

PLUS THERAPEUTICS™

ReSPECT CLINICAL TRIALS

2021 Society for NeuroOncology
PLUS Therapeutics Investigator Roundtable

2021 Society for NeuroOncology

Investigator Roundtable

11.18.2021

Boston, MA

- PLUS Therapeutics
  - Dr. Marc Hedrick, President & CEO PLUS Therapeutics
- Investigators
  - **CED**- Dr. Toral Patel, Associate Professor, UTSW, Neurosurgeon
  - **ReSPECT Trial**- Dr. Andrew Brenner, Professor UTHSCSA, Neuro Oncology

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

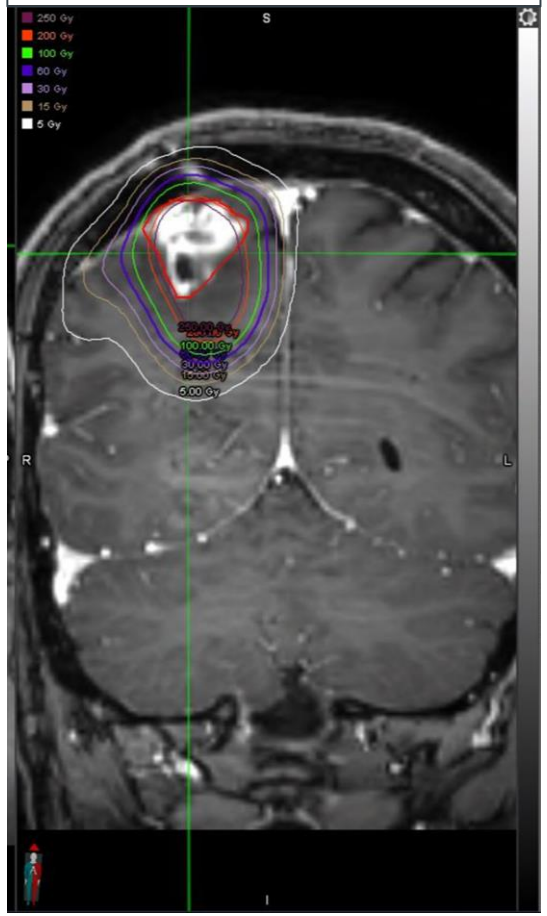


PLUS

Precision Targeted Radiation Therapy for Cancer

- Radiation therapy- 100 years of clinical use
- Approximately 40% of cancer patients receive radiation therapy
- Potentially any cancer can be cured if enough radiation delivered
- Precise, targeted delivery strategies can mitigate safety concerns
- Particle-based radionuclides- versatile, deliver very high radiation doses

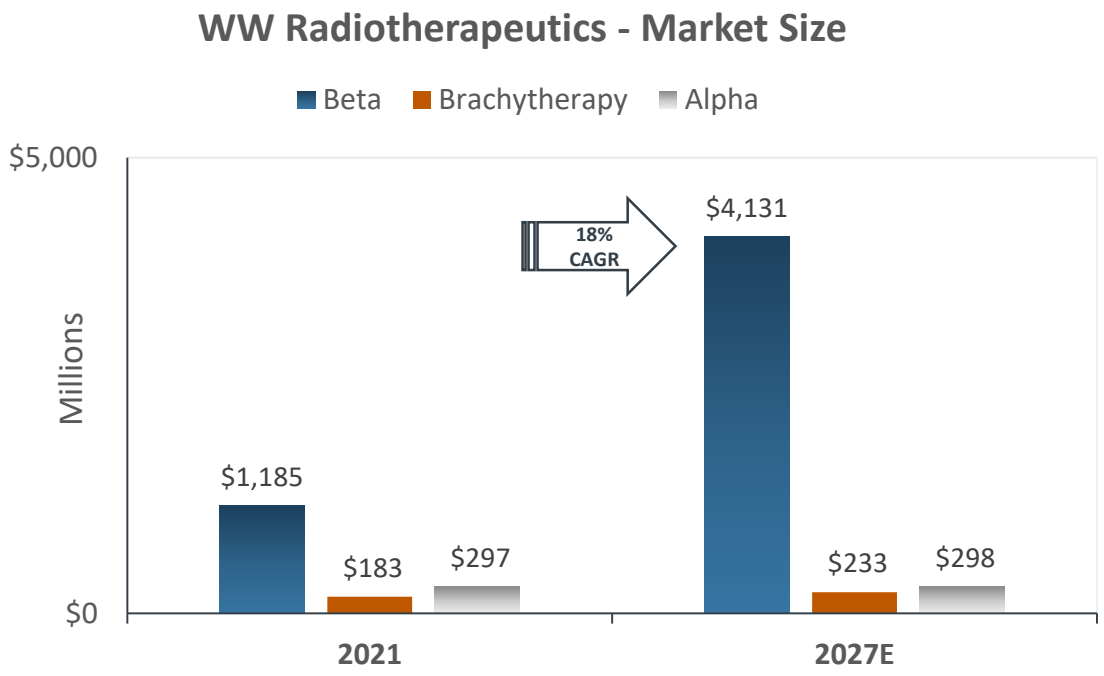
Targeted Delivery of ^{186}RNL



Source: American Cancer Society

Radiotherapeutic Market Growth Sparking Investment & Deals

Driven by Precision Targeting Technology



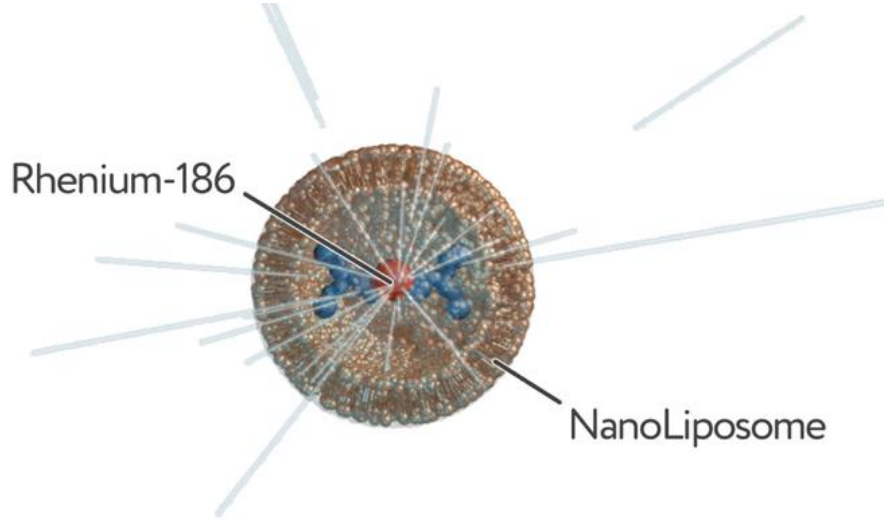
Transaction	Ownership	Date	Size
RayzeBio	Private (USA)	Jun 2021	$108M
Point Biopharma	Listed in NY (USA)	Jun 2021	$287M
Fusion Pharmaceuticals	Listed in NY (USA)	Jun 2021	$213M
Noria Therapeutics acquired by Bayer	Private (USA)	Jun 2021	N/A
PSMA Therapeutics acquired by Bayer	Private (USA)	Jun 2021	N/A
ITM-Munich	Private (Germany)	Jun 2021	$30M
Oncoinvent	Private (Norway)	Jun 2021	$29M
Nordic Nanovector	Listed in Oslo (Norway)	Apr 2021	$7M
Alpha-9 Theranostics	Private (Canada)	Apr 2021	$11M
Aktis Oncology	Private (USA)	Mar 2021	$72M
Y-mABS Therapeutics	Listed in NY (USA)	Feb 2021	$115M
Reflexion Medical	Private (USA)	Apr 2020	$100M
Blue Earth Diagnostics acquired by Bracco	Private (UK)	Jun 2019	$450M
Endocyte acquired by Novartis	Listed in NY (CH/USA)	Oct 2018	$2.1B
AAA acquired by Novartis	Listed in NY (CH/USA)	Jan 2018	$3.9B
Sirtex acquired by CDH	Private (China)	Jan 2018	$1.4B

Source: Nuclear Medicine/Radiopharmaceuticals Global Market

PLUS™ THERAPEUTICS

Lead Drug: Rhenium Nanoliposome or RNL™

Proprietary Nanoscale Compound with a Unique Isotope



Rhenium NanoLiposome™

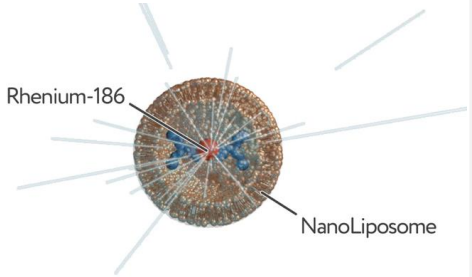
Current Disease Pipeline

+ Recurrent glioblastoma
+ Leptomeningeal metastasis
+ Pediatric brain cancer

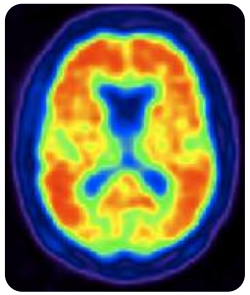
PLUS™ THERAPEUTICS

A Novel Approach to Intracranial Neoplasms

Marriage of New Developments Across Multiple Specialties



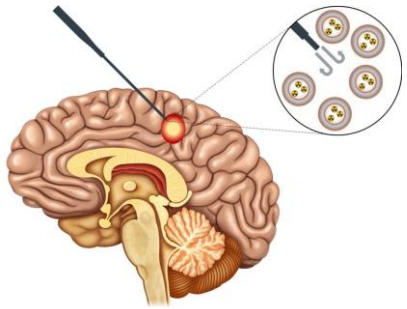
Nano Drug Delivery



Imaging & Nuclear Medicine



Radiation & Oncology

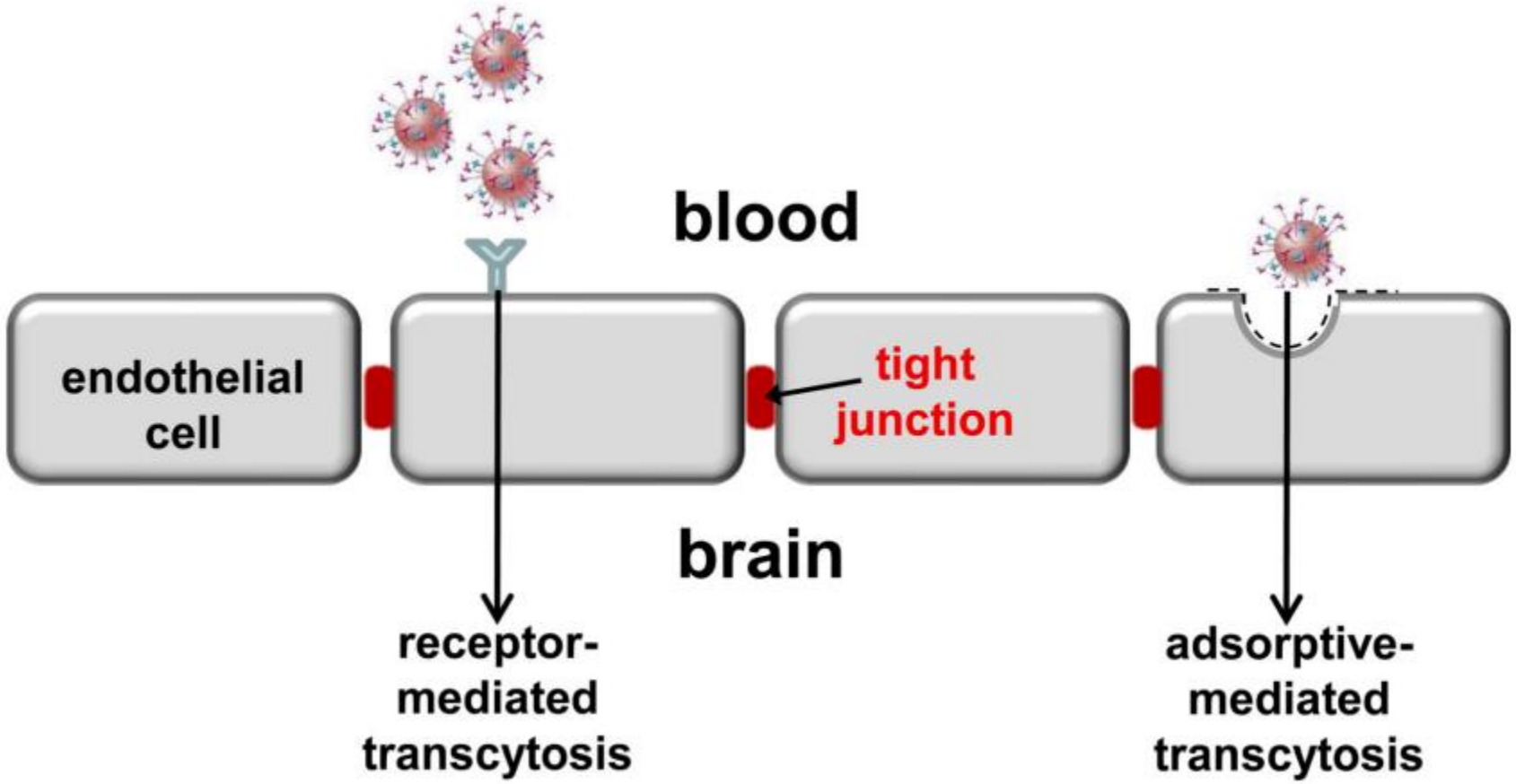


Neurosurgery

Convection-Enhanced Delivery in Neurosurgery

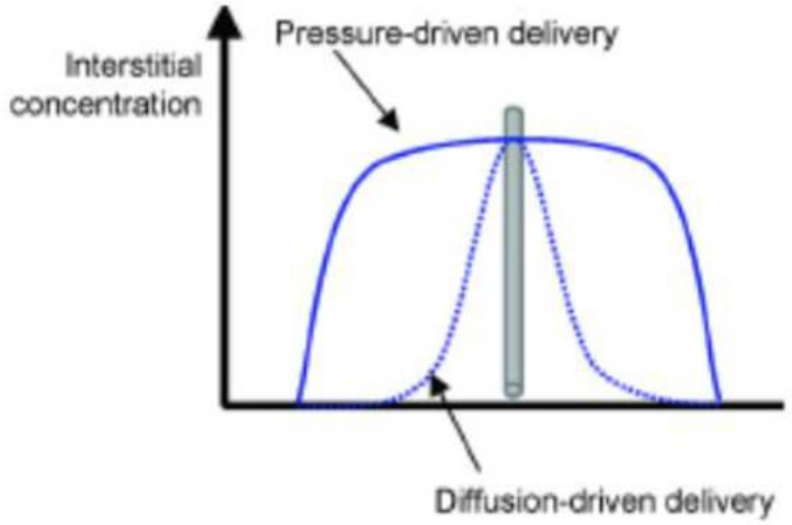
Toral R. Patel, MD
Associate Professor
Department of Neurological Surgery
UT Southwestern Medical Center

Drug Delivery to the CNS



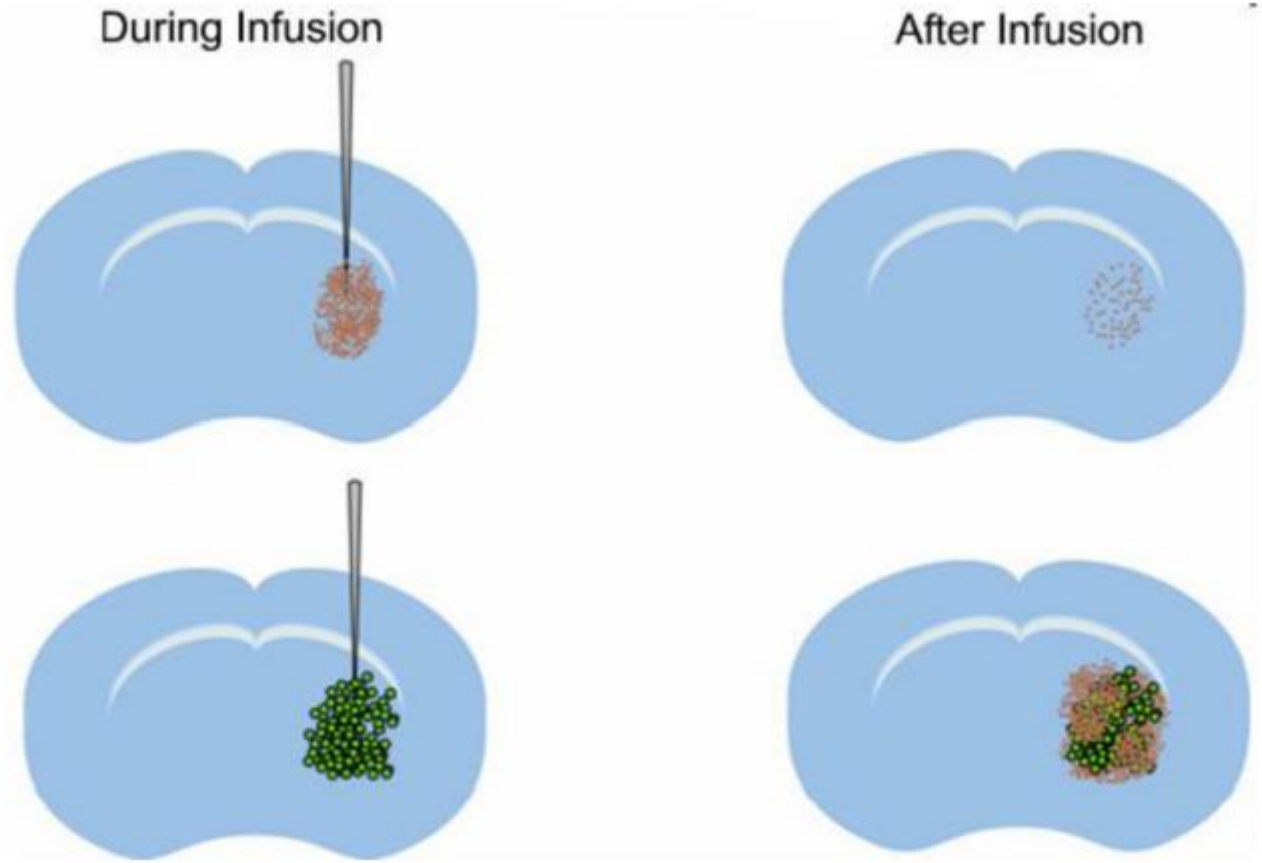
Adv Drug Deliv Rev. 2012 May 15; 64(7): 701–705. doi:10.1016/j.addr.2011.12.006.

Convection Enhanced Delivery



- Modeling approaches
  - Complicated modeling to optimize simulations for flow trajectory and infusion parameters
  - Simplified model to define clinical use (protocol development)
    - Darcy's Law: $q = -k/\mu * \Delta p$ → flow rate, volume

CED of Nanoparticles



Adv Drug Deliv Rev. 2012 May 15; 64(7): 701–705. doi:10.1016/j.addr.2011.12.006.

PRECISE Trial

Phase III randomized trial of CED of IL13-PE38QQR vs Gliadel wafers for recurrent glioblastoma†

Sandeep Kunwar, Susan Chang, Manfred Westphal, Michael Vogelbaum, John Sampson, Gene Barnett, Mark Shaffrey, Zvi Ram, Joseph Piepmeier, Michael Prados, David Croteau, Christoph Pedain, Pamela Leland, Syed R. Husain, Bharat H. Joshi, and Raj K. Puri; for the PRECISE Study Group‡

Neuro-Oncology 12(8):871–881, 2010.
doi:10.1093/neuonc/nop054
Advance Access publication February 4, 2010

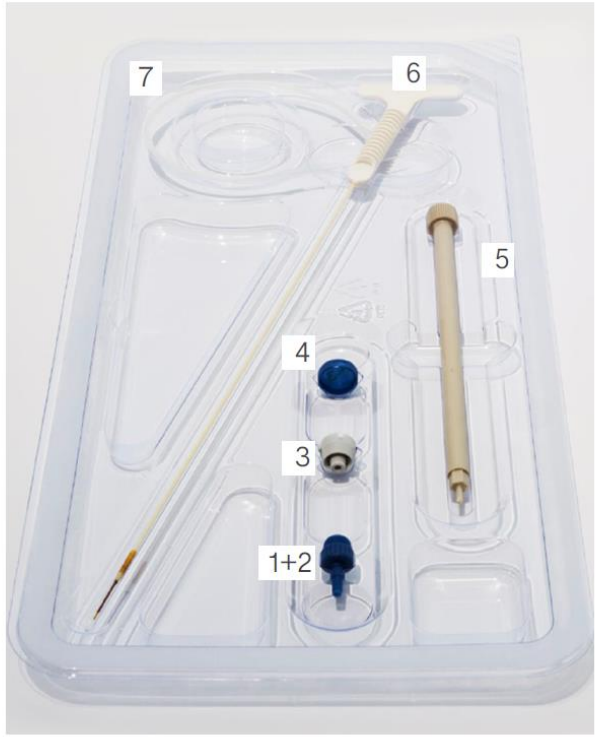
NEURO-ONCOLOGY

Catheter Design

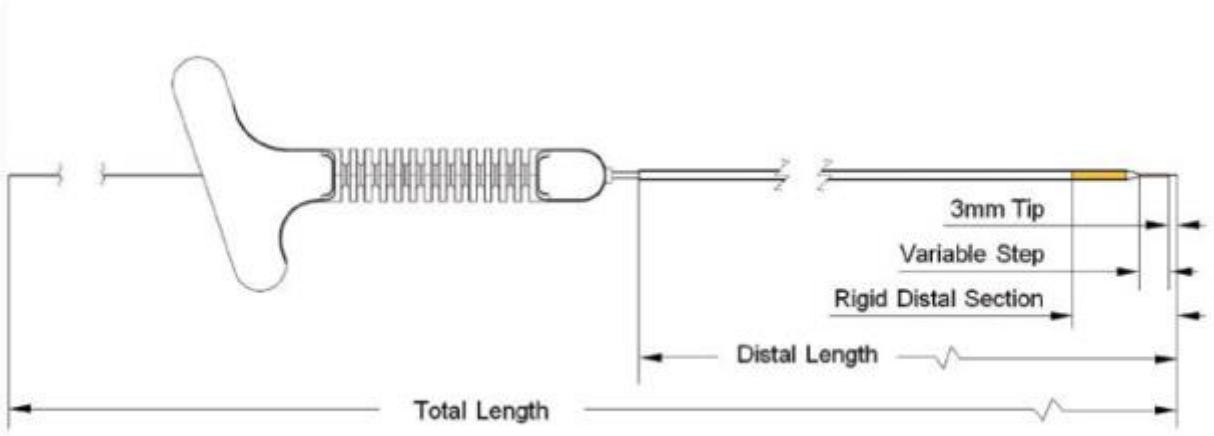
Brainlab flexible catheter

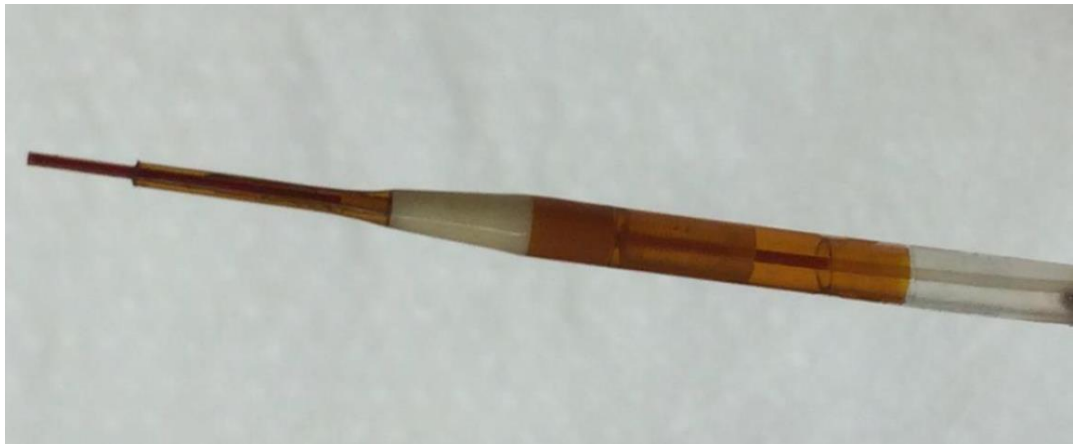
Components

1. Bone Anchor
2. Clear soft silicone seal inside the bone anchor
3. Compression cap
4. Cover
5. Driver
6. Catheter with inserted stylet
7. Inner fluid carrying lumen



Catheter Design



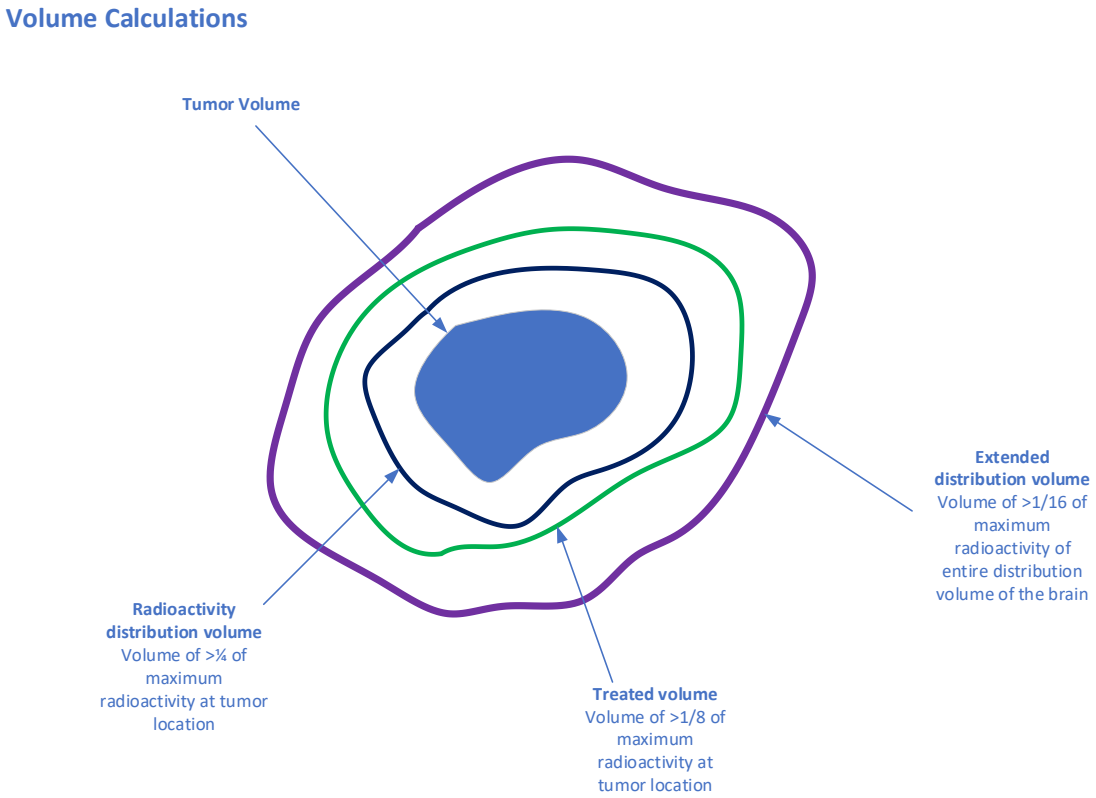


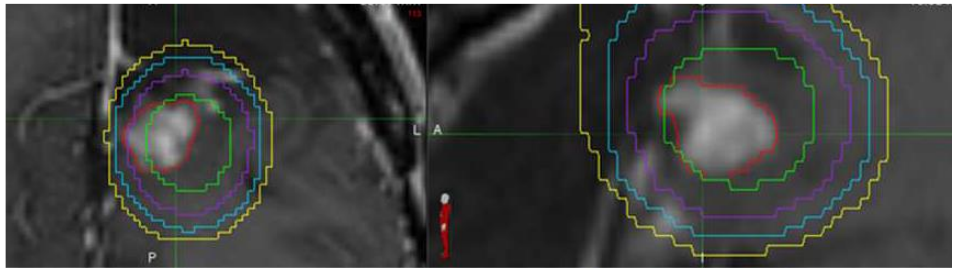
Goals for Optimization:

Full tumor coverage, including margin up to 2cm (occult microscopic disease).

Absorbed dose of all tumor cells ≥ lethal dose.

Volume of Distribution





Varioguide™ Drill Kit

Components

1. Device Guide
2. Drill Guide
3. Drill Bit
4. Lancet



TECHNICAL SPECIFICATIONS

Product Code			19769	19779
Drill guide	Length	inch	4.50	
		mm	114.3	
Drill bit	Outside Dia.	inch	0.134	
		mm	3.40	
	Length	inch	5.98	
		mm	151.9	
Lancet	Length	inch	5.92	
		mm	150.4	
Device guide	Inner Dia.	inch	0.075	0.085
		mm	1.90	2.16
	Outside Dia.	inch	0.310	
		mm	7.89	

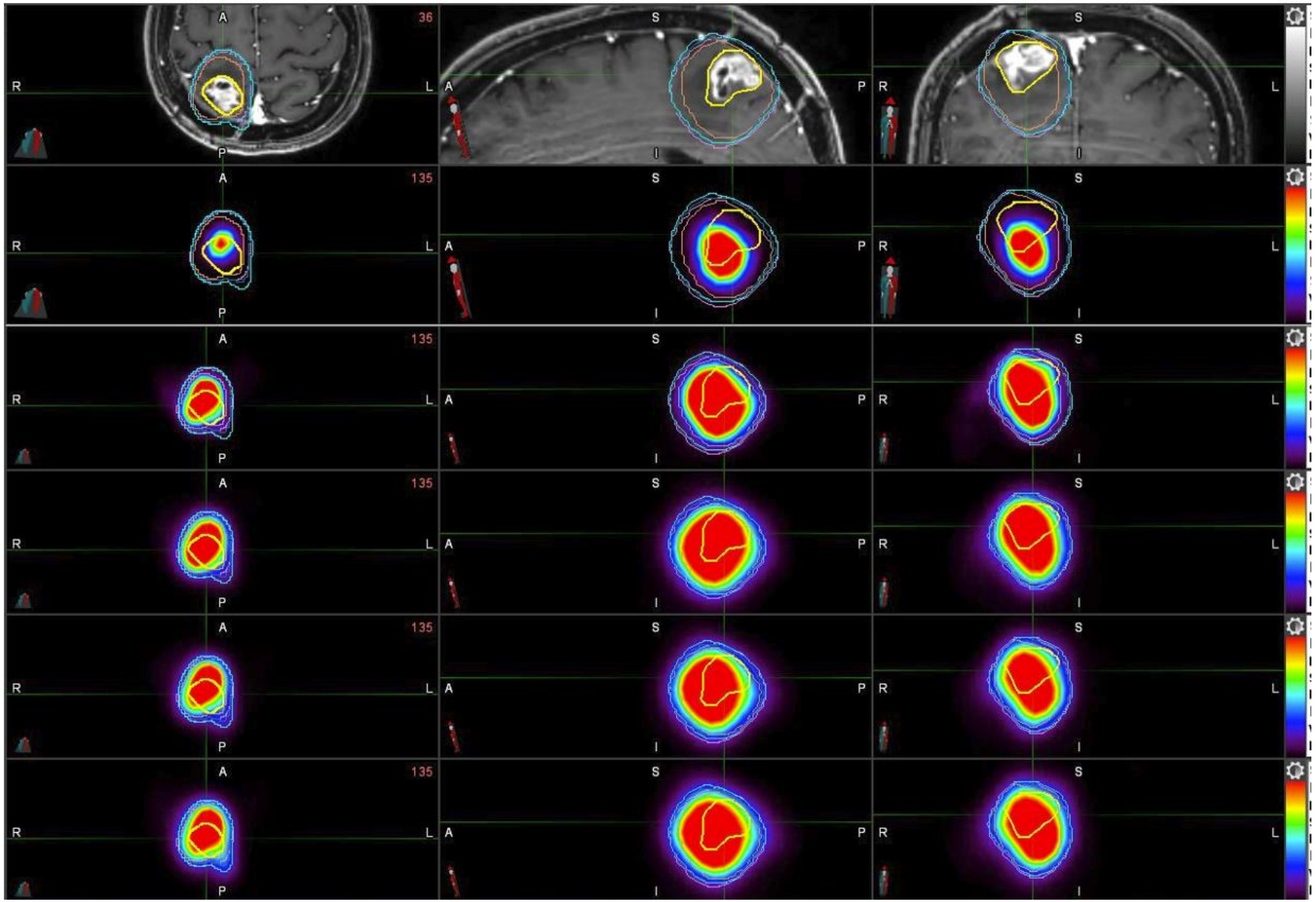
Table 1 – Nominal Device Dimensions

Dose Escalation Protocol

Cohort	Infused Volume (mL)	Total 186RNL Activity (mCi)	Concentration (mCi/mL)	Average Absorbed Dose (Gy)	Status
1	0.66	1.0	1.5	198	**Enrolling cohort 7** **(n = 22 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	
6*	**8.80**	**22.3**	**2.5**	**584**	
7	**12.30**	**31.2**	**2.5**	**TBD**	

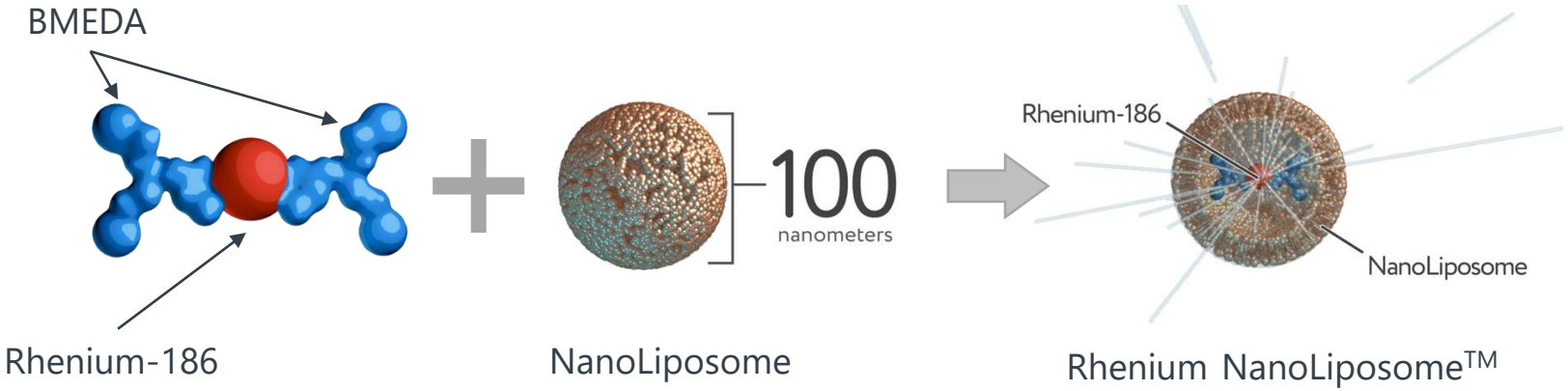
- 1-4 catheters used
- Maximum CED flow rate 5-20 µl/min

Clinical Experience



Rhenium Nanoliposome or RNL™

Proprietary Nanoscale Compound with a Unique Isotope

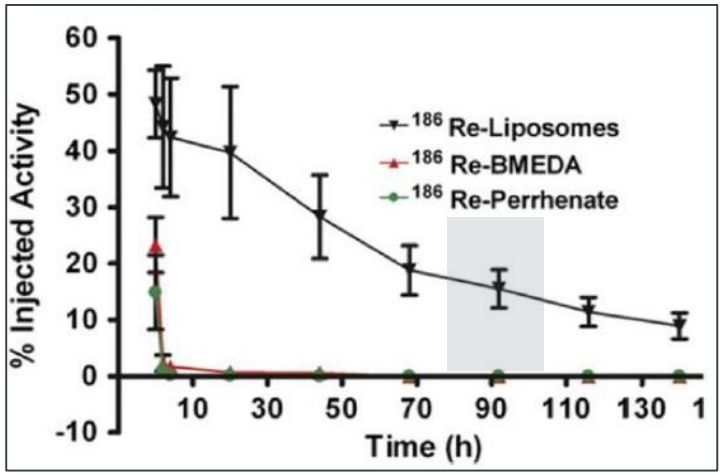


RHENIUM 186

- 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

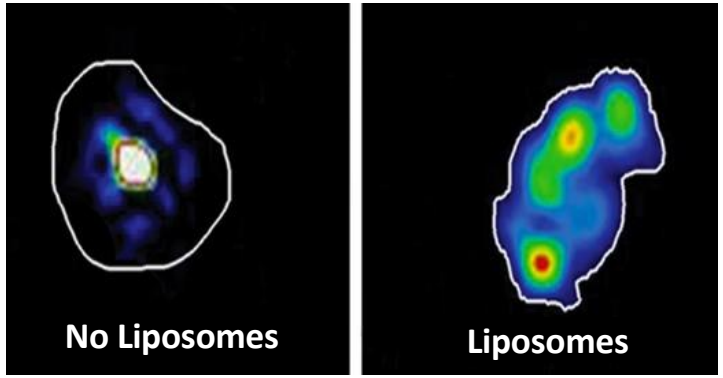
Spatiotemporal Behavior of RNL™ Following Brain Delivery

Prolonged Half-Life and Brain Retention



Tumor Retention

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



Tumor Dispersion

Liposomal encapsulation significantly extends rhenium-186 retention within the tumor and therefore improves dispersion characteristics in tissues.

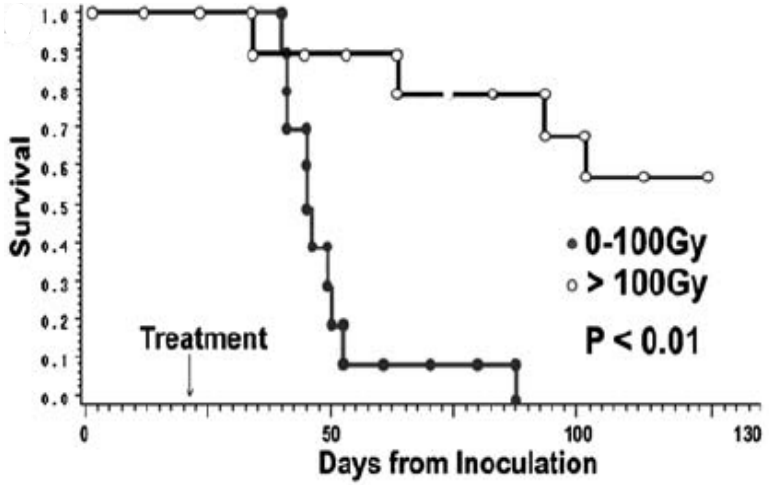
PLUS™ THERAPEUTICS

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

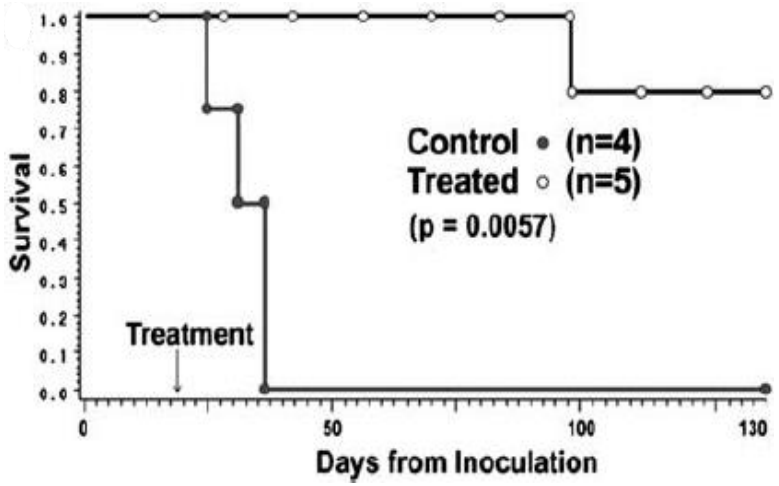
RNL™ Preclinical Data

RNL Significantly Prolongs Survival in U87 & U251 Intracranial Xenograft Models

U87



U251

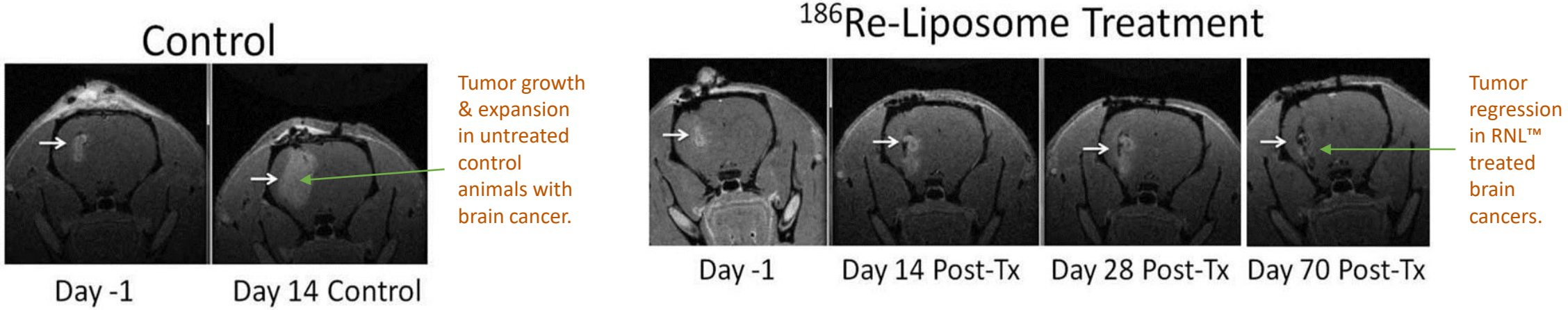


- Doses of up to 1,845 Gy were tolerated without weight loss or neurological deficit.
- No maximum tolerated dose of RNL reached.
- Statistically significant prolongation in survival, limited only be the end of the experiment.
- Blinded histologic analysis by neuropathologist showed no residual tumor all treated animals.

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

RNL™ Preclinical Data

Tumor Regression in U87 & U251 Intracranial Xenograft Models



- 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.

PLUS™ THERAPEUTICS

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

RNL™ for Recurrent Glioblastoma

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

ReSPECT CLINICAL TRIALS

Dose Escalation Scheme

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6*	**8.80**	**22.3**	**2.5**	**584**	
7	**12.30**	**31.2**	**2.5**	**TBD**	

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Key Patient Demographics

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 Bevucizumab	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%)	

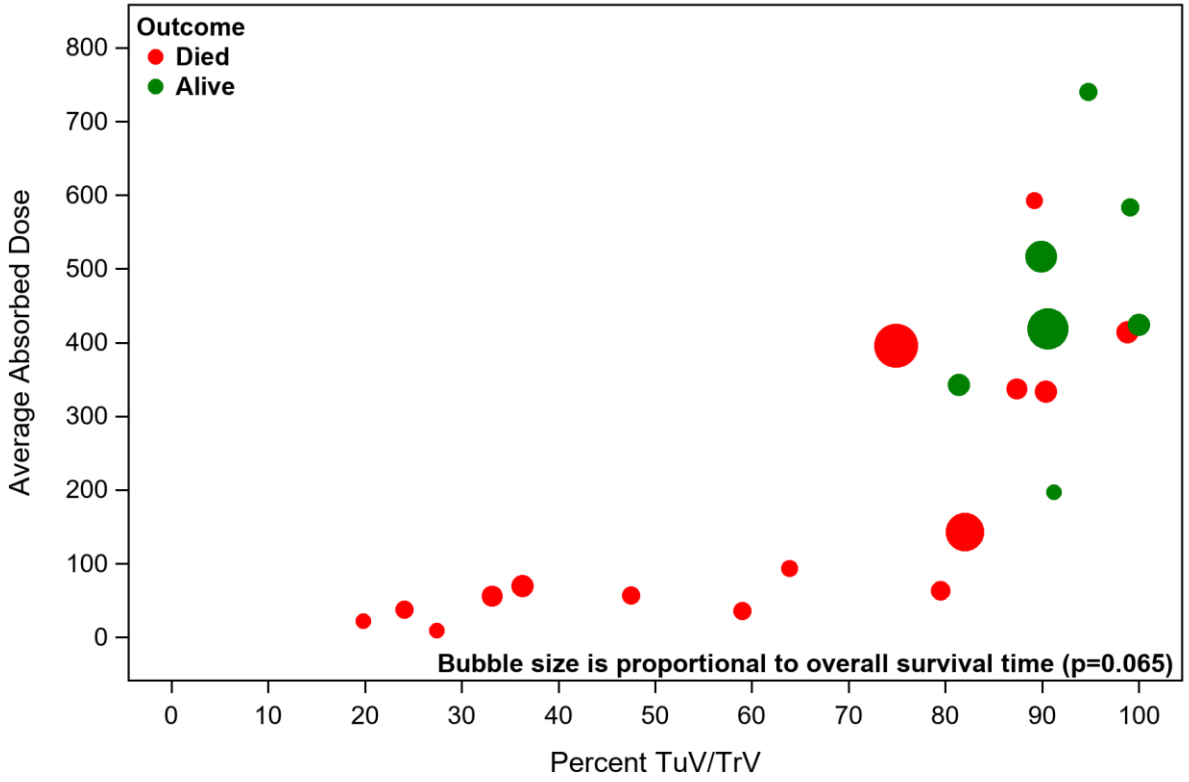
Convection Enhanced Delivery

- Twenty-two patients across 7 dosing cohorts received a range of 1.0-31.2 mCi in a volume of 0.6-12.3 mL.
- The maximum CED administration rate was 5-20 µl/min and 1-4 catheters were used per patient.
- Average absorbed radiation dose to the tumor (AARD) was 273 Gy (8.9-740 Gy) across all cohorts, while exposure outside the brain was negligible.
- In the 12 patients in cohorts 1-4, AARD >100Gy was 5/12 patients (42%) vs. 8/10 (80%) of patients treated thus far in cohorts 5-7.
- Tumor coverage or percent tumor volume (TuV) in the treated volume (TrV) aka. %TuV/TrV, was 71% (19.8%-100%) and correlated to AARD.
- In 5/22 patients receiving prior bevacizumab therapy, the AARD was 149 Gy and the %TuV/TrV was 47.9%. In 17 patients not receiving prior bevacizumab, AARD was 302 Gy and the percent TuV/TrV was 77.7%.

Safety

- **In 22 subjects with recurrent GBM receiving a single administration of 186RNL, we found that RNL to be safe and well-tolerated. No dose limiting toxicities observed.**
- There were no Adverse Events (AEs) with outcome of death, or discontinuations due to AEs. Most AEs were mild or moderate (Grade 1 or 2) in intensity and non-serious. The AEs with the highest incidence were: fatigue (50.0%), muscular weakness and headache (33.3% each) and gait disturbance (27.8%).
- Most AEs were deemed causally unrelated to 186RNL except one case of scalp discomfort, considered related to the surgical procedure, and one case of cerebral edema. Grade 3 AEs were leukocytosis, hyperglycemia, muscular weakness, seizure, brain edema, avascular necrosis of the shoulder (worsening), vasogenic cerebral edema and pneumonia. All were considered unrelated to 186RNL by the Principal Investigator with the exception of brain edema for one subject, considered possibly related to 186RNL.
- Serious Adverse Events (SAEs) were reported for two subjects in cohort 2 (seizure and vasogenic cerebral edema), one subject each in cohort 4 and cohort 5 (both seizure), and two subjects in cohort 6 (pneumonia, avascular necrosis of the shoulder (worsening) and cerebral edema). All SAEs were deemed unrelated to 186RNL by the Investigator except cerebral edema in one subject, considered possibly related to 186RNL and/or tapering of oral corticosteroids and none led to study discontinuation.
- We observed no meaningful differences or patterns in the incidence of treatment emergent AEs across cohort groups.

Threshold Effect: Correlation of Overall Survival to Drug Delivery



Overall survival in terms of Average Absorbed Radiation Dose to the tumor and tumor coverage measured by Percent TuV/TrV. The analysis was based on a proportional hazards model of overall survival in days in terms of average absorbed dose, percent TuV/Trv, and the interaction term, suggesting that survival time increases with both absorbed dose and percent TuV/Trv (p=0.065) based on a sample size N=22.

Overall Survival

	Days		Weeks		
	Mean	Median	Mean	Median	No. Alive
All 22 pts	336.6	231.5	48.1	33.1	7
13 Pts >100 Gy	453.8	330.0	64.8	47.1	7
9 Pts < 100Gy	167.3	156.0	23.9	22.3	0

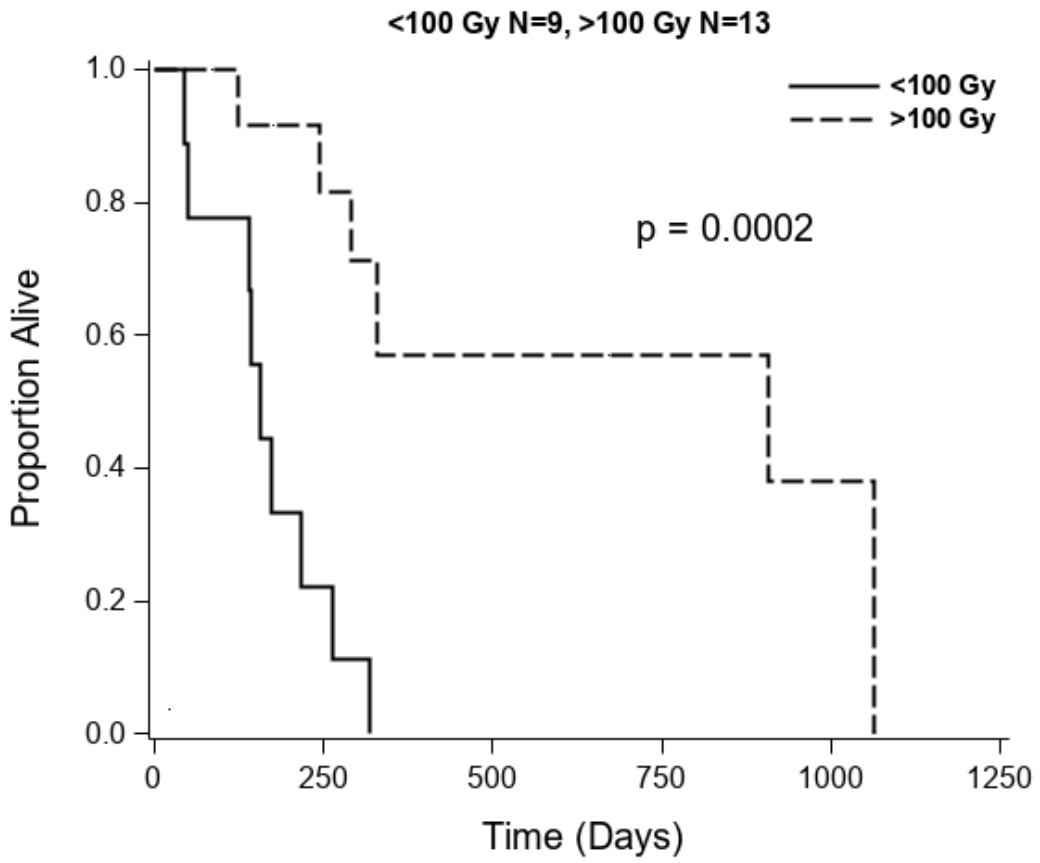
Comparative Overall Median Survival in 694 Recurrent GBM Patients

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**

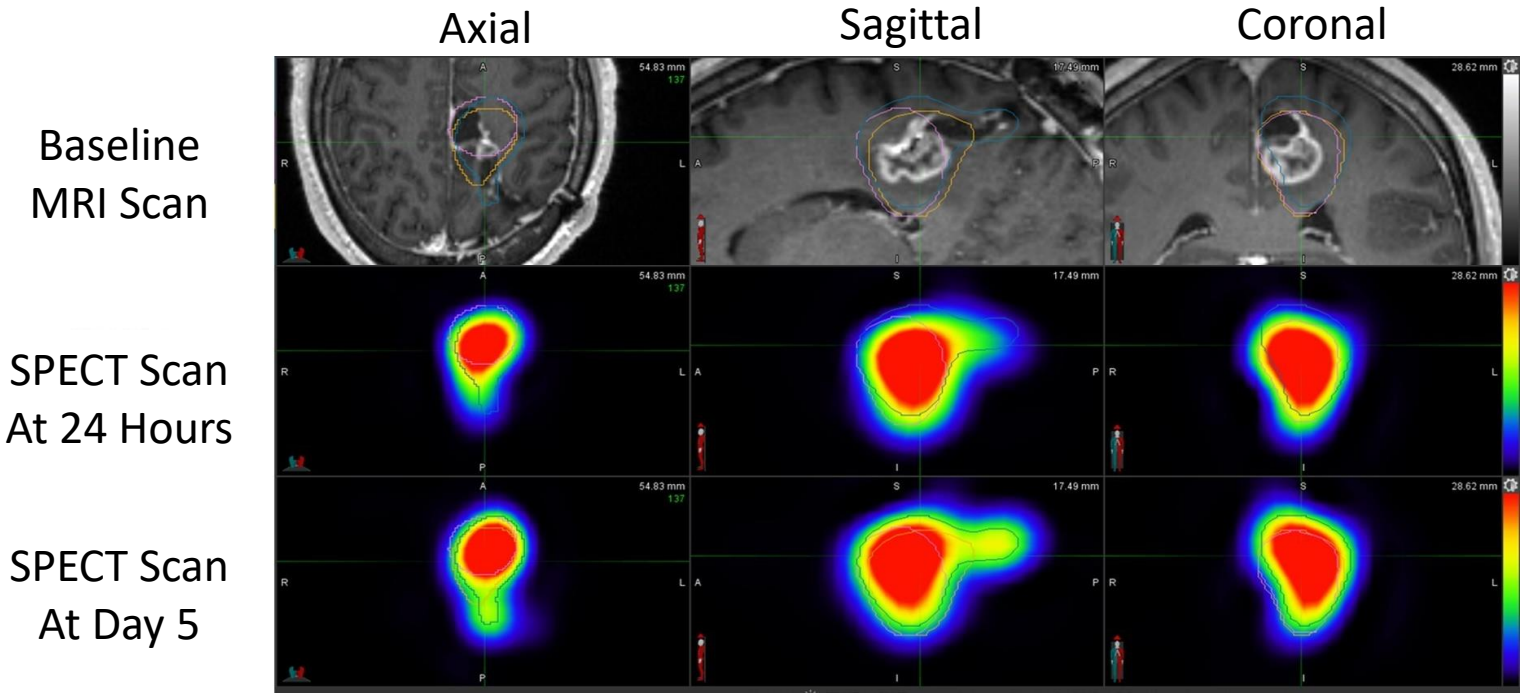
Abbreviations: ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance status; N, number of patients treated; NA = not applicable; RCT, randomized controlled trial; TThP, treatment through progression

Kaplan Meier- OS Therapeutic vs. Nontherapeutic Radiation



Tumor Coverage and Retention

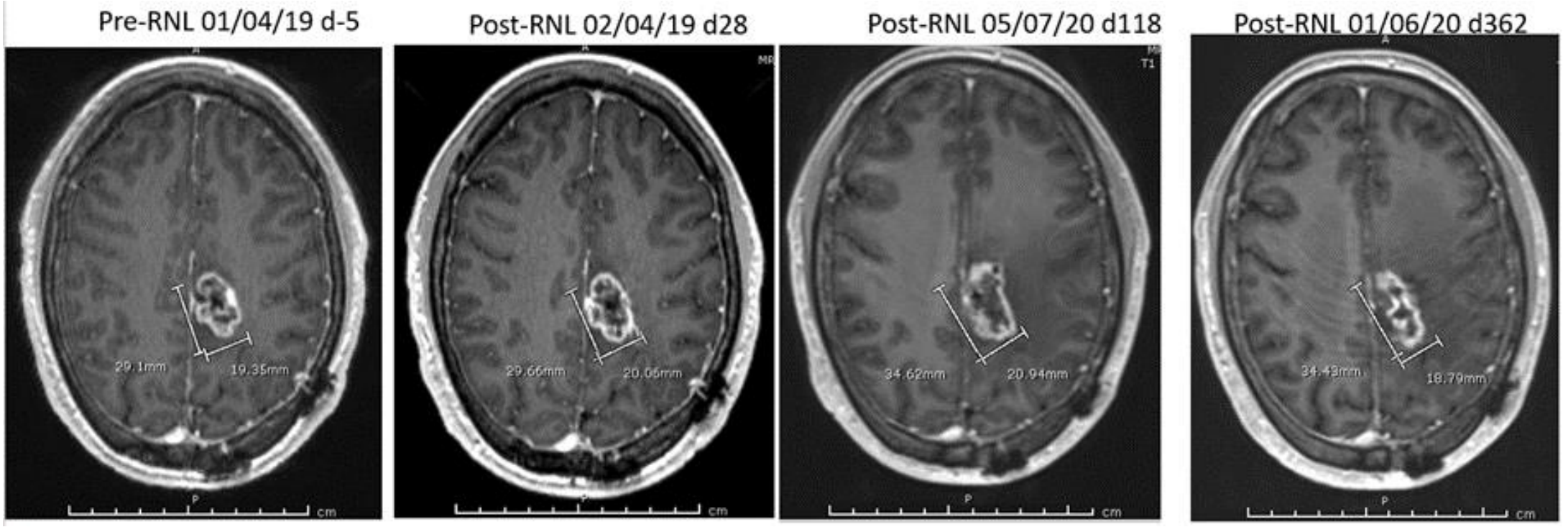
Subject 01-014



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

Natural History of Recurrent GBM Lesions After RNL™

Subject 01-014: Tumor Response Observed to Day 362



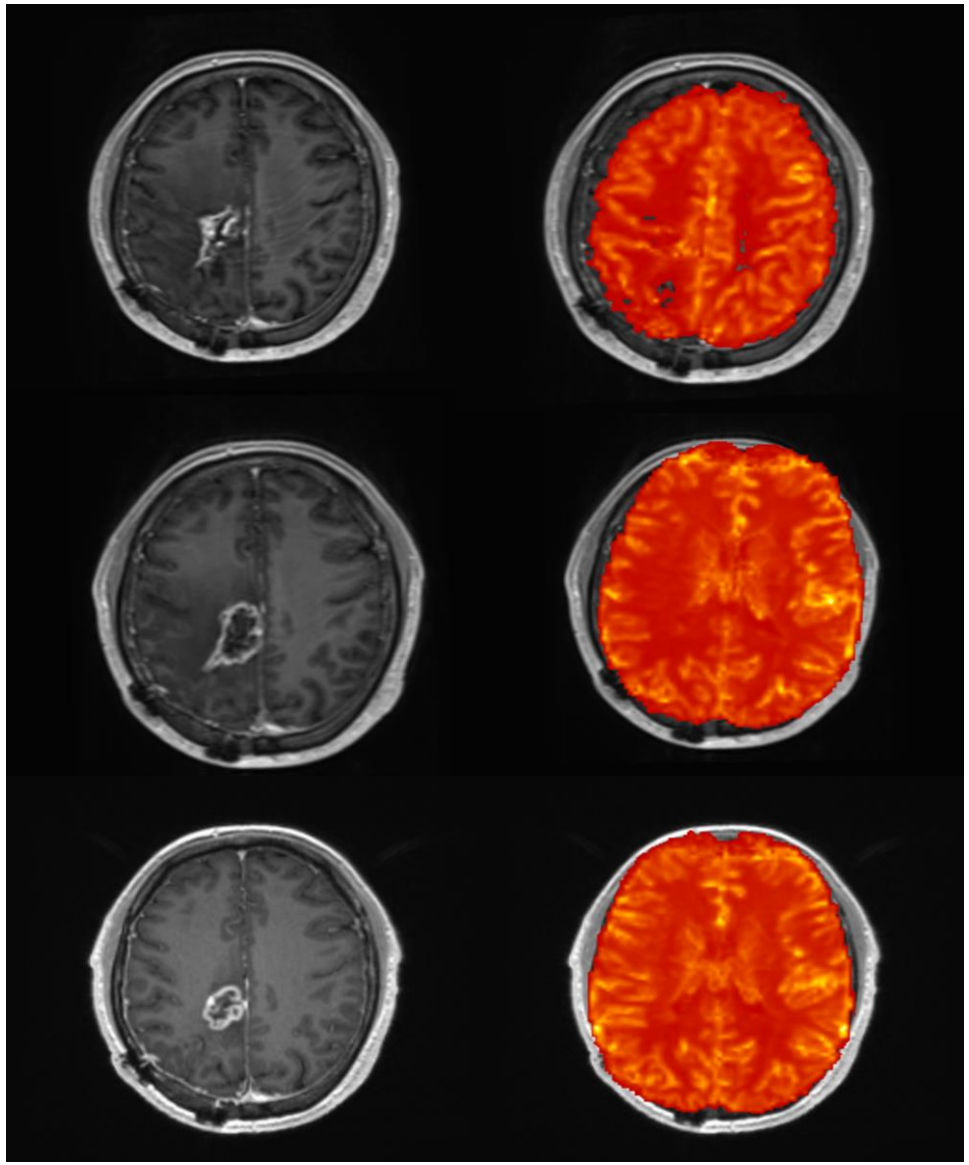
- MRI scans revealed an initial increase in size which peaked at Day 118, with some associated edema, followed by tumor shrinkage out to at least Day 362
- Patient remains alive (>900 days)

Pseudoprogression

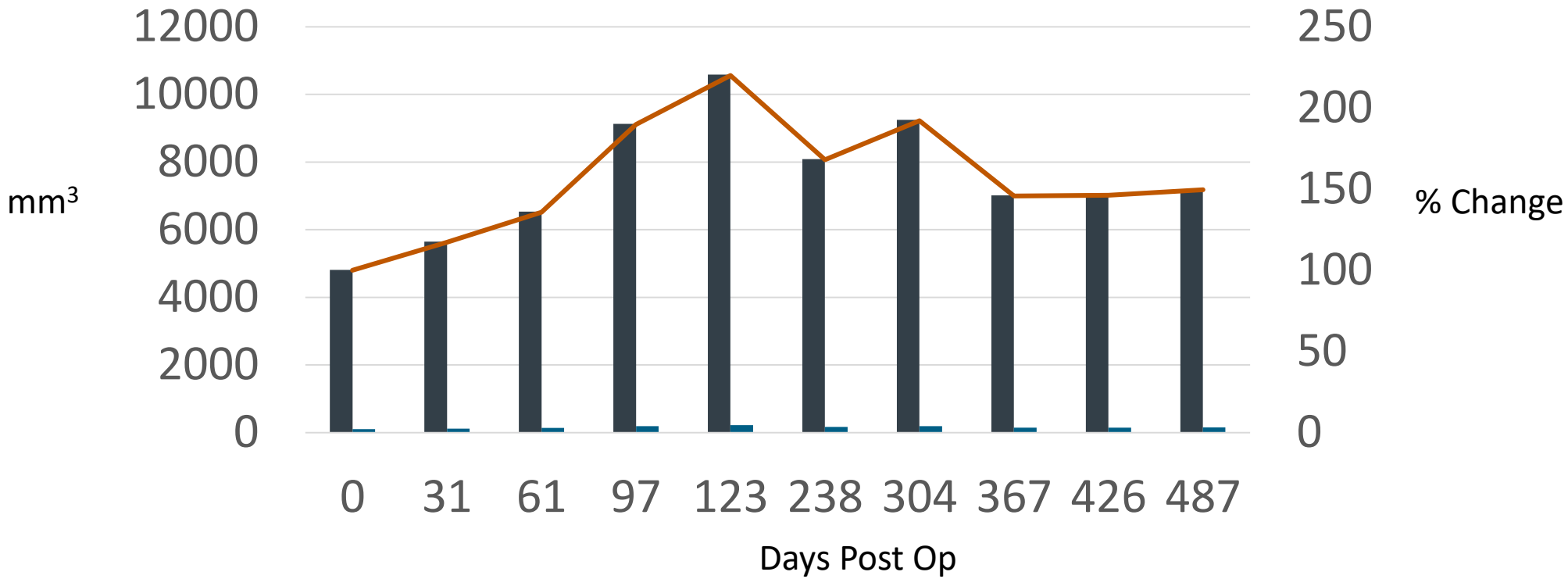
Baseline

Day 123

Day 367



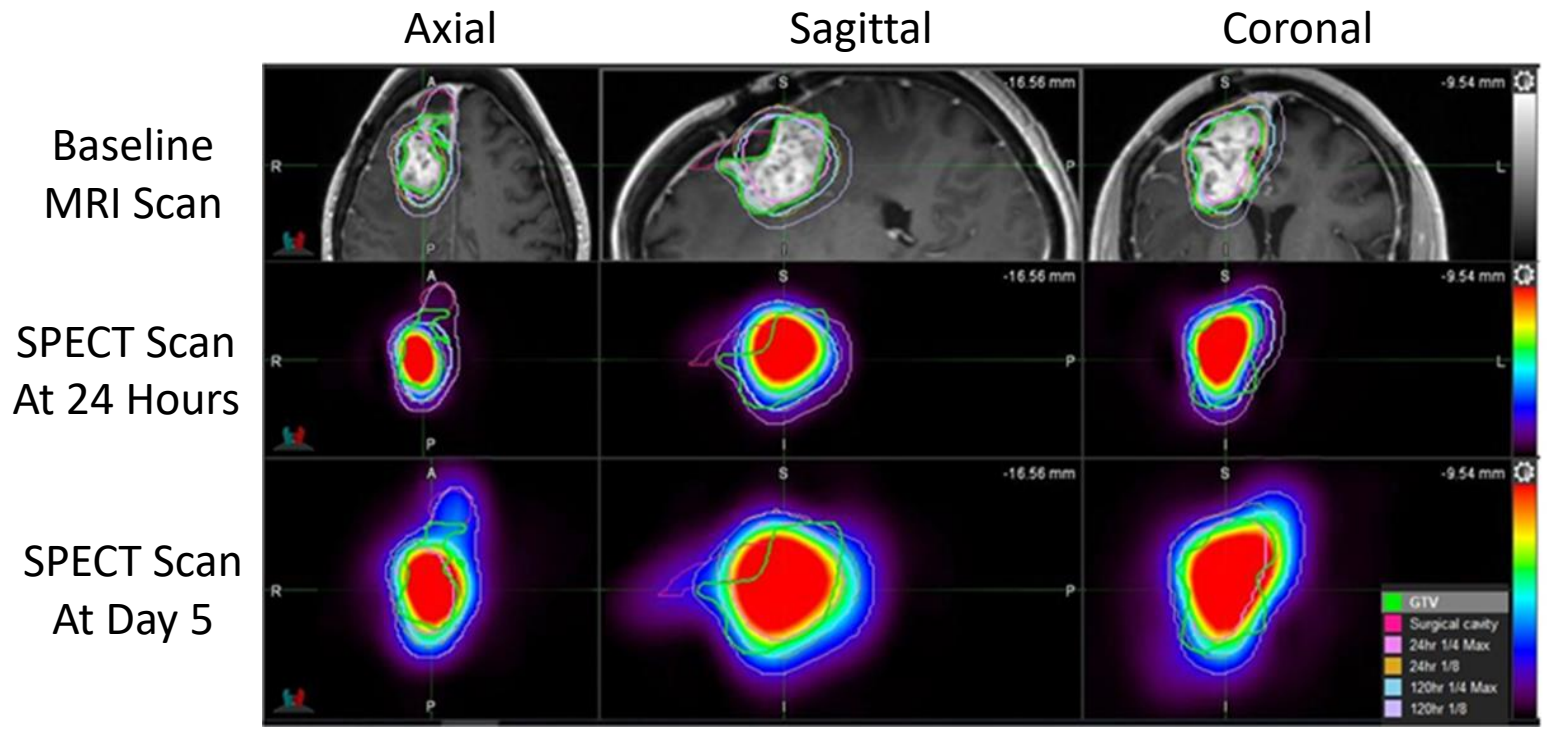
Pseudoprogression



Independent volumetric assessment for patient 01-017 demonstrating change in enhancing volume (left mm^3, right percent change) over time (days) without additional treatment consistent with pseudo-progression followed by lengthy stabilization.

Tumor Coverage and Retention

Subject 01-017

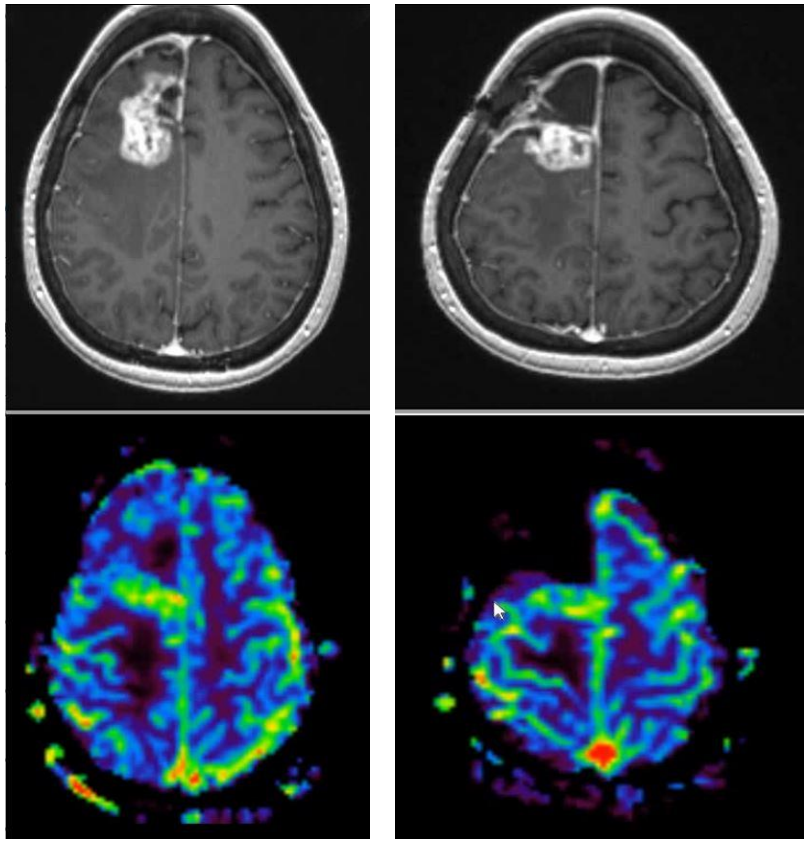


- Tumor volume was 18.8 mL and tumor coverage was 87%
- Absorbed dose delivered to tumor was 336 Gy

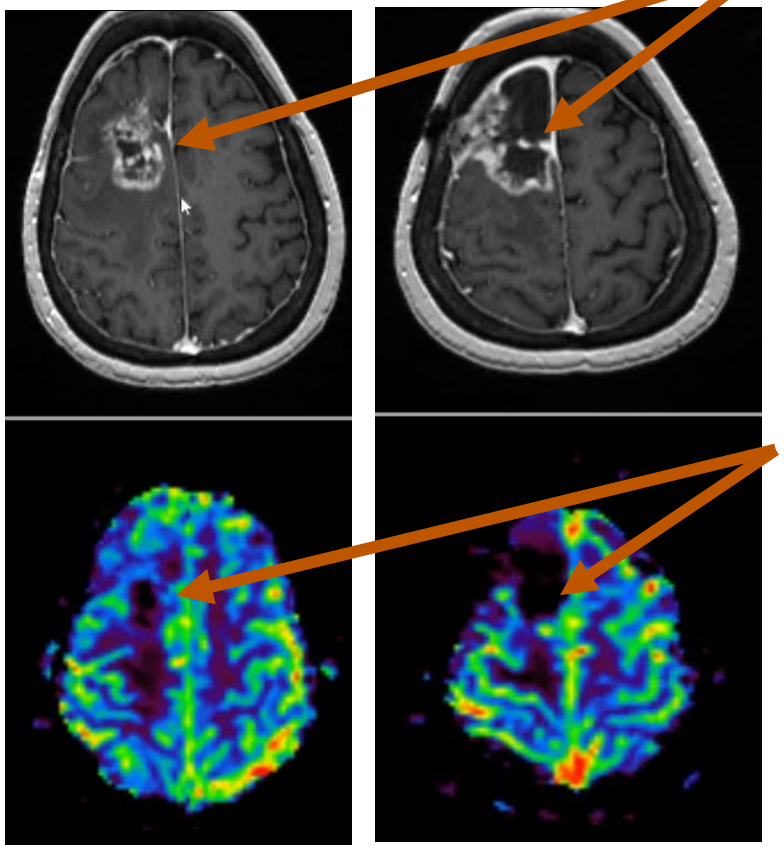
MRI & Perfusion Imaging

Subject 01-017: Tumor Ablation & Loss of Perfusion

Pre-Treatment



Day 56



CONCLUSIONS

- **Good safety profile- well tolerated, no dose limiting toxicities- in therapeutic range.**
- **Clear biological response in the best measure, overall survival.**
- **Favorable overall survival in patients with therapeutic dose compared to real meta-analysis.**
- Demographics
  - Heavily pretreated recurrent GBM population with disease attributes
- Delivery & Imaging
  - No dosing failures.
  - Single administration- up to 20x absorbed dose vs. EBRT (Max 740 Gy vs. 35 Gy).
  - SPECT/CT- reliable real-time visualization & dosimetry.
  - Tumor pseudo progression is common.
- Threshold effect at ~ 100 Gy absorbed dose.
- Survival
  - A statistically significant overall survival benefit in therapeutic doses (>100 Gy) vs. subtherapeutic ($p = 0.002$).
  - In cohorts 5-7 (higher volumes and doses), therapeutic dose achieved in 80% of patients.
  - Increasing drug volume and radiation correlate with improved OS.



Thank You

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