

Non-Technical Abstract

Cancers occur when previously normal cells grow and divide in an uncontrolled fashion. Many human cancers have been shown to have mutations in proteins that control cell growth and division. These mutations are required for the involved cell to become a cancer. One such mutant “cancer protein” is called Ras. The Ras protein is mutated in many human cancers including cancers of the colon, rectum, pancreas and lung, as well as in melanomas. There is evidence that the immune system can fight cancer. One of the cells in the immune system, a killer T cell, can recognize cancer cells that are making mutant proteins, including Ras. However, these killer cells do not appear to be stimulated effectively in cancer patients.

GlobeImmune has developed a novel immunotherapy product that stimulates killer T cells to fight cancers making the mutant Ras protein. To do this GlobeImmune scientists use recombinant DNA technology to modify ordinary Baker’s yeast such that the yeast produce the mutant Ras protein. The yeast are then heat killed. The product series is called GI-4000. The individual products which comprise GI-4000 are called GI-4014, GI-4015 and GI-4016. Extensive studies in mice using the GI-4000 product series have shown that injection of the heat-killed yeast stimulates a potent killer T cell response that can eradicate cancer cells that are making mutant Ras. In animal safety studies that are required by the FDA, the GI-4000 product series has been shown to have minimal toxicity – mostly limited to skin reactions at the injection site.

GlobeImmune is currently completing a phase 1 clinical trial in advanced stage gastrointestinal and lung cancer patients with the GI-4000 product series. In brief, GI-4000 has been injected under the skin of cancer patients whose cancers have been shown to be making the mutant Ras protein. The cancer patients have been monitored for any toxic effects or therapeutic benefits related to injection of GI-4000. To date, 25 subjects have been treated with one of the GI-4000 products at dose levels ranging from 0.1 YU to 40YU (1 YU=yeast unit contains 10,000,000 yeast cells). There have been no product related serious side-effects called serious adverse events (SAEs) in any of the treated subjects and possibly related non-serious side-effects have generally been limited to mild fatigue, fever, malaise, diarrhea, restlessness and mild injection site reactions. A majority of the patients in this study have demonstrated immune responses to the cancer target contained in the product.

We propose a phase 2 study (GI-4000-02) in patients with surgically treatable pancreatic cancer to compare GI-4000 plus standard chemotherapy to standard chemotherapy alone after successful surgery. Despite successful surgery, most patients have a recurrence of pancreas cancer and die within 18 to 24 months. After surgery patients are believed to be in a disease-reduced condition that should allow an immune-based treatment to have a beneficial effect on disease recurrence and survival. In this study patient tumors will be tested after surgery to determine suitability for treatment with GI-4000. Patients with tumors positive for mutant *ras* and with evidence of successful surgical removal of the tumor will be eligible for random assignment to either receive GI-4000 or salt water (called placebo or dummy product) in combination with standard chemotherapy called gemcitabine. The primary measure of effectiveness in the study will be the number of patients free of cancer at 15 months defined as the absence of detectable tumor by medical imaging techniques such as CT scan or MIU. Secondary measures of treatment

effectiveness include the number of patients free of chemical pancreas cancer markers in the blood (called CA19-9 and CEA) as well as the number of patients who survive to certain time-based milestones after surgery.