Safety and Feasibility of Rhenium-186 Nanoliposome (^{186}RNL) in Leptomeningeal Metastases Phase 1/2a Dose Escalation Trial

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Mays Cancer Center

UT Health San Antonio

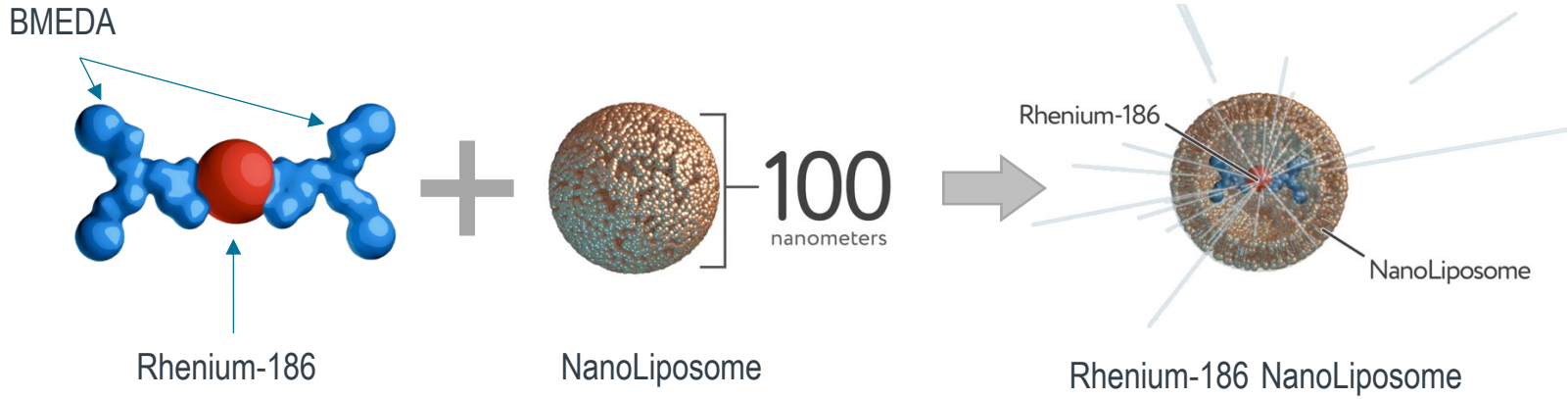
MD Anderson Cancer Center

Disclosures

- Dr. Andrew Brenner, William Phillips, and Ande Bao are Consultants to Plus Therapeutics, Inc. and hold stock in NanoTx, Inc.
- Marc Hedrick and Norman LaFrance are employees of Plus Therapeutics, Inc.

Rhenium-186 Nanoliposome (^{186}RNL)

A Proprietary Nanoscale Compound with a Unique Radioisotope

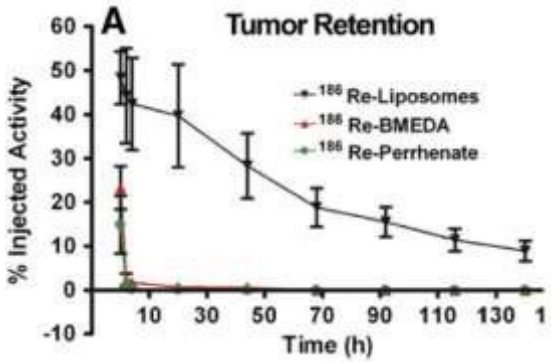


Rhenium-186

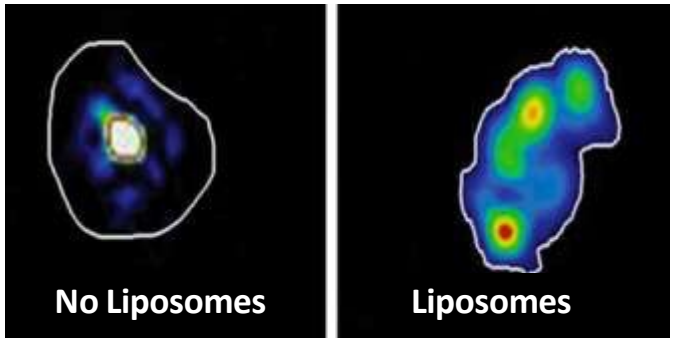
- Dual energy emitter - beta (cytotoxic) & gamma (imaging)
- Short average path length - precision
- Low dose rate - safer for normal tissues
- High radiation density - overwhelms innate DNA repair mechanisms

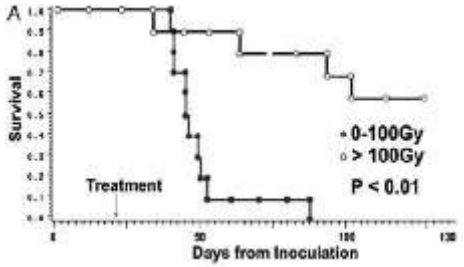
^{186}RNL Preclinical Science: Retention, Tumor Coverage, Efficacy, Safety

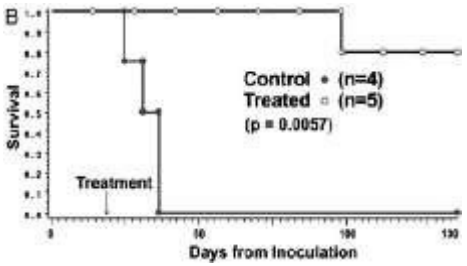
Liposomal encapsulation fundamentally changes both the **retention** within the tumor and the **dispersion** of the drug product.

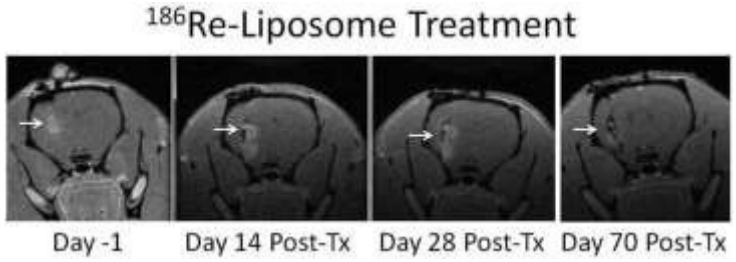


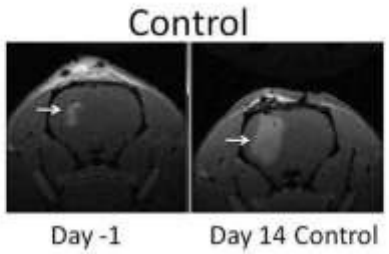
Tumor Dispersion











- Intracranial administration of 1, 3.5 or 6 mCi ^{186}RNL produced no significant pathologic changes at 24 hours or 14 days
- Highest absorbed dose was 360 Gy
- Based on these data, the no adverse effect limit (NOAEL), as related to brain pathology, was determined to be an absorbed dose of 360 Gy

Source: Phillips, W. et al Advanced Drug Delivery Reviews 2014

ReSPECT-GBM U.S. Phase 1 Clinical Trial

ReSPECT™ CLINICAL TRIALS

Multi-center, sequential cohort, open-label, volume and dose finding study of the safety, tolerability, and distribution of ^{186}RNL given by convection enhanced delivery to patients with recurrent or progressive malignant glioma after standard surgical, radiation, and/or chemotherapy treatment

- Study design: Single arm, prospective study utilizing a modified Fibonacci dose escalation scheme, followed by an expansion at the designated recommended phase 2 dose (RP2D)
- 24 patients treated to date:
  - Receiving up to 31.2 mCi in 12.3 mL
  - Average absorbed radiation dose to the tumor (AARD) of 273 Gy
  - In 17 patients not receiving prior bevacizumab, AARD was 302 Gy
  - No dose limiting toxicity was observed
  - Statistically significant overall survival benefit is observed in patients with AARD of >100 Gy to the tumor vs. those < 100 Gy
- Phase 2 will commence in second half of 2022

ClinicalTrials.gov: NCT01906385

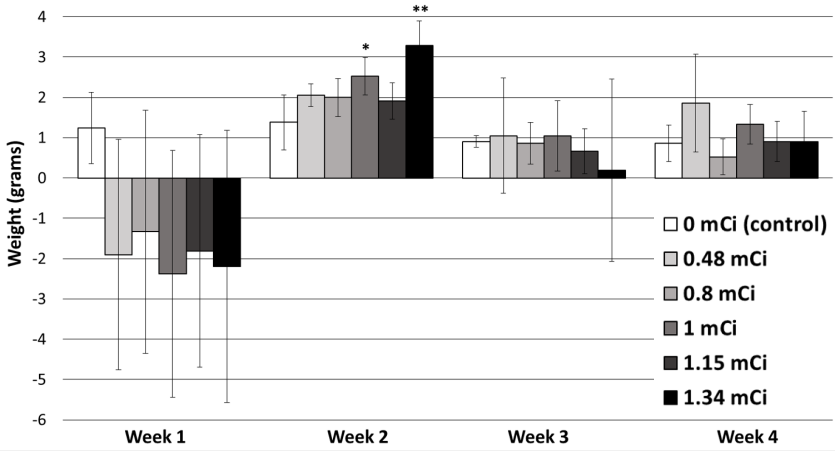
^{186}RNL Therapy in LM: Rationale

- 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.
- Liposomal encapsulation has been shown to prolong retention in the brain and CSF (e.g., DepoCyt®).
- ^{186}RNL should deliver high absorbed doses of radiation to disease within the leptomeningeal space while significantly limiting exposure to the brain, spinal cord, bone marrow and other non-target tissues.

^{186}RNL Preclinical Science: Retention, Tumor Coverage, Efficacy, Safety

- Preclinical evaluation of ^{186}RNL by intraventricular injection in non-tumor bearing rats with up to 1.34 mCi with corresponding absorbed doses of 1,075Gy was without significant toxicity. The only significant histologic finding among treated rats was thickening of the leptomeninges overlying the median eminence suggesting a mild reactive meningeal hypertrophy
- In 2 LM models (Wistar/C6 and NSG/MDA-MB-231) treatment with ^{186}RNL resulted in prolonged survival.

A.



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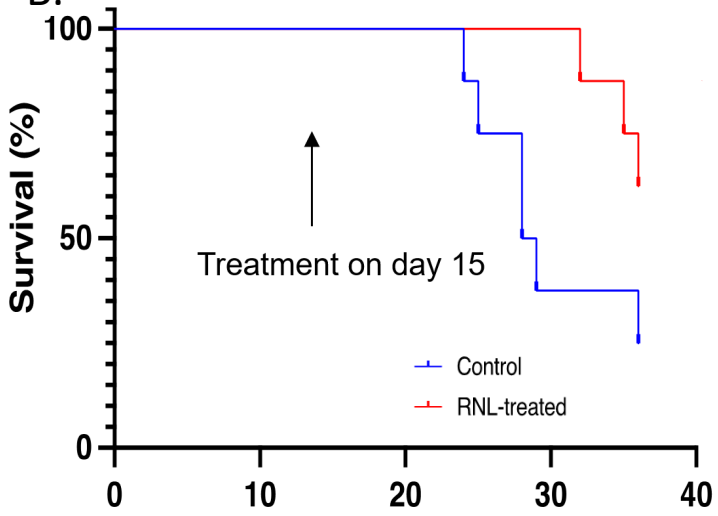

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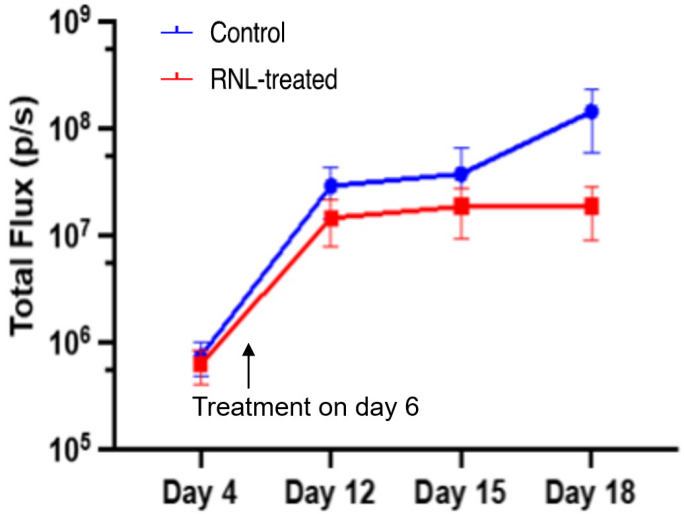

A. Weight post RNL in non-tumor bearing Wistar rats.
B. Survival curve for animals with intrathecal C6 treated with blank (blue) or RNL (red).
C. Bioluminescence of LM MDA-MB-231 in nude rats treated with blank (blue) or RNL (red)

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ReSPECT-LM U.S. Phase 1 Clinical Trial

ReSPECT™ CLINICAL TRIALS

Multicenter, Phase 1 dose-escalation study to establish the safety and tolerability of a single dose of ^{186}RNL by the intraventricular route (via Ommaya reservoir).

Study Design

- Primary objective is to determine a maximum tolerated dose (MTD) and/or maximum feasible dose (MFD).
- The study utilizes a modified 3+3 design. Dose Level (DL) 1 in the first cohort will based on the results of the preclinical pharmacokinetic/biodistribution/dosimetry and toxicology studies.
- Starting dose is up to 6.6 mCi as a single dose with a target absorbed dose of maximal possible dose of 50 Gy or less.
- Dose doubling for the first three cohorts, followed by a safety review prior to cohort 4.
- Expansion cohorts for Breast (n=20) and NSCLC (n=20)

Cohort	Infused Volume (mL)	Activity (mCi)	Concentration (mCi/mL)	Theoretical Max Absorbed Dose (Gy)	Increase (%)
1	5	6.6	1.32	50	N/A
2	5	13.2	2.64	100	100
3	5	26.4	5.28	200	100

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ReSPECT-LM U.S. Phase 1 Clinical Trial

Inclusion Criteria

1) Subject has proven and documented LM that meets the requirements for the study:
   - EANO-ESMO Clinical Practice Guidelines Type 1 and 2 (with the exception of 2D) LM of any primary type.
2) Karnofsky performance status of 60 to 100
3) Standard organ function requirements

Exclusion Criteria

1) Obstructive or symptomatic communicating hydrocephalus
2) Ventriculo-peritoneal or ventriculo-atrial shunts without programable valves or contraindications to placement of Ommaya reservoir
3) Patients who had any dose to the spinal cord or whole brain radiation therapy, regardless of when the radiation treatment was delivered.
4) Standard concomitant illness restrictions

ReSPECT-LM U.S. Phase 1 Clinical Trial

Post-Procedure Imaging and CSF Sampling

Assessment	Day 1	Day 2	Day 3	Day 7
Whole Body Planar	EOI* and EOI+3.5 hours	EOI+24 hours (± 6 hours)	EOI+48 hours (± 6 hours)	EOI+96 hours (± 2 days)
SPECT/CT	EOI+30 minutes (after WBP)	EOI+24 hours (± 6 hours)		

Assessment	Day 1	Day 2	Day 3
CSF for PK and Activity	5 hours post dose (± 20 minutes)	24 hours post dose (± 2 hours)	48 hours post dose (± 2 hours)

* End of Infusion

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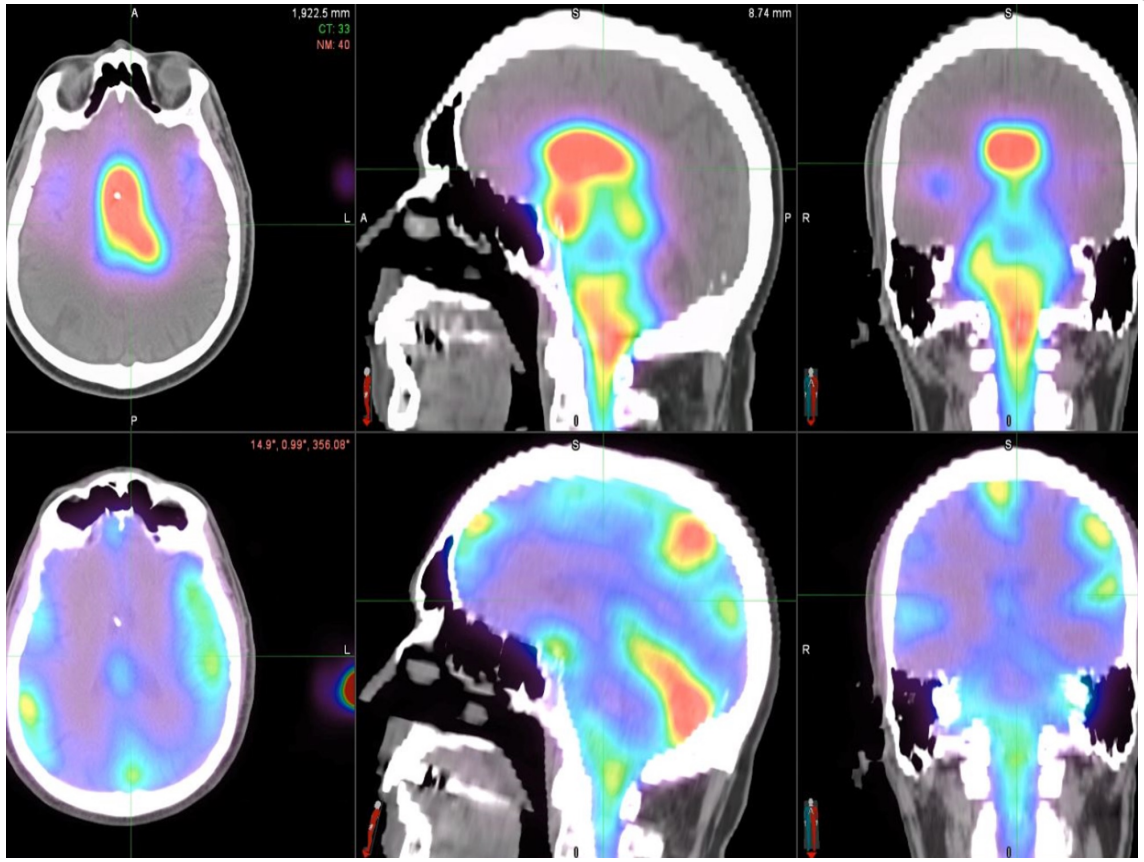
ReSPECT-LM Phase 1 Clinical Trial – Dose Escalation

Patient 02-101

- 70 year old white male
- Small cell carcinoma of the right oropharynx with metastases in the brain (Oligodendroglioma) and spinal cord, identified leptomeningeal disease on 12 February 2022
- Enrolled in Cohort 1 and treated with 6.6 mCi ^{186}RNL in 5.0 ml infusate on 16 March 2022

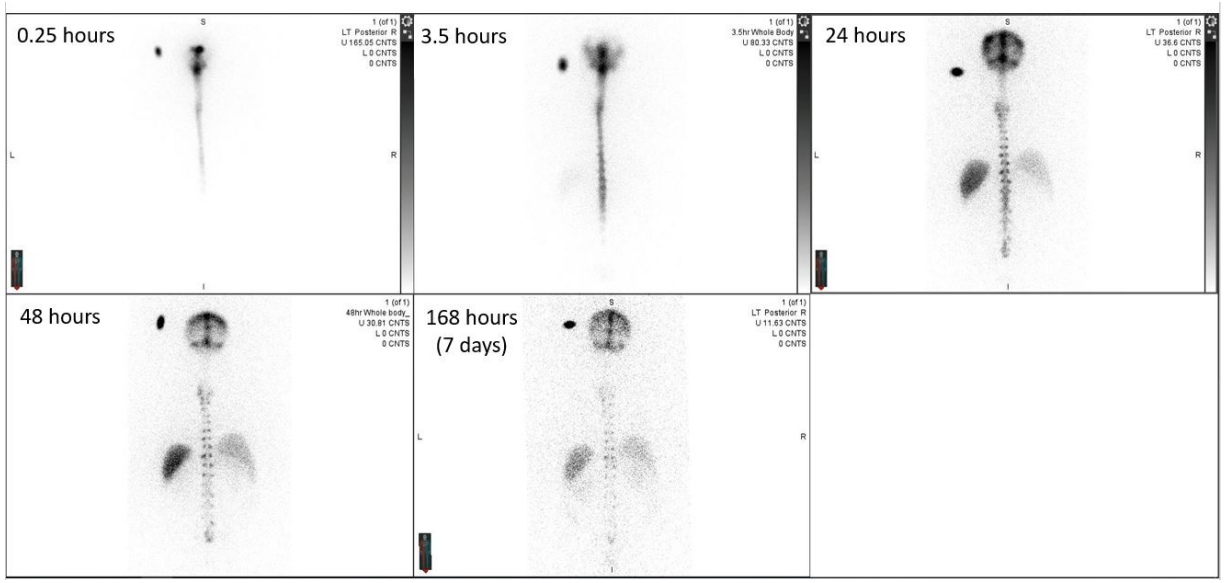


Region	Radiation Absorbed Dose (Gy)
Ventricles and cranial subarachnoid space	29.04
Ventricles (lateral, 3rd, and 4th)	14.52
Cranial subarachnoid space	37.27
Spinal Fluid	8.97

ReSPECT-LM Phase 1 Clinical Trial – Dose Escalation

Patient 02-101

Planar Imaging (Posterior-Anterior) Post-Treatment



Assessment: Tumor Cells/mL

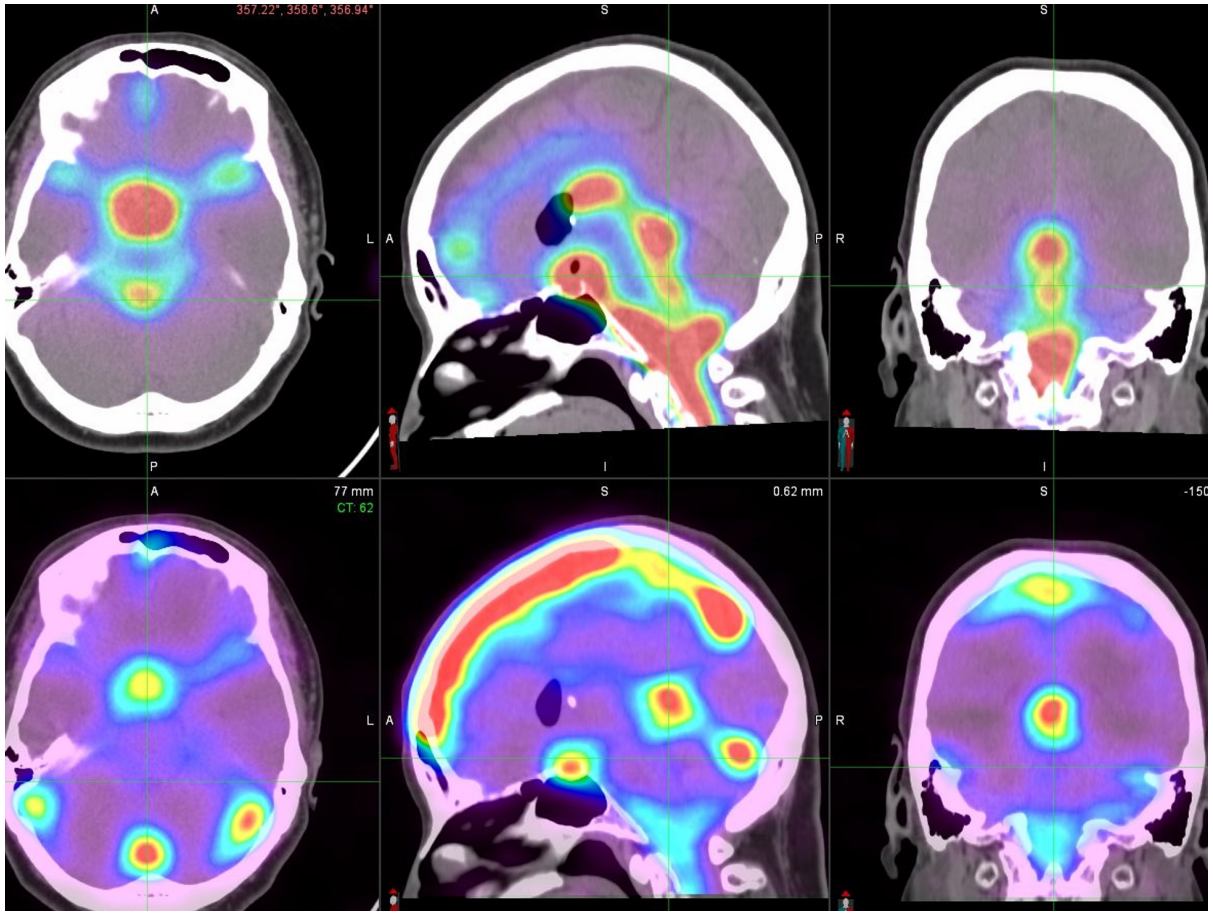
Pre	5 hrs	24 hrs	48 hrs	14 days	28 days	43 days	56 days
70.77	8.33	39.79	6.12	6.45	7.05	17.11	182.63

The subject was deceased following the last follow-up study visit (death due to progression of primary tumor on 18 June 2022), 95 days (13.6 weeks) after enrollment/treatment in the study.

ReSPECT-LM Phase 1 Clinical Trial – Dose Escalation

Patient 01-101

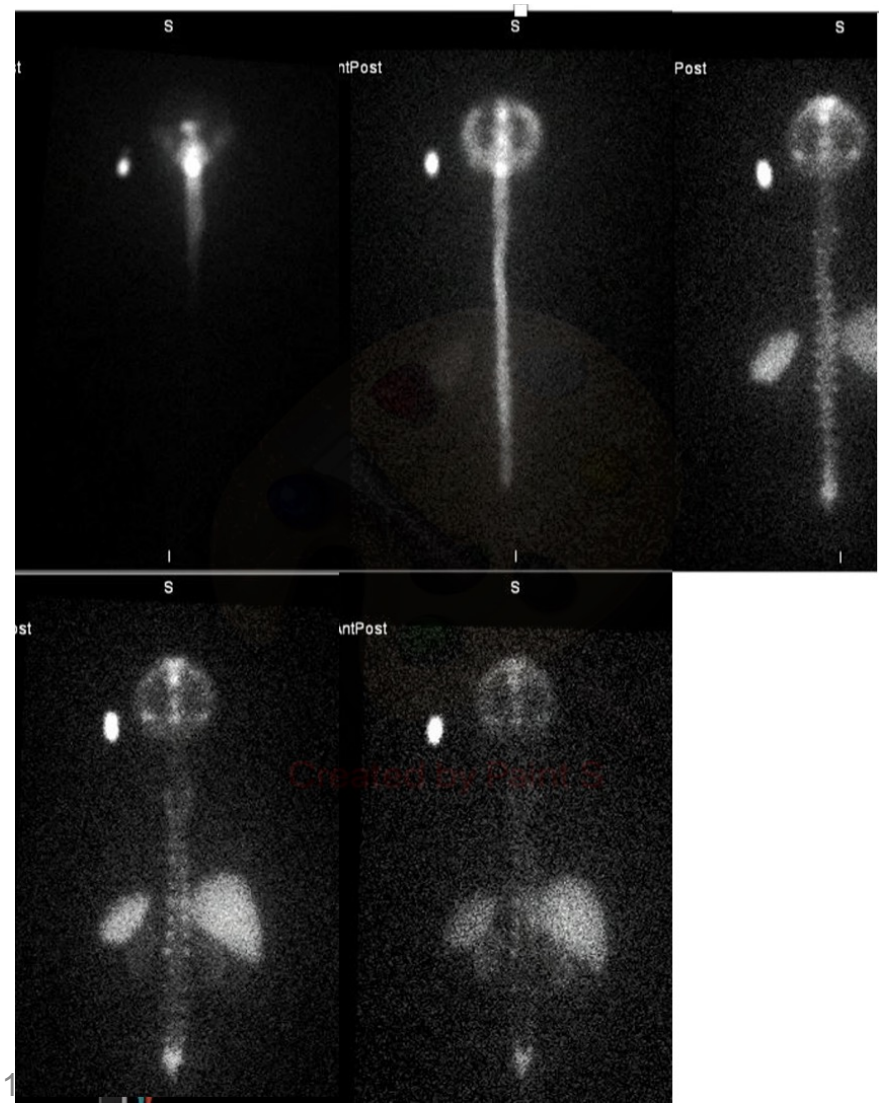
- 59 year old white female
- Cancer right upper quadrant diagnosis in 1998; metastatic breast cancer with unspecified estrogen receptor status (right HCC) diagnosis on 09 April 2018; leptomeningeal carcinomatosis, chest wall and regional lymph node metastases from her breast cancer on 02 November 2018
- Enrolled in Cohort 1 and treated with 6.6 mCi ^{186}RNL in 5.0 ml infusate on 27 April 2022



Region	Radiation Absorbed Dose (Gy)
Ventricles and cranial subarachnoid space	18.68
Ventricles (lateral, 3rd, and 4th)	6.83
Cranial subarachnoid space	25.32
Spinal Fluid	5.92

ReSPECT-LM Phase 1 Clinical Trial – Dose Escalation

Patient 01-101



Assessment: Tumor Cells/mL

Pre	5 hrs	24 hrs	48 hrs	14 days	28 days	43 days	56 days
85.94	155	133.13	14.35	Not Req	40.16	Not Req	30.83

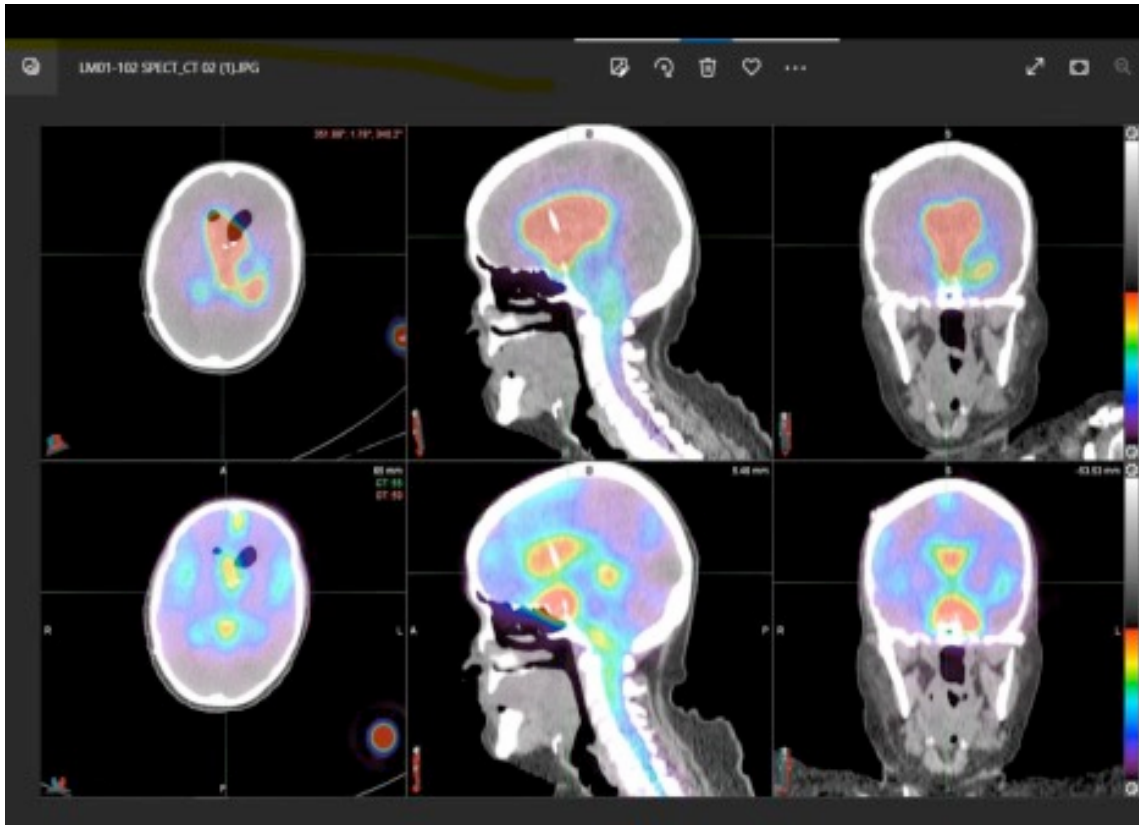
The subject was alive and last seen on 22 September 2022 for Day 112 follow-up.

ReSPECT-LM Phase 1 Clinical Trial – Dose Escalation

Patient 01-102

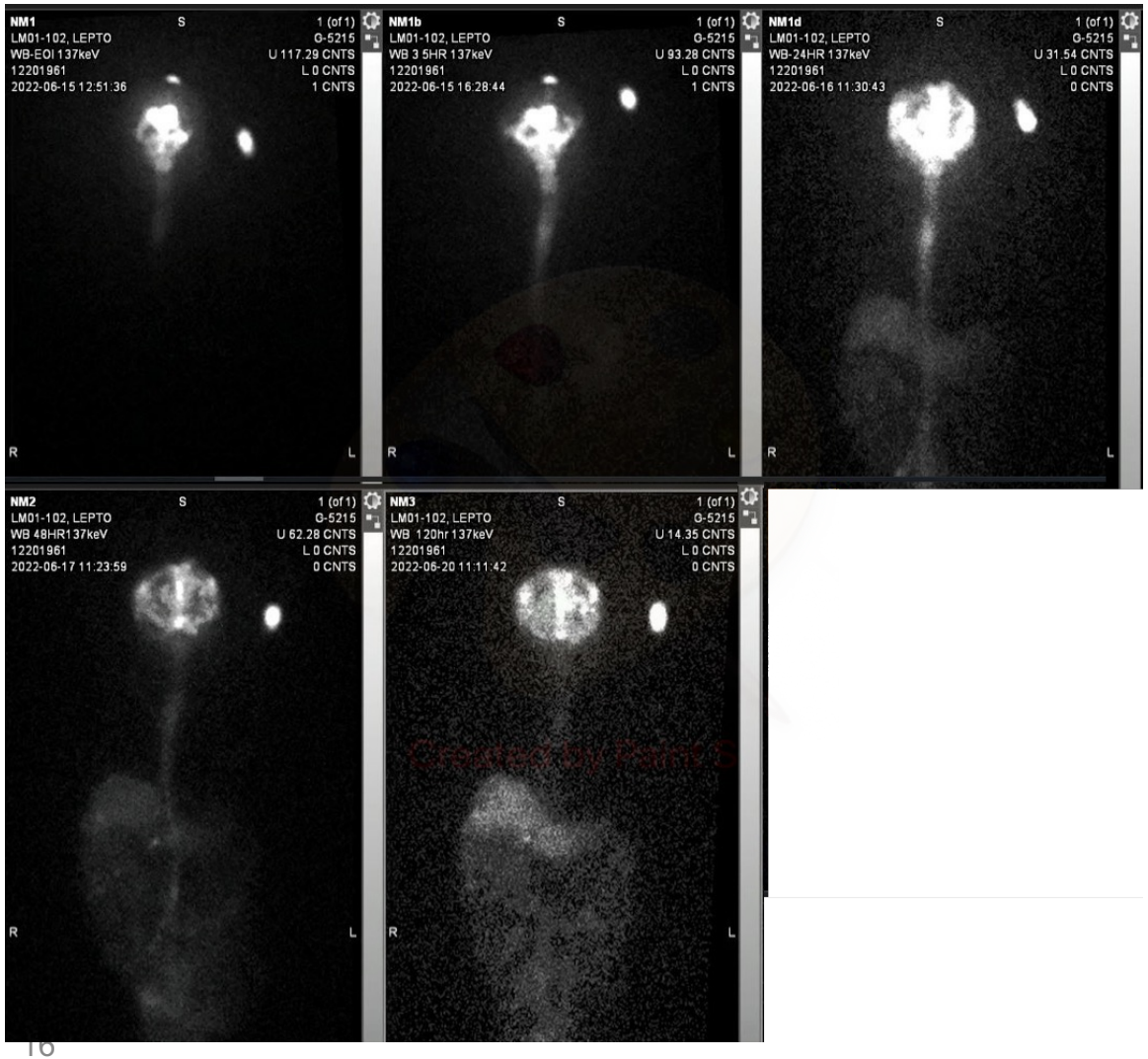
- 60 year old white female
- Stage III Invasive Lobular Breast Carcinoma of the right breast (2016); bone metastases (06/2020), leptomeningeal metastasis (01/2022)
- Previous treatment with total mastectomy (10/2016) followed by chemotherapy and radiation in 2016-2017
- Enrolled in Cohort 1 and treated with 6.6 mCi ^{186}RNL in 5.0 ml infusate on 15 June 2022

Region	Radiation Absorbed Dose (Gy)
Ventricles and cranial subarachnoid space	26.80
Ventricles (lateral, 3rd, and 4th)	36.44
Cranial subarachnoid space	21.25
Spinal Fluid	5.76



ReSPECT-LM Phase 1 Clinical Trial – Dose Escalation

Patient 01-102



Assessment: Tumor Cells/mL

Pre	5 hrs	24 hrs	48 hrs	14 days	28 days	43 days	56 days
839.13	551.03	455.29	506.73	Not Req	395.51	Not Req	1,133.40

The subject had disease progression as of 18 August 2022 and now is under survival follow-up. The subject started chemotherapy on 19 August 2022.

ReSPECT-LM Phase 1 Clinical Trial – Dose Escalation

Patient 02-102

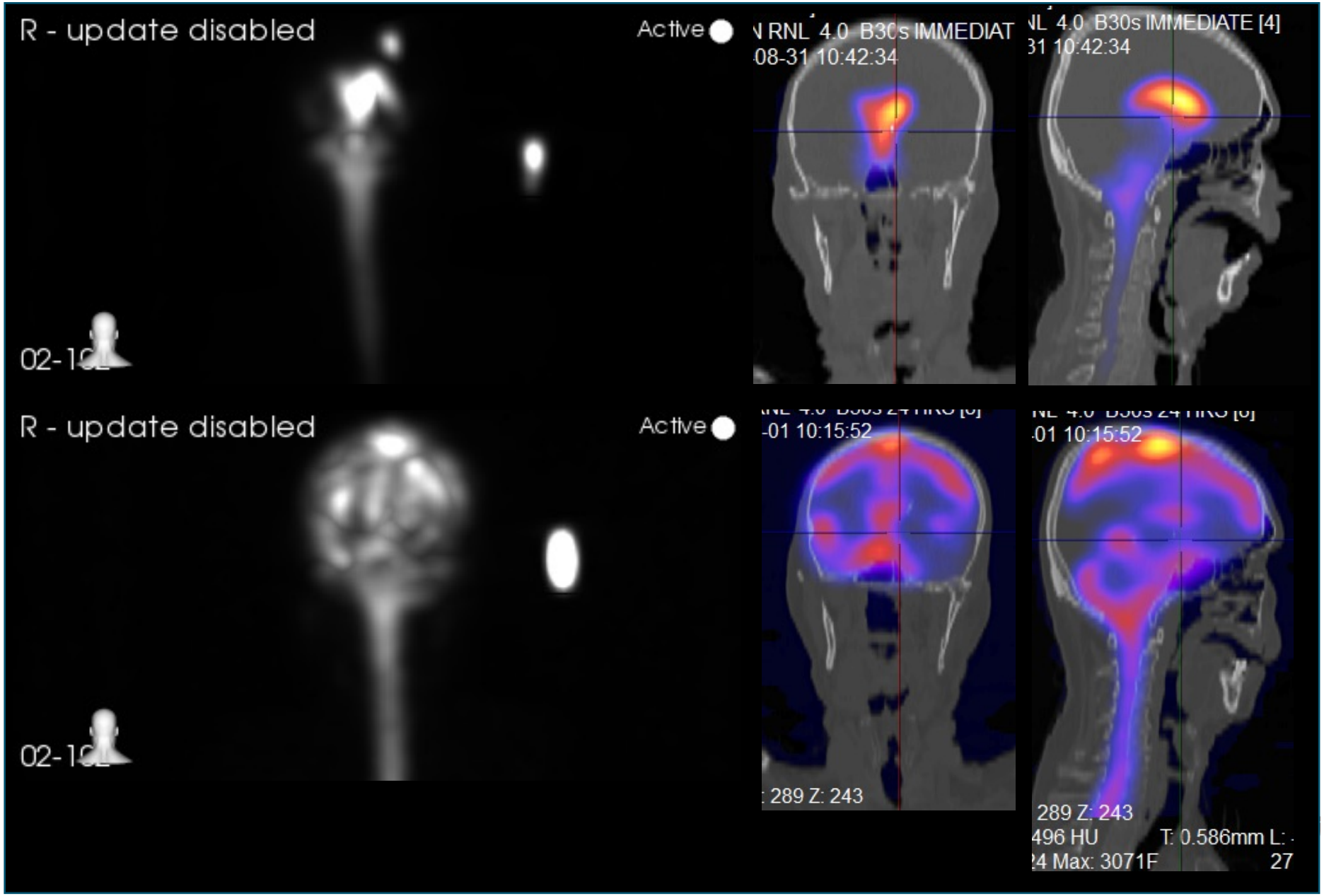
- 55 year old white male
- Leptomeningeal disease from lung adenocarcinoma (primary diagnosis 21 October 2021)
- Lobectomy 02 December 2021; chemotherapy 21 July 2022 – 15 August 2022
- Enrolled in Cohort 2 and treated with 13.2 mCi ^{186}RNL in 5.0 ml infusate on 31 August 2022

Assessment: Tumor Cells/mL

Pre	5 hrs	24 hrs	48 hrs	14 days	28 days	43 days	56 days
51.79	31.76	46.41	24.44	Not Req	48.46	Not Req	122.05

The subject is still alive. Patient is doing well, walking with minimal assistance (previously using wheelchair), no pain reported (was primary complaint pre-treatment), and reporting improved vision.

SPECT


EOI
R - update disabled
Active
RNL 4.0 B30s IMMEDIAT
08-31 10:42:34
NL 4.0 B30s IMMEDIATE [4]
31 10:42:34
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01 10:15:52
289 Z: 243
01 10:15:52
289 Z: 243
496 HU
T: 0.586mm L:
24 Max: 3071F
27

ReSPECT-LM U.S. Phase 1 Clinical Trial

^{186}RNL Safety through Cohort 1

- No trAEs greater than grade 1.
- Most common was headache.

01-101	Nausea	1
01-101	Vomiting	1
01-101	Headache	1
01-101	Intermittent Headaches	1
01-101	Brain Fogginess	1
01-102	Intermittent Headaches	1

ReSPECT-LM Summary

- ^{186}RNL is a nanoliposomal radiotherapeutic with a short pathlength allowing for a larger therapeutic window and higher safe absorbed doses than conventional radiation.
    - Preclinical experiments with absorbed doses as high as 1,000 Gy without toxicity
- ^{186}RNL is administered through a standard Ommaya reservoir, redistributes throughout the CSF, and retains in the leptomeninges through day 7
- A single administered dose of 6.6 mCi in 5.0 mL achieves absorbed doses of 18.7 to 29.0 Gy to the ventricles and cranial subarachnoid space
- ^{186}RNL at 6.6 mCi was well tolerated with no trAEs of greater than grade 1
- Patients experienced a decreased CSF cell count by microfluidic chamber assay after treatment, ranging from 46 to 92%
- Dose escalation is continuing, and repeated dosing will be explored

THANK YOU TO OUR PATIENTS

ReSPECT Study Team:

John Floyd MD (UTHSA)
William Phillips MD (UTHSA)
Ande Bao PhD (Case Western)
Toral Patel MD (UTSW)
Michael Youssef MD (UTSW)
Jeff Weinberg MD (MDACC)
All of our Study Coordinators

Plus Therapeutics

Norman LaFrance MD
Marc Hedrick MD
Melissa Moore PhD
Greg Stein MD

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