Safety & Feasibility of Rhenium-186 Nanoliposomes (186RNL) in Recurrent Glioma: the ReSPECT Phase 1 Trial

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INTRODUCTION

Glioblastoma (GBM) is the most common, aggressive primary malignant brain tumor in adults. The standard treatment for primary GBM is surgery, followed by concomitant chemotherapy with temozolomide and external beam radiation therapy (EBRT). EBRT is a central component of primary brain tumor management and the major contributor to survival in this regimen, but safety issues limited its use to maximum doses of approximately 80 Gy in the primary setting at 40 Gy following relapse. As most GBM recurrences occur within 2 cm of the resection margin, loco-regional therapies that bypass the blood brain barrier are attractive potential alternatives.

Rhenium-186 or 186Re is a potent source of electrons with short path length, low dose rate and high radiation density. More specifically, it is a beta ray-emitting therapeutic radionuclide with a 90-hour half-life, 1.8 mm radiation path range, and high β/γ-energy ratio suitable for cancer brachytherapy. Additionally, 186Re emits gamma energy sufficient to allow imaging of the *in vivo* radiopharmaceutical distribution with standard SPECT/CT.

Rationale drug carrier plus therapeutic radionuclide combinations such as liposomal nanoparticles (nanoliposomes) can increase absorbed dose by facilitating tumor sequestration and increase safety by slowing peripheral redistribution of active isotope. Rhenium-186 NanoLiposome (186RNL) has been formulated to enhance the delivery profile of long half-life 186Re energy to achieve long term tumor retention and achieve very high absorbed radiation doses to tumors. Preclinically, 186RNL administered via convection-enhanced delivery (CED) achieves very high doses of targeted radiation and a wide therapeutic index. We report the results of the first-in-man Phase 1 trial of 186RNL in recurrent glioblastoma (ReSPECT-GBM).

We report the clinical outcomes for the first 23 patients treated in the ReSPECT dose escalation clinical trial enrolling patients from 2015-2022.

PATIENTS & METHODS

Study Design

ReSPECT-GBM is a multi-center, sequential cohort, open-label, volume and dose-escalation Phase 1 clinical trial of the safety, tolerability, and distribution of 186RNL given by CED to patients with recurrent or progressive malignant glioma after standard surgical, radiation, and/or chemotherapy treatment. The study uses a modified Fibonacci dose escalation and a standard 3+3 design.

CED Planning, Catheter Placement and Drug Administration

Brainlab iPlan Flow software was used to plan SmartFlow catheter placement in the tumor volume while avoiding white matter tracts and CSF spaces (fissures, sulci, cisterns, ventricles and resection cavities). Frameless image-guided catheter placement was achieved with Brainlab Varioguide Stereotactic system. A single administration of 186RNL is delivered by CED utilizing 1 – 4 catheters at a maximum flow rate of up to 20 µL/min/catheter.

Imaging and Dosimetry

Serial 1-minute dynamic planar imaging was performed during the time of the infusion. SPECT/CT imaging and serial whole-body planar imaging scans were performed immediately following, and at 1, 3, 5, and 8 days after 186RNL infusion to assess the radiation absorbed dose to the tumor and other organs during the treatment. Serial blood samples and serial 24-hour urine collections were also counted for activity. Dosimetry was performed using region of interest data and OLINDA dose calculation software.

Dose Escalation Scheme

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 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	**12.30**	**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

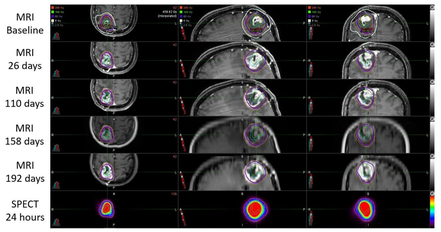
Demographics

Twenty-three patients across 7 dosing cohorts were treated from 2015 to 2022. Fifteen were male and eight were female. Average tumor size was 8.1 mL (range 0.9-22.8 mL). The average number of prior treatments (Txs) was 1.6 (range 1-3 Txs). Five patients received prior bevacizumab. The pathologic grade was Grade IV glioma in 21 patients and Grade III in 2 patients. IDH mutational status was wild type in 19 patients and mutated in 2 patients (2 patients had no status). MGMT status was methylated in 4 patients and unmethylated in 13 patients (6 patients had no status).

Convection-Enhanced Delivery (CED)

Twenty-three 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) while exposure outside the brain was negligible. In cohorts 1-4, an AARD of >100 Gy was achieved in 5/12 (42%) patients vs. 8/10 (80%) patients treated in cohorts 5-7. Tumor coverage or percent tumor volume (TuV) in the treated volume (TrV) [%TuV/TrV], was 71% (19.8%-100%) and correlated to AARD. In 5/23 patients receiving prior bevacizumab therapy, the AARD was 149 Gy and the %TuV/TrV was 47.9%. In 18 patients not receiving prior bevacizumab, AARD was 302 Gy and the %TuV/TrV was 77.7%.

Dosimetry

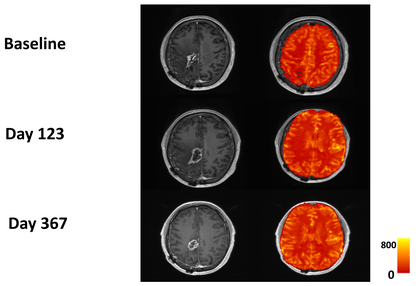


Patient 02-002: 3-D view of extent of radiation delivered measured in average absorbed dose distribution through 8 days posttreatment with 186RNL.

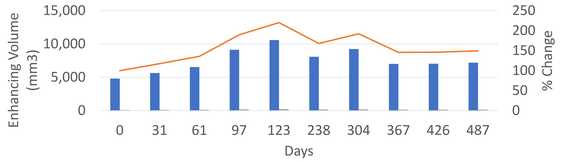
Safety

In 23 subjects with recurrent GBM receiving a single administration of 186RNL, we found 186RNL to be safe and well-tolerated. 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.

Imaging & Example Cases



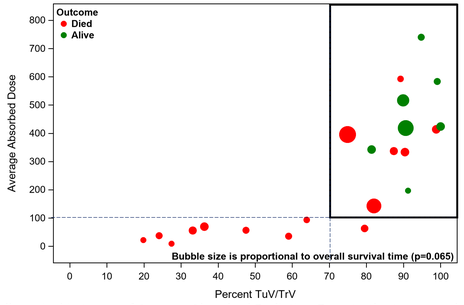
Patient 01-17. rGBM patient demonstrating an initial increase in enhancement (left) without increased rCBV (right) at day 123. With continued follow up this decreased over time consistent with pseudo-progression. The patient remains alive at day 1,040.



Independent volumetric assessment for patient 01-017 demonstrating change in enhancing volume (left mm3, right percent change) over time (days) without additional treatment consistent with pseudo-progression followed by lengthy stabilization.

RESULTS

Radiation Exposure, Tumor Coverage & Relative Overall Survival



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=23.

Overall Survival

In 23 subjects with recurrent Glioblastoma (GBM) receiving a single administration of 186RNL, 4 patients alive and 19 have died.

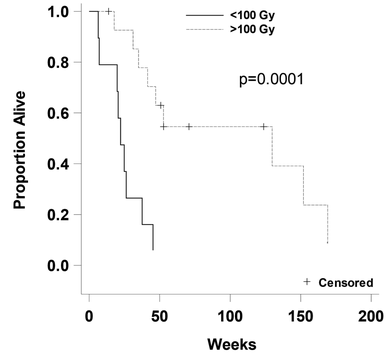
In a subset of 14 patients with AARD >100 Gy, the median and mean OS is 129.7 and 100.8 weeks respectively with 4 of 14 patients alive. In contrast, in the 9 patients with AARD <100 Gy, the median and mean OS is 22.3 and 24.6 weeks respectively and no patients remain alive.

Kaplan Meier curve comparing patients with adequate vs. inadequate coverage showed a statistically significant difference between the group (p=.0002).

Dose (Gy)	Overall Survival (weeks)			Patients Remain Alive
	Median	95% CI	Mean ± SE	
<100	**22.3**	6.4, 45.3	24.6 ± 4.8	0
>100	**129.7**	35, 169.1	100.8 ± 19	4

By comparison, **median overall survival of 32.1 weeks** reported in 8 study meta-analysis of 694 recurrent GBM patients treated with bevacizumab monotherapy

Correlation Absorbed Dose to Overall Survival



CONCLUSIONS

- Intra-tumoral convection enhanced delivery of 186RNL into the brain precisely delivers up to twenty times the absorbed dose of radiation that can be administered by EBRT.
- A single administration of 186RNL has been found to be safe without dose limiting toxicities.
- SPECT/CT can accurately and reliably visualize the location and residual radioactivity of the 186RNL during decay.
- Tumor pseudo progression is a common finding following treatment with 186RNL.
- A statistically significant overall survival benefit is observed in patients achieving adequacy in average absorbed radiation dose >100 Gy to the tumor vs. those <100 Gy.
- Adequacy in average absorbed radiation dose (>100 Gy) can be achieved in 80% of patients treated in cohorts 5-7.
- Increasing convected drug volume and radiation dose primarily in later dosing cohorts, correlate with improvement in overall survival.
- Cohort 7 with an increased dose of 186RNL over cohort 6 dose (31.2 mCi and infusate volume 12.3 mL) is enrolling.

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To learn more about 186RNL and the ReSPECT-GBM clinical trial, visit https://ReSPECT-Trials.com/gbm

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