

A PHASE I DOSE-ESCALATION TRIAL OF vvDD-CDSR (DOUBLE-DELETED VACCINIA VIRUS PLUS CD/ SMR) ADMINISTERED BY INTRATUMORAL INJECTION IN PATIENTS WITH SUPERFICIAL INJECTABLE 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.

The vvDD-CDSR virus that we will be using in this trial is such a virus designed for the treatment of cancer. This virus and its closely related parent virus show targeting to cancers and/ or effectiveness against cancers in mice, rats and/or rabbits. This virus 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 vvDD-CDSR virus was modified by taking out viral genes that are 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 cytosine deaminase (CD) that can convert a safe drug to a toxic drug at the tumor site, which shuts down virus replication, if necessary, and thereby increases safety, ("safety valve"). The second gene encodes for the somatostatin receptor (SR), which will allow a "tracer" to accumulate wherever the virus is active and allow us to visualize where the virus is in the body through a radiographic scan ("x-ray"). Thus, neither gene should be active until we administer the drug or tracer to the patient.

The main trial goals of the study are to determine the safety and the highest safe dose of the virus in patients. Other goals include determining tumor shrinkage, virus spread in blood, shedding into the urine or throat and the immune response (body's defense) to the virus.

Approximately 15-25 patients will be treated. These patients will have injectable superficial tumors that have failed standard treatments and are not curable by surgery or other treatments. This trial will be carried out at a single institution.

Because this specific virus has not been given to humans previously, we will give it directly into the tumor. This will maximize the potential for safety and efficacy. Tumors will be injected directly with virus through a needle. Local anesthesia will be used as required for pain. One to three tumors will be injected for each patient, and each tumor will be injected four times. If the injected tumor(s) have not progressed (i.e. are stable or shrinking), repeat injection cycles will be allowed up to a total of four cycles (administered every three weeks).

Doses will be escalated between patient groups (n=5 groups, or cohorts) using a standard Phase I dose escalation design; doses will increase from 3×10^7 (30 million) to 3×10^9 (3 billion) infectious units in five equal steps. Dose escalation will continue between patient groups until severe toxicities warrant halting dose escalation, should they occur.

Safety assessments, including blood testing (2-4 tablespoons per day blood is drawn), adverse event collection and physical examinations (including performance status assessment) are carried out every other day for one week following treatment and are assessed weekly thereafter through day 28 of their final cycle of treatment. The amounts of virus levels in blood, urine and throat will be assessed over time after treatment. Viral replication, gene expression and inflammatory cell infiltration will be assessed in tumors after treatment by obtaining a small piece of tumor tissue before and once after treatment (1-2 mm thickness and 5 mm long). Tumor responses (i.e. shrinkage) and time-to-tumor-progression at injected and non-injected tumor sites will be assessed.

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 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.