Preliminary Clinical data in the Phase 1/2a Dose Escalation Trial of ^{186}RNL (Rhenium-186 nanoliposome) (^{186}Re) Obisbemeda in Leptomeningeal Metastases (LM): the ReSPECT-LM Trial

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DISCLOSURES

- Consultant to Plus Therapeutics
- Officer and stock ownership of NanoTx, Inc.

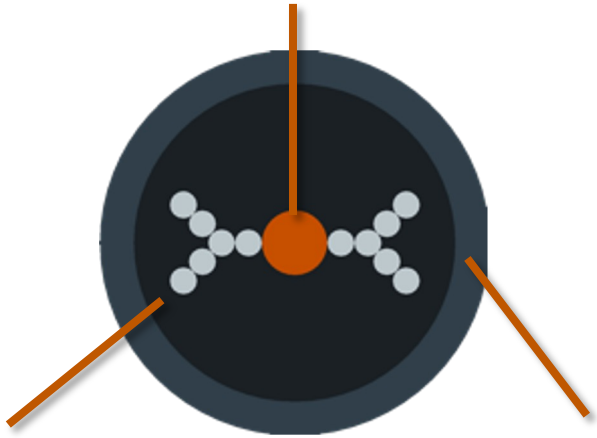
LEAD DRUG RHENIUM ^{186}RE OBISBEMEDA (^{186}RNL) PROLONGS RADIATION IN THE BRAIN & CSF

Rhenium ^{186}Re Obisbemeda, ^{186}RNL

Complementary technologies drive efficacy and safety profile

Rhenium-186 Radionuclide

Emits tumor destroying radiation over short distances while sparing healthy tissue



BMEDA Small Molecule

Chelates to Rhenium & is loaded into a NanoLiposome where it is irreversibly trapped

100 nm NanoLiposome

Carries BMEDA-Rhenium to target tumor & improves retention

^{186}RNL IN CLINICAL TRIALS

In addition to leptomeningeal metastases, there is a current trial using ^{186}RNL for the treatment of recurrent glioblastoma

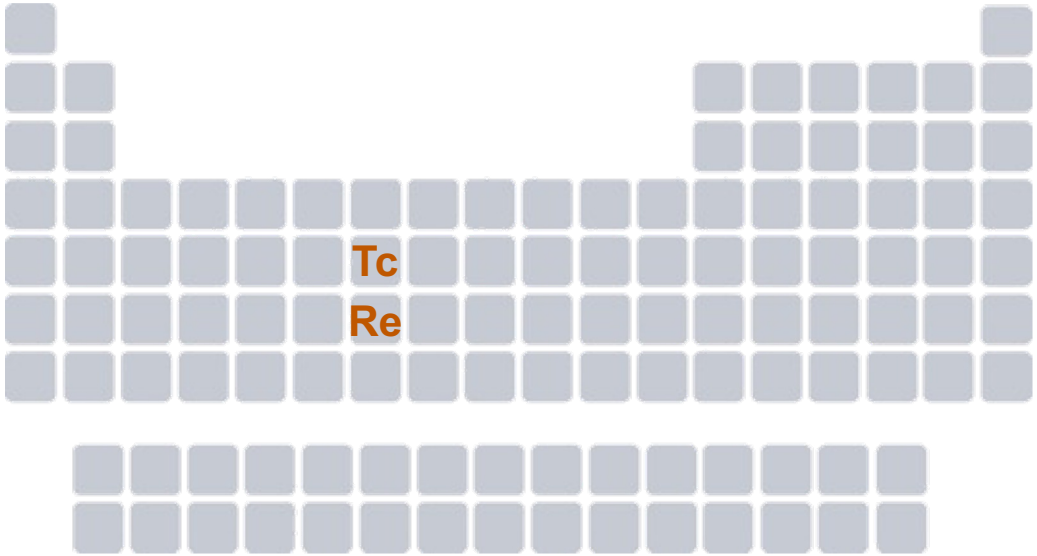
The initial phase I study was promising in terms of safety and efficacy, and is currently enrolling in a Phase 2

^{186}RNL also has the potential to treat other malignancies in addition to CNS malignancies

IDEAL RADIOISOTOPE FOR CNS TUMORS

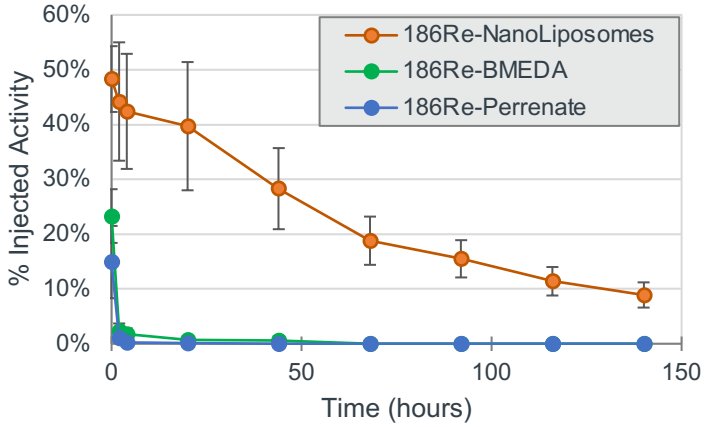
+ Two clinically relevant isotopes, Rhenium-186 & Rhenium-188
+ β is tumoricidal & 10% 137 keV γ for imaging
+ Rhenium/BMEDA chemistry is ideal for nanoliposome loading
+ Lacks affinity for bone
+ Majority of activity renally cleared. A portion is metabolized in the liver and spleen followed by renal clearance.

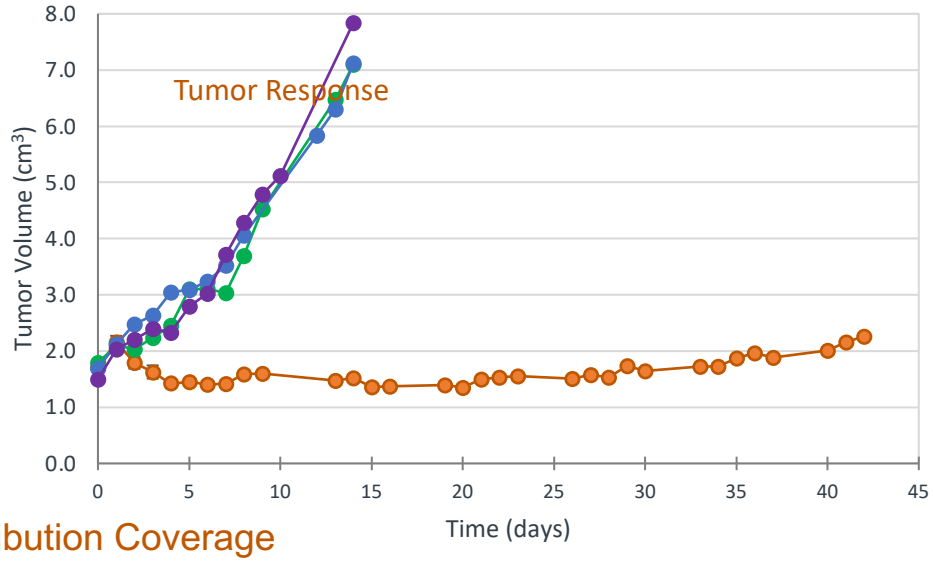
Specification	Rhenium-186	Rhenium-188
Average path length	~ 2 mm	~ 4 mm
Radiation half life	3.8 days	17 hours
Manufacture	Reactor	Generator



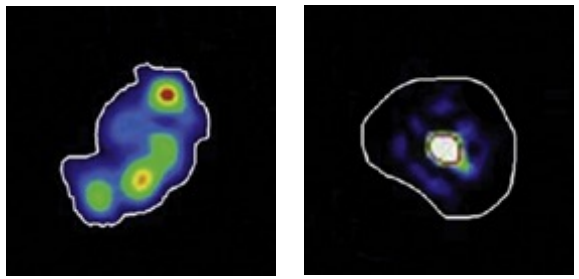
+ **Technetium (Tc) is adjacent in the periodic table to Rhenium (Re) and has similar properties**
+ **Tc is used in 40 million diagnostic procedures per year (80% of all nuclear medicine procedures globally)**

Tumor Retention



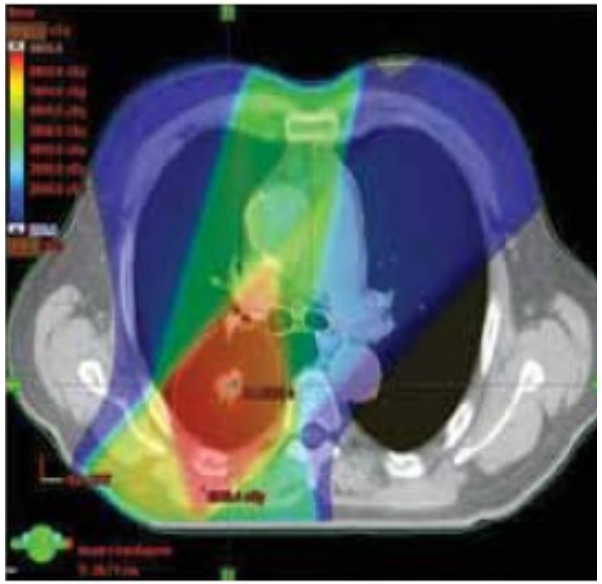


Improved Drug Distribution Coverage



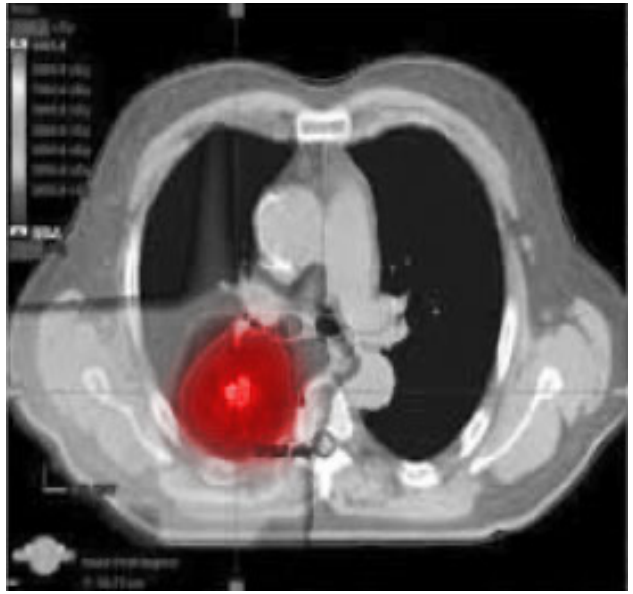
Sources: Phillips, W. et al. *Advanced Drug Delivery Reviews,* 2014

EXAMPLE OF A POTENTIAL FUTURE USE OF ^{186}RNL



Traditional Intensity Modulated Radiation Therapy (IMRT)

Proton Beam



Convection administered ^{186}RNL

- Ability to retreat patient due to low doses delivered to adjacent normal tissue.
- Potential for very high dose delivery to tumor

GOOD LOCAL RETENTION OF RNL IN THE BRAIN OVER TIME FOLLOWING INTRATUMORAL WITH CONVECTION

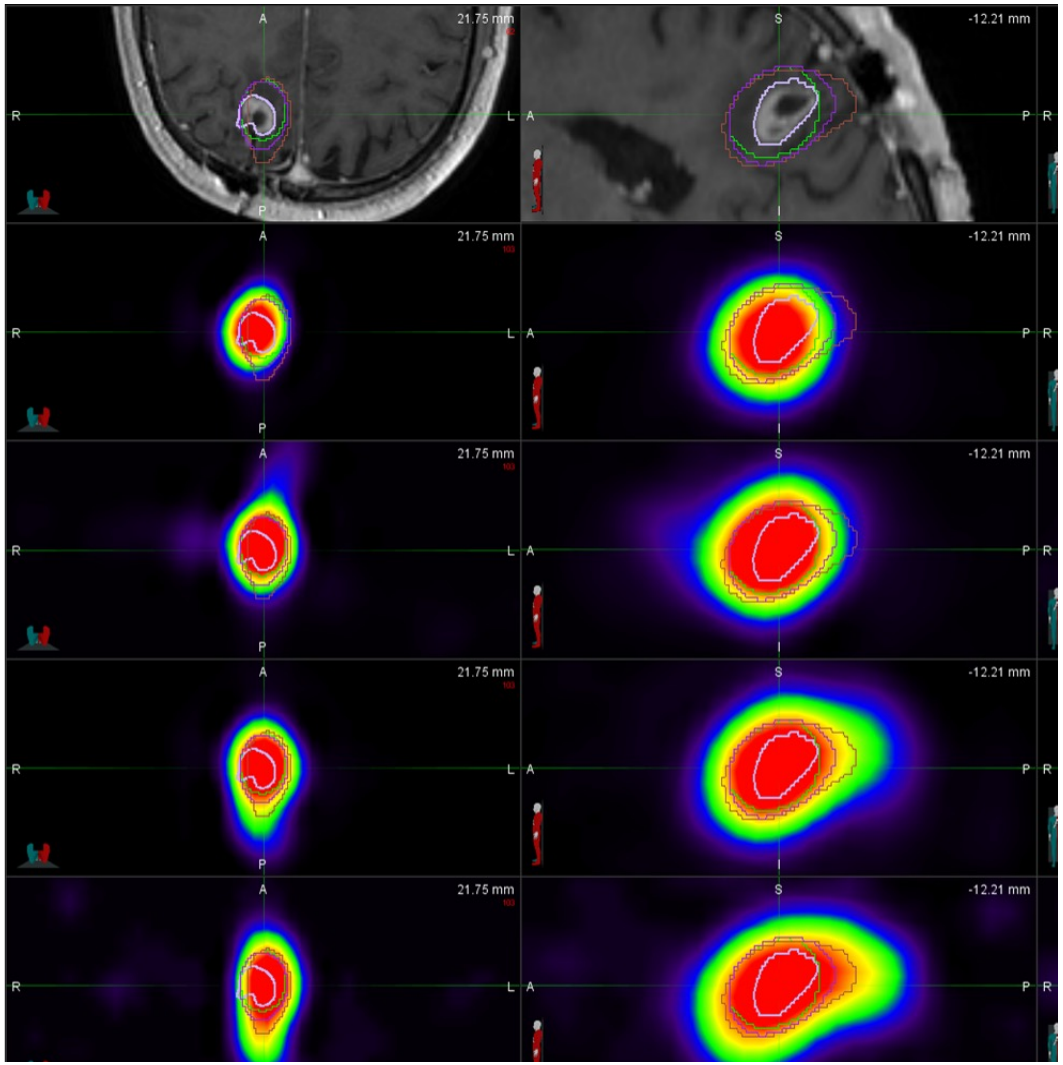
MRI
Baseline

SPECT
Mid-Infusion

SPECT
Post-Infusion

SPECT
24-hr Post-Infusion

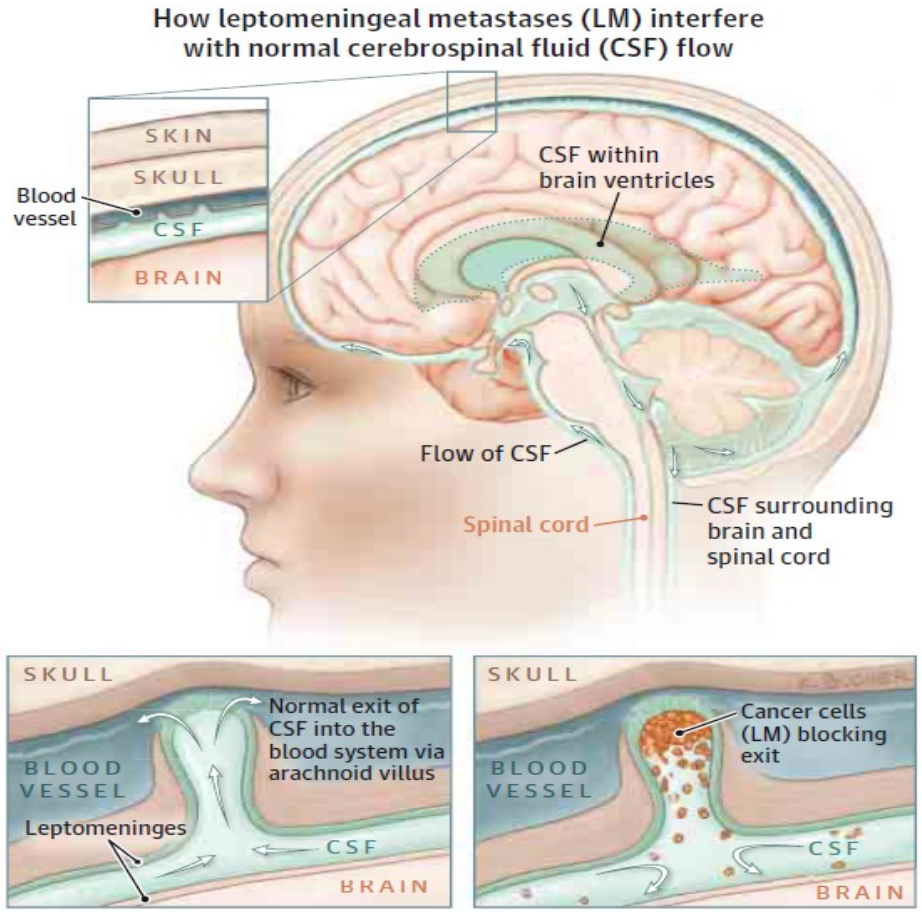
SPECT
120-hr Post-Infusion



Example of RNL for recurrent glioblastoma Therapy.
See Poster #EP-0612 (example of RWD)

LEPTOMENINGEAL DISEASE (LMD)

- Cancer of the pia/arachnoid and in the subarachnoid space/CSF (distinct from dura, parenchymal)
- Metastatic from solid and hematologic malignancies
- Symptoms of high ICP and/or spinal cord compression
- Cranial nerve symptoms
- Spinal cord and nerve roots: causing extremity weakness, paresthesia and/or pain.



JAMA Oncology, Zachary A et al. 04/2016

LMD TREATMENT APPROACH

Goals of Treatment

- **Symptomatic:** Reduce pressure on the brain caused by any CSF buildup, pain, neurologic deficits
- **Tumor Directed:** Reduce the number of cancer cells within the CSF

Treatment Modalities

- Surgery
- Radiation Therapy
- Medical Therapy (cytotoxics, targeted therapy, intrathecal etc)
- Palliative Care/Hospice

LEPTOMENINGEAL DISEASE PROGNOSIS

- Difficult to treat with poor overall survival (OS ~2-4 months)
- Without treatment survival can be 4-6 weeks
- 30-50% of her2+ breast cancer patients develop CNS mets, also seen more frequently in triple negative breast cancer
- Approximately 20% of her2+ breast cancer patients develop leptomeningeal disease
- No effective or approved therapies

CONSIDERATIONS IN LMD TREATMENT

Type of systemic cancer

- Solid versus hematologic malignancy
- Primary histology

State of systemic cancer

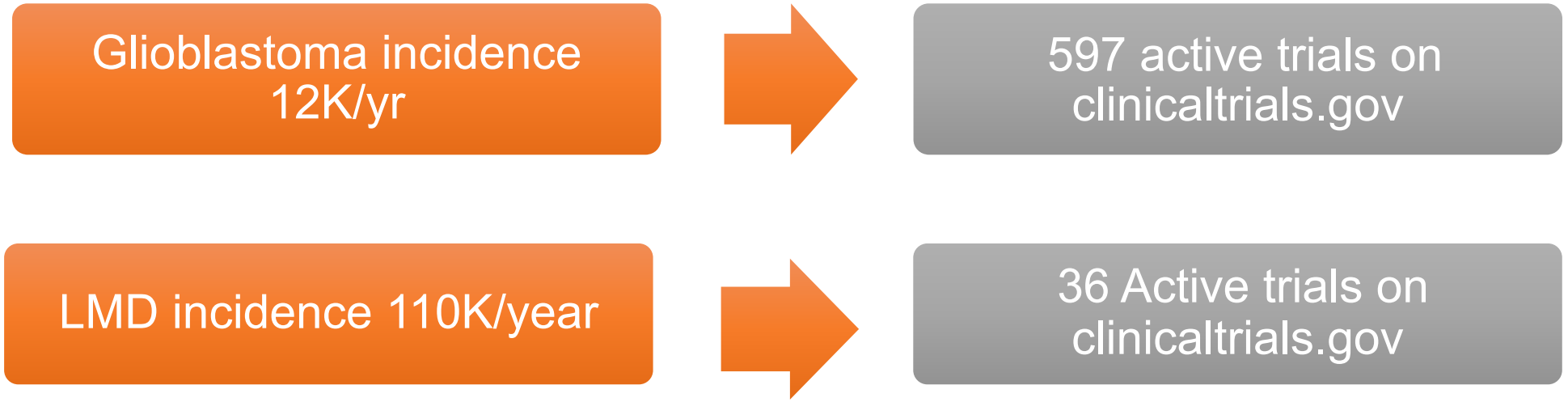
- Stable versus progressive disease

Bulky versus non-bulky metastases

Performance status

Patient Symptom Burden

LMD HAS BEEN UNDERSTUDIED: CLINICAL TRIALS



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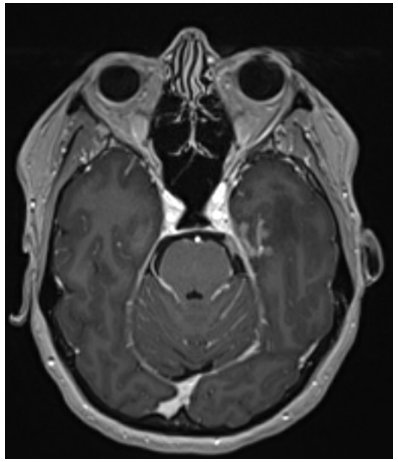
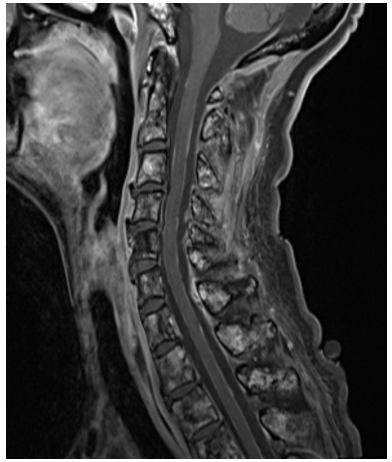
Current LMD Diagnostics

Three components:

1- Radiographic





2- Clinical Symptoms

3- CSF Cytology

Inconsistent and Confounding Clinical Symptoms

CSF Sample Viability

➢50% of viable cells after 30 minutes

➢10% after 90 minutes

Poor Sensitivity to CSF Cytology sensitivity for malignant cells

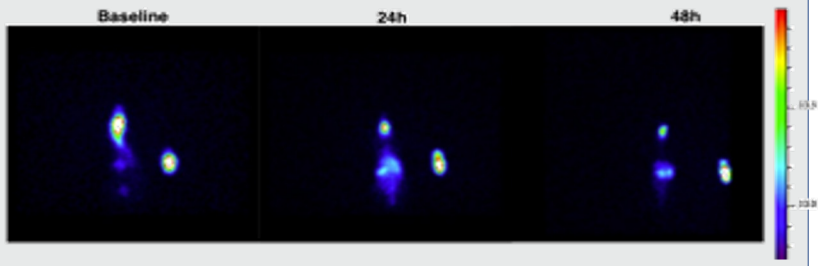
➢First LP: 45-60%

➢Third LP: up to 90%

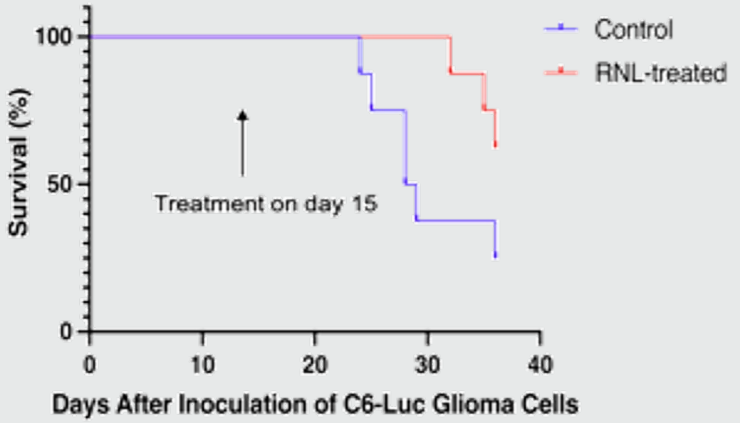
PRECLINICAL EVIDENCE FOR RHENIUM ^{186}RE OBISBEMEDA USE IN CNS CANCERS

Leptomeningeal Metastases
Wistar Rat Model

Radioactivity Visualized at 48 Hours;
Mean Absorbed Radiation Dose of 1,094 Gy



Statistically Significant Difference in Overall Survival with ^{186}RNL-Treated Animals Outliving the Controls



RESPECT-LM PHASE 1: TRIAL OVERVIEW

Dose escalation study for patients with leptomeningeal metastases

Study Design

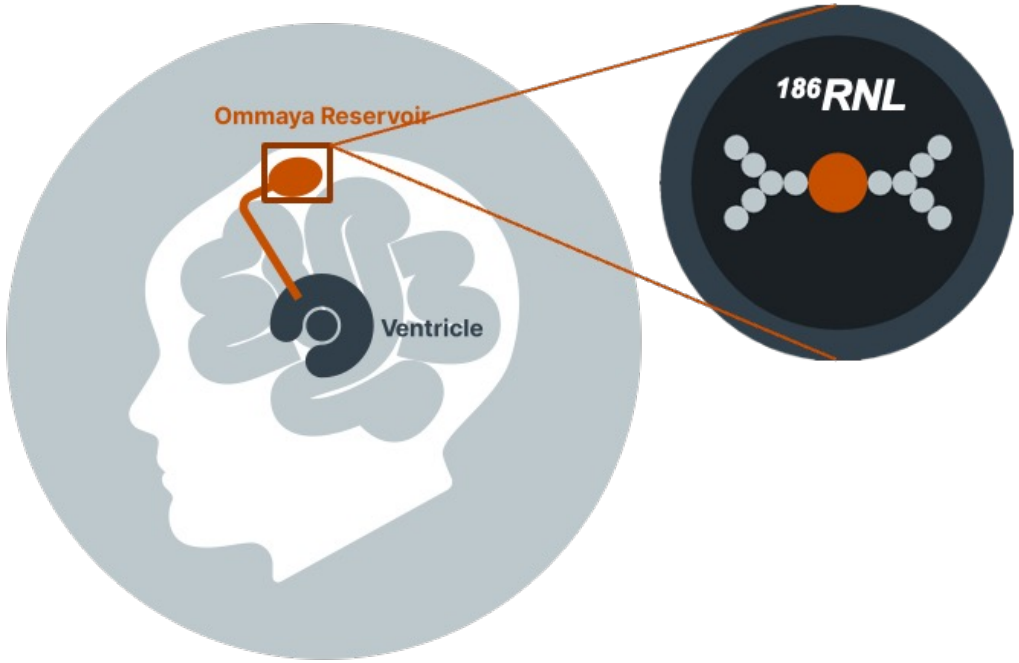
+ Multi-center, sequential cohort, open-label, dose-escalation, Phase 1 clinical trial to evaluate the safety and tolerability of a single dose of ^{186}RNL given by the intraventricular route (Ommaya reservoir) in adult LM patients
+ Primary objective is to determine a maximum tolerated dose (MTD)/maximum feasible dose (MFD) utilizing a modified 3+3 Fibonacci design
+ Each cohort received a single dose in a fixed volume by intraventricular catheter (Ommaya reservoir)
+ 1 patient (01-101) received a second dose under compassionate use

Inclusion Criteria

+ Proven and documented LM, meets requirements for the study (EANO-ESMO Clinical Practice Guidelines Type 1 and 2, except for 2D)
+ LM of <u>any</u> primary type
+ Karnofsky performance status of 60 to 100
+ Standard organ function requirements

Exclusion Criteria

+ Obstructive or symptomatic communicating hydrocephalus
+ Ventriculo-peritoneal or ventriculo-atrial shunts without programable valves or contraindications to placement of Ommaya reservoir
+ Any dose to the spinal cord or whole brain radiation therapy
+ Standard concomitant illness restrictions



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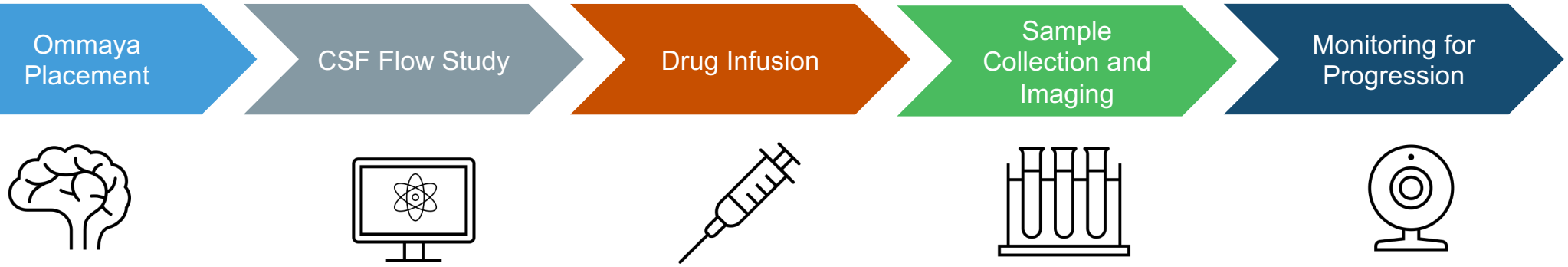
RESPECT-LM PHASE 1: WORKFLOW

Radiotherapy in a single outpatient visit



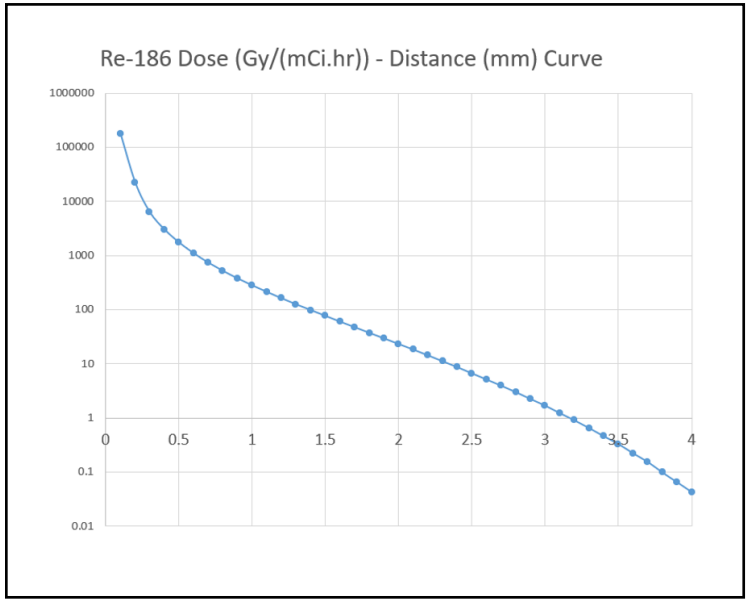
Week Prior to Treatment	Day -2 to -4	Day 1	Day 1-7	Day 28-End of Study
If not already present	^{111}In-DTPA CSF flow study to rule out flow obstruction	SSKI + single 5-minute injection of ^{186}RNL in outpatient setting	Blood, urine, CSF sample collection + whole body planar imaging (3.5-, 24-, 48-, and 168-hours post EOI) + SPECT/CT imaging (45-minutes and 24-hours post EOI)	MRI + RANO Day 28, Day 56, and every 56 days until progression

RESPECT-LM PHASE 1, PART A: DOSIMETRY

Absorbed dose in CNS spaces varied with administered dose, but organ doses remained low

Cohort	Blood Absorbed Dose (Gy)	Liver Absorbed Dose (Gy)	Spleen Absorbed Dose (Gy)	Ventricles and Cranial SA Space Absorbed Dose (Gy)	Ventricles (Lateral, 3rd, and 4th) Absorbed Dose (Gy)	Cranial SA Space Absorbed Dose (Gy)	Spinal Fluid Absorbed Dose (Gy)
1	0.02	0.38	1.82	24.84	19.26	27.95	6.88
2	0.02	0.64	3.61	40.86	25.43	49.49	20.73
3	0.07	1.47	2.40	63.83	25.96	85.73	44.07

+ Absorbed dose varied within patients for a given cohort, but the average absorbed dose for each region *increased* with administered dose
+ No ^{186}RNL or Re-186 accumulated in the bone marrow, and blood absorbed dose remained very low over each cohort
+ The liver and spleen are expected to be critical organs for normal tissue ^{186}RNL absorbed dose, but still significantly below any absorbed dose concerns for a critical organ
+ The beta radiation (therapeutic) from the ^{186}Re radionuclide has ~1-2 mm range, and 90% of radiation energy deposits within a 1.8 mm distance; there is a ~100X drop in dose at the 0.5 mm distance as shown in dose point kernel
+ Brain parenchyma and spinal cord have negligible absorbed dose and is not meaningfully affected by the circulating CSF fluid containing ^{186}RNL due to its short radiation pathlength of the beta emission



Dose point kernel of ^{186}Re radionuclide

RESPECT-LM PHASE 1: SAFETY SUMMARY

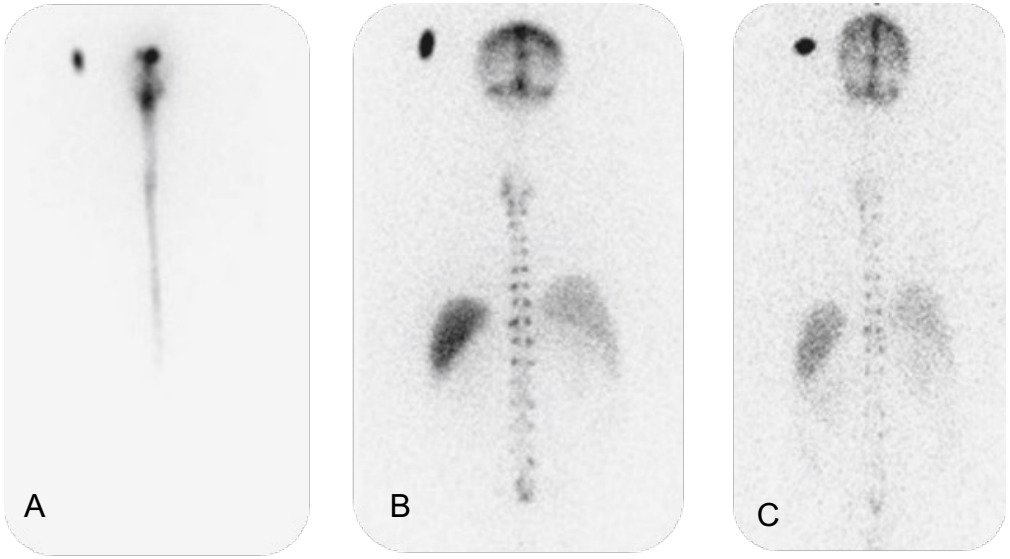
No DLTs were observed and the MTD/MFD was not reached

- 11 patients were treated over 4 cohorts, with one patient receiving a second treatment under compassionate use
- No DLTs observed
- MTD/MFD not reached
- Most AEs were mild (Grade 1, 58.7%) or moderate (Grade 2, 24%)
- 1 Grade 5 AE was due to systemic disease progression not related to study drug
- 8 SAEs observed, all but 1 deemed unrelated or unlikely related to study drug
- 1 SAE deemed possibly related was attributed to patient's pre-existing condition
- 5/10 treated patient remain alive and without evidence or report of radiation toxicity
- All 5 patient deaths were related to primary tumor progression

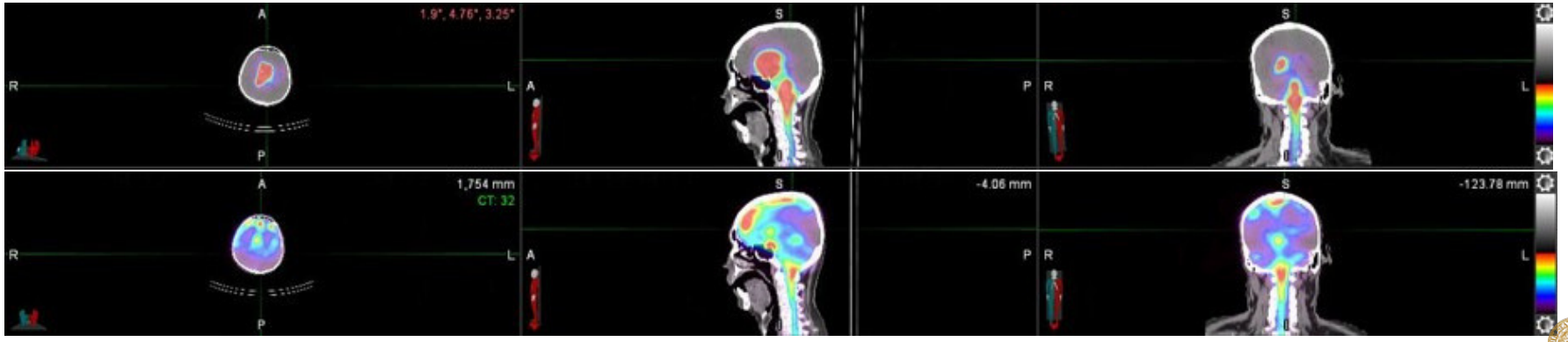
RESPECT-LM PHASE 1: IMAGING SUMMARY

^{186}RNL circulated throughout the CSF space and persisted for up to 7 days

+ Planar and tomographic (SPECT/CT) images collected using a dual-detector SPECT/CT camera
+ A sealed ^{186}Re radioactivity source was positioned next to each subject's head for in vivo radioactivity quantification
+ The planar and tomographic image acquisition uses low energy high resolution parallel-hole collimators (LEHR) with three energy windows settings – 137 keV, 119 keV, and 156 keV
+ ^{186}RNL was seen circulating throughout the CSF space by 1-hour following administration
+ ^{186}RNL persisted in the CSF for up to 7-days



Whole body planar image of LM patient at (A) 0.25-hours, (B) 48-hours, and (C) 7-days post intraventricular ^{186}RNL infusion through the Ommaya reservoir

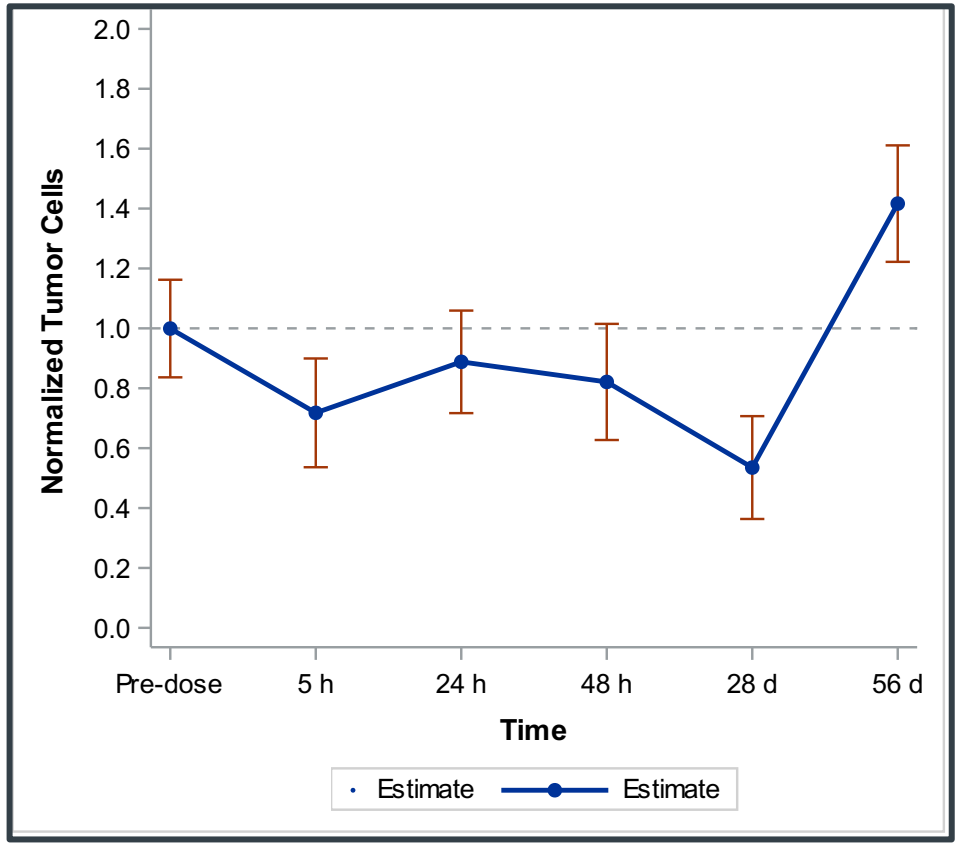


SPECT/CT of LM patient in cohort 2 (13.2 mCi injected activity) at 45-minutes and 24-hours post intraventricular ^{186}RNL infusion through the Ommaya reservoir

RESPECT-LM PHASE 1, PART A: TUMOR CELL ENUMERATION SUMMARY

Tumor cell counts decreased an average of 53% at Day 28 compared to predose level

- Exploratory endpoint included performing tumor cell enumeration on cerebral spinal fluid (CSF) pre- and post-administration of ^{186}RNL
- Tumor cell enumeration was performed by Biocept (CNSide, Biocept Inc., San Diego, CA)
- CSF tumor cells were captured using a biotinylated 10-antibody capture cocktail and immobilized in a streptavidin coated microfluidic channel
- Cells were quantified via digital analysis of the microfluidic channels
- Patients had up to 91% reduction in tumor cell count following treatment (max reduction at all time points measured)
- Patients had an average 53% reduction in tumor cell counts at Day 28 (compared to their predose level; range of 6% increase to 90% decrease)



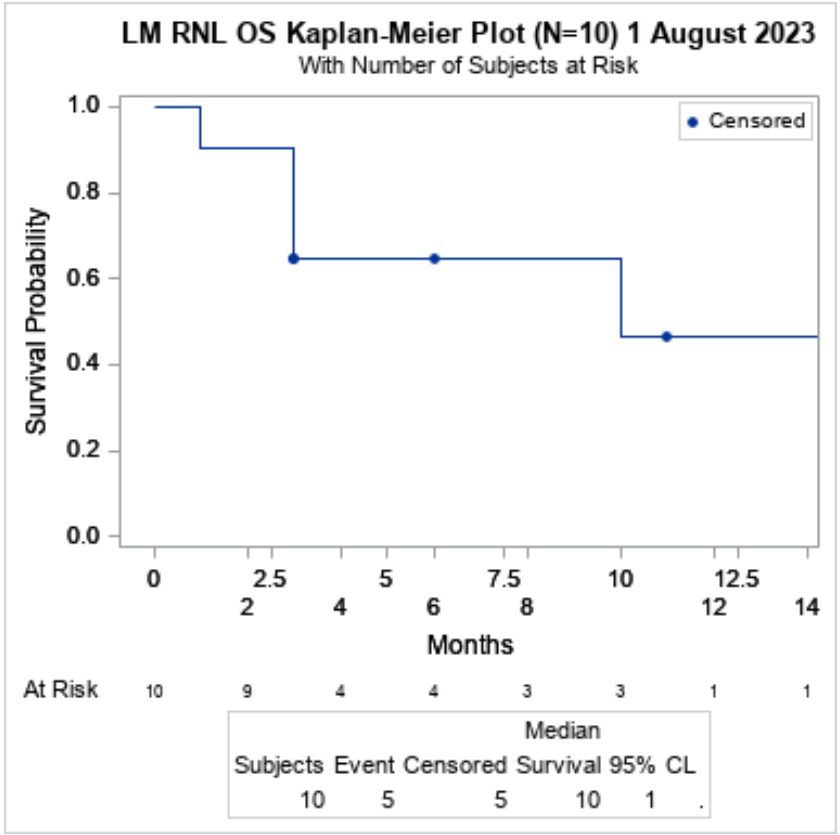
Normalized Tumor Cells by Time (N=10)

RESPECT-LM PHASE 1, PART A: OVERALL SURVIVAL

Treated patients had a median OS of 10 months

+ The median overall survival (OS) for N=10 patients treated with ^{186}RNL was 10 months with a 95% confidence interval (CI) of 1 month

+ 5 patients remained alive and were censored



Kaplan-Meier analysis of 10 LM patients treated with ^{186}RNL

OS cut off date 01Aug23

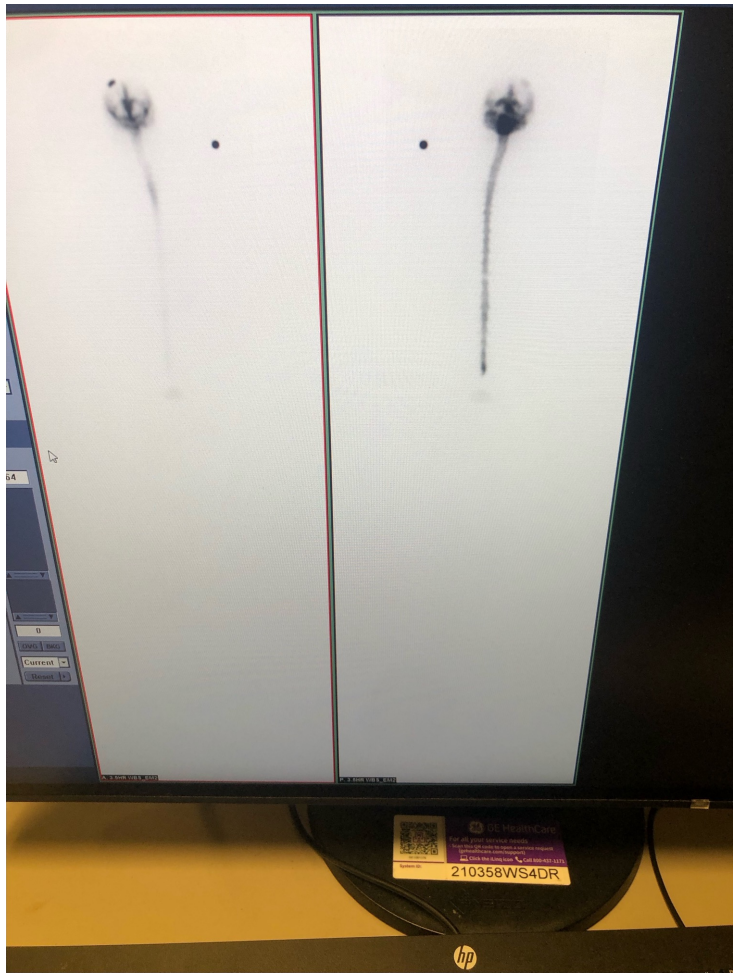
RESPECT-LM SUMMARY

Phase 1, Cohorts 1-3 are complete and Cohort 4 of Phase 1, Part B now enrolling

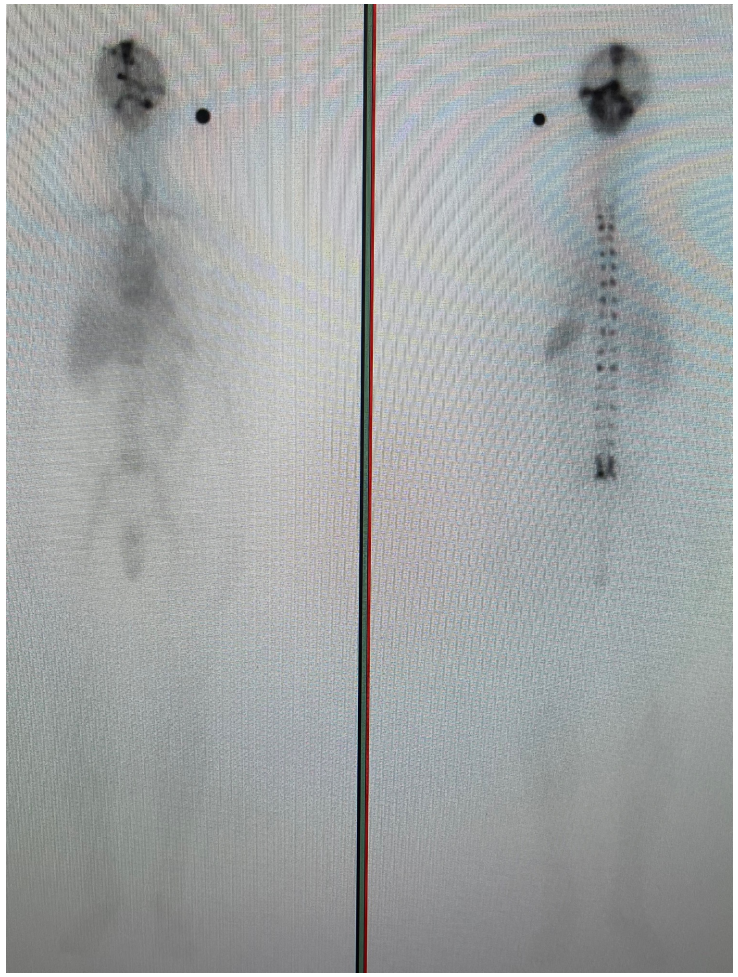
+ 10 of 14 patients with LM received a single intraventricular dose of ^{186}RNL between 6.6 and 26.4 mCi via indwelling Ommaya reservoir
+ In all treated patients, ^{186}RNL circulated throughout the CSF space by 1-hour following administration and persisted in the CSF for up to 7-days
+ An increase in administered dose correlated to a linear increase in absorbed dose to CNS structures
+ Overall organ radiation doses were low: liver, spleen, and bladder wall showed prominent ^{186}RNL clearance but as still significantly below any absorbed dose safety thresholds for critical organs
+ No DLTs were observed and MTD/MFD was not reached
+ Most AEs were Grade 1 and 2 with no SAEs attributed to study drug
+ CSF tumor cell enumeration decreased up to 91% following ^{186}RNL treatment (mean reduction 53% from baseline)
+ 5/10 treated patients remain alive, median OS of 10 months (95% CI of 1 month)
+ Continued dose escalation design to MTD/MFD (Phase 1, Part B; Cohorts 4-7) enrolling – 1 patient treated to date at 44.10 mCi
+ Multi-dose and retreatment protocols in process

Phase/Part	Cohort	Infused Volume (mL)	Total ^{186}RNL Activity (mCi)	Conc (mCi/mL)	% Increase
1	1	5	6.6	1.32	N/A
1	2	5	13.2	2.64	100
1	3	5	26.4	5.28	100
1	4	5	44.10	8.82	67
1	5	5	66.14	13.23	50
1	6	5	87.97	17.59	33
1	7	5	109.96	21.99	25

POST ^{186}RNL INFUSION IMAGING



3.5 hours



48 hours