Rhenium (^{186}Re) Obisbemeda (Rhenium Nanoliposome, ^{186}RNL) for the Treatment of Leptomeningeal Metastases (LM): Update on Phase 1 Dose Escalation Study

Andrew Brenner[1], Michael Youssef[2], Priya Kumthekar[3], Ande Bao[4], Joel Michalek[1], William Phillips[1], Toral Patel[2], John Floyd[1], Marc Hedrick[5], Leonardo Juverdianu[5], Barbara Blouw[5], Melissa Moore[5]

[1]UT Health San Antonio Mays Cancer Center, [2]UT Southwestern Medical Center, [3]Northwestern University, [4]Case Western Reserve University, [5]Plus Therapeutics

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. Prior studies have shown excellent tolerance with average absorbed doses as high as 734Gy for glioblastoma. Preclinical studies have shown similar excellent tolerance by direct intraventricular injection in rodents with NOAEL of 1mCi and absorbed doses over 1,000Gy.

Leptomeningeal metastasis (LM) is a devastating cancer of the CSF and membranes surrounding the brain and spinal cord. Median overall survival is 2-6 months with treatment and 4-6 weeks without treatment. Given the properties of ^{186}RNL that allow high CSF and cortical exposure with sparing of radiosensitive white matter (Figure 1) and preclinical efficacy, we embarked on a dose escalation phase 1 study in patients with LM.

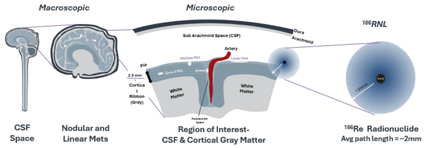


Figure 1. ^{186}RNL allows for the treatment of microscopic disease within the CSF and along the cortical matter with sparing of radiosensitive white matter.

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 186RNL 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 1).**

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%	Complete
6	5	75.00	15.00	13%	Enrolling
7	5	109.96	21.99	25%	Pending

Table 1. ReSPECT-LM dose escalation schema for cohorts 1-7. Cohort 6 is currently enrolling.

The starting dose level of 6.6 mCi (cohort 1) was based on the results of preclinical studies. The cohort 6 dose above is a modified dose escalation in agreement with the DSMB after the safety review of the cohort 5 data. One dose-limiting toxicity (DLT) was noted in cohort 5 (see Safety section) and a reduced escalation of 13% over the cohort 5 dose rather than the original 33% increase was proposed. Adjustments to the cohort 7 dose, if MTD/MFD are not reached in cohort 6, will be determined upon review with the DSMB after full enrollment in cohort 6.

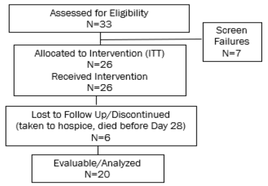
Patients included in the study are ≥ 18 years of age, have proven LM (EANO-ESMO Clinical Practice Guidelines Type 1 and 2, except for 2D), Karnofsky performance status of 60-100, and standard organ function. Patients with obstructive or symptomatic communicating hydrocephalus, ventriculoperitoneal or ventriculo-atrial shunts without programmable valves, contraindications to placement of Ommaya reservoir, any prior radiation dose to the spinal cord or whole brain radiation therapy, or standard concomitant illnesses are excluded from the study. Because 10-70% of subjects with LM have a CSF flow abnormality, all study participants require a diagnostic CSF flow study using 111In-DTPA or low dose (1 mCi) 186RNL following screening and 48-96 hours prior to 186RNL infusion. 186RNL was delivered intraventricularly through an Ommaya reservoir (5 mL, 1 mL/min infusion). Whole body planar imaging is completed at the end of infusion (EOI) and 3.5-, 24-, 48-, and 16 post-infusion. SPECT/CT imaging is completed 45 minutes and 24 hours after EOI. Samples of CSF are drawn via the Ommaya reservoir at intervals to monitor radioactivity, estimate absorbed dose, and perform PD studies. Urine samples are collected at 0-24 and 24-48-hour intervals for radioactivity measurements. Blood samples are collected after 186RNL 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.

Enrollment:
33 patients were consented and screened for enrollment in study cohorts 1-5. There were 7 screen failures, and an additional 6 patients were not evaluable for day 28 assessments. 20 patients were evaluable. Patients were treated with 186RNL over the first 5 cohorts, as described. Ages ranged (at time of treatment) between 29-76 years old. 65% were female and 35% male. Primary tumors were: 45% breast, 25% lung, and 30% other. The 9 evaluable patients with breast cancer had the biomarker profiles shown **(Table 2).**

ER+/HER2-	3
HER2+ (including ER+)	2
ER/PR/HER2-	4

Table 2 (left). Biomarker expression profiles of breast cancer patients (cohorts 1-5).

Flowchart (right). Enrollment paradigm.



Distribution

Planar and tomographic (SPECT/CT) images were collected from all subjects. Representative SPECT/CT images show initial activity within the lateral ventricle at 45m followed by redistribution throughout the leptomeningeal space by 24 hrs **(Figure 2, left).** Representative whole body planar imaging shows durable retention of 186RNL within the leptomeninges through day 7 **(Figure 2, right).**

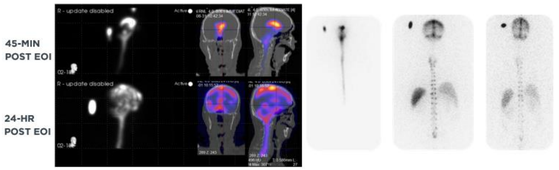


Figure 2. Whole body planar image of LM patient at 0.25 hours, 48 hours, and 7 days post intraventricular 186RNL infusion through the Ommaya reservoir.

Safety

A single DLT was noted thus far at 66.14 mCi administered dose (thrombocytopenia). 17 SAEs (7% of AEs) and 3 SARs (SAEs with at least a 'possible' attribution to study drug) were observed. Of the 3 SARs, there was: (A) encephalopathy (also attributed to steroid taper, resolved spontaneously), (B) headache (resolved with treatment), and (C) thrombocytopenia (resolved with treatment).

	Any Grade	Grade ≥3
	18 (100)	8 (44.4)
Headache	9 (50)	1 (5.6)
Vomiting	7 (38.9)	0
Nausea	4 (22.2)	0
Dizziness	3 (16.7)	0
Alanine Aminotransferase Increase	2 (11.1)	0
Gait Disturbance	2 (11.1)	0
Hypoalbuminemia	2 (11.1)	0
Lymphocyte Count Decreased	3 (16.7)	2 (11.1)
Platelet Count Decreased	2 (11.1)	1 (5.6)
White Blood Cell Count Decrease	2 (11.1)	1 (5.6)
Encephalopathy	1 (5.6)	1 (5.6)
Hydrocephalus	1 (5.6)	1 (5.6)
Left Eye Vision Loss	1 (5.6)	1 (5.6)

Table 3. Treatment-related AEs showing AE name, frequency, and percentage of patients over any grade and grade 3 or above.

**Safety data is partially unmonitored at the time of presentation.*

Absorbed Dose

A dose-dependent increase was observed in the absorbed dose to the cranial and spinal subarachnoid (SA) space, with clinically significant doses occurring in the first cohort and reaching an average absorbed dose to the cranial SA of 253Gy in cohort 5. Conversely, the average absorbed dose in the blood, liver, and spleen was not clinically significant with the exception of blood (bone marrow) absorbed doses approaching general toxicity limits of 2-3 Gy in cohort 5. Target/off-target radiation absorbed dose ratios of >100:1 were observed.

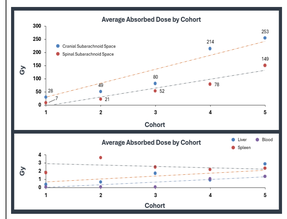


Figure 3. Average absorbed doses over 13 patients treated with a single dose of ^{186}RNL.

Response Assessment

Radiographic response data was available for 8 breast patients as of the data cutoff with 2 of those (25%) showing a response based on investigator assessment. An additional 4 patients showed stable disease through day 112 for a Clinical Benefit Rate (CR+PR+SD) of 75%. Additionally, a clinical response with evident decrease in disease symptoms was noted in 2 of 7 evaluable patients (29%), with 3 (43%) showing stable symptoms through day 112.

Exploratory endpoints included analysis on CSF tumor cells pre- and post-administration of 186RNL using Plus's CLIA-validated CNSide assay. CSF tumor cells were captured using a biotinylated antibody cocktail and immobilized in a streptavidin-coated microfluidic channel. Cells were quantified via immunofluorescent digital analysis of the microfluidic channels. Best response post-treatment as maximum percent change from predose to 28 days post-infusion plotted, with 1/15 showing a complete response and 12/15 showing a partial response **(Figure 4).** One progressed and one was stable. 7/8 breast cancer patients with CTC studies showed partial response, with 1/8 one stable.

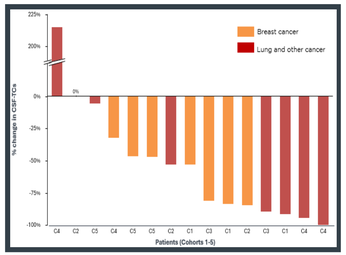


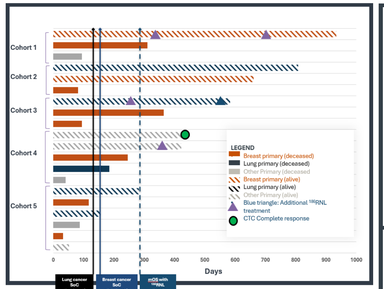
Figure 4. Best response following a single administration of ^{186}RNL .

Response Measure	Response	Stable Disease	Clinical Benefit Rate	Progression	Evaluable Patients	Data Not Available	Total Patients
CTC All	13	1	93%	1	15	5	20
CTC Breast	7	1	100%	0	8	1	9
MRI All	5	7	75%	4	16	4	20
MRI Breast	2	4	75%	2	8	1	9
Clinical All	2	10	86%	2	14	6	20
Clinical Breast	2	3	71%	2	7	2	9

Table 4. Single dose response assessed from pretreatment through 4 months (112 days) follow-up.

Overall Survival

The median overall survival (OS) for n=16 patients (cohorts 1-4) was 9 months (95% CI 1-NA) with 6 alive and censored patients at the time of analysis (November 14, 2024). Median OS for just the breast cancer patients was also 9 months (**Figure 6a and 6b,** respectively). 2/9 patients with breast cancer primaries are still alive at over 600 days post first dose (one has received two additional rounds of dosing as compassionate use). Cohort 5 is not mature and is therefore not included in the Kaplan-Meier analysis.



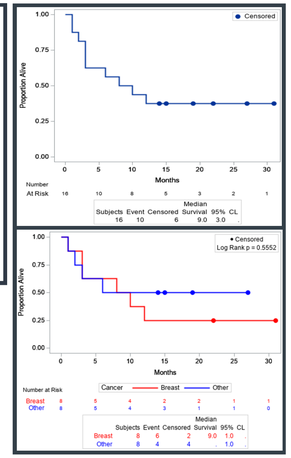


Figure 5 (left). Analysis by primary cancer and survival time in the 20 evaluable patients. 9 patients remain alive at time of analysis (November 2024). Tumors by primary disease Breast: 9 Lung: 5 Other: 6

Figure 6 (right). Kaplan-Meier analyses for 16 Phase 1 patients (**6a**, top) and breast cancer patients as a group compared to all other cancers (**6b,** bottom) in these cohorts.

Conclusions

- 26 patients with LM received a single intraventricular dose of 186RNL between 6.6 and 66.14 mCi through indwelling Ommaya reservoir
- Single dose 186RNL for patients with LM was well tolerated up to 66mCi/253Gy
- One DLT (Grade 4 thrombocytopenia) was observed and the MTD/MFD was not reached
- An objective response rate of 31% was observed with a median OS of 9 months supporting efficacy of 186RNL for leptomeningeal metastases
- CSF tumor cell enumeration decreased up to 100% following 186RNL treatment
- Within the breast cancer patients, response rate and survival are promising
- A multi-dose protocol has been agreed to with the FDA, with enrollment expected to begin in Q1/2025
- A single dose breast expansion cohort is expected to open concurrently in Q1 2025 to expand on single dose safety and efficacy

DR. ANDREW J. BRENNER at BRENNERA@UTHSCSA.EDU;
DR. MARC HEDRICK at MHEDRICK@PLUSTHERAPEUTICS.COM
CLINICAL TRIAL ID: 153715
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.