# Power and Precision in Cancer Radiotherapeutics

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# 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.

Risks and uncertainties for Plus include, but are not limited to: an inability or delay in obtaining required regulatory approvals for product candidates, which may result in unexpected cost expenditures; risks inherent in drug development in general; uncertainties in obtaining successful clinical results for product candidates and unexpected costs that may result therefrom; failure to realize any value of certain product candidates developed and being developed in light of inherent risks and difficulties involved in successfully bringing product candidates to market; inability to develop new product candidates and support existing products; the approval by the FDA and any other similar foreign regulatory authorities of other competing or superior products brought to market; risks resulting from unforeseen side effects; risk that the market for the combined company’s products may not be as large as expected; inability to obtain, maintain and enforce patents and other intellectual property rights or the unexpected costs associated with such enforcement or litigation; inability to obtain and maintain commercial manufacturing arrangements with third-party manufacturers or establish commercial scale manufacturing capabilities; loss of or diminished demand from one or more key customers or distributors; unexpected cost increases and pricing pressures; economic recession and its negative impact on customers, vendors or suppliers; uncertainties of cash flows, expenses and inability to meet working capital needs; and other risks and uncertainties detailed in the risk factors section of Plus’ Form 10-K and Forms 10-Q filed with the SEC, as well as other filings Plus makes with the SEC from time-to-time. Many of these factors that will determine actual results are beyond Plus’ ability to control or predict. Plus disclaims any obligation to update information contained in these forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

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

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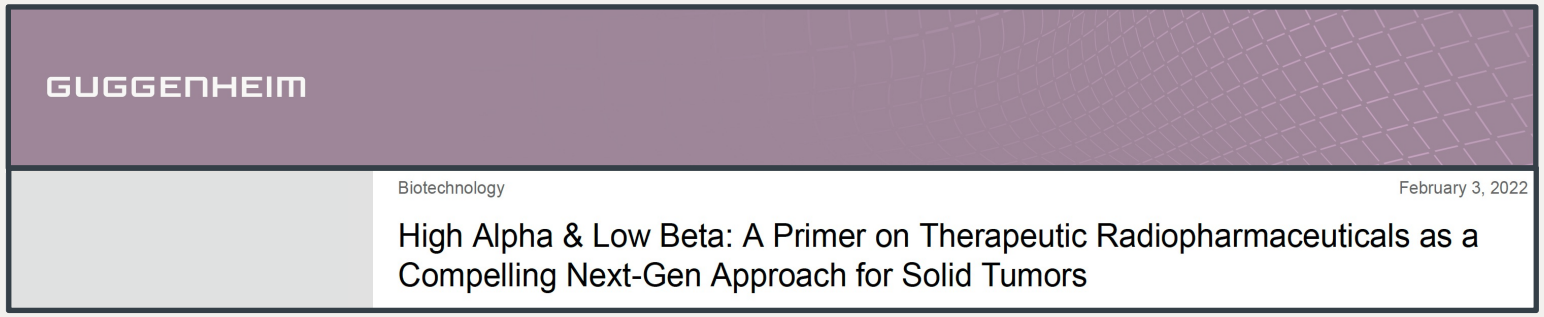
# Radiopharmaceuticals for Cancer




*"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

*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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# Targeted Radiation Therapy & Mechanism of Action

## Types of Radiation

External Beam Radiation

Internal Targeted Radiation

## Absorbed Radiation & DNA Damage

**1 Gray Radiation**

=

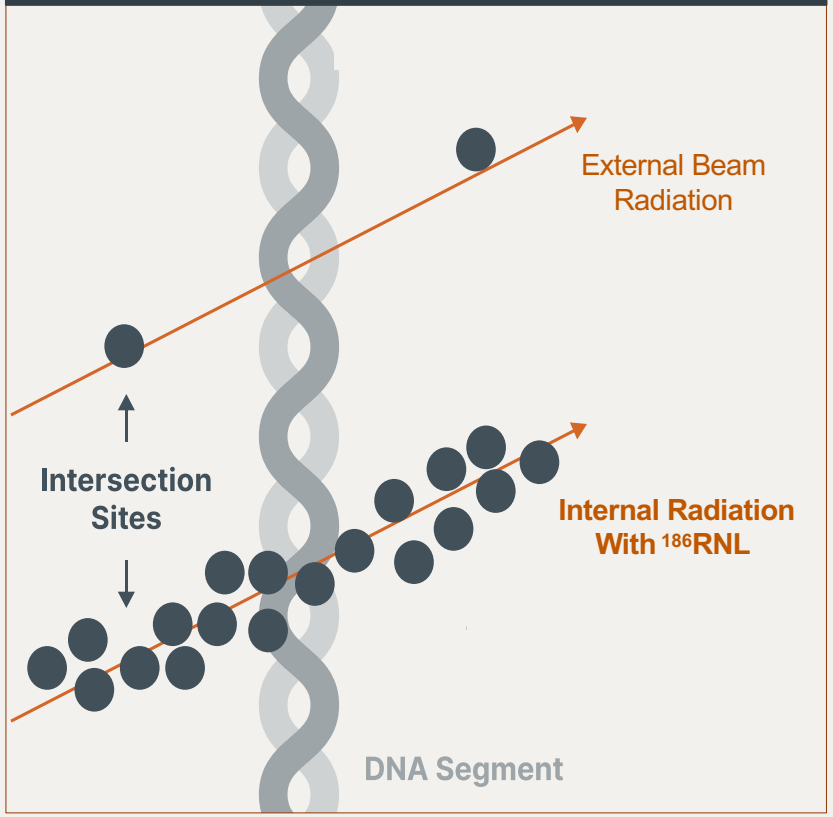
$10^5$ Ionizations

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 (35Gy) | 700 - 1,400 |
| **$^{186}$RNL (600 Gy)** | **12,000 - 24,000** |

## Radiation Mechanism of Action

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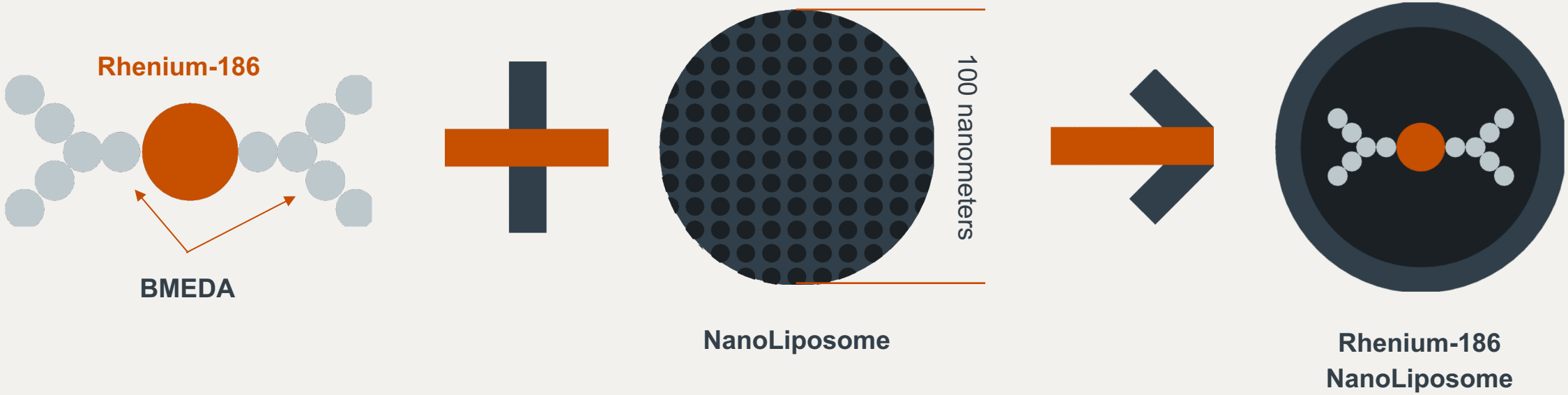
# Lead Investigational Drug: Rhenium-186 NanoLiposome ($^{186}$RNL)

## Rhenium-186

+ 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

## Proprietary Nanoscale Compound with a Unique Isotope

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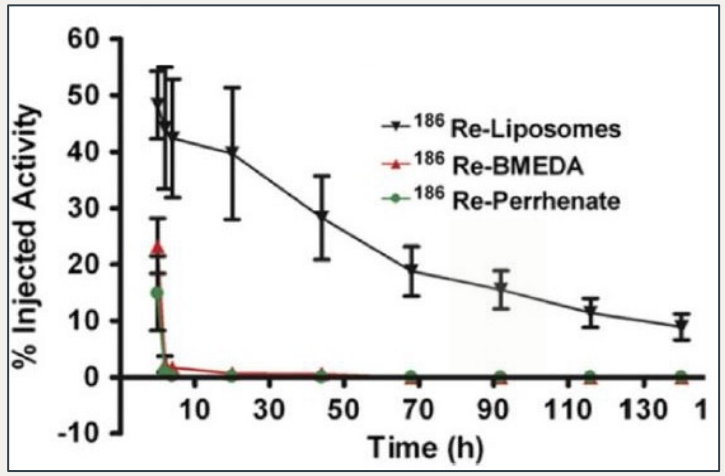
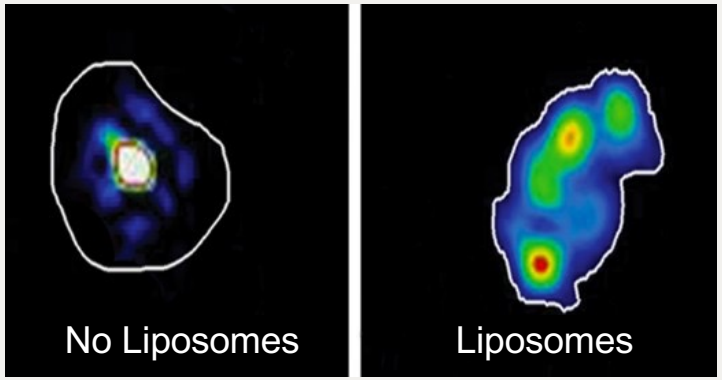
# Spatiotemporal Behavior of $^{186}$RNL Following Direct Brain Delivery

## 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.

**Reduced Tumor Dispersion**
Liposomal encapsulation significantly extends Rhenium-186 retention within the tumor and therefore improves dispersion characteristics in tissues.

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

# 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

## FACTS ABOUT CNS TUMORS

**Glioblastoma:** deadliest, most common brain cancer in adults

**Leptomeningeal Metastases:** late complication in 5% of cancer patients

**Pediatric Brain Cancer:** 2nd most common type of cancer in children

## FACTS ABOUT LIVER 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

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*Sources: CBTRUS Statistical Report, NBTS, NCI*

# Plus Therapeutics Pipeline

| Investigational Drug | Indication | FDA Designation(s) | External Funding | Stage | Status |
|---|---|---|---|---|---|
| $^{186}$RNL | Recurrent Glioblastoma | Orphan Drug<br>Fast Track | NIH/NCI to Phase 2 | Phase 1<br>Dose Escalation | Enrolling |
| | Recurrent Glioblastoma (22.3 mCi) | Orphan Drug<br>Fast Track | NIH/NCI to Phase 2 | Phase 2 | 2022 |
| | Recurrent Glioblastoma- retreatment | | | | Submitted 2021 FDA |
| | Leptomeningeal Metastases | Fast Track | — | Phase 1 | Enrolling |
| | Pediatric Brain Cancer | — | — | Pre-IND | IND Submission 2022 |
| $^{188}$RNL-BAM | Hepatocellular Carcinoma | Pre-clinical | | | IND Enabling<br>CMC & Pre-clinical |
| | Liver Metastases | Pre-clinical | | | IND Enabling<br>CMC & Pre-clinical |

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

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# Glioblastoma

## A Rare, Incurable, and Fatal Brain Cancer with No Good Treatment Options


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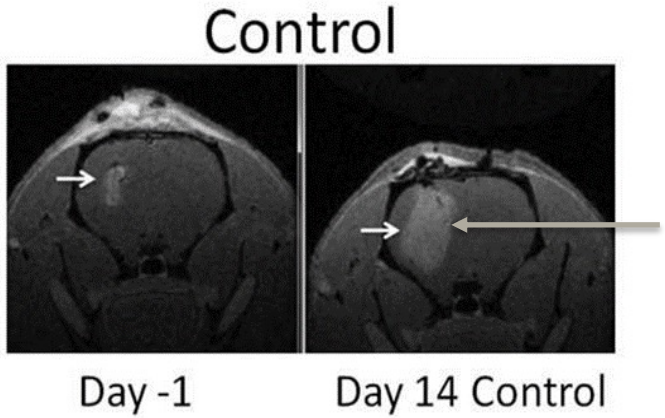
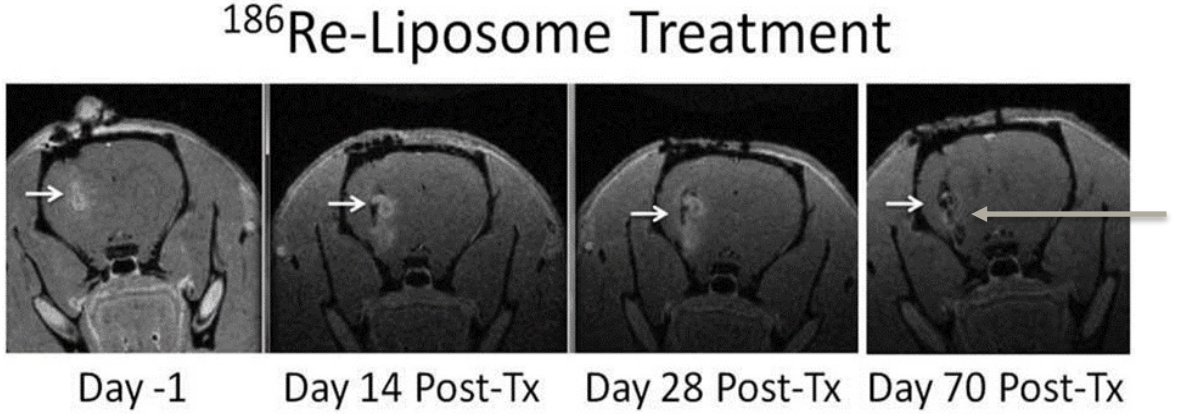
# $^{186}$RNL Preclinical GBM Data

## Tumor Regression in U87 & U251 Intracranial Xenograft Models




Tumor growth & expansion in untreated control animals with brain cancer.




Tumor regression in $^{186}$RNL treated brain cancers.

- Bioluminescence assay showed many of the treated animals had a loss of activity to background levels suggesting complete eradication of the tumor.
- MRI analysis (above) supported the observation of tumor eradication.
- Blinded histologic evaluation by neuropathologist showed no residual disease.

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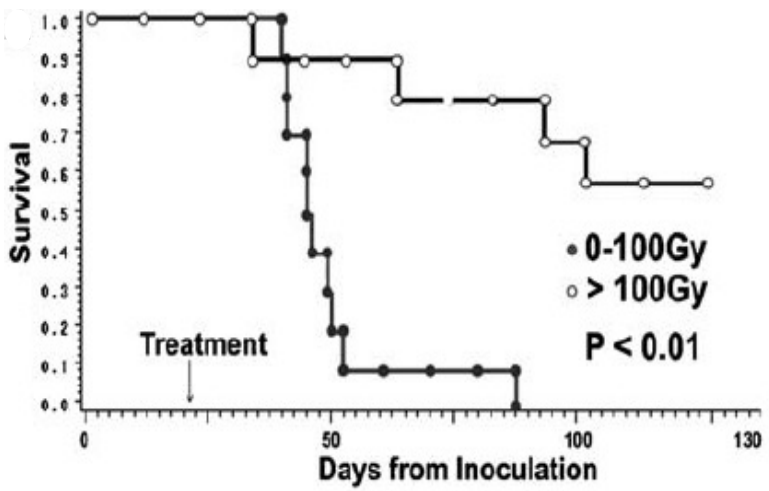
Source: Phillips, W. et al Advanced Drug Delivery Reviews 2014

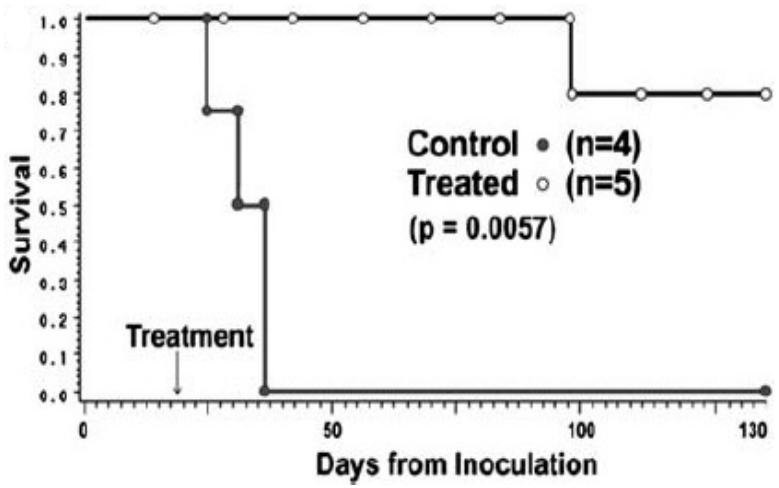
# $^{186}$RNL Preclinical GBM Data

## $^{186}$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.

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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.

National Institutes of Health

UT Health San Antonio

UT Southwestern Medical Center

The University of Texas MD Anderson Cancer Center

Making Cancer History

ClinicalTrials.gov: NCT01906385

# $^{186}$RNL for Recurrent Glioblastoma

## Potential Advantages Compared to External Beam Radiation Therapy


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# 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%) |

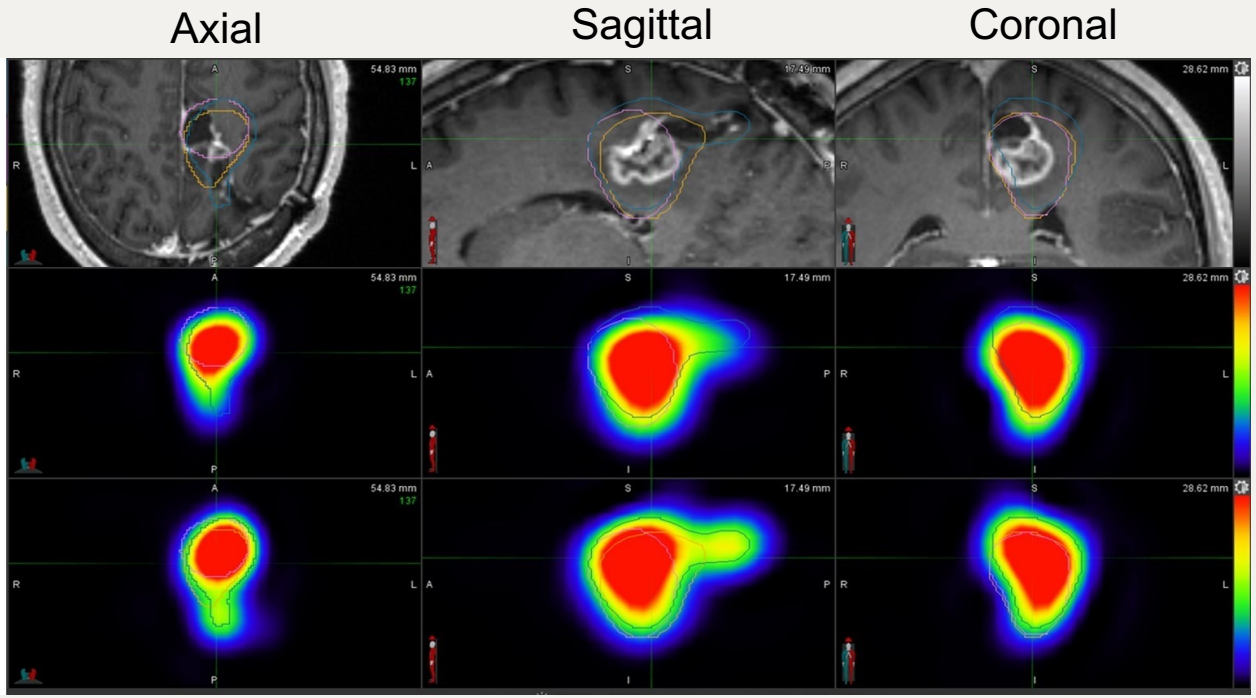
## Updated Trial Enrollment

| 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

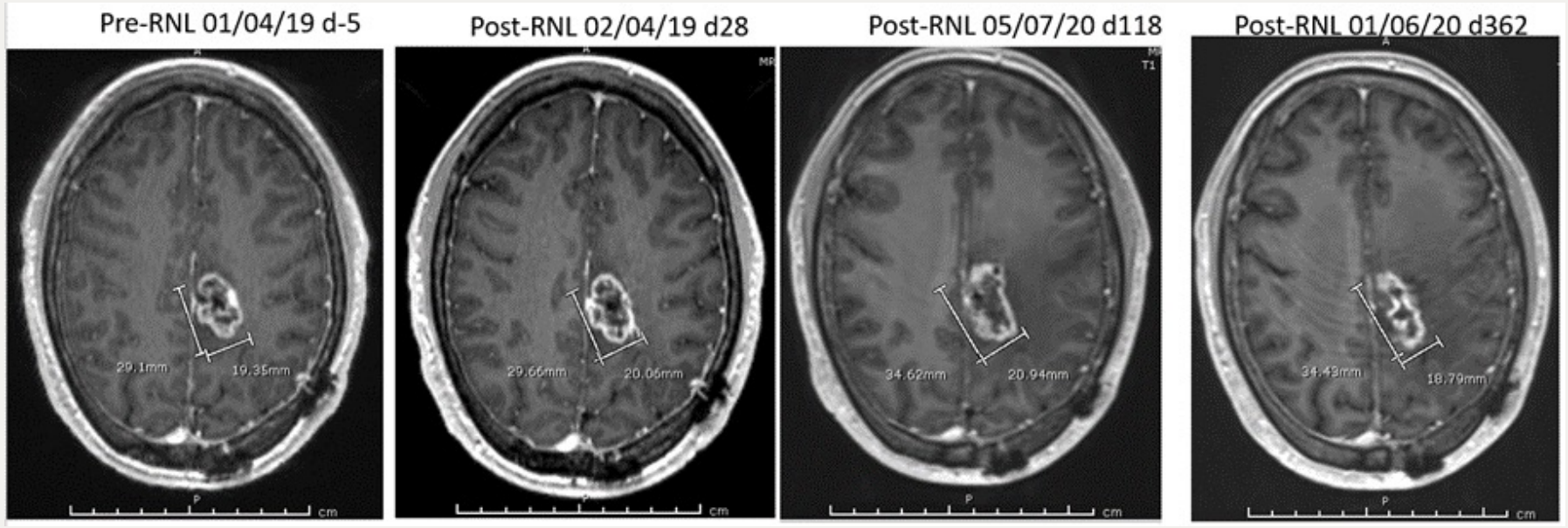
## Cohort 5/Subject 01-014: MRI & SPECT/Radiation Dosimetry




- 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)

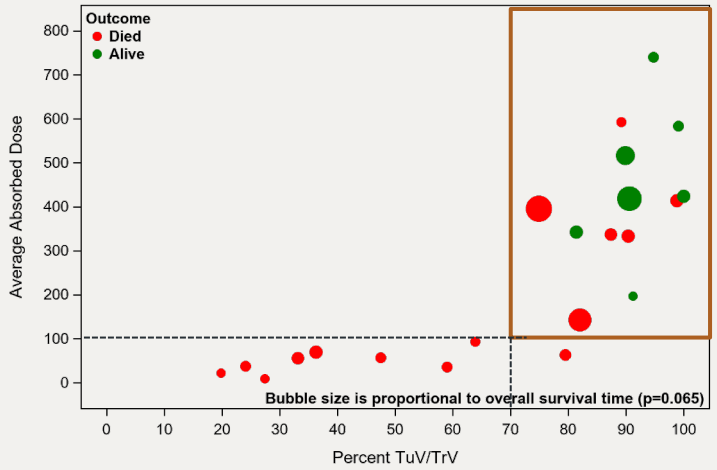
## A Technique that Generates a Pressure Gradient To Deliver Therapeutics Through the Interstitial Spaces of the Central Nervous System

| Evolution of Key Delivery Parameters | Absorbed Radiation Dose Correlates with OS | Delivery Reliability in Later Cohorts |
|---|---|---|

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** |

Therapeutic Threshold > 100Gy




P = 0.065

**Cohort 1-4**

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

**Cohort 5-7**

+ 12 patients treated
+ 9/11 82% > 100Gy

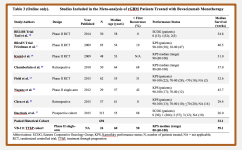
# ReSPECT-GBM Updated Efficacy Data Since SNO 2021

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

**Overall Survival Data, N=23**
(Stratification by Radiation Dose & Cohort)

| Dose | Cohort | N | OS Weeks Median | OS Weeks Mean | Alive | FPI | LPI | Duration |
|---|---|---|---|---|---|---|---|---|
| >100 Gy | 1 to 5 | 8 | 82 | 88 | 2 | 3/10/15 | 7/22/20 | 280 |
| >100 Gy | 6 to 7 | 6 | 44 | 40 | 5 | 10/22/20 | 1/12/22 | 64 |
| | **Subtotal** | **14** | **46** | **67** | **7** | | | |
| <100 Gy | 1 to 5 | 7 | 22 | 23 | 0 | 3/10/15 | 7/22/20 | 280 |
| <100 Gy | 6 to 7 | 2 | 23 | 23 | 0 | 10/22/20 | 1/12/22 | 64 |
| | **Subtotal** | **9** | **22** | **23** | **0** | | | |

***Mono Tx Bevucizamab 32.1**



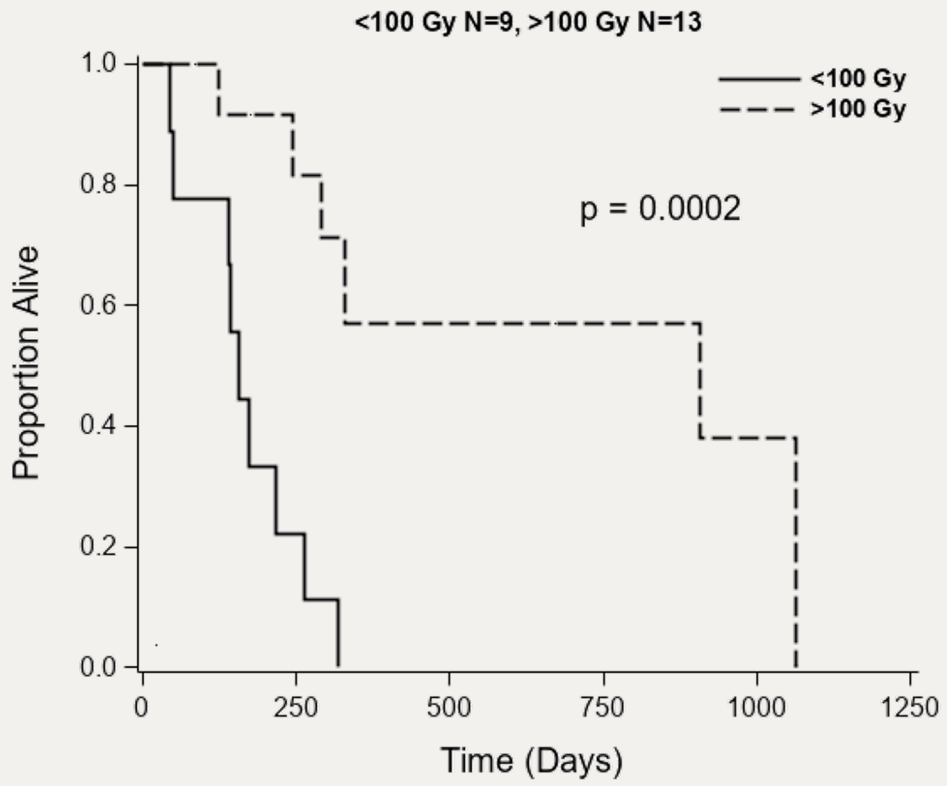
**Key Points**

- Cohorts 1-5 represent patients treated from 2015 to 2020
  - 2 pts. still alive
  - The median & mean survival is between 2-3 times monotherapy with Bevacizumab
- Cohorts 6-7 have been treated recently, since October 2020
  - Low overall survival related to recent enrollment
  - 5/6 still alive
- Empirically, patients with rGBM receiving >100 Gy survive longer than those receiving <100 Gy & longer than those receiving monotherapy bevacizumab

* *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

## Comparative OS Based on Average Absorbed Radiation Dose



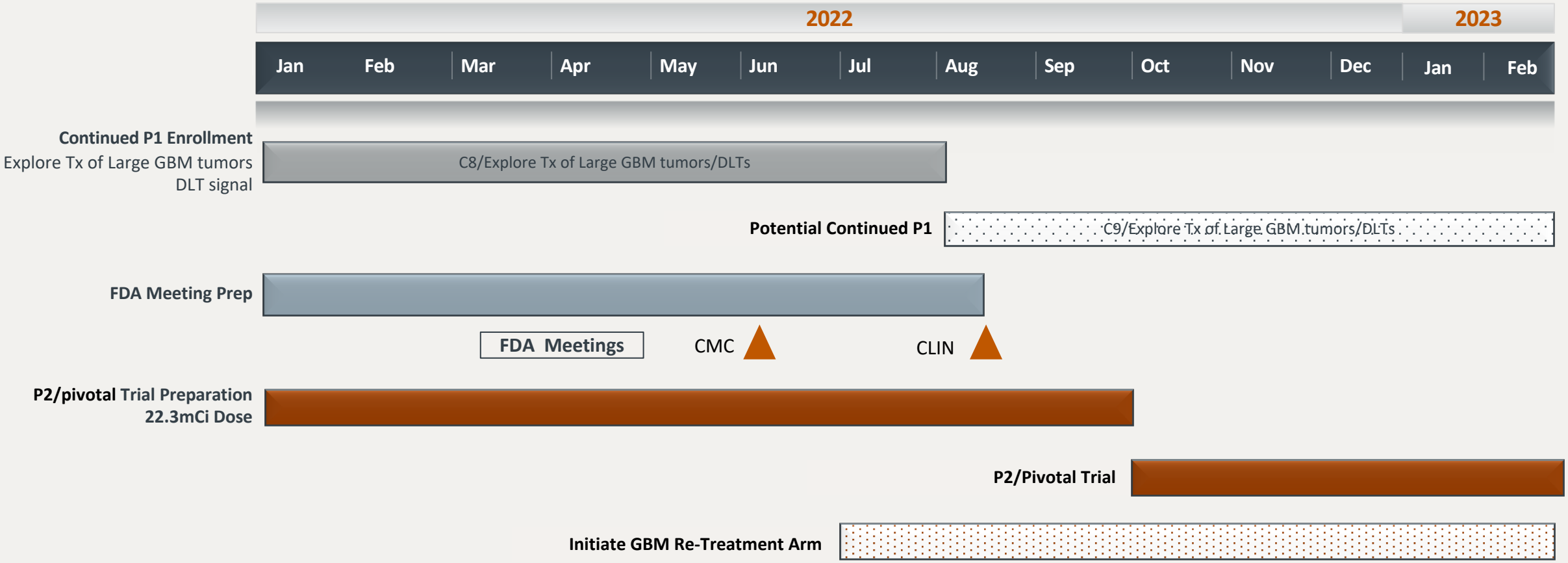

**Summary**

- No DLTs, favorable safety & tolerability profile
- Delivery > 100Gy radiation correlates with increased OS
- Recent cohorts (5-7) > 80% delivery success
- Radiation distribution volume in cohort 6/7 treats >50% market of rGBM
- At cohort 6/7 level

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

- Plan: Take cohort 6/7 22.3mCi dose to Phase 2/pivotal

# 2022 ReSPECT-GBM Clinical Timeline



# $^{186}$RNL in Leptomeningeal Cancer

## Disease Background

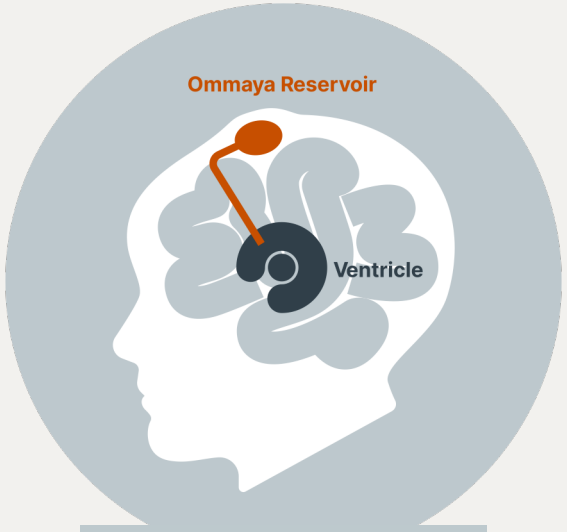
+ Leptomeningeal cancer, also known as carcinomatosis, is a cancer that starts in one part of the body spreads to the leptomeningeal lining of the brain and spinal cord surrounding the cerebrospinal fluid (CSF) space.

## 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
+ 1st site at UTSW enrolling
+ Planned 5 sites
+ 5 cc delivered via Omaya reservoir
+ Feasibility & safety




Delivery via Standard Ommaya Reservoir

# ReSPECT-LM Trial Protocol Synopsis

## 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 Sampling**
- **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)

**Innovative, targeted radiotherapeutics for patients with** liver tumors.

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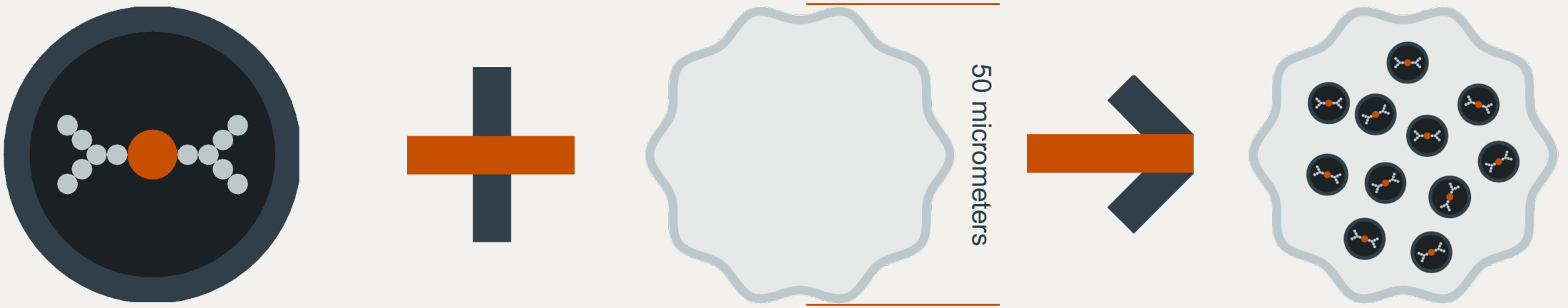
# Second Investigational Drug: Rhenium-188 NanoLiposome Biodegradable Alginate Microsphere ($^{188}$RNL-BAM)

## 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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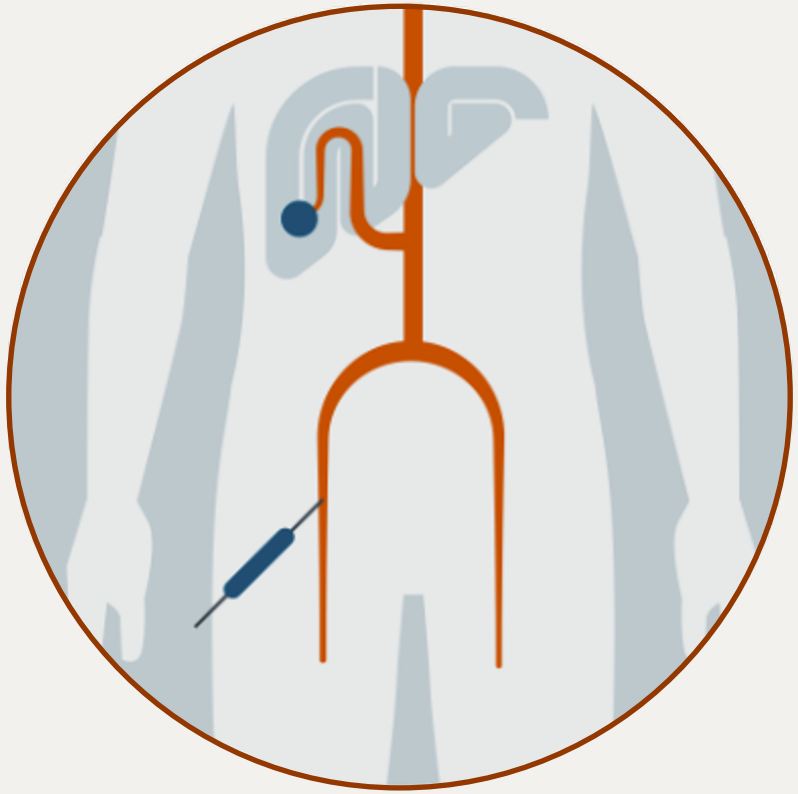
# $^{188}$RNL-BAM Radioembolization Therapy

## 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/pivotal ReSPECT-GBM trial
  - FDA CMC & Clinical Meetings
  - Complete CMC activities for $^{186}$RNL for GMP/Phase 3 drug supply
  - Initiate ReSPECT-GBM P2/pivotal trial
- ReSPECT-GBM Phase I trial of $^{186}$RNL, dose escalation and report data
- Initiate & open ReSPECT-GBM retreatment protocol
- 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
- Actively exploring opportunities for pipeline expansion, extension and partnering

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# Capitalization Summary

## Select Data

| As of September 30, 2021 | |
|---|---|
| **Cash** | $21.3M |
| **Common Shares Outstanding** | 15,360,025 |
| **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