date, we have not reached MTD/MFD. The majority of AEs are mild or moderate with only one AE of Grade 5 (systemic disease progression) with an attribution of unrelated to study drug. All SAEs re not related or unlikely related to study drug except for one. The one possibly related SAE was also attributed to the patient's pre-existing condition.

Absorbed Dose: Table 4 reports the average absorbed dose of cranially located, subarachnoid cerebral spinal fluid for the ventricles and cranial subarachnoid (SA) space, ventricles (Lateral, 3rd, and 4th), and cranial subarachnoid space. Additionally, we measured the average absorbed dose in the spinal fluid, liver, and spleen. Organ doses remain low while absorbed dose to the CNS increased with administered dose.

Cohort	Ventricles and Cranial Subarachnoid Space Absorbed Dose (Gy)	Ventricles (Lateral, 3rd, and 4th) Absorbed Dose (Gy)	Cranial Subarachnoid Space Absorbed Dose (Gy)	Spinal Fluid Absorbed Dose (Gy)
1	24.84	19.26	27.95	6.88
2	40.86	25.43	49.49	20.73
3	63.83	25.96	85.73	44.07
4	164.96	77.07	213.86	77.78
5	207.44	90.11	273.62	142.12

Table 4. Average absorbed doses treated with a single dose of ^{186}RNL. Cohort 5 is still enrolling,

Summary:

+ Over 4 Cohorts, Rhenium (^{186}Re) Obisbemeda has shown to be well tolerated with the majority of AEs as mild or moderate and the MTD/MFD has not been reached
+ SPECT/CT imaging shows that the drug circulates throughout the CSF space by 1-hour following administration and persists in the CSF for up to 7-days
+ High radiation doses are delivered to areas of tumor, with low organ doses
+ Cohort 5 is currently enrolling

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CLINICAL TRIAL IDS: ReSPECT-GBM 116117, ReSPECT-LM 153715

CLINICALTRIALS.GOV IDENTIFIERS: ReSPECT-GBM NCT01906385, ReSPECT-LM NCT05034497

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

DISCLOSURES: THESE STUDIES WERE SUPPORTED BY AN NCI AWARD 1R01CA235800, A PILOT AWARD FROM MAYS CANCER CENTER P30CA054174, COMMERCIALIZATION AWARDS FROM CPRIT DP150021 AND CPRIT DP220039, AND PLUS THERAPEUTICS. ^{186}RNL IS AN INVESTIGATIONAL TREATMENT.