ReSPECT-GBM: Phase I/IIa Dose Escalation Trial of Rhenium-186 NanoLiposome (186RNL) in Recurrent Glioma via CED

- **Andrew Brenner, UT Health San Antonio**
- Toral Patel, UT Southwestern
- Jeffrey Weinberg, UT MD Anderson
- Ande Bao, Case Western Reserve University
- William Phillips, UT Health San Antonio
- Marc Hedrick, Plus Therapeutics
- Norman LaFrance, Plus Therapeutics
- Michael Youssef, UT Southwestern
- John Floyd, UT Health San Antonio

Mays Cancer Center

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MD Anderson Cancer Center

Disclosures

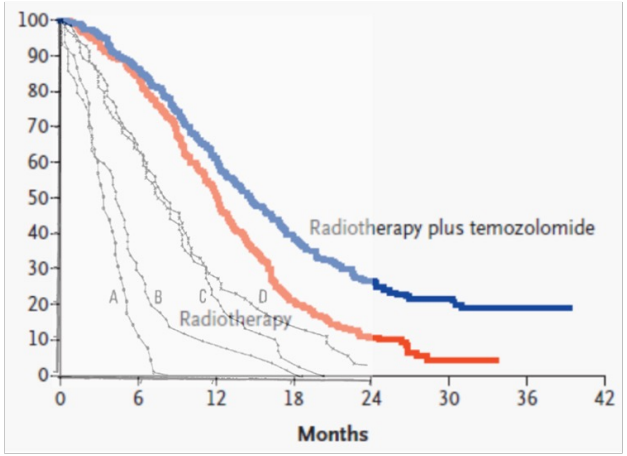
- Dr. Andrew Brenner, William Phillips, and Ande Bao are Consultants to Plus Therapeutics, Inc. and hold stock in NanoTx, Inc.
- Marc Hedrick and Norman LaFrance are employees of Plus Therapeutics, Inc.

Rhenium-186 Nanoliposome (^{186}RNL)

Why Develop a Targeted Radiotherapeutic for Glioblastoma?

- Up to a point, survival time for external beam radiation therapy (EBRT) correlates with the total dose delivered.
- The therapeutic window for EBRT is limited by increasing late normal tissue damage.
- Due to the short path length & dose rates, intra-tumoral beta emitters have the potential to dramatically widen the therapeutic window, increase delivered dose, & extend survival time.
- Considering that 90% of recurrences are located within 2 cm of the enhancing edge of the original tumor, treatments that increase the dose or dose effectiveness to a localized tumor without increasing radiation to the adjacent normal brain tissue are attractive approaches.

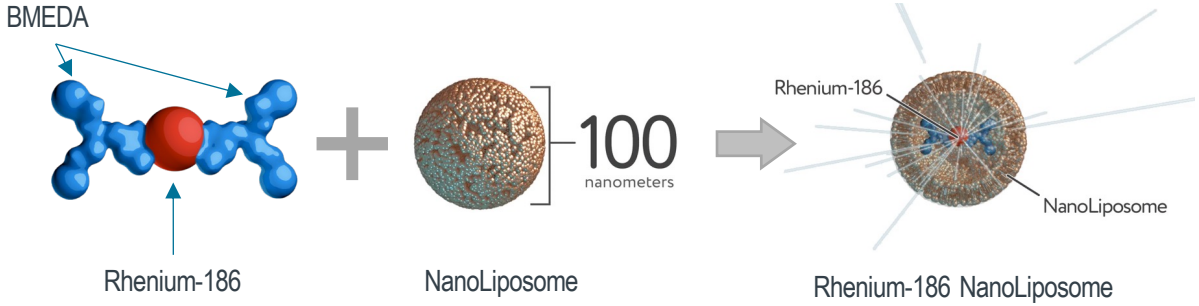
GBM treatment from 1975-2005:
Radiotherapy has made the most impact but has reached the maximum therapeutic window



Overall survival of patients over time with best supportive care (A), BCNU chemotherapy (B), radiation (C,D), and more recent radiation approaches including tomotherapy (red) or that plus Temodar (blue)

Rhenium-186 Nanoliposome (^{186}RNL)

A Proprietary Nanoscale Compound with a Unique Radioisotope

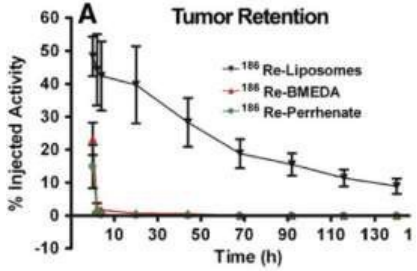


Rhenium-186

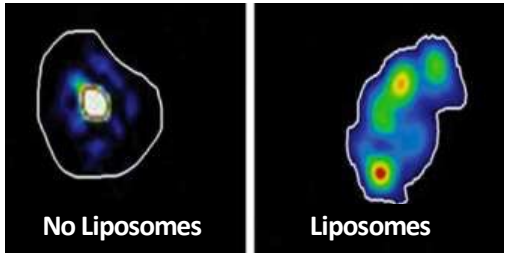
- Dual energy emitter - beta (cytotoxic) & gamma (imaging)
- Short average path length - precision
- Low dose rate - safer for normal tissues
- High radiation density - overwhelms innate DNA repair mechanisms

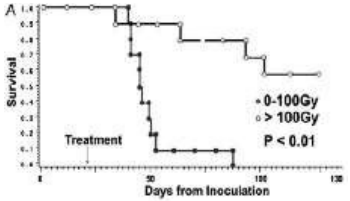
^{186}RNL Preclinical Science: Retention, Tumor Coverage, Efficacy, Safety

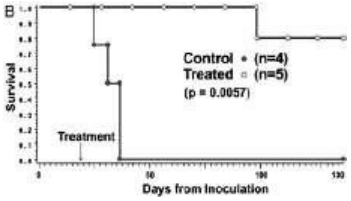
Liposomal encapsulation fundamentally changes both the **retention** within the tumor and the **dispersion** of the drug product.



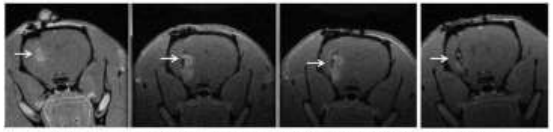
Tumor Dispersion







^{186}Re-Liposome Treatment



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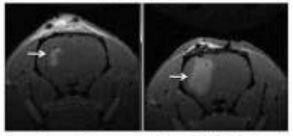

- Intracranial administration of 1, 3.5 or 6 mCi ^{186}RNL produced no significant pathologic changes at 24 hours or 14 days
- Highest absorbed dose was 360 Gy
- Based on these data, the no adverse effect limit (NOAEL), as related to brain pathology, was determined to be an absorbed dose of 360 Gy

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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

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Standard Inclusion/Exclusion Enrollment Criteria

- No prior bevacizumab (excluded from cohort 5 onward)
- Progression by RANO criteria following both standard combined modality treatment with radiation & temozolomide chemotherapy.
- Patients who receive treatment with antiepileptic medications must have a 2 week history of stable dose of antiepileptic without seizures prior to dosing
- Patients with corticosteroid requirements to control cerebral edema must be maintained at a stable or decreasing dose for a minimum of two weeks without progression of clinical symptoms
- A volume of enhancing tumor which falls within the treatment field volume being evaluated in the respective cohort
- Restricted to glioblastoma from cohort 6 forward (1 patient with AO & 1 with AA in early cohorts)
- Standard organ function requirements
- ECOG 0-2

ReSPECT-GBM U.S. Phase 1 Clinical Trial

Demographics & Dose-Escalation Scheme

Gender	
Male	16 (66%)
Female	8 (33%)
Tumor Volume (cm^3)	Average = 8.6; Range = 0.9 to 22.8
Prior Treatments	Average = 1.6; Range = 1 to 3
Prior Bevacizumab	5 (21%)
IDH Mutational Status	
Wild type	20 (83%)
Mutated	2 (8%)
None	2 (8%)
MGMT Status	
Methylated	5 (20%)
Unmethylated	15 (63%)
None	4 (17%)
Glioma grade	
Grade IV	22 (92%)
Grade III	2 (8%)

Cohort	Infused Volume (mL)	Total ^{186}RNL Activity (mCi)	Concentration (mCi/mL)	Average Absorbed Dose (Gy)	Status
1	0.66	1.0	1.5	199	Enrolling Cohort 8 (n=24 subjects)
2	1.32	2.0	1.5	122	
3	2.64	4.0	1.5	233	
4	5.28	8.0	1.5	171	
5	5.28	13.4	2.5	423	
6	8.80	22.3	2.5	287	
6b	8.80	22.3	2.5	462	
7	12.3	31.2	2.5	308	
8	16.34	41.5	2.5	TBD	

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

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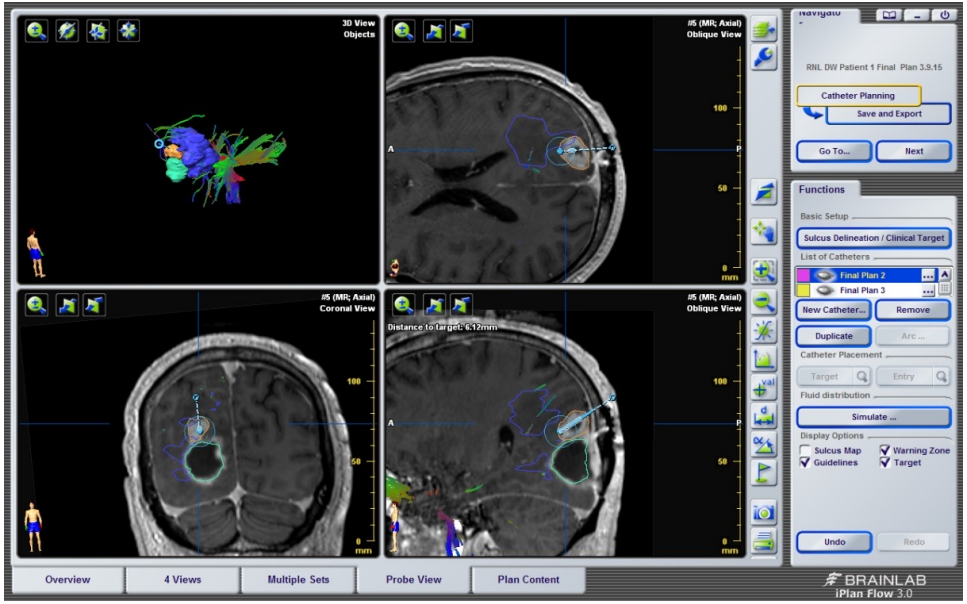
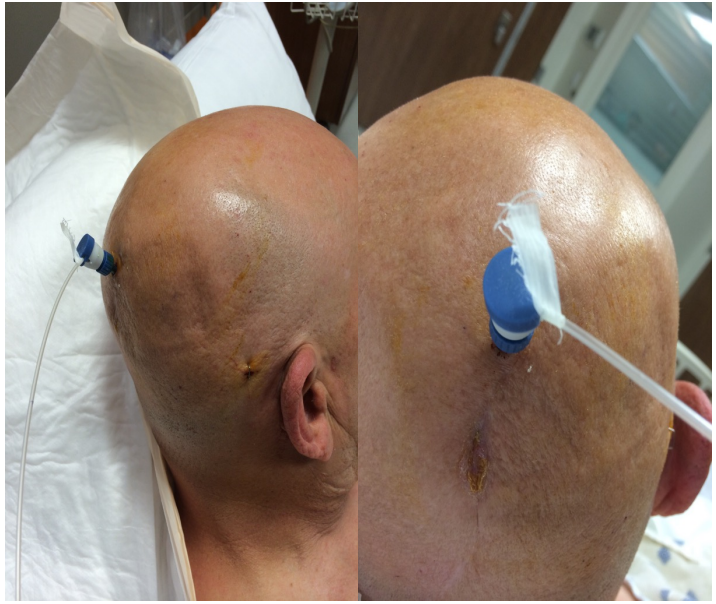
Treatment Administration by Convection-Enhanced Delivery





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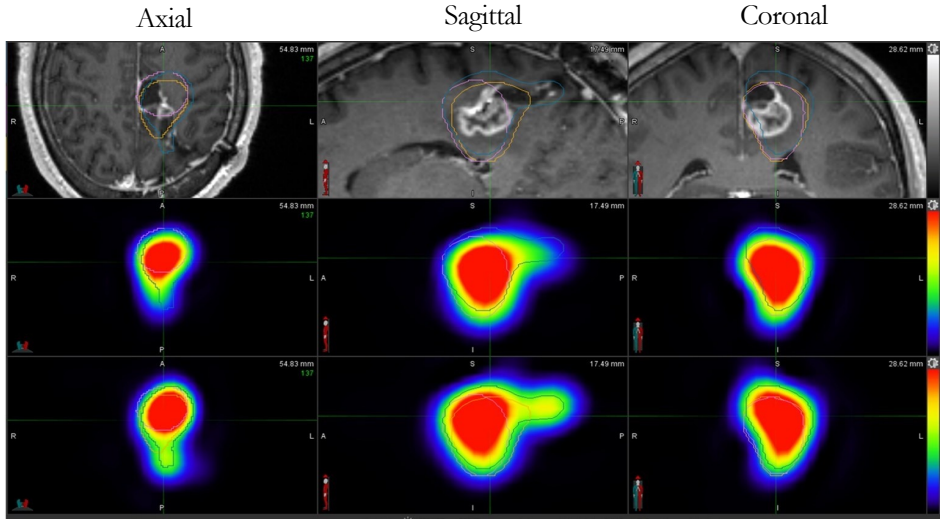
Example 01-014



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

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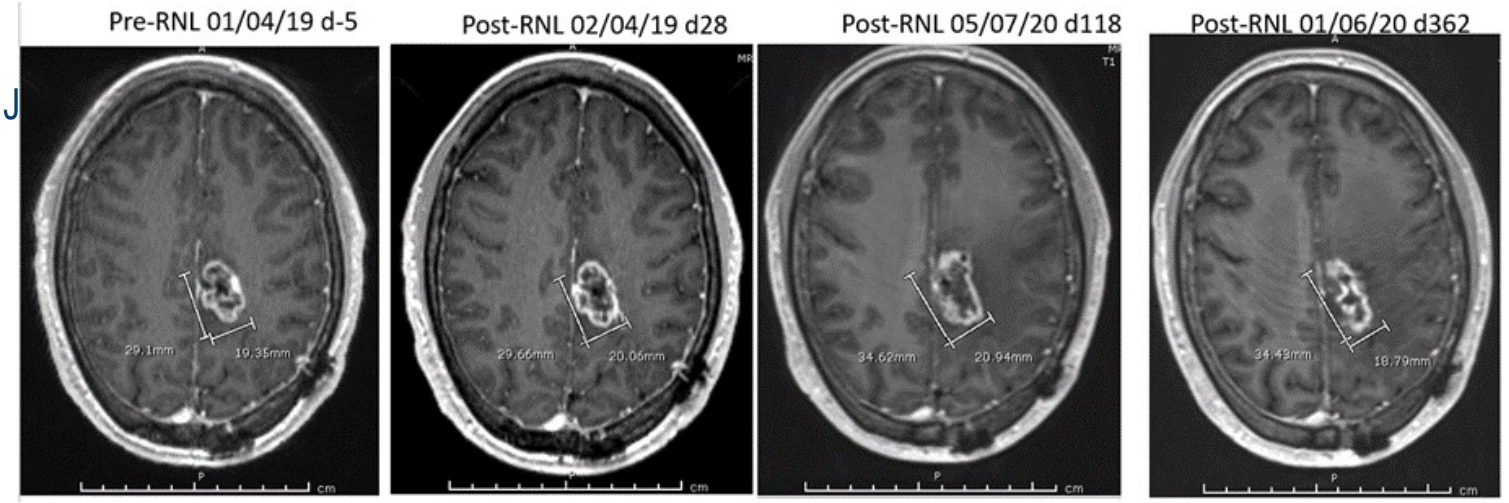
Example 01-014

Andrew J



- MRI scans revealed an initial increase in size which peaked at Day 118, with some associated edema, followed by tumor shrinkage out to at least Day 362
- Patient survival >950 days

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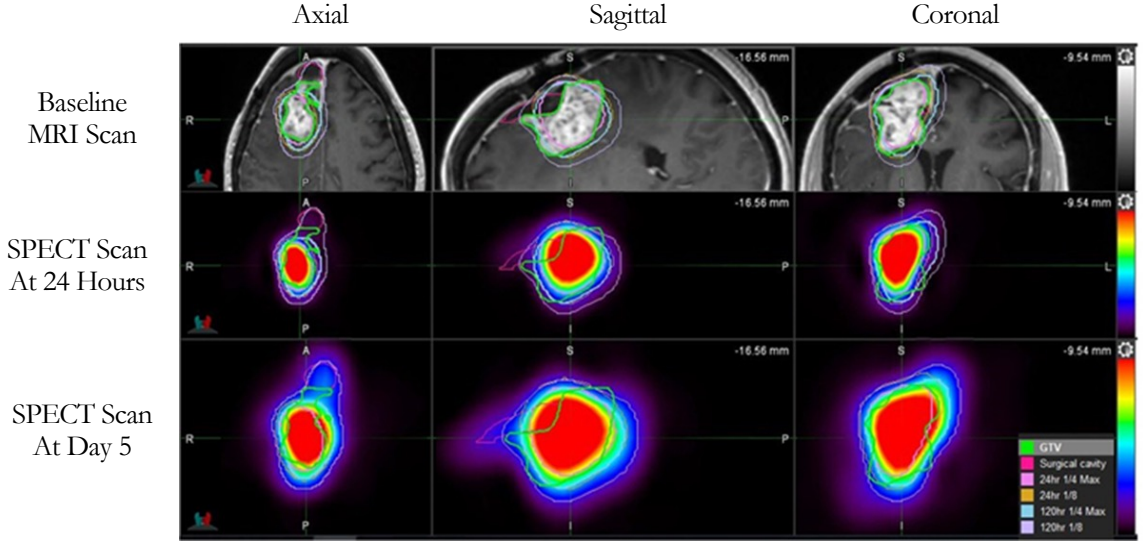
Example 01-017



- Tumor volume was 18.8 mL & tumor coverage was 87%
- Absorbed dose delivered to tumor was 336 Gy

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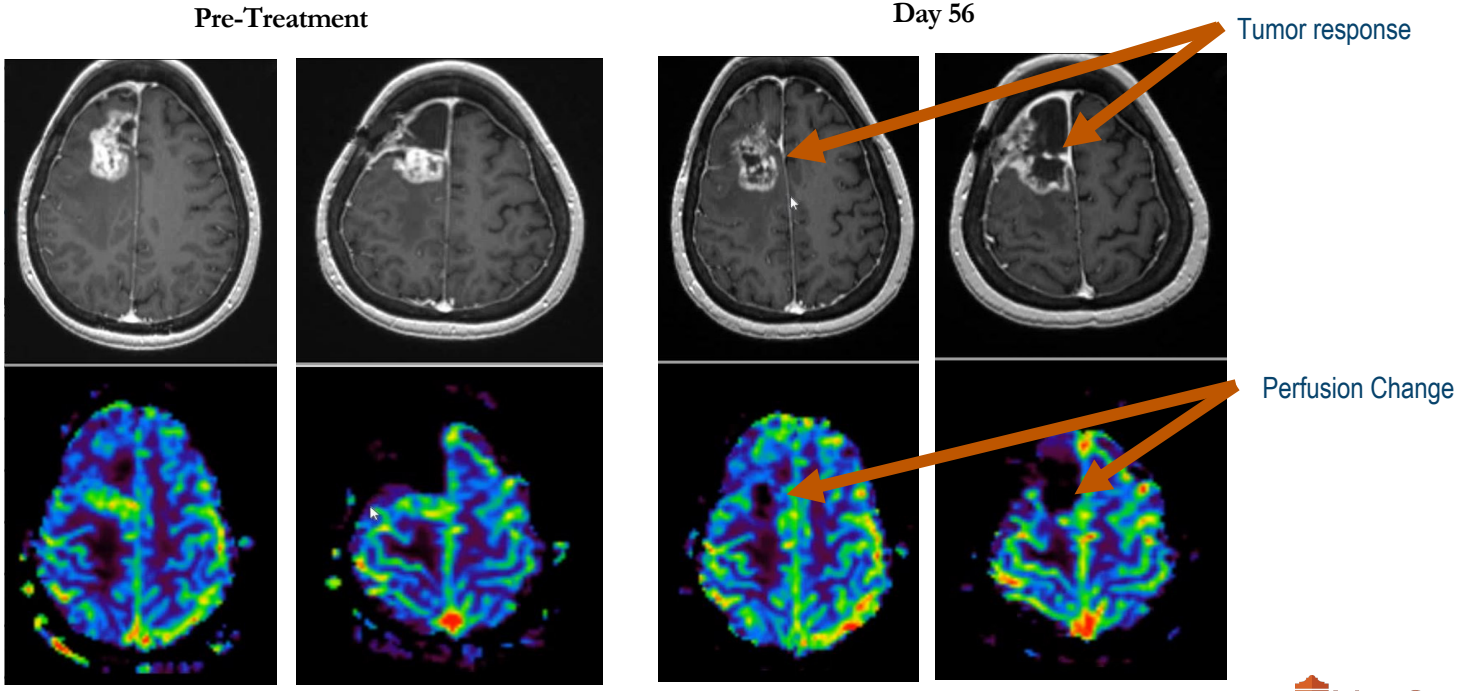
Example 01-017



Andrew J Brenner MD,

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No Significant Extracranial Exposure

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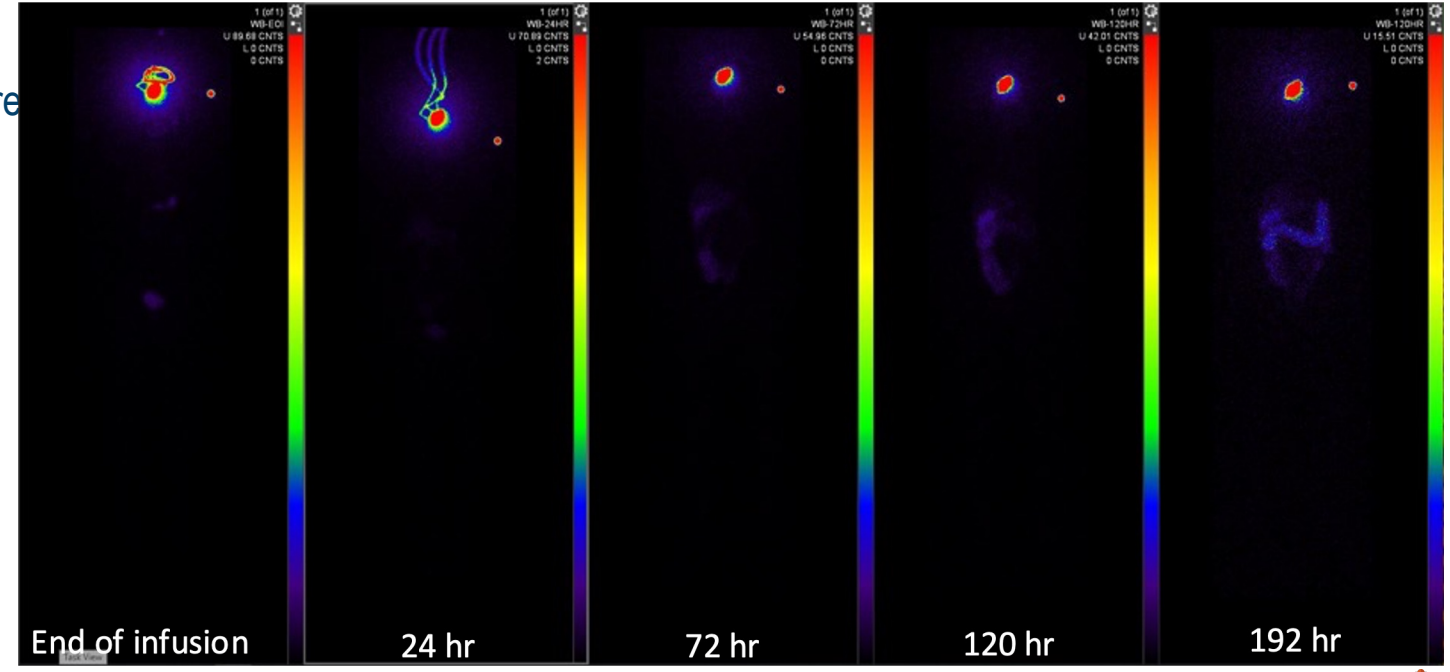

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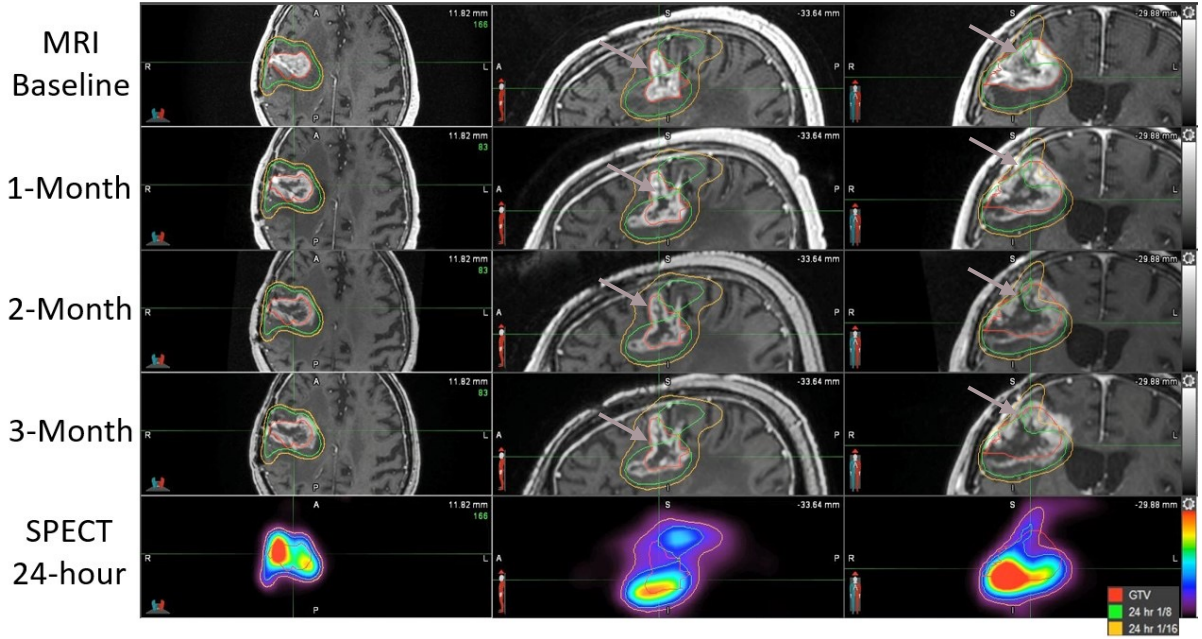
Coverage Correlates with Response



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Safety

- There have been no dose limiting toxicities
- Minimal systemic radiation exposure
- The majority of AEs reported were mild or moderate (Grade 1 or 2) in intensity.
- Most AEs considered causally unrelated to ^{186}RNL except scalp discomfort -- considered related to the surgical procedure.

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	3	0	0	**4**
Vasogenic cerebral edema	0	0	3	0	0	**3**
Pneumonia	0	0	1	0	0	**1**

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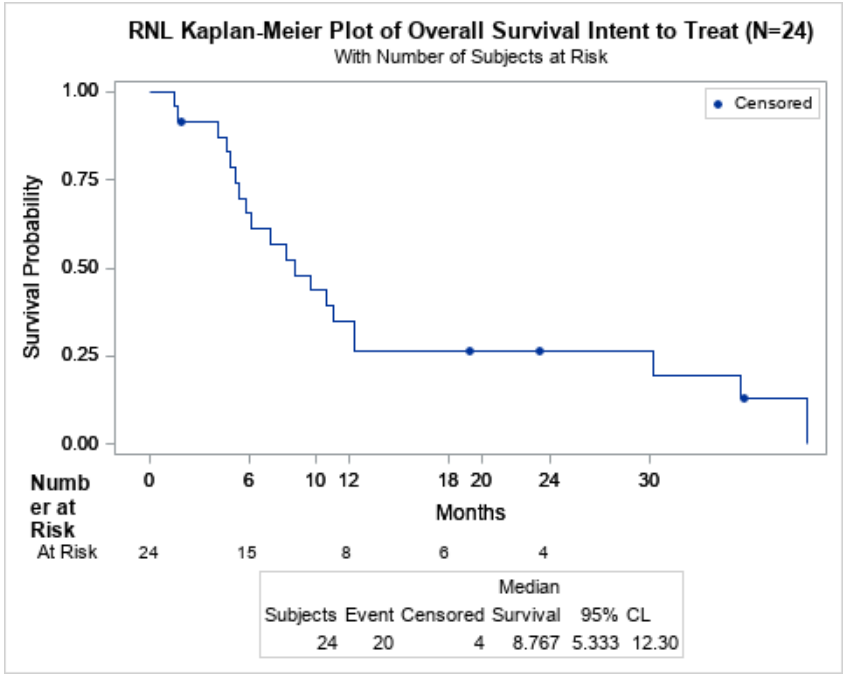
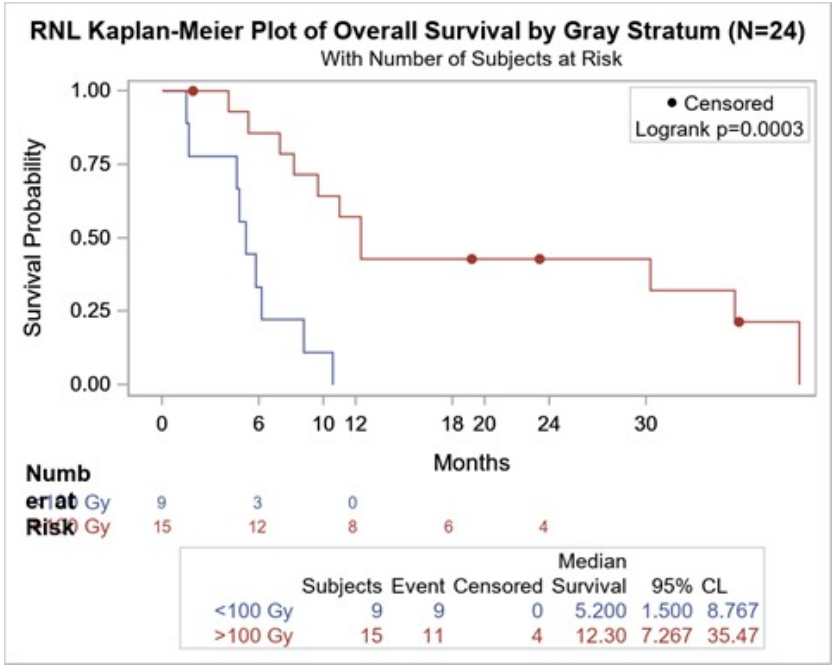
Efficacy





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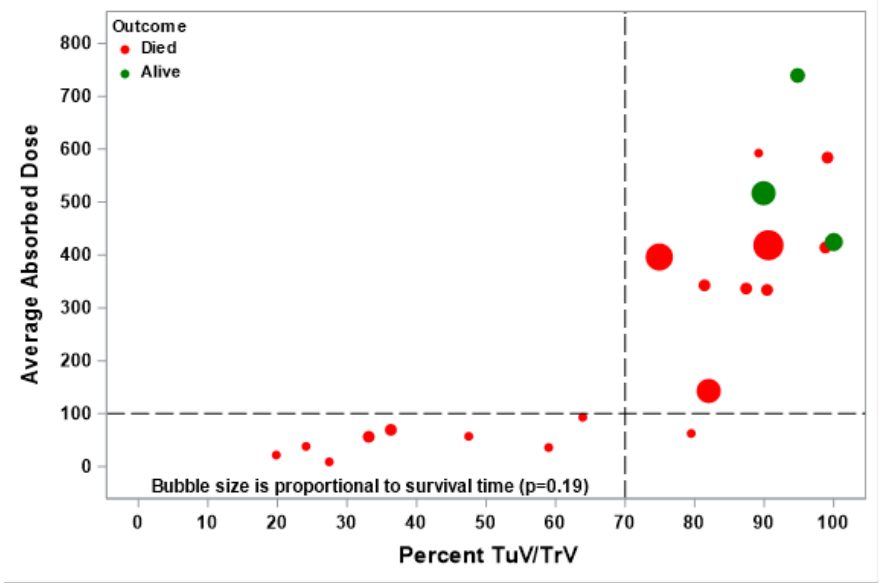
Efficacy



Overall Survival, N=23		
Dose	**Median OS (months)**	**95% CI**
All	**9.4**	5.8, 13.2
<100 Gy	**5.6**	1.6, 9.4
>100 Gy	**22.9**	8.8, 42.3

Patients Remain Alive

>100 Gy - 3 patients

< 100 Gy - none

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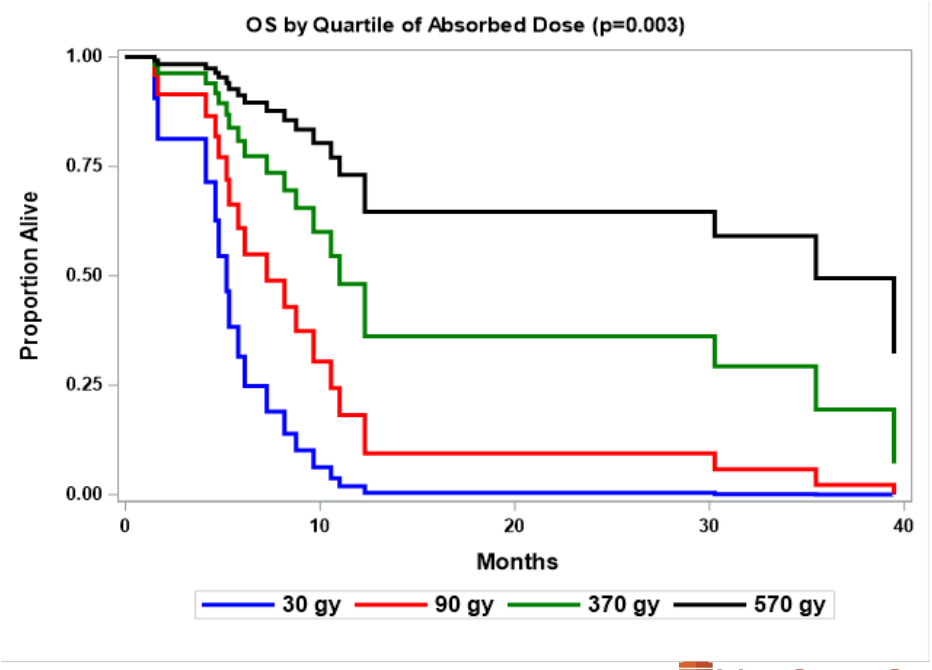
Cox Proportional Hazards Modeling

Model	Variable	beta±SE	HR	95% CI	p-value
1	Absorbed dose	-0.291±0.192	0.747	0.513, 1.089	0.13
	Tumor Volume	0.018±0.026	1.019	0.968, 1.072	0.48
	Percent Treated	-0.016±0.015	0.984	0.956, 1.012	0.27
2	Absorbed dose	-0.416±0.154	0.66	0.488, 0.892	0.007
	Tumor Volume	0.022±0.027	1.022	0.97, 1.077	0.41
3	Absorbed dose	-0.306±0.188	0.736	0.509, 1.065	0.1
	Percent Treated	-0.017±0.014	0.984	0.957, 1.011	0.24
4	Tumor Volume	0.024±0.026	1.025	0.974, 1.078	0.34
	Percent Treated	-0.032±0.011	0.969	0.947, 0.99	0.005
5	Tumor Volume	0.045±0.026	1.046	0.995, 1.101	0.08
6	Percent Treated	-0.033±0.011	0.967	0.947, 0.988	0.002
7	Absorbed dose	-0.442±0.149	0.643	0.48, 0.861	0.003



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Summary

Safety - well tolerated, no dose limiting toxicities - in therapeutic range.

Delivery & Imaging

- No dosing failures.
- Single administration- up to 20x absorbed dose vs. EBRT (maximum 740 Gy vs. 35 Gy).
- SPECT/CT- reliable real-time visualization & dosimetry.

Survival

- A statistically significant OS benefit in therapeutic doses (>100 Gy) vs. subtherapeutic ($p = 0.002$).
- In cohorts 5-7 (higher volumes & doses), therapeutic dose achieved in 80% of patients.
- Increasing drug volume & radiation correlate with improved OS.

Going Forward

- Phase II is enrolling with 22.3mCi in 8.8mL for rGBM less than 20mL in total volume
- Phase I will allow for higher dosing volumes for patients with rGBM greater than 20mL

THANK YOU TO OUR PATIENTS

ReSPECT Study Team:

John Floyd MD (UTHSA)
William Phillips MD (UTHSA)
Ande Bao PhD (Case Western)
Toral Patel MD (UTSW)
Michael Youssef MD (UTSW)
Jeff Weinberg MD (MDACC)
All of our Study Coordinators

Plus Therapeutics

Norman LaFrance MD
Marc Hedrick MD
Melissa Moore PhD
Greg Stein MD

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