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

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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.

Leptomeningeal Metastases (LM)

- Diagnosed in approximately 5% of subjects with metastatic cancer; affects over 110,000 subjects per year in the U.S. alone.
- Typical treatment strategies include optimal systemic therapy for the primary disease, as well as neuroaxis directed therapies, which may include intrathecal chemotherapy or radiotherapy.
- 30 Gray (Gy) given in 10 fractions is a typical radiation dosing scheme. However, no survival benefit of whole brain radiotherapy (WBRT) was observed in most retrospective studies of subjects with LM.
- Craniospinal radiotherapy is rarely an option for adult subjects with LM from solid cancers because of the risk of bone marrow toxicity, enteritis, and mucositis in a context of concomitant systemic disease and the need of systemic pharmacotherapy.
- Survival for subjects with LM is poor, limited to a few months in most subjects. The median survival has been estimated at:
    - 3.8 - 5.4 months for LM from breast cancer
    - 3 - 8.7 months for LM from lung cancer
    - 5.2 months for LM from melanoma

Why Develop a NanoLiposomal Radiotherapeutic?

- Up to a point, survival time for external beam radiation correlates with the total dose delivered.
- The therapeutic window for external beam radiation is limited by increasing late normal tissue damage.
- In LM, radiotherapy is limited by toxicity including myelopathy and marrow suppression given the dose to the brain, cord, and surrounding tissues.
- Recent studies, such as those with proton craniospinal irradiation suggest incremental improvements in CNS PFS and OS can be achieved with more conformal techniques.
- Due to the short path length, intra-tumoral administration of beta emitters have the potential to dramatically widen the therapeutic window, increase delivered dose, and extend survival time.

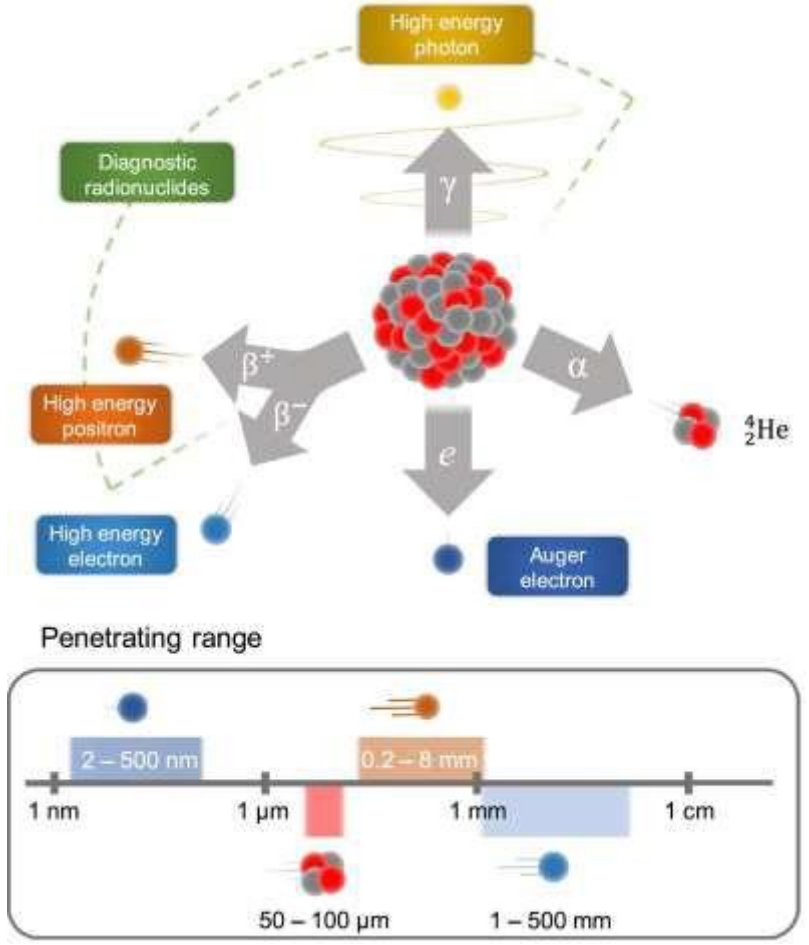
Rhenium-186 is a β-emitting Radionuclide

Rhenium-186 (Re-186, ^{186}Re) Properties

- 89.3-hour half-life (3.72 days)
- Beta energy: 1077 keV (71%), 939 keV (22%)
- Gamma energy: 137 keV (9%)
- Max. penetration in tissue: 4.5 mm (average 1.1 mm)
- Re-186 HEDP is used for palliative treatment of bone metastases originating from breast or prostate cancer (MTD = 65 mCi)

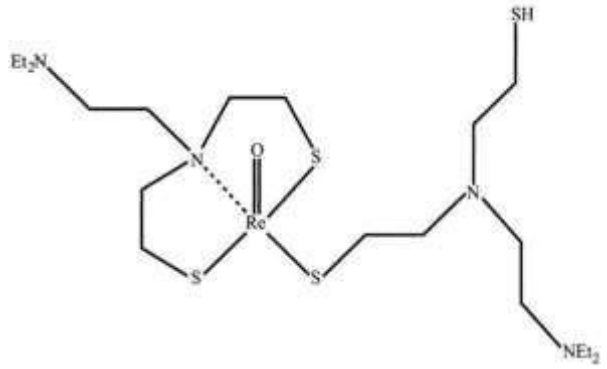
For comparison, Iodine-131 (I-131, ^{131}I) Properties

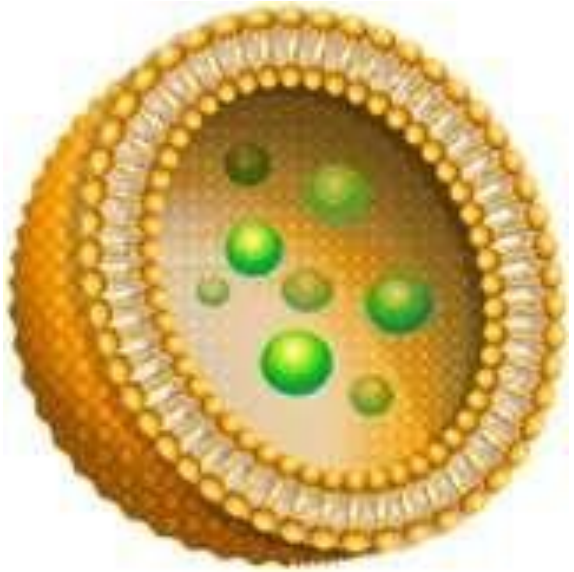
- 192.5-hour half-life (8.02 days)
- Beta energy: 606 keV (90%)
- Gamma energy: 364 keV (10%)
- Penetration in tissue: 0.6 to 2.0 mm
- I-131 is used for the treatment of thyrotoxicosis and some types of thyroid cancer (typical empiric dose = 200 mCi)



Rhenium-186 Nanoliposomes (^{186}RNL)

- Investigational product is N,N-bis(2-mercaptoethyl)-N',N'-diethyl-ethylenediamine (BMEDA)-chelated ^{186}Rhenium encapsulated within lipid vesicles (liposomes).
- BMEDA is an SNS pattern ligand with a tridentate structure that has one nitrogen and three sulfur atoms. These three atoms donate electrons to ^{186}Rhenium, resulting in a lipophilic complex in a neutral state.

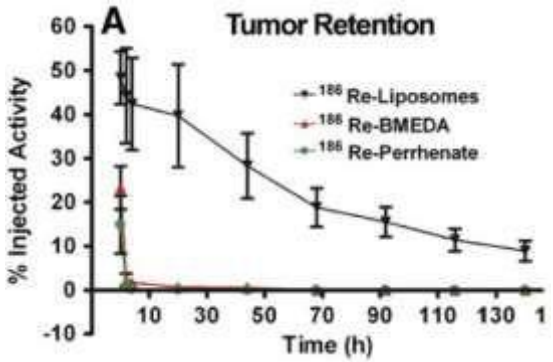




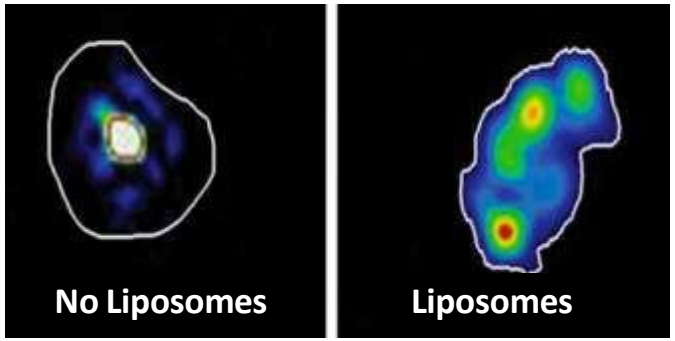
- Nanoliposomes are composed of an 80 – 130 nm diameter lipid bilayer of distearoylphosphatidylcholine (DSPC) and cholesterol and confer drug delivery control on the chelated ^{186}Rhenium.

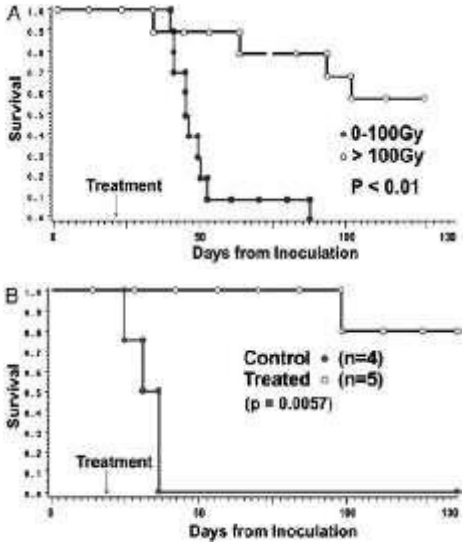
^{186}RNL Preclinical Science: Retention, Tumor Coverage, Efficacy, Safety

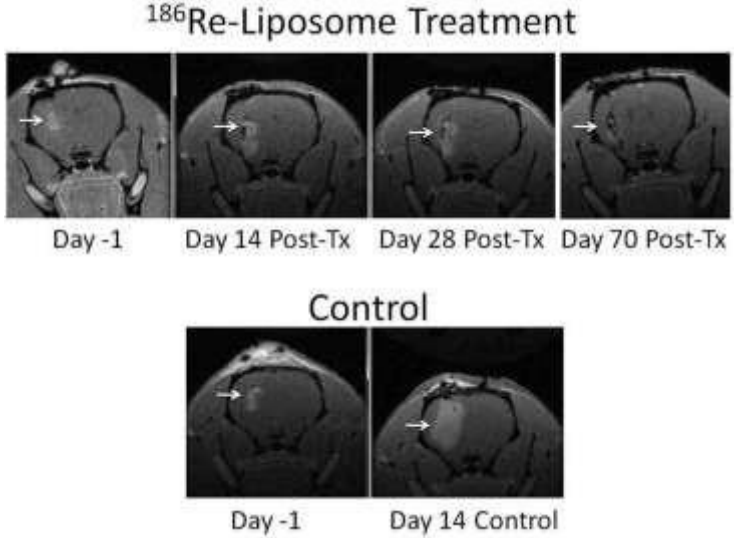
Liposomal encapsulation fundamentally changes both the **retention** within the tumor and the **dispersion** of the drug product.



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

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ReSPECT-GBM U.S. Phase 1 Clinical Trial

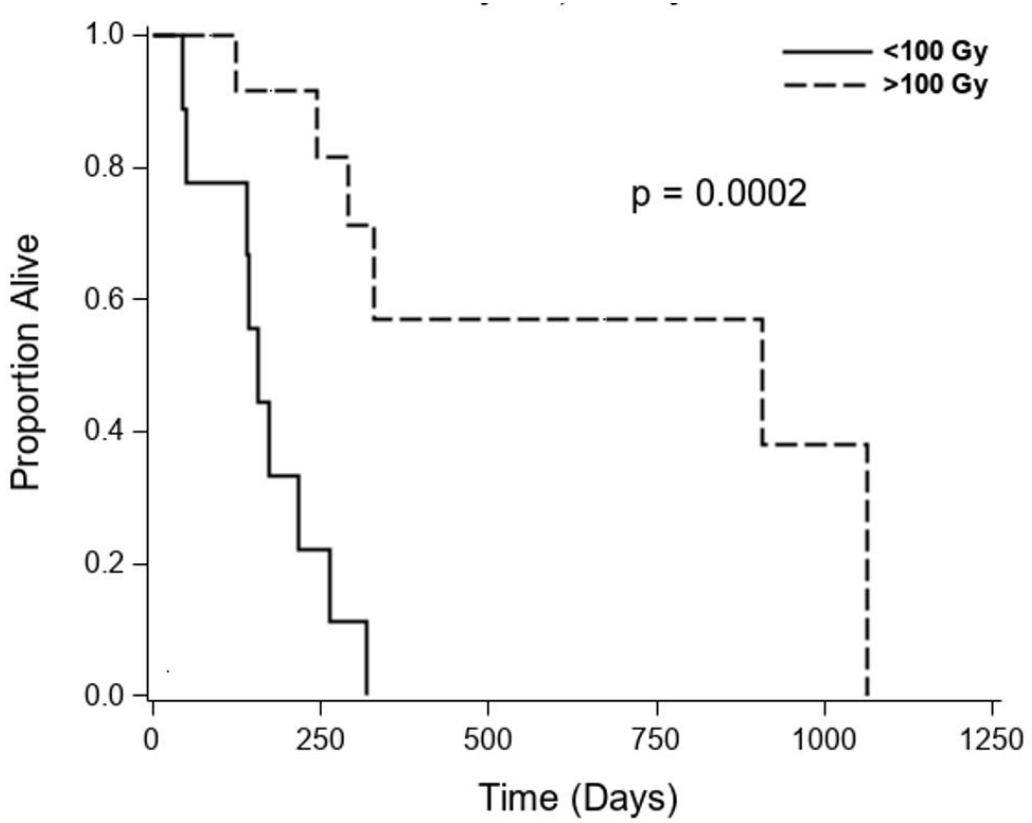
ReSPECT™ CLINICAL TRIALS

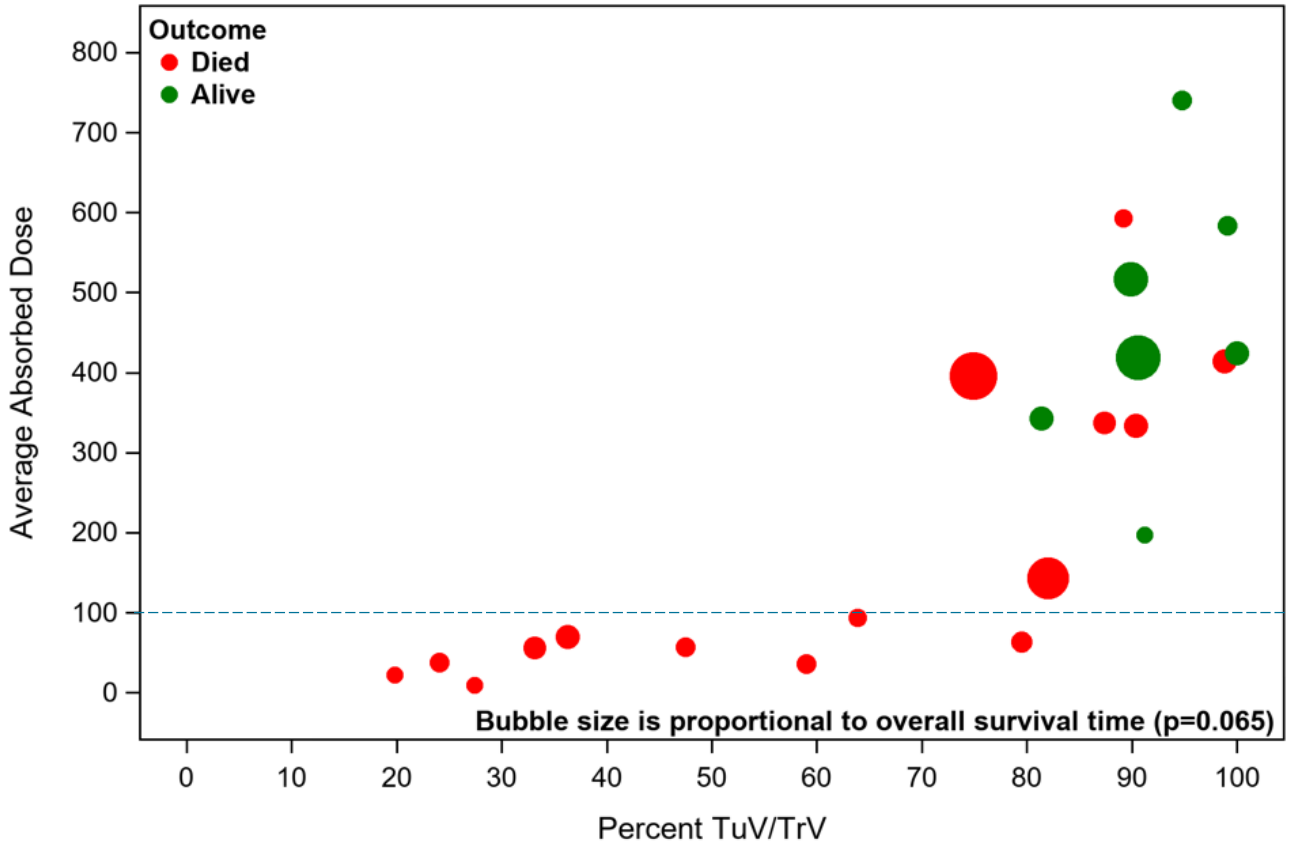
Multi-center, sequential cohort, open-label, volume and dose finding study of the safety, tolerability, and distribution of ^{186}RNL given by convection enhanced delivery to patients with recurrent or progressive malignant glioma after standard surgical, radiation, and/or chemotherapy treatment

- 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)
- 23 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

ReSPECT-GBM U.S. Phase 1 Clinical Trial





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ClinicalTrials.gov: NCT01906385

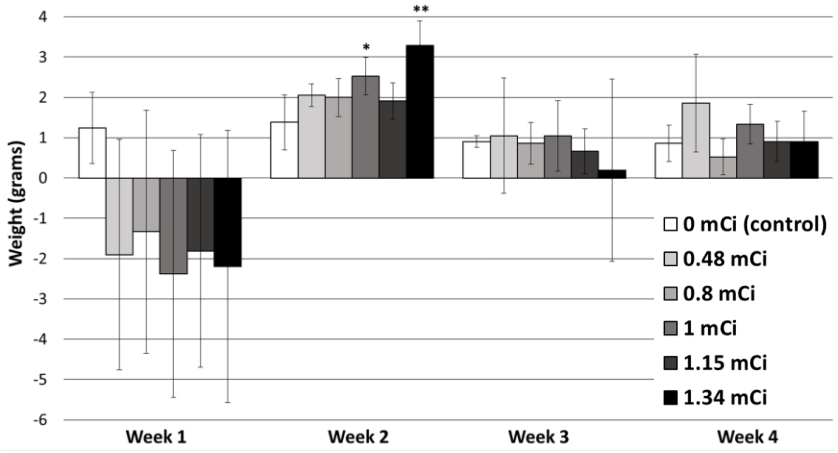
^{186}RNL Therapy in LM: Rationale

- 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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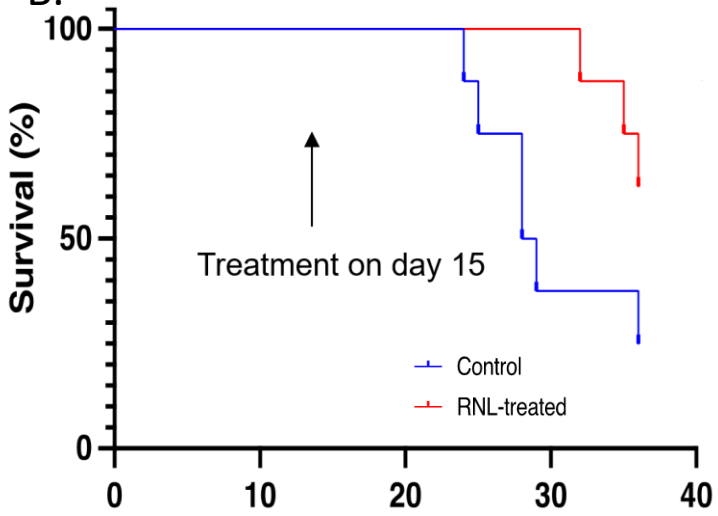

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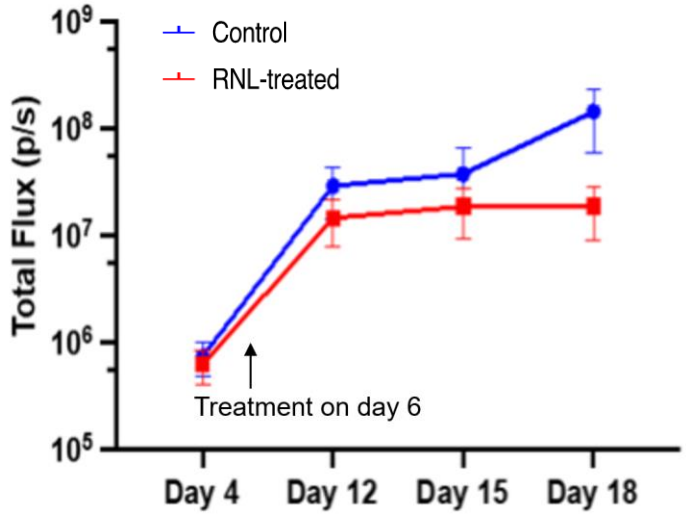

A. Weight post RNL in non-tumor bearing Wistar rats.
B. Survival curve for animals with intrathecal C6 treated with blank (blue) or RNL (red).
C. Bioluminescence of LM MDA-MB-231 in nude rats treated with blank (blue) or RNL (red)

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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.
  - Conservative scenario was assumed in that there will be minimal to no clearance or diffusion of the investigational product through the CSF volume
  - In the Phase 1 recurrent GBM study, absorbed doses above 740 Gy appear to be safe and well tolerated, including in certain clinical cases in which the ^{186}RNL leaked into the leptomeningeal space.
- Dose doubling for the first three cohorts, followed by a safety review prior to cohort 4.

Status

- 3 patients treated to date

ReSPECT-LM U.S. Phase 1 Clinical Trial

Dose Escalation

Cohort	Infused Volume (mL)	Activity (mCi)	Concentration (mCi/mL)	Theoretical Maximal Absorbed Dose in CSF (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

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

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)		

* End of Infusion

ReSPECT-LM U.S. Phase 1 Clinical Trial

Post-Procedure Blood Collection

- Blood PK specimen collected into two 3 mL blue top tubes (sodium citrate) for each timepoint
- Label tube with patient's study ID number, patient initials, and collection date and time
- No processing required
- Because of the small amount of radioactivity in the blood samples, they can be stored in the nuclear medicine hot room after they are collected until shipped to Reference Laboratory (PK Lab)
- After last draw, ship per Laboratory Manual (bulk shipment - multiple timepoints/per study subject)

Assessment	Day 1	Day 2	Day 3
Blood	1, 2, 3.5 hours post dose	24 hours post dose (± 2 hours)	48 hours post dose (± 2 hours)

ReSPECT-LM U.S. Phase 1 Clinical Trial

Post-Procedure CSF Collection

- Samples of the CSF will be drawn via the Ommaya reservoir into a 5 mL aliquot tube for each timepoint
- Label tube with subject's study ID number, patient initials, and collection date and time
- No processing required
- Because of the small amount of radioactivity in the blood samples, they can be stored in the nuclear medicine hot room after they are collected until shipped to Reference Laboratory (PK Lab)
- After last draw, ship per Laboratory Manual (bulk shipment - multiple timepoints/per study subject)

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)

ReSPECT-LM U.S. Phase 1 Clinical Trial

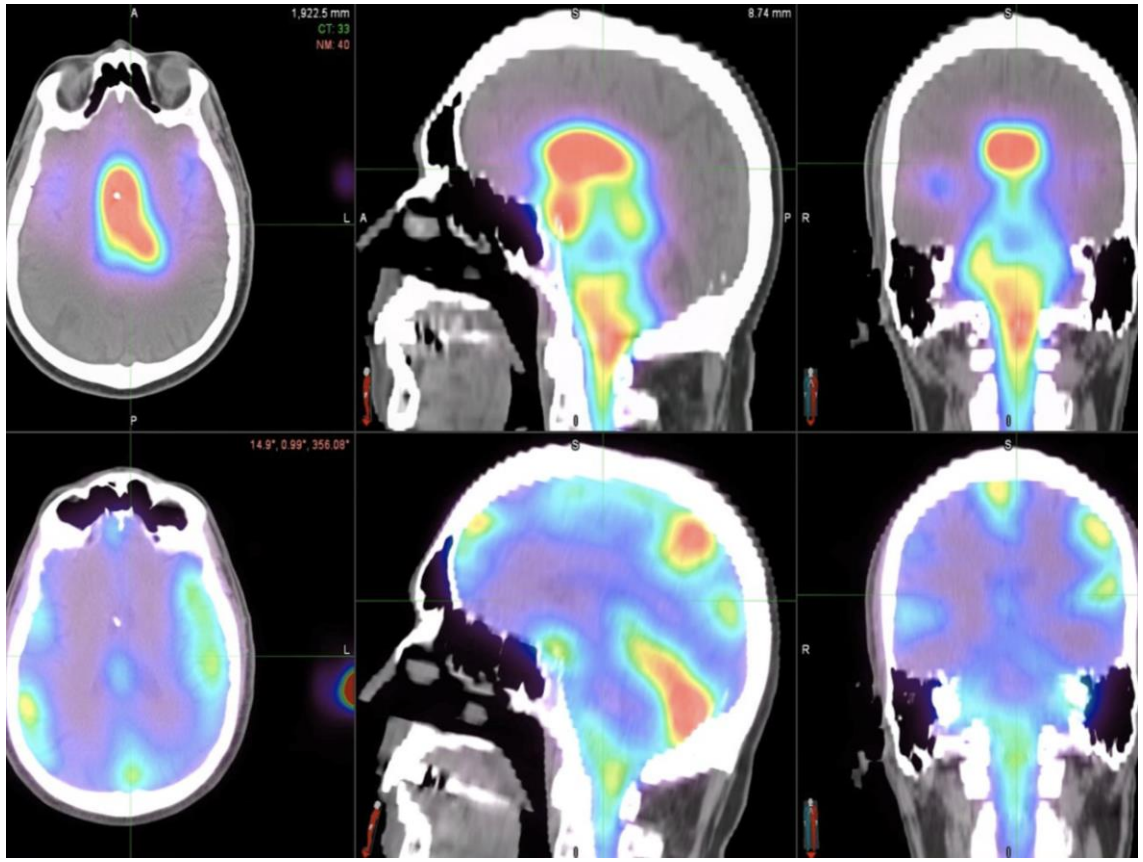
Patient 02-101

70 year old white male with small cell carcinoma of the right oropharynx with LM of the brain and spinal cord.

Enrolled in Cohort 1 receiving 6.6 mCi ^{186}RNL in 5.0 ml infusate on March 16, 2022.

Radiation absorbed dose:

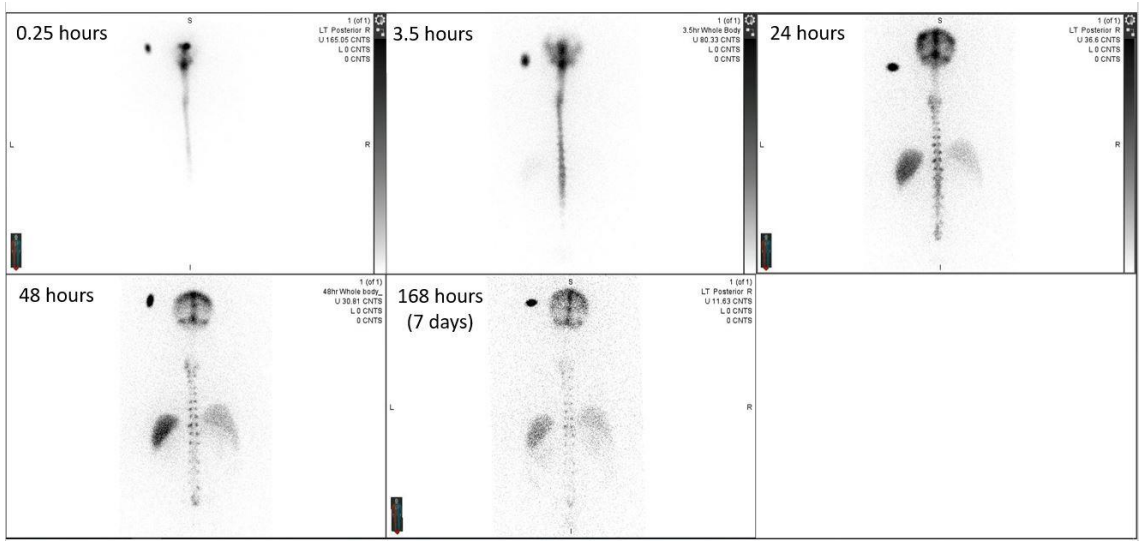
- Ventricles and cranial subarachnoid space = 29.04 Gy
- Ventricles (lateral, 3rd, and 4th) = 14.52 Gy
- Cranial subarachnoid space = 37.27 Gy
- Spinal Fluid = 8.97 Gy



ReSPECT-LM U.S. Phase 1 Clinical Trial

Patient 02-101

Planar Imaging (Posterior-Anterior) Post-Treatment



Assessment: Tumor Cells / mL

Pre	5 Hours	24 Hours	48 Hours	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 deemed due to progression of primary tumor and not LM), 95 days (13.6 weeks) after enrollment/treatment in the study.

ReSPECT-LM U.S. Phase 1 Clinical Trial

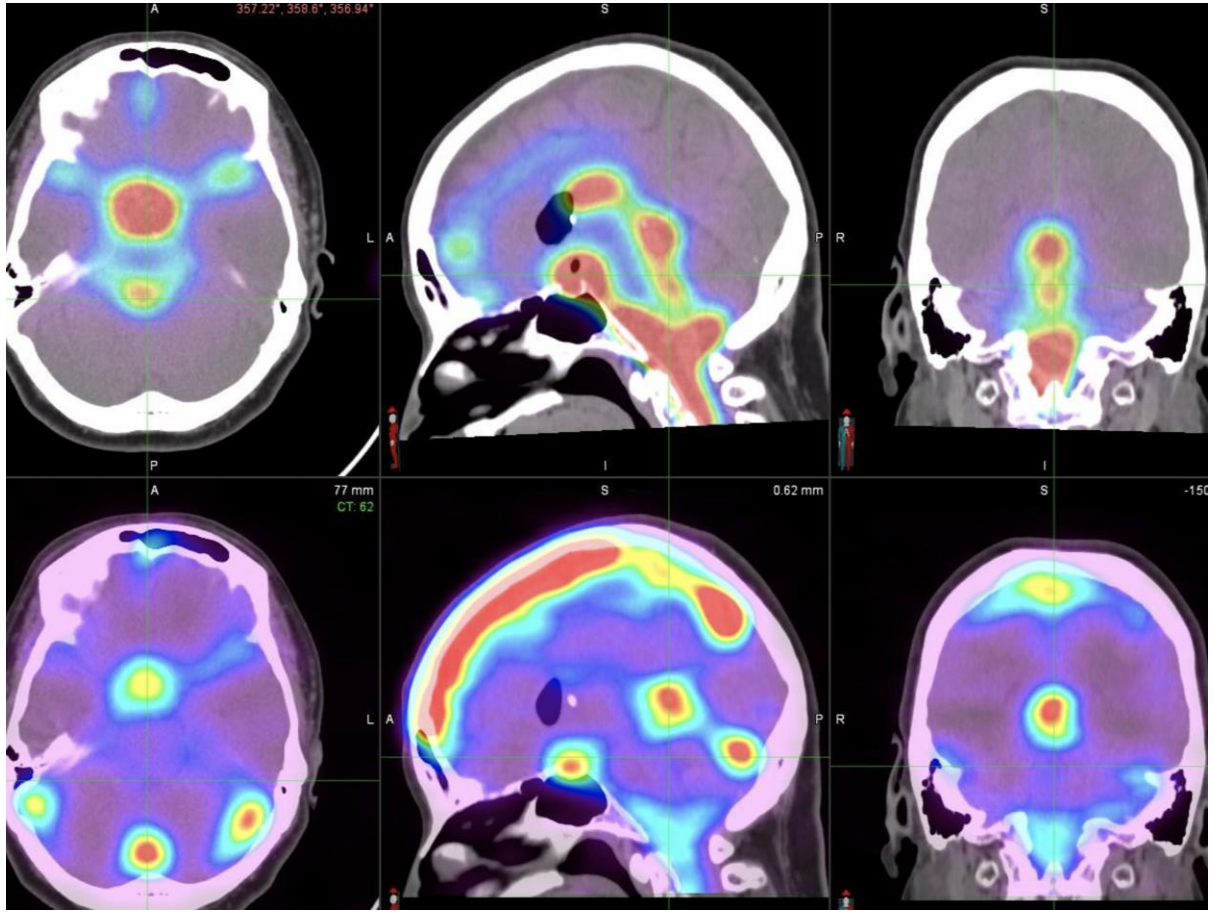
Patient 01-101

59 year old white female with triple negative breast cancer right upper quadrant diagnosis with chest wall and regional lymph node recurrence followed by craniospinal leptomeningeal metastases.

Enrolled in Cohort 1 receiving 6.6 mCi ^{186}RNL in 5.0 ml infusate on April 27, 2022.

Radiation absorbed dose:

- Ventricles and cranial subarachnoid space = 18.68 Gy
- Ventricles (lateral, 3rd, and 4th) = 6.83 Gy
- Cranial subarachnoid space = 25.32 Gy
- Spinal Fluid = 5.92 Gy



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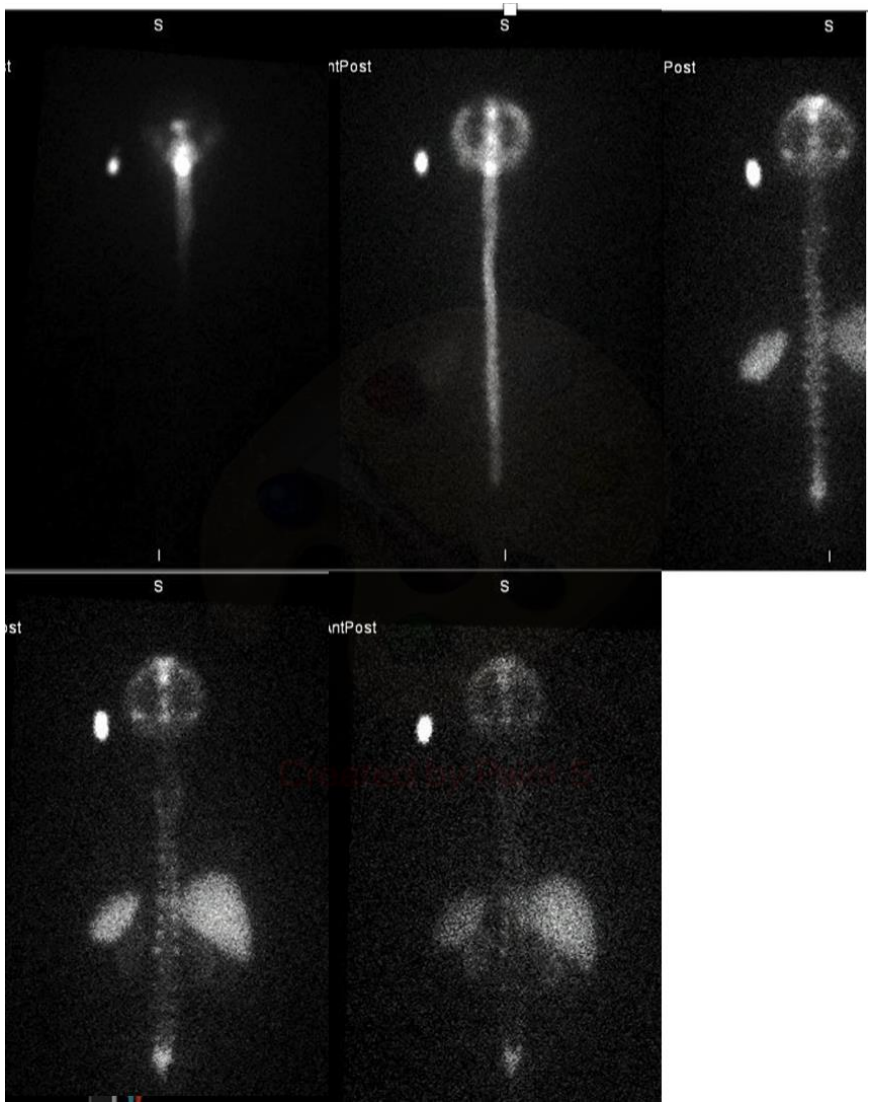
Patient 01-101



Assessment: Tumor Cells / mL

Pre	5 Hours	24 Hours	48 Hours	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 clinically stable as of the last follow-up at day 90 after treatment.

ReSPECT-LM U.S. Phase 1 Clinical Trial

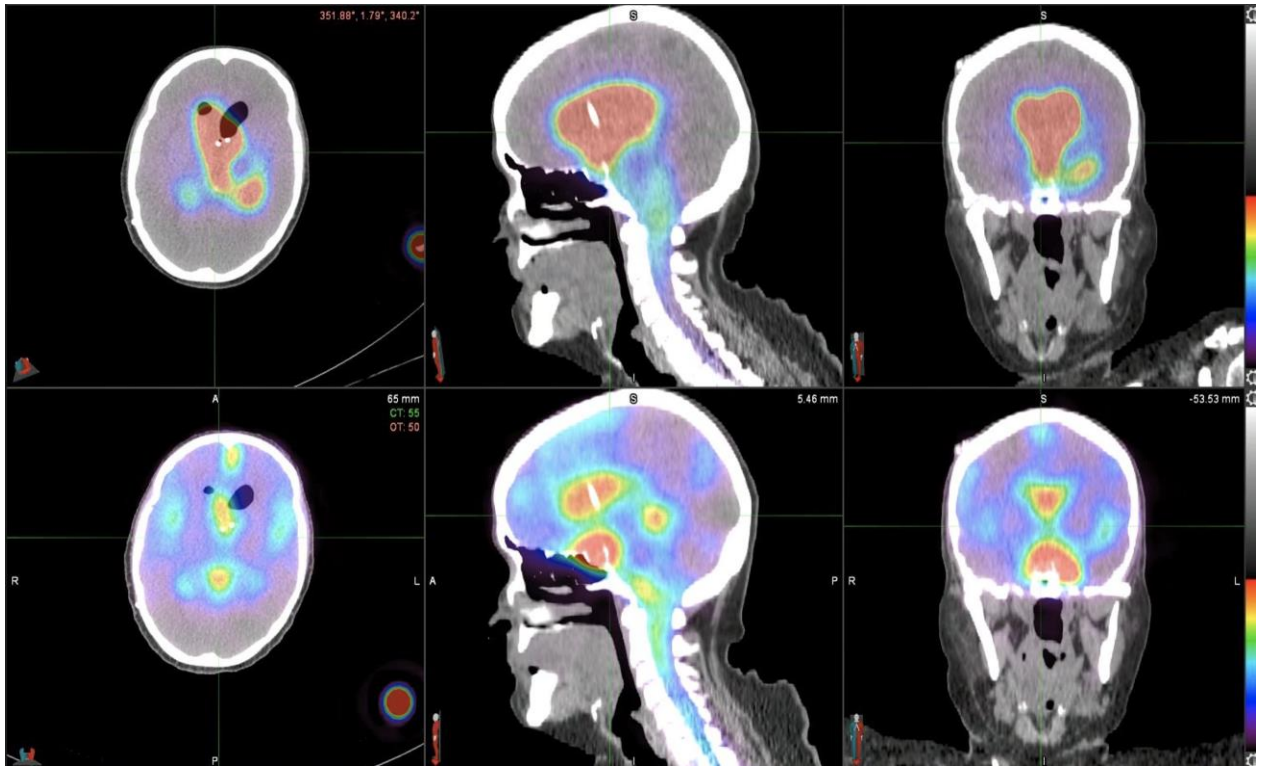
Patient 01-102

60 year old with Stage III Invasive Lobular Breast Carcinoma of the right breast (2016); bone metastases (06/2020), leptomeningeal metastasis (01/2022) with conversion to triple negative within the CSF.

Enrolled in Cohort 1 receiving 6.6 mCi ^{186}RNL in 5.0 ml infusate on June 15, 2022.

Radiation absorbed dose:

- Ventricles and cranial subarachnoid space = 26.80 Gy
- Ventricles (lateral, 3rd, and 4th) = 36.44 Gy
- Cranial subarachnoid space = 21.25 Gy
- Spinal Fluid = 5.76 Gy



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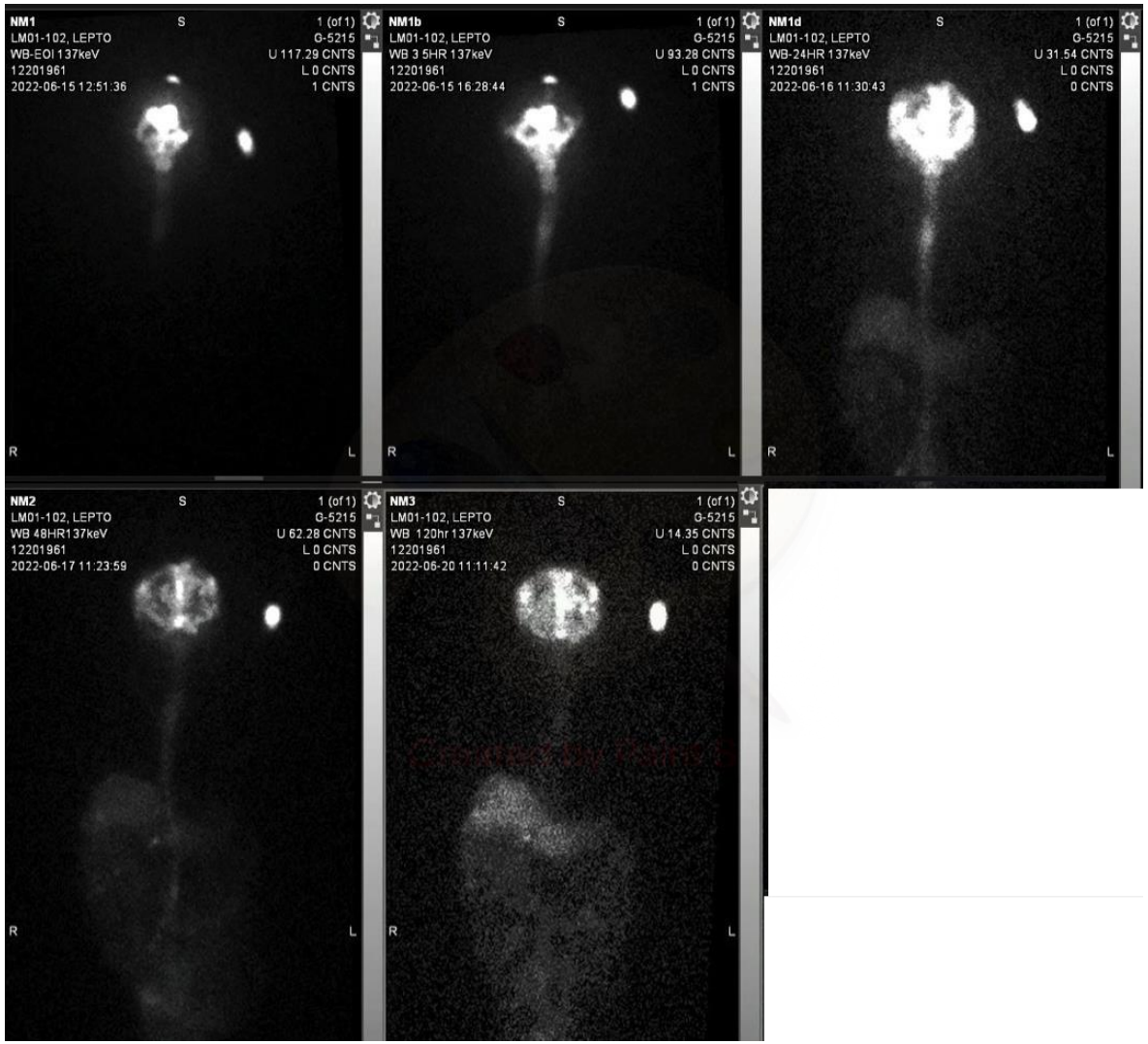
Patient 01-102



Assessment: Tumor Cells / mL

Pre	5 Hours	24 Hours	48 Hours	14 Days	28 Days	43 Days	56 Days
839.13	551.03	455.29	506.73	Not Req	395.1	Not Req	TBD

The subject was alive and clinically stable as of the last follow-up at day 39 after enrollment/treatment in the study.

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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 intraventricular catheter, 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
- 3 of 3 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