Cancer Prevention & Research Institute of Texas

Phase 1 Multicenter Study of Multiple Doses of Rhenium (186Re) Obisbemeda (Reyobiq) for Leptomeningeal Metastases: Rationale, Design, and Preliminary Cohort 1 Data

Andrew Brenner[1], Priya Kumthekar[2], Michael Schulder[3], Eva Galvan[1], Ande Bao[4], Joel Michalek[1], Penny Vroman[1], William Phillips[1], John Floyd[1], Jonathan Yang[5], Michael Rosol[6], Marc Hedrick[6], Michael Youssef[7]

Affiliations: 1) UTHealthSanAntonio, 2) Northwestern Medicine, 3) Hofstra/Northwell Health, 4) Case Western Reserve University, 5) New York University, 6) Plus Therapeutics, 7) UT Southwestern Medical Center

PLUS THERAPEUTICS

Background

- Leptomeningeal metastases (LM) are a devastating complication of solid tumors with limited treatment options and poor survival outcomes.
- Rhenium (186Re) obisbemeda (186RNL) has been studied for the treatment of LM in the recently completed ReSPECT-LM single dose escalation trial (NCT05034497).
- In that trial a single dose of 186RNL was well-tolerated up to a MTD of 66mCi, a recommended phase 2 dose of 44.1 mCi, and absorbed doses delivered of >300 Gy were observed.
- Given the success of the single dose study, we have initiated a multicenter, open-label Phase 1 study to evaluate the safety and efficacy of multiple 186RNL doses and dose levels administered via intraventricular catheter in patients with LM from any primary solid tumor.

Introduction

- Rhenium (186Re) obisbemeda (186RNL), a next generation radiotherapeutic, is BMEDA-chelated 186Re encapsulated in liposomal nanoparticles. 186Re 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 186RNL 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.

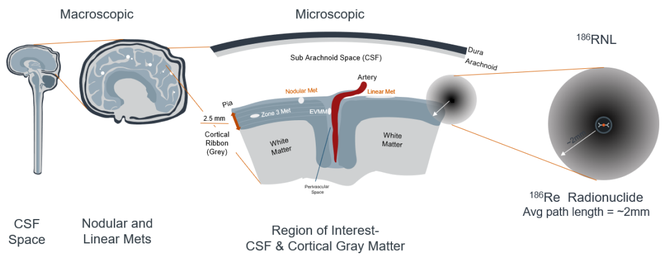


Figure 1. 186RNL allows for treatment of microscopic disease within the CSF and along the cortical matter with sparing of radiosensitive white matter.

ReSPECT-LM Single Dose Design and Results

- Dose escalation: 3+3 modified Fibonacci
- Primary objective: Safety and tolerability
  - Maximum Tolerated Dose (MTD) / Maximum Feasible Dose (MFD) via Ommaya reservoir
- Secondary objectives: Efficacy
  - Overall Response Rate (ORR)
  - Duration of Response (DoR)
  - Progression Free Survival (PFS)
  - Overall survival (OS)
- Other objectives: Analysis on CSF, pK
  - CSF circulating tumor cells (CTCs)
  - Pharmacodynamic (PD) markers & dosimetry

ReSPECT-LM Single Dose Design and Results

	Cohort	Administered Volume (mL)	Administered Activity (mCi)	Administered Concentration (mCi/mL)
	1	5	6.6	1.32
	2	5	13.2	2.64
	3	5	26.4	5.28
RP2D	4	5	44.10	8.82
	5	5	66.14	13.23
Trial Stopped	6	5	75.00	15.00
	7	5	109.96	21.99

Single Administration Phase 1 Dose Escalation Plan

Summary

- Study completed
- 29 patients dosed over 6 cohorts
- Demonstrated feasibility, safety, and showed efficacy signal

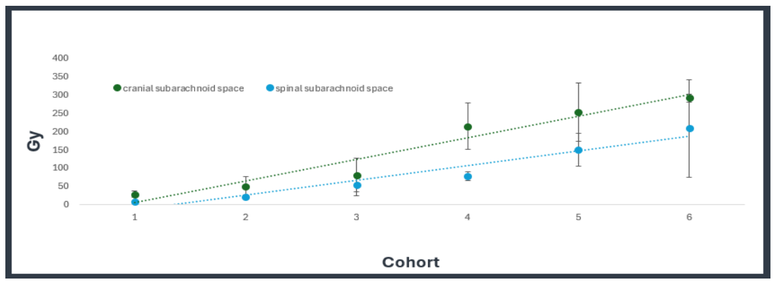
Safety

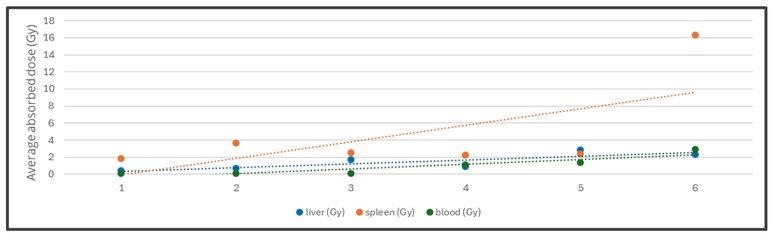
- 1 DLT in cohort 5, 1 DLT in cohort 6
- 1 death due to sepsis deemed unlikely related in cohort 6
- No DLTs or SAEs in cohort 4
- DSMB review of cohort 6 Feb 2025
- RP2D (44.1 mCi) and MFD determined

Results

- Median OS of 9 months in cohorts 1-4 (RP2D) (2-6 months commonly reported in lit.)
- CSF tumor cell enumeration decreased up to 100% following Reyobiq treatment
- 5 of 7 patients with >80% reduction in CTC by CNSide survived at least 1 year

General toxicity limits: Liver: ~35-50 Gy; Spleen: ~40 Gy; Bone marrow: ~2–5 Gy





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 >250Gy by cohort 5. Average absorbed doses in the blood, liver, and spleen were not clinically significant with the exception of blood (bone marrow) absorbed doses approaching general toxicity limits of 2-3 Gy by cohort 5.

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	8	13	4	17	3	20
Clinical	2	11	13	2	15	5	20

Clinical Benefit Rate (CR+PR+SD). CTC response: 93% (14/15); MRI Imaging response: 76% (13/17); Clinical response: 87% (13/15)

ReSPECT-LM Multiple Dose Design

Title: A Multicenter Phase 1/2 Study to Determine the Safety and Efficacy of Multiple Doses at Defined Intervals of Rhenium (186Re) Obisbemeda (Rhenium-186 NanoLiposome, 186RNL) Administered via Intraventricular Catheter for Any Primary Solid Tumor Cancer with Leptomeningeal Metastases (NCT 07098806)

Primary Objective: Phase 1

To characterize the safety and tolerability of multiple doses at defined intervals of 186RNL administered via intraventricular catheter (i.e., Ommaya reservoir) for patients of any primary solid tumor cancer with leptomeningeal metastases and identify an MTD/MFD for a given dose, interval duration, and number of doses

Primary Objective: Phase 2

To characterize the efficacy of multiple doses of the optimal dose/interval selected in the Phase 1/Expansion of 186RNL for participants of any primary solid tumor cancer with leptomeningeal metastases by assessing response using CSF tumor cell enumeration

Dose Level	Dosing Interval (days)	Dose (mCi)	Doses/ Subject	Total Administered Dose (mCi)
Low	56	13.2	3	39.6
	28	13.2	3	39.6
	14	13.2	3	39.6
Medium	56	26.4	3	79.2
	28	26.4	3	79.2
	14	26.4	3	79.2
High	56	44.1	3	132.3
	28	44.1	3	132.3

Phase 1b: Dose Optimization
Dose levels and intervals to be tested. Need minimum of 3 per cohort (can go up to 6 per cohort).

Summary

- We have initiated a multicenter, open-label Phase 1 study to evaluate the safety and efficacy of multiple 186RNL doses administered via intraventricular catheter in patients with LM from any primary solid tumor.
- The study aims to identify the maximum tolerated/feasible dose (MTD/MFD) across varying dosing intervals.
- Enrollment has begun into Cohort 1; with delivery of 13.2 mCi 186RNL at 3 time points, separated by 56 days.
- 3 patients have been enrolled as of data cutoff; 1 patient has received all 3 doses in the 1st cohort without a DLT, with a 2nd completing a 2nd dose.
- This study builds on single-dose findings, aiming to optimize dosing regimens to improve outcomes for LM patients, addressing an unmet clinical need with a novel radiotherapeutic approach.

Acknowledgements

UT Health San Antonio Health Sciences
UT Southwestern Medical Center
Northwell Health

TO LEARN MORE ABOUT RHENIUM (186RE) OBISBEMEDA AND THE RESPECT CLINICAL TRIALS, VISIT: RESPECT-TRIALS.COM