KOL Roundtable on Leptomeningeal Metastases: An Obvious Disease Target for Radiotherapeutic Intervention

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Participants: **Priya Kumthekar, M.D.**, Associate Professor of Neurology and Medicine at Northwestern University's Feinberg School of Medicine

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August 11, 2023

The Emerging Radiopharmaceutical Landscape

Commercial Promise

- PSMA-targeting in Prostate Cancer
  - PLUVICTO: $240M in 2Q23 sales
  - PYLARIFY: $211M in 2Q23 sales
  - Illuccix: $78M in 2Q23 sales
- SSTR-targeting in Neuroendocrine tumors (NETs)
  - LUTATHERA: $150M in 2Q23 sales
- Bone metastases
  - Xofigo: €408M peak sales (€242M in the U.S.) in 2017

Clinical Promise

- ~50% of cancer patients in the U.S. receive some form of radiation therapy
  - Radiopharmaceuticals offer potential for directing more radiation and more potent types of radiation to tumor cells and less to healthy cells than external beam radiotherapy
- PSMAfore and SPLASH trials reading out in the pre-chemo mCRPC in 2H23
- Phase III SIERRA trial demonstrates potential in stem cell transplant conditioning
- Multiple next-generation products being tested in PSMA+ and SSTR+ patients

Expanding Radioisotope Diversity

- Therapeutic radioisotopes:
  - Lu-177 (PLUVICTO, LUTATHERA)
  - Ra-223 (Xofigo)
  - I-131 (AZEDRA, Bexxar)
  - Others approved: Y-90, Sr-89, Sm-153
  - Others of interest: Cu-67, At-211, Sn-117m, Tb-161, Ho-166, Er-169, Re-186, Re-188, Pb-212, Ra-224, Ac-225
- Imaging radioisotopes:
  - F-18 (F-18 FDG, Axumin, PYLARIFY, POSLUMA)
  - Ga-68 (Illuccix, LOCAMETZ, NETSPOT)
  - Others approved: Cu-64, Tc-99m, I-125, I-123, In-111, C-11, C-14, Xe-133, Tl-201, Rb-82, N-13
  - Others of interest: Zr-89, Pb-203

Opportunities

- Alternatives to molecular targeting (e.g., nanoparticle delivery, natural accumulation of radioactive salts, sealed or open brachytherapy)
- Pan-cancer targets (e.g., FAP, CXCR4, EGFR, IGF-1R)
- Biomarker imaging for patient selection and outcome monitoring
- Use in difficult to treat cancers (e.g., CNS cancers, pancreatic cancer, colorectal cancer, and aggressive blood cancers)
- Use in combinations with strong mechanistic rationale (e.g., immuno-oncology and DNA damage repair inhibitors)

JonesTrading

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Jones Research

Leptomeningeal Disease

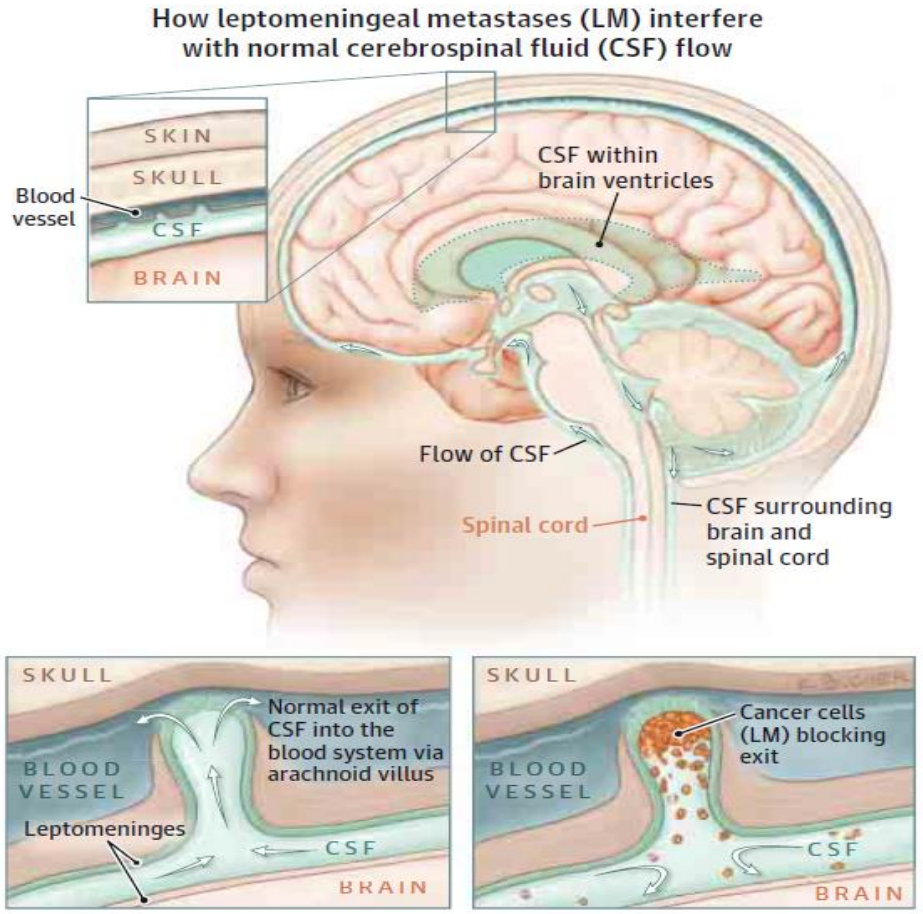
August 11, 2023

Priya Kumthekar, MD

Leptomeningeal Disease (LMD)

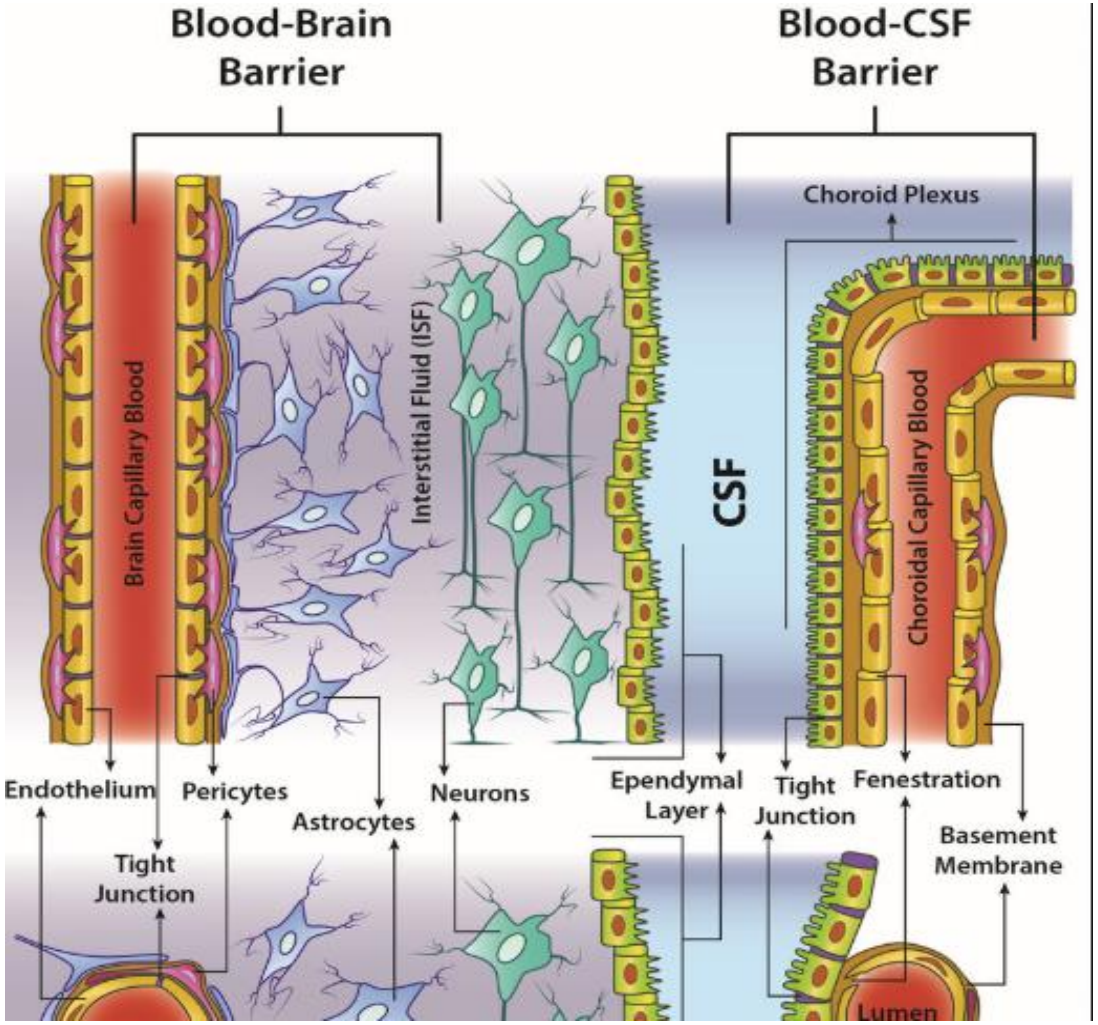
- Cancer of the pia/arachnoid and in the subarachnoid space/CSF (distinct from dura, parenchymal)
- Solid and Hematologic malignancies
- Symptoms of high ICP and/or spinal cord compression
- Cranial nerve symptoms
- Spinal cord and nerve roots: causing extremity

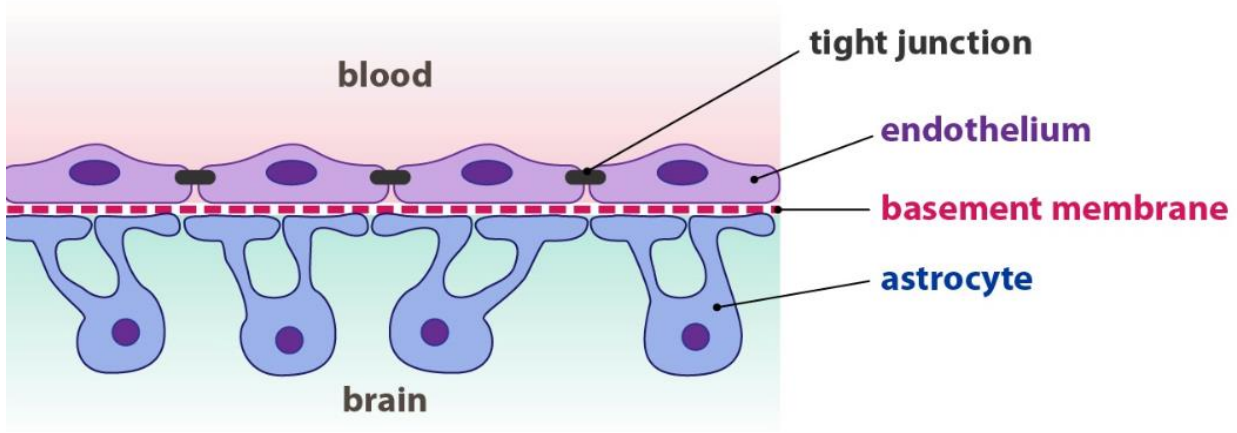
weakness, paresthesia and/or pain.

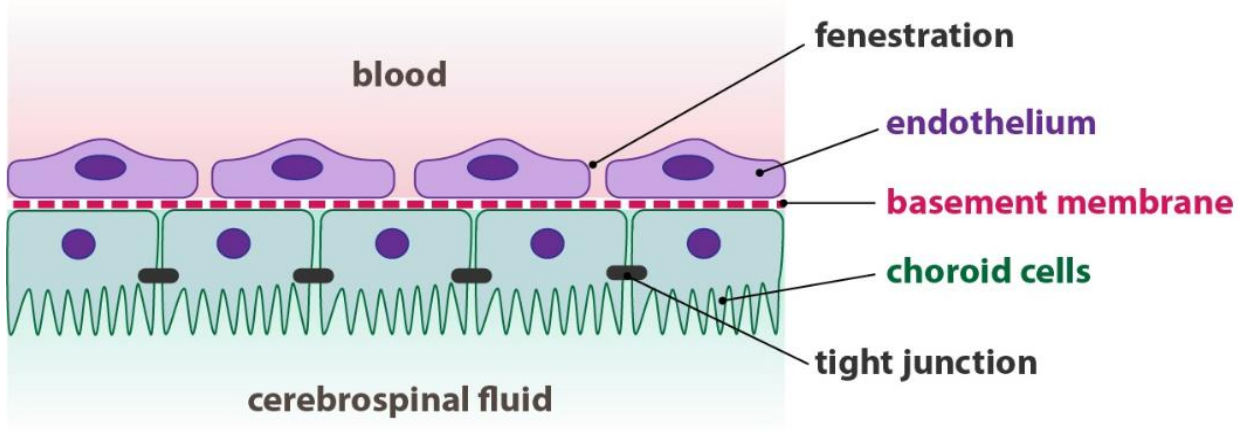


JAMA Oncology, Zachary A et al. 04/2016

The Challenges in LMD Treatment







CNS Cancer: Models, Markers, Prognostic Factors, Targets, and Therapeutic Approaches (pp.577-613), DOI: 10.1007/978-1-60327-553-8_25. May 2009

LMD Treatment Approach: Birdseye View

Goals of Treatment

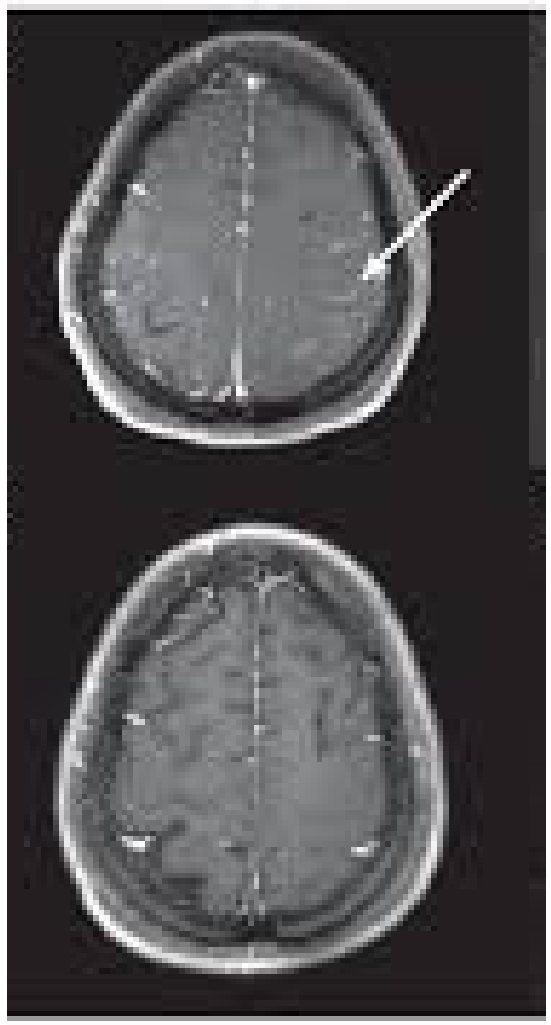
- Symptomatic: Reduce pressure on the brain caused by any CSF buildup, pain, neurologic deficits
- Tumor Directed: Reduce the number of cancer cells within the CSF

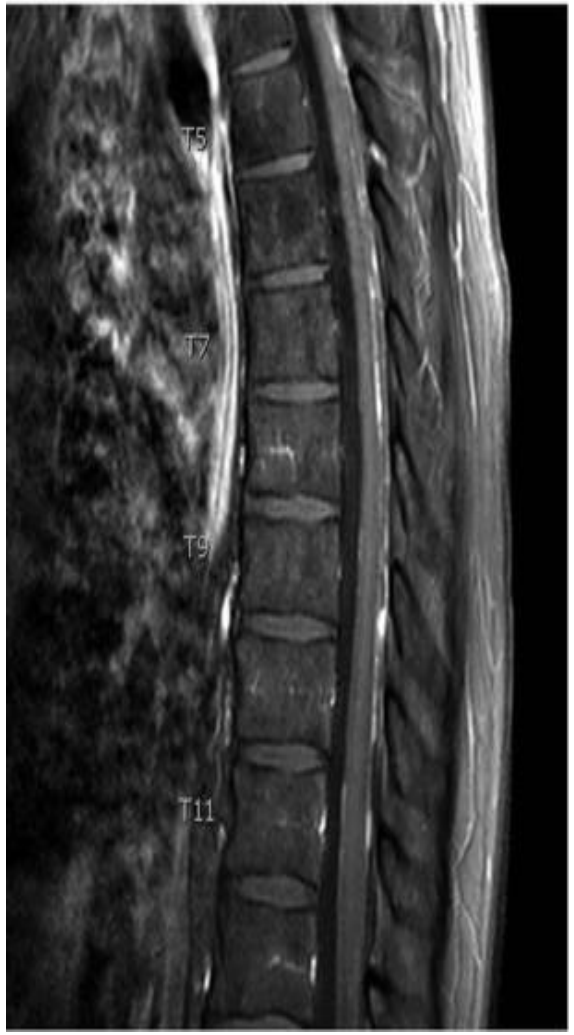
Treatment Modalities

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

Leptomeningeal Disease (LMD) 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 freq in TN breast ca
- 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

CNS metastases have been understudied: Clinical Trials

Glioblastoma incidence 12K/yr* → 324 INTERVENTIONAL and RECRUITING trials on clinicaltrials.gov

LMD incidence 110K/year* → 94 trials on clinicaltrials.gov*

*date censored 9-11-22

THE FINE PRINT:

- 38 recruiting studies (tripled from 2020)
- 10 active not recruiting
- 4 observational only

*in the United States

Nayer et al Oncotarget 2017 Sep 22; 8(42): 73312–73328

Northwestern Medicine | Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Change Is Happening

- Routinely excluded from clinical trials
  - Concern for CNS toxicity
  - Challenges in trial design and appropriate endpoints

- CNS Mets spotlighted
  - More advanced imaging techniques
  - Improved agents for systemic disease and prolonged survival
  - CNS disease alone

- Agents beyond traditional cytotoxic chemotherapy
  - Targeted drugs
  - Immunotherapy

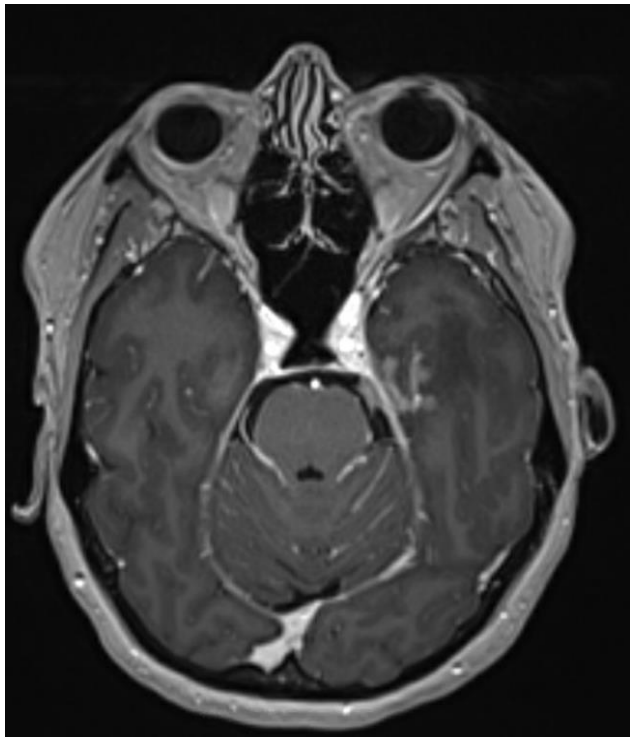
Current LMD Diagnostics: Challenges

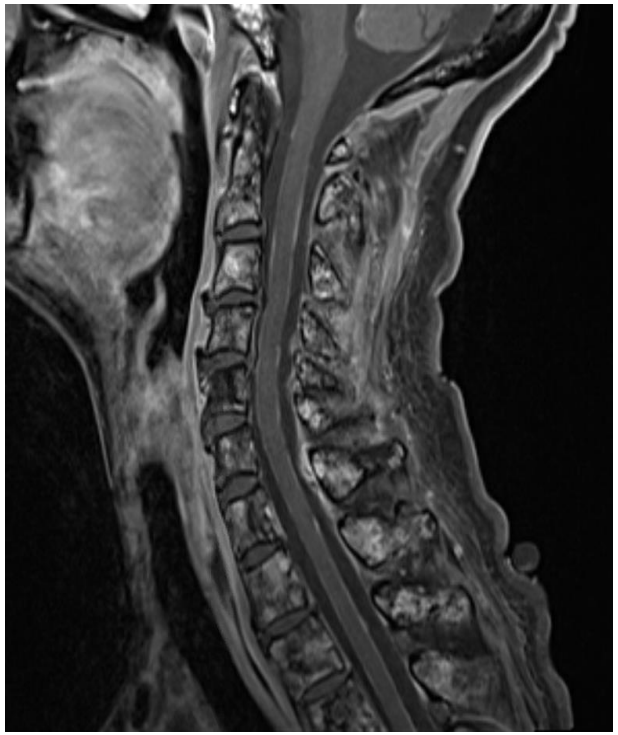
Three components:

1- Radiographic

2- Clinical

3- CSF Cytology





Inconsistent and Confounding Clinical Symptoms

CSF Sample Viability

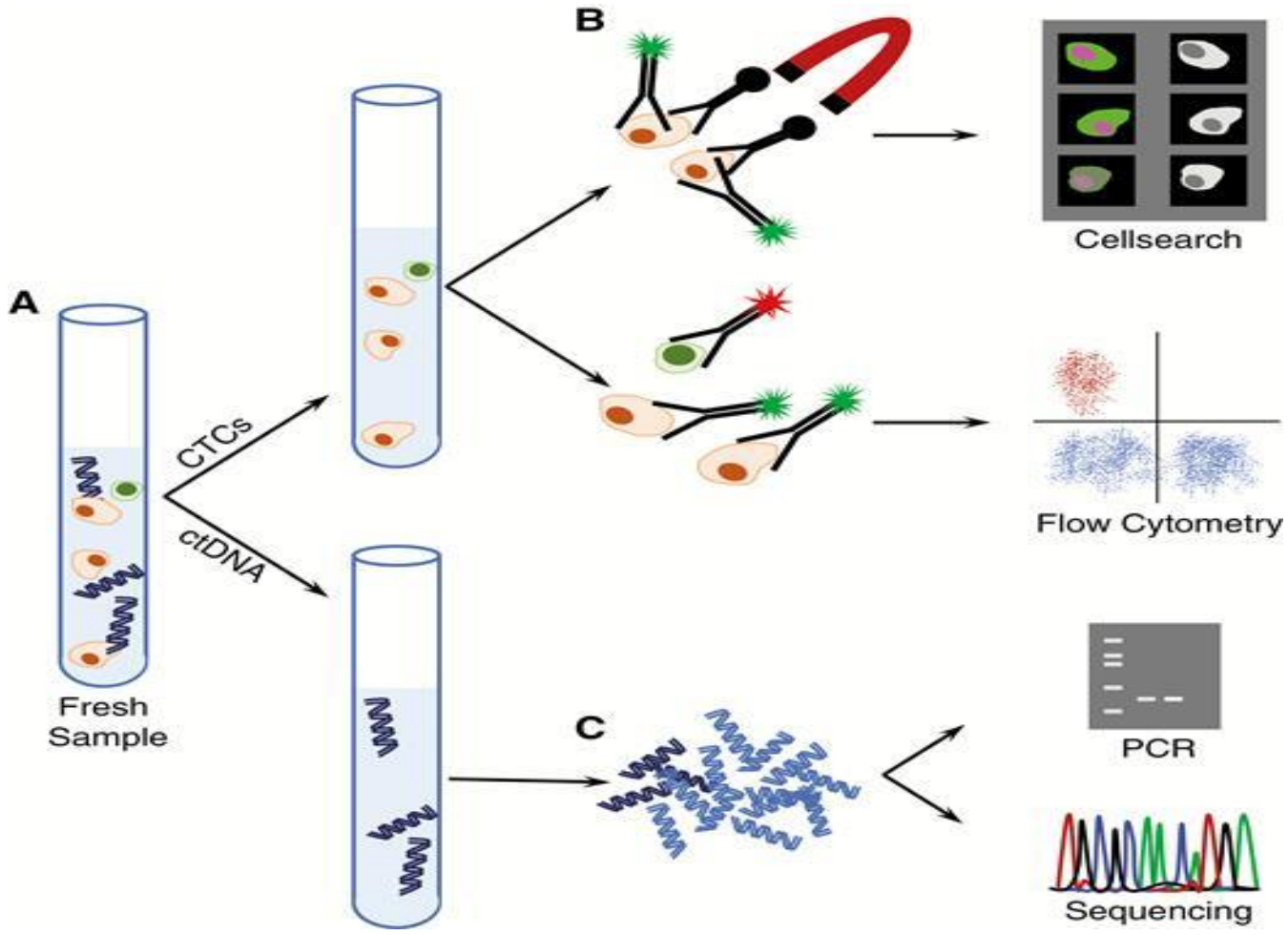
- **50% of viable cells after 30 minutes**
- **10% after 90 minutes**

Poor Sensitivity to CSF Cytology sensitivity for malignant cells

- **First LP: 45-60%**
- **Third LP: up to 90%**

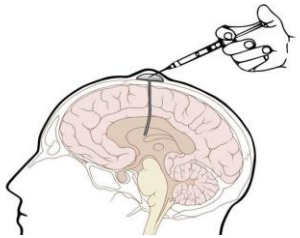
Can we do better?

- **Novel methods to isolate circulating tumor cells**
  - Using Cellsearch System or
  - Flow cytometry
- **CSF cell free DNA (ct DNA)**
  - Acellular material/ctDNA in the supernatant can be amplified and analyzed with PCR



Boire et al Neuro Oncology Jan 2019

A Therapy Treatment Response Trial in Patients With LMD: **FORESEE Study (**NCT05414123)



Is there a tumor?

Is there a target?

Is there a trend?

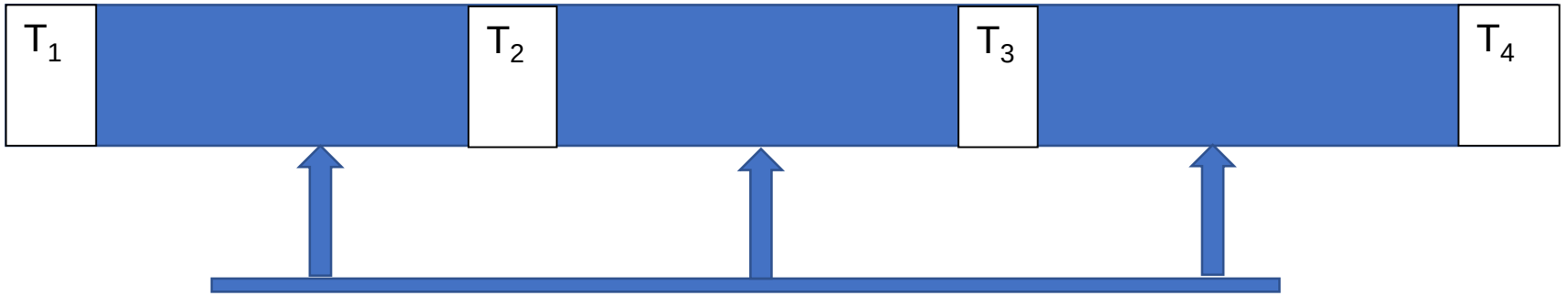
Serial monitoring

- CSF tumor cells
- ctDNA/RNA
- And current SOC diagnostics

Trial Schema:

Time Point 1 (Baseline)
CSF collection
CNSide testing
Radiographic imaging
Clinical evaluation
Cytology

Consecutive Time Points (At each clinician visit)
CSF collection
CNSide testing
Radiographic imaging
Clinical evaluation
Cytology



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Power and precision
in cancer radiotherapeutics

2023 SNO/ASCO Meeting
AUG 11, 2023

Andrew J. Brenner, M.D., Ph.D.,
Professor of Medicine, Neurology, and Neurosurgery at The University of Texas, Health Services Center at San Antonio

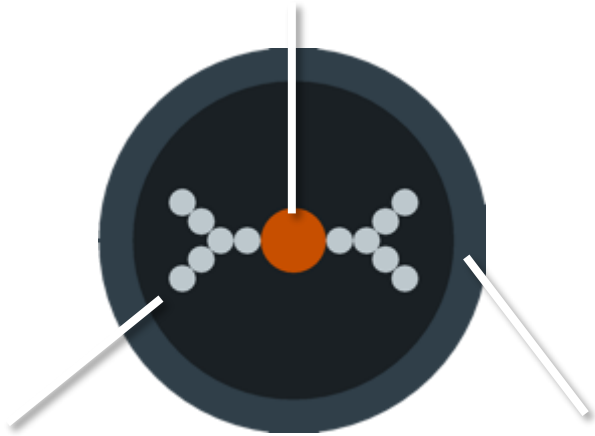
LEAD DRUG RHENIUM ^{186}RE OBISBEMEDA PROLONGS RADIATION IN THE BRAIN & CSF

Complementary technologies drive efficacy & safety profile

Rhenium Re^{186} Obisbemeda

Rhenium-186 Radionuclide

Emits tumor destroying radiation over short distances while sparing healthy tissue



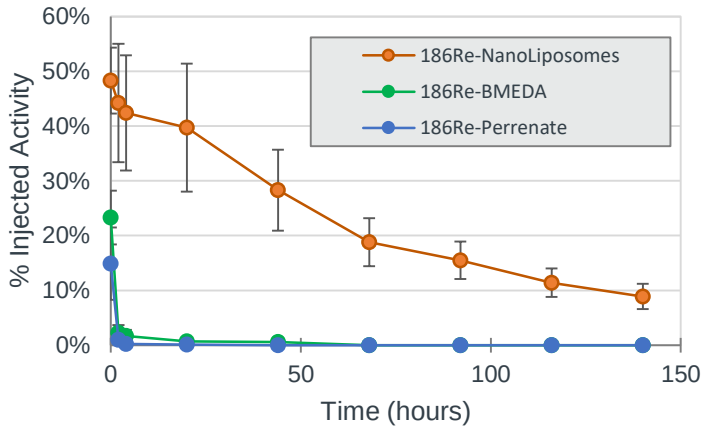
BMEDA Small Molecule

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

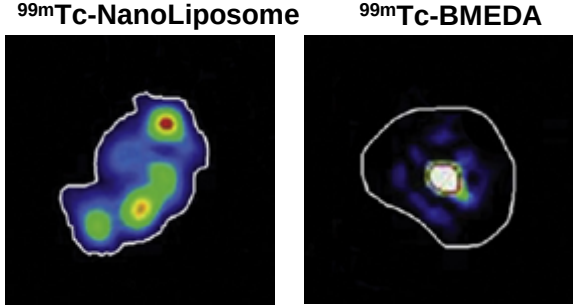
100 nm NanoLiposome

Carries BMEDA-Rhenium to target tumor & improves retention

Tumor Retention



Improved Drug Distribution Coverage



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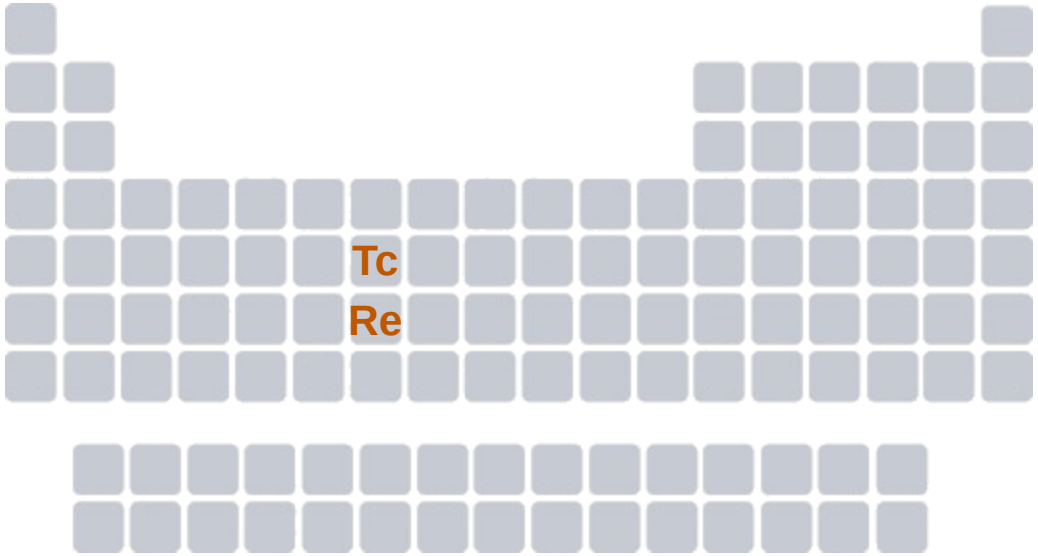
Sources: Phillips, W. et al. *Advanced Drug Delivery Reviews,* 2014

ISOTOPIC RHENIUM IDEAL FOR CNS INDICATIONS

Ideal radioisotope for CNS tumors

+ Two clinically relevant isotopes, Rhenium-186 & Rhenium-188
+ ‘Goldilocks’ energy profile between Yttrium-90 & Lutetium-177
+ Dual energy: β is tumoricidal & γ for imaging
+ Rhenium/BMEDA chemistry is ideal for nanoliposome loading
+ Lacks affinity for bone & thyroid
+ Rapid clearance
+ High radiation density & optimal half-life
+ Mature, redundant supply chain

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)**

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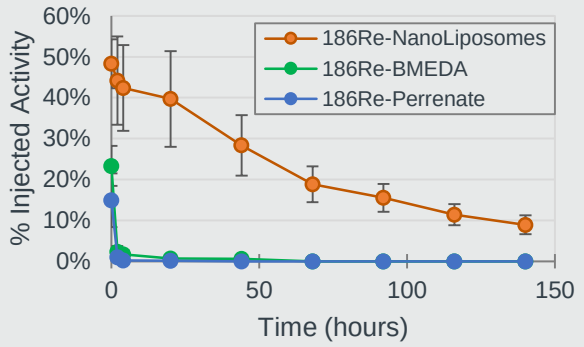
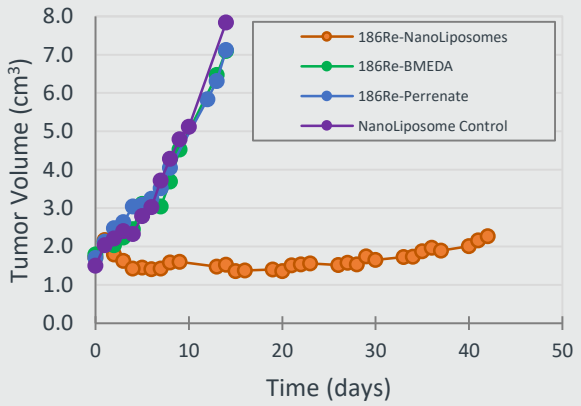
PRECLINICAL EVIDENCE FOR RHENIUM ^{186}RE OBISBEMEDA USE IN CNS CANCERS

Nanoliposome Enhances Tumor Dispersion & Response

Tumor Retention

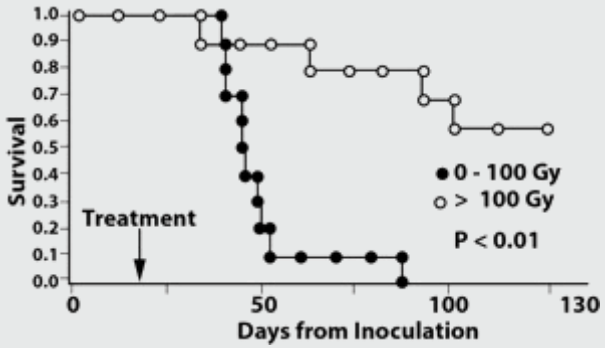


Tumor Response



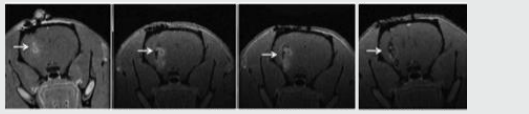
Glioblastoma Intracranial Xenograft Model

Clear Separation in Rat Survival at a Radiation Dose of 100 Gray

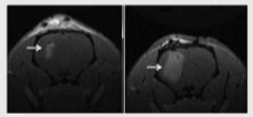


^{186}Re Treated Tumors Progressively Disappear Over Time

186Re-Liposome Treatment

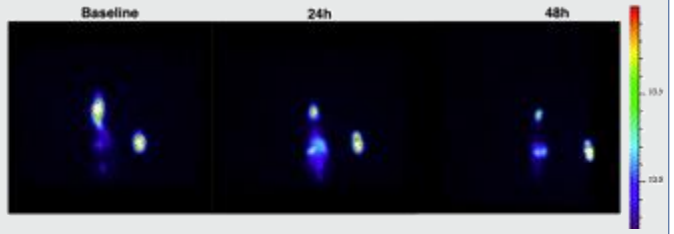


Control

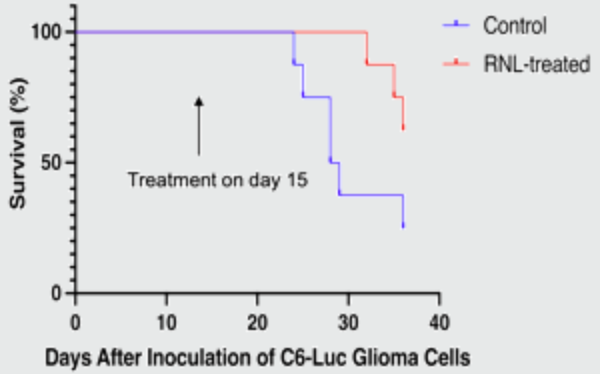


Leptomeningeal Metastases Wistar Rat Model

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



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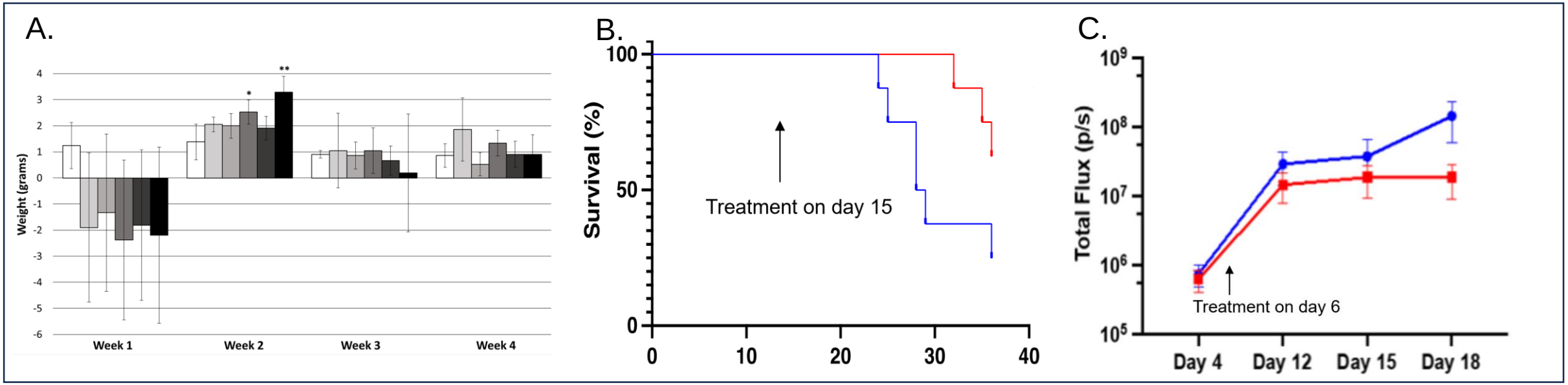
Sources: Phillips, W. et al. *Advanced Drug Delivery Reviews,* 2014; Phillips, W. et al. *Neuro-Oncology*, 2012; Balinda, H. et al. *SNO Brain Metastases Meeting,* 2021

RHENIUM ^{186}RE OBISBEMEDA PRECLINICAL SCIENCE: RETENTION, TUMOR COVERAGE, EFFICACY, SAFETY

+ **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
+ **EFFICACY:** In 2 LM models (Wistar/C6 and NSG/MDA-MB-231) treatment with ^{186}RNL resulted in prolonged survival.



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 PHASE 1, PART A: TRIAL OVERVIEW

Dose escalation study for patients with leptomeningeal metastases

Study Design

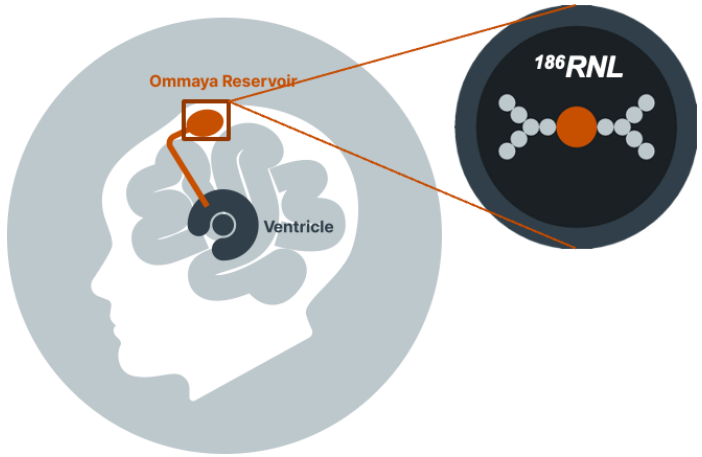
+ Multi-center, sequential cohort, open-label, dose-escalation, Phase 1 clinical trial to evaluate the safety and tolerability of a single dose of ^{186}RNL given by the intraventricular route (Ommaya reservoir) in adult LM patients
+ Primary objective is to determine a maximum tolerated dose (MTD)/maximum 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 any 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



Phase/Part	Cohort	Infused Volume (mL)	Total ^{186}RNL Activity (mCi)	Conc (mCi/mL)	% Increase
1A	1	5	6.6	1.32	N/A
1A	2	5	13.2	2.64	100%
1A	3	5	26.4	5.28	100%

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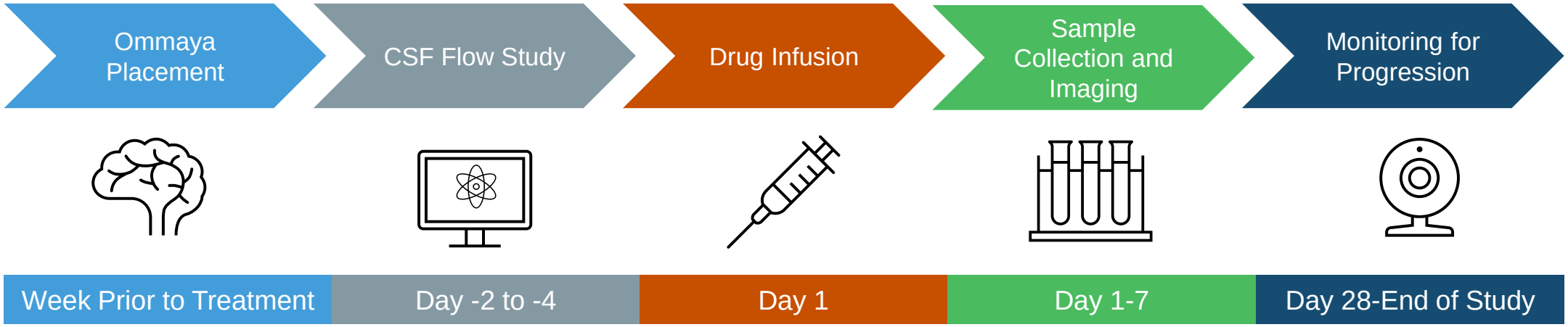
RESPECT-LM PHASE 1, PART A: WORKFLOW

Radiotherapy in a single outpatient visit



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RESPECT-LM PHASE 1, PART A: ENROLLMENT + DEMOGRAPHICS

10 subjects treated with ^{186}RNL

Patients

+ 13 patients were screened between March 2022 and March 2023
+ 10 patients were treated with ^{186}RNL between March 2022 and April 2023
+ 9 patients received a single dose
+ 1 patient received a second dose (retreatment)
+ 5 patients remain alive

Demographics

+ Most treated patients were white (80%), women (70%), and between 41-60 years of age

Primary Cancer Diagnosis

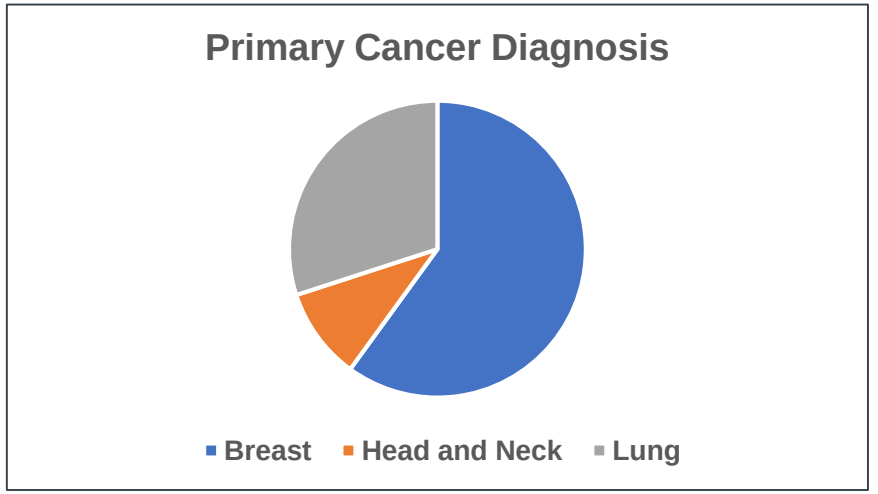
+ Primary cancer diagnosis was breast (60%), lung (30%), and head and neck (10%)
+ Most breast cancer patients were triple negative (ER-/PR-/HER2-)

LM Diagnosis

+ Most patients presented with neurologic symptoms (dizziness, weakness, back pain, etc.) and subsequent work-up with MRI and tumor cell enumeration (CNSide, Biocept Inc., San Diego, CA) were diagnostic of LM

Patient Status	Number of Subjects
Consented and Screened	13
Withdrew Consent	1
Screen Failures	2
Treated with ^{186}RNL	10
Deceased	5
Alive	5

Patient Accrual by Site	Number of Subjects
UTHSCSA	5
UTSW	3
NW	1



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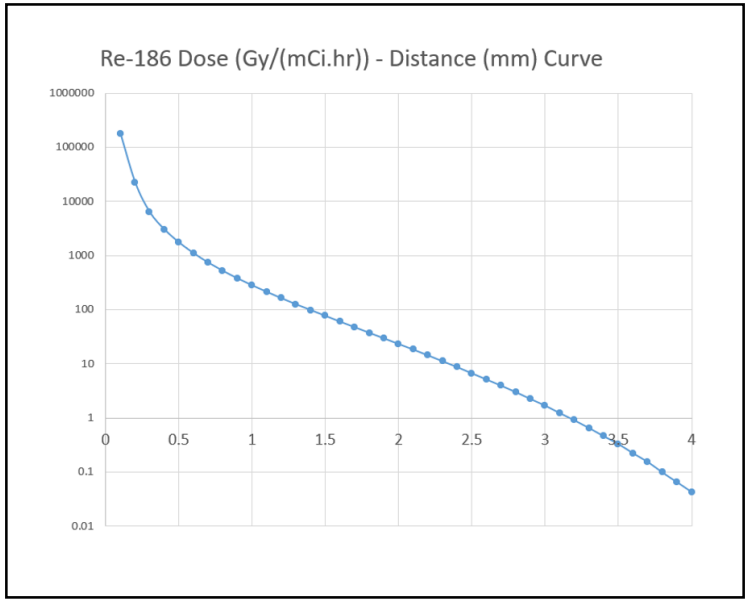
RESPECT-LM PHASE 1, PART A: DOSIMETRY

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

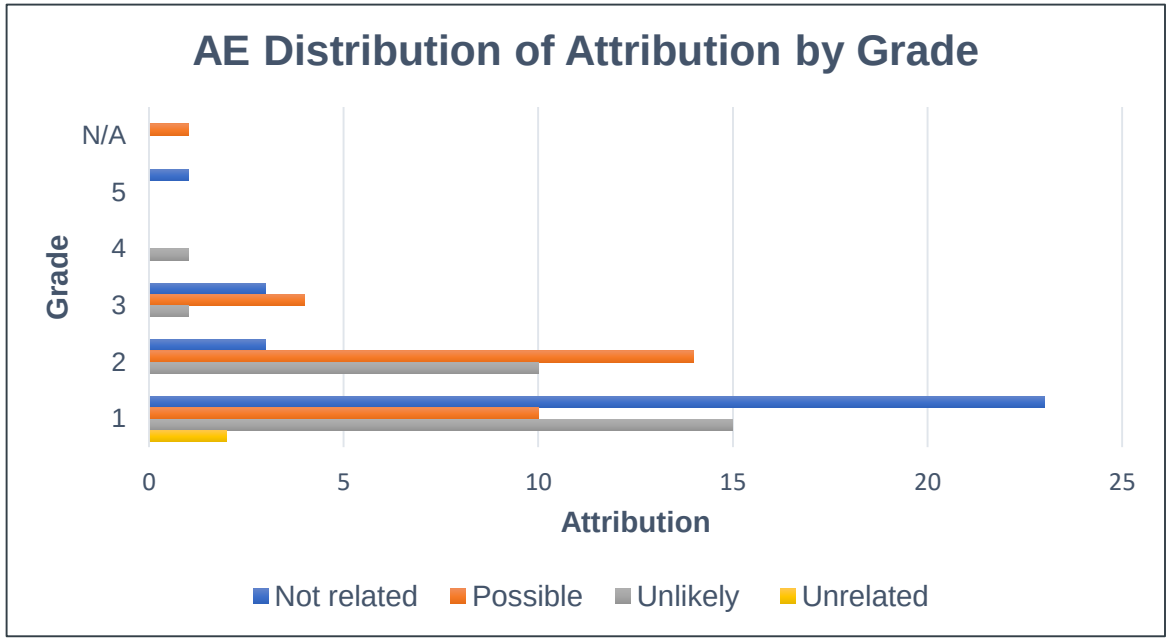


Dose point kernel of ^{186}Re radionuclide

RESPECT-LM PHASE 1, PART A: SAFETY SUMMARY

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

- 10 patients were treated over 3 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



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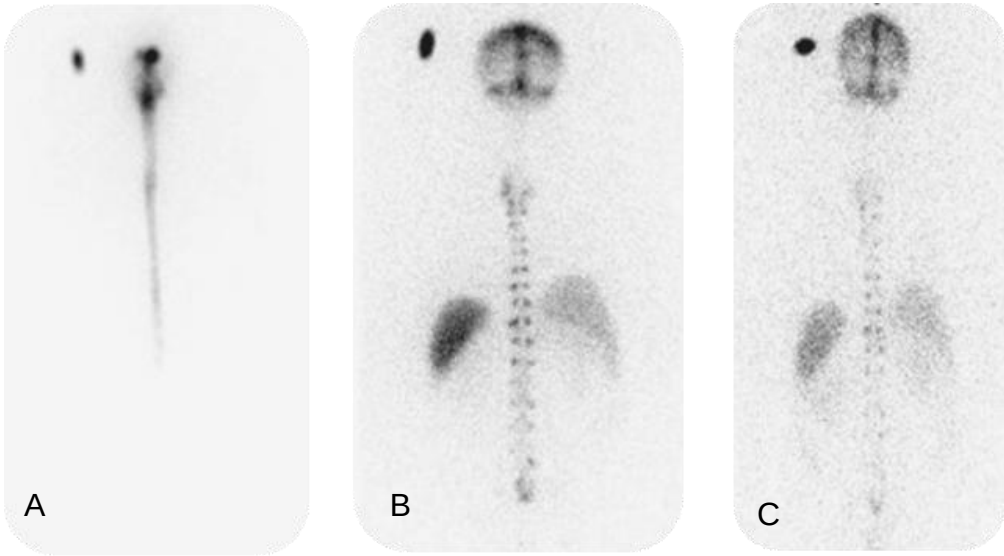
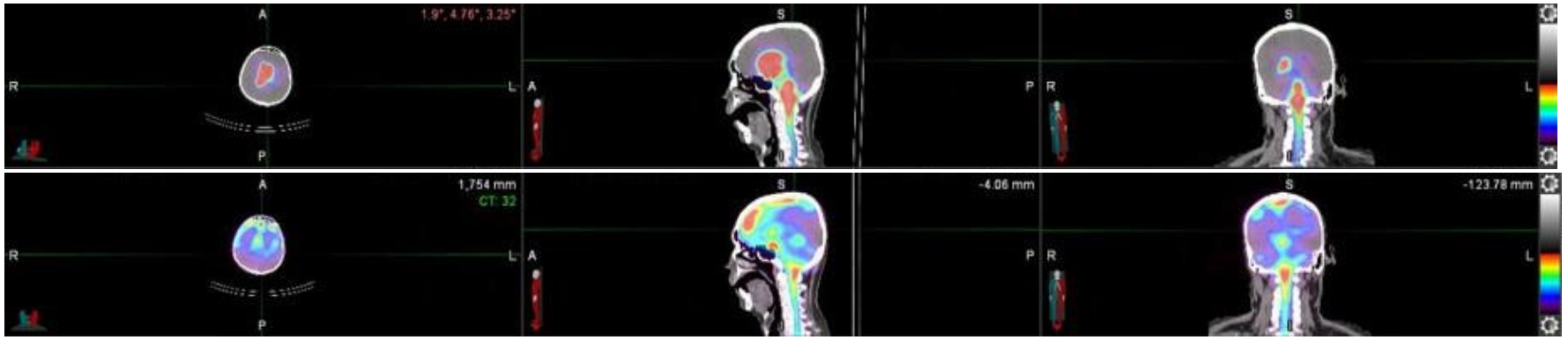
RESPECT-LM PHASE 1, PART A: IMAGING SUMMARY

^{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

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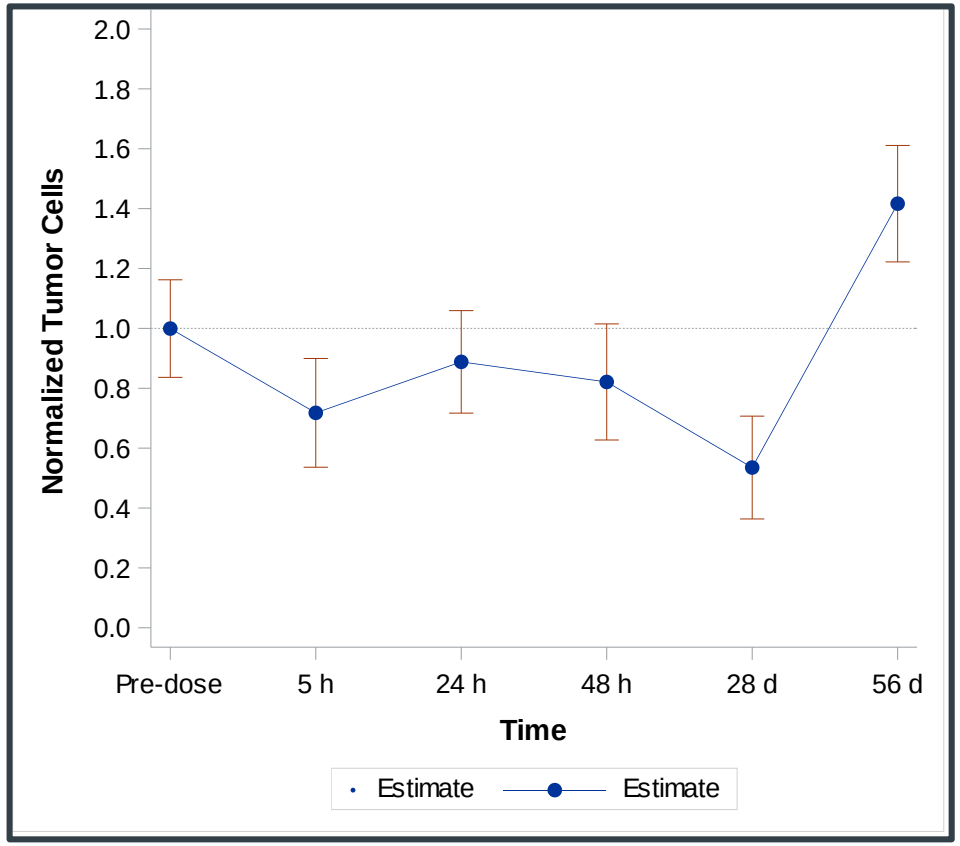
RESPECT-LM PHASE 1, PART A: TUMOR CELL ENUMERATION SUMMARY

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)

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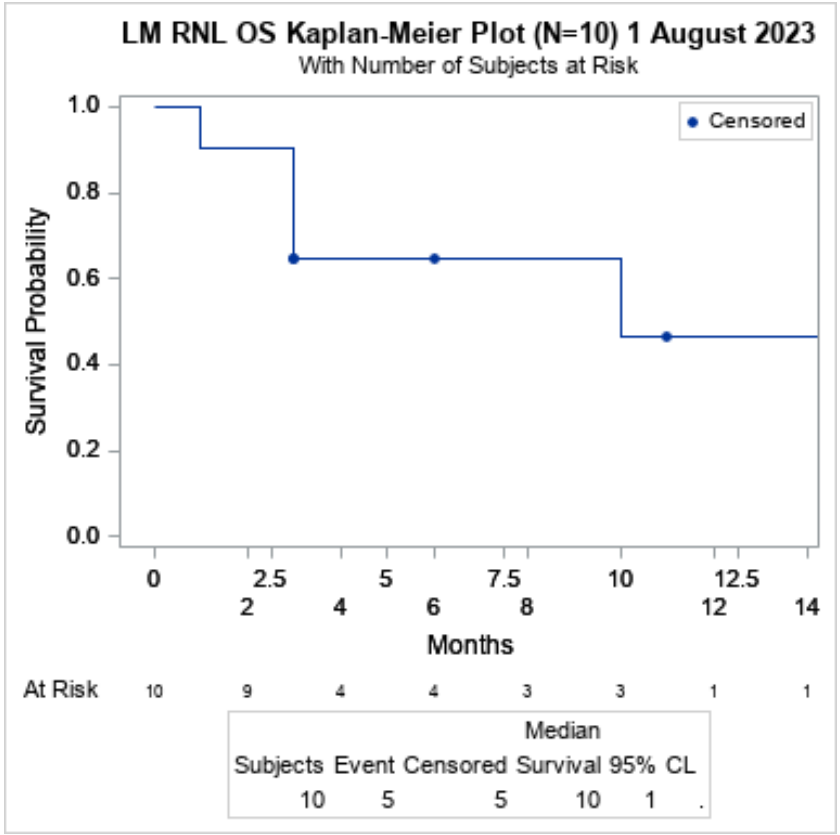
RESPECT-LM PHASE 1, PART A: OVERALL SURVIVAL

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, Part A is complete and Cohort 4 of Phase 1, Part B now enrolling

+ 10 of 13 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
+ Multi-dose and retreatment protocols in process

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

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KOL Roundtable on Leptomeningeal Metastases: An Obvious Disease Target for Radiotherapeutic Intervention

Moderator: **Justin Walsh, Ph.D.**, Vice President, Jones Research

Participants: **Priya Kumthekar, M.D.**, Associate Professor of Neurology and Medicine at Northwestern University's Feinberg School of Medicine

Andrew J. Brenner, M.D., Ph.D., Professor of Medicine, Neurology, and Neurosurgery at The University of Texas, Health Services Center at San Antonio

Marc Hedrick, M.D., President and Chief Executive Officer, Plus Therapeutics

Norman LaFrance, M.D., Chief Medical Officer, Plus Therapeutics

August 11, 2023