Treatment of Recurrent Glioblastoma via Convection Enhanced Delivery with Rhenium (^{186}Re) Obisbemeda: *ReSPECT-GBM Phase 1/2 Trial Update*

John Floyd, MD
Associate Professor
Chair of the Department of Neurosurgery
University of Texas Health Science Center San Antonio

Andrew Brenner, UTHSCSA
Toral Patel, UTSW
Ande Bao, Case Western Reserve University
William Phillips, UTHSCSA
Joel Michalek, UTHSCSA
Shiliang Huang, UTHSCSA
Jeffrey Weinberg, MDA
Carlos Kamiya Matsuoka, MDA
Barbara Blouw, Plus
Leonardo Juverdianu, Plus
Marc Hedrick, Plus
Melissa Moore, Plus

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Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

Disclosures

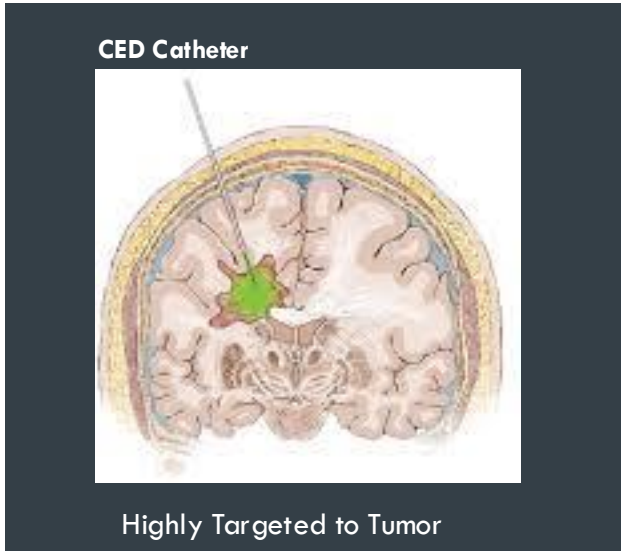
- None

Convection enhanced delivery bypasses the blood brain barrier to target CNS cancers with local, targeted delivery of therapeutics

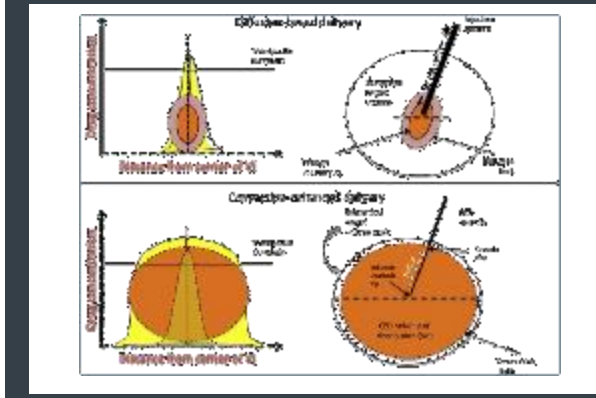
- FDA-approved and used for 20+ years with a wide variety of compounds
- Can target glioblastoma and other brain tumors
- Bypasses the BBB, allowing for larger treatment volumes than can be resected during surgery
- Personalized procedure based on pathology and anatomy
- Relies on a pressure gradient generated by a pump-catheter system (“bulk flow”)
- Enables homogenous delivery of high concentration therapeutics with a tissue penetration of a few centimeters
- Steep concentration fall-off at border of convective volume
- Controlled pressure and flow are optimal for drug delivery to region of interest
- Several catheters and software driven planning tools available

CED for glioblastoma

Stereotactic placement of one or more catheters in region of interest. Pumps connected to catheters apply positive pressure infusion of drug via bulk flow.



Highly Targeted to Tumor



Diffusion vs. Convection

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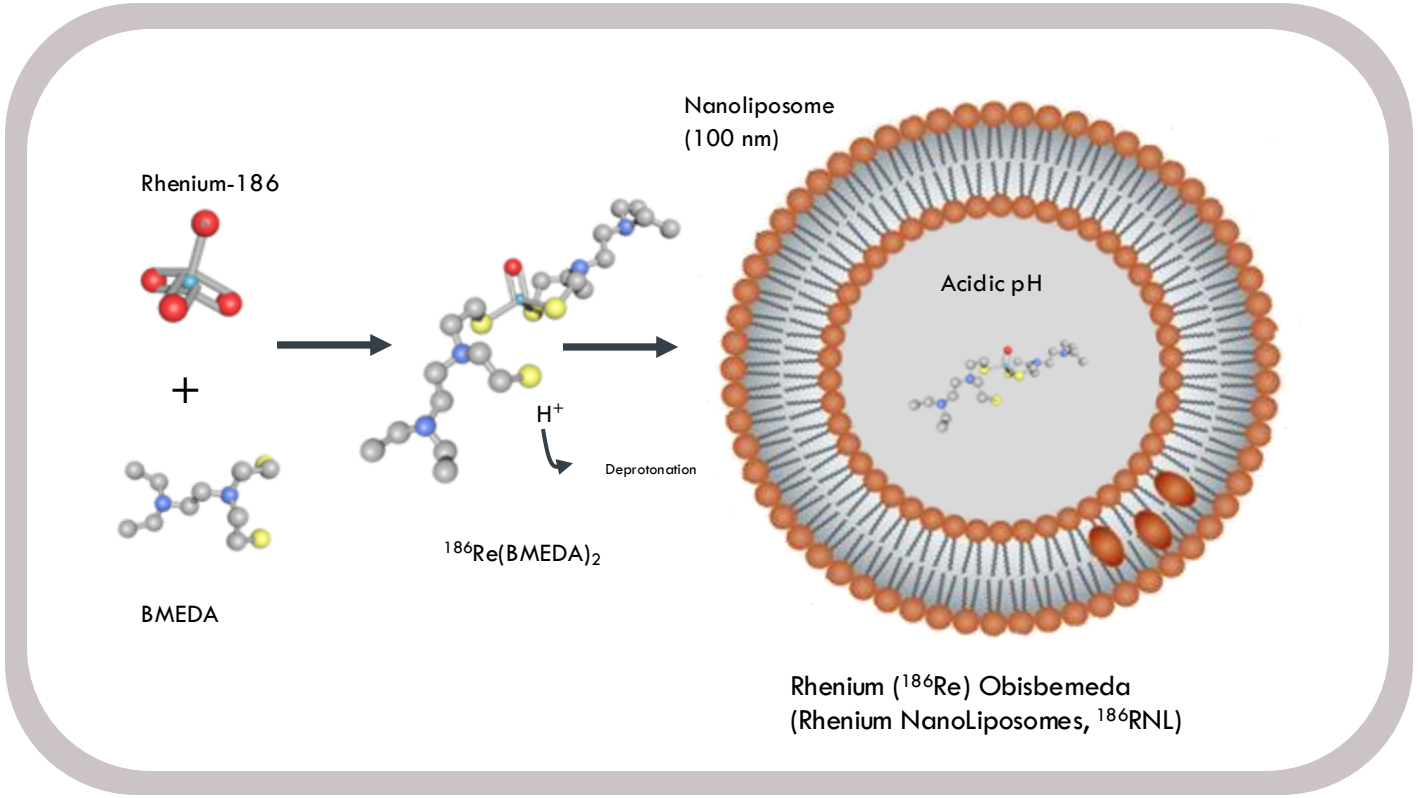
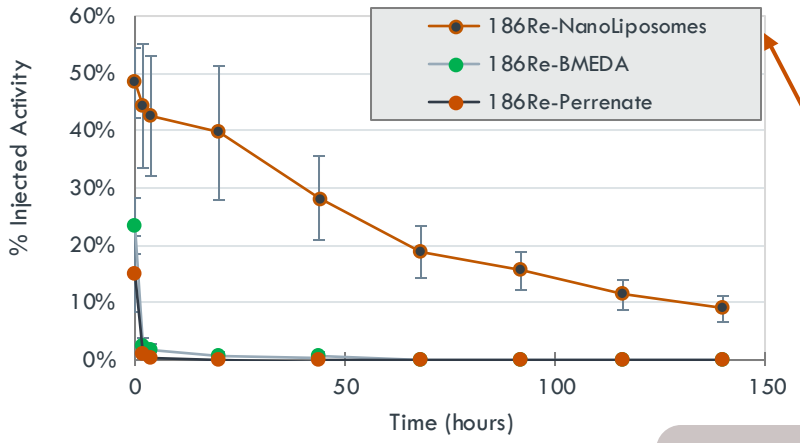
Jerusha Naidoo, Massimo Fiandaca, Russell R. Lonser, Krystof Bankiewicz, Chapter 16 - Convection-Enhanced Drug Delivery in the Central Nervous System, Nervous System Drug Delivery, Academic Press, 2019, Pages 335-350, ISBN 9780128139974.
Shinde, Shrikant & Mahale, Nitin & Chaudhari, S & Thorat, R. (2019). Recent Advances In Brain Targeted Drug Delivery System:A Review. J Neurooncol. 2021 February ; 151(3): 415–427. doi:10.1007/s11060-020-03408-9.

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



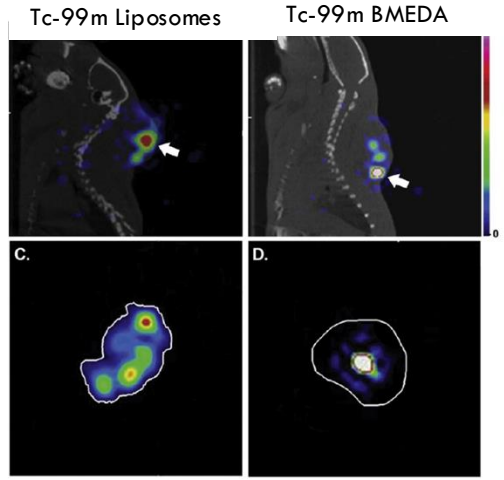
1. Rhenium-186: Emits tumor-destroying radiation over short distances while sparing healthy tissue
2. BMEDA: Small molecule that chelates to rhenium and is loaded into the nanoliposome where it's irreversibly trapped
3. Nanoliposome: Carries the trapped BMEDA-chelated ^{186}Re to tumor

Improved Tumor Retention



Nanoliposomes improve retention and distribution of ^{186}RNL

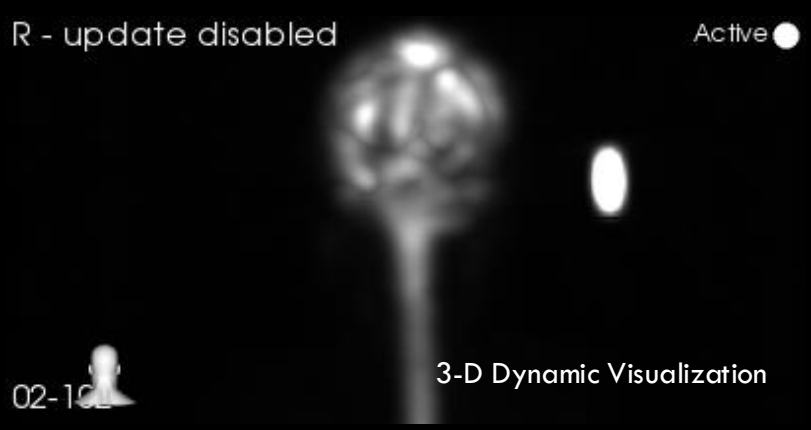
Improved Drug Distribution



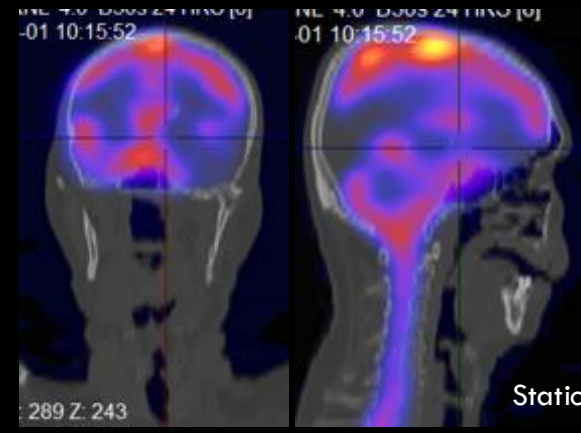
^{186}RNL allows direct visualization of drug application and quantification, with dual beta (therapeutic) and gamma (diagnostic) characteristics

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

Leptomeningeal Metastases

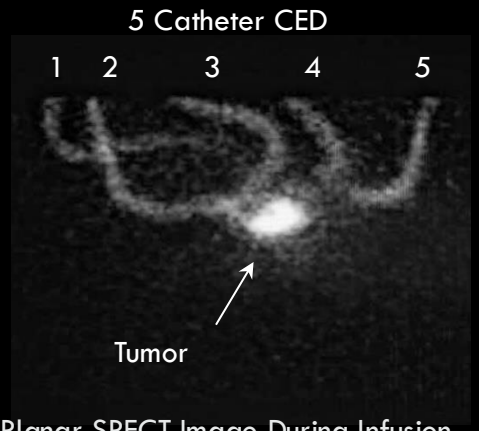


3-D Dynamic Visualization

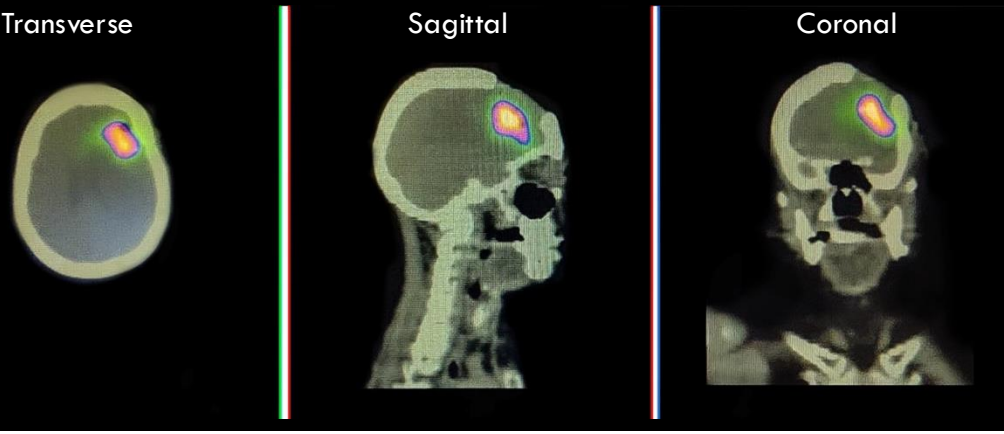


Static AP & Lateral

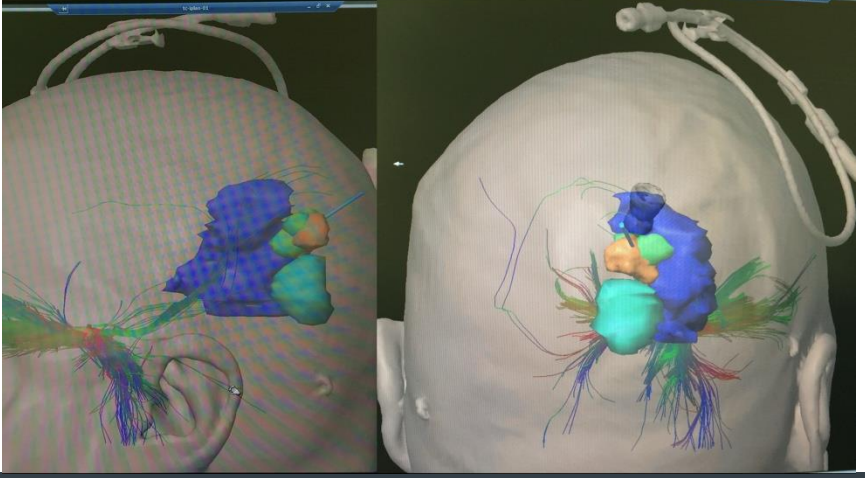
Glioblastoma

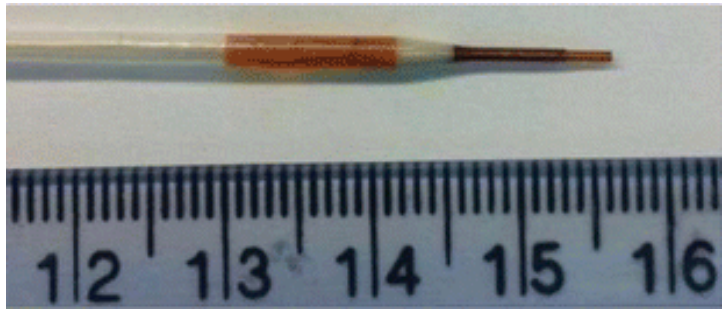


Planar SPECT Image During Infusion

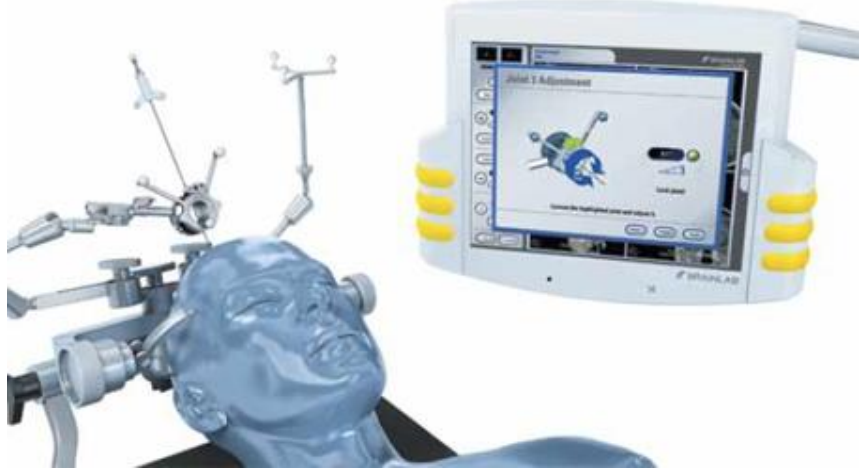


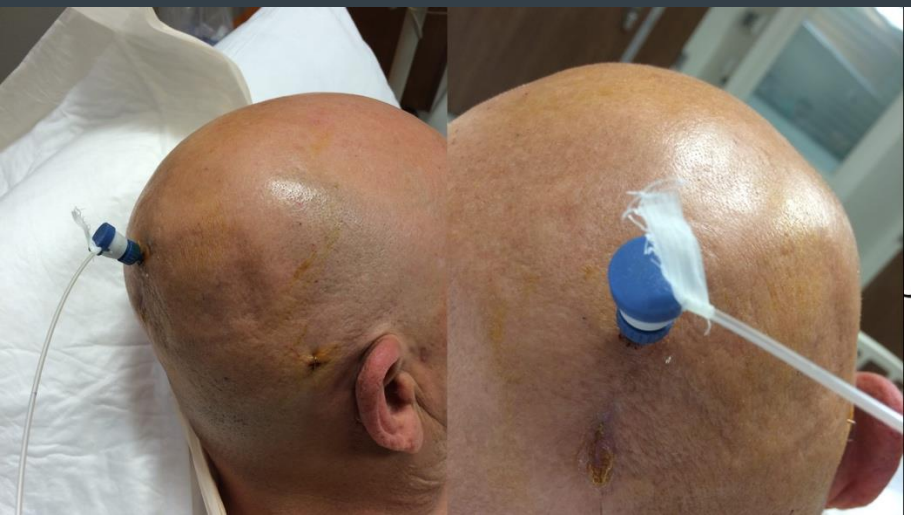
SPECT/CT Image at 20% Total Infusion



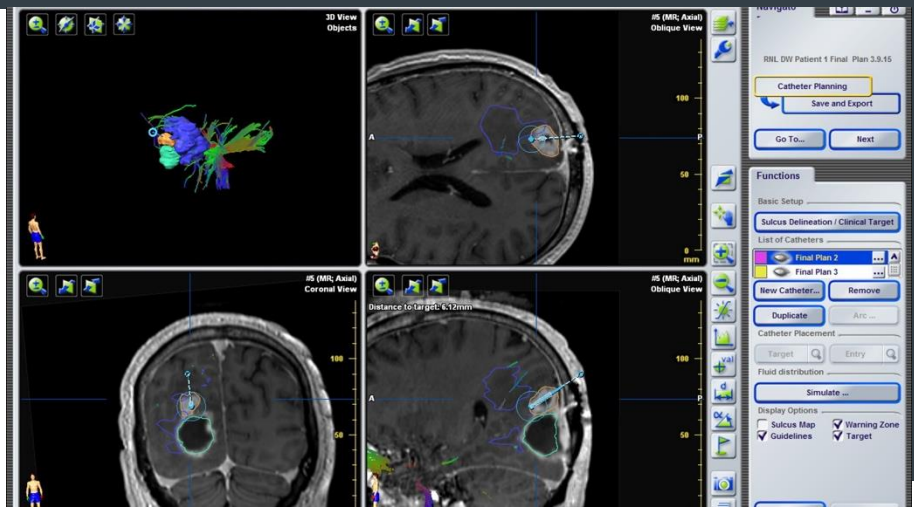


Brainlab Single Lumen Catheter





BRAINLAB



Commercial planning and neuronavigation software and hardware enables personalized placement of catheters based on treatment planning MRI

ReSPECT-GBM phase 1 dose escalation trial shows safety and efficacy signal and RP2D

- Multi-center, single arm, open-label
- Volume and dose finding study of the safety, tolerability, and distribution of ^{186}RNL given by CED
- Patients with recurrent or progressive malignant glioma
- Supported by a NIH/NCI grant

Cohort	Patients	Volume (mL)	Dose (mCi)	Conc. (mCi/mL)	Status
1	3	0.66	1.0	1.5	Complete
2	3	1.32	2.0	1.5	Complete
3	3	2.64	4.0	1.5	Complete
4	3	5.28	8.0	1.5	Complete
5	3	5.28	13.4	2.5	Complete
6	**6**	**8.80**	**22.3**	**2.5**	**RP2D**
7	3	12.3	31.2	2.5	Complete
8	5	16.34	41.5	2.5	Enrolling

ReSPECT CLINICAL TRIALS

NIH National Institutes of Health

Phase 1 Sites

UT Health San Antonio

UT Southwestern Medical Center

The University of Texas MD Anderson Cancer Center Making Cancer History

Mays Cancer Center UT Health San Antonio MD Anderson Cancer Center

ReSPECT-GBM clinical workflow

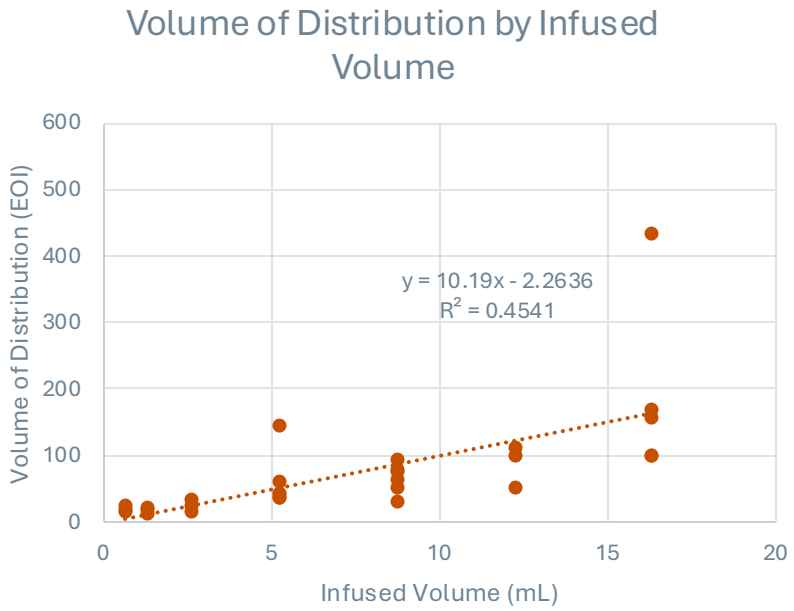
Prior to Treatment	Day 0	Day 1	Day 2-3
MRI imaging to assess and plan catheter number, trajectory, and flow rate	Standard of care biopsy followed by catheter placement in OR	Single ~4-hour infusion and real-time imaging in hospital Nuclear Medicine department	Catheter removal and patient discharged

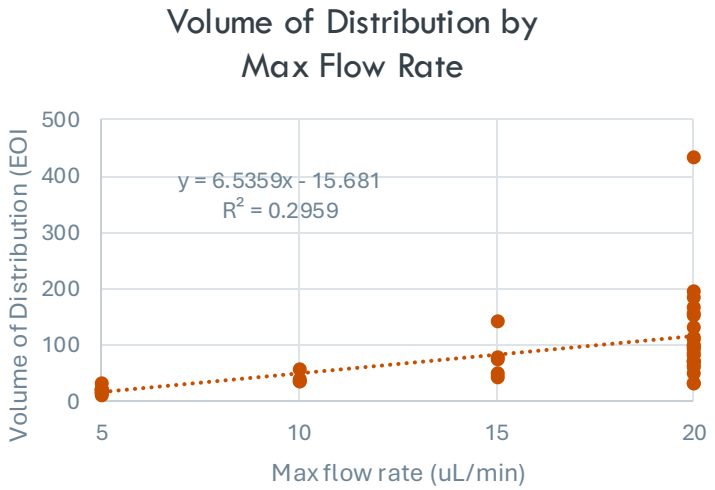
Phase 1 demographics

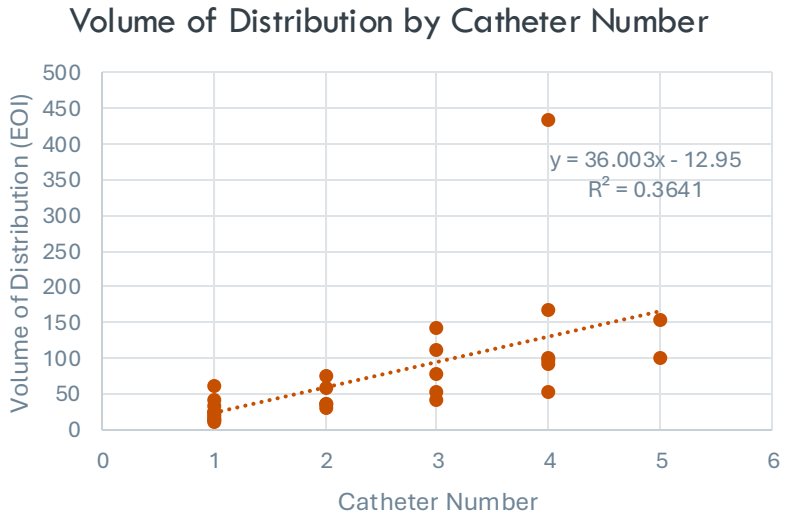
- Cohorts 1-8 (n=29)
- Heavily pretreated patient population
- Mean tumor volume 11.45 mL (tumor sizes up to 33 mL treated)
- Patient population heavily skewed to IDM wild type, MGMT unmethylated, and grade IV histology

Gender	
Male	18 (62.1%)
Female	11 (37.9%)
Tumor Volume (mL)	
Average	11.45
Range	0.88-33
IDH Mutational Status	
Wild type	23 (79.3%)
Mutated	3 (10.3%)
Quantity Not Sufficient	2 (6.9%)
Unknown	1 (3.5%)
MGMT Status	
Methylated	7 (24.1%)
Unmethylated	18 (62.1%)
Quantity Not Sufficient	2 (6.9%)
Unknown	2 (6.9%)
Glioma Grade	
Grade IV	27 (93.1%)
Grade III	2 (6.9%)

Infused volume, flow rate, and catheter number influence Vd







Absorbed dose to tumor and percent tumor coverage

- All patients received rhenium (^{186}Re) obisbemeda
- All patients received at least 1 catheter (generally for smaller tumors), max 5 catheters
- No significant complications from catheter placement
- Dosimetry analysis allows measurement of absorbed dose to the tumor and percent of tumor treated
- Cohort 6 was chosen as RP2D to ensure adequate volume of distribution (to maximize average absorbed dose to tumor and percent tumor coverage) for med-to-large tumors

Cohort	Patients	Average absorbed dose to tumor (Gy)	Percent of tumors with > 100 Gy	Percent of tumors with > 70% coverage	Tumor size (avg, mL)
1	3	199	67%	67%	1.82
2	3	122	33%	33%	4.23
3	3	233	33%	33%	13.05
4	3	171	33%	33%	8.00
5	3	423	100%	100%	11.70
6	6	374	67%	67%	9.48
7	3	308	100%	67%	10.85
8	5	178	60%	60%	25.24

Strong safety profile across all cohorts with minimal off-target toxicity

Adverse Event	AEs > 5%
Headache	6.09%
Fatigue	6.09%
Dizziness	3.04%
Seizure	3.04%
Nausea	2.61%
Gait disturbance	2.61%
Vomiting	2.61%
Dysphasia	2.17%
Alanine aminotransferase increased	2.17%
Pain	2.17%
Diarrhea	2.17%
Edema cerebral	2.17%
Muscle weakness lower limb	1.74%
Constipation	1.74%
Anorexia	1.74%
Aspartate aminotransferase increased	1.30%
Anxiety	1.30%
Edema limbs	1.30%
Paresthesia	1.30%
Generalized muscle weakness	1.30%
Thromboembolic event	1.30%
Tinnitus	1.30%

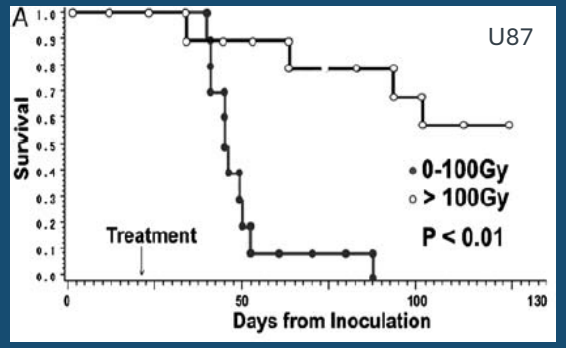
- Administration of rhenium (^{186}Re) obisbemeda has a strong safety profile
- Majority of AEs and SAEs are unrelated or unlikely related or to rhenium (^{186}Re) obisbemeda
- Cohort 8 had 1 DLT

Adverse Event	Grade	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	Cohort 7	Cohort 8
Edema cerebral	3	0	1	0	0	1	1	0	0
Seizure	3	0	1	0	0	1	0	0	0
Generalized muscle weakness	3	0	0	0	1	0	0	0	0
Hyperglycemia	3	0	0	0	1	0	0	1	0
Leukocytosis	3	0	0	0	1	0	0	0	0
Muscle weakness right-sided	3	0	0	0	1	0	0	0	0
Avascular Necrosis of the Shoulder	3	0	0	0	0	0	1	0	0
Lung infection	3	0	0	0	0	0	1	0	0
Fracture	3	0	0	0	0	0	0	1	0
Lymphocyte count decreased	3	0	0	0	0	0	0	0	2
	Totals	0	2	0	4	2	3	2	2

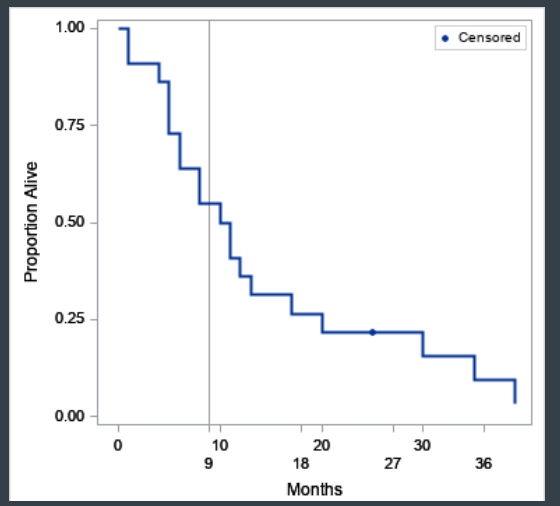
Relation	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	Cohort 7	Cohort 8
Definite	1	0	0	0	0	0	0	0
Probable	0	0	0	0	0	1	0	0
Possible	2	0	0	3	3	12	2	10
Unlikely	3	0	1	3	7	15	3	10
Unrelated	19	34	26	15	7	10	27	9
Pending	0	0	0	0	0	0	0	7
Totals	25	34	27	21	17	38	32	36

Efficacy – Phase 1

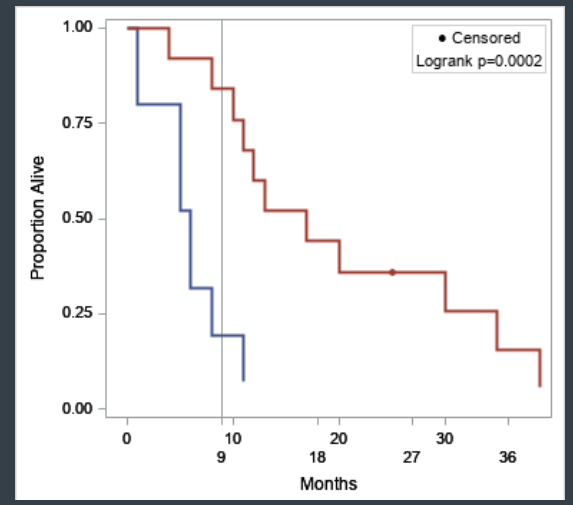
- Based on preclinical data demonstrating increase on OS for >100 Gy, analyzed both ITT and dichotomized
- Median overall survival (mOS) was 11 months in all patients treated in the dose escalation phase (Cohorts 1-6)
- When mOS data was dichotomized based on absorbed radiation dose (less than or greater than 100Gy):
  - <100 Gy: 6 months
  - >100 Gy: 17 months
  - P = 0.0002
- After adjustment for age, baseline ECOG status, baseline volume administered, and baseline tumor volume (AFT model):
  - OS increased by 27% for each 10% increase in the percentage of tumor covered
  - OS increased by 31% for each 100Gy increased in the absorbed dose
- Cohort 7 mOS (n=3): 167.5 (range 114-218)
- Cohort 8* mOS (n=5): 128 (range 43-341, 1 patient still alive at time of reporting)



100Gy efficacy threshold observed in preclinical research



For all patients, the mOS was 11.0 m (95% CI 5.0-17.0 m, OS9=0.55±0.11)

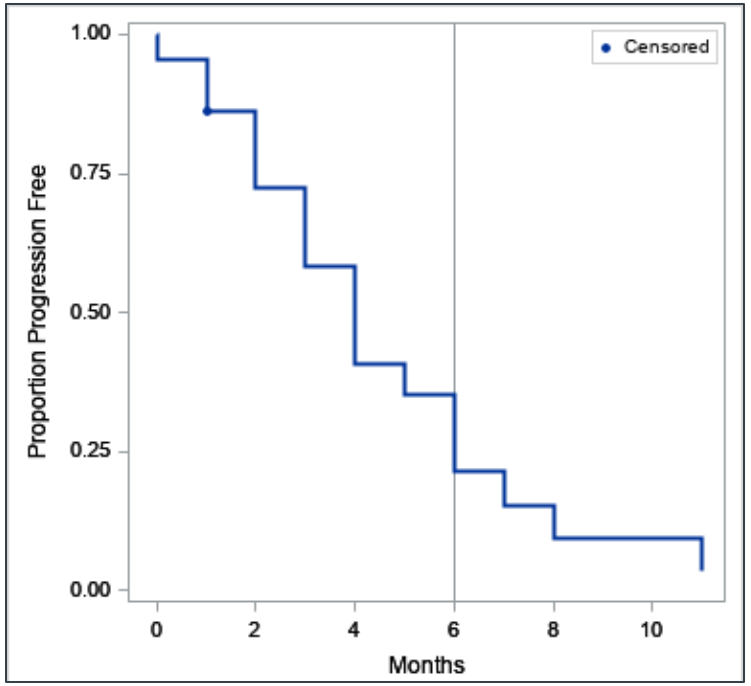


Patients who received <100Gy had a mOS of 6.0 m (95% CI 1.0-11.0 m, OS9=0.19±0.18) (blue) and those with ≥100Gy had a mOS of 17.0 m (95% CI 8.0-35.0 m, OS9=0.84±0.11) (red)

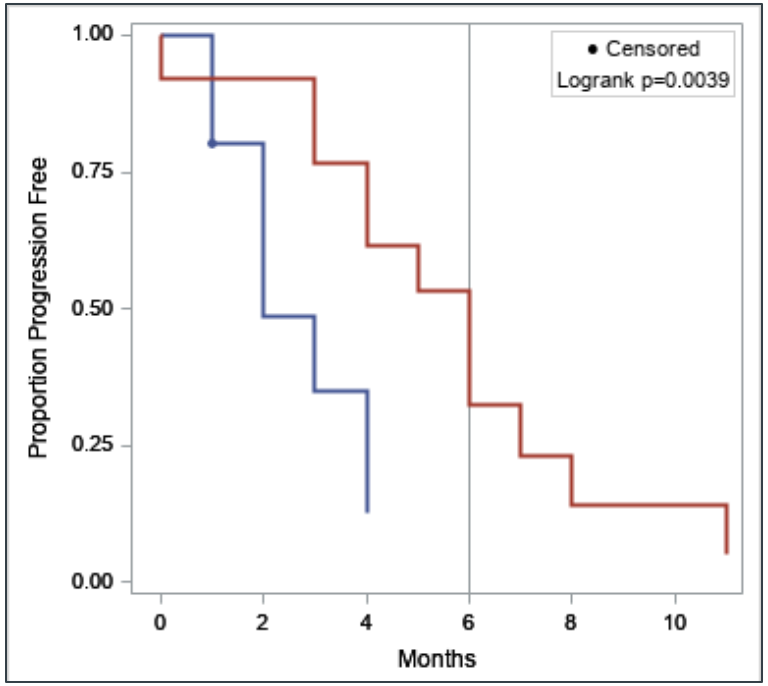
*as of 26Sep24 for alive patients

Efficacy – Phase 1

- Median progression free survival (mPFS) was 4 months in all patients treated in the dose escalation phase (Cohorts 1-6)
- When mPFS data was dichotomized based on absorbed radiation dose (less than or greater than 100Gy):
  - <100 Gy: 2 months
  - >100 Gy: 6 months
  - P = 0.0039
- After adjustment for age, baseline ECOG status, baseline volume administered, and baseline tumor volume (AFT model):
  - PFS increased by 15% for each 10% increase in the percentage of tumor covered
  - PFS increased by 19% for each 100Gy increased in the absorbed dose



For all patients, the mPFS was 4.0 m (95% CI 2.0-6.0 m, PFS6=0.21±0.11)



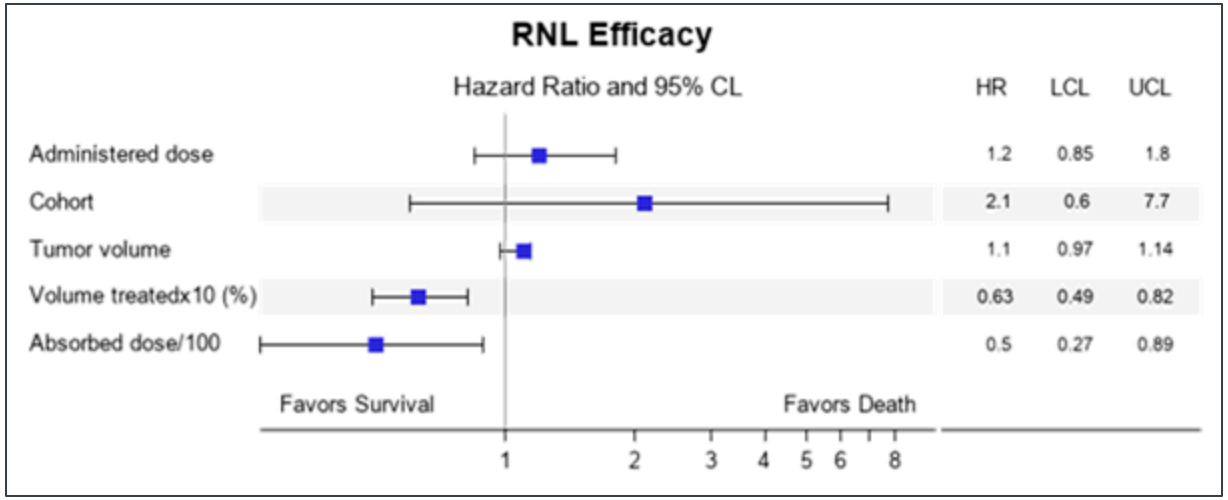
Patients who received <100Gy had a mPFS of 2.0 m (95% CI 1.0-4.0 m, PFS6=0.0) (blue) and those with ≥100Gy hand a mPFS of 6.0 m (95% CI 3.0-8.0 m, PFS6=0.32±0.16) (red)

Efficacy – Phase 1

Results

- Increased absorbed radiation dose (p=0.003) and percent tumor volume treated (p=0.002) correlates with improvement in overall survival
- Therapeutic absorbed radiation dose (>100 Gy) was reliably achieved in >80% of patients treated in high dose cohorts

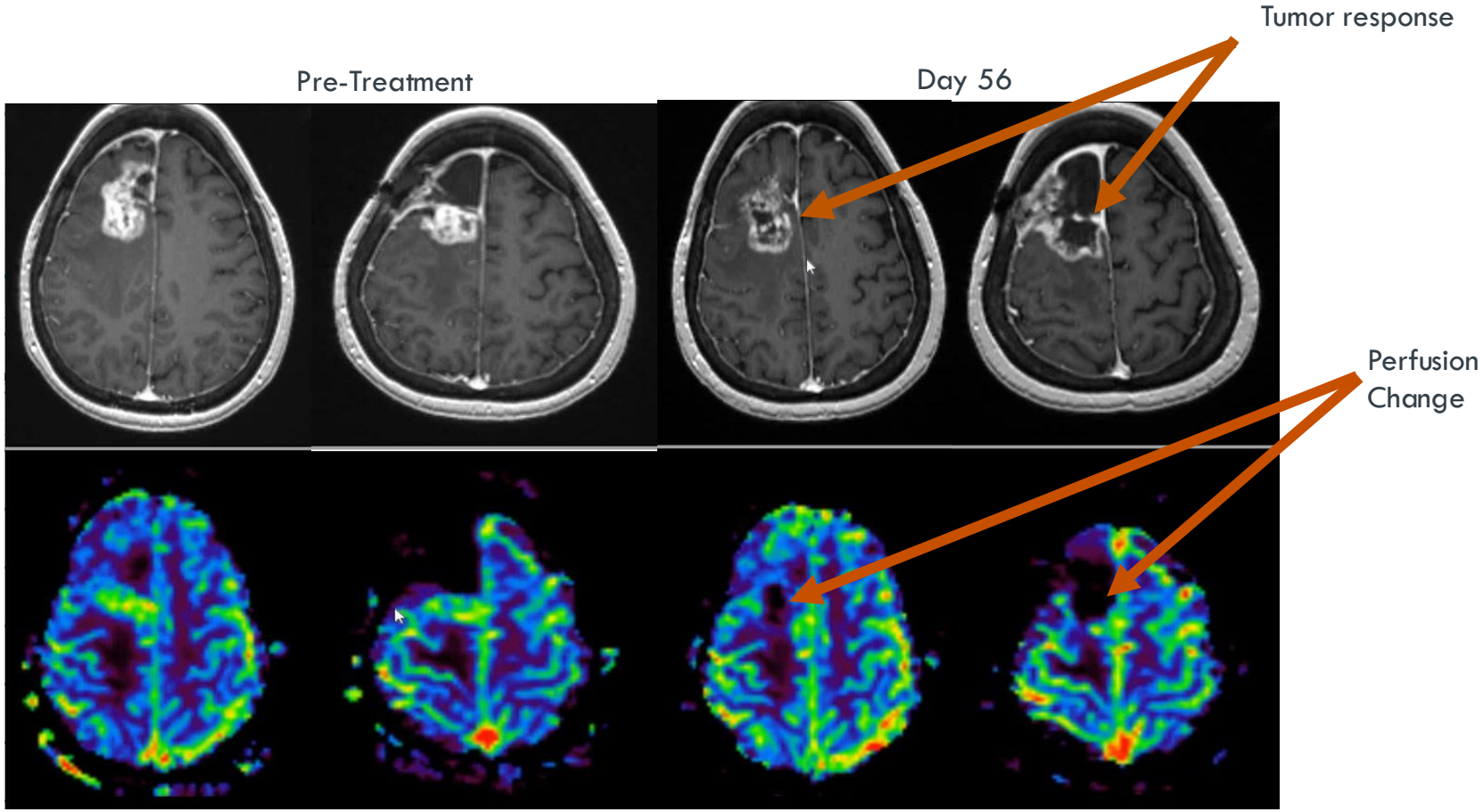
Hazard Ratio Model (Cox)



- For each 100 Gy increase of Total Dose in Distribution Volume, the risk of death decreases by 45.6% (p=0.003)
- For each 10% increase in the Ratio of Treated to Total Tumor Volume, the risk of death decreases by 66.9% (p=0.002)

Tumor response data: qualitative response using rCBV analysis

- Relative cerebral blood volume (rCBV) and treatment response assessment maps (TRAM) used to assess tumor response
- Phase 1, Cohort 5, 13.4mCi ^{186}RNL in 5.28mL (01-017)
- Tumor volume was 15.3mL and tumor coverage was 98.1%
- Average absorbed dose delivered to tumor was 336.6Gy



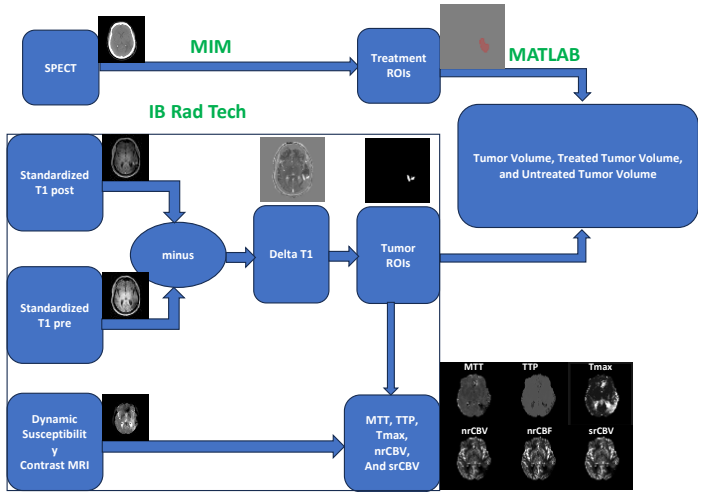
The colors are representative of perfusion, with black/blue as low perfusion and yellow/red as medium to high perfusion. Arrows indicate post-treatment tumor response.

Tumor response data: quantitative response - treated vs. untreated tumor by patient

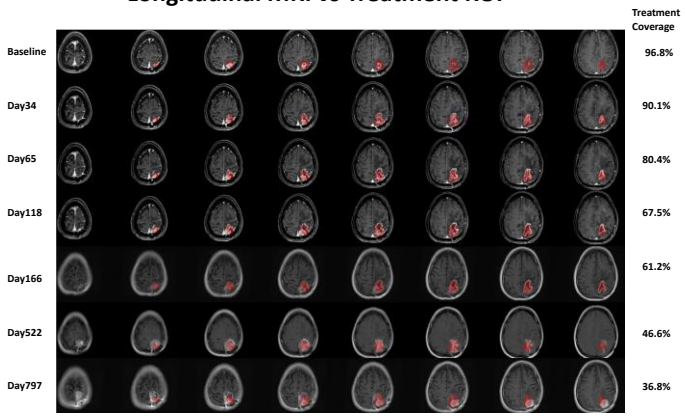
- Workflow for quantitation of response:
  - Overlay the SPECT image with isodose lines of absorbed dose to the MRI images taken at various time points following treatment
  - Perform subtraction mapping for pre and post treatment

- In 11 patients analyzed to date, a statistically significant difference in tumor volume rate change was seen in tumors receiving > or < 100 Gy
  - Where there is >100 Gy absorbed dose and sufficient tumor coverage, tumor is controlled
  - Conversely, regrowth appears outside this coverage range

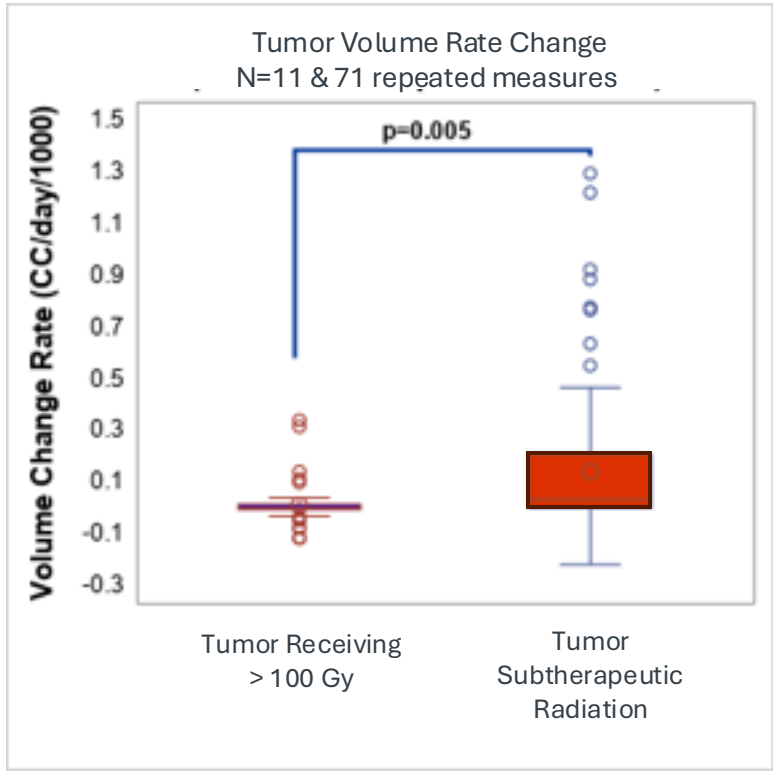
- Evaluation supports hypothesis that tumor coverage is the most important variable for outcome in rGBM patients receiving ^{186}RNL



Longitudinal MRI vs Treatment ROI



Tumor Volumetric Response*



*At time of analysis, November 2023

Phase 2 trial for small-medium sized tumors at Phase 1 cohort 6 variables (RP2D)

- Open at 3 sites: UTHSCSA, UTSW, and Northshore
- Currently enrolling with 19 patients treated at the RP2D
- Histologically confirmed glioblastoma, WHO 2021 IDH wild type, grade IV
- Limited to 1 recurrence
- Tumor sizes 20cm^3 or less
- 1-5 catheters
- Bevacizumab-naïve
- 34 patients planned
- Safety and efficacy data to date following P1 data trends (Cohorts 1-6)

^{186}RNL mL	^{186}RNL mCi	^{186}RNL mCi/mL	Status
8.80	22.3	2.5	Enrolling
Gender			
Male	12 (60%)		
Female	7 (40%)		
Tumor Volume (mL)			
Average	7.49		
Range	0.90 to 22.76		
IDH Mutational Status			
Wild type	19 (100%)		
MGMT Status			
Methylated	9 (47.3%)		
Unmethylated	10 (52.6%)		
Glioma Grade			
Grade IV	19 (100%)		

Summary

- CED bypasses the BBB to target CNS cancers with local, targeted delivery of therapeutics, including radiopharmaceuticals and is commercially available
- ^{186}RNL, 186Re encapsulated in nanoliposomes, is a novel therapeutic for the treatment of recurrent glioblastoma via CED and leptomeningeal metastases via intraventricular catheter
- ^{186}RNL allows direct visualization of drug application and quantification, with dual beta (therapeutic) and gamma (diagnostic) characteristics
- ReSPECT-GBM is a multi center, single arm, open label Phase 1/2 study to evaluate safety and efficacy of ^{186}RNL given by CED for patients with recurrent glioblastoma
- 29 patients over 8 dosing cohorts have been treated with ^{186}RNL in the Phase 1 study
- Majority of AEs and SAEs were unrelated or unlikely related or to ^{186}RNL
- After adjustment for age, baseline ECOG status, baseline volume administered, and baseline tumor volume (AFT model), PFS and OS were increased for patients who received > 100 Gy compared to those who received < 100 Gy; likewise, this was also seen with percentage of tumor covered
- The recommended phase 2 dose at cohort 6 was determined based on maximizing volume of distribution (and therefore percent tumor coverage and absorbed dose to tumor) for tumors < 20cm3
- Cohort 8 shows a decrease in average absorbed dose and percent tumor coverage compared to other cohorts, potentially indicating an upper limit of tumor size for the technology
- Phase 2 is currently enrolling at 3 institutions: UTHSCSA, UTSW, and Northshore and seeking additional patients for the study

Thank you

Patients and Caregivers

Investigators

Plus Therapeutics

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

John Floyd, UTHSCSA

Andrew Brenner, UTHSCSA
Toral Patel, UTSW
Ande Bao, Case Western Reserve University
William Phillips, UTHSCSA
Joel Michalek, UTHSCSA
Shiliang Huang, UTHSCSA
Jeffrey Weinberg, MDA
Carlos Kamiya Matsuoka, MDA
Barbara Blouw, Plus
Leonardo Juverdianu, Plus
Marc Hedrick, Plus
Melissa Moore, Plus

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

UTHSCSA Contact | John Floyd, MD | floydj@uthscsa.edu
PLUS Contact | Melissa Moore, PhD | mmoore@plustherapeutics.com