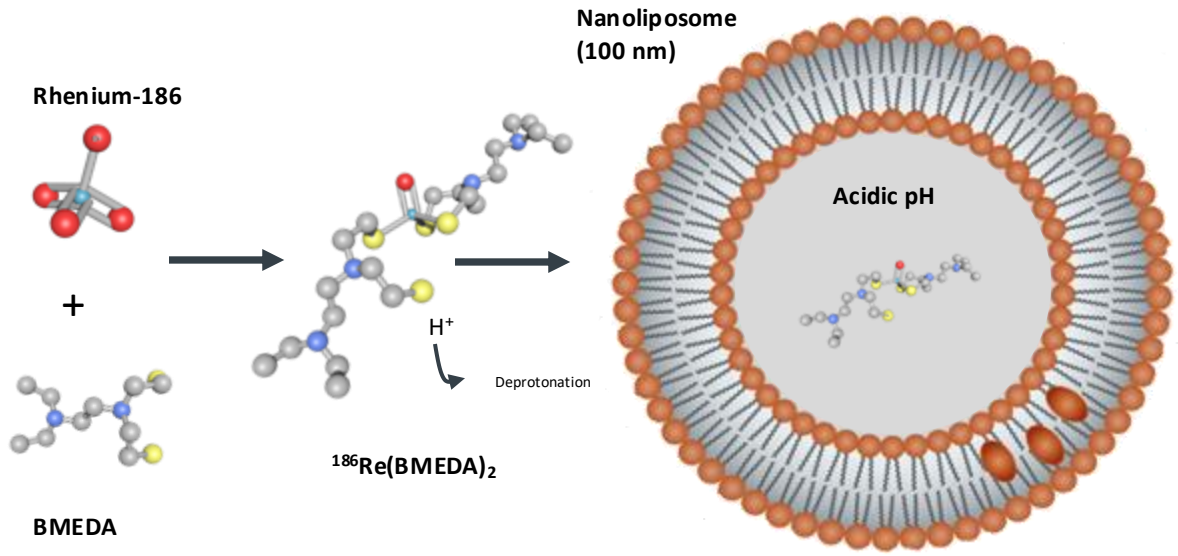
Phase 1 Dose Escalation of Rhenium (^{186}Re) Obisbemeda (Rhenium Nanoliposome, ^{186}RNL) for the Treatment of Leptomeningeal Metastases (LM)

Andrew Brenner, MD, PhD
SNO/ASCO 2024

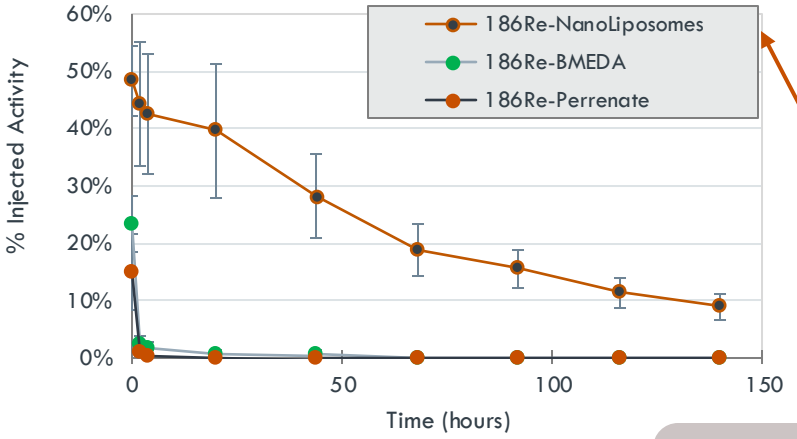
Michael Youssef, UT Southwestern
Ande Bao, Case Western Reserve University
Joel Michalek, UT Health San Antonio
William Phillips, UTHSCSA
Toral Patel, UTSW
Priya Kumthekar, Northwestern
John Floyd, UTHSCSA
Melissa Moore, Plus Therapeutics

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

Direct targeted Rhenium NanoLiposomes (^{186}RNL) for CNS malignancies

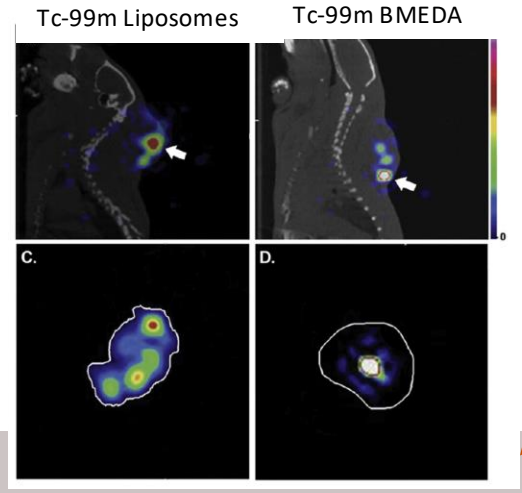


Improved Tumor Retention



Nanoliposomes improve retention and distribution of ^{186}RNL

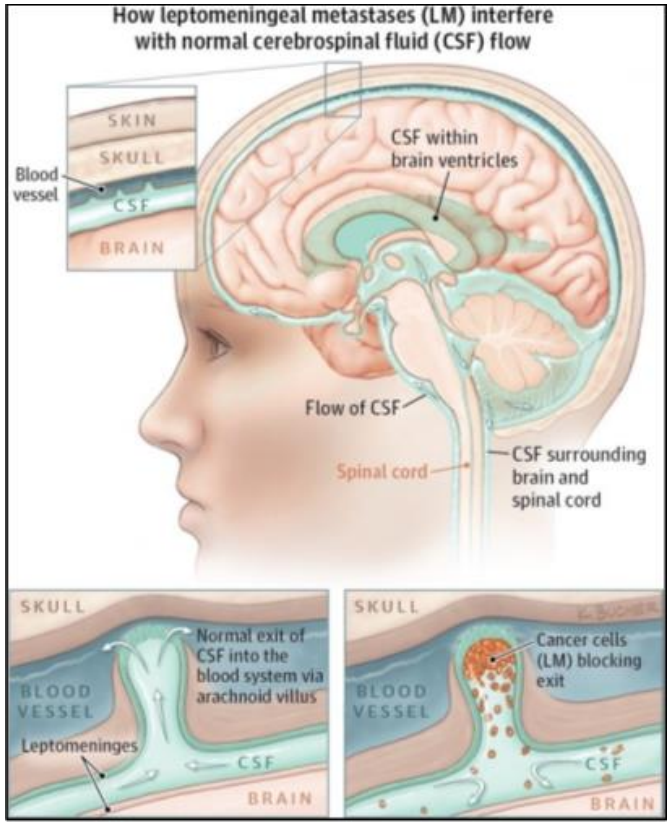
Improved Drug Distribution



1. **Rhenium-186:** Emits tumor-destroying radiation over short distances while sparing healthy tissue
2. **BMEDA:** Small molecule that chelates to rhenium and is loaded into the nanoliposome where it's irreversibly trapped
3. **Nanoliposome:** Carries the trapped BMEDA-chelated ^{186}Re to tumor

Rationale of ^{186}RNL for the treatment of leptomeningeal metastases (LM)

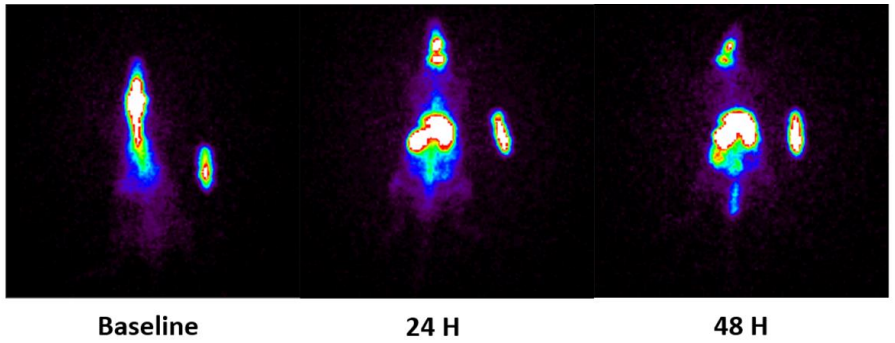
- Rhenium-186 is an ideal radionuclide for CNS indications because of its long half-life (~90 hours), short path length of the beta particles (~2mm), low dose rate, and high radiation density
- Liposomal encapsulation has been shown to prolong retention in the brain and CSF (e.g., DepoCyt®)
- ^{186}RNL 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.

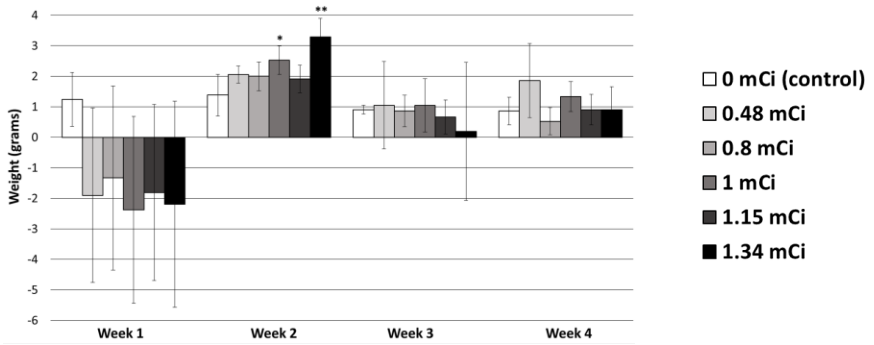


JAMA Oncol. 2016;2(6):839.oi:10.1001/jamaoncol.2015.3502

Preclinical studies demonstrate efficacy and safety

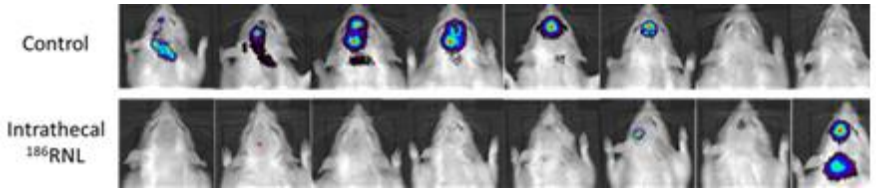
Preclinical evaluation of ^{186}RNL by intraventricular injection in non-tumor bearing rats with up to 1.34 mCi with corresponding absorbed doses of 1,075Gy was without significant toxicity



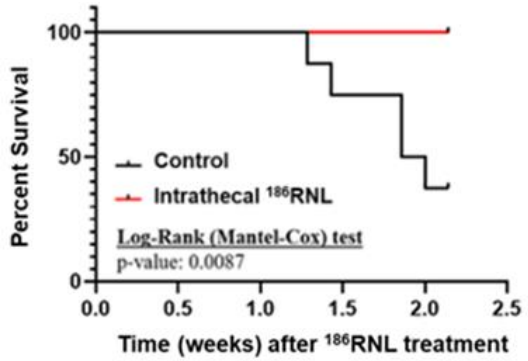


In 2 LM models (Wistar/C6 and NSG/MDA-MB-231) treatment with ^{186}RNL resulted in prolonged survival

A.



B.



A. Bioluminescence of LM MDA-MB-231 in nude rats treated with blank or ^{186}RNL
B. Survival curve for animals with intrathecal C6 treated with blank (blue) or ^{186}RNL (red)

ReSPECT-LM Phase 1, single dose trial design

- Dose escalation: 3+3 modified Fibonacci with back filling of cohorts to 6 to determine therapeutic range

- Primary objective
  - Maximum Tolerated Dose (MTD) / Maximum Feasible Dose (MFD)

- Secondary objectives
  - Overall Response Rate (ORR)
  - Duration of Response (DoR)
  - Progression Free Survival (PFS)
  - Overall survival (OS)

- Exploratory objectives: Analysis on cerebral spinal fluid (CSF) pre- and post-administration
  - CSF tumor cell enumeration
  - Pharmacodynamic (PD) markers
  - QoL assessments

- Funding: $17.6M grant from CPRIT

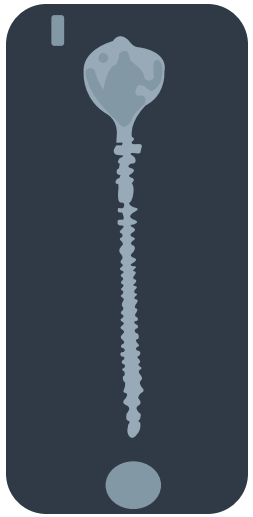
Single Administration Phase 1 Dose Escalation Plan

Cohort	Administered Volume (mL)	Administered Activity (mCi)	Administered Concentration (mCi/mL)
1	5	6.6	1.32
2	5	13.2	2.64
3	5	26.4	5.28
4	5	44.10	8.82
5	5	66.14	13.23
6	5	87.97	17.59
7	5	109.96	21.99

Cohort 5 currently enrolling

Treatment workflow

Treatment Planning	Drug Infusion	Patient Monitoring
Prior to Treatment	**Day 1**	**Day 2-3**
CSF flow study to confirm no flow obstruction	Single 5-minute injection in outpatient setting	Imaging and PK/PD assessments



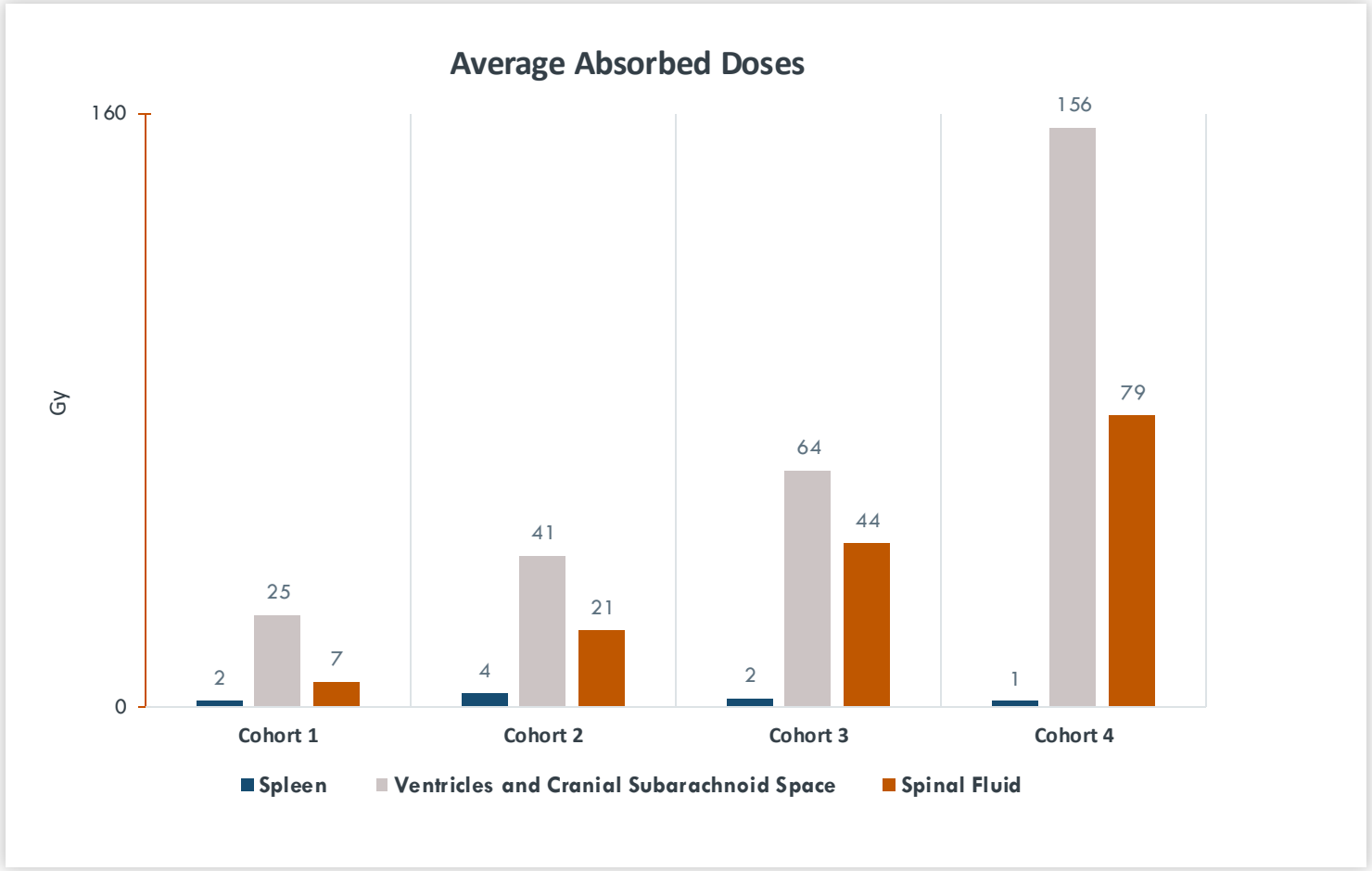
Results: Demographics

- 25 Total dosed to date
- 68% female / 32% male
- Median Age 55 (29-70)
- KPS: Median 90 (60-100)

KPS 90-100	52%
KPS 80	24%
KPS 70	12%
KPS 60	12%

Histology	N
Breast	12
Lung	6
Pineal parenchymal tumor	1
Primary Effusion Lymphoma	1
Oropharyngeal Squamous cell carcinoma neck	1
Moderately differentiated adenocarcinoma esophageal	1
Melanoma	1
Renal cell carcinoma	1

Pharmacokinetics: Linear Correlation between Administered and Absorbed Dose



Safety: Adverse Events by Cohort

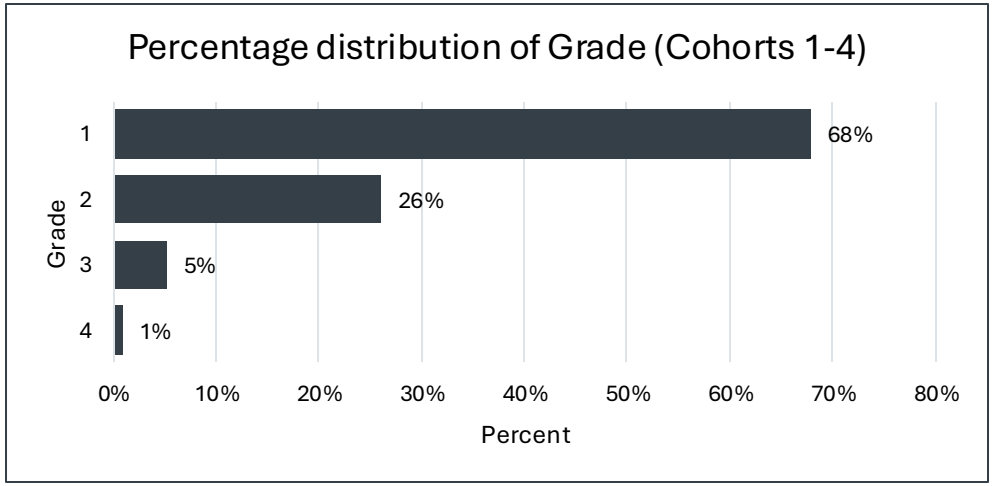
All Adverse Events Grades 1 – 4 by Cohort

Adverse Event	*Cohort 1*	*Cohort 2*	*Cohort 3*	*Cohort 4*
Anorexia	1	0	1	2
Constipation	1	0	1	0
Dizziness	0	0	1	2
Dysphasia	1	0	0	1
Epistaxis	1	0	0	1
Fatigue	1	0	0	2
Headache	2	0	2	3
Hyperglycemia	0	0	1	4
Hypertension	0	0	3	0
Hypertriglyceridemia	0	0	0	7
Hypoalbuminemia	1	0	1	2
Lymphocyte count Decreased	0	0	1	2
Nausea	1	0	1	1
Pain in extremity	0	0	1	1
Paresthesia	0	0	1	1
Scalp pain	0	0	1	1
Urinary tract infection	0	0	1	1
Vomiting	1	0	1	2
Weight loss	1	0	0	1

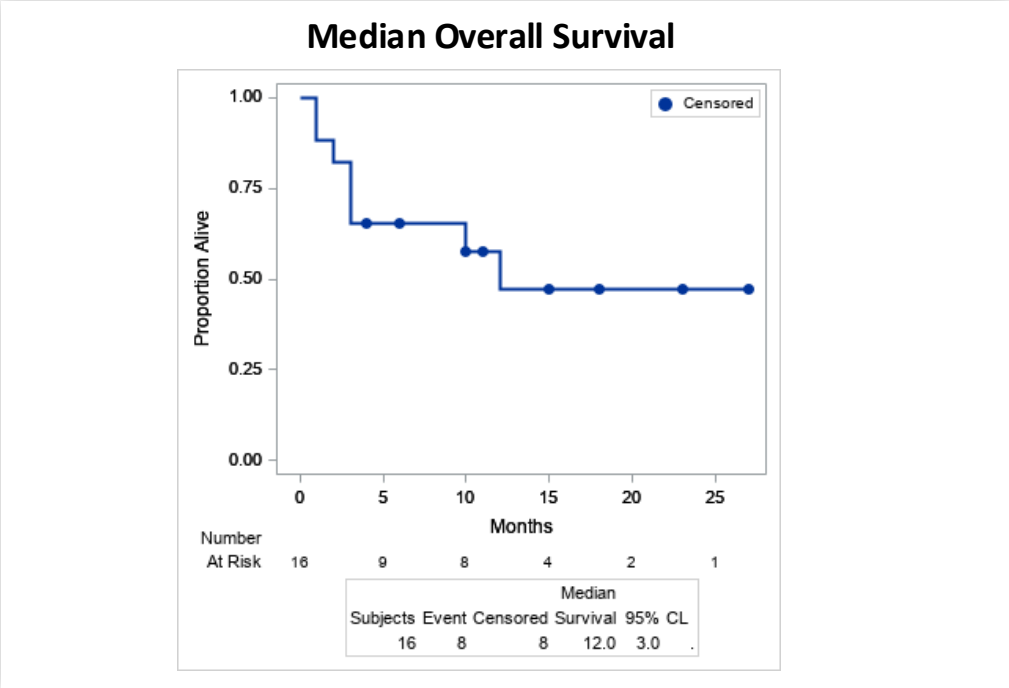
Relatedness	*Cohort 1*	*Cohort 2*	*Cohort 3*	*Cohort 4*
Definite	0	0	0	1
Possible	5	3	16	20
Unlikely	17	1	12	24
Unrelated	0	0	16	18

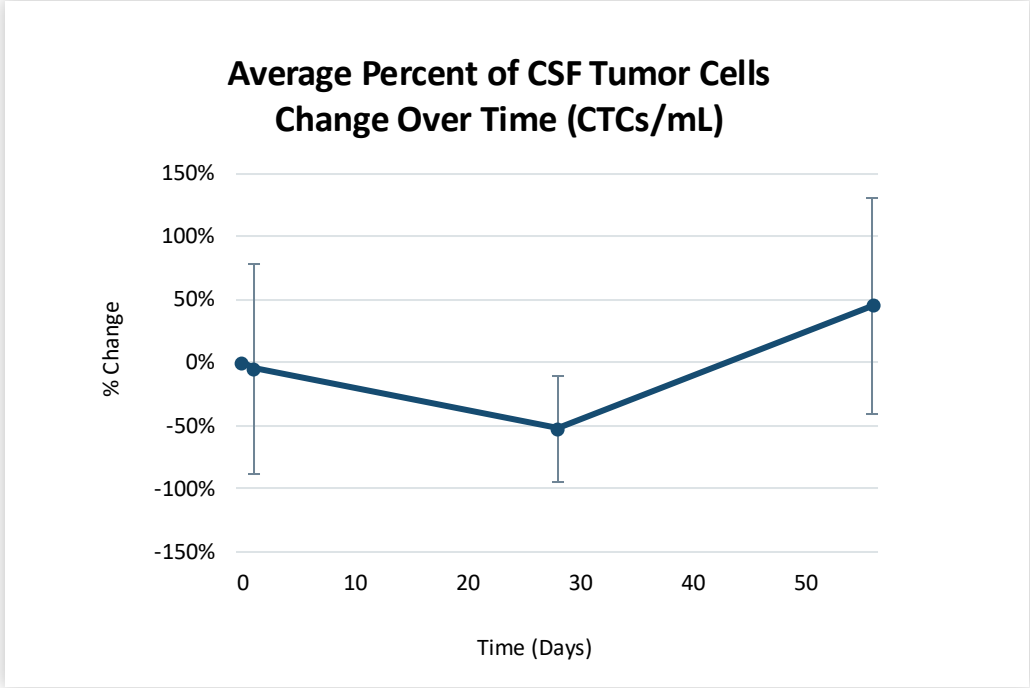
Grades 3 – 4 Adverse Events by Cohort

Adverse Event	*Grade*	*Cohort 1*	*Cohort 2*	*Cohort 3*	*Cohort 4*
Encephalopathy	3	0	1	0	0
Hypertension	3	0	0	1	0
Lymphocyte count Decreased	3	0	0	1	0
Pneumonia	3	1	0	0	0
Polyuria	3	0	0	1	0
Stridor	4	1	0	0	0
Urinary tract infection	3	0	0	1	0



Efficacy: Median overall survival and CSF tumor cell changes





- N = 16 patients, Cohorts 1-4
- mOS of 12 months, compared to 2-4 months SOC
- 8 patients remain alive*

- Max percent reduction in CSF tumor cells at D28 was 90%
- Average of 53% CSF tumor cell reduction at D28
- N = 13 patients, Cohorts 1-3
- Testing was discontinued after Cohort 3 and started again after Cohort 4

*As of 01 Jul2024

Case study: Patient 02-101

- Cohort 1 patient, 6.6 mCi administered dose
- 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
- Patient lived 94 days post-treatment

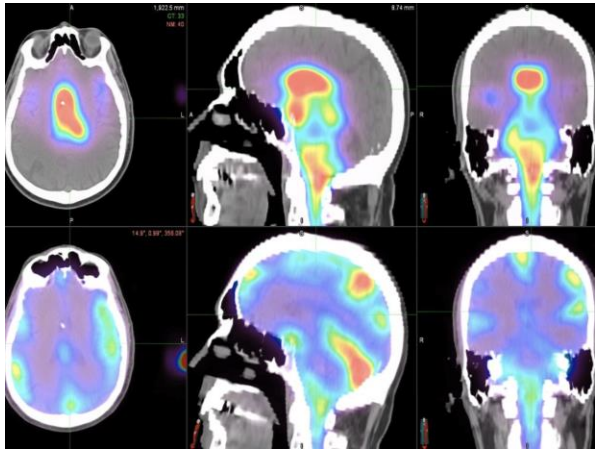
Radiation Absorbed Dose

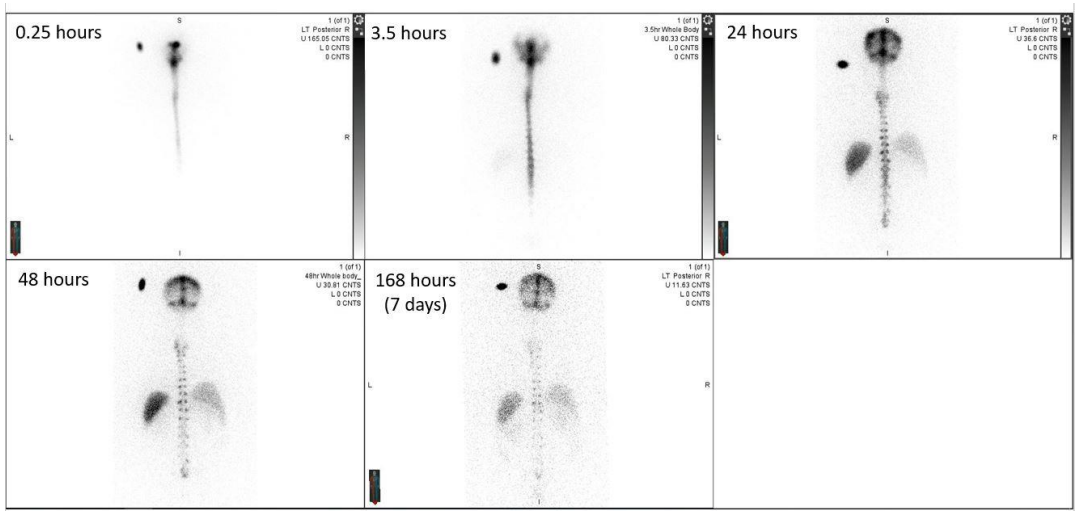
Region	Radiation Absorbed Dose (Gy)
Ventricles and cranial subarachnoid space	29.04
Ventricles (lateral, 3rd, and 4th)	14.52
Cranial subarachnoid space	37.27
Spinal Fluid	8.97

Assessment: Tumor Cells/mL

Pre	5-h	24-h	48-h	14-d	28-d	43-d	56-d
70.77	8.33	39.79	6.12	6.45	7.05	17.11	182.63

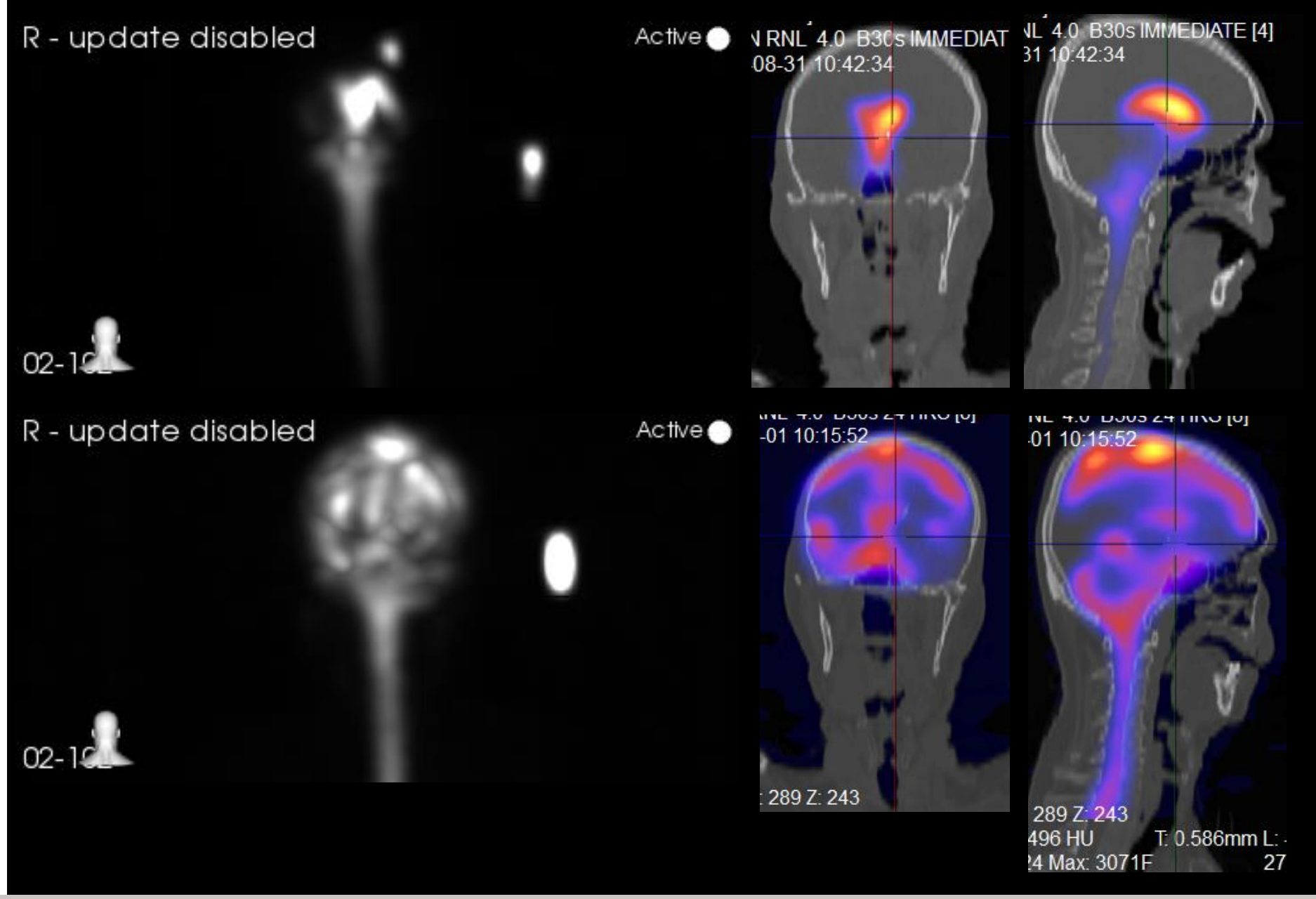
Imaging Post Treatment





Case study: Patient 02-101

SPECT IMAGING



Conclusions and Future Plans

- No DLT through administered dose of 44mCi
- Achieved average absorbed doses of 176 Gy to the cranial leptomeninges and 76Gy to the leptomeninges
- Preliminary evidence of efficacy seen early with decreased CSF cell counts and patient survival
- Currently in Cohort 5 at 66mCi (50% increase over cohort 4) with 5 evaluable patients and 1 patient remaining

- Single dose phase 2 for Breast Ca and NSCLC to begin after confirming RP2D
- Phase 1 multidose study to be opened early 2025 with 3 consecutive doses
- Exploring ICI combination cohort (preclinical)

GBM

- Currently in Phase 2

Ovarian

- Preclinical work underway

Pleural

- Mesothelioma
- Metastatic disease

Thank you

Patients and Caregivers

Principal Investigators

Plus Therapeutics

Funding by CPRIT, NIH/NCI, Plus Therapeutics

ReSPECT-LM Investigators and Collaborators, Study Team, and Brenner Lab

Michael Youssef, MD
William Phillips, MD
Joel E Michalek, PhD, FASA
Ande Bao, PhD
John Floyd MD
Priya Kumthekar, MD
Beth Goins, PhD
Henriette Balinda, PhD
Eva Galvan, MD
Mays IDD Team

UT Health San Antonio | Mays Cancer Center

UT Southwestern Medical Center

Northwestern Memorial Hospital

Contact | Andrew Brenner, MD, PhD | brennera@uthscsa.edu