

Scientific Abstract

GlobeImmune has generated recombinant yeast cell-based immunotherapeutics that target mutated Ras oncoproteins. Mutations in the human *K-ras* gene and its encoded Ras oncoprotein have been implicated in the pathogenesis of multiple solid tumors, including pancreatic, colorectal, non-small cell lung cancer, ovarian cancer, and melanoma. The most common mutations in ras occur at codons 12, 13, and 61, all three of which result in constitutive activation of the Ras/epidermal growth factor receptor (EGFR) pathway and uncontrolled cell division. Because these mutations are not random, but are required for carcinogenesis, these mutated oncoproteins represent ideal targets for cancer immunotherapy.

GlobeImmune has developed a series of yeast (*Saccharomyces cerevisiae*) based mutated Ras immunotherapy products targeting these common mutations and has demonstrated in non-clinical models that these immunotherapeutics block the growth of tumors expressing mutations at the target positions in an antigen-specific fashion. Yeast are efficiently taken up by dendritic cells, resulting in an enhanced cell-mediated immune response aimed at cancer cells expressing mutant Ras protein. The GI-4000 series of Ras products is made up of three different immunotherapeutics, each of which carries the two most common mutated amino acid substitutions at the 61 position and one of the three most common mutations at the 12 position. These products have been tested in non-clinical safety studies in animals and been found to have minimal toxicity, generally limited to reactions at the injection site. The sponsor has filed an Investigational New Drug Application (Filed May 12, 2004, BB-IND #: 11653) to initiate the evaluation of these products in patients with Ras-mutation bearing solid tumors.

The GI-4000 series is being studied in a Phase I clinical trial (GI-4000-01). This study, conducted at five centers in the U.S. includes patients with Stage III or IV refractory colorectal, pancreatic or non-small cell lung cancers. Eligible subjects had to have failed at least first-line chemotherapy and were skin tested to rule out immediate hypersensitivity to *S. cerevisiae*. Subjects had a sample of their tumor analyzed by genomic DNA sequencing and, if they possessed a mutation in *ras* contained in one of the three GI-4000 products, were administered 5 weekly subcutaneous doses of the corresponding GI-4000 product in ascending dose cohorts from 0.1YU to 40YU (1 YU [yeast unit] = 10 million yeast) in an open label fashion and followed for 85 days for safety, immunogenicity, and efficacy. To date, 138 subjects signed an informed consent and were skin tested for allergy to *S. cerevisiae* (number of consented subjects includes recently collected interim data from the 20YU and 40YU cohorts). Of this group, there were 0 positive skin tests noted. To date, 25 subjects have been administered one of the GI-4000 products at dose levels up to 40YU (the highest dose anticipated). 7 of the 21 subjects from the first 4 dose groups (0.1, 0.3, 1.0, and 10YU) have completed the 85 day follow up phase of the study. There have been no product related serious adverse events (SAEs) and possibly related adverse events have generally been limited to mild fatigue, fever, malaise, diarrhea, restlessness and mild injection site reactions. A majority of the patients in this trial have demonstrated antigen specific T cell responses by at least one of two different assays to antigens contained in the product; lymphocyte proliferation assay and intracellular cytokine staining for IFN γ .

We propose a multicenter, double blind, randomized phase 2 study (GI-4000-02) to evaluate GI-4000 versus placebo in patients with resectable pancreatic cancer in combination with standard of

care surgery + gemcitabine adjuvant chemotherapy. The post-resection population represents a disease-diminished study population for which an immune-based approach can be expected to have a clinically meaningful impact in clearing microscopic residual tumor at the surgical margin as well as occult malignant cells at sites distant from the primary tumor. In this study patient tumors will be sequenced after surgery to determine eligibility. Patients with tumors positive for mutant Ras and with a resection status of R0 (no evidence of disease at the margin) or R1 (only microscopic disease at the margin) will be eligible for randomization. 100 patients will be randomized 1:1 to begin GI-4000 therapy (or placebo) two weeks following surgery and remain on weekly GI-4000 mono-therapy during their holiday prior to the initiation of gemcitabine. Once adjuvant gemcitabine has been initiated additional monthly injections of GI-4000 will be administered during the two-week holiday between monthly gemcitabine cycles. The primary efficacy endpoint of the study will be recurrence free survival at 15 months, with secondary endpoints including biochemical recurrence using the biochemical marker CA19-9 as well as median overall survival.