CLTR-06 — ReSPECT-LM: Pharmacokinetic and Pharmacodynamic Assessment of Rhenium Obisbemeda in Leptomeningeal Metastases with Emerging Data from Repeated Dosing (ReSPECT-LMM)

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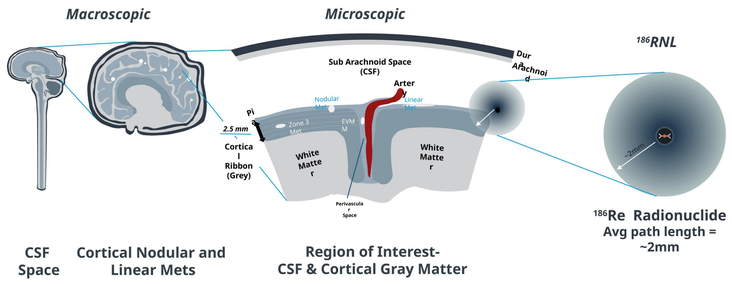
Background

- LM carries a poor prognosis and has limited therapeutic options.
- Rhenium Obisbemeda (^{186}RNL; Reyobiq) is a nanoliposomal radiotherapeutic administered intraventricularly through an Ommaya reservoir.
- The ~2 mm beta-particle pathlength is well suited to the leptomeningeal space while limiting dose to deeper brain.
- Objectives: characterize PK, PD, dosimetry, safety, and early activity; summarize emerging repeated-dosing development.

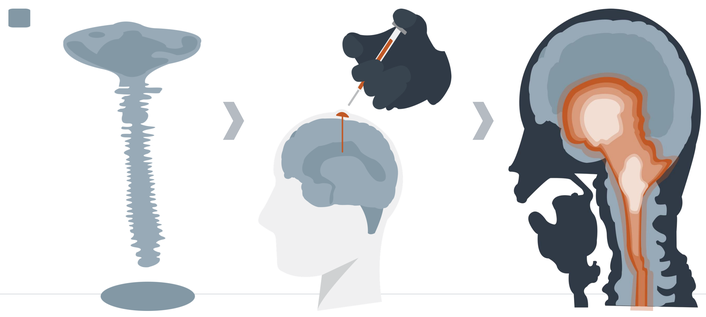
Why ^{186}RNL for LM?



The ~2 mm pathlength of ^{186}Re beta particles targets the leptomeninges while limiting dose to deeper brain structures.

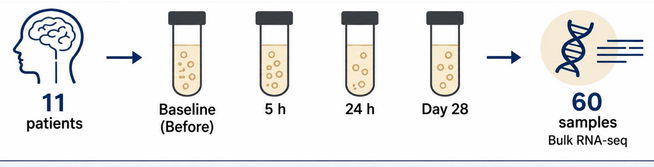
Treatment Workflow

Treatment Planning	Drug Infusion	Patient Monitoring
Prior to Treatment	Day 1	Day 2–3
CSF flow study confirms unobstructed flow	5-minute outpatient injection through the Ommaya reservoir	SPECT/CT imaging and PK/PD assessments



CSF Bulk RNA-seq Pharmacodynamics

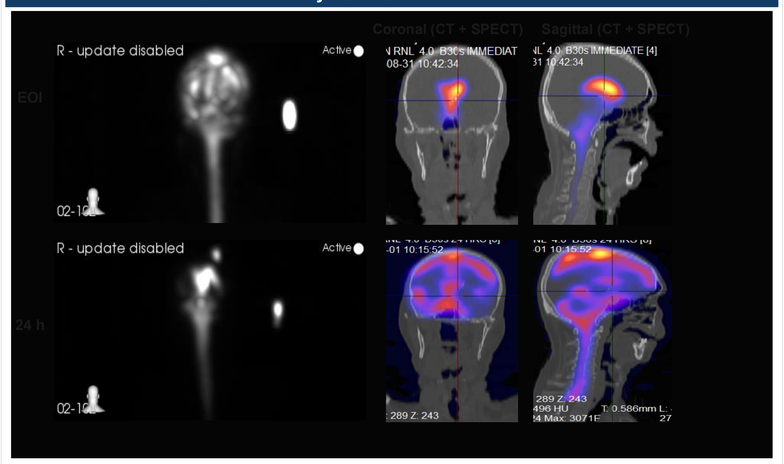
11 patients • 60 serial CSF samples • Baseline, 5 h, 24 h, Day 28 • Bulk RNA-seq with ssGSEA



Methods

- Phase 1, modified Fibonacci 3+3, single-administration dose escalation.
- Intraventricular administration through a standard Ommaya reservoir; dose levels 6.6–75.0 mCi.
- Primary endpoint: safety/tolerability and determination of MFD/RP2D.
- Secondary: ORR, duration of response, PFS, and OS. Exploratory: CSF CTCs, PD markers, PK, and dosimetry.

Distribution by 3D SPECT/CT Reconstruction



Single-Dose Safety and Activity

Dose Escalation Overview

Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
6.6 mCi	13.2 mCi	26.4 mCi	44.1 mCi	66.1 mCi	75.0 mCi

37 enrolled; 29 intent-to-treat; 22 treatment evaluable.

Two DLTs: G4 thrombocytopenia at 66 mCi (blood dose 3 Gy); G4 lymphocytopenia/neutropenia at 75 mCi (5 Gy).

Common AEs: headache, vomiting, and nausea.

Most AEs were grade 1–2 and unrelated or unlikely related.

Maximum Feasible Dose (MFD): 66.1 mCi.

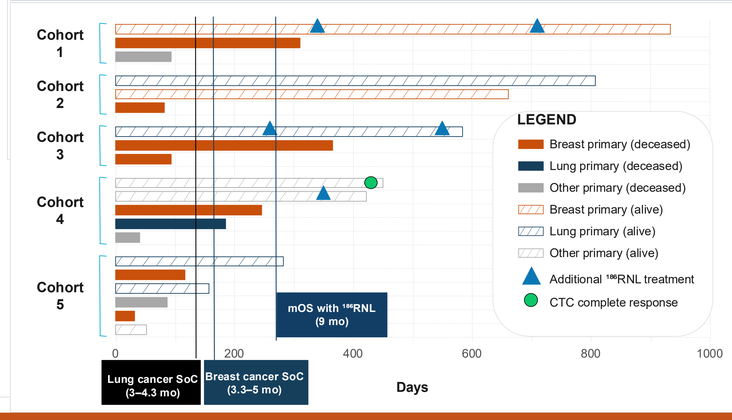
Single-administration RP2D: 44.1 mCi.

Response Through 4 Months After Single Administration

Measure	Rate
CTC Response	93% (14/15)
MRI CR+PR	31% (5/16)
Clinical CR+PR	13% (2/15)

Response assessed through Day 112.

Survival / Clinical Course

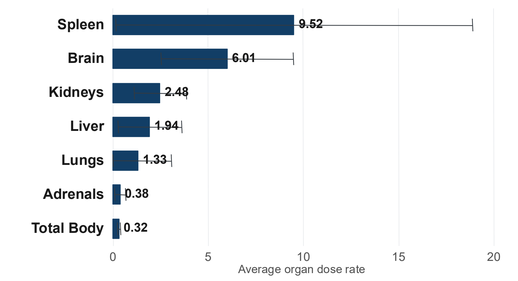


PK / Dosimetry and Repeated Dosing

Updated PK / Dosimetry

Average Organ Dose Rate (n=8)

(mGy/MBq; mean ± SD)



Blood Redistribution Patterns

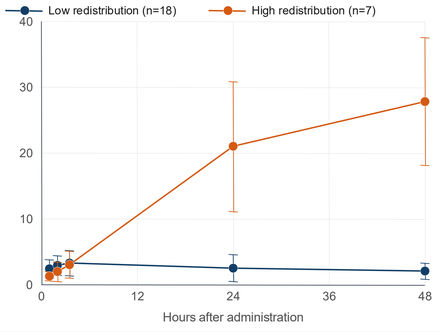
Low Redistribution (n=18)

Blood absorbed dose <50 cGy over 168 h
No blood cell count changes

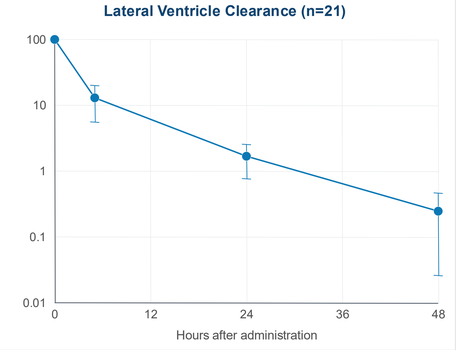
High Redistribution (n=7)

Blood absorbed dose 119.6–347.7 cGy over 168 h
Dose-dependent blood count decreases by 30 days

%ID in Blood Over Time

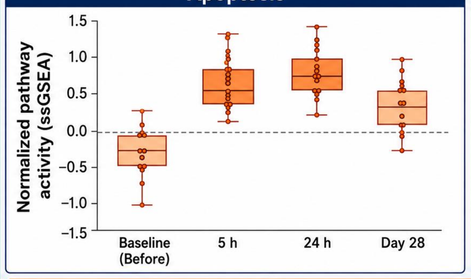


Lateral Ventricle Clearance (n=21)

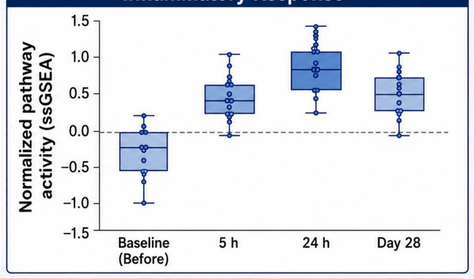


- Biphasic, dose-independent ventricular clearance: t½ 1.7 h (0–5 h) and 7.5 h (5–48 h).
- Mean lateral-ventricle absorbed dose: 1.3 Gy/mCi.
- %ID measurements are prior to decay correction.

Apoptosis



Inflammatory Response



Bulk RNA-seq showed induction of cell-death programs and inflammatory response after 186RNL.

- Early enrichment of apoptosis
- Increased inflammatory-response signaling
- Supports on-target pharmacodynamic activity in CSF tumor cells

Emerging Repeated-Dosing Program (ReSPECT-LMM)

Dose Level	Cohort	Dosing Interval (days)	Dose (mCi)	Doses / Participant	Total Administered Dose (mCi)
Low	1a	56	13.2	3	39.6
	1b	28	13.2	3	39.6
	1c	14	13.2	3	39.6
Medium	2a	56	26.4	3	79.2
	2b	28	26.4	3	79.2
	2c	14	26.4	3	79.2
High	3a	56	44.1	3	132.3
	3b	28	44.1	3	132.3

- **Cohort 1a cleared with no DLT.**
- **Current enrollment: Cohort 1b and Cohort 2a.**

★ *Repeated-dosing study ongoing; expansion planned at the recommended dose / interval.*

Conclusions

Single-dose ^{186}RNL was tolerated to 66.14 mCi; the single-administration RP2D is 44.1 mCi.

Cytopenia—especially thrombocytopenia—was dose-limiting and correlated with blood / marrow dose.

No serious treatment-attributable neurologic sequelae were observed.

ORR 31%, median OS 9 months, and CSF tumor-cell declines support continued development.

PK supports broad CSF distribution with limited systemic exposure in most patients and continued repeated dosing.

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