

1. Scientific Abstract

The objective of the proposed clinical study is to evaluate the safety and feasibility of immunotherapy using ETBX-021 (Ad5 [E1-, E2b-]-HER2/neu) in patients with advanced or metastatic human epidermal growth factor receptor 2 (HER2/neu)-expressing malignancies. ETBX-021 is an adenovirus serotype 5 (Ad5) vector that has been modified by removal of the E1, E2b and E3 genes and insertion of a modified HER2/neu gene (1, 2). HER2/neu is a 185-kDA protein receptor with tyrosine kinase activity and has extensive homology to epidermal growth factor receptor (EGFR). HER2/neu is a self-protein expressed in high levels during fetal development and in low levels on a few normal adult tissues, including breast, uterus, vagina and digestive tract epithelium (4). In normal adult tissue the HER2/neu gene is present as a single copy but amplification of the gene or over-expression of the protein plays a role in malignant transformation by contributing to the transformation of normal cells into cancer cells (4,5). HER2/neu over-expression has been described in a variety of different tumor types including 25 to 30% of breast cancers as well as gastric, ovarian, non-small cell lung, renal cell, prostate, pancreas, colon, salivary, bladder and oral squamous cell carcinomas (4,6). HER2/neu over-expression is regarded as a poor prognostic factor associated with aggressive tumor progression, shorter relapse time following treatment and reduced survival (6, 7). Current interventions including therapy with monoclonal antibodies against HER2/neu is effective in some patients with HER2 positive Stage III and IV breast cancer; however, many patients do not respond to antibody therapy, and patients who do respond ultimately relapse (8). ETBX-021 is designed to induce T cell-mediated immune responses in addition to polyclonal antibody induction in patients and may have a different spectrum of effectiveness than current therapies.

We are currently performing a Phase I/II clinical trial of ETBX-011 (Ad5 [E1-, E2b-]-CEA) under FDA-IND#14325, which employs the same Ad5 vector backbone that expresses the tumor associated antigen carcinoembryonic antigen (CEA). Currently we have reached a maximum dose of 1×10^{11} viral particles without any test drug related toxicity including dose-limiting toxicity (DLT). CEA-specific T cell induction measured by ELISpot has been observed in more than 50% of patients treated with ETBX-011. The safety profile from multiple treatments of patients having over-expressing CEA cancers using the Ad5 [E1-, E2b-] vector backbone gives us confidence to advance the same Ad5 backbone expressing HER2/neu (ETBX-021) for the treatment of patients with cancers over-expressing HER2/neu to evaluate the safety and effectiveness.

The primary objectives of the proposed Phase I/II clinical study are to evaluate the safety and feasibility of immunotherapy with ETBX-021 in patients who have advanced or metastatic HER2/neu over-expressing malignancies. In this Phase I/II study, three cohorts will receive dosage levels of ETBX-021 in an increasing manner to assess the safety of the product (Phase I component). In the Phase II component, the highest tolerated dose will be administered to a larger cohort of patients. The study drug, ETBX-021, will be given by subcutaneously (SC) injection every 3 weeks for 3 treatments. The dose escalation component of ETBX-021 therapy will take place in cohorts of three to six patients. Cohort 1 will contain three patients, which will each receive three treatments of 5×10^9 virus particles. Cohort 2 will contain three patients which will each receive three treatments of 5×10^{10} virus particles per immunization and Cohort 3 will contain six patients which will receive three treatments of the highest dose of 5×10^{11} virus particles per immunization. There will be no intra-patient dose escalation. Assessment of DLT for dose escalation will be made after all patients in a cohort have had a study visit at least 3 weeks after receiving their first dose of ETBX-021. In the Phase II cohort, an additional 12 patients will receive ETXB-021 at the maximum tolerated dose (MTD) every 3 weeks for 3 immunizations. This study will determine the MTD of ETBX-021 and will also evaluate the level of induction of cell mediated immune responses against HER2/neu via testing peripheral blood mononuclear cells in IFN- γ expressing ELISpot, proliferation and multi-parameter flow cytometric assays. Anti-tumor effectiveness will also be determined by clinical evaluations.