PARIS 2022 ESMO congress

The ReSPECT-GBM Phase 1/2a Trial of Rhenium-186 NanoLiposome (^{186}RNL) in Recurrent Glioma via Convection-Enhanced Delivery (CED)

Abstract 277O

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Declaration of Interests

Andrew Brenner, MD, PhD

Dr. Brenner has disclosed receipt of intellectual property rights/patent holder & ownership interest with NanoTX Therapeutics, & stock interest in Plus Therapeutics; honoraria from Vascular Biogenics, Alamab Therapeutics, Novalis, & Plus Therapeutics.

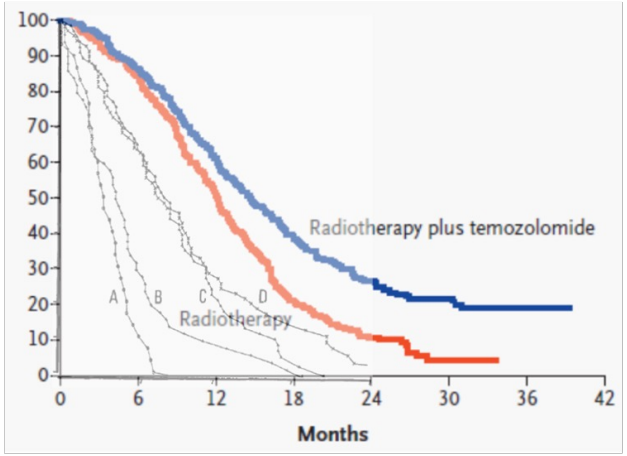
These relationships will not impact his ability to present an unbiased presentation.

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.

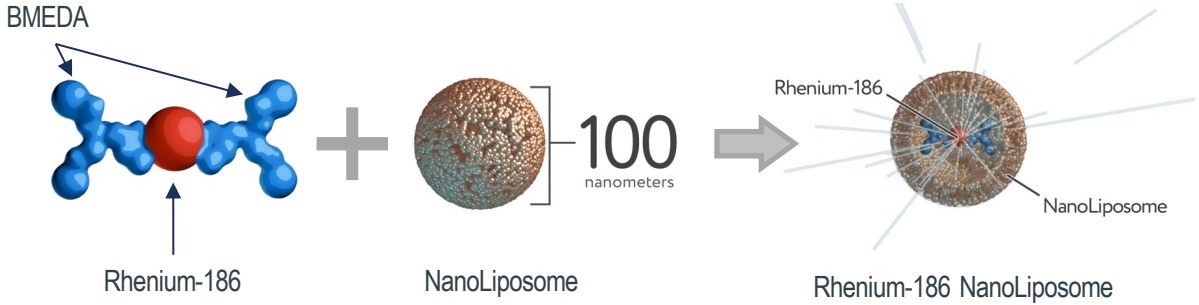
GBM treatment from 1975-2005:
Radiotherapy has made the most impact but has reached the maximum therapeutic window



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



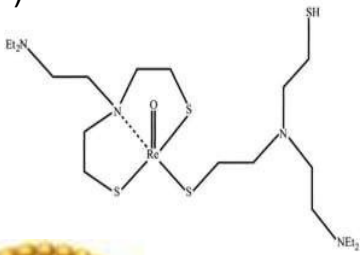
Rhenium-186

- 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

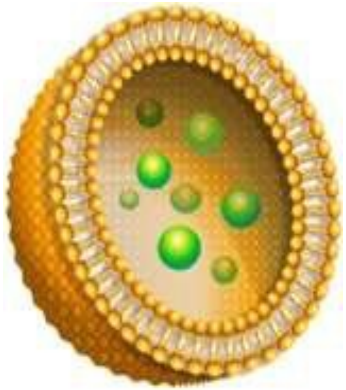
Rhenium-186 NanoLiposome (^{186}RNL)

Drug Product & Characteristics

- Investigational product is N,N-bis(2-mercaptoethyl)-N',N'-diethyl-ethylenediamine (BMEDA)-chelated Rhenium-186 encapsulated within lipid vesicles (liposomes).
- BMEDA is an SNS pattern ligand with a tridentate structure that has 1 nitrogen & 3 sulfur atoms. These 3 atoms donate electrons to Rhenium-186, resulting in a lipophilic complex in a neutral state.



- Rhenium-186 is an ideal radioisotope for therapy with features including 89 hour half-life (3.72 days), beta energy 1,077 keV & 939 keV, non-therapeutic gamma energy of 137 keV (imaging), safety similar to ^{131}I, & penetration in tissue averaging 1.1 mm.
- Nanoliposomes are composed of an 80 – 130 nm diameter lipid bilayer of distearoylphosphatidylcholine (DSPC) & cholesterol & confer drug delivery control on the chelated Rhenium-186.

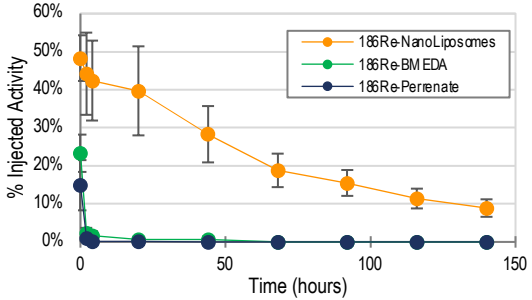


^{186}RNL in Glioblastoma

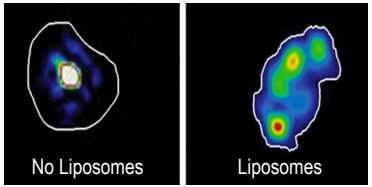
Preclinical Findings: Retention, Distribution, Safety & Efficacy

- NanoLiposome encapsulation fundamentally changes both the retention within the tumor & the dispersion of the drug product
- 186Re-NanoLiposome tumors progressively disappeared over time; survival improved at >100 Gy

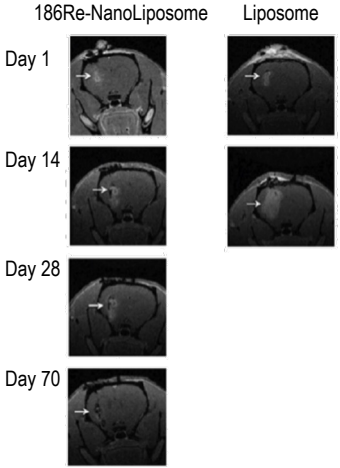
Tumor Retention



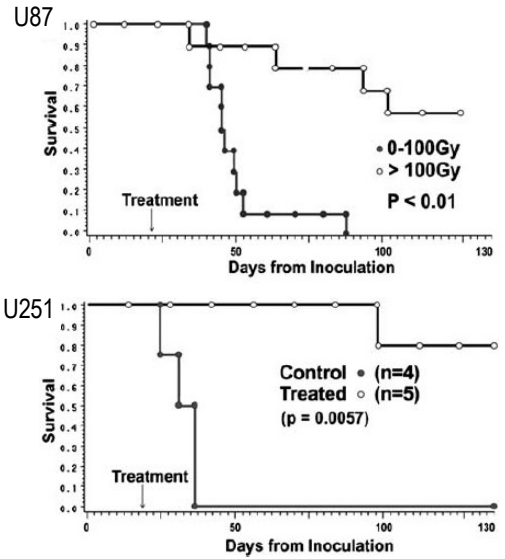
Tumor Dispersion



Tumor Size & Growth



Animal Survival



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ReSPECT-GBM U.S. Phase 1 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

ReSPECT-GBM U.S. Phase 1 Clinical Trial

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

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Demographics & Dose-Escalation Scheme

Gender	
Male	15 (65%)
Female	8 (35%)
Tumor Volume (cm^3)	Average = 8.1; Range = 0.9 to 22.8
Prior Treatments	Average = 1.6; Range = 1 to 3
Prior Bevacizumab	5 (23%)
IDH Mutational Status	
Wild type	19 (83%)
Mutated	2 (9%)
None	2 (9%)
MGMT Status	
Methylated	4 (17%)
Unmethylated	13 (57%)
None	6 (26%)
Glioma grade	
Grade IV	21 (91%)
Grade III	2 (9%)

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

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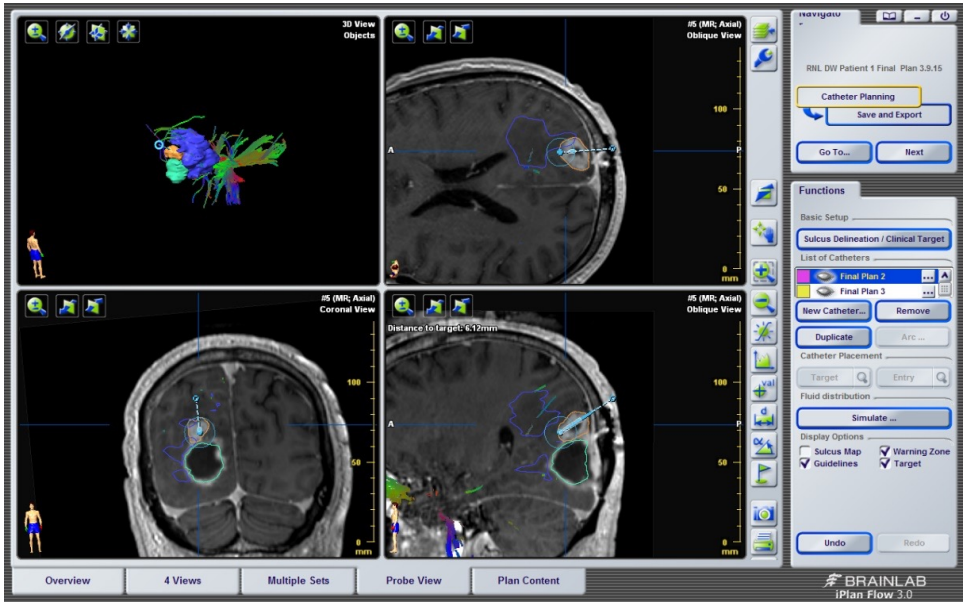
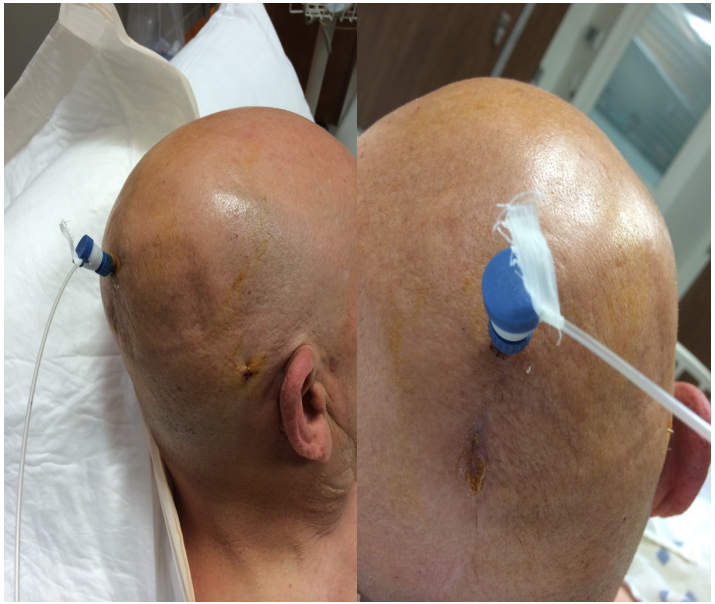
Treatment Administration by Convection-Enhanced Delivery





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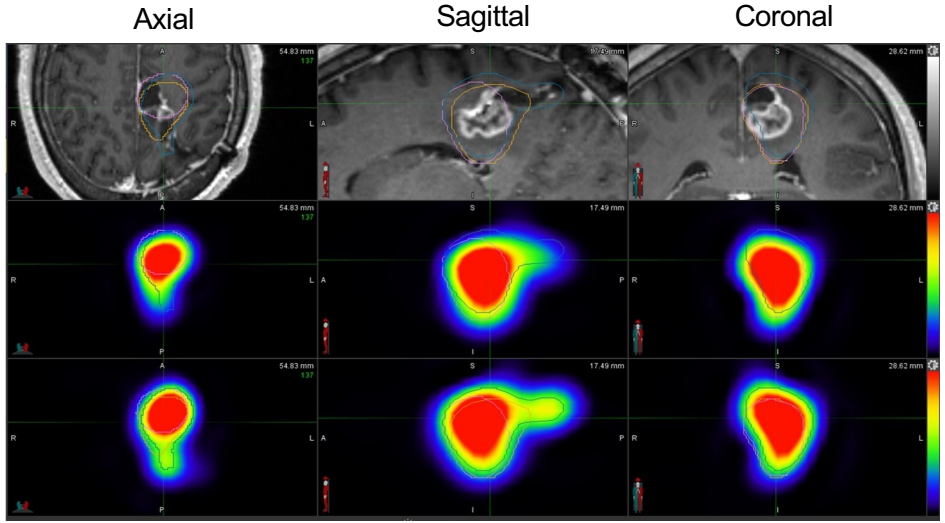
Example 01-014



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

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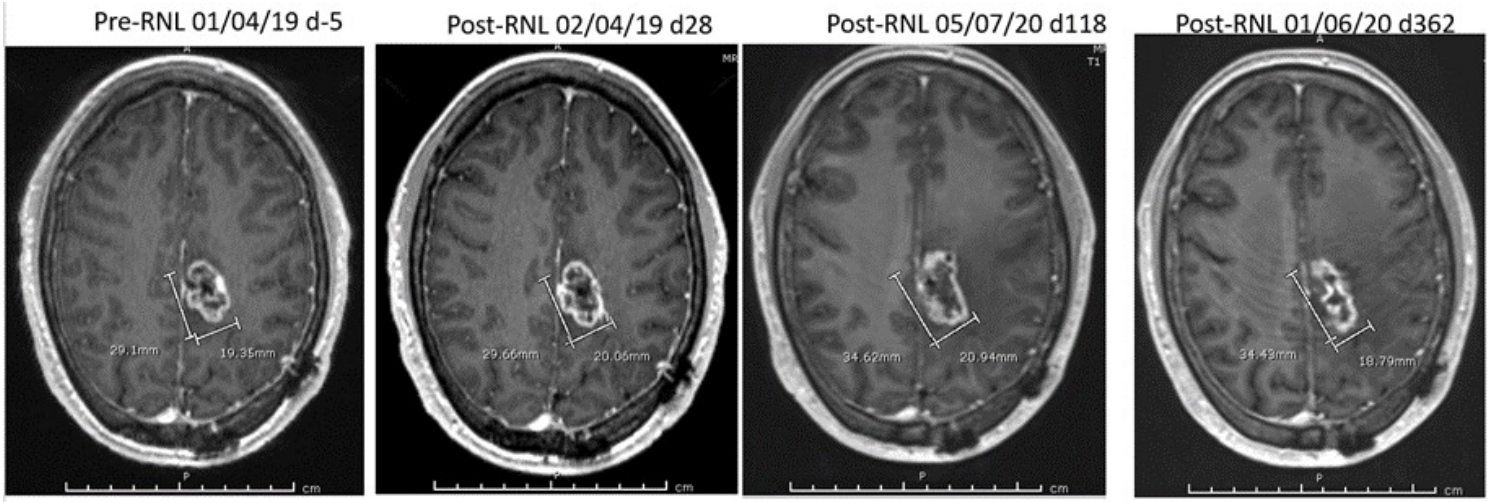
Example 01-014



- 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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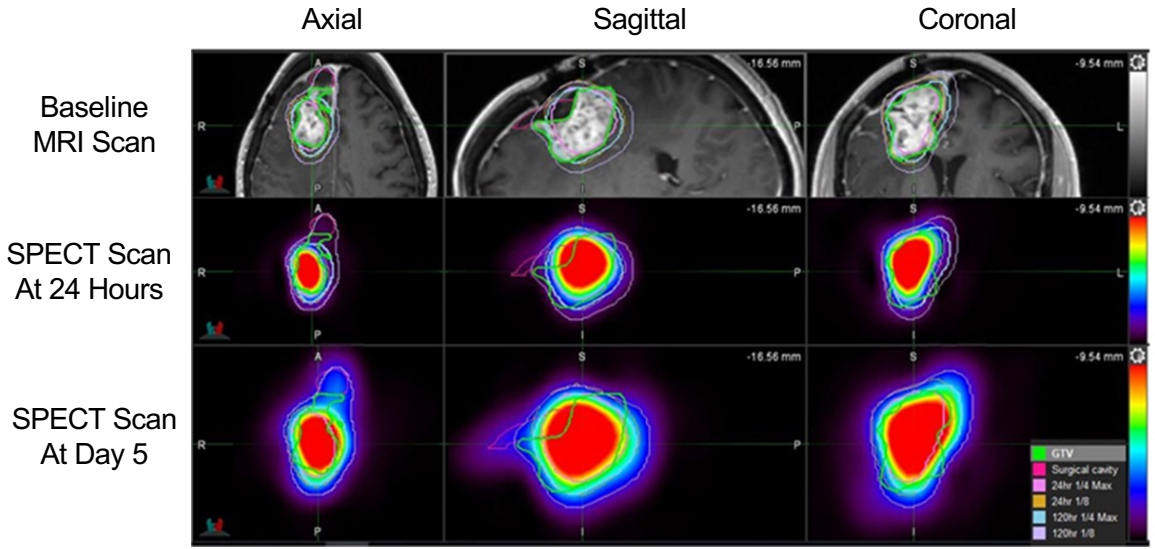
Example 01-017



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

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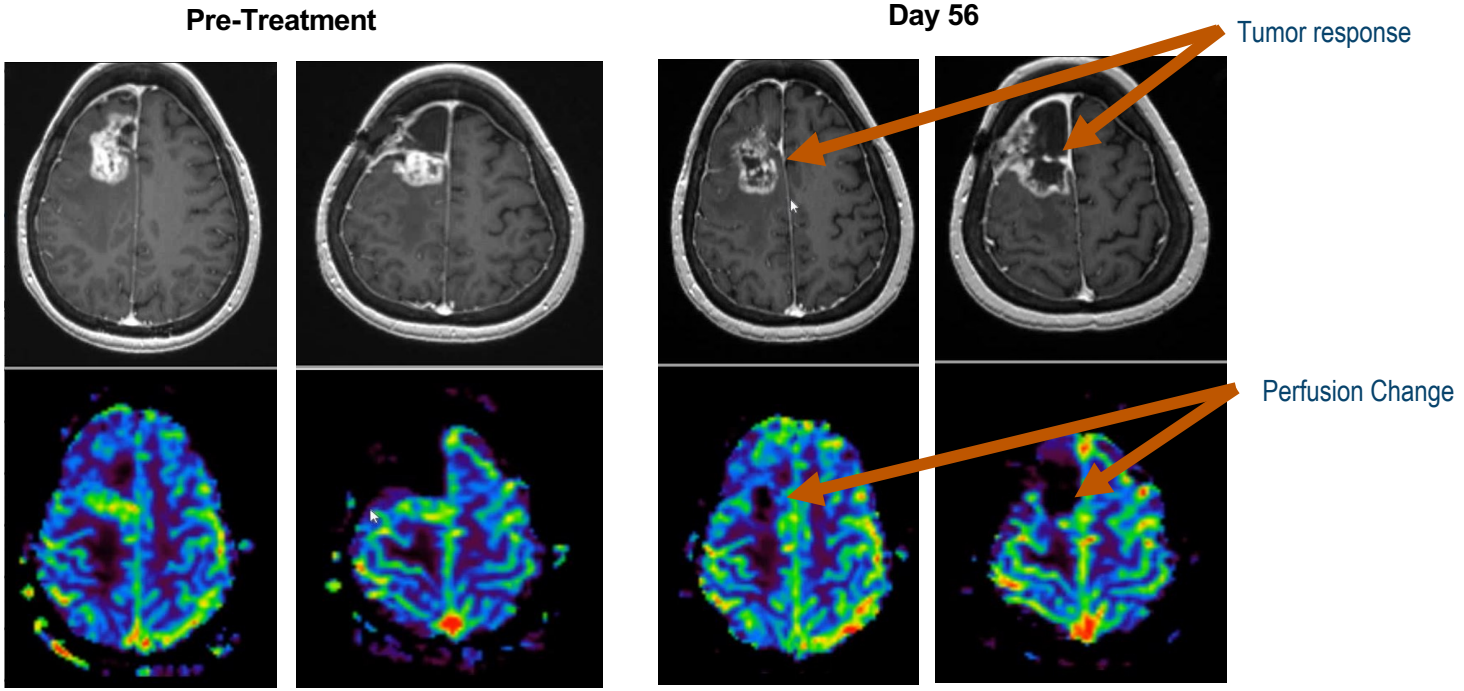
Example 01-017



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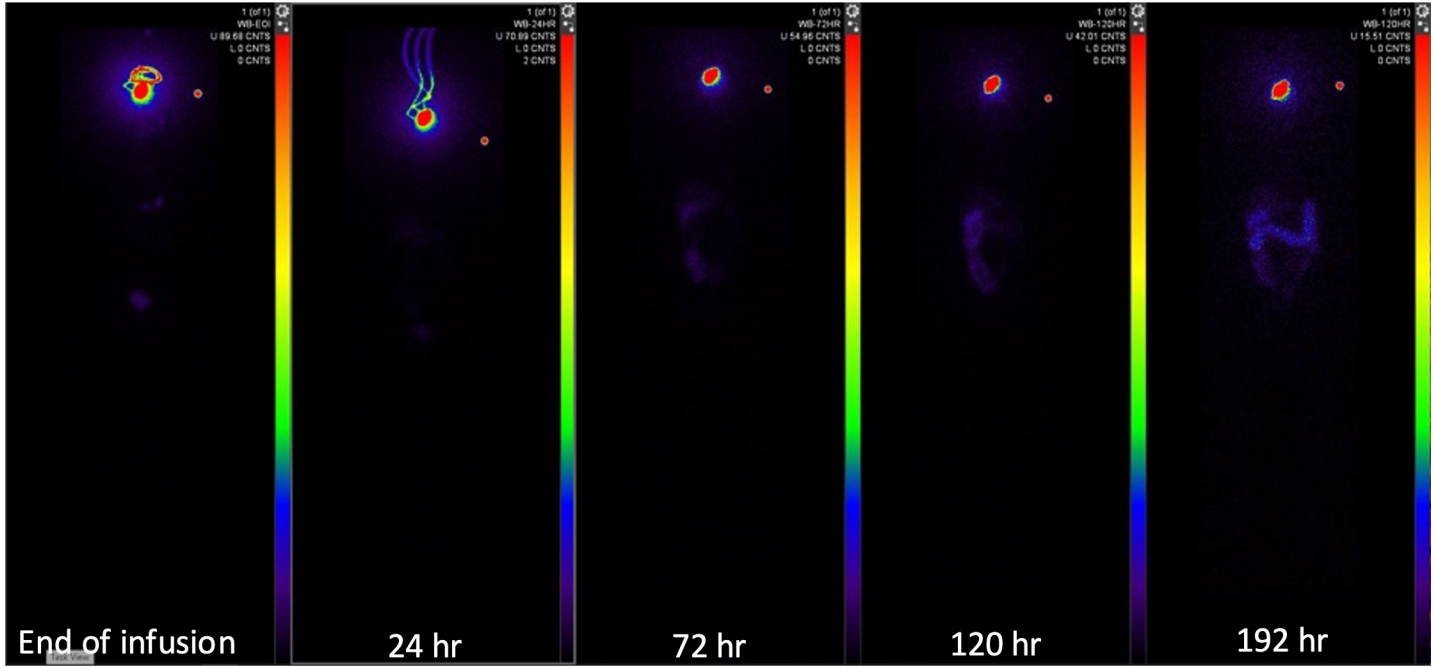
No Significant Extracranial Exposure



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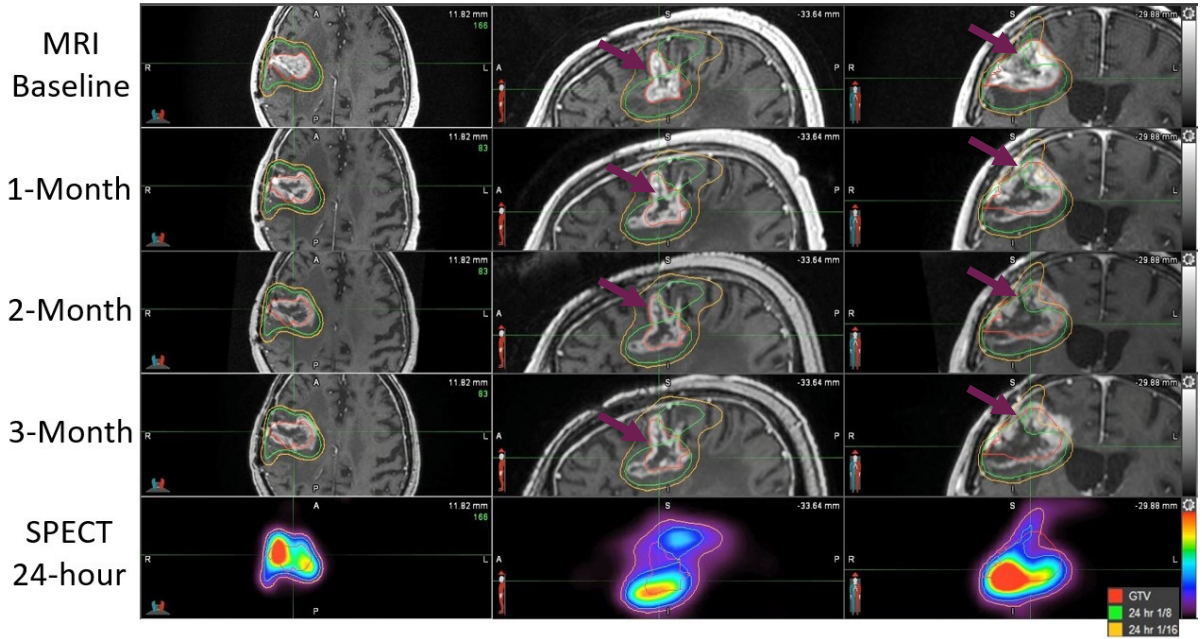
Coverage Correlates with Response



ReSPECT-GBM U.S. Phase 1 Clinical Trial

Patient	Gender	Dose (mCi)	Vol. (mL) Vi	Conc. (mCi/mL)	Catheters per Treatment plan	Catheters used in Treatment	Max Flow rate (µL/min)	iPLAN™ Tumor Volume (mL) TuV1	Treated Tumor Volume Percent TuV in TrV (%)*	Absorbed Dose to TuV2 (Gy [J/kg])	Patient	Alive	OS (days)	OS (weeks)
1	M	1.0	0.66	1.5	1	1	5.0	3.50	82.01%	143.00	1	N	909	130
2	M	1.0	0.66	1.5	1	1	5.0	1.08	74.91%	396.30	2	N	1065	152
3	M	1.0	0.66	1.5	1	1	5.0	0.88	33.11%	56.40	3	N	264	38
4	F	2.0	1.32	1.5	1	1	5.0	8.50	27.44%	8.90	4	N	51	7
5	M	2.0	1.32	1.5	1	1	5.0	2.20	90.40%	334.00	5	N	331	47
6	M	2.0	1.32	1.5	1	1	5.0	2.00	19.82%	21.85	6	N	46	7
7	F	4.0	2.63	1.5	1	1	5.0	18.20	36.30%	69.50	7	N	318	45
8	M	4.0	2.63	1.5	1	1	5.0	18.44	24.10%	38.17	8	N	175	25
9	M	4.0	2.63	1.5	1	1	5.0	2.50	89.20%	592.70	9	N	125	18
10	F	8.0	5.28	1.5	1	1	10.0	2.40	47.50%	57.20	10	N	145	21
11	M	8.0	5.28	1.5	2	2	10.0	15.10	59.00%	36.00	11	N	157	22
12	M	8.0	5.28	1.5	2	2	10.0	6.50	90.60%	418.60	12	N	1185	169
13	M	13.4	5.28	2.5	2	2	10.0	3.85	89.90%	516.90	13	Y	958	137
14	F	13.4	5.28	2.5	3	3	15.0	15.30	87.40%	336.60	14	N	246	35
15	M	13.4	5.28	2.5	3	3	15.0	15.96	98.80%	414.20	15	N	291	42
16	M	22.3	8.8	2.5	2	1 Cath Fail - Ended with 1	15.0	5.20	63.90%	93.20	16	N	140	20
17	F	22.3	8.8	2.5	4	4	15.0	22.00	81.40%	342.70	17	N	370	53
18	M	22.3	8.8	2.5	3	3	15.0	1.00	100.00%	424.60	18	Y	587	84
19	F	22.3	8.8	2.5	4	1 Cath Fail - Ended with 3	20.0	22.76	79.50%	62.60	19	N	185	26
20	F	22.3	8.8	2.5	2	2	20.0	3.50	94.80%	739.50	20	Y	461	66
21	M	22.3	8.8	2.5	2	1 Cath Fail - Ended with 1	20.0	2.40	99.10%	584.20	21	N	370	53
22	F	31.2	12.3	2.5	3	3	20.0	4.00	91.20%	197.00	22	N	219	31
23	M	31.2	12.3	2.5	3	3	20.0	9.84	69.20%	468.10	23	N	161	23

ReSPECT-GBM U.S. Phase 1 Clinical Trial

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	2	0	0	**3**
Vasogenic cerebral edema	0	0	2	0	0	**2**
Pneumonia	0	0	1	0	0	**1**

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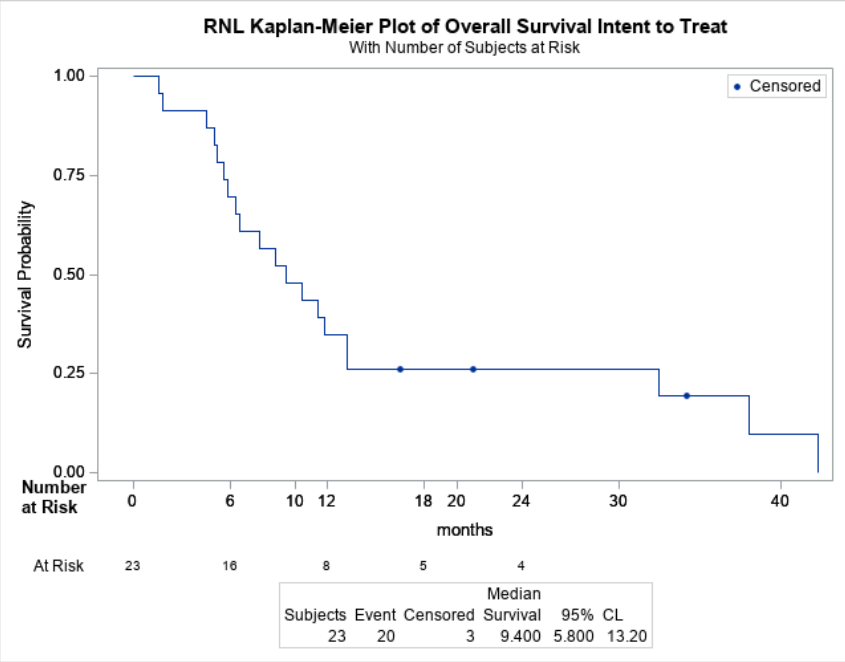
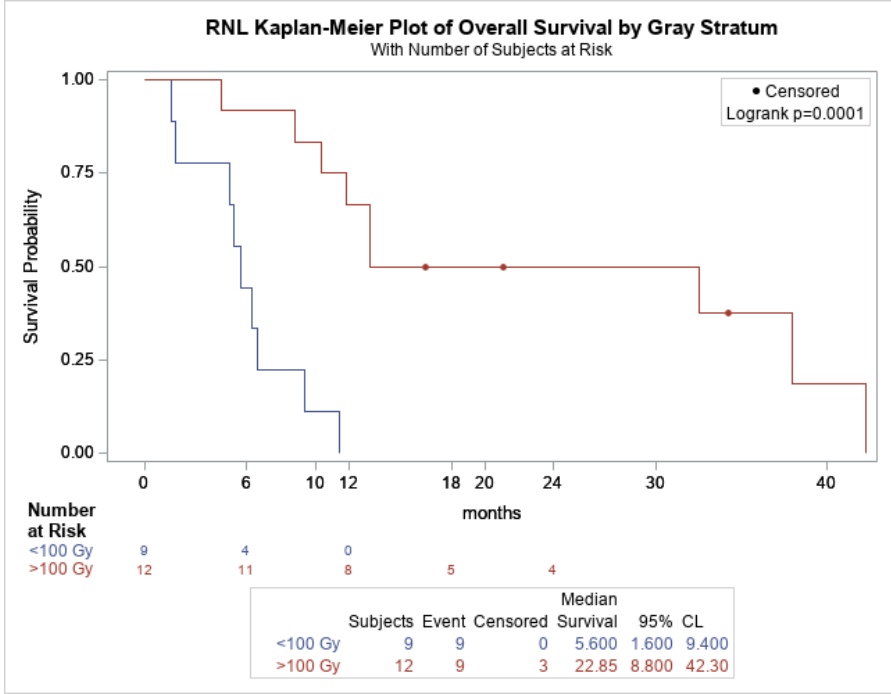
Efficacy





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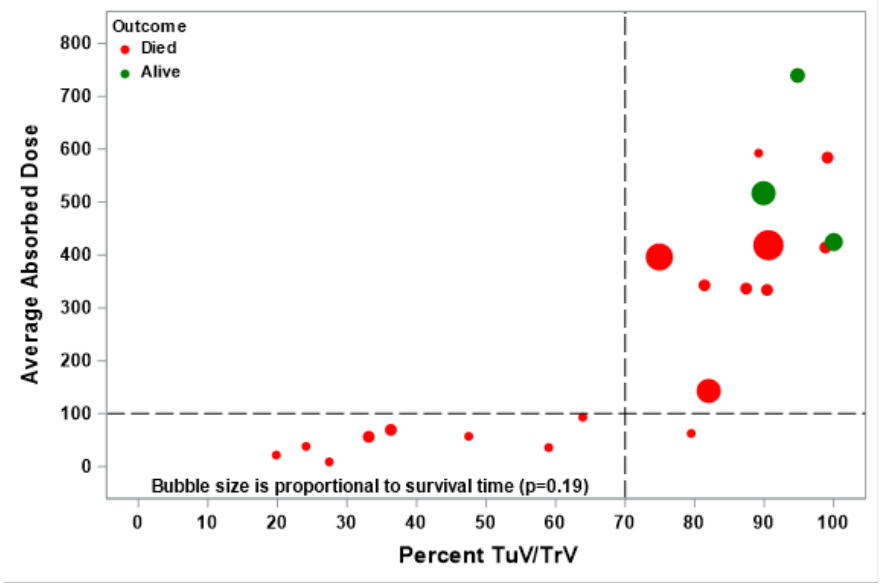
Efficacy



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

ReSPECT-GBM U.S. Phase 1 Clinical Trial

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 commencing with 22.3mCi in 8.8mL for rGBM less than 20mL in total volume

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THANK YOU

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