ReSPECT-LM: Maximum tolerated dose, safety, and efficacy of intraventricular Rhenium-186 Nanoliposome (^{186}RNL) for Leptomeningeal metastases

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Introduction

- Leptomeningeal metastases (LM) are a rare but typically fatal complication of advanced cancer affecting the fluid-lined or intrathecal structures of the central nervous system (CNS). Despite affecting over 110,000 subjects per year in the United States alone [1], highly effective, approved treatments are not available.
- Typical treatment strategies include optimal systemic therapy for the primary disease, as well as neuroaxis directed therapies, which may include intrathecal chemotherapy or radiotherapy. Thirty Gray (Gy) given in 10 fractions is a typical radiation dosing scheme [1]. However, no survival benefit of whole brain radiotherapy (WBRT) was observed in most retrospective studies of subjects with LM [2].
- Rhenium 186 is an ideal radionuclide for CNS indications because of its long half-life (~90 hours), short path length of the beta particles (~2mm) low dose rate and high radiation density that overwhelms proliferating cellular innate DNA repair mechanisms. Furthermore, liposomal encapsulation has been shown to prolong retention in the brain and CSF.
- Preclinical studies in rat model of LM show tolerance to Rhenium-186 Nanoliposomes with doses as high as 1075Gy. No significant toxicity was observed and an MTD was not established in these studies. Treatment led to marked reduction in tumor burden in both C6 and MDA-231 LM models.

Study Design

- Multi-center, sequential cohort, open-label, dose escalation study of the safety, tolerability, and distribution of ^{186}RNL via intrathecal infusion to the ventricle to patients with LM after standard surgical, radiation, and/or chemotherapy treatment
- Modified Fibonacci dose escalation, followed by an expansion at the MTD to determine efficacy with a starting dose of 6.6 mCi in a volume of 5 mL
- Primary endpoints are the incidence and severity of adverse events (AE) and dose limiting toxicities (DLT)
- Secondary endpoints of Overall response rate (ORR), Duration or response (DoR), Progression free survival (PFS), and Overall survival (OS)
- Exploratory objectives are the pharmacokinetic and dosimetry profile of a single dose of 186RNL when administered intraventricularly via Ommaya reservoir

Patients and Treatment

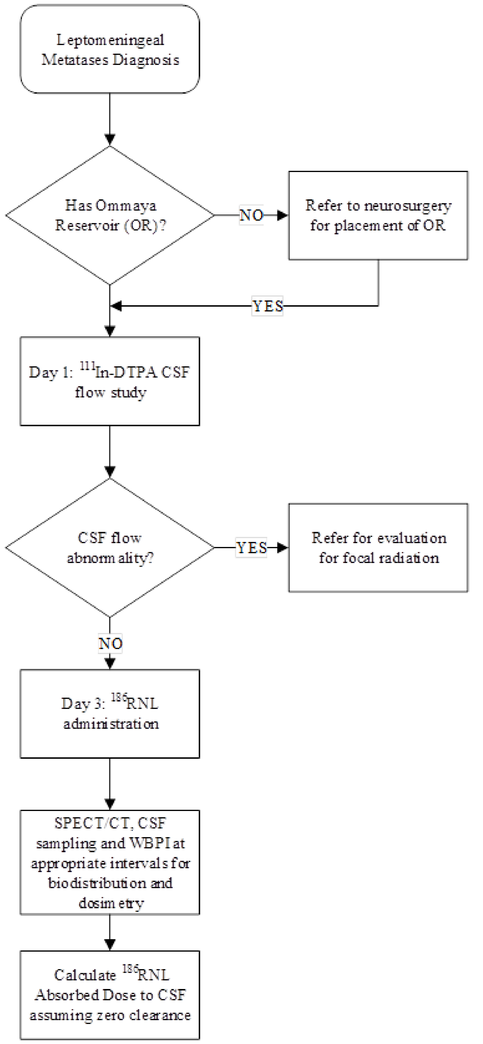
KEY ELIGIBILITY CRITERIA

- Subject has proven and documented LM that meets the requirements for the part of the study they will participate in:
  - a. Part 1: EANO-ESMO Clinical Practice Guidelines Type 1 and 2 (with the exception of 2D) LM of any primary type.
  - b. Part 2, Cohort A: Type 1A/1C breast cancer leptomeningeal metastases
  - c. Part 2, Cohort B: Type 1A/1C non-small cell lung cancer leptomeningeal metastases
- Karnofsky performance status of ≥60
- Acceptable organ function
- No obstructive or symptomatic communicating hydrocephalus
- No ventriculo-peritoneal or ventriculo-atrial shunts without programable valves or contraindications to placement of Ommaya reservoir
- No craniospinal irradiation (for intraparenchymal or dural metastasis) or intrathecal cytotoxic anti-cancer therapy less than 3 weeks prior to first dose of RNL

DRUG ADMINISTRATION

- ^{186}RNL from 6.6 to 82.5mCi will be administered intraventricularly via ommaya reservoir at a fixed volume of 5ml.

Schema



Analytical Methods

Following administration, whole body A/P SPECT imaging will be performed and repeated at 4 hours, 24 hours, and 48 hours. A 3% standard will be placed adjacent to the subject's right ear and anterior and posterior whole images will be obtained simultaneously. The calculation of radiation absorbed dose will be as previously described [3].

Study Status

The study is planned to begin accrual in Q4 2021. Site selection remains ongoing. Interested sites should contact study Principal Investigator brennera@uthscsa.edu or Lisa Sereno lsereno@plustherapeutics.com at Plus Therapeutics.

References

1. Groves, M. D. (2011). Leptomeningeal disease. Neurosurgery Clinics of North America, 22(1), 67–78.
2. Le Rhun, E., Preusser, M., Van Den Bent, M., Andratschke, N., & Weller, M. (2019). How we treat subjects with leptomeningeal metastases. ESMO Open, 4, 4–8.
3. Wang, S.X., et al., Intraoperative 186Re-liposome radionuclide therapy in a head and neck squamous cell carcinoma xenograft positive surgical margin model. Clin Cancer Res, 2008. 14(12): p. 3975-83.