Power and precision
in cancer radiotherapeutics

PLUS™ THERAPEUTICS

BIO International Convention

June 15, 2022

Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Any statement in this document that is not a historical fact is a “forward-looking statements” within the meaning of Section 27A of the Securities Act & Section 21E of the Securities Exchange Act & are usually identified by the use of words such as “anticipates,” “believes,” “estimates,” “expects,” “intends,” “may,” “plans,” “projects,” “seeks,” “should,” “will,” & variations of such words or similar expressions. We intend these forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 27A of the Securities Act & Section 21E of the Securities Exchange Act of 1934, as amended, & are making this statement for purposes of complying with those safe harbor provisions. These forward- looking statements reflect our current views about our plans, intentions, expectations, strategies & prospects, which are based on the information currently available to us & on assumptions we have made. Although we believe that our plans, intentions, expectations, strategies & prospects as reflected in or suggested by those forward-looking statements are reasonable, we can give no assurance that the plans, intentions, expectations or strategies will be attained or achieved. Furthermore, actual results may differ materially from those described in the forward-looking statements & will be affected by a variety of risks & factors that are beyond our control.

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We believe in the critical importance in developing & delivering innovative, targeted radiotherapeutics for patients battling rare & central nervous system cancers.

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Radiopharmaceuticals for Cancer

*High Alpha & Low Beta: A Primer on Therapeutic Radiopharmaceuticals as a **Compelling Next-Gen Approach for Solid Tumors***

GUGGENHEIM

*"Theoretically, any cancer can be cured if **enough radiation** can be **delivered** to it."*

Andrew Brenner, MD PhD
Professor Neuro Oncology & Neurosurgery
Kolitz/Zachry Endowed Chair Neuro-Oncology Research
UT Health San Antonio

*"In 2016, there were an estimated 3.05 million cancer survivors treated with radiation, accounting for **29% of all cancer survivors**."*

Cancer Epidemiol Biomarkers Prev 2017 Jun;26(6):963-970

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Rare & Difficult-to-Treat Cancers

Responsible for Substantial Morbidity & Mortality Worldwide

+ Rare cancers represent 27% of all cancers; all pediatric cancers are rare
+ Rare cancers account for 25% of all cancer deaths; 5-year survival rate is lower for patients with a rare cancer than those with a more common cancer
+ Treatments for rare cancers are eligible for orphan drug designations

^{186}RNL FOR CNS TUMORS

Glioblastoma: deadliest, most common brain cancer in adults (TAM $2.1B)

Leptomeningeal Metastases: late complication in 5% of cancer patients (TAM $8.4B)

Pediatric Brain Cancer: 2nd most common type of cancer in children (TAM $106M)

^{188}RNL-BAM FOR LIVER & SOLID TUMORS

Primary Liver Cancer: 42k cases diagnosed annually in U.S. with 5-year survival of 20%

Secondary Liver Cancer: ~50-60% of colorectal cancer patients develop metastases to liver (TAM $1.3B)

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Sources: CBTRUS Statistical Report, NBTS, NCI

Targeted Radiation Therapy & Mechanism of Action

Types of Radiation

External Beam Radiation

Internal Targeted Radiation

Absorbed Radiation & DNA Damage

1 Gray Radiation

=

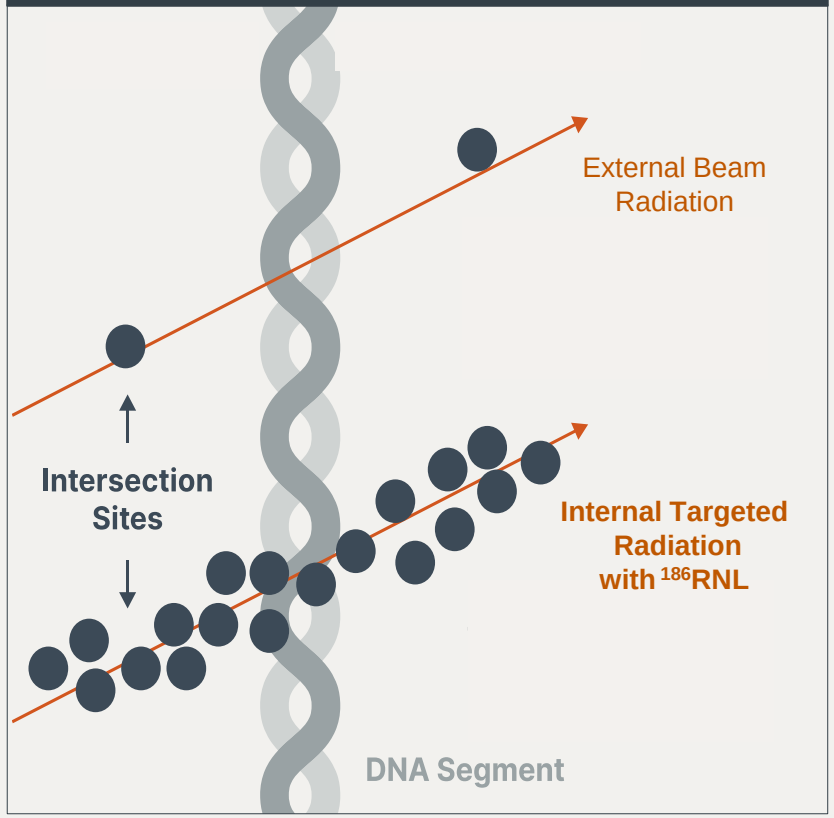
10^5 Ionizations

1,000 damaged DNA bases
1,000 single strand (SS) breaks
20-40 double strand (DS) breaks

Absorbed Radiation & Recurrent GBM

	DS DNA Breaks
EBRT (35 Gy)	700-1,400
^{186}RNL (600 Gy)	**12,000-24,000**

Radiation Mechanism of Action



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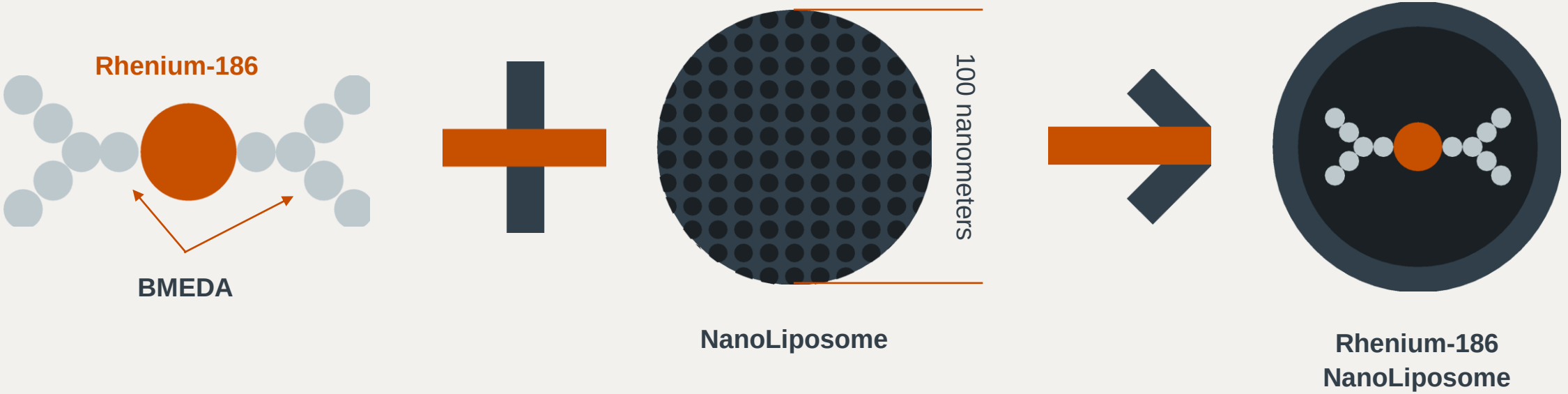
Lead Investigational Drug: Rhenium-186 NanoLiposome (^{186}RNL)

Proprietary Nanoscale Compound with a Unique Isotope



Rhenium-186 Isotope

+ Dual energy emitter: beta (cytotoxic) & gamma (imaging)
+ Short average path length (1.8 mm): high precision
+ Low dose rate: safer for normal tissues
+ High radiation density: overwhelms innate DNA repair mechanisms

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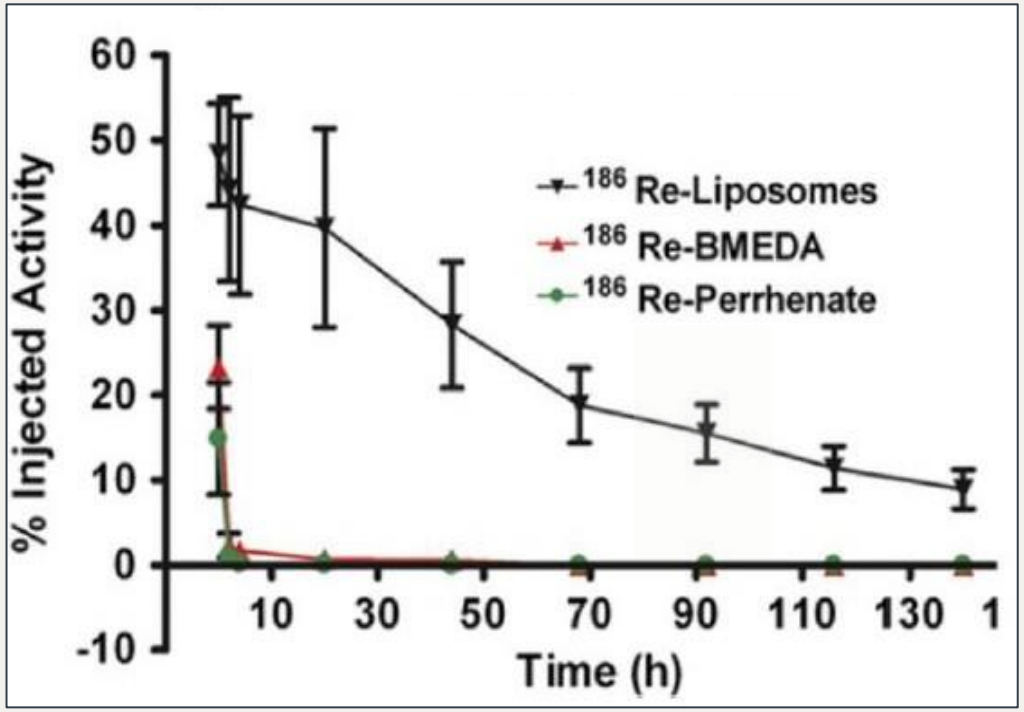
Spatiotemporal Behavior of ^{186}RNL Following Direct Brain Delivery

Prolonged Half-Life & Brain Retention



Prolonged Tumor Retention

Liposomal encapsulation significantly extends the *in vivo* intracranial half-life of Rhenium-186 (90 hours) & decreases clearance rate from the brain.

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

Investigational Drug Pipeline

Radiotherapeutic	Indication	FDA Designation(s)	External Funding	Stage	Status
^{186}RNL	Recurrent Glioblastoma (dose escalation)	Orphan Drug Fast Track	NIH/NCI Phase 2	Phase 1/2a	Enrolling
	Recurrent Glioblastoma (22.3 mCi dose)	Orphan Drug Fast Track	NIH/NCI Phase 2	Phase 2b/registration	2022
	Recurrent Glioblastoma (multi-dose extension trial)	Orphan Drug Fast Track	—	Phase 2b	2022
	Leptomeningeal Metastases	Fast Track	—	Phase 1	Enrolling
	Pediatric Brain Cancer	—	—	Pre-IND	IND Submission 2022
^{188}RNL-BAM	Hepatocellular Carcinoma	—	—	Preclinical	IND Enabling CMC & Preclinical
	Liver Metastases	—	—	Preclinical	IND Enabling CMC & Preclinical

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Innovative, targeted radiotherapeutics for patients with central nervous system tumors.

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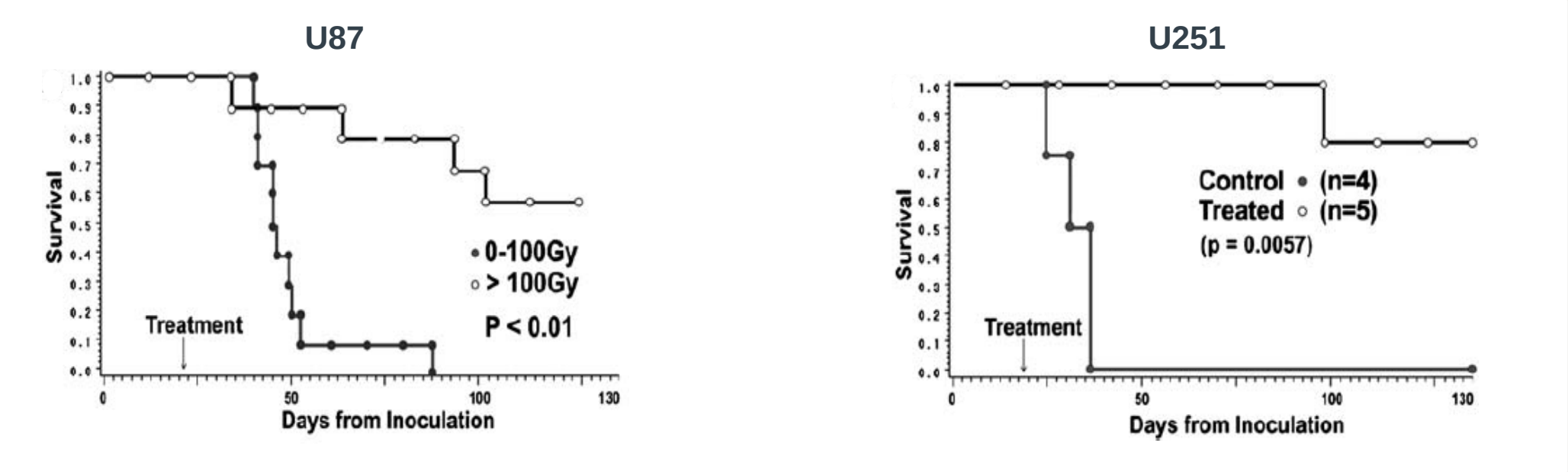
^{186}RNL Preclinical Data in Glioblastoma (GBM)

^{186}RNL Significantly Prolongs Survival in Intracranial Xenograft Models



+ Doses of up to 1,845 Gy were tolerated without weight loss or neurological deficit.
+ No maximum tolerated dose of ^{186}RNL reached.
+ Statistically significant prolongation in survival, limited only be the end of the experiment.
+ Blinded histologic analysis by neuropathologist showed no residual tumor all treated animals.

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

ReSPECT-GBM Phase 1/2 Clinical Trial Design

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

+ Single arm, prospective Phase 1/2 study utilizing a modified Fibonacci dose escalation scheme, followed by an expansion at the designated recommended phase 2 dose (RP2D).
+ Maximum number of planned subjects: up to 55 subjects (including patients enrolled in the Phase 1 dose escalation trial & a subsequent cohort at the RP2D).
+ Supported by a NIH/NCI grant through Phase 2.

ClinicalTrials.gov: NCT01906385

ReSPECT-GBM Patient Demographics & Dose Escalation

Patient Demographics (N=22)

Gender	
Male	14 (64%)
Female	8 (36%)
Tumor Volume (cm^3)	Average = 8.3 Range = 0.9 - 22.8
Prior Treatments	Average = 1.7 Range = 1 - 3
Prior Bevacizumab	5 (23%)
IDH Mutational Status	
Wild type	18 (90%)
Mutated	2 (10%)
MGMT Status	
Methylated	4 (25%)
Unmethylated	12 (75%)
Glioma grade	
Grade IV	20 (91%)
Grade III	2 (9%)

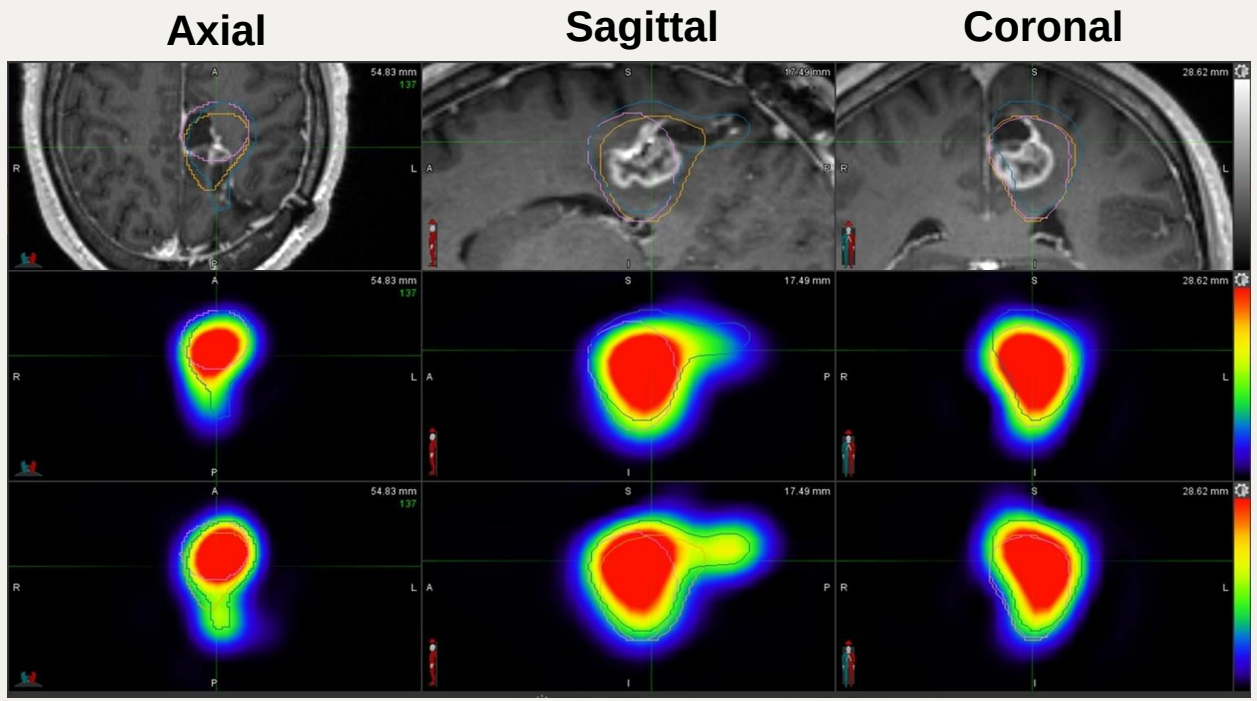
Dose Escalation

Cohort	Infused Volume (mL)	Total ^{186}RNL Activity (mCi)	Concentration (mCi/mL)	Average Absorbed Dose (Gy)	Status
1	0.66	1.0	1.5	198	Enrolling Cohort 8 (n = 23 subjects)
2	1.32	2.0	1.5	122	
3	2.64	4.0	1.5	234	
4	5.28	8.0	1.5	171	
5	5.28	13.4	2.5	423	
6	8.80	22.3	2.5	287	
7*	8.80	22.3	2.5	584	
8	12.3	31.2	2.5	TBD	

* Cohort 7 utilized same volume & dose as cohort 6 but with increase in maximum flow rate to 20 microliters/minute

ReSPECT-GBM Case Study: Tumor Coverage & Retention

Cohort 5 / Subject 01-014: MRI & SPECT / Radiation Dosimetry

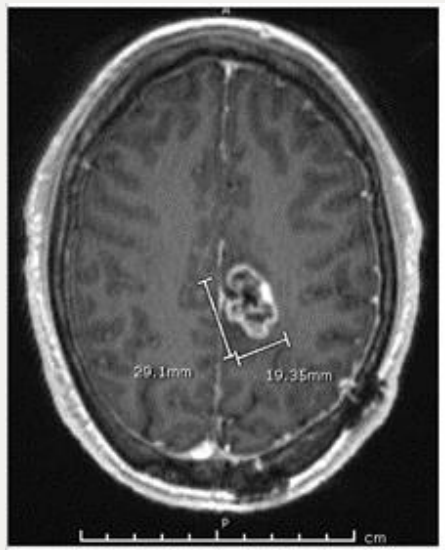


+ Deep brain tumor recurrence
+ Tumor volume: 6.5 mL
+ Tumor coverage: >90%
+ Absorbed dose delivered to tumor: 419 Gy

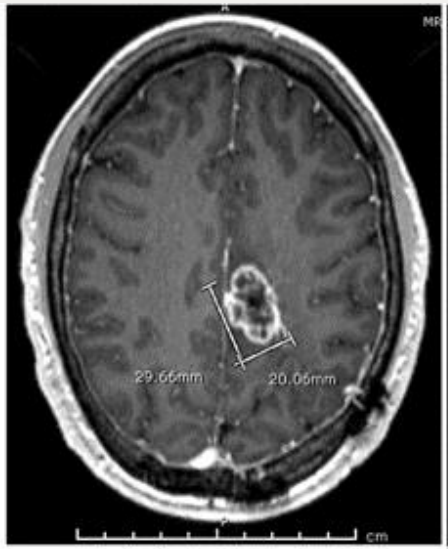
Natural History of Recurrent GBM Lesions After ^{186}RNL

Cohort 5 / Subject 01-014: Tumor Response Observed to Day 362

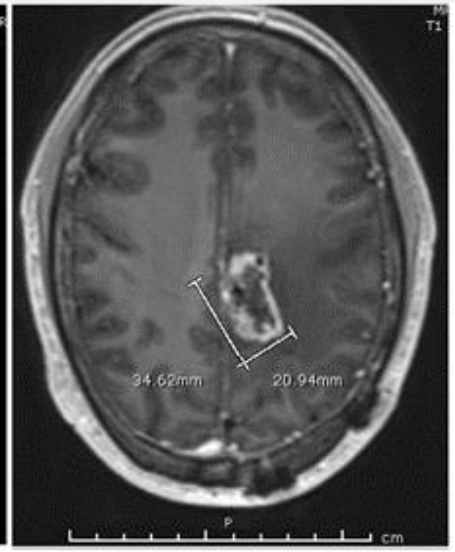
Pre-^{186}RNL 1/4/19 d-5



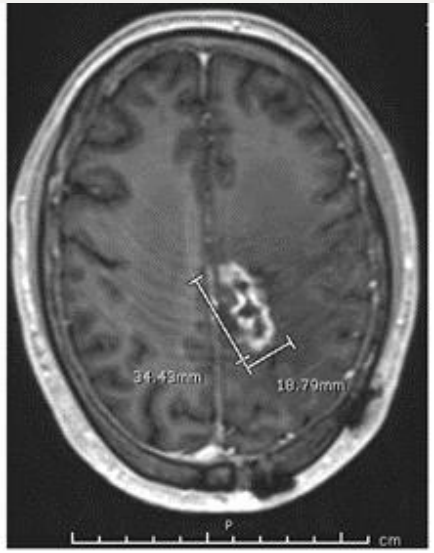
Post-^{186}RNL 2/4/19 d28



Post-^{186}RNL 5/7/19 d118



Post-^{186}RNL 1/6/20 d362



+ MRI scans revealed an initial increase in size which peaked at Day 118, with some associated edema, pseudo-progression
+ Tumor shrinkage out to at least Day 362
+ Remains alive at 160 weeks after single treatment

ReSPECT-GBM Patient Safety

^{186}RNL Appears to be Safe & Well Tolerated

Thus far, in the Phase 1 study of 23 subjects in 8 dosing cohorts with recurrent glioblastoma receiving a single dose of ^{186}RNL:

+ There have been no dose limiting toxicities.
+ Most AEs reported were mild or moderate (Grade 1 or 2) in intensity.
+ Most AEs were considered causally unrelated to ^{186}RNL except scalp discomfort, which was considered related to the surgical procedure.
+ Serious adverse events:

Serious Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Osteonecrosis (Left Shoulder)	0	0	1	0	0	**1**
Seizure	0	1	2	0	0	**3**
Vasogenic cerebral edema	0	0	2	0	0	**2**
Pneumonia	0	0	1	0	0	**1**

Convection-Enhanced Delivery (CED)

A Technique that Generates a Pressure Gradient To Deliver Therapeutics Through the Interstitial Spaces of the Central Nervous System

Evolution of Key Delivery Parameters → Increasing Delivery Success → Absorbed Radiation Dose Correlates with OS

Activity	1.0 – 31.2 mCi
Volume	0.6 – 12.3 mL
Max Flow Rate	5 – 20 ul/min
CED Catheters	1 – 4 per patient

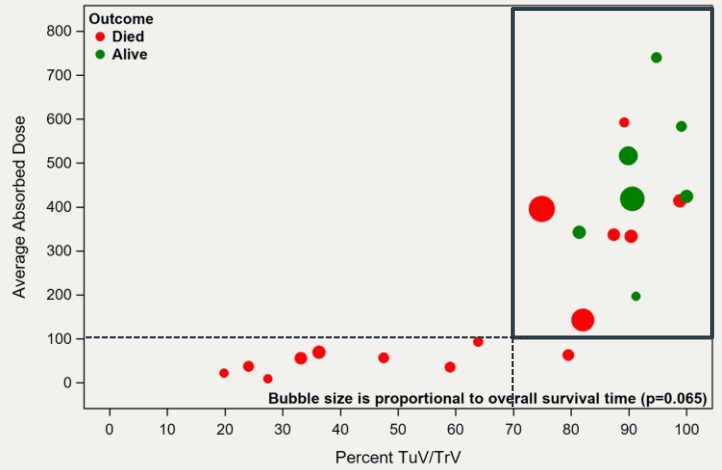
Cohort 1-4 (low dose & volume)

+ 12 patients treated
+ 5/12 (42%) >100 Gy

Cohort 5-7 (high dose & volume)

+ 11 patients treated
+ 9/11 (82%) >100 Gy

Therapeutic Threshold >100 Gy

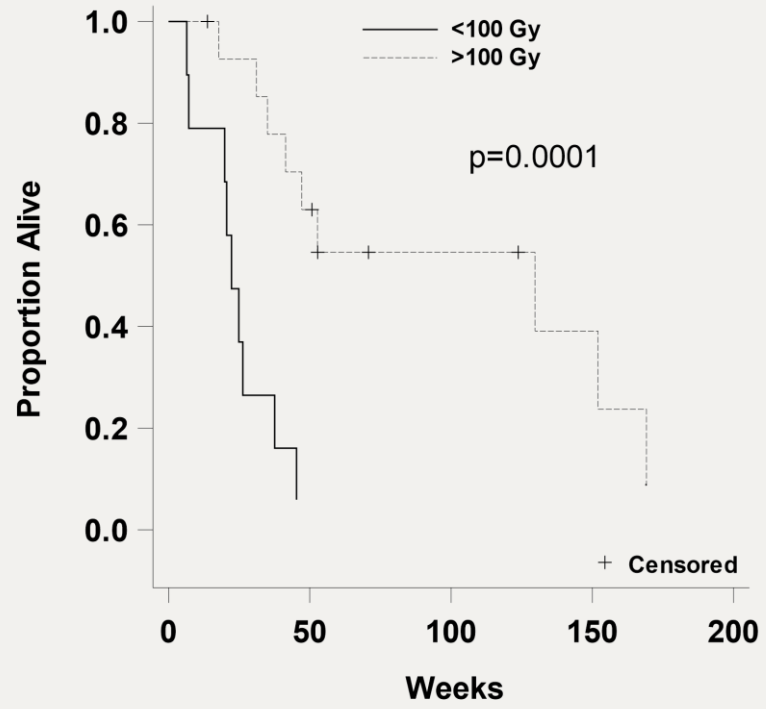


P = 0.065

ReSPECT-GBM Updated Efficacy Data Since SNO 2021

Current Enrollment is 23 Patients Across 7 Dosing Cohorts (Feb 2022)

Kaplan Meier Analysis



Dose (Gy)	Overall Survival (weeks)			Patients Remain Alive
	Median	95% CI	Mean ± SE	
<100	**22.3**	6.4, 45.3	24.6 ± 4.8	0
>100	**129.7**	35, 169.1	100.8 ± 19	4

By comparison, **median overall survival of 32.1 weeks** reported in 8 study meta-analysis of 694 recurrent GBM patients treated with bevacizumab monotherapy

Neuro-Oncology, 22(5), May 2020: 694–704, 705-717.
Oncol Lett, 14(1), Jul 2017: 1141–1146.

ReSPECT-GBM Summary & Next Steps

Summary

+ No DLTs, favorable safety & tolerability profile
+ Recent cohorts (5-7) >80% delivery success
+ ~20x radiation to tumor vs. EBRT
+ Statistically significant OS improvement in >100 Gy radiation absorbed dose
+ Very favorable OS >100 Gy vs. published data

Next Steps

1) Take Cohort 6 dose & volume to Phase 2b/registrational trial in late 2022 for small to medium sized tumors (~2/3 of all recurrent GBM patients)
2) Continue to dose escalate in larger tumors to DLT (~1/3 of all recurrent GBM patients)
3) Initiate multi-dose extension trial to investigate additional ^{186}RNL doses in previous ^{186}RNL-treated recurrent GBM patients

Recommended Phase 2 Dose (from Cohort 6)

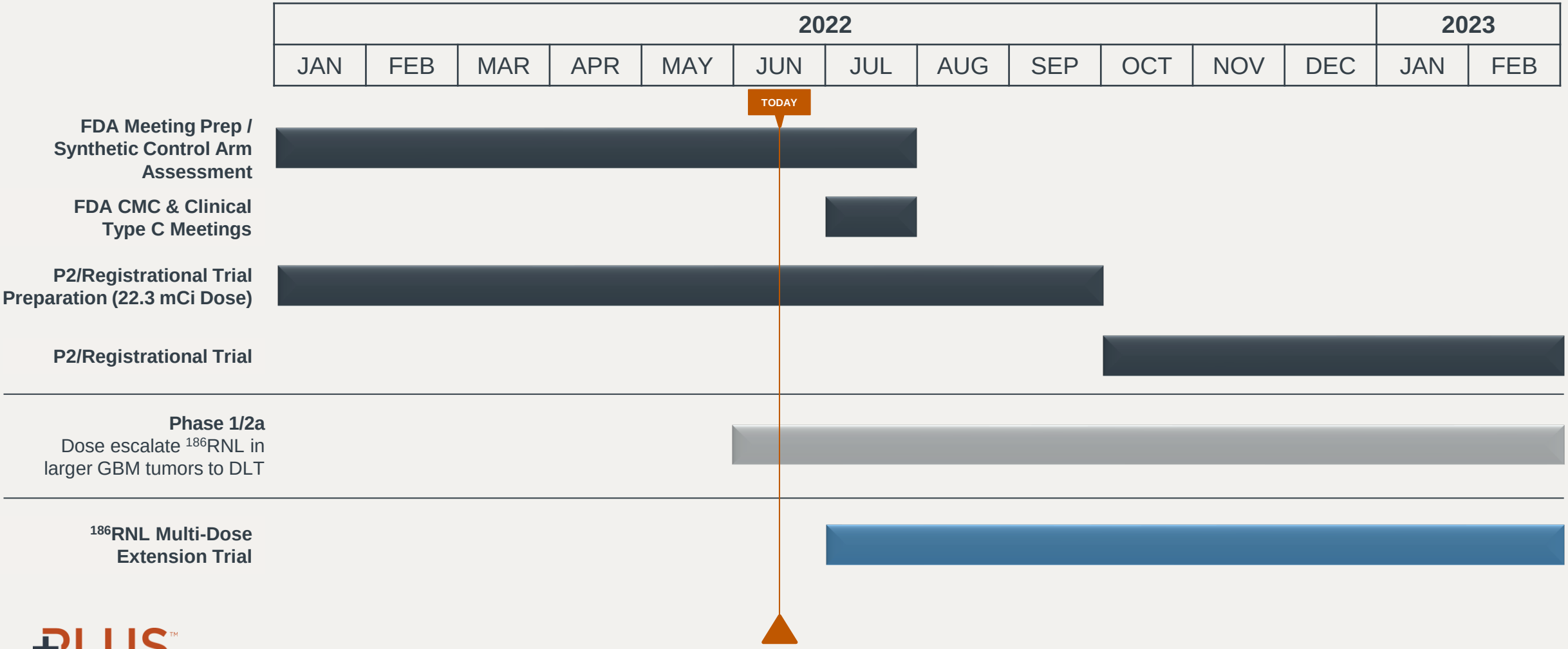
+ Infused Volume: 8.80 mL
+ Total ^{186}RNL Activity: 22.3 mCi
+ Concentration: 2.5 mCi/mL
+ Average Absorbed Dose: 584 Gy

Phase 2b/Registrational Trial *

+ Active Patients: ~100
+ Randomization ~3:1 (^{186}RNL treatment : synthetic control or standard of care)
+ Enrollment duration: 18-24 months
+ Primary Endpoint: overall survival

* subject to FDA feedback

ReSPECT-GBM Timeline



ReSPECT-LM Phase 1 Clinical Trial Design

A two-part, multi-center Phase 1 study to determine the maximum tolerated dose/ maximum feasible dose, safety, & efficacy of single dose Rhenium-186 NanoLiposome (^{186}RNL) administered via the intraventricular route for leptomeningeal metastases (LM).

Primary Objective

Characterize the safety & tolerability of a single dose of ^{186}RNL by the intraventricular route & to identify a maximum tolerated dose (MTD) and/or maximum feasible dose (MFD).

Secondary Objectives

+ Characterize the pharmacokinetic & dosimetry profile of a single dose of 186RNL when administered intraventricularly via Ommaya reservoir.
+ Develop a multiple dosing strategy of 186RNL for subsequent clinical trials.
+ Determine the overall response rate (ORR) defined as the proportion of all evaluable patients achieving a response as the best overall response at the time of progression.
+ Determine the duration or response (DoR) defined as the time from first response to LM progression.
+ Determine progression free survival (PFS) defined as the time from first treatment to date of LM progression or death from any cause.
+ Determine the overall survival (OS) define as the time from first treatment to date of death.

Primary Endpoints

+ Incidence & severity of adverse events (AE) & serious adverse events (SAE).
+ Incidence of dose limiting toxicities (DLT).

ClinicalTrials.gov: NCT05034497

^{186}RNL in Leptomeningeal Metastases

Disease Background

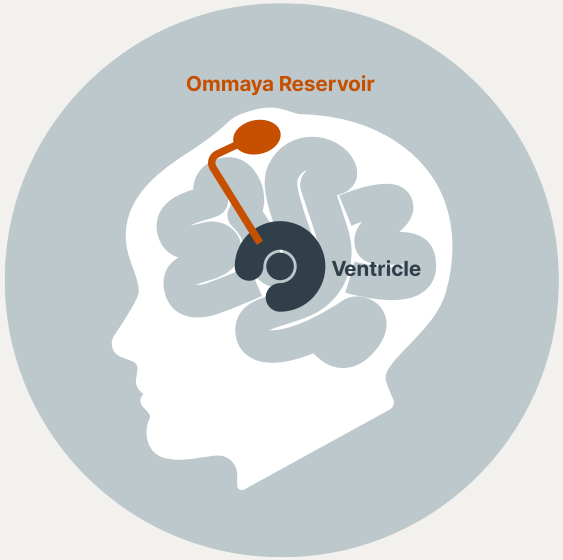
+ Leptomeningeal cancer, also known as carcinomatosis, is a cancer that starts in one part of the body spreads to the leptomeningeal lining of the brain & spinal cord surrounding the cerebrospinal fluid (CSF) space.

100 nm NanoLiposomes in Cerebrospinal Fluid (CSF)

+ Circulate feely throughout the CSF.
+ Migrate to meningeal surfaces where LM is located.
+ Have an extended half life - several weeks vs. hours with unencapsulated drugs.
+ Safe & effective in preclinical models

Phase 1 Clinical Trial

+ 2-part dose escalation trial
+ 2 sites enrolling
+ Planned 5 sites
+ 5 cc delivered via Ommaya reservoir
+ Feasibility & safety



Delivery via Standard Ommaya Reservoir

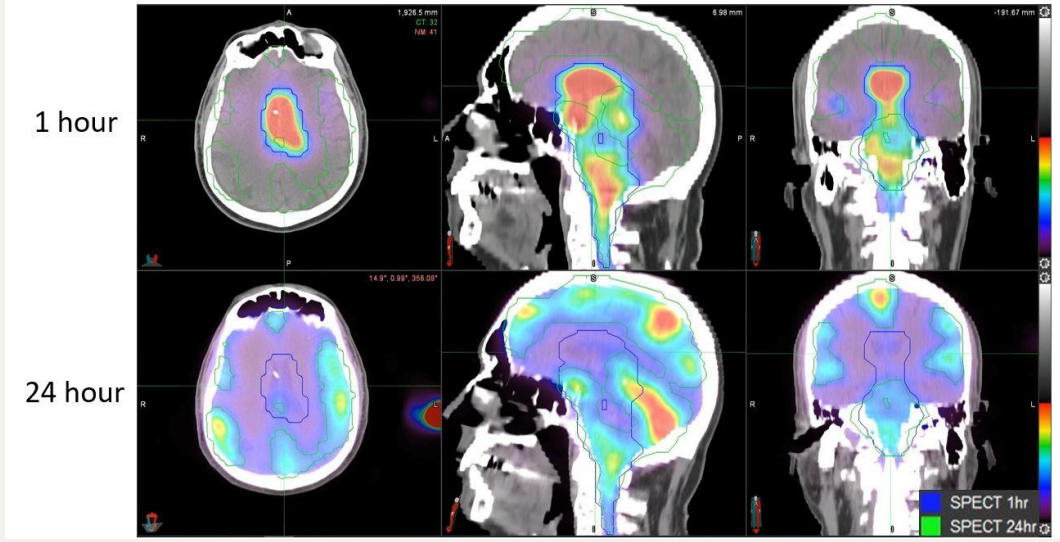
ReSPECT-LM Initial Patient Report

Cohort 1 / Subject 02-101: Post ^{186}RNL Treatment

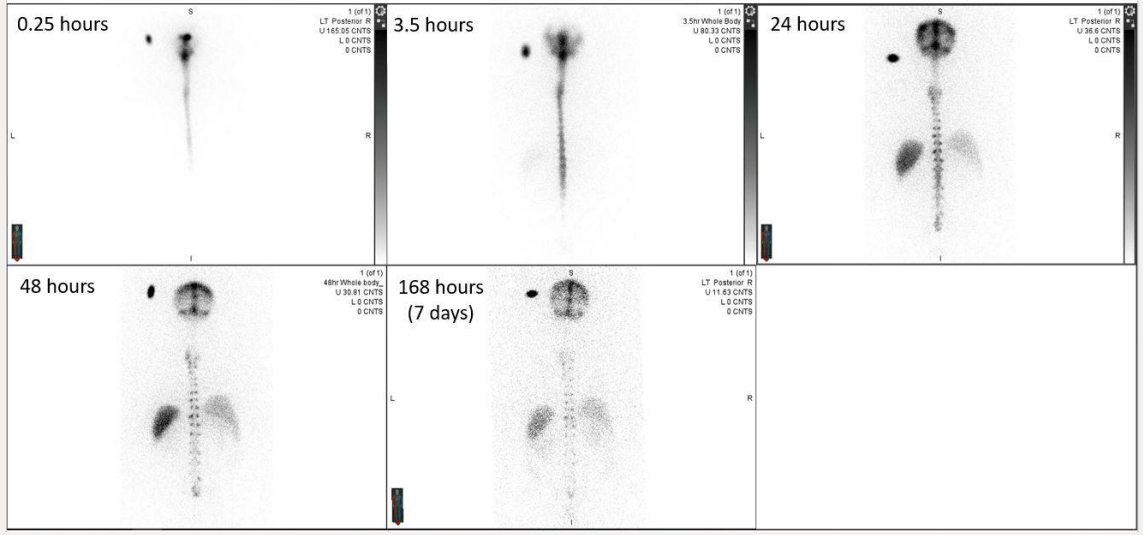
+ Rapid & full CSF circulation by 4 hours after treatment
+ Well-tolerated & no safety concerns (no DLTs) as of recent study visit
+ CSF isotopic activity through at least 7 days after treatment
+ Stable 90% reduction in tumor cells at 4 weeks

CSF Cell Based Assay	Predose	24 Hours	48 Hours
Tumor Cells Per mL	70.77	39.79	6.12

SPECT/CT Imaging Post-Treatment



Planar Imaging (Posterior-Anterior) Post-Treatment



Innovative, targeted radiotherapeutics for patients with liver tumors.

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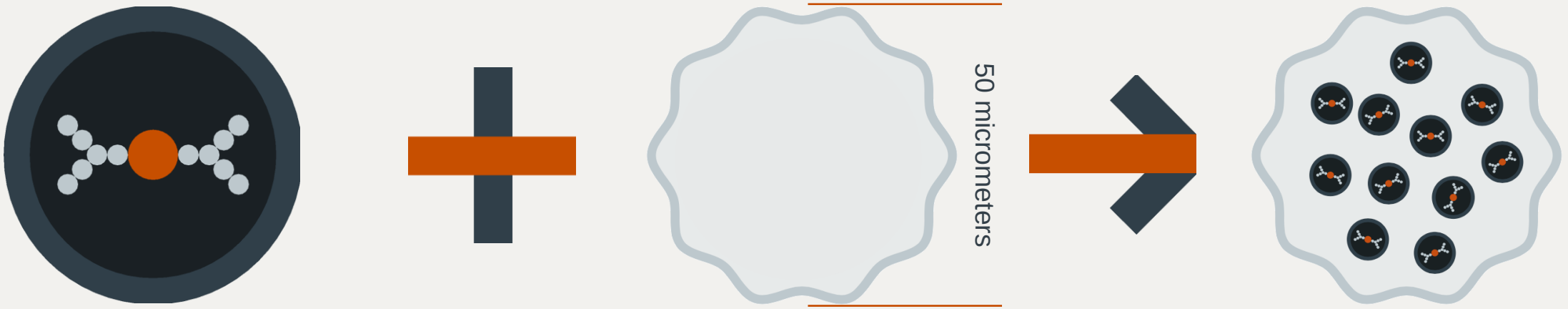
Second Investigational Drug: Rhenium-188 NanoLiposome Biodegradable Alginate Microsphere (^{188}RNL-BAM)

Proprietary Microscale Compound with a Unique Isotope

Rhenium-188

+ Dual energy emitter: beta (cytotoxic) & gamma (imaging)
+ Short average path length (3.1 mm): offers greater precision
+ Low dose rate: safer for normal tissues
+ High radiation density: overwhelms innate DNA repair mechanisms
+ Generator-produced for quick availability



Rhenium-188 NanoLiposome

Biodegradable Alginate Microsphere

Rhenium-188 NanoLiposome Biodegradable Alginate Microsphere

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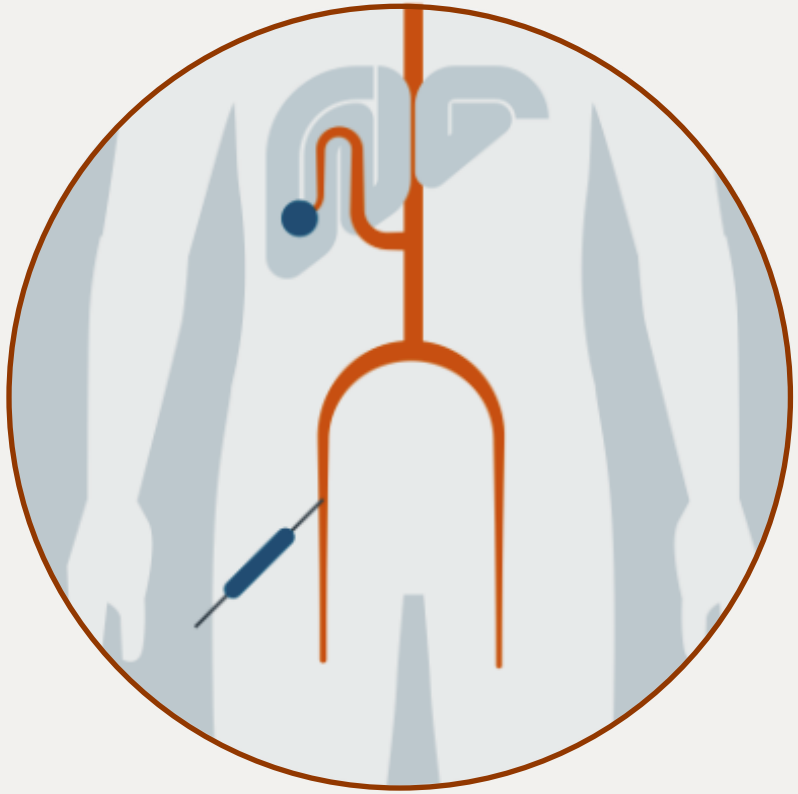
^{188}RNL-BAM Radioembolization Therapy

In Development as a Non-Surgical Locoregional Treatment Option for Solid Organ Tumors

The **Approach**

A single intra-arterial injection of ^{188}RNL-BAM in which biodegradable microspheres block the blood flow to the targeted solid organ tumors & simultaneously deliver a therapeutic payload of radiation.



The **Potential Advantages**

Compared to 2 radioembolization therapies currently available, ^{188}RNL-BAM may offer:

1) Biodegradable microspheres
2) Higher quality imaging
3) Work-up predictive of final clinical outcome
4) Shorter production time
5) Improved patient access
6) Higher margins
7) Better translate to other indications

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^{188}RNL-BAM Radioembolization Therapy: Initial Targets

Liver Cancer is the 6th Most Common & 3rd Deadliest Cancer

The Challenges

Hepatocellular Carcinoma

The most common type of primary liver cancer.

+ Incidence: 42k
+ 5-Year Survival: 20%

Metastatic Colorectal Cancer

A secondary form of liver cancer with a high level of severity.

+ Incidence: 150K
+ 5-Year Survival: 14%

The Opportunities

Pursue new & relevant routes of administration & mechanisms of delivery/action.

Extend the life of patients with liver cancer through a safer, more targeted, & convenient treatment approach.

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2022 Corporate Milestones

- ReSPECT-GBM Phase 2 / registrational trial for small to medium tumors
  - FDA CMC & clinical Type C meetings
  - Complete CMC activities for ^{186}RNL for GMP/registrational drug supply
  - Initiate enrollment
- ReSPECT-GBM Phase 1 dose escalation for large tumors
- ReSPECT-GBM ^{186}RNL multi-dose extension trial
- ReSPECT-LM Phase 1 initial cohort enrollment, feasibility assessment completion
- ReSPECT-PBC IND approval & Phase 1 trial initiation for pediatric ependymoma & high-grade glioma
- ^{186}RNL-BAM technology transfer & key CMC, FDA IND-enabling studies
- Complete additional preclinical studies
- Planned data presentations in H2 2022: ASCO/SNO Brain Mets, ESMO, EANO, SNO

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Capitalization Summary

Select Data as of March 31, 2022	
Cash	$21.2M
Common Shares Outstanding	22,197,635
Series U warrants	2,141,000

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+ Headquarters: Austin, Texas
+ Manufacturing: San Antonio, Texas
+ Nasdaq: PSTV
+ Corporate Website: PlusTherapeutics.com
+ ReSPECT™ Website: ReSPECT-Trials.com