Safety and feasibility of rhenium-186 nanoliposome (^{186}RNL) in recurrent glioma: The ReSPECT™ phase 1 trial

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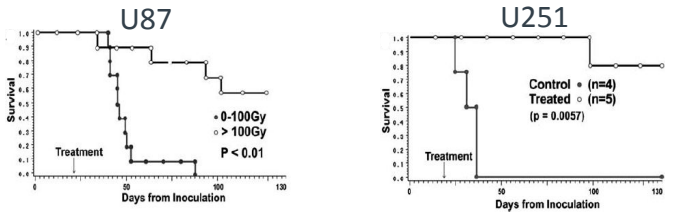
Introduction

High grade gliomas 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 primary brain tumors, it is limited by tolerance of the surrounding normal brain tissue. Rhenium-186 NanoLiposome (^{186}RNL) permits the selective delivery of beta-emitting radiation of high specific activity with excellent retention in the tumor. In a Phase 1 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 in patients with prior treatment. Responses have been observed supporting the clinical activity.

Preclinical Data: Treatment of Glioblastoma Xenograft Models

Rhenium nanoliposomes (RNL™) 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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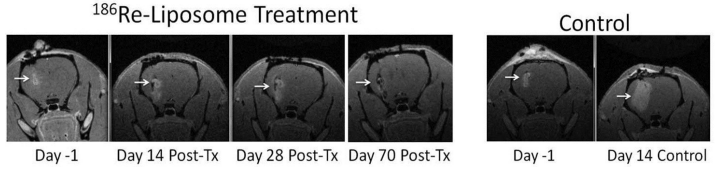
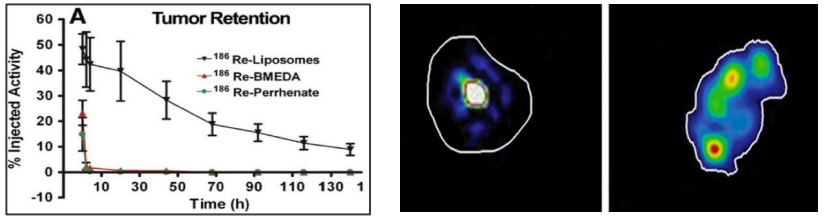
Bioluminescence assay showed loss of activity compared to background levels suggesting complete eradication of the tumor. MRI analysis (below) and histology supported this observation.



Preclinical Data: Spatiotemporal Behavior of ^{186}RNL 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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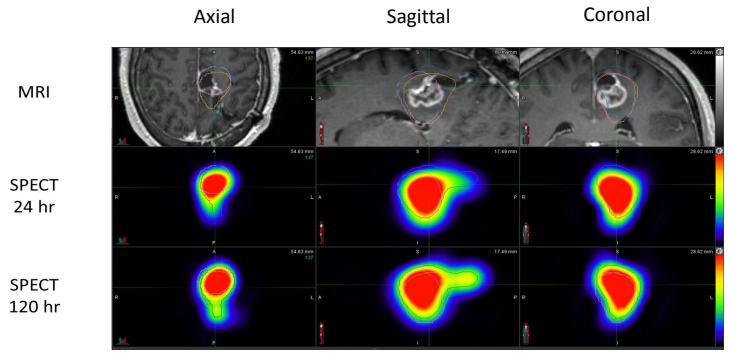
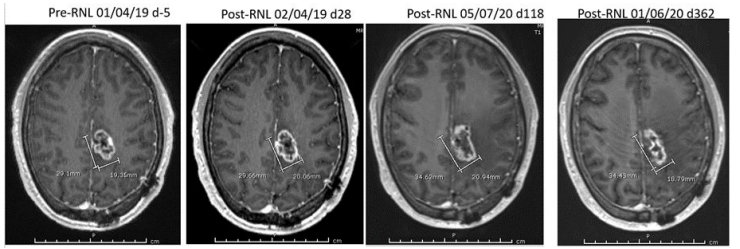
Current Clinical Experience

In the current adult Phase I/II clinical trial, ^{186}RNL 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 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 seven of ten patients still alive.



Subject 01-014

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



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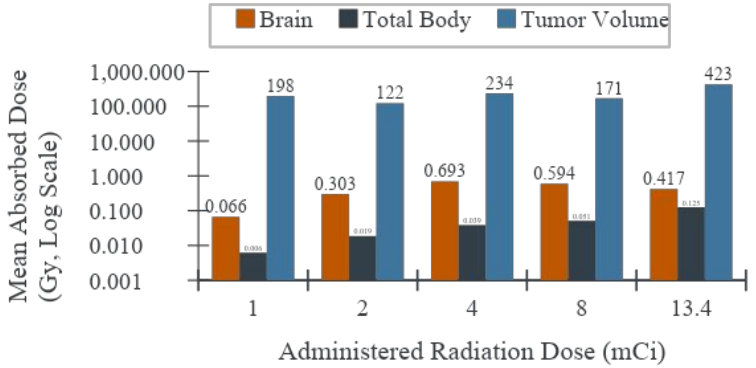
Relative Radiation Exposure

The absorbed dose (Gy) to tumor volume: mean 239 Gy (range 9-593 Gy) and the ratio of mean tumor volume AD/mean total body AD in cohorts 4 & 5, ≥ 3,000 fold.



Conclusions

^{186}RNL administered by CED to patients with recurrent glioma results in a very high absorbed dose of radiation to the tumor compared to EBRT, without significant toxicity.

Final data through the final cohort (cohort 6) is being evaluated and will be presented at the SNO Annual meeting.