

1. SCIENTIFIC ABSTRACT

Prostate cancer is the most common cancer and the second leading cause of cancer deaths in men in the US. Approximately 220,900 new diagnoses of and 28,900 deaths from prostate cancer in the US are projected for 2003. (Jemal, 2003) Treatment for prostate cancer is based a variety of clinical factors related to the cancer, as well as the patient's age, and any comorbid illnesses. Approximately 80% of patients in the US are diagnosed with localized or regional disease, which is most commonly treated with surgery (radical prostatectomy) and/or radiation therapy. Patients with metastatic prostate cancer generally undergo a period of 18-24 months of hormone responsiveness during which androgen deprivation therapies are effective. Unfortunately, in most patients this is followed by a period of androgen-unresponsiveness (androgen-independent prostate cancer, AIPC). Current treatments for AIPC are unsatisfactory. Chemotherapy regimens although active are thus far of only palliative benefit. The application of immunotherapy to the treatment of prostate cancer has been proposed based on the identification of well characterized tumor-associated antigens and the advent of increasingly sophisticated vectors for presenting antigen to the immune system. The majority of prostate tumor cells express high levels of prostate specific antigen (PSA), which can be measured in peripheral blood. Several recent studies have identified HLA-restricted PSA epitopes that can be targeted by T-cells derived from patients vaccinated with PSA-specific vaccines. Based on these studies a single HLA-A2-restricted epitope was identified and a single amino acid modification of that epitope resulted in improved recognition by the PSA-specific T-cell receptor, and this modification has been incorporated into the PSA coding sequence used in viral construction. While numerous vaccine approaches have been described, the use of poxvirus vectors expressing tumor antigens such as PSA, carcinoembryonic antigen (CEA), and mucin-1 (MUC-1) have been evaluated in previous clinical trials demonstrating safety, evidence for the induction of T-cell responses in a proportion of vaccinated subjects, and early suggestions of clinical effectiveness. Basic research on T-cell biology has now revealed that activation of T-cells depends on delivery of two signals. The first signal is derived from processed antigens that are presented by tumor cells or professional antigen-presenting cells. The second signal is provided by a distinct set of cell surface proteins collectively referred to as co-stimulatory molecules. Several co-stimulatory molecules have now been described, including B7.1, ICAM-1, LFA-3, and others. The combined expression of B7.1, ICAM-1, and LFA-3 in both vaccinia and fowlpox viruses have demonstrated superior activity in the initiation of T-cell proliferative responses and the combination was superior to single gene vectors in eradicating animal tumors in pre-clinical studies. The expression of co-stimulatory molecules with tumor antigens is easily accomplished in poxviruses and several trials have demonstrated the safety and potential increased clinical effectiveness of using this approach. Previous trials have tested vaccinia and fowlpox vectors

expressing PSA in a prime/boost approach and confirmed pre-clinical data supporting this as a strategy for enhancing immune and clinical responses. The goal of this protocol is to determine the safety and efficacy of a prime/boost approach using a vaccinia virus expressing PSA and a triad of co-stimulatory molecules (B7.1, ICAM-1, and LFA-3, designated PROSTVAC-V) followed by six booster doses of fowlpox virus expressing PSA and the same triad of co-stimulatory molecules. (designated PROSTVAC-F). A randomized, double-blind, controlled Phase II clinical trial is proposed. Patients randomized to the control arm will receive the empty viral vector as the control. Recent reports of antigen spreading suggest that an immune response against one antigen may enhance, or "spread" to other antigens also expressed by established tumors. The incorporation of several important methods into this vaccine trial builds on previous knowledge of tumor vaccines and immunology, including the prime/boost strategy with different vectors, the inclusion of multiple co-stimulatory molecules, and the PSA modification for enhanced recognition. Further clinical development of the prostate cancer vaccine program has been supported by the recent completion of a Phase I trial. The vaccines comprising PROSTVAC-VF/TRICOM have been evaluated in a Phase I clinical trial. Preliminary safety information has been compiled and shows no dose-limiting toxicities related to the investigational product. The safety of the vaccine components has also been established through extensive clinical experience with related vaccine products.

Replicating and non-replicating pox virus-based vaccines have a well established history of effective use and an established safety profile. The worldwide elimination of smallpox is attributed to effective vaccination strategies using these well-characterized vectors. More recently, given their genetic stability, ease of administration, and suitability as stable, non-integrating recombinant vectors, pox viruses are seeing novel application as core components of therapeutic vaccines. Over the last nine years, the Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD) at the National Cancer Institute (NCI) have sponsored multiple Phase I and II clinical trials using various cancer vaccines prepared by Therion which are based on the same parental viruses as those used to generate PROSTVAC-VF/TRICOM. The unmodified PSA gene, as well as the genes encoding the TRICOM co-stimulatory molecules (B7.1, ICAM-1, and LFA-3), have also been incorporated in other Therion vaccines evaluated in human clinical trials by CTEP. Over 600 cancer patients have participated in clinical trials of the following related vaccines: rV-PSA, rF-PSA, rV-CEA, rV-CEA(6D)/TRICOM, rF-CEA(6D)/TRICOM, MAGEVAC, rV-MART-1, rF-MART-1, rV-gp100, rF-gp100, rF-Mgp100, rF-gp100P209; rV-TYR, rF-TYR, rV-MUC-1, rV-B7.1, and rV-TRICOM. Specific clinical experience is discussed in the Investigator's Brochure.