PLUS THERAPEUTICS

WELCOME

SCAN TO RECORD ATTENDANCE

*not needed if you pre-registered

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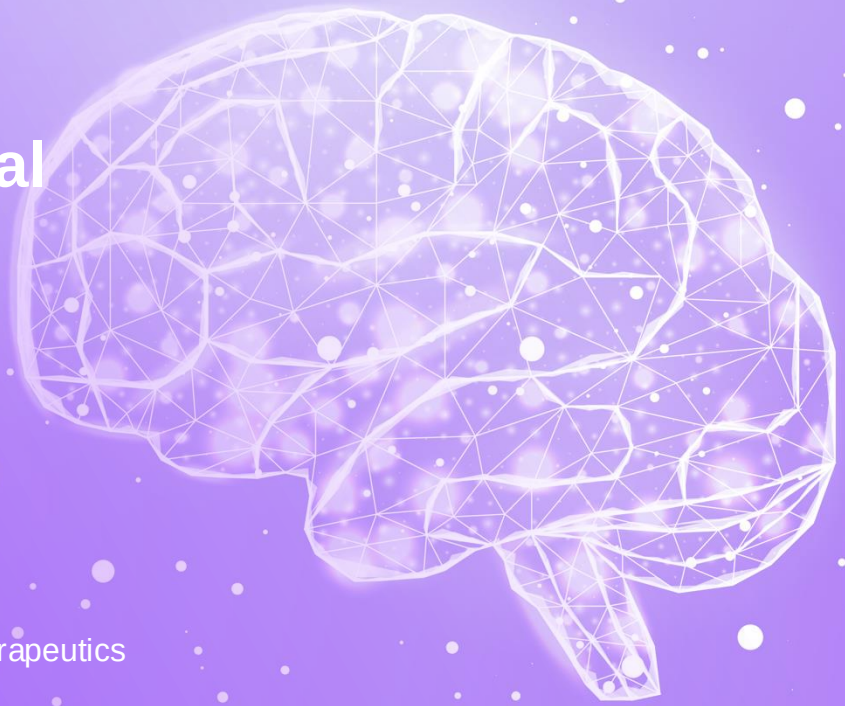
Radiation-based Therapeutic Approaches to Leptomeningeal Metastasis



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Department of Radiation Oncology
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Perlmutter Cancer Center

Disclosures

Employer: NYU School of Medicine

Research funding: AstraZeneca, Kazia Therapeutics, Natera, Debiopharm, Cantex Therapeutics, Biocept

Consulting/Advisory Board: AstraZeneca, Debiopharm, Galera Therapeutics, Nanocan Therapeutics, Plus Therapeutics

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Radiation Therapy for the Management of Leptomeningeal Metastasis (LM)

- **Long served as a pillar in the management of LM**

- **For patients with select primary CNS malignancies, craniospinal irradiation is considered the standard-of-care for patients with known or at risk of leptomeningeal dissemination with goal of disease control and cure.**
  - Medulloblastoma
  - Intracranial and spinal ependymoma
  - CNS germ cell tumors

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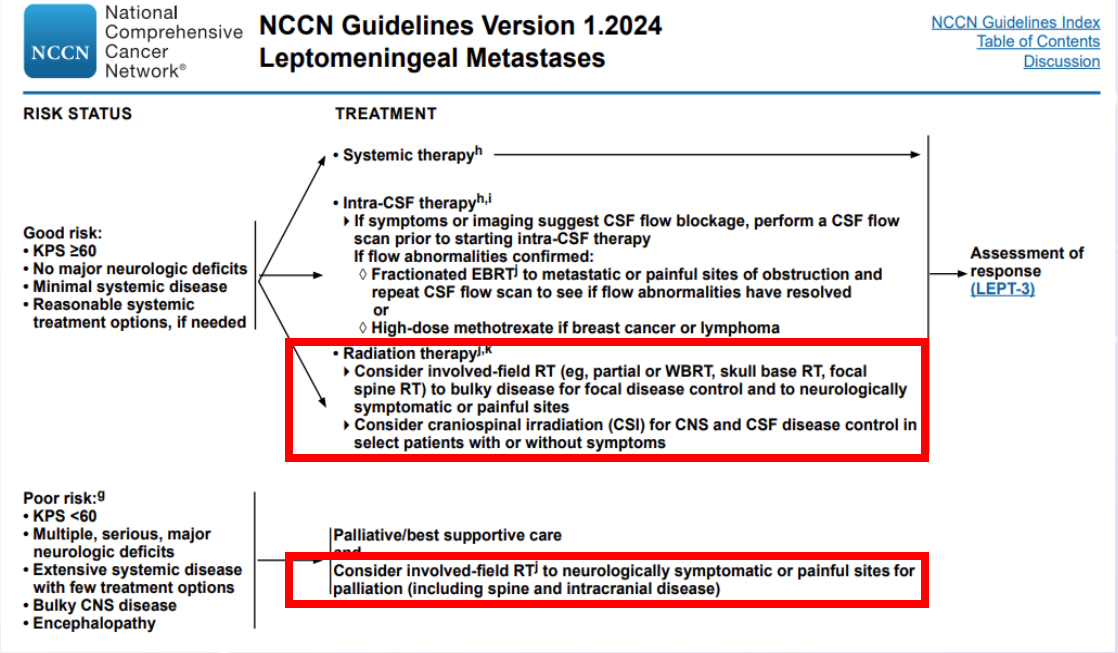
Radiation Therapy for the Management of LM

- **Long served as a pillar in the management of LM**
- **For patients with leptomeningeal dissemination from solid tumors, palliative radiation therapy has an essential role for symptom management and disease control.**



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IFRT

- **Most prescribed form of RT for the management of solid tumor LM**
- **Used in both good and poor risk patients with LM**
- **Treatment sites guided by radiographic and/or clinical findings**
- **Does not seem to improve overall survival**

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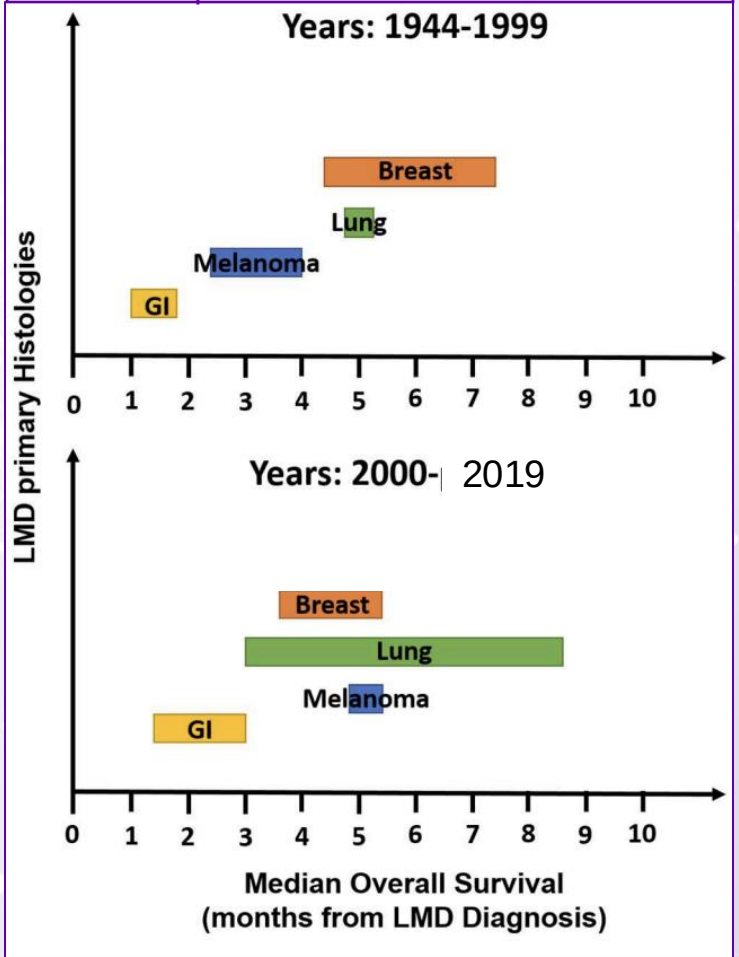
Studies involving IFRT for LM

Adapted from Buszek et al. 2019

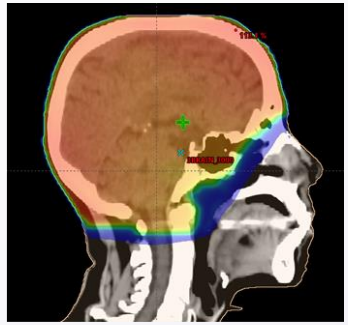


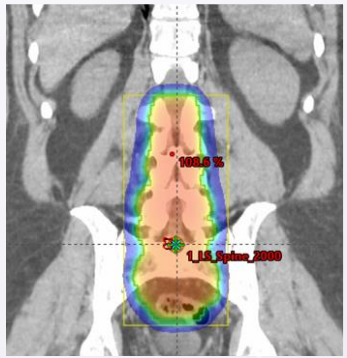
Goal-Directed Radiation Therapy for the Management LM

Symptom and local disease management → CNS and CSF disease control

Involved-field radiotherapy (IFRT):

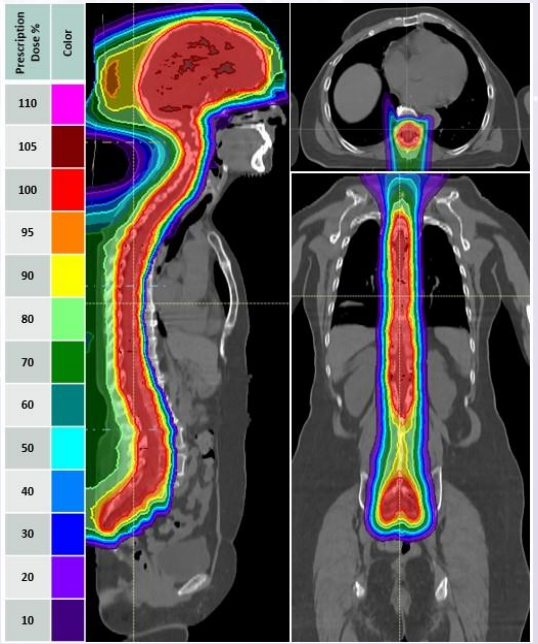
- Does not stop LM progression along the CNS axis and does not seem to improve survival
- Safe and effective in partially treating the CNS compartment





Craniospinal irradiation (CSI):

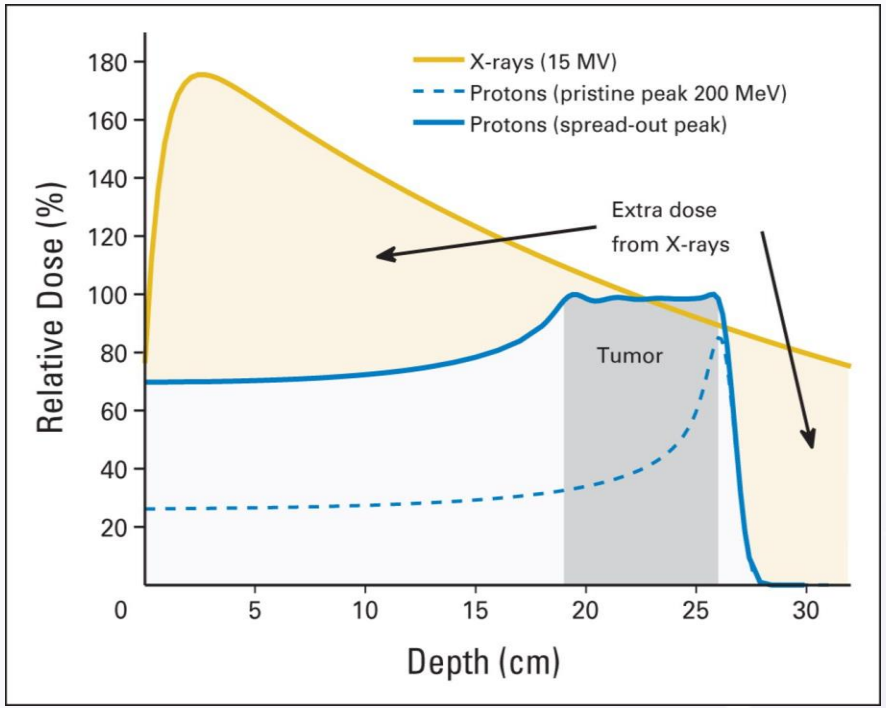
- Can potentially stop LM progression along the CNS axis and can potentially improve survival
- How do we safely treat the entire compartment in patients who tend to be heavily pretreated and needing to get back on systemic therapy quicky?

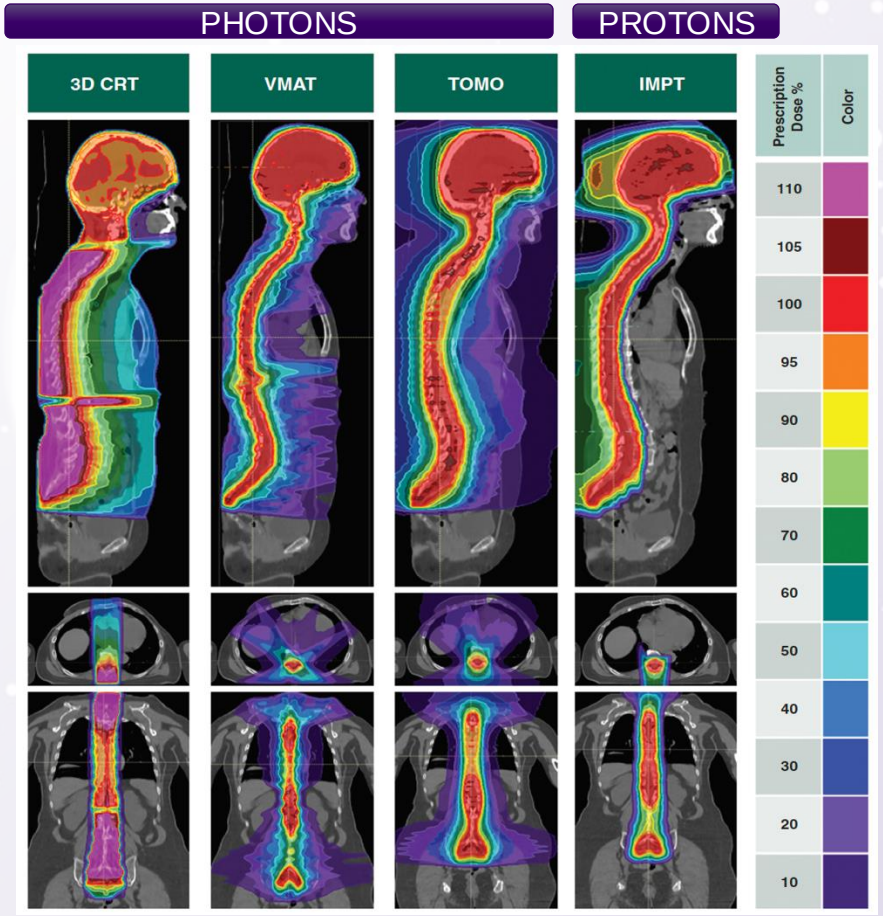


Lessons Learned from Traditional CSI Delivery Techniques

Study	Diagnosis	Patient number	Outcomes
Brown et al. 2014	Adult medulloblastoma	• 21 with 3DCRT photon CSI • 19 with proton CSI	**Proton vs. Photon CSI:** • >5% weight loss 16% vs. 64% • Grade 2+ nausea and vomiting 26% vs. 71% • Grade 3+ esophagitis 5% vs. 57%
Breen et al. 2024	Adult medulloblastoma	• 20 with photon CSI (9 with 3DCRT, 11 with IMRT) • 19 with proton CSI	**Proton vs. Photon CSI:** • acute dysphagia of any grade: 5% vs. 35% • weight loss during radiation: +1.0 vs. -2.8 kg
Harada et al. 2014	Solid tumors	17 with **photon CSI**	• 41%, 35% and 6% Grade 3-4 leukopenia, thrombocytopenia and anemia, respectively • 24% Grade 3-4 nausea and anorexia
El Shafie et al. 2019	Solid tumors	25 with tomortherapy **photon CSI**	32% with Grade 3 myelosuppression
Devecka et al 2020	Solid tumors	19 with **photon CSI** (3 with 3DCRT, 16 with tomotherapy)	9 patients did not complete RT, with 5 patients due to Grade 3-4 cytopenia

Differences Between Photon and Protons





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Mitin and Zietman. JCO 2014
Kotecha, La Rosa and Mehta Neuro Oncology 2024

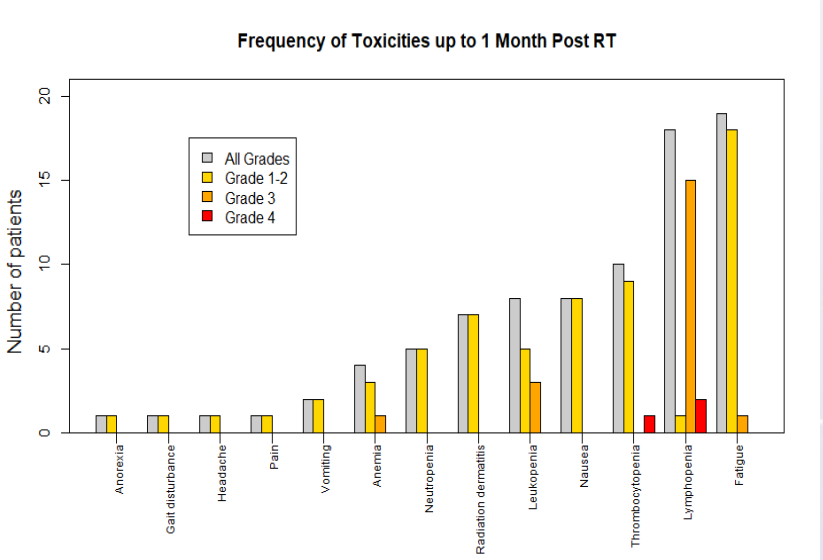
Proton CSI Phase I Trial

- **Between June 2018- April 2019, 21 patients enrolled**
- Median age 52 (30-67)
- Median KPS 70 (60-90)
- Most common histologies NSCLC (52%) and breast (33%)

- **1 patient was censored at 24 months**

- **Median OS= 9 months (95% CI: 6-22 months)**

- **Median CNS PFS= 7 months (95% CI: 5-13 months)**



Symptoms	Grade 3	Grade 4
Anemia	1 (5%)	0 (0%)
Leukopenia	3 (15%)	0 (0%)
Thrombocytopenia	0 (0%)	**1 (5%)**
Lymphopenia	15 (75%)	**2 (10%)**
Fatigue	**1 (5%)**	0 (0%)

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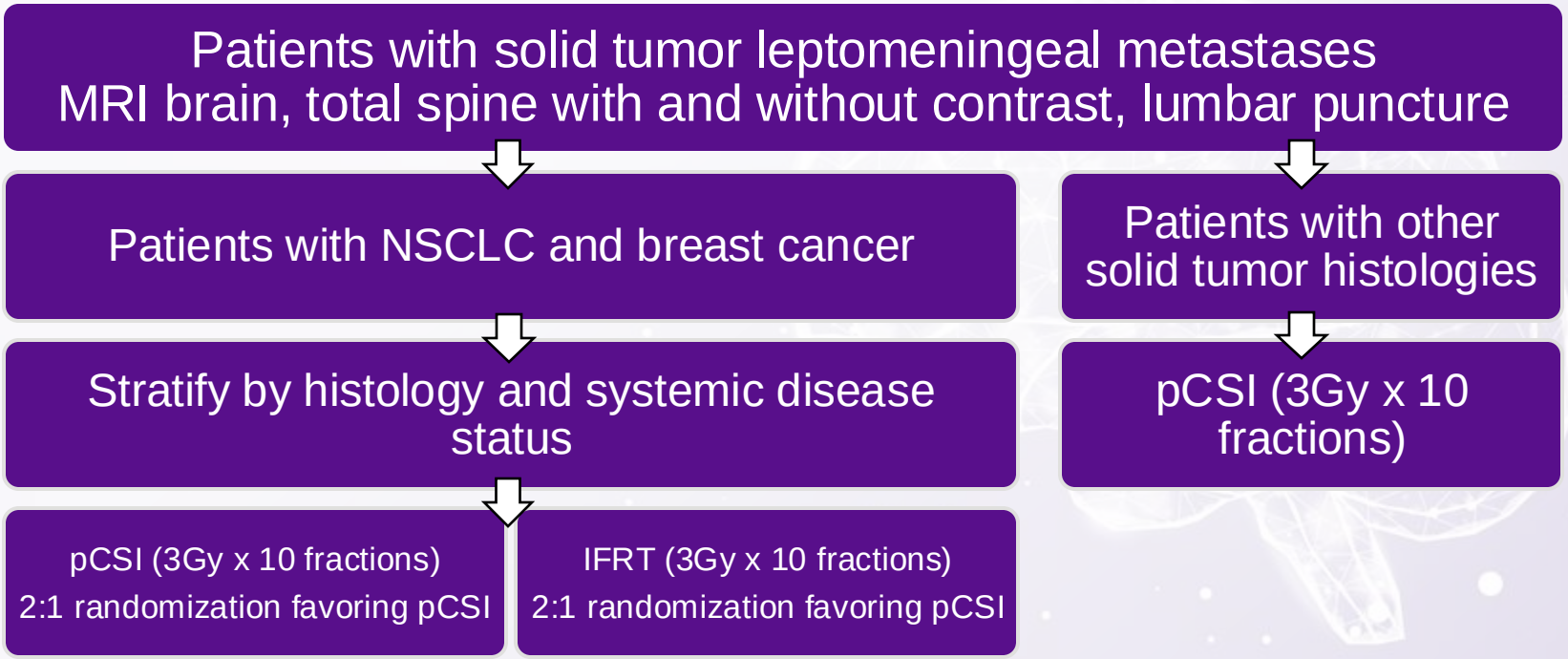
Yang et al., Neuro Oncology 2021

Randomized Phase II Trial of proton CSI vs. IFRT



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Yang et al., JCO 2022

Phase II Trial- Randomized Groups

Characteristic	pCSI (N=42)	Photon IFRT (N=21)
Age (median, range)	56 (49-55)	61 (54-65)
Sex		
Female	34 (81%)	18 (86%)
Male	8 (19%)	3 (14%)
Primary Disease		
NSCLC	24 (57%)	12 (57%)
EGFR+	12 (29%)	7 (33%)
Breast	18 (43%)	9 (43%)
HER2+	6 (14%)	4 (19%)
Systemic Disease Status		
Active	22 (52%)	11 (52%)
Stable/None	20 (48%)	10 (48%)

Characteristic	pCSI (N=42)	Photon IFRT (N=21)
KPS (median, range)	80 (60-90)	80 (60-90)
Newly diagnosed LMD	35 (83%)	18 (86%)
At Enrollment		
Positive MRI	38 (91%)	21 (100%)
Positive Cytology	28 (67%)	11 (52%)
Positive CSF CTC	36 (86%)	17 (81%)
Brain Metastases		
Yes	28 (67%)	15 (71%)
No	14 (33%)	6 (29%)
Median Lines of Prior Systemic Therapy	2 (0-8)	2 (0-8)
IFRT Fields		
WBRT		9 (43%)
Spinal RT		1 (5%)
Both		8 (38%)

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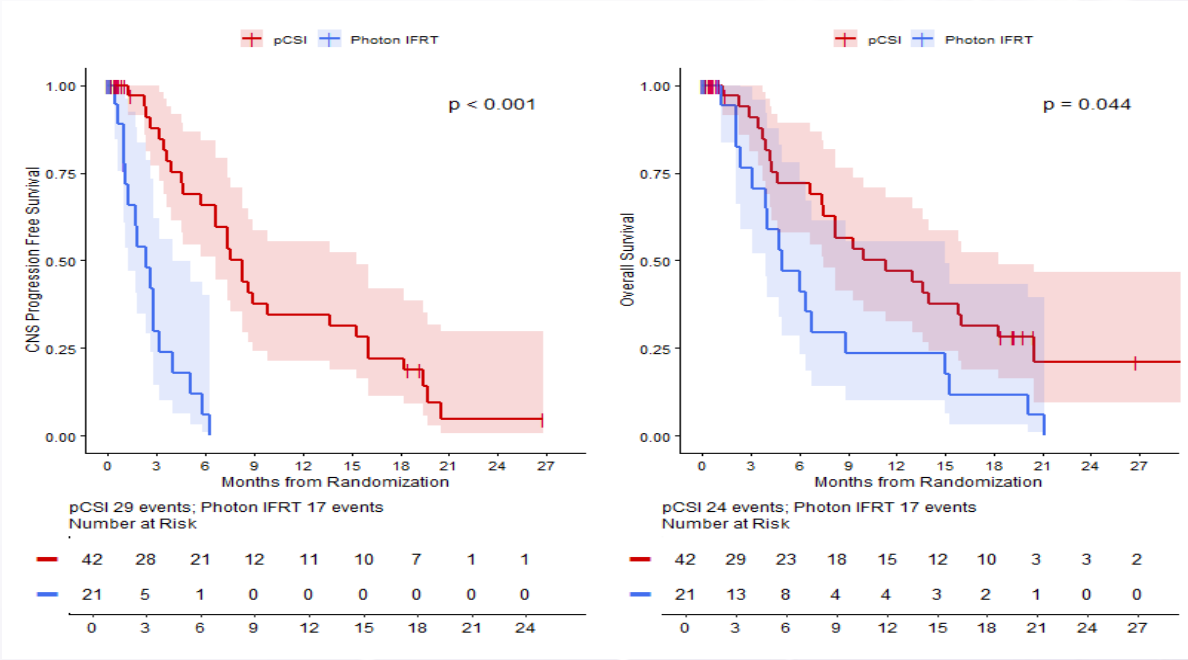
Yang et al., JCO 2022

Final Analysis Survival Outcomes



Median CNS PFS: 8.2 vs. 2.3 months

Median OS: 11 vs. 4.9 months

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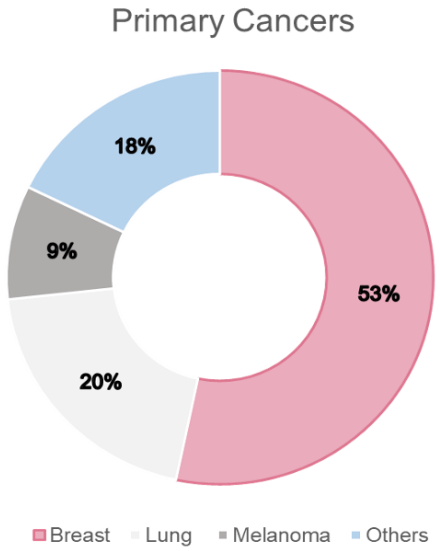
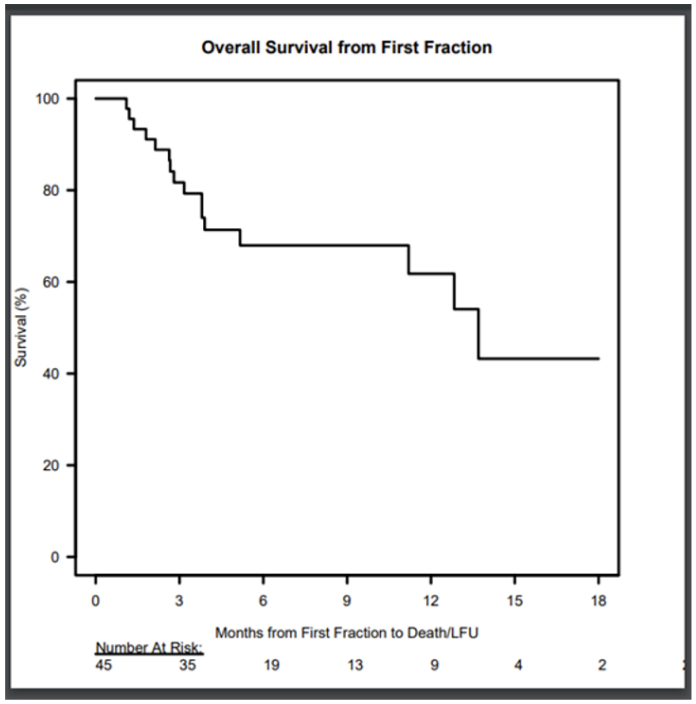
Yang et al., ASTRO 2024

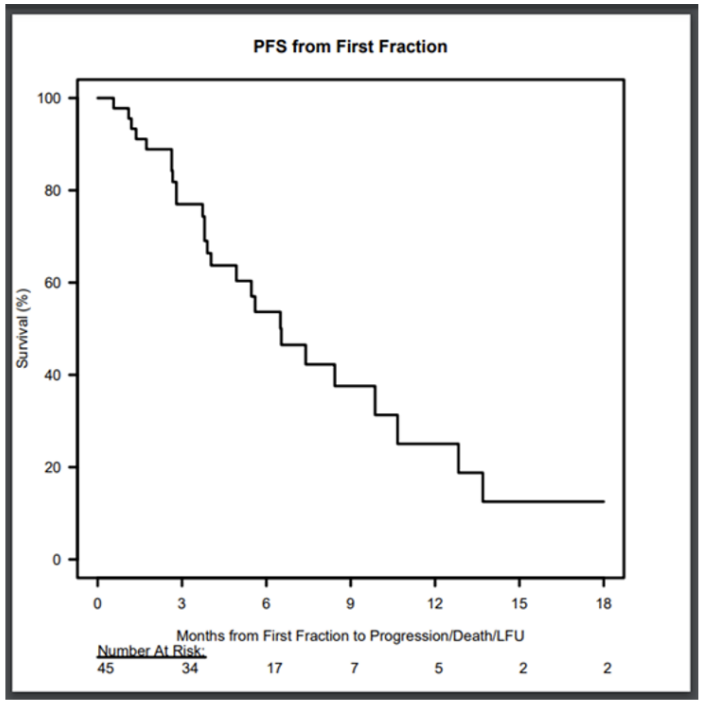
Results: Baseline Patient Characteristics

- 45 patients completed pCSI
- Median age 54 years (range, 23-79)
- 73% female
- 53% lived >100 miles away
- mKPS prior to pCSI was 80 (range, 50-90)



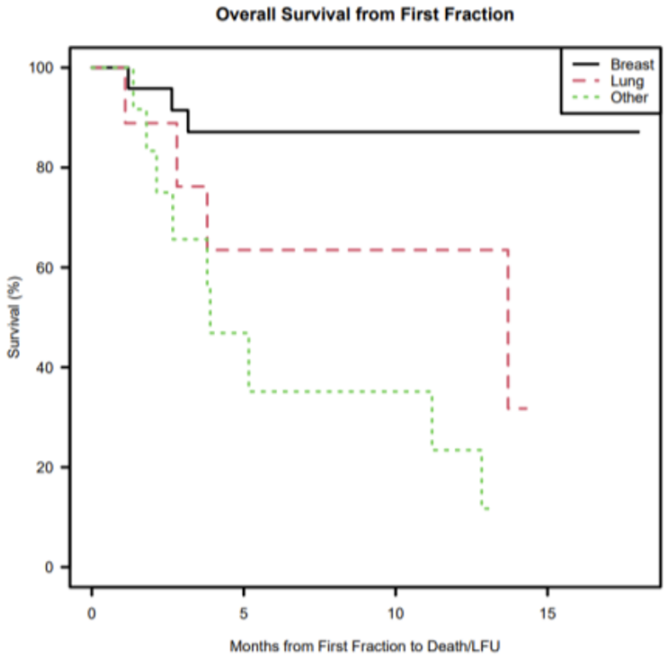


mOS: 13.7 months (95% CI, 11.2 to not reached)



mPFS: 6.5 months (95% CI, 4.9 to 12.8)

Results: Survival by Primary Cancer



- mOS for breast cancer: Not reached
- mOS for lung cancer: 13.7 months (95% CI, 3.8 to not reached)
- For all others, mOS 3.9 months (95% CI, 2.7 to not reached)

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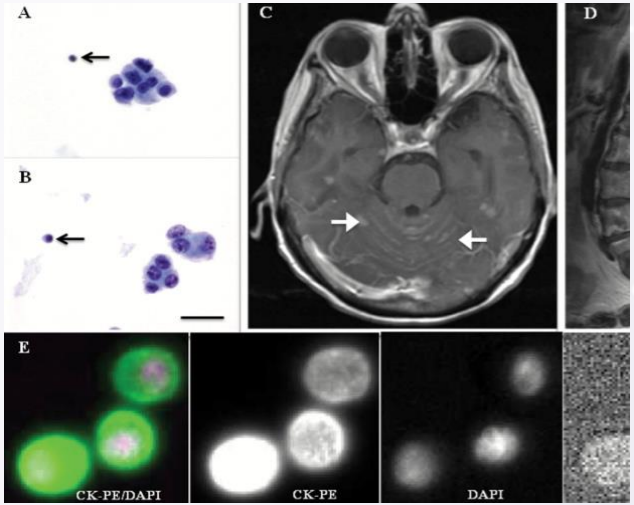
Lam et al. SNO 2024

CSF Circulating Tumor Cells

- Circulating tumor cells (CTCs) in the CSF is a potential diagnostic and treatment response assessment tool.
- In a prospective clinical trial evaluating intrathecal Trastuzumab for HER2+ epithelial cancer LM, dynamic changes in CSF CTCs were observed with increased CSF CTCs preceded MR changes with disease progression

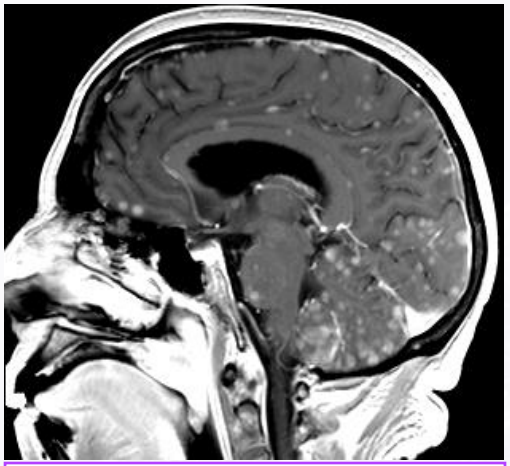


- Consecutive case series of 58 solid tumor LM patients who were treated with proton CSI between January 2018 and December 2020.
- **No increases in CSF CTCs immediately after proton CSI**
- Most favorable group: **low baseline CSF CTCs (**baseline CSF CTC <53 cells/3mL, CellSearch), **median CNS PFS=12 months, OS= 17 months**
- Favorable group: **high baseline CSF CTCs, large CSF CTCs decrease after proton CSI** (baseline CSF CTC ≥53 cells/3mL and decrease ≥37 cells/3mL after proton CSI), **median CNS PFS=7 months, OS=11 months**)
- Unfavorable group: **high baseline CSF CTCs, small CSF CTCs decrease after proton CSI** (baseline CSF CTC ≥53 cells/3mL and decrease<37 cells/3mL after proton CSI), **median CNS PFS=4 months, OS=5 months**

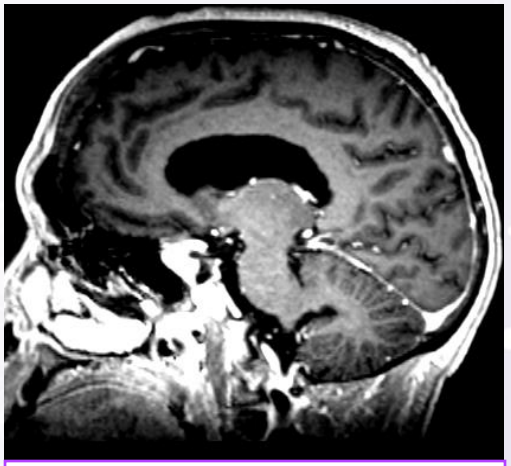
Lin et al. Neuro Oncol. 2017.
Diaz et al. Neuro-oncology Advances 2020
Wijetunga et al. Neuro-oncology Advances 2021

CSF CTCs

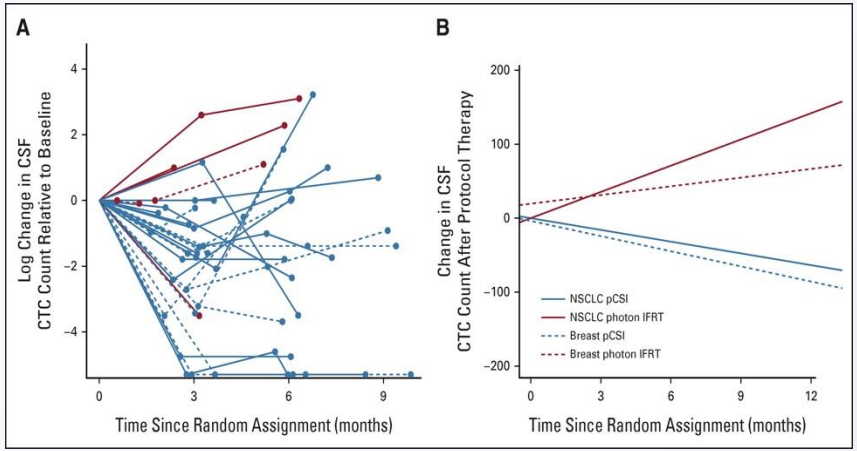
- In the phase II randomized trial, mean CSF CTCs declined among patients treated with proton CSI and increased among patients treated with IFRT.
- For IFRT patients, the increase in CSF CTCs was significantly associated with worse time to CNS progression, CNS PFS, and OS.
- **Treating the entire CNS compartment is needed to meaningfully reduce the CSF disease burden**

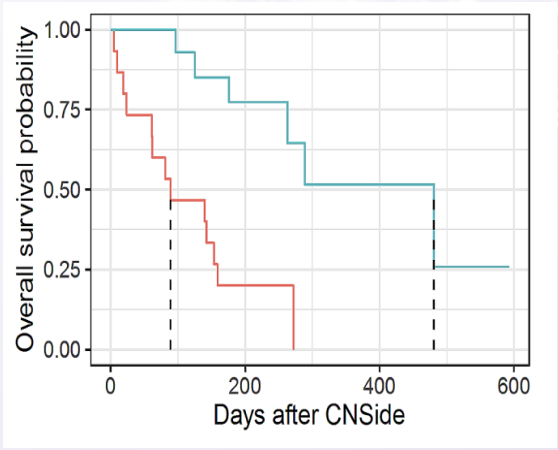


Pre-treatment MRI (extensive disease)
4,590 cells in total, and 1,092 per mL



8 weeks post-treatment (no measureable disease)
12 cells in total, and 2 per mL





Yang et al. JCO 2022
Barbour et al. Journal of NeuroOnc 2024
Example of MRI and CNSide numeration courtesy of Dr. Kotecha

Modern CSI Delivery for Solid Tumor LM

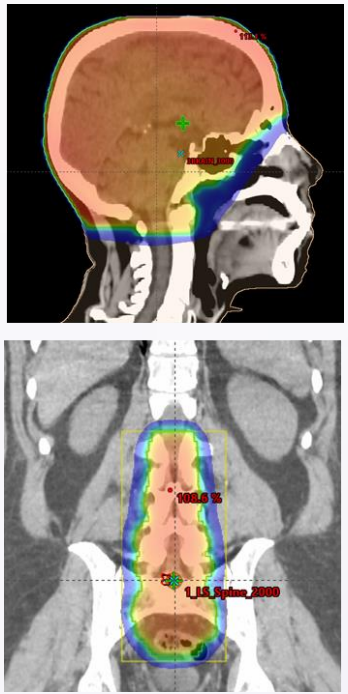
Study	Diagnosis	Patient number	Outcomes
Yang et al. 2021	Solid tumors	24 with **proton CSI**	5% and 10% Grade 4 thrombocytopenia and lymphopenia, respectively 5% Grade 3 fatigue Median CNS PFS=7.0 months, OS=8.0 months
Yang et al. 2022	Arms A and B: Breast cancer and NSCLC Arm C: all other solid tumors	Arms A and B: 42 with proton CSI 21 with IFRT Arm C: 35 with proton CSI	Arms A and B **Proton CSI vs. IFRT**: • Grade 3-4 toxicities low and comparable • Median CNS PFS: 8.2 vs. 2.3 months • Median OS: 11 vs. 4.9 months Arm C **Proton CSI**: Median CNS PFS=5.8 months OS=7.0 months
Kotecha et al. 2024	Solid tumors	23 with **proton CSI**	9% and 4% Grade 4 lymphopenia and thrombocytopenia respectively Median CNS PFS=9.0 months, OS=9.0 months
Lam et al. 2024	Solid tumors	45 patients with **proton CSI**	Predominantly grade 1-2 toxicities (nausea, headaches, fatigue) Median CNS PFS=6.5 months, OS=13.7 months
Perlow et al. 2024	Solid tumors	10 with **vertebral body sparing VMAT photon CSI**	No Grade 3 or above toxicities 1 patient with Grade 2 neutropenia, 9 with Grade 1 hematologic toxicity

Evolution of Radiation Therapy for Solid Tumor LM

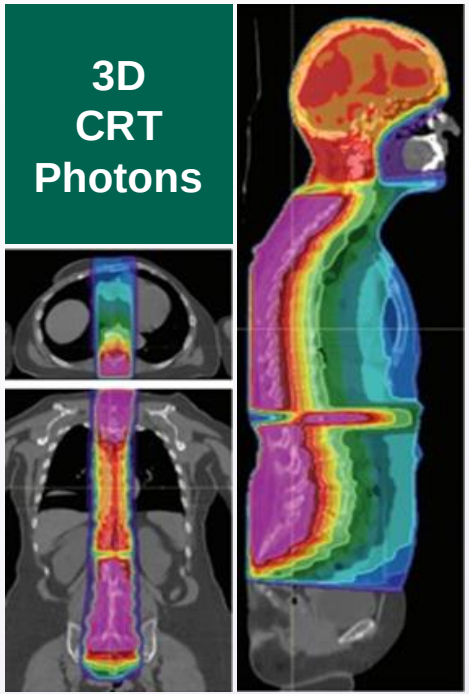
Partial CNS treatment

Traditional Comprehensive CNS treatment

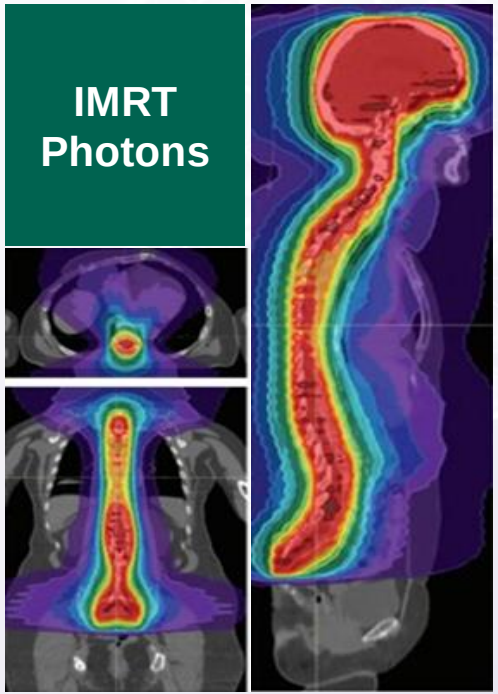
Modern Comprehensive CNS treatment



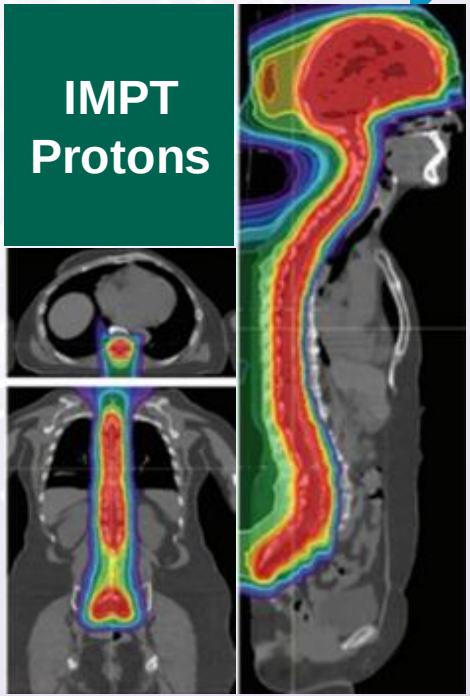
3D CRT Photons



IMRT Photons



IMPT Protons



Conclusions

- **Radiation therapy has a critical role in the management of LM.**
- **For focal symptom and local CNS disease management, IFRT remains and important treatments for all patients with solid tumor LM.**
- **For CNS and CSF disease control, radiation to the entire CNS compartment is needed with potential improvement in patient survival.**
  - For external beam radiation therapy, modern and sophisticated radiation delivery techniques (proton CSI, vertebral body sparing VMAT photon CSI) are needed to adequately treat the CNS compartment while reduce/avoid radiation doses to bone marrow and anterior organs.
  - Other forms of targeted radiation delivery techniques to the entire CNS compartment, including intrathecal radionuclides such as rhenium (186Re) obisbemeda, should be investigated as patients may derive similar benefits as external beam radiation therapy to the entire CNS compartment.
- **Circulating tumor cells (CTCs) in the CSF is a clinically important diagnostic and treatment response assessment tool and should be incorporated the management of patients with LM.**

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Thank You

Jonathan.Yang@nyulangone.org

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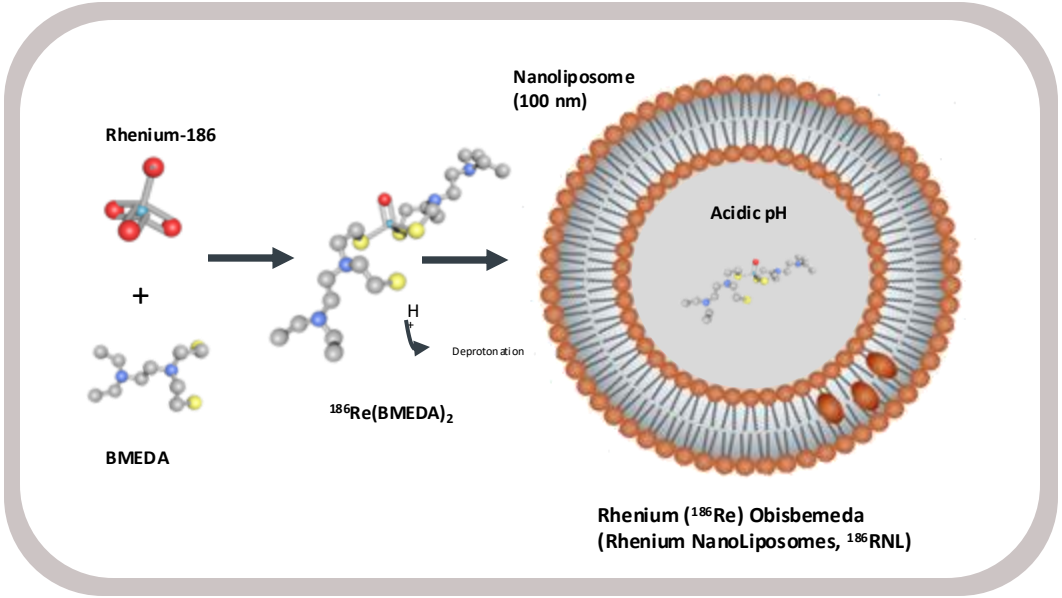
Rhenium (^{186}Re) Obisbemeda (^{186}RNL) for the Treatment of Leptomeningeal Metastases (LM)

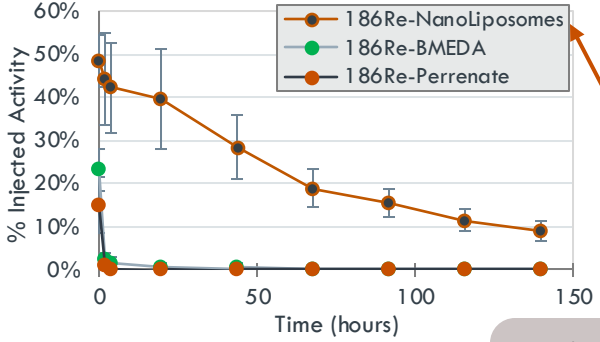
Andrew Brenner, MD, PhD
SNO 2024

Ande Bao, Case Western Reserve University
Priya Kumthekar, Northwestern
Joel Michalek, UTHSCSA
William Phillips, UTHSCSA
John Floyd, UTHSCSA
Michael Youssef, UTSW
Toral Patel, UTSW

Rhenium (^{186}Re) Obisbemeda (^{186}RNL)

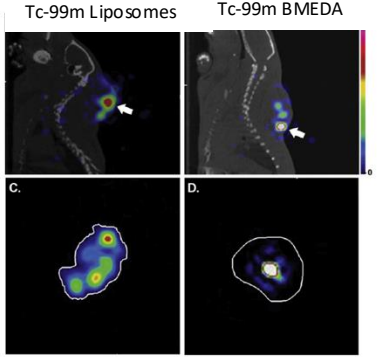


Improved Tumor Retention



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

Beta Emitter Rhenium-186 is a Differentiated Radionuclide

Chemistry, imaging, and tumoricidal characteristics optimal for CNS cancers

Rhenium vs. Field

Optimal Features	^{186}Re (β)	^{225}Ac (α & β)	^{212}Pb (α)	^{131}I (β)	^{177}Lu (β)	^{90}Y (β)
Tumor Visualization *Emits gamma particle*	✓	✓	✓			
Treatment Depth *2 mm avg path length*	✓					
Optimal Tx Index *Moderate KeV (~175-340 KeV)*	✓	✓	✓	✓		
Optimal Tx Index *Moderate half-life ($T_{½}$ = 90h)*	✓			✓	✓	
Optimal chemistry *High-drug loading efficiency*	✓					

EU Rhenium Experience

+ Extensive clinical data supports the safety and efficacy of rhenium[1]
+ Rhenium has been used safely and effectively for over 30 years in Europe to treat various cancers [2]

^{186}Re Decay

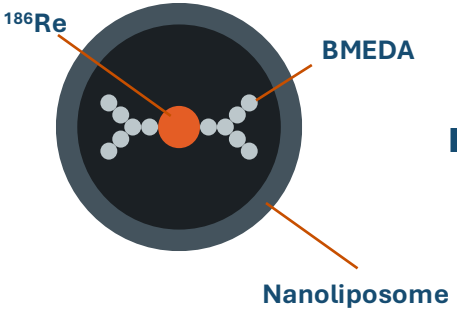
^{186}Re = beta particle + ^{186}Osmium + antineutrino

Delivery of ^{186}RNL

Potentially high therapeutic index for multiple CNS cancers

^{186}RNL: Lead Investigational Drug

Chelator (BMEDA) and Rhenium-186 Radionuclide (half-life = 90 hours)



Encapsulated in 100 Nanometer Liposome

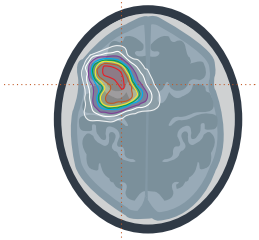
2 Delivery Modalities

CSF Malignances
Ex. LM

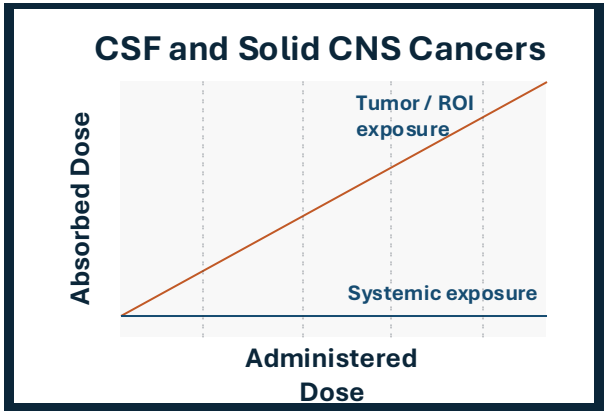
Intraventricular catheter (Ommaya reservoir)

Solid Tumors
Ex. GBM

Convection Enhanced Delivery (CED)



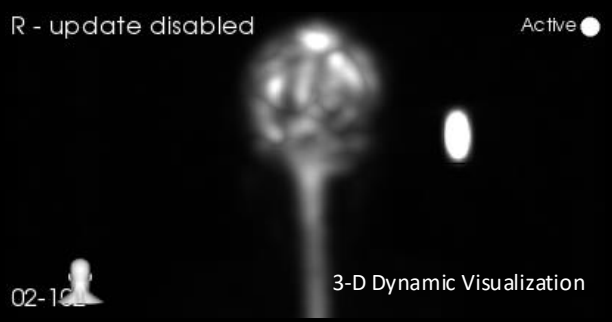
Therapeutic Impact



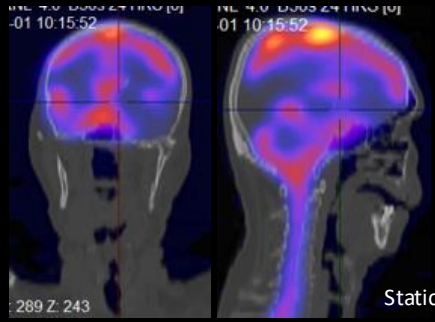
Direct Visualization of Drug Application and Quantification

Targeting, localization, and quantification ensures optimal dosing at the time of administration

Leptomeningeal Metastases

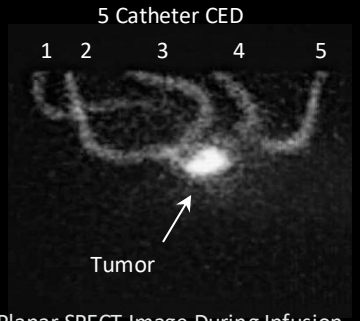


3-D Dynamic Visualization

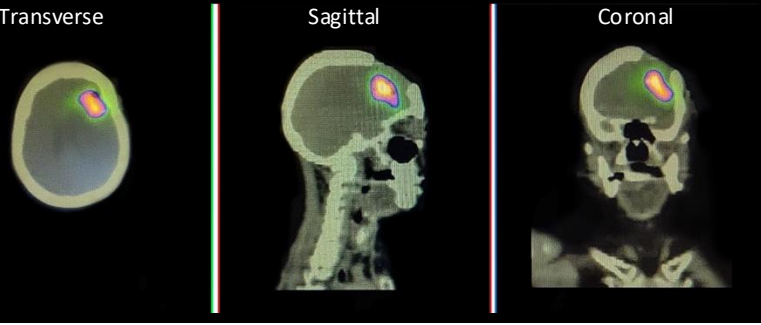


Static AP & Lateral

Glioblastoma



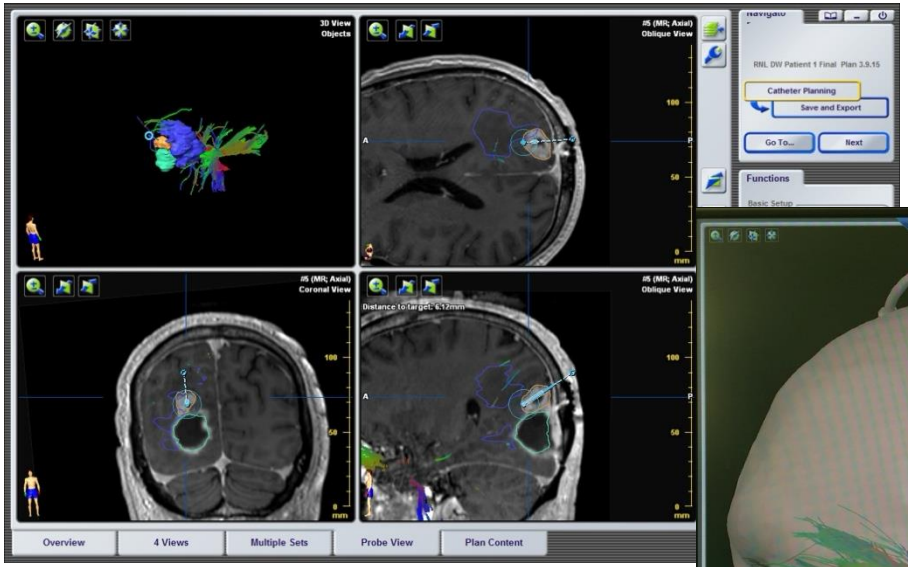
Planar SPECT Image During Infusion

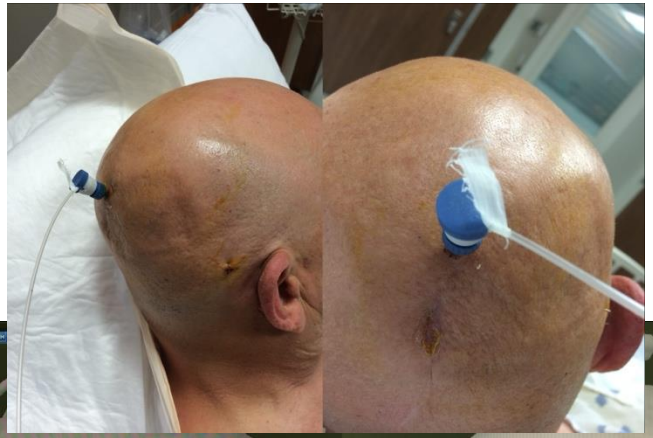


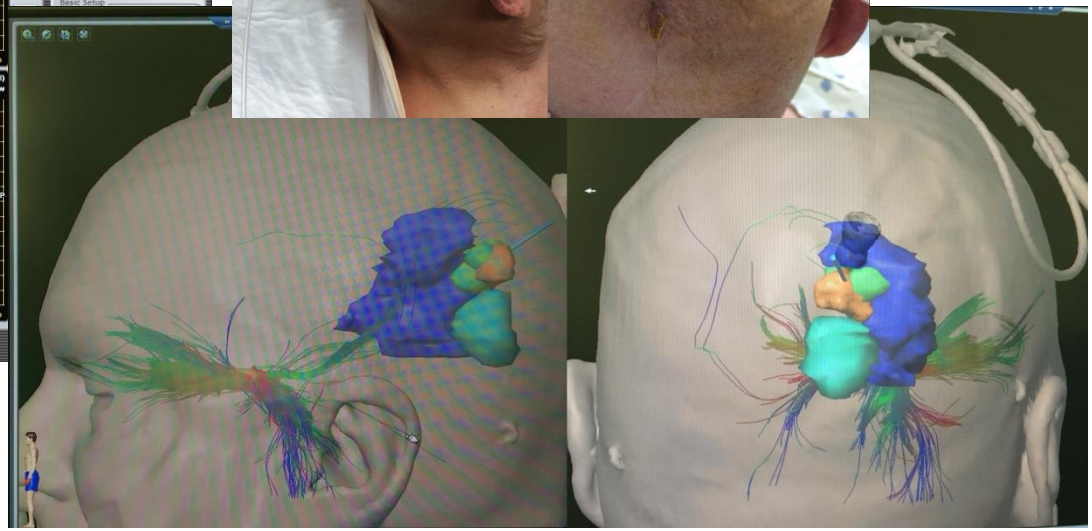
SPECT/CT Image at 20% Total Infusion

In Silico Case Planning for the ReSPECT-GBM Trial

Trial Patient 1



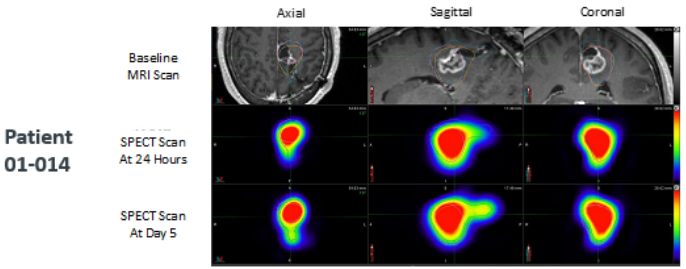




ReSPECT-GBM Phase 1, Single Dose Trial Design

Single administration of Rhenium (^{186}Re) Obisbemeda by Convection Enhanced Delivery (CED)

Example of rGBM Treatment: MRI and SPECT/CT



- Tumor volume was 6.5 mL & tumor coverage was > 90%
- Absorbed dose delivered to tumor was 419 Gy

ReSPECT-GBM Trial Design

- **Funding: NIH/NCI grant through Phase 2**
- **Dose escalation: 3+3 modified Fibonacci, currently enrolling in cohort 8**
- **Primary objective: Safety and tolerability**
  - Maximum Tolerated Dose / Maximum Feasible Dose
- **Secondary objectives: Efficacy**
  - Dose distribution
  - Overall Response Rate (ORR)
  - Progression Free Survival (PFS)
  - Overall survival (OS)
  - Imaging

Single Administration Phase 1 Dose Escalation Plan

Cohort	Administered Volume (mL)	Administered Activity (mCi)	Administered Concentration (mCi/mL)
1	0.66	1.0	1.5
2	1.32	2.0	1.5
3	2.64	4.0	1.5
4	5.28	8.0	1.5
5	5.28	13.4	2.5
6	**8.80**	**22.3**	**2.5**
7	12.3	31.2	2.5
8	16.34	41.5	2.5

ReSPECT-GBM Phase 1 Single Administration Dose Escalation Trial

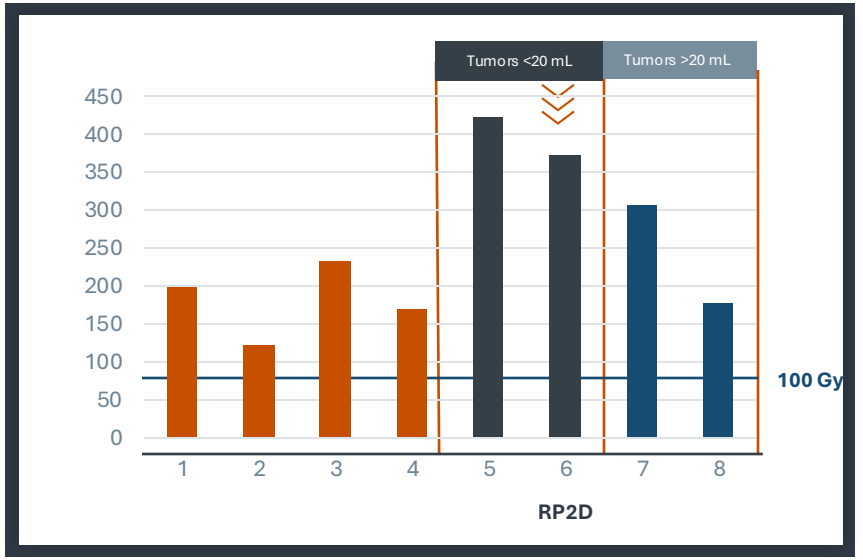
Favorable safety signal in Phase 1/2 and selection of RP2D for small to medium tumor sizes (20 mL or less)

Phase 1 Safety Summary

Grade	%	Most common AEs	SAEs
Grade 1	65.7%	Headache Fatigue	18 (only 2 possibly related)
Grade 2	25.2%		
Grade 3	6.5%		
Grade pending	2.6%		

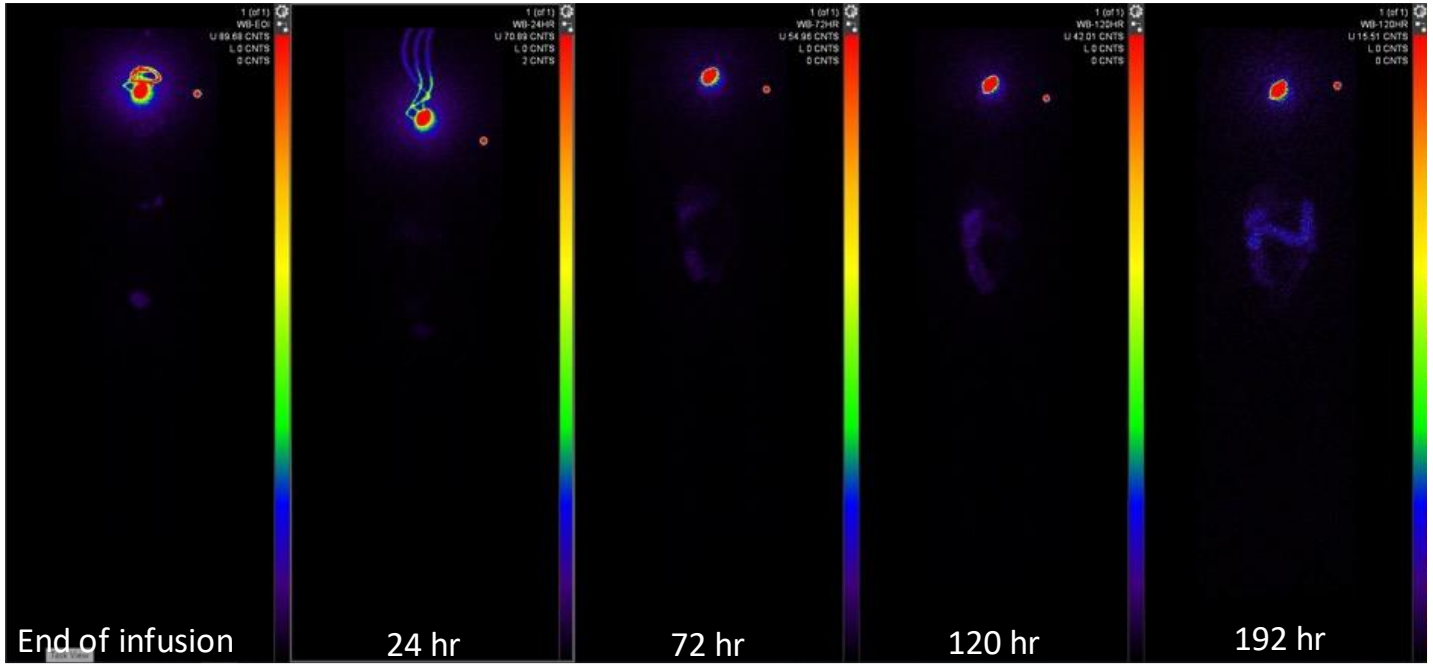
- Generally safe and well tolerated over 29 patients in 8 Phase 1 dosing cohorts
- 1 DLT in cohort 8 (hemiplegia)
- Most Phase 1 adverse events (AEs) were mild/moderate, unrelated/unlikely related to study drug, and resolved with treatment
- Increasing tumor size lowers average absorbed dose (cohorts 7 and 8)
- 19 (out of 34) patients treated at the RP2D
- Phase 2 safety profile consistent with Phase 1 data

Average Absorbed Dose to Tumor by P1 Cohort



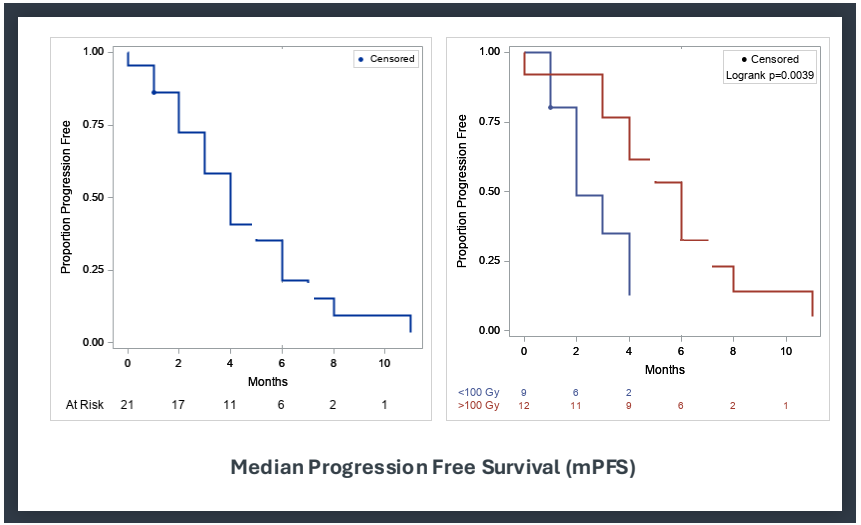
- The average absorbed dose to the tumor for all Phase 1 patients was 258 Gy (range: 8.9-739.5 Gy)
- P2 average absorbed dose to the tumor (n=19) of 300 Gy to date

ReSPECT-GBM Safety: Retention and Distribution



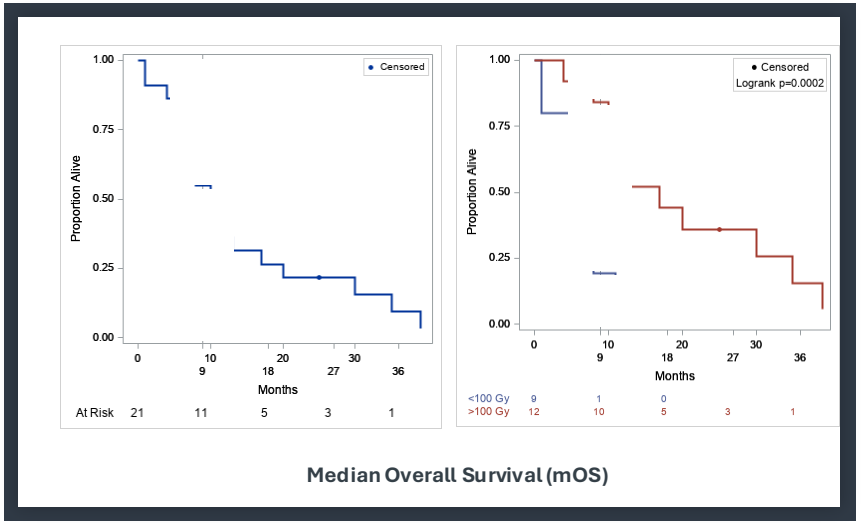
ReSPECT-GBM Phase 1 Single Administration Dose Escalation Trial

Statistically significant survival benefit in patients meeting or exceeding delivery 'threshold' parameters



Median Progression Free Survival (mPFS)

+ All patients: 4.0 months
+ <100 Gy: 2.0 months (blue)
+ **≥100 Gy: 6.0 m (red)**



Median Overall Survival (mOS)

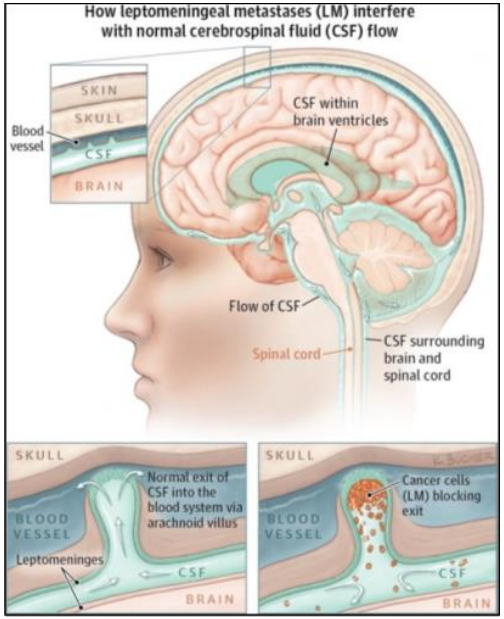
+ All patients: 11.0 months
+ <100 Gy: 6.0 months (blue)
+ **≥100 Gy: 17.0 months (red)**

+ OS increased by **27%** for each **10% increase** in the ***percentage of tumor covered*** (p<0.001)[1]
+ OS increased by **31%** for each **100 Gy increase** in the ***absorbed dose*** (p<0.001)[1]

1. Cox Proportional Hazards Model after adjustment for age, baseline ECOG status, baseline volume administered, and baseline tumor volume at time of analysis, November 2023

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

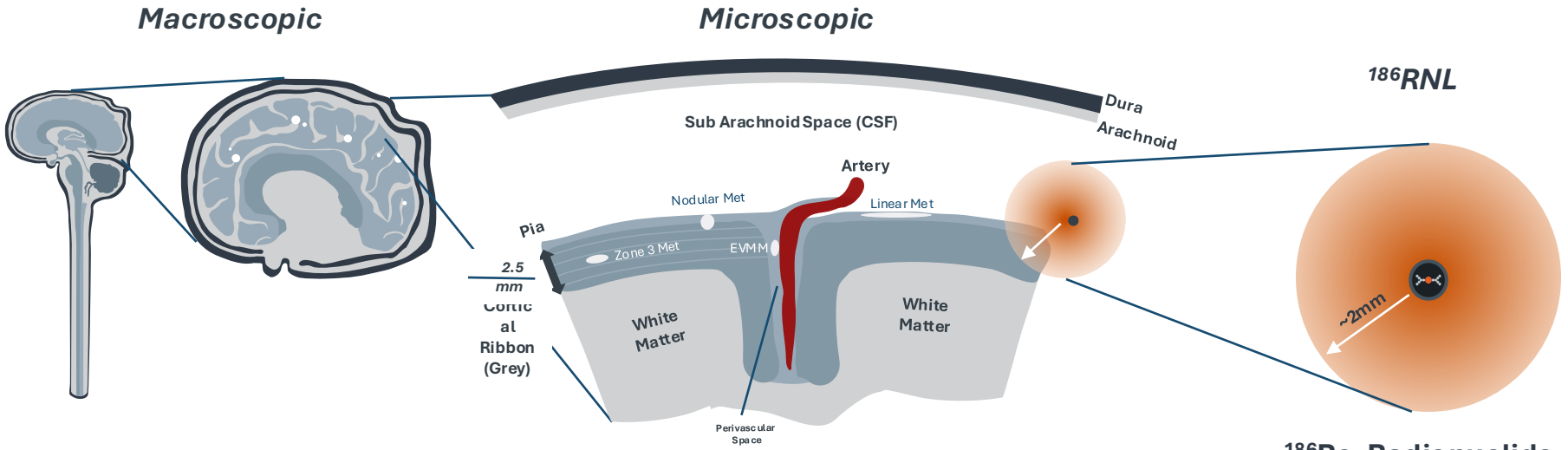
- Rhenium-186 is an ideal radionuclide for CNS indications because of its long half-life (~90 hours), short path length of the beta particles (~2mm), low dose rate, and high radiation density
- Liposomal encapsulation has been shown to prolong retention in the brain and CSF (e.g., DepoCyt®)
- ^{186}RNL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

Pathology of Leptomeningeal Disease Drives Therapeutic Approach

Rhenium-186 energy profile and pathlength treats unique CNS anatomy & region of interest



CSF Protected Dead Space

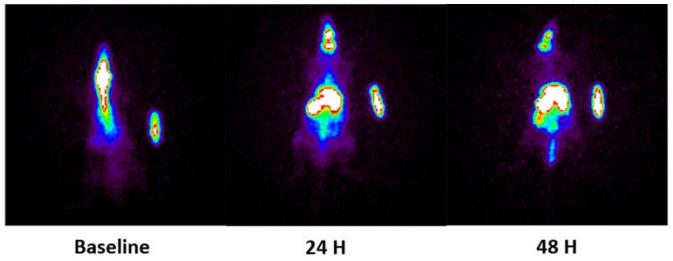
Nodular and Linear Mets

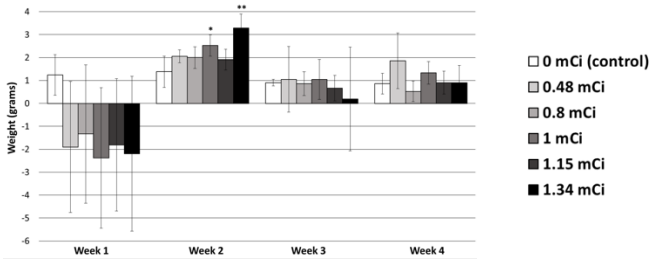
Region of Interest- CSF & Cortical Gray Matter

^{186}Re Radionuclide
Avg path length = ~2mm

Preclinical Safety and Efficacy

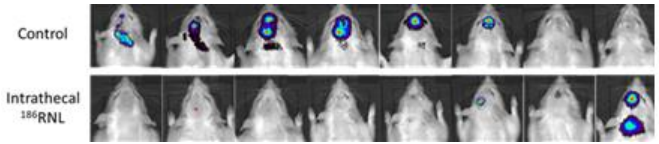
Preclinical evaluation of ^{186}RNL by intraventricular injection in non-tumor bearing rats with up to 1.34 mCi with corresponding absorbed doses of 1,075Gy was without significant toxicity



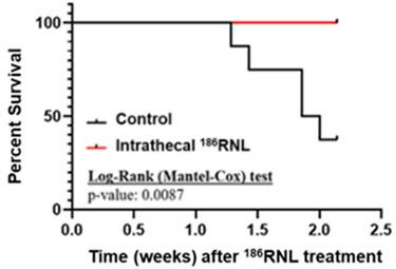


In 2 LM models (Wistar/C6 and NSG/MDA-MB-231) treatment with ^{186}RNL resulted in prolonged survival

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 Administration Dose Escalation Trial

Trial design: single administration delivery via standard Ommaya reservoir

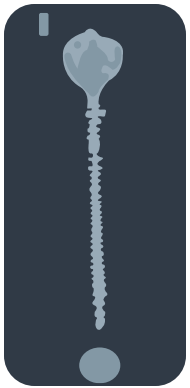
- **Dose escalation:** 3+3 modified Fibonacci
- **Primary objective:** Safety and tolerability
  - Maximum Tolerated Dose (MTD) / Maximum Feasible Dose (MFD) via Ommaya reservoir
- **Secondary objectives:** Efficacy
  - Overall Response Rate (ORR)
  - Duration of Response (DoR)
  - Progression Free Survival (PFS)
  - Overall survival (OS)
- **Other objectives:** Analysis on CSF, pK
  - CSF circulating tumor cells (CTCs)
  - Pharmacodynamic (PD) markers & dosimetry
- **Funding:** CPRIT

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**	**75.0**	**15.00**
7	5	TBD	TBD

Cancer Prevention & Research Institute of Texas

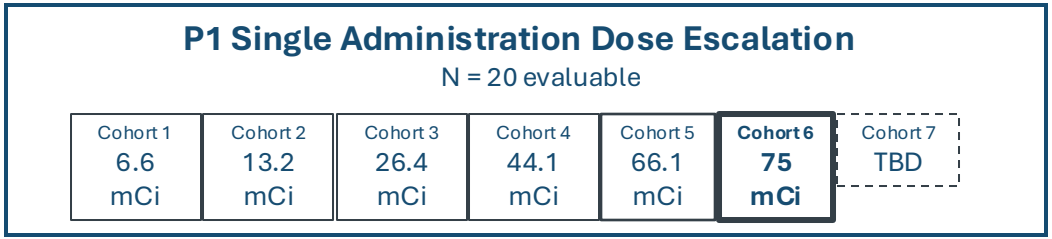
Treatment workflow

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



ReSPECT-LM Phase 1 Single Administration Dose Escalation Trial

Safety summary shows ^{186}RNL well tolerated through Cohort 5



- N = 33 enrolled, 7 screen failures, 26 intent to treat, 20 per treatment evaluable, 1st patient treated in Cohort 6
- A single DLT noted thus far at 66.14 mCi administered dose (thrombocytopenia)
- Adverse Events
  - Most common AEs (>20% of patients): headache, vomiting, nausea
  - Most AEs mild (grade 1, 60%) and moderate (grade 2, 28%)
  - Most AEs unrelated (38%) or unlikely related (28%) to study drug
  - Two AEs (headache) deemed definitely related to study drug (1 was grade 3 and resolved with treatment)
- Serious Adverse Events
  - 17 SAEs (7% of AEs)
  - 3 SARs[1] (SAEs with at least 'possible' attribution) – (1) encephalopathy (also attributed to steroid taper, resolved spontaneously), (2) headache (resolved with treatment), and (3) thrombocytopenia (resolved with treatment)

1. Serious adverse reaction

ReSPECT-LM Phase 1 Single Administration Dose Escalation Trial

Safety summary shows ^{186}RNL well tolerated through Cohort 5

Serious Adverse Events: 17 (7% of AEs):

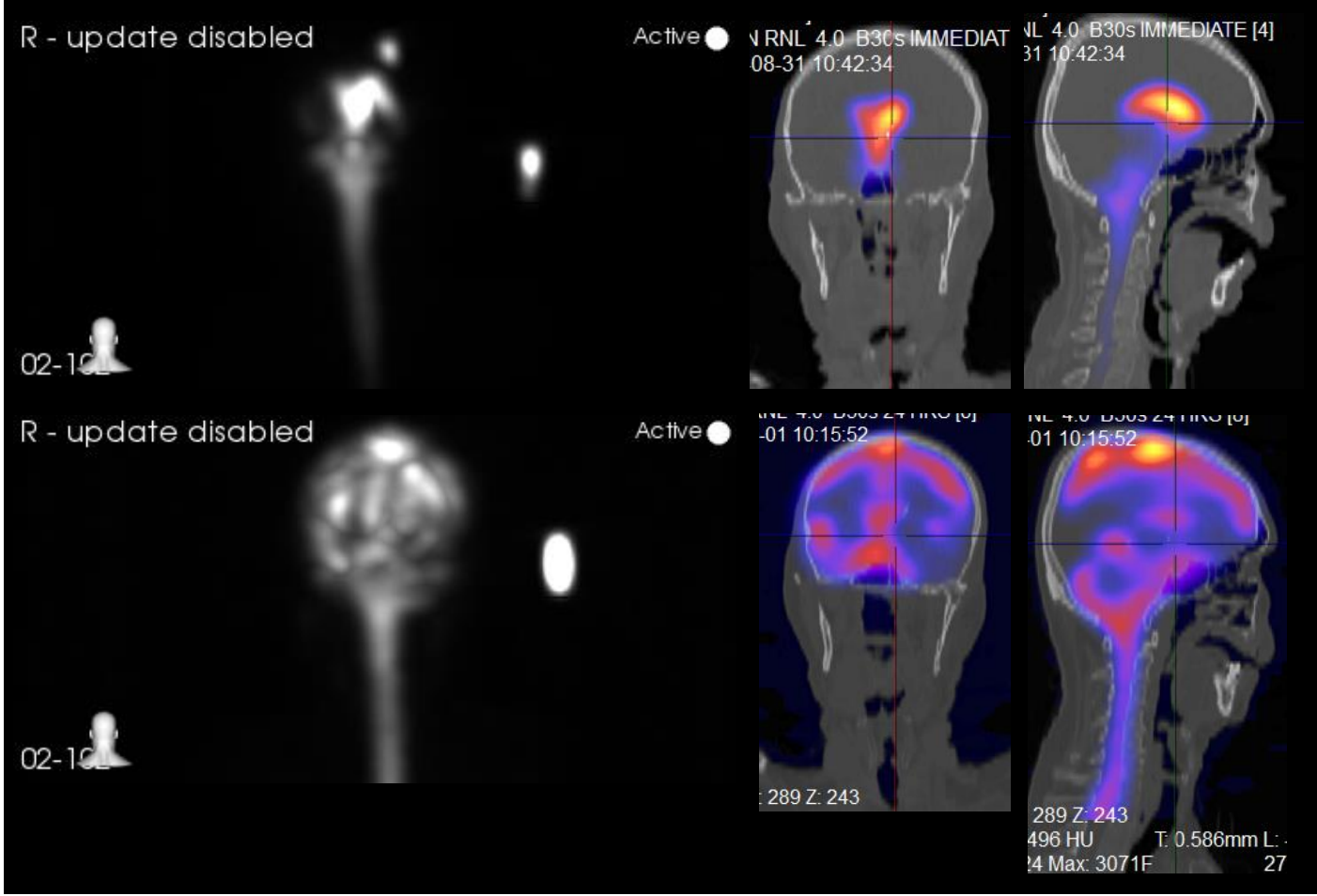
3 SARs (SAEs with at least 'possible' attribution) – (1) encephalopathy (also attributed to steroid taper, resolved spontaneously), (2) headache (resolved with treatment), and (3) thrombocytopenia (resolved with treatment)

	All grades, No. (%) N=85	Grade 3/4, No. (%) 9 (11%)
Headache, intermittent headaches	10 (12%)	1 (1%)
WBC, lymphocyte count decreased	9 (11%)	3 (4%)
Vomiting	7 (8%)	
Hypoalbuminemia	5 (6%)	
Platelet count decreased	5 (6%)	3 (4%)
Other	49 (58%)	2 (2%)

Note: Safety data partially unmonitored at time of presentation- 11/22/2024

Case study: Patient 02-101

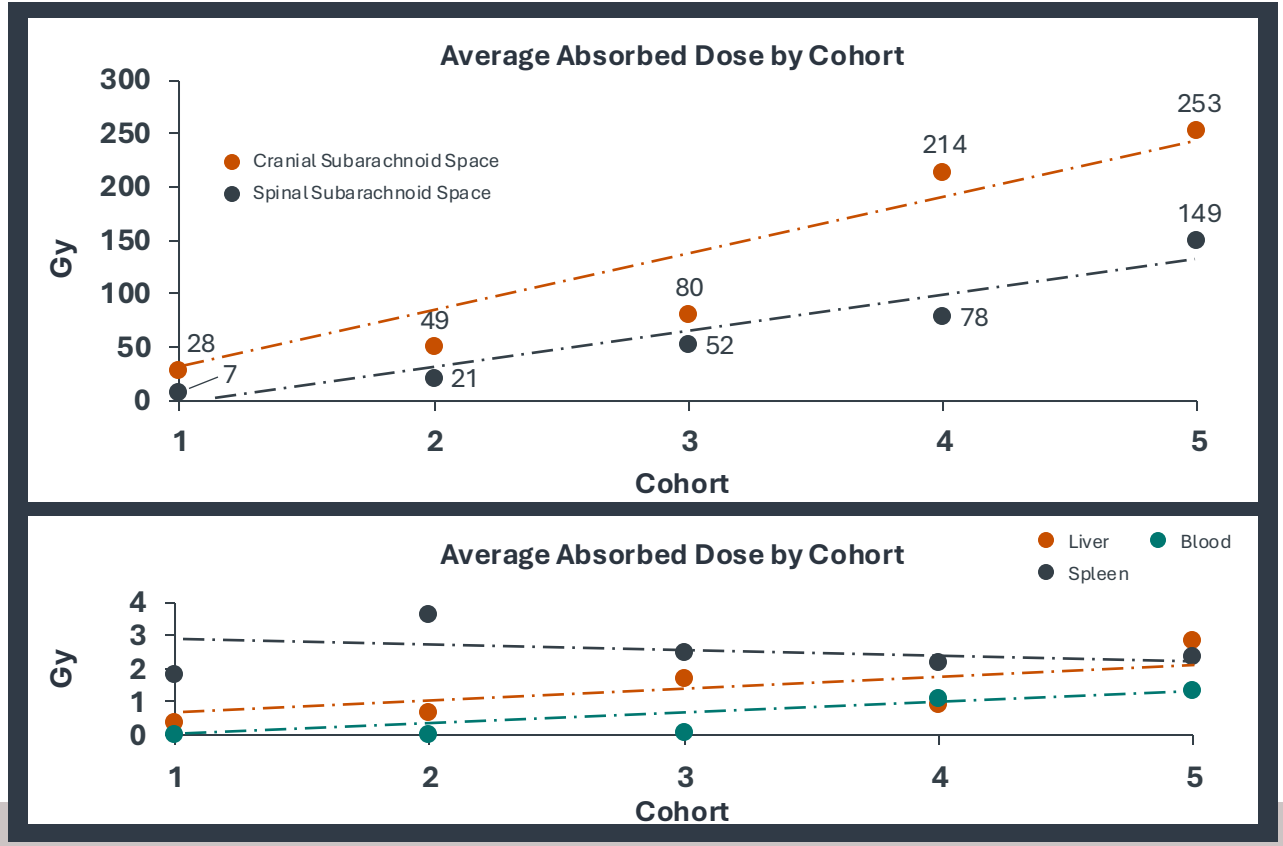
SPECT IMAGING



ReSPECT-LM Phase 1 Single Administration Dose Escalation Trial

Dosimetry & pK shows linear increase in absorbed & limited systemic dose

- Target/off-target radiation absorbed dose ratio >100/1
- Low radiation exposure to critical organs
- Radiation measured in CSF space for 7 days
- Complete CSF circulation of drug seen by 3.5-hour imaging timepoint
- **General toxicity limits[1]:**
  - Liver: ~35-50 Gy
  - Spleen: ~40 Gy
  - Bone marrow: ~2–5 Gy



1. J Nucl Med. 2021 Dec;62(Suppl 3):23S-35S. doi: 10.2967/jnumed.121.262751.

ReSPECT-LM Phase 1 Single Administration Dose Escalation Trial

Combined best response vs. baseline after single administration – through 4 months

- **Clinical Benefit Rate (CR+PR+SD)**
  - CTC response: 93% (14/15)
  - MRI Imaging response: 75% (12/16)
  - Clinical response: 86% (12/14)

Single dose response assessed from pretreatment through 4 months (112 days) follow-up

Response Measure[1]	Response	Stable Disease	Clinical Benefit Rate	Progression	Evaluable Patients	Data Not Available	Total Patients
CTC	13	1	14	1	15	5	20
Imaging	5	7	12	4	16	4	20
Clinical	2	10	12	2	14	6	20

CR = Complete response
PR = Partial response
SD = Stable disease
CTC = Circulating tumor cells

ReSPECT-LM Phase 1 Single Administration Dose Escalation Trial

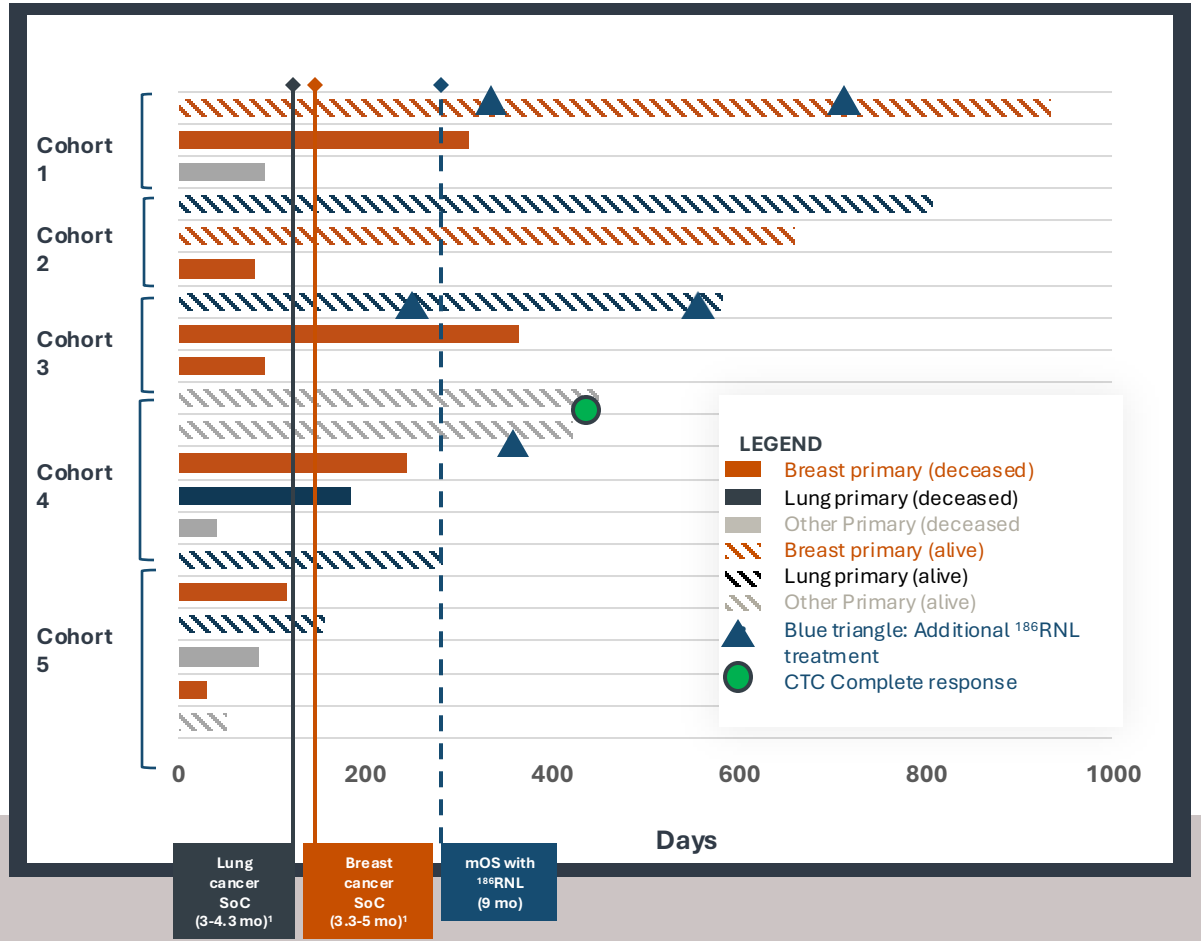
Swimmer's plot shows survival by cohort & primary cancer

Analysis by primary cancer and survival time in the dose escalation phase

- n = 20 evaluable patients
- 9 patients alive at analysis
- Tumors by primary disease
  - Breast: 9
  - Lung: 5
  - Other: 6

Key point

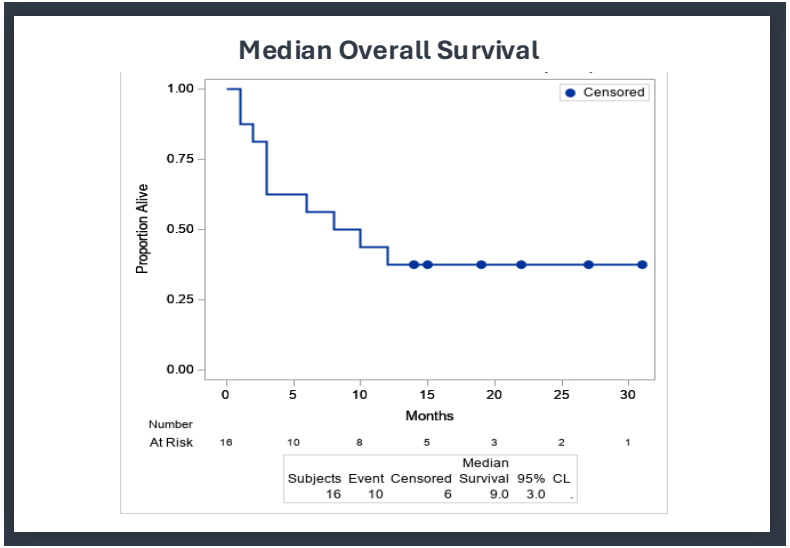
- Multiple long-term survivors including those receiving multiple doses through compassionate use



ReSPECT-LM Phase 1 Single Administration Dose Escalation Trial

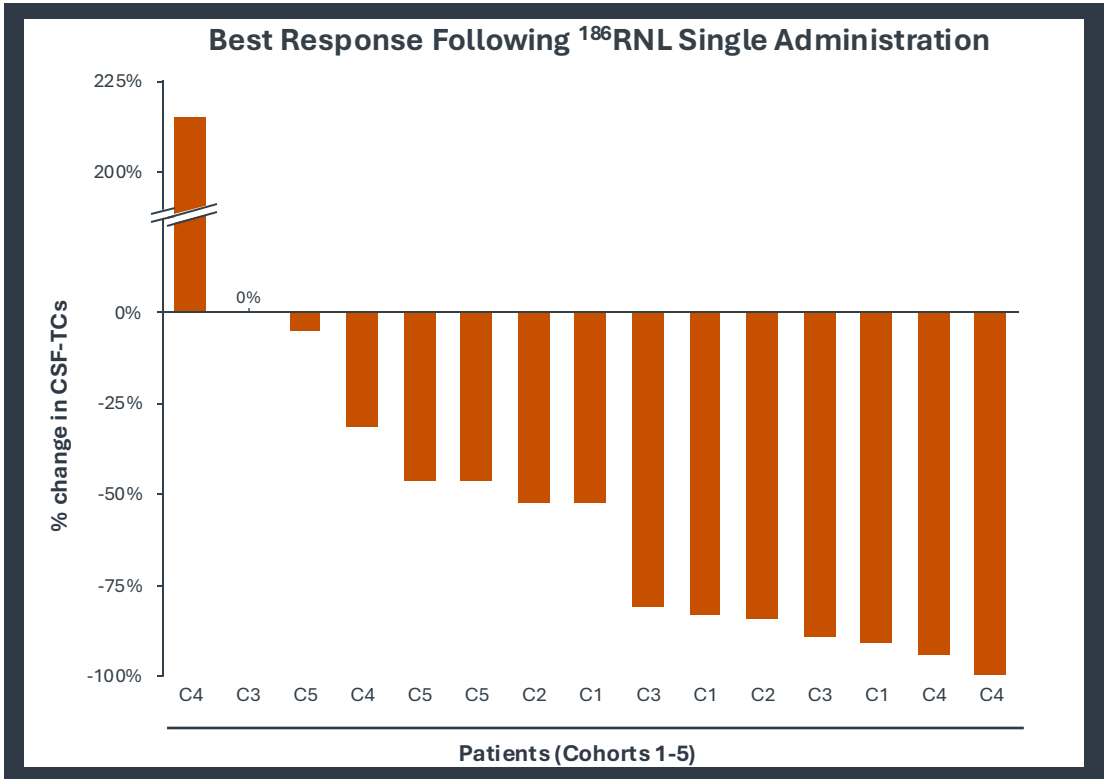
Median overall survival of 9 months through Cohort 4

- Positive mOS signal in dose escalation phase
- mOS of 9 months, compared to 4-6 months reported survival
- n = 16 patients, Cohorts 1-4
- 6 patients remain alive at analysis[1]



ReSPECT-LM Phase 1 Single Administration Dose Escalation Trial

Best response in tumor cells (CTCs) vs. baseline



Conclusions and Future Plans

- A single DLT noted thus far at 66.14 mCi administered dose (thrombocytopenia)
- Achieved average absorbed doses >250Gy to the cranial leptomeninges
- Radiographically 5 of 16 with response, 12 of 16 stable or better at 4 months
- Clinically 2 of 14 with neurologic improvement and 12 of 14 stable or better
- Median OS 9months through cohort 4 with one-third of patients still alive
- Currently in Cohort 6 at 75mCi
- 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 at varying intervals
- CNSide assay appears to have the greatest sensitivity for detecting response

Thank you

Patients and Caregivers

Principal Investigators

Plus Therapeutics

Funding by CPRIT, NIH/NCI, Plus Therapeutics

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UT Health San Antonio | Mays Cancer Center
UT Southwestern Medical Center
The Ohio State University Wexner Medical Center
Northwestern Memorial Hospital
NYU Langone Health
Johns Hopkins Medicine
Cleveland Clinic

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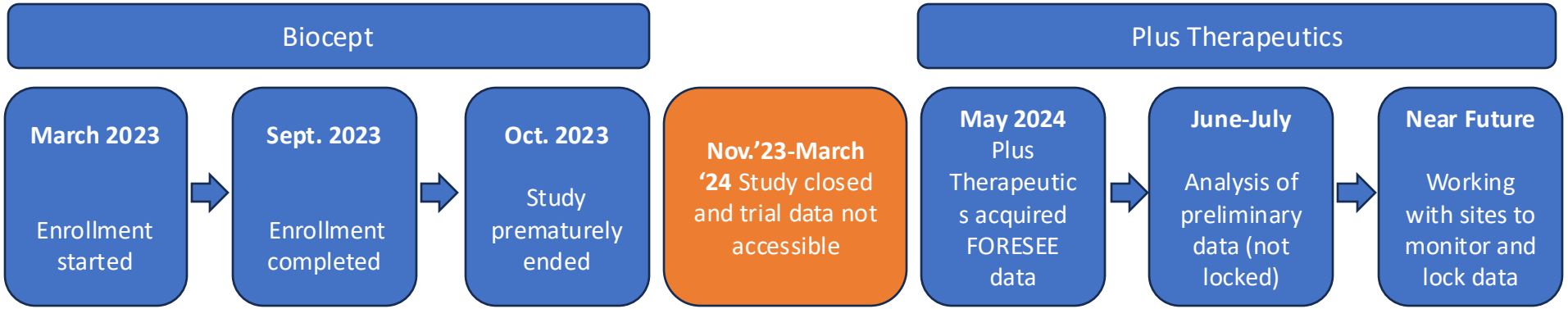
CSF Tumor Cell (CSF-TC) Detection, Quantification and Biomarker assessment helps in clinical management of breast cancer and Non-Small Cell Lung cancer patients having Leptomeningeal Disease (FORESEE Study, NCT05414123)

Northwestern Medicine®

Robert H. Lurie Comprehensive Cancer Center of Northwestern University

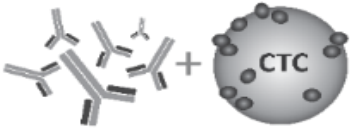
Timeline of the FORESEE Study



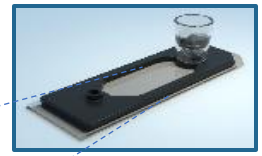
CNSide CSF Diagnostic Platform

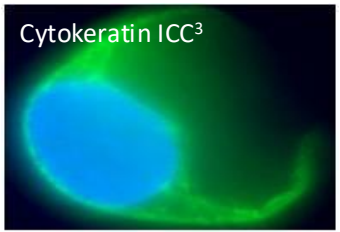
Tumor Cell Detection Workflow

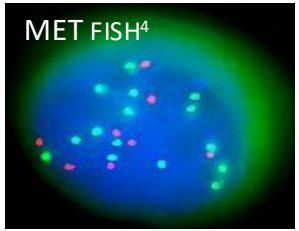
Antibody Cocktail Tumor Cell Isolation[1, *]

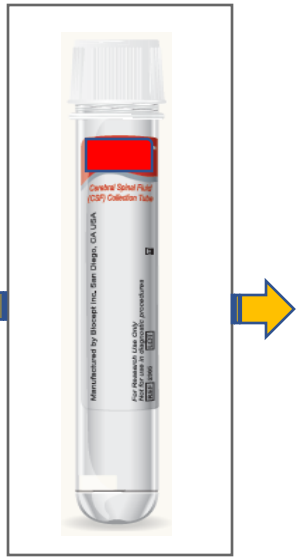


Patented Microfluidic Channel [2,*]







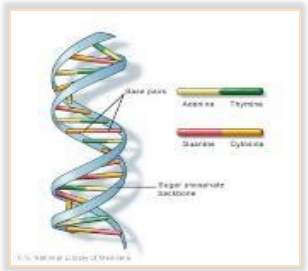


Collection tube for ambient shipping up to 4 days

*Unique cell capture technology for FISH and protein expression assays

cfDNA Detection Workflow

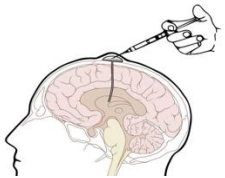
CSF cfDNA Isolation



NGS on CSF cfDNA

[1] Mikolajzyk et al. JCO (2011), [2] Dickson et al. Microfluidics (2011)
[3] Pecot et al. Cancer Discovery (2011), [4] Mayer et al. Cancer Genetics (2011)

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

- At each visit, CNSide's contribution to a clinical decision was evaluated via a Questionnaire
- Treatment decisions were at Physician discretion
- Enrollment goal: 20 patients with breast cancer, 20 with NSCLC

PI Kumthekar

FORESEE Study: Study End Points

Primary End Point

- Evaluate if CNSide contributes to a clinical decision (Target: 20% of decisions)

Secondary End Point

- Evaluate tumor cell detection by CNSide as a therapy response monitoring tool
- Sensitivity, Specificity, NPV and PPV of CNSide compared to CSF cytology

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

FORESEE Study: Inclusion and Exclusion criteria

Inclusion Criteria

- Positive breast cancer or NSCLC diagnosis
- Suspected or confirmed LMD diagnosis
- Willingness to sign informed consent
- Positive or negative for Parenchymal brain metastasis

Exclusion criteria

- Patients with any other cancer than breast cancer or NSCLC cancer
- Patients with a primary brain tumor

Precedence for Clinical Utility Trial Design

Title	NCT#	Primary End Point	Type of Test
BESPOKE Study of ctDNA Guided Immunotherapy	04761783	Percent of Melanoma, - NSCLC and Colorectal patients who have their immunotherapy treatment regimen changed due to the SIGNATERA ctDNA test result	Patient tailored gene panel to detect cfDNA from the blood
Treatment Decision Impact of OncotypeDx in HR+, N- Breast Cancer Patients (SWITCH)	01446185	Impact of OncotypeDx Recurrent Score on treatment decisions	21-gene test that predicts recurrence of early-stage breast cancer
Study of the Clinical Utility of PSMA Imaging in the Evaluation of Men With Prostate Cancer	02825875	Changes to clinical management of patients with prostate cancer after Physician reviews a PET/CT scan of PSMA	PSMA Imaging by PET/CT
Prospective Clinical Utility Study to Assess the Impact of Decipher on Treatment Decisions after Surgery (PRO-IMPACT)	02080689	Number of participants for which the Urologist changed the patient's treatment plan based on Decipher test results	Next Generation Sequencing of tumor tissue
Decision Impact Study of PreciseDx Breast (PDxBRUTILITY)	06309615	Proportion of Physicians who utilized PBxBR results in their management of patients with invasive breast cancer (target: 20%)	Combination of Artificial Intelligent grading of histology and clinical data that predicts recurrence in early-stage breast cancer patients

FORESEE Study: Physician Questionnaire

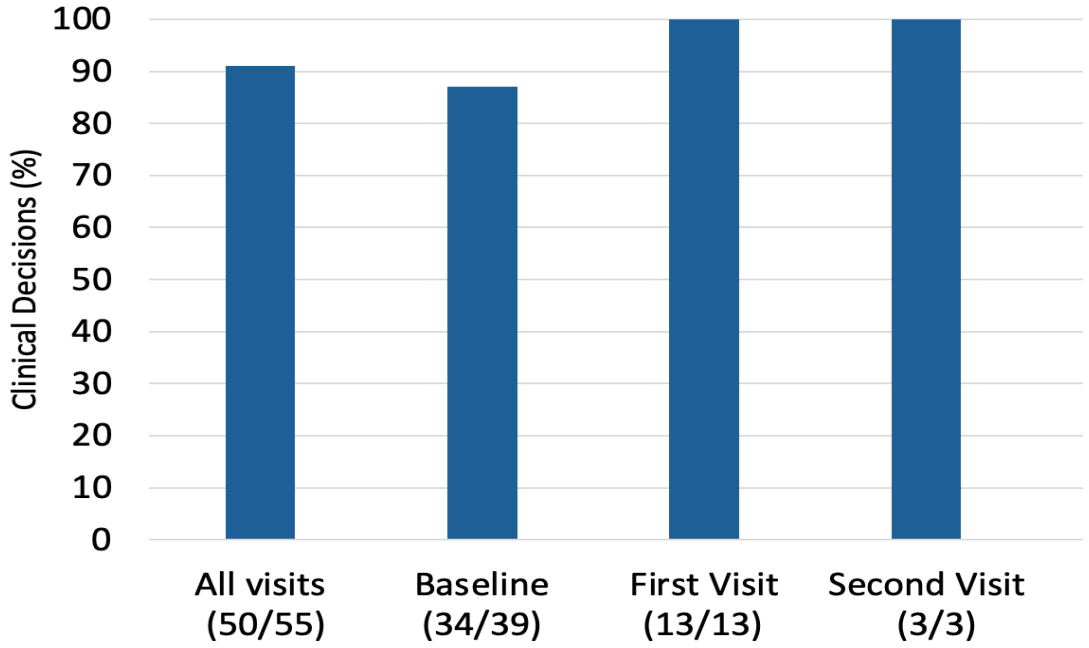
Baseline:

1. Was the patient diagnosed with LM prior to Baseline visit (yes, no)
   a. If no, is the patient diagnosed with LM at the Baseline visit (yes, no)
   b. If yes, what is the status of the LM tumor at this visit (No Change, Progression, Resolution)
2. Did CNSide contribute to this assessment? (yes, no)
3. Did CNSide inform the specific drug selected for treatment? (yes, no)

Subsequent visits:

1. What is the status of the LM tumor (No Change, Progression, Resolution)
2. Did CNSide contribute to this assessment? (yes, no)
3. Did CNSide inform the specific drug selected for treatment? (yes, no)

Take Home #1:
CNSide helped make clinical decisions in LMD patients



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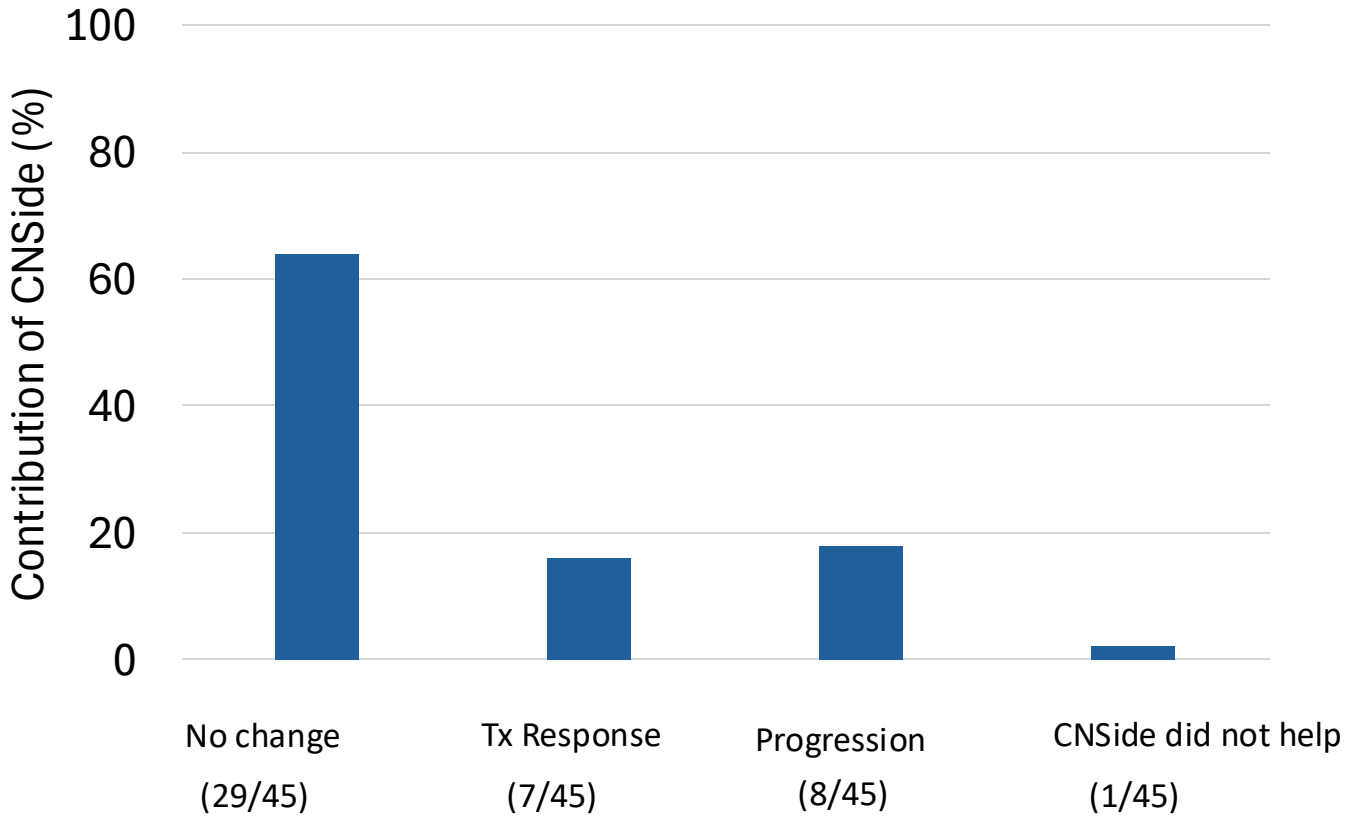
Take Home #2: CNSide helped to diagnose LMD

- N=10 patients not diagnosed with LMD prior to trial enrollment
  - These patients were deemed LMD positive or negative after the baseline visit based on investigator assessment

- LMD Positive Patients (N=7)
  - Cytology Positive, CNSide Positive: N=2
  - Cytology Negative, CNSide Positive: N=5

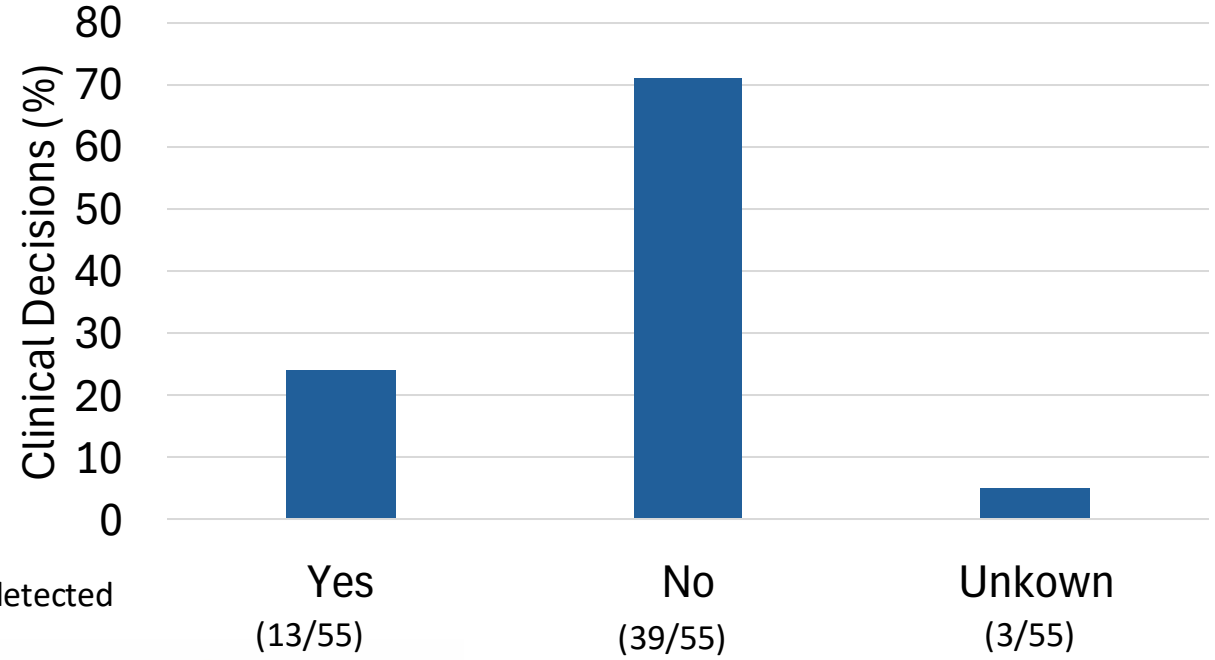
- LMD Negative Patients (N=3)
  - All three patients were cytology negative and CNSide negative
    - Investigators noted on the questionnaire that CNSide helped to rule out LMD

Take Home #3: CNSide helped to evaluate the status of the LMD tumor (45 questionnaires)*



*N=35 pts

Take Home #4:CNSide identified mutations used to make a specific drug selection



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Improved tumor cell detection in LMD patients* of CNSide compared to Cytology** in matched samples (n=45)

CNSide

- Detected cells in 80% (36/45) samples of LMD Positive Patients (N=36)
- Did not detect cells in LMD Negative Patients (N=3)

Cytology

- Detected cells in 29% (13/45) samples of LMD Positive Patients (N=36)
- Detected Atypical or Suspicious cells in (4/45) samples of LMD Positive Patients
- Did not detect cells in LMD Negative Patients (N=3)

*LMD based on investigator assessment

**Cytology Atypical and Suspicious for Malignant cells included

RESULTS: To be presented on Sunday

Abstract Code: BIOM-70

Abstract Title: CSF tumor cell (CSF-TC) detection, quantification and biomarker assessment helps in clinical management of breast cancer and non-small cell lung cancer patients having leptomeningeal disease (FORESEE Study, NCT05414123)

Oral Abstract Session - Clinical Trials - Non Immunologic, 24th November 2024, 10:15am - 10:25am, Grand Assembly B

Conclusions and Next Steps

Preliminary Conclusions

- FORESEE study met primary end point
- CNSide helped to make a clinical decision in 91% (50/55) of decisions
- CNSide helped to inform therapy selection in 24% (13/55) of decisions
- Compared to cytology in matched samples, CNSide more than

Next steps

- Working with the sites to obtain mature data to be presented/published in near future

Acknowledgements

- All patients who were enrolled in FORESEE trial
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PLUS THERAPEUTICS

THANK YOU!

SCAN TO RECORD ATTENDANCE

*not needed if you pre-registered