

A two-part, Phase I study of Rhenium-186 Nanoliposomes (¹⁸⁶RNL) delivered by convection enhanced delivery (CED) for recurrent, refractory, or progressive ependymoma and high-grade glioma (HGG)

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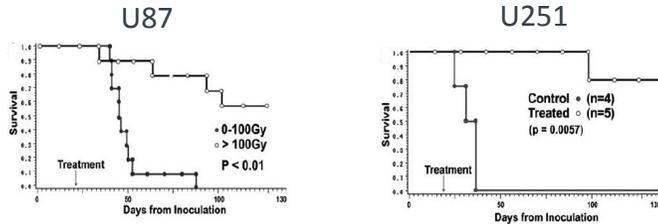
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Introduction

Ependymoma and high grade glioma (HGG) are gliomas that are often difficult to treat, frequently aggressive, and in recurrent settings can carry an extremely poor prognosis. While external beam radiation therapy (EBRT) remains a central component of the management of pediatric gliomas, it is limited by tolerance of the surrounding normal brain tissue. Rhenium-186 NanoLiposome (¹⁸⁶RNL) permits the selective delivery of beta-emitting radiation of high specific activity with excellent retention in the tumor. In a Phase I trial in adults with recurrent glioblastoma (NCT01906385), the mean absorbed dose to the tumor when coverage was 75% or greater (n=10) was 392 Gy (CI 306 – 478). Thus far, the therapy has been well tolerated, no dose-limiting toxicity has been observed, and no treatment-related serious adverse events have occurred despite markedly higher absorbed doses typically delivered by EBRT (n=18). As a result, a pediatric Phase I clinical trial will soon follow with focus on ependymoma and HGG.

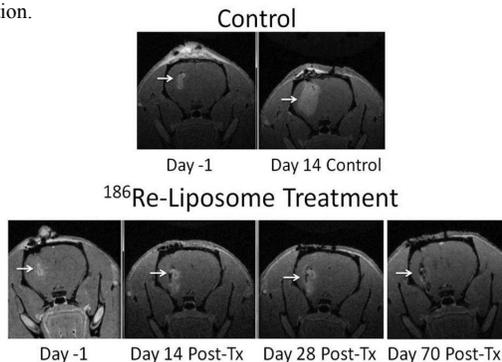
Preclinical Data: Treatment of Glioblastoma Xenograft Models

Rhenium nanoliposomes (RNLTM) prolongs survival in U87 and U251 glioblastoma xenograft models. Animals tolerated up to 1,845 Gy without significant weight loss or neurologic deficits. In this experiment, blinded histologic analysis by a neuropathologist showed no residual tumor in all treated animals.



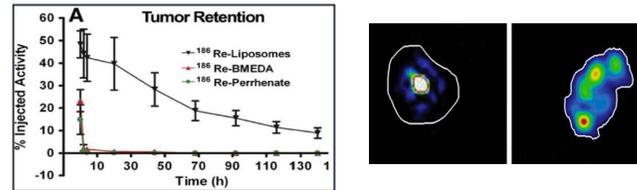
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Bioluminescence assays showed loss of activity compared to background levels suggesting complete eradication of the tumor. MRI analysis (below) supported this observation.



Preclinical Data: Spatiotemporal Behavior of RNLTM Following Brain Delivery

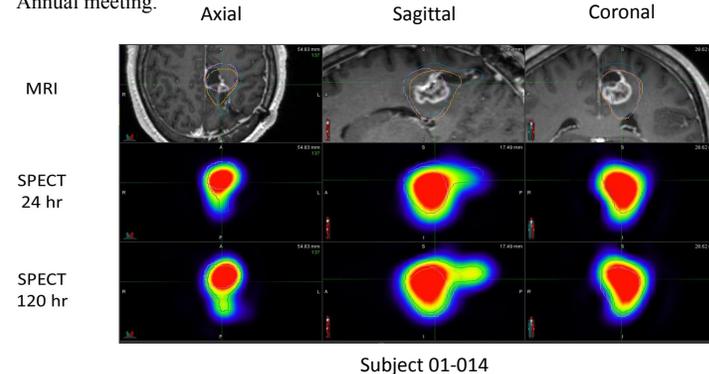
Liposomal encapsulation significantly extended *in vivo* intracranial half life of rhenium-186 (90 hours) and decreased clearance from the brain. Liposomal encapsulation also extended rhenium-186 retention within the tumor resulting in improved dispersion characteristics within brain tissue.



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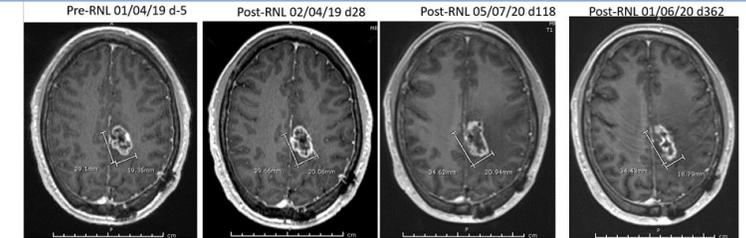
Adult Clinical Trials: Current Clinical Experience

In the current adult Phase I/II clinical trial, ¹⁸⁶RNL is given by convection enhanced delivery (CED) to patients with recurrent or progressive malignant glioma after standard surgery, radiation, and/or chemotherapy treatment. Through cohort 5, no treatment-related serious adverse events (SAE's) or dose limiting toxicities (DLT's) have been observed. The mean absorbed dose of the tumor where coverage was 75% or greater (n = 10) was 392 Gy (CI 306-478). Currently, there are 3 long term survivors at 33, 30, and 29 months and 7 survivors over 10 months. Seven of ten patients were still alive. Final data through the final cohort (cohort 6) is being evaluated and will be presented at the 2021 SNO Annual meeting.

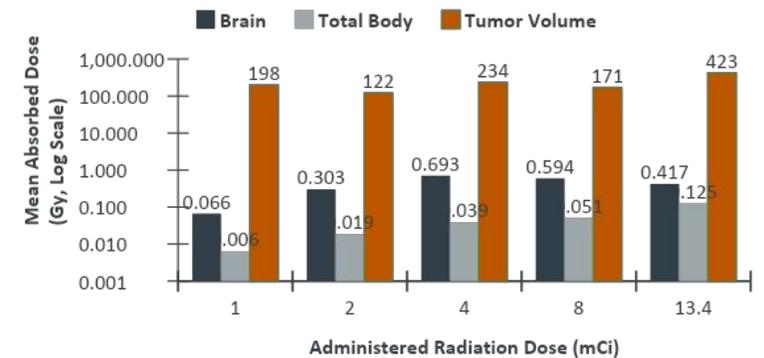


Patient	Activity (mCi)	Infusate Volume (mL)	Concentration (mCi/mL)	Catheters	Maximum Flow rate (μL/min)	Tumor Volume (mL)	Post-Inf Distribution Volume (mL)	Post-Inf Treated Volume (mL)	Percent TuV in TrV (%)	Absorbed Dose to TuV (Gy [J/kg])	Prior Tx (Gy)	Avastin Failure	Alive
Average	NA	NA	10.15	9.4	15.6	30.6	66%	239.0	1.7	1.0	7	7	
Minimum	1.0	0.66	1.5	1	5.0	1.1	1.6	24%	22.0	1.0			
Maximum	22.3	8.8	2.5	4	20.0	23.4	54.2	98.0	100%	593.0	3.0		

Through cohort 6 only



Subject 01-014



Pediatric Brain Tumors: Proposed Clinical Trial

Primary Objectives:

Part 1: to determine the maximal feasible dose (MFD) of ¹⁸⁶RNL administered by convection enhanced delivery (CED) in subjects with recurrent, refractory, or progressive ependymoma or HGG

Part 2: to determine the overall response rate (ORR) by radiographic assessment in pediatric neuro-oncology (RAPNO) criteria following ¹⁸⁶RNL administration in subjects with recurrent, refractory, or progressive ependymoma or HGG

Schema

Part 1A "Safety Lead-In": Up to six subjects with supratentorial tumors and tumor size limited to maximum diameter of 2cm and a volume of 4.2 mL will be treated with a single CED catheter

Part 1B: Up to 12 subjects with tumors up to 4 cm in longest diameter and volume of 14.0 mL

Part 2 Expansion cohorts: Cohort A (ependymoma) and Cohort B (HGG)

Acknowledgements

PLUS Therapeutics

