1. SCIENTIFIC ABSTRACT

The identification of unique tumor-associated antigens capable of eliciting cytotoxic T-lymphocyte (CTL) responses has led to new methods of immunotherapy for cancer. One method is the insertion of a tumor antigen cDNA clone into a live virus that can be used in active immunization protocols. This approach was used to generate a vaccinia virus that expressed the human carcinoembryonic antigen (CEA) gene. Vaccinia was chosen as a vector because of its ability to accept a large amount of foreign DNA, its replicative stability, its ability to generate strong CD8+ CTL responses, and its success as an immunizing agent in the smallpox eradication program. The recombinant vaccinia-CEA virus (rV-CEA) was shown to have therapeutic effectiveness in the prophylaxis and treatment of an established CEA-expressing murine adenocarcinoma tumor. Furthermore, the construct elicited both anti-CEA antibodies and CTL directed against CEA in mice. The vaccine induced similar immune responses in a non-human primate model and was shown to be safe with few side effects.

The FDA and RAC granted permission to perform a clinical trial in human patients with this vaccine in 1992. The National Cancer Institute (NCI) has conducted four studies using either ALVAC-CEA or ALVAC-CEA/B7.1:

1. A Phase I study in cancer patients of a replication-defective avipox recombinant vaccine that expresses human carcinoembryonic antigen; conducted by John Marshall et al.1

2. A pilot study of sequential vaccinations with ALVAC-CEA and vaccinia-CEA with the addition of IL-2 and GM-CSF in patients with CEA-expressing tumors; conducted by John Marshall, Jeffrey Schlam and Alfred Tsang 2.

3. A Phase I pilot study of ALVAC-CEA/B7.1 immunization in patients with advanced adenocarcinomas expressing CEA; conducted by Margaret von Mehren et al3.


Some of these studies are still ongoing, and therefore not all results are available. In general, the treatments were well tolerated, with no significant product-related toxicities. The results demonstrated the ability of both ALVAC-CEA and ALVAC-CEA/B7.1 to induce CEA-specific CTL responses in patients with CEA-expressing carcinomas. The results to date from these studies can be summarized as follows:

Vaccination with ALVAC-CEA or ALVAC-CEA/B7.1 of patients with CEA-expressing tumors is safe and does not induce autoimmunity or serious adverse events, except for mild local reactions and some grade 4 toxicities such as fatigue, fever, and myalgia.

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Increases in T-cell precursor frequency, as demonstrated by limiting dilution assays, have been documented after vaccination. Frequency of T-cell responders and magnitude of the response may be increased by: adding GM-CSF as an immunoadjuvant, priming with vaccinia-CEA and then boosting with ALVAC-CEA, incorporating the B7.1 co-stimulatory molecule into the ALVAC-CEA construct.

The current study will investigate the administration of ALVAC-CEA/B7.1 concomitantly with chemotherapy.