Update Report of the ReSPECT-GBM Phase 1 Dose Escalation Trial of Rhenium (^{186}Re) Obisbemeda (^{186}RNL) in Recurrent Glioma via Convection Enhanced Delivery

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INTRODUCTION

Recurrent glioma, including histologically confirmed glioblastoma (GBM), is the most aggressive or primary brain tumors in adults. Bevacizumab (anti-VEGF monoclonal antibody), granted provisional approval under FDA's accelerated approval program in May 2009 and full approval in December 2017, remains the only currently approved therapeutic for salvage treatment, however the median progression-free survival (PFS) is <4 months and median overall survival (OS) is ~8 months. This has prompted the National Comprehensive Cancer Network (NCCN), patient advocacy groups, and other oncology medical societies to unanimously recommend treatment in clinical trials for these patients.

Rhenium (^{186}Re) obisbemeda (^{186}RNL) 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).

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 recurrent 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 tumor absorbed radiation doses. ^{186}RNL is administered via Convection Enhanced Delivery (CED) (**Figure 1**).

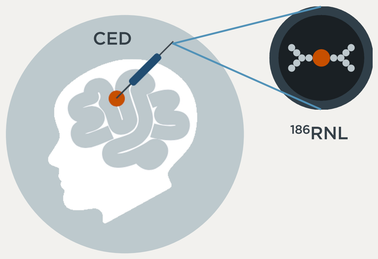

Figure 1. ^{186}RNL is BMEDA-chelated ^{186}Re encapsulated in nanoliposomes. For the treatment of GBM, it is directly delivered to the tumor by Convection Enhanced Delivery.

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 1 study** was to determine an **MTD/MFD** utilizing a modified 3+3 Fibonacci design (**Table 1**). *Data provided herein includes 28 Phase 1 patients treated to date.*

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

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 (Abstract 1567102).

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.

PATIENTS

28 adult recurrent glioma patients were enrolled in the Phase 1 study across three study sites: UT Heath San Antonio (21), UT Southwestern Medical Center (6), and MD Anderson (1) between June 2015 and May 2023. Eligible participants were at least 18 years of age, had recurrent glioma of any number of recurrence, were able to provide written consent, had histologically confirmed recurrent WHO Grade 3 or 4 glioma (per 2016 WHO classification), and had an enhancing tumor volume within the treatment field volume in the respective cohort. 18 patients were male, 92.9% were white, and 89.3% were non-Hispanic. The protocol was modified after Cohort 4 to exclude patients with Grade 3 glioma or prior bevacizumab treatment (5 early patients with prior bevacizumab therapy correlated with poor ^{186}RNL convection to the tumor, lower tumor coverage and lower tumor absorbed dose).

26 patients had Grade 4 glioma and two had Grade 3. For those genotyped, IDH mutational status was WT in 21 patients and mutated in three patients (two were not otherwise specified and two had insufficient quantity to process). MGMT status was methylated in seven patients and unmethylated in 17 patients (two had insufficient quantity to process and two were unknown).

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**.

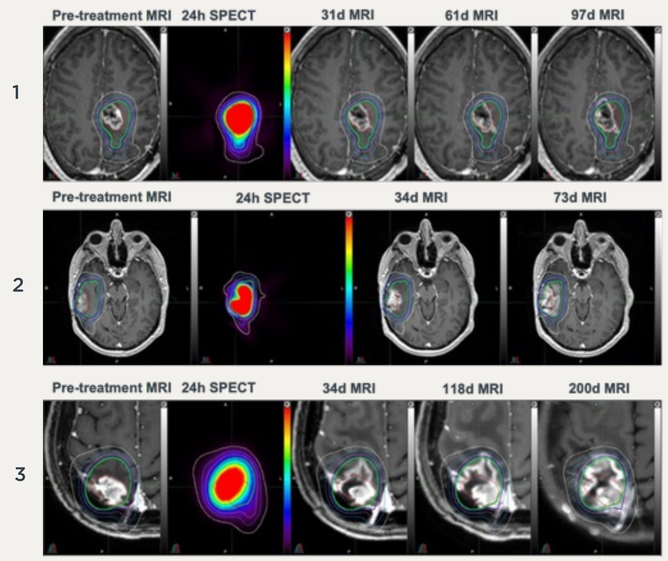

Figure 2. Pretreatment MRI, 24-hr post-treatment SPECT, and post-treatment MRI. (1) Phase 1 patient, cohort 4. (2) Phase 1 patient, cohort 5. (3) Phase 1 patient, cohort 6. Overall survival ranged from 750-1200 days.

ABSORBED DOSE, PERCENT TUMOR COVERAGE, AND VOLUME OF DISTRIBUTION

Early cohorts 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 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) (**Table 2**). An average absorbed dose of greater than or equal to 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 greater than or equal 70% tumor coverage.

Cohort	Average Absorbed Dose (Gy)	Average Percent of Treated Tumor Volume	Average Volume of Distribution (mL)	Average Tumor Volume (mL)
1	199	79.60%	18.83	1.82
2	122	32.25%	16.96	4.23
3	233	47.03%	23.63	13.05
4	171	61.87%	44.90	8.00
5	423	95.47%	73.87	11.70
6	374	76.98%	65.57	9.48
7	308	76.40%	87.50	10.85
8	Enrolling	Enrolling	Enrolling	Enrolling

Table 2. Cohort 8 is still enrolling so average numbers across the completed full cohort are not available.

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. 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 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.

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 (**Table 3**).

ORGAN	Cohort 1 cGy/mCi	Cohort 2 cGy/mCi	Cohort 3 cGy/mCi	Cohort 4 cGy/mCi	Cohort 5 cGy/mCi	Cohort 6 cGy/mCi	Cohort 7 cGy/mCi	Cohort 8 cGy/mCi	All 28 Patients cGy/mCi
Adrenals	0.17	0.01	0.05	0.02	0.06	0.03	0.05	0.14	0.07
Breasts	0.17	0.01	0.04	0.02	0.05	0.03	0.04	0.12	0.06
Gallbladder Wall	0.18	0.02	0.06	0.03	0.07	0.04	0.05	0.15	0.07
LLI Wall	0.17	0.54	0.98	1.54	2.66	2.28	0.59	2.70	1.43
Small Intestine	0.17	0.21	0.35	0.73	1.89	1.58	0.43	1.94	0.91
Stomach Wall	0.17	0.01	0.05	0.64	0.33	1.42	1.77	0.27	0.58
ULI Wall	0.17	0.36	0.60	0.87	1.71	1.44	0.39	1.76	0.91
Heart Wall	0.17	0.01	0.04	0.02	0.65	0.75	0.50	0.70	0.36
Kidneys	0.17	0.01	0.05	0.06	6.43	0.98	0.67	0.27	1.08
Liver	1.07	0.87	3.45	1.82	1.95	2.36	2.13	4.56	2.27
Lungs	0.39	0.01	0.04	0.02	0.33	0.03	0.04	0.13	0.13
Muscle	0.17	0.02	0.04	0.02	0.06	0.03	0.05	0.13	0.06
Prostate	0.17	0.01	0.04	0.02	0.06	0.04	0.05	0.13	0.07
Pancreas	0.17	0.01	0.05	0.03	0.06	0.04	0.05	0.14	0.07
Red Marrow	0.14	0.03	0.05	0.03	0.06	0.04	0.04	0.10	0.06
Osteogenic Cells	0.40	0.10	0.15	0.08	0.14	0.10	0.13	0.27	0.17
Skin	0.17	0.02	0.04	0.02	0.06	0.03	0.05	0.12	0.06
Spleen	0.76	0.77	9.58	3.09	4.30	0.76	1.64	15.49	4.55
Testes	0.17	0.00	0.03	0.01	0.05	0.02	0.02	0.02	0.04
Thymus	0.17	0.01	0.04	0.02	0.05	0.03	0.04	0.12	0.06
Thyroid	0.19	0.03	0.05	1.42	0.06	0.66	0.05	0.13	0.33
Urinary Bladder Wall	1.00	0.48	1.02	2.45	1.73	6.41	5.02	2.76	2.61
Uterus	0.17	0.01	0.04	0.02	0.06	0.04	0.05	0.13	0.07

Table 3. Normalized average absorbed organ doses per Cohort. Values in cGy/mCi.

CONCLUSION

- A single dose of ^{186}RNL was safe and well tolerated.
- No dose limiting toxicities were found.
- The MTD was not reached.
- 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.
- Greater than 100 Gy absorbed dose to the tumor was received in ~64% of patients.
- Greater than 70% of the tumor volume was treated in ~70% of patients.
- Critically, our Phase 1 data shows a robust safety and tolerability signal, favorable efficacy, and a clear path for retreatment of tumors that did not receive optimal absorbed dose and/or percent tumor coverage.
- Phase 1, Cohort 8 is enrolling concurrently with our Phase 2 (tumor size ≤20 cm3) study.

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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.