Rhenium (^{186}Re) Obisbemeda (Rhenium Nanoliposome, ^{186}RNL) for the Treatment of Leptomeningeal Metastases (LM): Summary of the Phase 1 Dose Escalation Study and Phase 2 Administered Dose Selection

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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. 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 (Fig 1) and preclinical efficacy, we embarked on a dose escalation phase 1 study in patients with LM.

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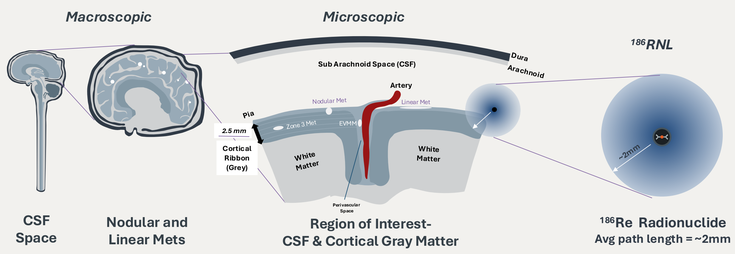


Figure 1. ^{186}RNL allows for treatment of microscopic disease within the CSF and along the cortical matter with sparing of radiosensitive white matter.

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 ^{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 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	TBD	TBD	TBD	Pending

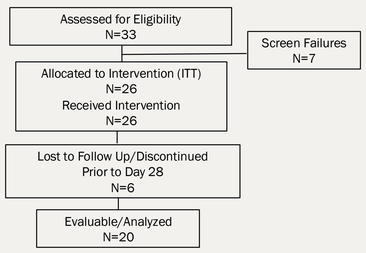
Table 1. ReSPECT-LM dose escalation schema for cohorts 1-7. Cohort 6 is currently enrolling.

The starting dose level of 6.6 mCi (cohort 1) was based on results of preclinical studies. The cohort 6 dose above is a modified dose escalation in agreement with the DSMB after 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 planned 33% increase was proposed. 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 on 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, ventriculo-peritoneal 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 ^{111}In-DTPA or low dose (1 mCi) ^{186}RNL following screening and 48-96 hours prior to ^{186}RNL infusion. ^{186}RNL was delivered intraventricularly through an Ommaya reservoir (5 mL, 1mL/min infusion). Whole body planar imaging 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 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 ^{186}RNL infusion at various timepoints to estimate absorbed dose to red marrow. Study subjects are routinely assessed by MRI (standard of care) until disease progression according to RANO criteria.

PATIENTS

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 ^{186}RNL over the first 5 cohorts, as described. Ages ranged (at time of treatment) between 29-76 years old. 35% were male and 65% female. Primary tumors were: 45% breast, 25% lung, and 30% other.



SAFETY

- A single DLT was noted thus far at 66.14 mCi administered dose (thrombocytopenia).
- Serious Adverse Events*: 17 (7% of AEs).
- 3 SARs (SAEs with at least 'possible' attribution) – (1) encephalopathy (also attributed to steroid taper, resolved spontaneously), (2) headache (resolved with treatment), and (3) thrombocytopenia (resolved with treatment).

*Safety data partially unmonitored at time of presentation- 11/22/2024

	Total N=18	
	Any Grade	Grade ≥ 3
Any TRAE	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 2. Treatment-related adverse events showing AE name, frequency, and percentage of patients over any grade and grade 3 or above.

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 ^{186}RNL within the leptomeninges through day 7 (**Figure 2, right**).

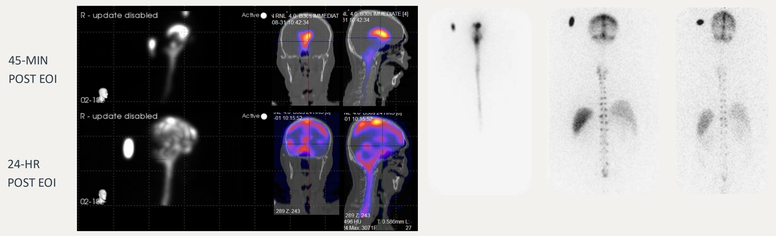


Figure 2. Whole body planar image of LM patient at 0.25-hours, 48-hours, and 7-days post intraventricular ^{186}RNL infusion through the Ommaya reservoir.

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.

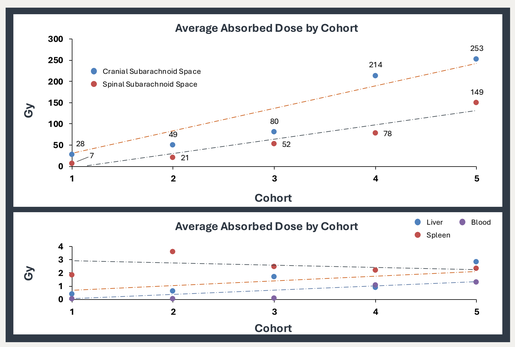


Figure 3. Average absorbed doses over 13 patients treated with a single dose of ^{186}RNL.

RESPONSE ASSESSMENT

Radiographic response data was available for 16 patients as of the data cutoff with 5 of those (31%) showing a response based on investigator assessment. An additional 7 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 14 evaluable patients (14%), with 10 showing stable symptoms through day 112 for a benefit rate of (86%).

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

Response Measure[1]	Response	Stable Disease	Clinical Benefit Rate	Progression	Evaluable Patients	Data Not Available	Total Patients
CTC	13	1	14	1	15	5	20
Imaging	5	7	12	4	16	4	20
Clinical	2	10	12	2	14	6	20

Table 3. Combined best response vs. baseline after single administration – through 4 months.

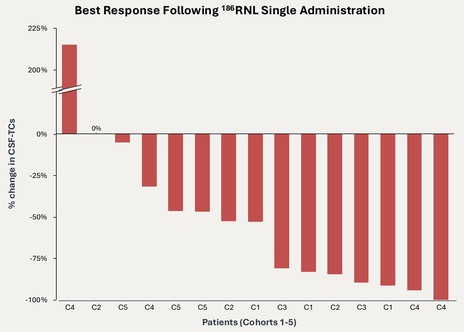


Figure 4. Response in CSF CTCs following ^{186}RNL treatment: 1/15 showed complete response; 12/15 showed partial response.

Exploratory endpoints included analysis on CSF tumor cells pre- and post-administration of ^{186}RNL 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.

OVERALL SURVIVAL

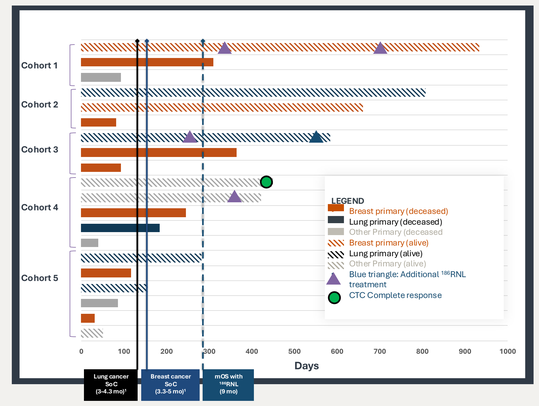


Figure 5. Analysis by primary cancer and survival time in the 20 evaluable patients. 9 patients remain alive at time of analysis (November 2024). Tumors by primary disease Breast: 9 Lung: 5 Other: 6

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) (Figure 6). Cohort 5 is not mature and is therefore not included in the Kaplan-Meier analysis.

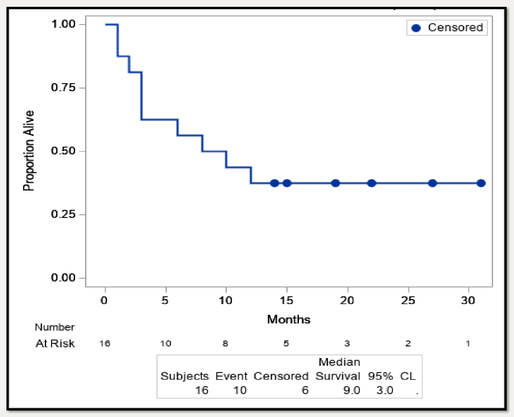


Figure 6. Kaplan-Meier analysis for 16 Phase 1 patients.

SUMMARY AND CONCLUSIONS

+ 26 patients with LM received a single intraventricular dose of ^{186}RNL between 6.6 and 66.14 mCi through indwelling Ommaya reservoir
+ Single dose ^{186}RNL 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 ^{186}RNL for leptomeningeal metastases
+ CSF tumor cell enumeration decreased up to 100% following ^{186}RNL treatment
+ Dose escalation continues at 75mCi with planned dose expansion in breast and lung cancers
+ A multi-dose protocol has been agreed to with the FDA, with enrollment expected to begin in Q1/2025

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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.