Rhenium NanoLiposome (RNL™)

OVERVIEW

PLUS THERAPEUTICS plans to develop, manufacture, and commercialize nanoliposome-encapsulated BMEDA-chelated radioisotope drugs to treat various types of cancer. Our initial focus is on developing BMEDA-chelated Rhenium NanoLiposome (RNL™) for the treatment of recurrent glioblastoma – a rare, incurable, and fatal disease.

Rhenium Radionuclide

Rhenium-186 (186Re) (half-life 90 hours) is a reactor produced isotope with great potential for medical therapy. It is in the same chemical family as Technetium-99m (99mTc), a radioactive tracer that is the most commonly used isotope for diagnostic scintigraphic imaging in nuclear medicine. Like 99mTc, rhenium is not taken up by bone and is readily cleared by the kidneys.

While 186Re emits therapeutic beta particles, every 10th isotope decay also produces a gamma photon. The average 186Re beta particle path length in tissue of 2 millimeters is ideal for treatment of solid tumors. Additionally, the emitted gamma photon has some similar photon energy to those emitted by 99mTc, allowing for imaging of the isotope within the body on standard nuclear imaging equipment available in routine medical practice. Therefore, the 186Re isotope has great potential in Convection Enhanced Delivery (CED) applications of local therapy of solid tumors. However, a carrier is needed to deliver the isotope to the brain and maintain its localization at the desired site, as otherwise it would quickly disperse and be carried away from the site of injection by the circulatory system.

Rhenium, discovered in 1925, is a silvery-grey, heavy, transition metal and one of the rarest elements in the Earth's crust.

NanoLiposomes

Liposomes are spontaneously forming lipid nanoparticles that have been well studied for over 30 years. Although larger liposomes can be manufactured, the most useful size range for drug carrier applications is 80-100 nanometers. Liposomes of this size are often referred to as nanoliposomes and have the ability to facilitate retention at the site of injection. Several marketed products use liposomes as drug carriers and liposomes are expected to be widely used both clinically and commercially for the foreseeable future. This is likely due to the fact that liposomes are made of naturally occurring lipid bilayers which are nearly identical to the lipid membranes of normal cells. This means that there are natural degradation pathways in the human body for these lipid nanoparticles.

Rhenium-Labeled NanoLiposomes

Liposomes in the 100 nanometer size range have been the most investigated carrier for CED drug delivery to the brain. These studies include the use of CED-delivery of nanoliposomes carrying chemotherapeutic agents directly to brain tumor, including drugs such as irinotecan and topotecan.

If nanoliposomes are to be utilized as a carrier for radioisotopes, a method for the efficient loading of liposomes with the radioisotopes is needed. Such a method has been developed for the loading of nanoliposomes with radiotherapeutic rhenium radionuclides to very high levels of specific activity. This novel approach uses a specially developed molecule known as BMEDA-2 to chelate with 186Re and carry it into the interior of a liposome where it is irreversibly trapped.

DISEASE TARGET – RECURRENT GLIOBLASTOMA

Glioma

Glioma is a type of tumor that occurs in the brain and spinal cord. According to the NIH/NCI, brain and other nervous system tumors account for 1.4% of all new cancer cases and 2.9% of all cancer-related deaths. In 2019, an estimated 23,820 new cases of will be diagnosed and 17,760 patients will die from these tumors.

Approximately 50% of all primary brain tumors originate from astrocytes, one of the subtypes of the normal supportive glial cells of the brain. Primary brain tumors that develop from astrocytes are called astrocytomas. The World Health Organization (WHO) classifies astrocytomas into four distinct grades (I,II,III,IV) on the basis of how quickly the cells grow and spread and how the cells appear under a microscope. Collectively, the Grade III and IV gliomas are referred to as high grade gliomas. Glioblastoma (Grade IV astrocytoma) is the most common and most aggressive of the primary malignant brain tumors in adults.

Glioblastoma – A High Grade (Most Serious) Glioma

According to the most recent CBTRUS Statistical Report, annually there are approximately 12,900 cases of glioblastoma diagnosed, with historical 1 year and 5 year relative survival rates of 40.8% and 6.8%, respectively. The poor survival is attributable partly to the nature of the tumor. The infiltrative nature of glioblastoma results in difficulty eliminating microscopic disease despite macroscopic gross total resection, with 90% of patients having recurrence at the original tumor location. The location of the tumor also makes drug delivery difficult with only small or lipophilic molecules able to cross the blood brain barrier to reach the tumor. Of those agents that are able to reach the tumor, glioblastomas have shown to be resistant to most cytotoxic agents and to quickly develop resistance when initially sensitive. The most significant advance in treatment for glioblastoma over the last several years has come from concomitant chemoradiotherapy with temozolomide which can result in increased median survival of 14.6 months with radiotherapy plus temozolomide compared to 12.1 months with radiotherapy alone. However, this still leaves much to be desired with an improvement in median survival of only 2.6 months over radiotherapy alone. In the recurrent and progressive setting there is no clear standard of care. More recent studies have shown that some benefit can be seen at the time of progression with angiogenesis inhibitor bevacizumab, achieving median progression free survivals of 22- 23 weeks, and median overall survivals of 40 to 54 weeks. Nevertheless, despite recent advances, glioblastoma remains incurable with a life expectancy of less than 24 months despite all efforts.

References:

- Hou et al. 2006
- Stupp et al. 2005
- Grill et al. 2007
- Kong et al. 2007

Additional Resources

Note: all external links

- American Brain Tumor Association
- American Cancer Society
- Brain Tumor Network
- Dictionary of Cancer Terms
- End Brain Cancer Initiative
- MedlinePlus (NIH)
- National Brain Tumor Society
- National Cancer Institute
- National Comprehensive Cancer Network
- Support Groups Listing
- The Brain Tumour Charity
- Trial Connect
- VirtualTrials.com
- Voices Against Brain Cancer

Standard Treatment for Glioblastoma

Glioblastoma (Grade IV astrocytoma) is the most common and most aggressive of the primary malignant brain tumors in adults, and hence the primary target of drug development for intracranial malignancy. Currently, front-line treatment consists of a multi-modality approach that includes maximal surgical resection, adjuvant radiation therapy of 54-60 Gy with concurrent temozolomide at 75 mg/m2, 6 months of single-agent temozolomide at up to 200 mg/m2 with tumor treatment fields (TTF). This multimodal approach results in a median overall survival of 19.6 months in the intent to treat population. While this is an improvement, it is clear that radiation remains the most effective component of the combined approach with multiple randomized studies showing a 5 month improvement in survival with XRT alone compared to an additional 2.5 months with the addition of chemotherapy and 3 months for TTF.

Once a patient fails standard front-line therapy, prognosis is very poor. The only currently approved therapeutic for salvage treatment is bevacizumab, a recombinant humanized monoclonal antibody against VEGF with an associated median overall survival time of 8.7-9.2 months. After bevacizumab failure, survival is only approximately 120 days.

References:

- Stupp et al. 2005
- Stupp et al. 2015
- Chang et al. 2007
- Friedman et al. 2009
- Quant et al. 2009

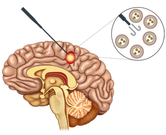
DEVELOPMENT RATIONALE

Rhenium-labeled nanoliposomes (RNL) have shown great promise in preclinical studies of glioblastoma that surpassed results typically seen with current standard treatment modalities such as oral temozolomide or intravenous bevacizumab. Glioblastoma remains incurable with limited benefit despite aggressive treatment. Investigation of RNL safety and tolerability is warranted.

RNL's lipid nanocarrier is an essential component for radionuclide retention. The ability to treat the whole tumor is also greatly enhanced by the 2 millimeter average path length of the beta particle radiation which compensates for mild inhomogeneities in the CED dispersion of the nanoparticles within the tumor. The 2 millimeter pathlength means that therapy delivered to one cell has the potential of moving through 80 cell diameters since an average cell diameter is 25 microns (25 x 80 cell diameters = 2 millimeter pathlength). Another theoretical advantage for the local administration of rhenium-labeled nanoliposomes is that the glial originating cells of the tumor retain their phagocytic ability and may be actively ingesting the nanoparticles which would result in a specific targeting of glioblastoma cells as compared with normal glial and neuronal cells.

References:

- Bao A et al. 2003
- French J et al. 2010
- Wang S et al. 2008
- Wang S et al. 2009



Rhenium-labeled nanoliposomes (RNL) intracranially administered by convection-enhanced delivery (CED) using cannulas specifically designed for use in the brain.

ReSPECT™ CLINICAL TRIAL – RECRUITING PATIENTS

Trial Design

Part 1.

This is a multi-center, sequential cohort, open-label, volume and dose escalation study of the safety, tolerability, and distribution of RNL™ given by convection enhanced delivery to patients with recurrent or progressive malignant glioma after standard surgical, radiation, and/or chemotherapy treatment. The study uses a modified Fibonacci dose escalation, followed by an expansion at the maximum tolerated dose (MTD) to determine efficacy. The starting absorbed dose is 1mCi in a volume of 0.660 mL. This dose and volume have been selected after careful consideration by the investigators.

Part 2.

This is a multicenter, single arm, non-blinded, prospective study of RNL™ by convection enhanced delivery (CED) in patients experiencing their first or second recurrence following standard multimodal therapy. Patients will receive a single treatment with infusion utilizing from 1 to 4 catheters based upon tumor size, shape, and results of treatment simulation. Simulation will be performed and iterative modulation to the simulation algorithm performed as needed. The primary endpoint will be overall survival. This endpoint was selected based upon the possibility of increased enhancement on MRI as a result of treatment, and lack of currently available salvage therapies with proven survival benefit following initial treatment. The secondary end points will be median overall response rate, safety, and quality of life.

Trial Locations

1. UT Health Science Center (San Antonio) – now enrolling patients
2. UT Southwestern (Dallas) – now enrolling patients
3. MD Anderson (Houston) – not yet recruiting patients

Patient Population

There are no effective established treatments for high grade glioma available after progression on standard therapy, and to date only radiation, alkylating chemotherapy, and tumor treating fields have improved survival. These patients invariably recur and have a dismal prognosis.

In this study, patients with recurrent high-grade glioma with no standard treatment options will be eligible for enrollment. For the Phase 2 portion, patients will be further restricted to first recurrence following conventional treatment per Stupp protocol and be bevacizumab naive to allow for survival comparison with historical controls.

Primary Objectives

1. To determine the maximum tolerated dose of RNL™ by convection enhanced delivery (CED) at the time of planned stereotactic biopsy (Part 1)
2. To determine median overall survival following RNL™ in bevacizumab naïve recurrent glioblastoma (Part 2)

Secondary Objectives

1. To assess the safety of single dose RNL™ by CED
2. To assess the dose distribution of RNL™ by CED
3. To determine the overall response rate by Radiographic Assessment in Neuro-Oncology (RANO) criteria following RNL treatment
4. Disease specific progression-free survival after RNL™ treatment

References:

- Clinicaltrials.gov

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Full Name (required)

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I am a:

- Patient
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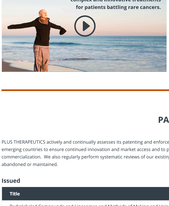
REGULATORY STATUS

PLUS THERAPEUTICS is conducting the ReSPECT™ clinical study under a U.S. FDA approved Investigational New Drug (IND) application.

In September 2020, PLUS THERAPEUTICS announced that the U.S. FDA granted both an Orphan Drug designation and a Fast Track designation for its lead investigational drug, Rhenium NanoLiposome (RNL™) for the treatment of patients with recurrent glioblastoma.

The FDA's Office of Orphan Drug Products grants orphan status to support development of medicines for underserved patient populations, or rare disorders, that affect fewer than 200,000 people in the U.S. Orphan drug designation provides to the Company certain benefits, including market exclusivity upon regulatory approval, exemption of FDA application fees, and tax credits for qualified clinical trials.

The FDA's Fast Track process is designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious conditions.



"This Fast Track designation further validates the importance of developing this novel radiotherapeutic for patients with recurrent glioblastoma who currently have no compelling treatment options."

Marc Hedrick, MD
President & CEO

PATENTS

PLUS THERAPEUTICS actively and continually assesses its patenting and enforcement strategy for new product candidates and technologies in both developed and emerging countries to ensure continued innovation and market access and to protect the investments made in research, development, manufacturing, and commercialization. We also regularly perform systematic reviews of our existing patents to verify a patent's therapeutic value and to evaluate if a patent should be abandoned or maintained.

Issued

Title	Country	Patent Number	Filing Date
Radiolabeled Compounds and Liposomes and Methods of Making and Using the Same	United States	7,718,160	6/7/005
Radiolabeled Compounds and Liposomes and Methods of Making and Using the Same	Australia	2003241598	5/22/03
Radiolabeled Compounds and Liposomes and Methods of Making and Using the Same	Canada	2,490,959	5/22/03
Radiolabeled Compounds and Liposomes and Methods of Making and Using the Same	France	1536843	5/22/03
Radiolabeled Compounds and Liposomes and Methods of Making and Using the Same	Germany	60335469.6	5/22/03
Radiolabeled Compounds and Liposomes and Methods of Making and Using the Same	United Kingdom	1536843	5/22/03

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