A PHASE I DOSE-ESCALATION TRIAL OF JX-594 (THYMIDINE KINASE-DELETED VACCINIA VIRUS PLUS GM-CSF) ADMINISTERED BY INTRAVENOUS INFUSION IN PATIENTS WITH REFRACTORY SOLID TUMORS

Non-Technical Abstract

Novel treatments are needed for cancer. Oncolytic, replication-selective viruses hold promise as novel anti-cancer therapeutics that can destroy tumors. These viruses are engineered to multiply and spread efficiently in cancer tissues but not in normal tissues. JX-594 is one of these viruses.

The JX-594 virus that we will be using in this trial is engineered from a virus called vaccinia that was used to eradicate smallpox worldwide. Millions of individuals received vaccinia virus smallpox vaccinations safely with only rare complications. In addition, over 90 cancer patients have safely received various vaccinia viruses by intratumoral injection. The JX-594 virus was modified by taking out a viral gene that is critical for virus multiplication in normal cells in the body, thus making this virus even safer than "wild-type" vaccinia. Nevertheless, this virus still multiplies and spreads in cancer tissues and can cause tumor destruction. In addition, this virus is "armed" with two genes. The first of these encodes for GM-CSF (granulocyte-macrophage colony stimulation factor) a growth hormone for white blood cells that increases the response of the immune system to tumor cells. The second gene encodes for an enzyme, β-galactosidase, which will allow us to visualize where the virus is located within the tumor when we analyze tumor biopsies.

JX-594 was found to be well tolerated in a Phase I/II clinical trial of seven patients with metastatic melanoma in which patients received multiple intra-tumoral injections (biweekly for at least six weeks). Five of seven (71%) patients had tumor responses at a site of injection, including two complete responses (one led to complete surgical resection). At time of entry into the trial, four patients had dermal metastases that subsequently regressed, even though they were never injected. These results suggest that oncolytic viral vaccines, and specifically JX-594, have the potential to treat distant metastatic disease. Two patients remained disease-free for at least one-and-one-half and six years after treatment, respectively (M. Mastrangelo, personal communication).

A Phase I clinical trial of JX-594 is currently ongoing under a Physician-sponsored IND in South Korea in patients with injectable tumors within the liver, that are not responding to standard therapies. Six patients have been treated to date (through July 2006) and no dose-limiting toxicities or serious adverse events have been reported. These patients have consistently experienced mild to moderate flu-like symptoms, including aches/pain, anorexia, chills, fatigue, fever, nausea, and vomiting. Flu-like symptoms began within three days or less following the JX-594 injection and had an average duration of 2-3 days. Patients were consistently found to have transient mild to moderate leucopenia, neutropenia, lymphopenia, and/or thrombocytopenia directly following injection with JX-594; values were consistently found to return to baseline at Day 5 (injection = day 1).

In the proposed, Phase I clinical research study (JX594-IV-004), the target patient population is patients with advanced/metastatic solid tumors refractory to standard therapy. This is a dose-ranging study, which is being conducted to determine the safest and most effective dose of JX-594 when treated by intravenous infusion. We expect approximately 15-21 patients will be treated.

Patients will receive up to 6 cycles of treatment. A cycle is defined as 7 days and treatment with JX-594 is given on the first day of each cycle. Doses will be escalated between patient groups (n=4 groups, or cohorts) using a standard Phase I dose escalation design; doses will increase from a starting dose of 1×10^8 (100 million) to a top dose of 3×10^9 (3 billion) infectious units in four approximately equal steps. Dose escalation will continue between patient groups until severe toxicities warrant halting dose escalation, should they occur, or until the maximum dose is achieved, as discussed in the protocol.

Safety assessments, including blood testing (2-4 tablespoons per day blood is drawn), adverse event collection and physical examinations (including performance status assessment) will be carried out at all study visits. The amounts of virus levels in blood, urine and throat will be assessed over time after treatment. Immune response will be assessed over time post-treatment. Viral replication, GM-CSF gene expression and inflammatory cell infiltration will be assessed in tumors after treatment by obtaining a small piece of tumor tissue at the specified visit day during Cycles 1 and 4. Tumor responses (i.e. shrinkage) and time-to-tumor-progression will be assessed. CT scans to measure response will be performed at the end of Cycle 6 and every 6 weeks thereafter until disease progression, death, or the patient initiates a new cancer treatment. If the patient has superficial tumors, photographs will be taken at baseline and at the end of every cycle if changes are observed.

Before any study related procedures are done, patients will have the study explained to them by the investigator and/or study coordinator and they will be able to ask questions. If they decide to enroll, they will be asked to read and sign, if they wish, a written informed consent form approved by the Institutional IRB. They will receive a copy of this form. Screening blood tests, urine, x-rays, ECG, medical history and physical examinations will then be carried out to determine patient eligibility for the trial. Patients will be actively involved in the study for approximately three months. Patients will return for follow-up visits every 6 weeks until the patient has disease progression, initiates a new cancer therapy, or dies.