

#### **D. TECHNICAL ABSTRACT**

This scientific abstract has been updated to reflect changes made to the protocol.

#### **A PHASE I/II DOSE ESCALATION AND EFFICACY TRIAL OF GVAX PROSTATE CANCER VACCINE IN PATIENTS WITH METASTATIC HORMONE-REFRACTORY PROSTATE CANCER**

Prostate cancer (PCA) is the most common form of non-skin-cell cancer in adult males in the United States, eclipsing lung cancer incidence, as reported by Ries et al (Cancer. 2000; 88[10]:2398-2424). In 1996, a new case of PCA was diagnosed on an average of every 3 minutes in the United States, and a death from PCA occurred every 15 minutes. In 1997, the National Center for Health reported a US prevalence of prostate cancer of 609,000, an incidence of 330,200, and a mortality of 32,891. To date, radical prostatectomy and radiation therapy are recognized curative treatments of clinically localized prostate cancer. No curative systemic therapy exists for metastatic disease. Moreover, despite the established efficacy of hormonal therapy as first-line treatment of metastatic prostate cancer, virtually all patients eventually develop disease progression.

#### **OBJECTIVES:**

- Phase I:** To evaluate clinical and laboratory safety in patients receiving 4 different doses of GVAX Prostate Cancer Vaccine in order to determine a maximum tolerated dose (MTD) for use in Phase II trials  
To evaluate the pharmacokinetics of serum GM-CSF levels after vaccinations in at least 3 patients
- Phase II:** To further evaluate clinical and laboratory safety of GVAX Prostate Cancer Vaccine in two treatment groups at the Phase II dose  
To evaluate the efficacy of GVAX Prostate Cancer Vaccine in two treatment groups at the Phase II dose as measured by PSA response, time to progression by PSA, clinical and composite criteria, and survival

#### **PATIENT POPULATION:**

Up to 80 eligible patients with metastatic hormone-refractory prostate cancer confirmed by bone scan or other radiologic assessment without bone pain.

#### **STUDY DESIGN:**

This is an open label, Phase I/II, dose escalation and efficacy trial. The dose escalation phase of the trial will have 4 dose levels. The efficacy phase of the trial will have two

treatment groups, in which the vaccine will be administered at the dose level that was established in the dose escalation phase.

#### **TREATMENT PLAN AND SCHEDULE:**

**Phase I:** In the dose escalation phase of the trial, patients will be enrolled in cohorts of at least 3 patients each. The first 3 patients who are enrolled will be assigned to Dose Level 1. If there are no dose-limiting toxicities experienced by the 3 patients in a cohort during the first week after the first vaccination, patients will be entered in the next dose level. Entry of patients in the next dose level will not occur until at least 1 week after the last patient in the previous cohort received his first dose of vaccine. If a patient withdraws from the trial before receiving at least 3 doses, another patient may be enrolled at that dose level. If a dose-limiting toxicity (DLT) occurs, an additional 3 patients may be enrolled at the dose level at which the DLT occurred. Participants in the dose-escalation phase receiving Dose Levels 1 and 2 will receive 6 doses at intervals of 28 ( $\pm$  4) days. Participants in the dose-escalation phase receiving Dose Level 3 will receive 12 doses at intervals of 14 ( $\pm$  2) days. Participants in the dose-escalation phase receiving Dose Level 4 will receive a prime vaccination and 11 boost vaccinations at intervals of 14 ( $\pm$  2) days.

**Phase II:** Two treatment groups will be enrolled for a total of 55 patients at the dose level established in the Phase I dose escalation. Group A patients will receive 6 doses of vaccine at intervals of 28 ( $\pm$  4) days. After the 30<sup>th</sup> patient has enrolled into Group A, the next 25 sequential patients will be assigned to Group B. Group B patients will receive 12 doses of vaccine at intervals of 14 ( $\pm$  2) days.

#### **DOSE:**

**Dose Level 1:** Each vaccination will consist of 2 intradermal injections of PC-3 cells to deliver a total of  $50 \times 10^6$  cells, and 2 intradermal injections of LNCaP cells to deliver  $50 \times 10^6$  cells, for a total of  $100 \times 10^6$  cells per dose.

**Dose Level 2:** Each vaccination will consist of 3 intradermal injections of PC-3 cells to deliver a total of  $100 \times 10^6$  cells, and 3 intradermal injections of LNCaP cells to deliver  $100 \times 10^6$  cells, for a total of  $200 \times 10^6$  cells per dose.

**Dose Level 3:** Each vaccination will consist of up to 6 intradermal injections of PC-3 cells to deliver  $150 \times 10^6$  cells, and up to 6 intradermal injections of LNCaP cells to deliver  $150 \times 10^6$  cells, for a total of  $300 \times 10^6$  cells per dose.

**Dose Level 4:** The prime vaccination will consist of up to 10 intradermal injections of PC-3 cells to deliver  $250 \times 10^6$  cells, and up to 10 intradermal injections of LNCaP cells to deliver  $250 \times 10^6$  cells, for a total of  $500 \times 10^6$  cells per dose. The boost vaccinations will consist of up to 5 intradermal injections of PC-3 cells to deliver  $150 \times 10^6$  cells, and up to 5 intradermal injections of LNCaP cells to deliver  $150 \times 10^6$  cells, for a total of  $300 \times 10^6$  cells per dose.

### **DOSE-LIMITING TOXICITY:**

Dose-limiting toxicity (DLT) is defined as any treatment-related grade 3 or 4 non-hematological toxicity, excluding alopecia, or any grade 4 hematological toxicity that does not resolve in less than 5 days.

**Phase I:** If a DLT occurs in a patient during the dose escalation phase of the trial, treatment of that patient will be stopped and an additional 3 patients may be enrolled at the dose level at which the DLT occurred. In the event that an additional DLT is identified in patients at that dose level, the previous dose level will be defined as the maximum tolerated dose (MTD). All subsequent doses will be decreased to the MTD. If there are no additional DLTs within 1 week of the first vaccine dose, dose escalation will proceed to the next level.

**Phase II:** In the event that dose-limiting toxicity is identified in more than 1/3 of patients during the efficacy phase of the trial, then the next lower dose will be defined as the new MTD, and all subsequent doses will be decreased to the new MTD.

### **ADVERSE EVENT REPORTING PERIOD:**

The treatment period is defined as starting with the first vaccination and ending 4 weeks after the last dose of vaccine. During this period, adverse events will be assessed at each clinic visit, and all adverse events will be reported.

The follow-up period is defined as starting 4 weeks after the last dose of vaccine that the patient receives and ending 7 months after the last vaccine, or when the patient begins new treatment for prostate cancer. During this period, adverse events will be assessed at each clinic visit and all serious adverse events, all new malignancies, all new diagnoses of autoimmune disease and all adverse events that may be related to vaccine will be reported.

### **ENDPOINTS:**

#### **Safety:**

- Adverse events
- Safety laboratory values

#### **Efficacy:**

- PSA Response Rate
- Time to PSA Progression
- Time to Clinical Progression
- Time to Composite Progression
- Survival
- Serum GM-CSF levels

### **PRODUCT:**

GVAX<sup>®</sup> Prostate Cancer Vaccine has two components, PC-3 Cells (CG1940) and LNCaP Cells (CG8711), which are administered at the same time. Each of the components is a prostate carcinoma cell line that has been transduced ex vivo with a recombinant adeno-associated virus (rAAV). The vector contains the human genomic GM-CSF gene, under the transcriptional control of a cytomegalovirus promoter.