Phase 1/2 ReSPECT-GBM Trial of Rhenium (186Re) Obisbemeda in Recurrent Glioblastoma: Safety and Efficacy from the Phase 1 and Update on Phase 2

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Background

Rhenium (186Re) Obisbemeda (186RNL; Reyobiq), is a novel radiotherapeutic consisting of 186Re encapsulated in nanoliposomes under investigation for convection enhanced delivery in recurrent glioblastoma (GBM) in the Phase 1/2 ReSPECT-GBM trial (IND 116117).

Introduction

Rhenium (^{186}Re) obisbemeda (^{186}RNL), a next generation radiotherapeutic, is BMEDA-chelated ^{186}Re encapsulated in liposomal nanoparticles. ^{186}Re is a beta-emitting therapeutic radionuclide with a 90-hour half-life, ~2 mm tissue path length, and optimal 137 keV γ-decay that allows real-time imaging of in vivo drug distribution by SPECT/CT. Durable, localized treatment with beta emitters, like ^{186}Re, has the potential to dramatically widen the therapeutic window, increase the delivered dose, and avoid normal tissue exposure. ^{186}RNL uses Direct Targeted Delivery, which deposits high doses of radiation non-systemically and locoregionally to achieve thorough tumor coverage and retention with high, localized absorbed radiation doses.

ReSPECT-GBM: Traditionally, radiation exposure to adjacent normal brain tissue limits the use of External Beam Radiation Therapy (EBRT) to typical doses of ~30-50 Gray (Gy). As most glioma recurrences are within 2 cm of the resection margin, radiopharmaceuticals that can be delivered directly to the tumor and minimize adjacent exposure to healthy tissues are attractive treatment alternatives. Molecularly targeted radiation therapy improves upon EBRT, but is reliant on receptor specificity, is delivered systemically, and few cross the blood brain barrier (BBB). These limitations can lead to off-target effects and inefficient tumor treatment. In preclinical models of glioma, ^{186}RNL delivered directly to the tumor eradicated transplanted tumor cells with absorbed dose of >100 Gy, with no evidence of neurologic compromise or other safety and toxicity markers. Furthermore, a study in beagles to assess toxicity of an intracranial, single dose administration of ^{186}RNL showed no test article-related pathologic changes at the highest administered amount (6 mCi). For rGBM, ^{186}RNL is administered via Convection Enhanced Delivery (CED) (Figure 1).

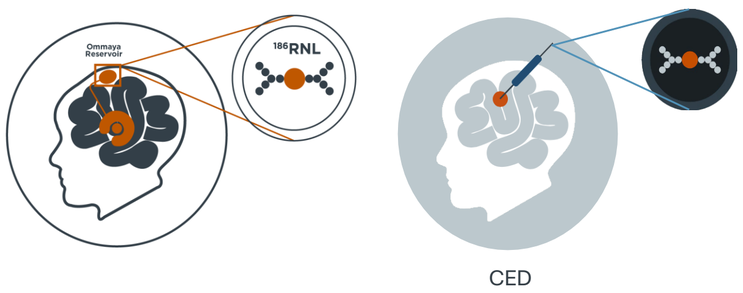

Figure 1. ^{186}RNL is BMEDA-chelated ^{186}Re encapsulated in nanoliposomes. For the treatment of GBM, it is directly delivered to the tumor by Convection Enhanced Delivery. For LM, it is directly delivered by intraventricular catheter (Ommaya reservoir).

Study Design

Study Design: ReSPECT-GBM is an ongoing, first-in-human, open-label, Phase 1/2 study investigating dose escalation and other delivery parameters (i.e., number of catheters (1-5), infusion rates, drug volumes, and drug concentrations) to determine the maximum tolerated dose (MTD), maximum feasible dose (MFD), safety, and efficacy of ^{186}RNL in recurrent adult glioma (IND 116117). The primary objective of the Phase 1 study was to determine an MTD/MFD utilizing a modified 3+3 Fibonacci design. The primary objective of the Phase 2 study is to assess overall survival (OS) following ^{186}RNL administration. Table 1provides the administered dose, volume, and concentration over the dosing cohorts, with the recommended phase 2 dose (RP2D) derived from Cohort 6's parameters.

	Cohort	Infused Volume (mL)	Total ^{186}RNL Activity Infused (mCi)	Concentration (mCi/mL)
	1	0.66	1.0	1.5
	2	1.32	2.0	1.5
	3	2.64	4.0	1.5
	4	5.28	8.0	1.5
	5	5.28	13.4	2.5
RP2D	6	8.80	22.3	2.5
	7	12.3	31.2	2.5
	8	16.34	41.5	2.5

Table 1. ReSPECT-GBM Trial with dose escalation for Cohorts 1-8. Cohorts 1-8 are complete with the Cohort 6 dose the RP2D.

Methods: Brainlab iPlan Flow software was used to plan BrainLab Flexible Catheter placement in the tumor while avoiding white matter tracts and CSF spaces. Catheter placement was achieved with Brainlab Varioguide Stereotactic system. Patients were given supersaturated potassium iodide (SSKI) prior to treatment. A single administration of ^{186}RNL was delivered by CED utilizing 1-5 catheters at a maximum flow rate of up to 20 uL/min/catheter. 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 at end of infusion (EOI) and at 1-, 3-, 5-, and 8-days after ^{186}RNL infusion to assess the radiation absorbed dose to the tumor and other organs during the treatment. Serial blood samples and urine collections were also counted for activity. Dosimetry was performed using region of interest data and OLINDA dose calculation software. Progression was determined by Radiographic Assessment in Neuro-Oncology (RANO) criteria following standard treatment.

Results

The Phase 1 dose-escalation study, employing a modified 3+3 design, was completed and enrolled 29 patients across eight cohorts. Doses escalated from 1.0 mCi (0.66 mL) to 41.5 mCi, achieving a maximum absorbed tumor dose of 739.5 Gy. Only one dose-limiting toxicity (DLT; Grade 4 hemiplegia) was observed in Cohort 8, with the Cohort 6 dose (22.3 mCi) selected as the recommended Phase 2 dose (RP2D) due to its favorable safety profile. Across all patients treated in both Phase 1 and 2 (n=47 to date), most treatment-related adverse events (TRAEs; 114 total) were Grade 1 or 2, including lymphopenia (7.9%), cognitive disorder (7.0%), and headache (7.0%), with no treatment-related deaths or study discontinuations due to serious adverse reactions (SARs). Preliminary efficacy data from Phase 1 cohorts 1 to 6 (N=21) showed a median overall survival (mOS) of 17.0 months (95% CI 8.0–35.0) for patients receiving ≥100 Gy (n=12), compared to 6.0 months (95% CI 1.0–11.0) for those receiving <100 Gy (N=9), surpassing historical bevacizumab monotherapy outcomes (mOS ~7.4–9.2 months).

Results

Imaging: Planar and tomographic (SPECT/CT) images were collected from all subjects using a dual-detector SPECT/CT camera. A sealed ^{186}Re radioactivity vial with known ^{186}Re radioactivity (~5% of injected radioactivity) was positioned next to each subject's head and well inside the image field of view at each time of image acquisition for in vivo radioactivity quantification. Representative SPECT/CT images are shown in Figure 2.

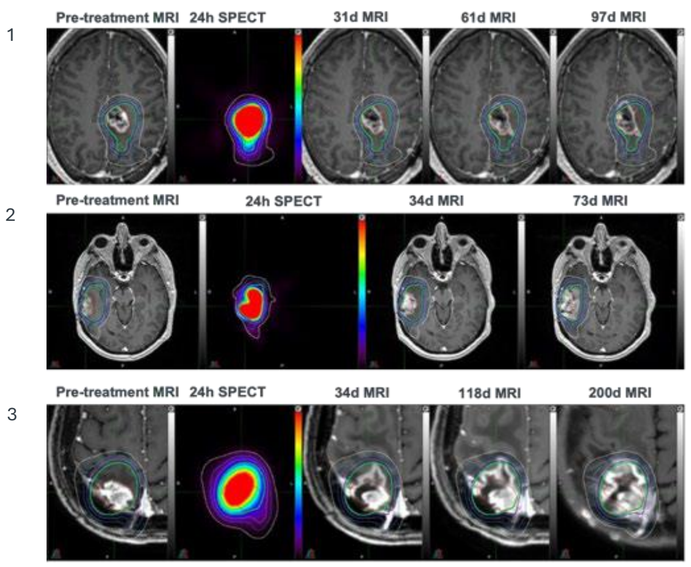

Figure 2. Pretreatment MRI, 24-hr post-treatment SPECT, and post-treatment MRI. (1) Phase 1 patient, Cohort 4. (2) Phase 1 patient, cohort 5. (3) Phase 1 patient, Cohort 6. Overall survival ranged from 750-1200 days.

The ongoing Phase 2 study has enrolled 24 of a planned 34 patients as of data cutoff, continuing to evaluate safety and efficacy at the RP2D.

SPECT/CT imaging continues to confirm high tumor-specific radiation retention, with minimal systemic exposure. Phase 2 patients are further restricted to histologically confirmed recurrent glioblastoma (1 recurrence), bevacizumab-naïve, with tumors ≤20cm^3.

Summary

- Efficacy data from Phase 1 cohorts 1 to 6 (N=21) showed a median overall survival (mOS) of 17.0 months (95% CI 8.0–35.0) for patients receiving ≥100 Gy (n=12), compared to 6.0 months (95% CI 1.0–11.0) for those receiving <100 Gy (N=9), surpassing historical bevacizumab monotherapy outcomes (mOS ~7.4–9.2 months).
- Phase 2 continues to enroll, with 24 of a planned 34 patients enrolled as of data cutoff.
- 186RNL has demonstrated a promising safety and efficacy profile in this trial, warranting continued investigation as a novel therapeutic for recurrent GBM, addressing this critical unmet medical need.

Acknowledgements

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