

Tau Therapeutics LLC Article for the Musella Foundation

Tau Therapeutics LLC joins National Cancer Institute to Study Interlaced Therapy™ In Patients with Recurrent High-Grade Glioma

Tau Therapeutics LLC, a pharmaceutical company developing T-type calcium channel inhibitors for the treatment of solid tumors, has opened enrollment for a Phase Ib clinical trial with the National Cancer Institute's Adult Brain Tumor Consortium (ABTC) using the company's novel cancer drug mibefradil in patients with recurrent high-grade glioma. This dose escalation trial will evaluate the safety and pharmacokinetics of mibefradil when sequentially administered with temozolomide – a novel proprietary approach Tau calls Interlaced Therapy™.

Interlaced Therapy™ is a potentially synergistic cancer therapy involving sequential administration of a T-type calcium channel blocker and a cytotoxic agent. In Interlaced Therapy™, a T-type calcium channel blocker is administered to arrest cancer cells at the G1/S checkpoint of the cell cycle. Then, administration of the T-type calcium channel blocker is stopped and administration of chemotherapy begins. Many conventional cytotoxic chemotherapies exert their effect during S or M phases of the cell cycle. The T-type calcium channel blocker synchronizes the cells and increases the number of cancer cells entering S phase at the same time. As a result, the number of cancer cells susceptible to the toxic effect of the various S phase cytotoxins is greatly increased. Without a T-type calcium channel blocker, the number of tumor cells destroyed is limited to those cells that happen to be in S or M phase during the period of chemotherapy treatment. By synchronizing the cell cycle with a T-type calcium channel blocker first and then withdrawing it and administering a cytotoxic drug, tumor cell destruction increases without increasing patient exposure to chemotherapy and its side effects. This sequential administration results in magnifying the effects of conventional cancer chemotherapies on cancer cells while having no adverse effect on healthy cells. If these benefits are clinically demonstrated and approved for market, Interlaced Therapy™ may greatly increase the efficacy of current chemotherapies and help overcome resistance to them.

The trial is already enrolling at ABTC sites Johns Hopkins University, Wake Forest University and Henry Ford Health System, and will commence soon at Emory University, University of Pennsylvania and University of Pittsburgh. Patients eligible for the trial must be 18 years old with the following disease characteristics:

- Histologically proven high-grade glioma (glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, mixed anaplastic oligoastrocytoma, anaplastic ependymoma) that is recurrent following standard upfront radiation therapy + temozolomide
- Measurable contrast-enhancing progressive or recurrent high-grade glioma (single or multiple lesions) by MRI imaging within 30 days of starting treatment

- Must have a plan for retreatment with temozolomide at 150-200 mg/m² for 5 days per cycle; each cycle = 28 days.
- Must have previously tolerated at least one cycle of adjuvant temozolomide therapy in the prior treatment of the glioma

Additional requirements of patients are detailed on clinicaltrials.gov, number NCT01480050: <http://clinicaltrials.gov/ct2/show/NCT01480050>.

Patients who participate in this clinical trial will receive the standard of care treatment for brain cancer but with the addition of mibefradil, a T-type calcium channel blocker, interlaced into the standard of care treatment by administration just prior to the chemotherapeutic agent temozolomide. Patients will receive mibefradil orally (PO) 4 times a day on days 1-7 (days 1-8 on first course) and temozolomide PO on days 8-12 (days 9-13 on first course). Treatment will repeat every 28 days in the absence of disease progression or unacceptable toxicity. Blood samples will be collected during the first course for pharmacokinetic studies.

In addition, patients in the dose-expansion cohort will undergo [18F]-3'-fluoro-3'-deoxy-L-thymidine (FLT)-positron emission tomography (PET) at baseline and on day 7 of the first course of therapy. After completion of study therapy, patients will be followed up every 2 months.