Phase 1A of the ReSPECT-LM Trial: Rhenium (^{186}Re) Obisbemeda (^{186}RNL) in Leptomeningeal Metastases (LM)

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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.

Leptomeningeal metastases (LM) is diagnosed in approximately 5% of patients with metastatic cancer. Survival is poor and limited to a few months in most patients. LM is a devastating clinical complication that occurs when cancer cells invade the leptomeninges and cerebrospinal fluid (CSF) of patients with malignant tumors. Typical treatment strategies include optimal systemic therapy for the primary disease, as well as neuroaxis-directed therapy, which may include intrathecal chemotherapy or radiotherapy, External Beam Radiation Therapy (EBRT) is limited to ~30-50 Gray (Gy) over multiple fractions to limit toxicity including myelopathy and marrow suppression given the dose to the brain, spinal cord, and surrounding tissues.

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 LM. ^{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. For LM, ^{186}RNL is infused via Ommaya reservoir (intraventricular catheter) (**Fig. 1**).

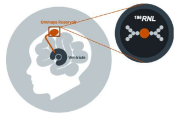

Figure 1. ^{186}RNL is BMEDA-chelated 186rhenium encapsulated in nanoliposomes. For the treatment of LM, it is directly delivered to the CSF via intraventricular catheter (Ommaya reservoir).

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 LM patients. The primary objective of the **Phase 1, Part A** study was to determine a maximum tolerated dose (MTD)/maximum feasible dose (MFD) over 3 cohorts utilizing a modified 3+3 Fibonacci design (**Table 1**).

Phase/Part	Cohort	Infused Volume (mL)	Total ^{186}RNL Activity (mCi)	Concentration (mCi/mL)	Increase
1A	1	5	6,6	1,32	N/A
1A	2	5	13,2	2,64	100%
1A	3	5	26,4	5,28	100%
1B	4	5	44,10	8,82	67
1B	5	5	66,14	13,23	50
1B	6	5	87,97	17,59	33
1B	7	5	109,96	21,99	25

Table 1. ReSPECT-LM Trial with dose escalation for cohorts 1-7. Phase 1, Part A included cohorts 1-3 and is complete. Phase 1, Part B is enrolling.

Phase 1, Part A included cohorts 1-3. Dose level 1 (6.6 mCi) in the first cohort was based on results of the preclinical studies, with dose doubling for cohorts 2 and 3. Patients included on study were at least 18 years of age, had proven and documented LM (EANO-ESMO Clinical Practice Guidelines Type 1 and 2, with the exception of 2D), Karnofsky performance status of 60-100, and standard organ function requirements. For the Phase 1 study, patients with any primary cancer were included. Patients with obstructive or symptomatic communicating hydrocephalus, ventriculo-peritoneal or ventriculo-atrial shunts without programable valves, contraindications to placement of Ommaya reservoir, any prior radiation dose to the spinal cord or whole brain radiation therapy, or standard concomitant illness restrictions were excluded from the study.

Because between 10% and 70% of subjects with LM have some sort of CSF flow abnormality, all study participants required a diagnostic CSF flow study using Indium-111 diethylenetriaminepentaacetic acid (^{111}In-DTPA) following screening and 48-96 hours prior to ^{186}RNL infusion. Failure of the radionuclide to appear in a given CSF compartment was operationally defined as CSF flow block and the patient was classified as a screen fail.

Patients were given supersaturated potassium iodide (SSKI) prior to treatment. 186RNL was delivered intraventricularly through an Ommaya reservoir (5 mL, 1mL/min infusion). Whole Body Planar was completed at end of infusion (EOI) and 3.5-, 24-, 48-, and 168-hours post-infusion. SPECT/CT imaging was completed 45-minutes and 24-hours after EOI.

Samples of the CSF were 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 counts, and other cytology studies. Urine samples were collected at 0-24-hour and 24-48-hour intervals for radioactivity measurements. Likewise, blood samples were collected after the end of infusion at various timepoints to estimate the absorbed dose to red marrow.

PATIENTS

13 patients were consented and screened between March 07, 2022 and March 20, 2023. 10 patients were treated over 3 cohorts between March 16, 2022 and April 12, 2023 (1 withdrew consent and 2 were screen failures). Patients were treated over three study sites: UT Heath San Antonio (5 patients), UT Southwestern (3 patients), and Northwestern (1 patient).

70% of patients were women and 80% were white. Patients ranged in age (at time of treatment) between 35 and 70 years old.

Patients of all primary tumors were included in the Phase 1, Part A of the study. The majority of the patients had breast cancer as their primary tumor (60%), followed by lung (40%).

TUMOR CELL ENUMERATION

Exploratory endpoints included performing analysis on cerebral spinal fluid (CSF) pre- and post-administration of ^{186}RNL to evaluate pharmacodynamic (PD) markers of ^{186}RNL efficacy. For tumor cell enumeration, Biocept's CNSide assay was used. CSF 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 are defined as DAPI positive, CD45 negative, Cytokeratin positive or negative and Streptavidin positive. The entire platform is CLIA validated. **Figure 2** provides the percent change of tumor cell counts to predose at 24-hours, 48-hours, 28-days, and 56-days post infusion for 9/10 patients with reported data. Patients had up to 91% reduction in tumor cell count (max reduction at all time points measured), with an average of 53% reduction at Day 28 (compared to predose; range of 6% increase to 90% decrease).

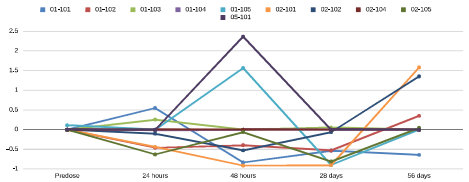

Figure 2. Tumor cell counts by percent change from predose over time for 9 LM patients treated with ^{186}RNL.

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. The planar and tomographic image acquisition uses low energy high resolution parallel-hole collimators (LEHR) with three energy windows setting: 1) Primary energy window: 137 keV (± 10%); 2) Low energy scattering window: 119 keV (± 3.5%); and 3) High energy scattering window: 156 keV (± 3.5%). Representative SPECT/CT images at the two acquisition time points (45-min post EOI and 24-hr post EOI) are shown in **Figure 3**.

Representative whole body planar imaging in **Figure 4** shows durable retention of ^{186}RNL out to 7 days.

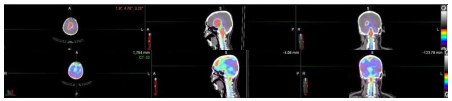

Figure 3. SPECT/CT of LM patient in cohort 2 (13,2 mCi injected activity) at 45-min and 24-hours post intraventricular ^{186}RNL infusion through the Ommaya reservoir.

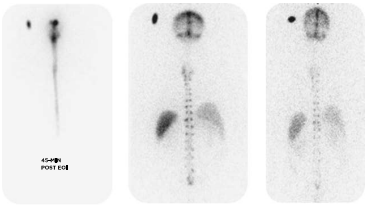

Figure 4. Whole body planar image of LM patient at 0.25-hours, 48-hours, and 7-days post intraventricular ^{186}RNL infusion through the Ommaya reservoir.

SAFETY

10 patients were treated over 3 cohorts, with one patient receiving a second treatment (retreatment protocol) under compassionate use. To date, we have had no DLTs and have not reached MTD/MFD. Of the 10 patients treated, across all three Cohorts, the majority of AEs were mild (Grade 1, 58.7%) or moderate (Grade 2, 24%) with only 1 AE of Grade 4 (stridor) with an attribution of unlikely related to the study drug. Only 8 SAEs were found, and all were 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.

Of the 10 patients enrolled since April 2022, 5 are alive and without evidence or report of radiation toxicity. Additionally, all 5 patient deaths were due to their primary tumor progression.

ABSORBED DOSE

Table 2. Average absorbed doses.

Cohort	Blood Absorbed Dose (Gy)	Liver Absorbed Dose (Gy)	Spleen Absorbed Dose (Gy)	Ventricles and Cranial SA Space Absorbed Dose (Gy)	Ventricles (Lateral, 3rd, and 4th) Absorbed Dose (Gy)	Cranial SA Space Absorbed Dose (Gy)	Spinal Fluid Absorbed Dose (Gy)
1	0.02	0.38	1.82	24.84	19.26	27.95	6.86
2	0.02	0.64	3.61	41.95	25.43	49.49	20.73
3	0.07	1.47	2.40	63.83	25.96	66.73	44.07

Table 2 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.

OVERALL SURVIVAL

The median overall survival (OS) for N=10 patients was **10 months with a 95% confidence interval of 1 month.** 5 patients remained alive and were censored (**Figure 5**).

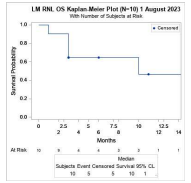

Figure 5. Kaplan-Meier analysis for 10 Phase 1, Part A patients.

CONCLUSION

- 10 of 13 patients with LM received a single intraventricular dose of ^{186}RNL between 6.6 and 26.4 mCi through indwelling Ommaya reservoir.
- In all 10 patients, ^{186}RNL circulated throughout the CSF space by 1-hour following administration and persisted in the CSF for up to 7-days.
- Variability was seen in the absorbed dose in CNS structures but there was a linear increase with increasing administered dose.
- As expected with a nanoliposome formulation, overall organ radiation doses were low, with the liver, spleen, and bladder wall having the most prominent ^{186}RNL clearance but still significantly below any absorbed dose concerns for a critical organ.
- No DLTs were observed and the MTD/MFD was not reached.
- Most AEs were Grade 1 and 2.
- CSF tumor cell enumeration decreased up to 91% following ^{186}RNL treatment.
- Currently, 5/10 treated patients remain alive with a median OS of 10 months (95% confidence interval of 1 month).
- A continued dose escalation design to MTD/MFD (Phase 1, Part B; Cohorts 4-7) is open and enrolling.
- Multi-dose and retreatment protocols are in process.

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CLINICALTRIALS.GOV IDENTIFIER: NCT05034497

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

DISCLOSURES: THIS STUDY WAS SUPPORTED BY CPRIT DP220039. ^{186}RNL IS AN INVESTIGATIONAL PRODUCT UNDER AN APPROVED FDA IND.