Power and Precision in Cancer Radiotherapeutics

Marc Hedrick, MD, MBA
President & CEO

PLUS™ THERAPEUTICS

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 and Section 21E of the Securities Exchange Act and are usually identified by the use of words such as “anticipates,” “believes,” “estimates,” “expects,” “intends,” “may,” “plans,” “projects,” “seeks,” “should,” “will,” and 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 and Section 21E of the Securities Exchange Act of 1934, as amended, and 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 and prospects, which are based on the information currently available to us and on assumptions we have made. Although we believe that our plans, intentions, expectations, strategies and 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 and will be affected by a variety of risks and factors that are beyond our control.

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We believe in the critical importance in developing and delivering innovative, targeted radiotherapeutics for patients battling rare and CNS cancers.

Radiopharmaceuticals for Cancer

"Compelling Next-Gen Approach for Solid Tumors"


GUGGENHEIM

Biotechnology February 3, 2022

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

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

Dr. Andrew Brenner
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 and Difficult-to-Treat Cancers

Responsible for Substantial Morbidity and 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}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

=

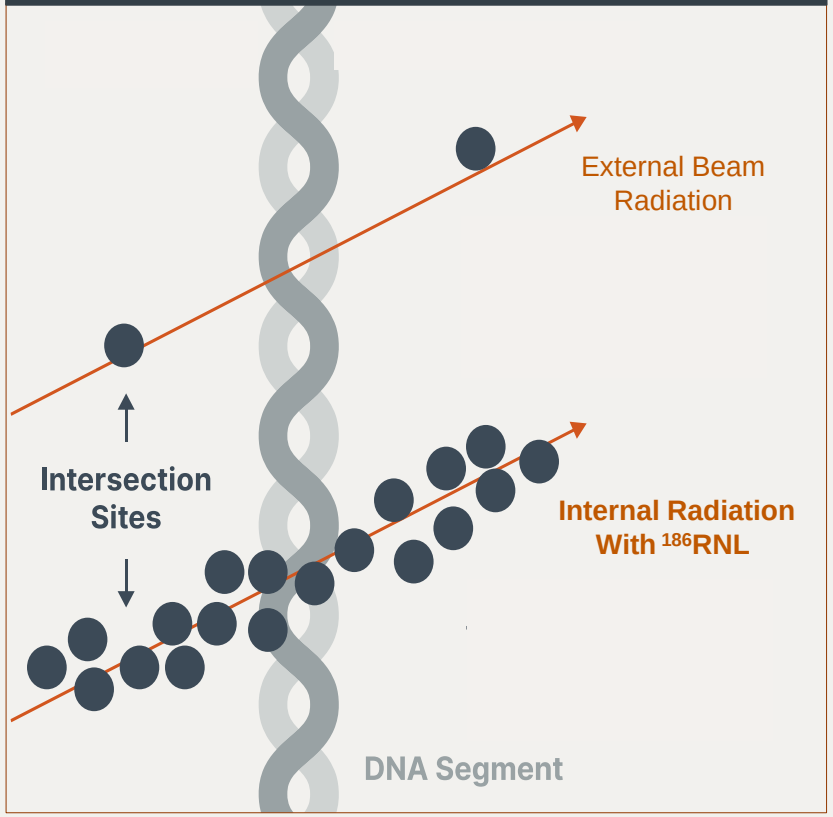
10^5 Ionizations

1000 damaged DNA bases
1000 single strand (SS) breaks
20-40 double strand (DS) breaks

Absorbed Radiation & Recurrent GBM

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

Radiation Mechanism of Action



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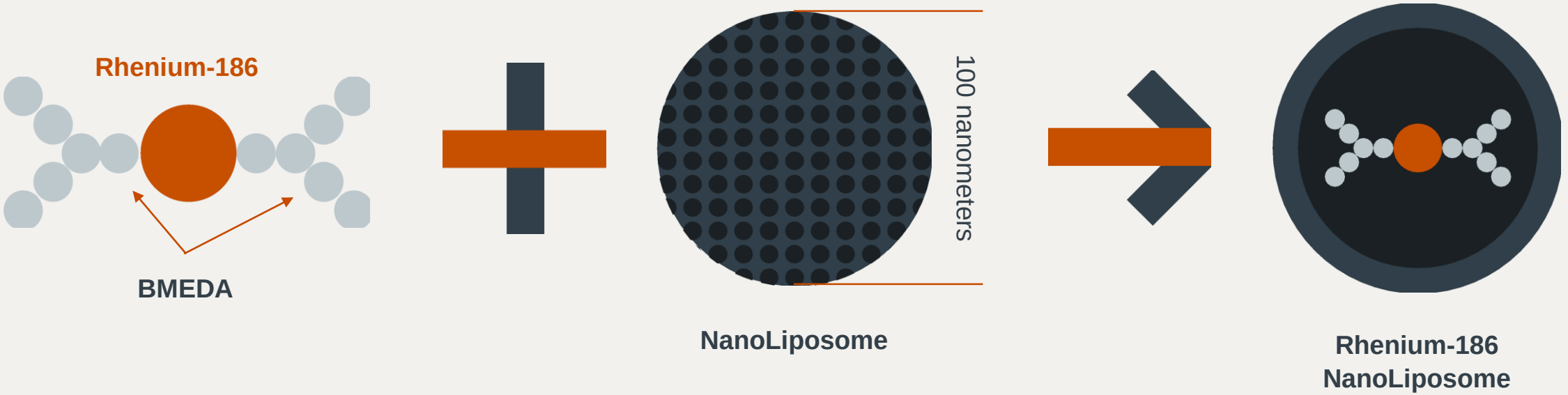
Lead Investigational Drug: Rhenium-186 NanoLiposome (^{186}RNL)

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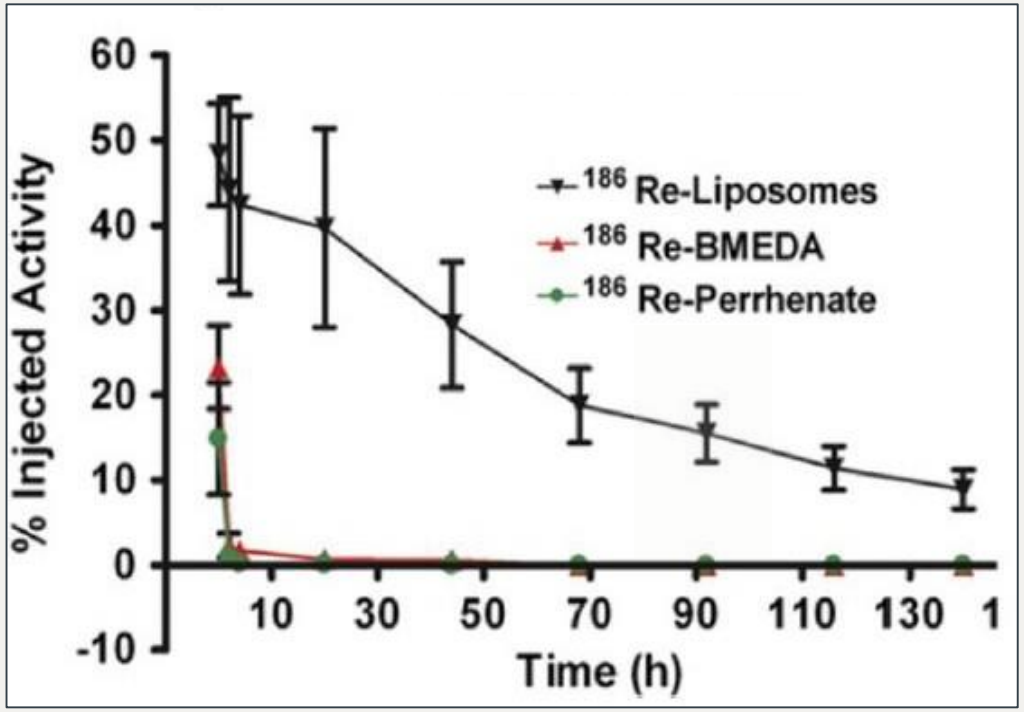
Spatiotemporal Behavior of ^{186}RNL Following Direct Brain Delivery

Prolonged Half-Life and Brain Retention



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

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

Plus Therapeutics Pipeline

Investigational Drug	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 Dose Escalation	Enrolling
	Recurrent Glioblastoma (22.3mCi)	Orphan Drug Fast Track	NIH/NCI Phase 2	Phase 2b/ registration	2022
	Recurrent Glioblastoma- multidose 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		Pre-clinical		IND Enabling CMC & Pre-clinical
	Liver Metastases		Pre-clinical		IND Enabling CMC & Pre-clinical

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

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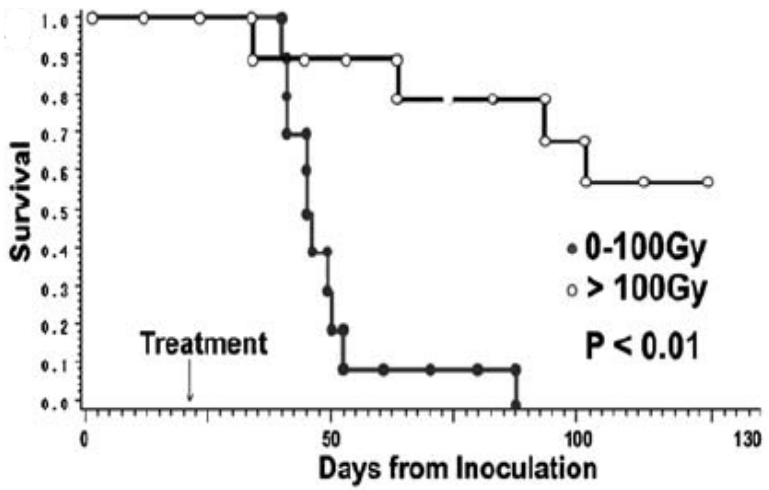
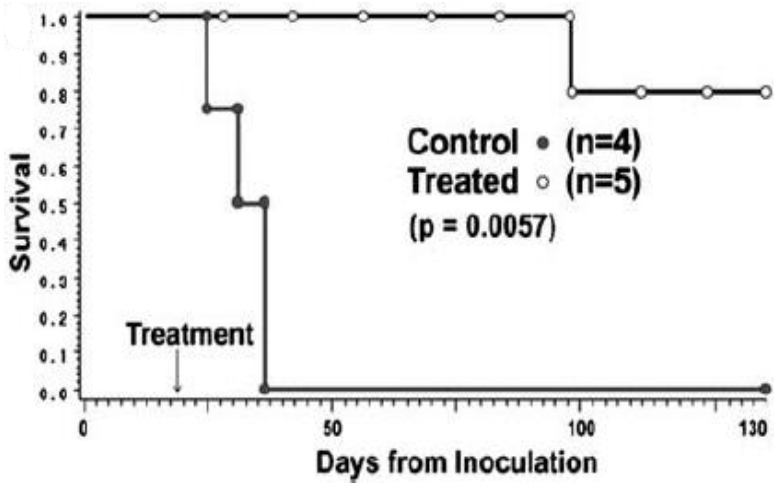
^{186}RNL Preclinical GBM Data

^{186}RNL Significantly Prolongs Survival in U87 & U251 Intracranial Xenograft Models

U87



U251



- Doses of up to 1,845 Gy were tolerated without weight loss or neurological deficit.
- No maximum tolerated dose of 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.

PLUS THERAPEUTICS

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

Phase 1/2 Clinical Trial Design

Multi-center, sequential cohort, open-label, volume and dose finding study of the safety, tolerability, and 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 and a subsequent cohort at the RP2D).
- Supported by a NIH/NCI grant through Phase 2.

ClinicalTrials.gov: NCT01906385

Trial Enrollment & Patient Demographics

Patient Demographics
(n = 22)

Gender	
Male	14 (64%)
Female	8 (36%)
Tumor Volume	Average = 8.3 cc; Range = 0.9 cc - 22.8 cc
Prior Treatments	Average = 1.7 treatments; Range = 1 – 3 treatments
Prior Bevacizumab	N = 5 patients
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%)

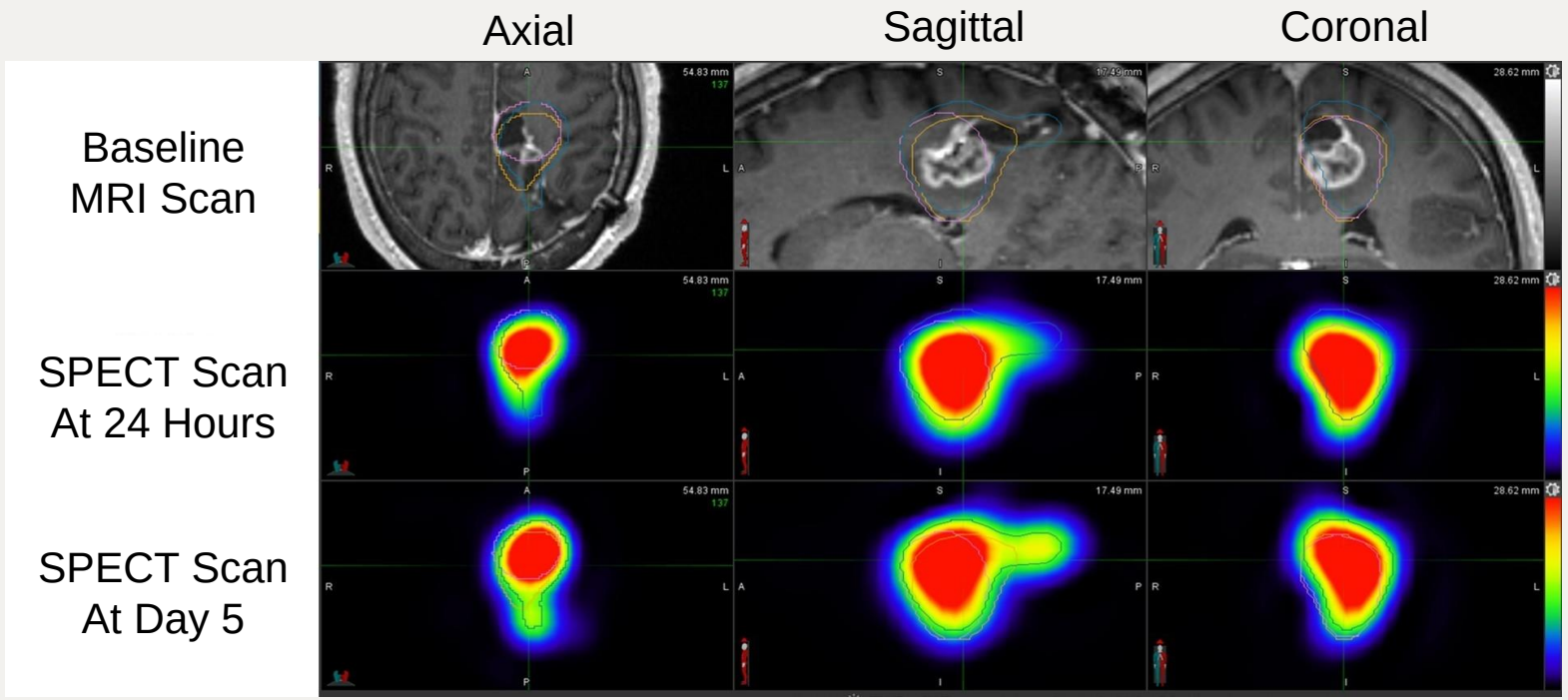
Dose Escalation Plan

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 and dose as cohort 6 but with increase in maximum flow rate to 20 microliters/minute

Case Study: Tumor Coverage and Retention

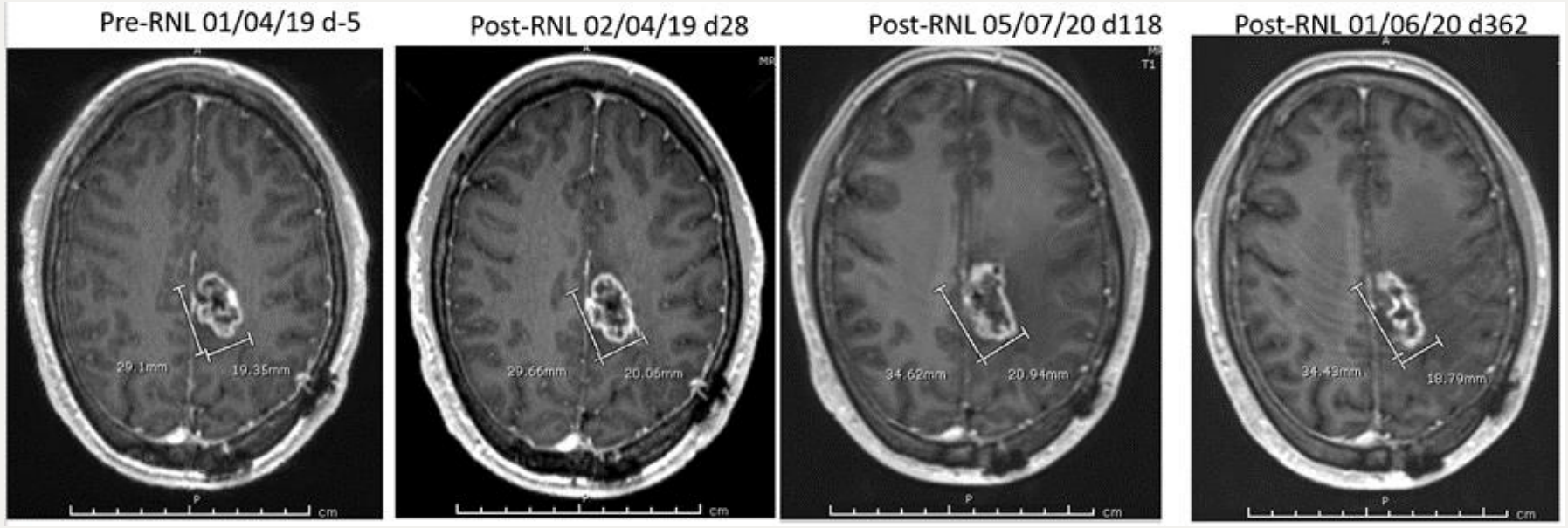
Cohort 5/Subject 01-014: MRI & SPECT/Radiation Dosimetry



+ 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 RNL™

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



- 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

Patient Safety

^{186}RNL Appears to be Safe and 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.
- The majority of AEs reported were mild or moderate (Grade 1 or 2) in intensity.
- Most AEs were considered causally unrelated to 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

Targeted Delivery

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

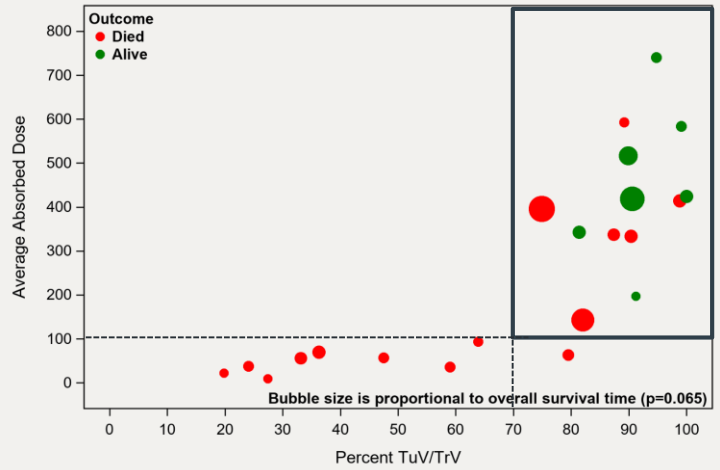
Cohort 1-4 (low dose & volume)

- 12 patients treated
- 5/12 42% > 100Gy

Cohort 5-7 (high dose & volume)

- 11 patients treated
- 9/11 82% > 100Gy

Therapeutic Threshold > 100Gy

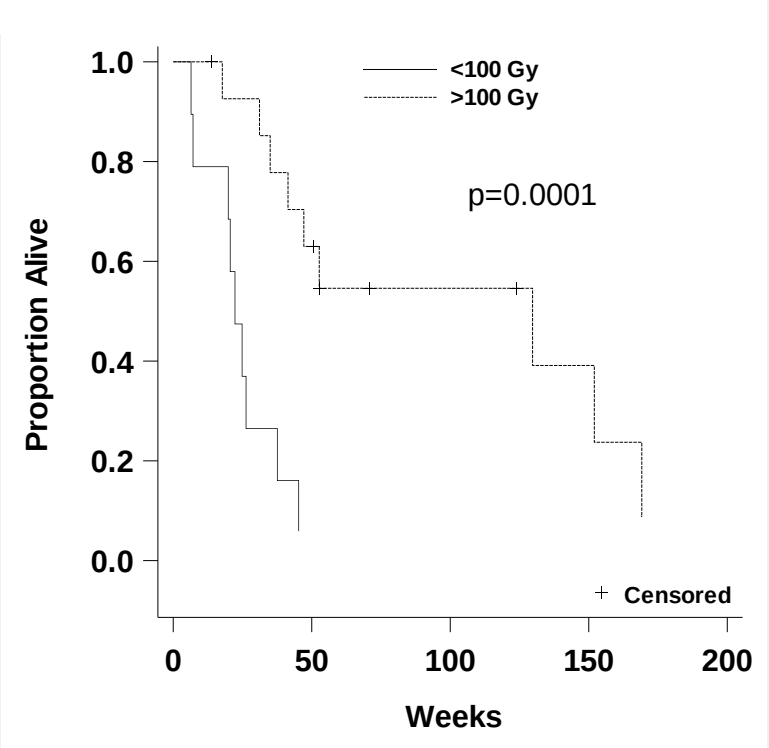


P = 0.065

ReSPECT-GBM Updated Efficacy Data Since SNO 2021

Current Enrollment is 23 in 7 Dosing Cohorts (Feb 2022)

Kaplan Meier Analysis



Overall Survival Data, N = 23
(Stratification by Radiation Dose, OS in weeks)

Gy	Median	95% CI	Mean±SE
<100 Gy	**22.3**	6.4, 45.3	24.6±4.8
>100 Gy	**129.7**	35, 169.1	100.8±19

>100Gy- 4 patients remain alive, none >100Gy

* Best comparative recurrent GBM published data:
~700 pts. meta analysis of mono therapy w/ Bevucizamab

Overall Survival = 32.1weeks

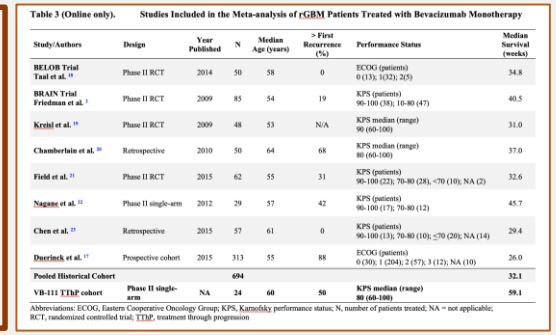


Table 3 (Online only). Studies Included in the Meta-analysis of rGBM Patients Treated with Bevacizumab Monotherapy

Study/Authors	Design	Year Published	N	Median Age (years)	> First Recurrence (%)	Performance Status	Median Survival (weeks)
BELOB Trial Taal et al. [18]	Phase II RCT	2014	50	58	0	ECOG (patients) 0 (13); 1(32); 2(5)	34.8
BRAIN Trial Friedman et al. [3]	Phase II RCT	2009	85	54	19	KPS (patients) 90-100 (38); 10-80 (47)	40.5
Kreisl et al. [19]	Phase II RCT	2009	48	53	N/A	KPS median (range) 90 (60-100)	31.0
Chamberlain et al. [20]	Retrospective	2010	50	64	68	KPS median (range) 80 (60-100)	37.0
Field et al. [21]	Phase II RCT	2015	62	55	31	KPS (patients) 90-100 (22); 70-80 (28), <70 (10); NA (2)	32.6
Nagane et al. [22]	Phase II single-arm	2012	29	57	42	KPS (patients) 90-100 (17); 70-80 (12)	45.7
Chen et al. [23]	Retrospective	2015	57	61	0	KPS (patients) 90-100 (13); 70-80 (10); <70 (20); NA (14)	29.4
Duerinck et al. [17]	Prospective cohort	2015	313	55	88	ECOG (patients) 0 (30); 1 (204); 2 (57); 3 (12); NA (10)	26.0
Pooled Historical Cohort			694				32.1
VB-111 TThP cohort	Phase II single-arm	NA	24	60	50	KPS median (range) 80 (60-100)	59.1

Abbreviations: ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; N, number of patients treated; NA = not applicable; RCT, randomized controlled trial; TThP, treatment through progression

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

ReSPECT-GBM Clinical Trial

Summary & Next Steps

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

Recommended Phase 2 Dose				
Cohort	**Infused Volume (mL)**	**Total ^{186}RNL Activity (mCi)**	**Concentration (mCi/mL)**	**Average Absorbed Dose (Gy)**
6	8.80	22.3	2.5	584

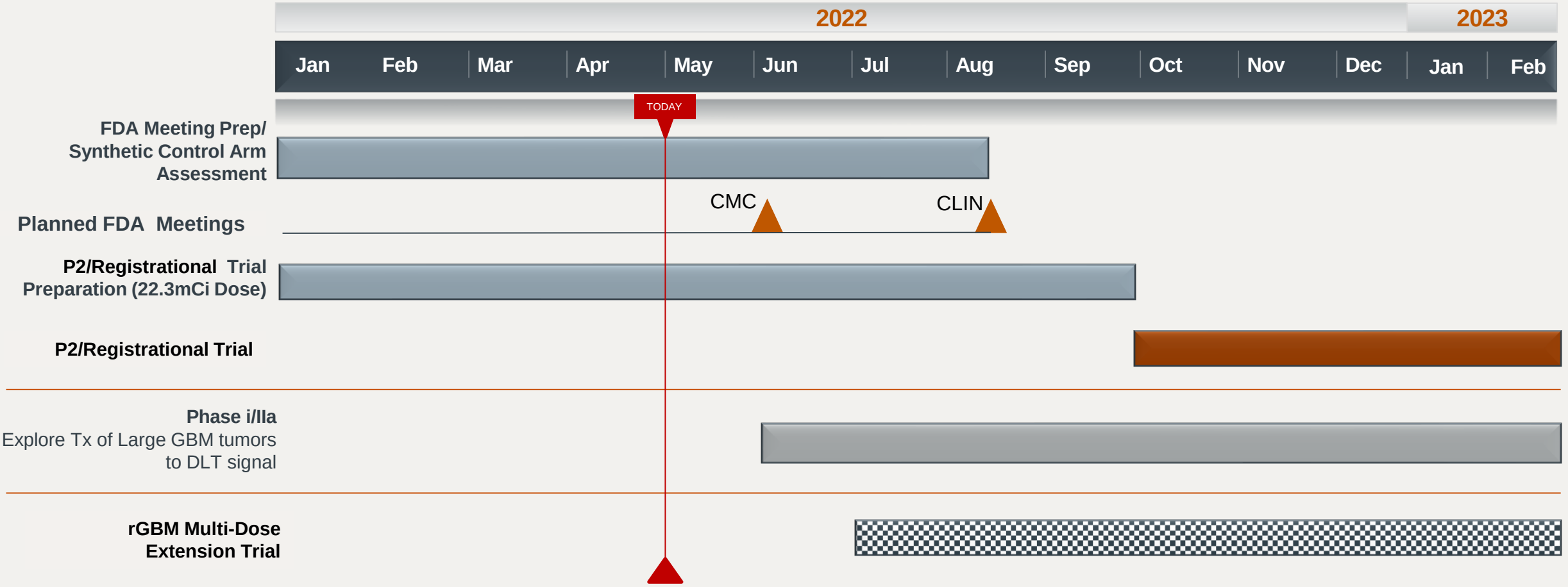
Phase 2b/registrational trial

Patients: ~100
Primary Endpoint: Overall survival
Randomization/Control: >1:1, synthetic control arm, MD preference
Timing: Q4 2022 start, enrollment ~18 months
Cost: ~ $10M

- 3 Part Plan:

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

2022 ReSPECT-GBM Clinical Timeline



ReSPECT-LM Trial Protocol- Now Enrolling

Leptomeningeal Metastases

A Two-Part, Multicenter 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 Metastasis

Primary Objectives

To 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).

Development collaboration with BioCept for CSF Biomarker Analysis

Secondary Objectives

Characterize the pharmacokinetic & dosimetry profile of a single dose of ^{186}RNL when administered intraventricularly via Ommaya reservoir.

Develop a multiple dosing strategy of ^{186}RNL 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.

Endpoints

Primary Endpoints

Incidence & severity of adverse events (AE) & serious adverse events (SAE)

Incidence of dose limiting toxicities (DLT)

^{186}RNL in Leptomeningeal Cancer

Disease Background

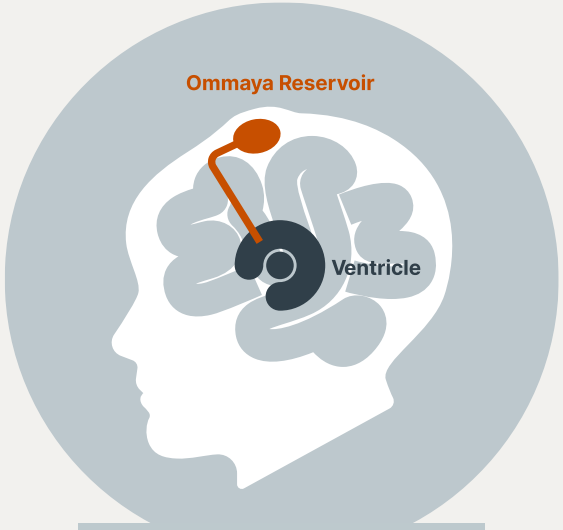
+ Leptomeningeal cancer, also known as carcinomatosis, is a cancer that starts in one part of the body spreads to the leptomeningeal lining of the brain and spinal cord surrounding the cerebrospinal fluid (CSF) space.

100 nm NanoLiposomes in CSF

+ Circulate feely throughout the CSF.
+ Migrate to meningeal surfaces where LMC 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 Omaya reservoir
+ Feasibility & safety



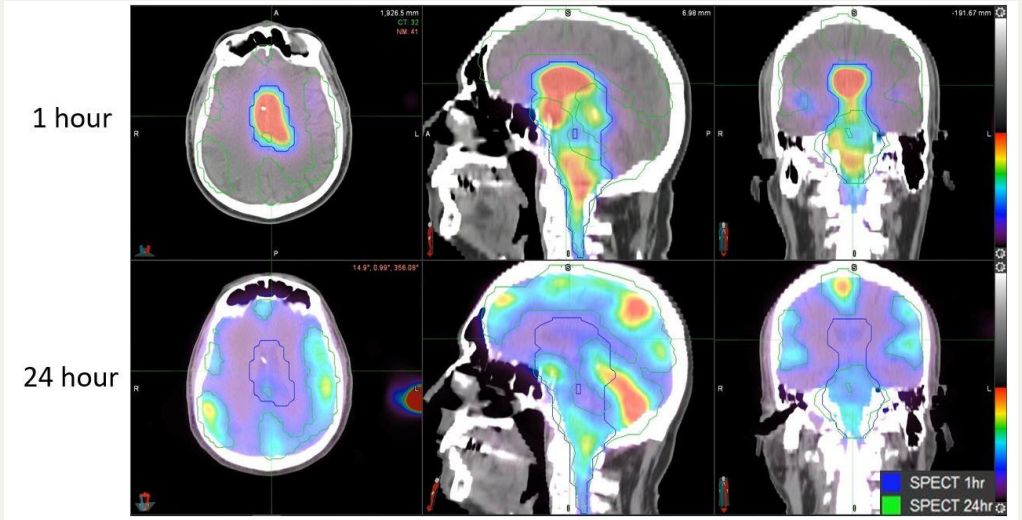
Delivery via Standard Ommaya Reservoir

ReSPECT-LM Trial- Initial Patient Report

ReSPECT-LM Phase 1 Clinical Trial Data: Subject 02-101 Post ^{186}RNL Treatment

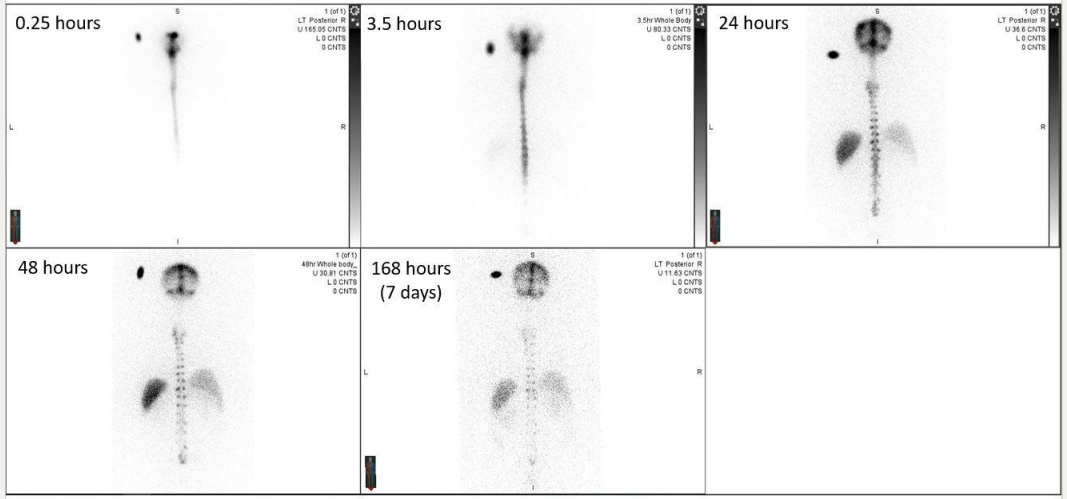
- Rapid and full CSF circulation by 4 hours after treatment
- Well-tolerated & no safety concerns (no DLTs) as of recent study visit
- CSF isotopic activity through at least 7 days after treatment
- Stable 90% reduction in tumor cells at 4 weeks

Spect CT



SPECT/CT images of patient brain at 1 and 24 hours post-186RNL administration

Planar Imaging Post ^{186}RNL Treatment



Posterior – Anterior Planar Image Summary

CSF Liquid Biopsy Data

CSF Cell Based Assay	Predose	24 Hours Post ^{186}RNL	48 Hours Post ^{186}RNL
Tumor Cells (cells per mL)	70.77	39.79	6.12

Innovative, targeted radiotherapeutics for patients with liver tumors.

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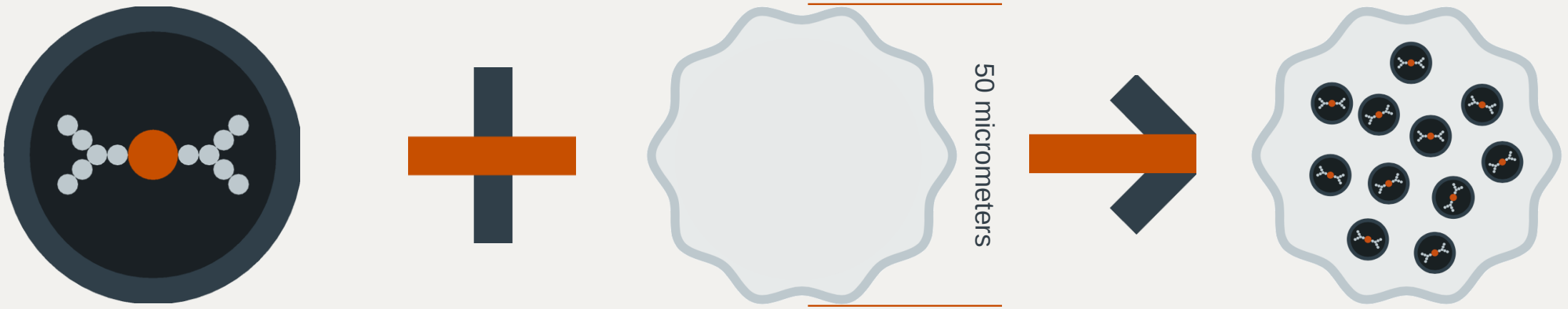
Second Investigational Drug: Rhenium-188 NanoLiposome Biodegradable Alginate Microsphere (^{188}RNL-BAM)

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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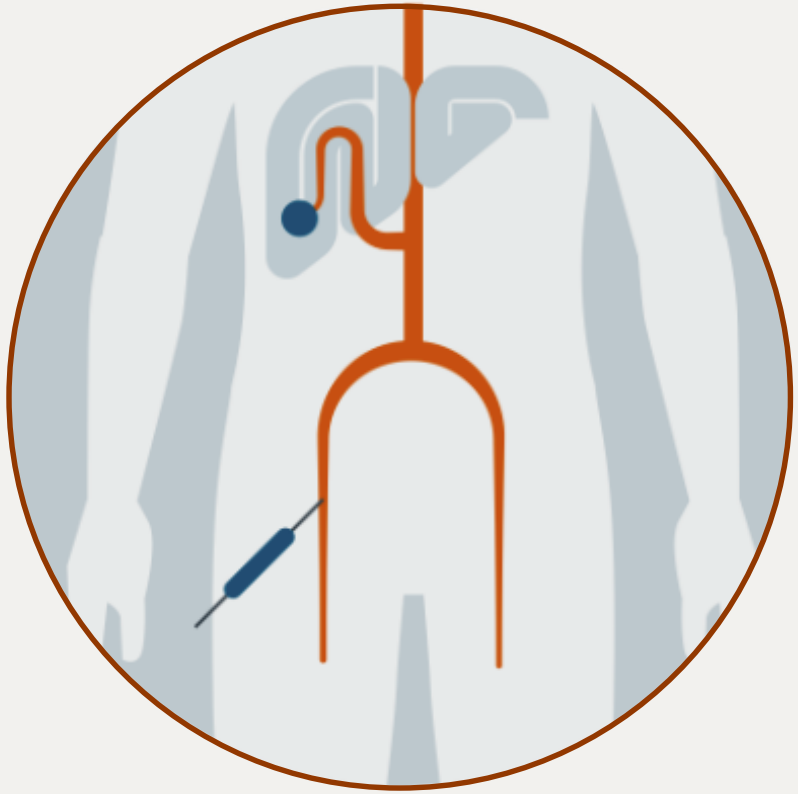
^{188}RNL-BAM Radioembolization Therapy

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 and 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 and 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 and relevant routes of administration and mechanisms of delivery/action.

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

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2022 Corporate Milestones

- Phase 2/ registrational ReSPECT-GBM trial for small to medium sized tumors
  - FDA CMC & Clinical Meetings
  - Complete CMC activities for ^{186}RNL for GMP/registrational drug supply
  - Initiate ReSPECT-GBM P2/ registrational trial
- ReSPECT-GBM Phase I trial of ^{186}RNL, dose escalation for large tumors
- Initiate ReSPECT-GBM multidose extension trial
- Complete initial cohort enrollment, feasibility assessment in ReSPECT-LM Phase 1 trial
- Obtain FDA IND approval and initiate ReSPECT-PBC Phase 1 trial of ^{186}RNL
- Complete technology transfer & key CMC, FDA IND-enabling studies for ^{188}RNL-BAM asset
- Complete additional preclinical studies
- 2022 Planned data presentations: SNMMI, SNO Brain Mets, ESMO, EANO, SNO

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Capitalization Summary

Select Data

As of March 31, 2021	
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