

A Phase III Randomized, Open-Label Study of CG1940 and CG8711 Versus Docetaxel and Estramustine in Patients with Metastatic Hormone-Refractory Prostate Cancer who are Chemotherapy-Naïve

Scientific Abstract

Prostate cancer is the most common form of non-skin cell cancer in adult males in the U.S., eclipsing lung cancer in incidence (Ries, et al, Cancer, 2000; 88[10]: 2398-2424). In 2003, the estimated incidence and mortality rate in the United States was 220,900 new cases and 28,900 deaths. Radical prostatectomy and radiation therapy are currently recognized curative treatments of clinically localized prostate cancer (Olsson, et al, Mosby Year Book, 1993. Nelson, et al, Urol Clin North Amer, 1996; 23[4]: 685-696). Approximately 70% of patients will have metastases at some time during the course of their disease, limited to the bone in 80-90% of patients. No curative systemic therapy exists for metastatic disease. Despite the established efficacy of hormonal therapy as first-line treatment of metastatic prostate cancer, virtually all patients will eventually develop disease progression.

OBJECTIVES:

This phase III, randomized, open-label study will be conducted in chemotherapy-naïve patients with metastatic hormone-refractory prostate cancer and will compare a regimen of CG1940 and CG8711 to the chemotherapy regimen of docetaxel and prednisone. The primary objective of the study is to compare the duration of survival between the two treatment arms. The secondary objectives are to compare between treatment groups the proportion of patients experiencing bone-related events (spinal cord compression, bone surgery, local radiation to the bone, or skeletal fracture), the proportion of patients experiencing progression of bone metastases, and the time to onset of bone pain.

PATIENT POPULATION:

The study will enroll approximately 600 chemotherapy-naïve patients with metastatic hormone-refractory prostate cancer. Eligible patients will have an ECOG performance status of 0-2 and detectable metastases by bone scan, CT scan or MRI. Patients with moderate or severe cancer-related pain and taking analgesics (ketorolac, opioids, and/or acetaminophen/opioid combinations) for pain management will not be eligible for the study.

STUDY DESIGN:

All patients will be randomized to one of two treatment arms to receive either a series of 13 vaccinations of CG1940 and CG8711 or 9 cycles of dexamethasone, docetaxel, and prednisone. At randomization, patients will be stratified based on screening results for ECOG performance status (0 vs. 1 or 2), Gleason score (≤ 7 vs. ≥ 8), and alkaline phosphatase level (\leq upper limit of normal vs. $>$ upper limit of normal, based on central laboratory normal ranges). All patients will be assessed for bone-related events, and undergo a complete skeletal x-ray at week 28 and week 52 following the first treatment visit. In addition, all patients will complete a 7-day analgesic-diary prior to each treatment visit. Patients will also have a tumor evaluation and assessment of clinical response approximately every 12 weeks, including bone scan.

TREATMENT PLAN AND SCHEDULE:

Patients randomized to the CG1940 and CG8711 vaccination arm will receive a prime vaccination followed by 12 boost vaccinations at 14-day treatment intervals. Patients in this arm will receive a total of 13 vaccinations. Patients with stable or improved disease at the completion of 13 vaccinations may receive additional boost vaccinations monthly, at the discretion of the investigator. CG1940 and CG8711 should be administered as intradermal injections in an outpatient setting.

Patients randomized to the chemotherapy treatment arm will receive dexamethasone, docetaxel, and prednisone every 21 days for up to 9 cycles. Patients with stable or improved disease at the completion of 9 cycles may receive additional cycles at the discretion of the investigator.

DOSE:

Vaccination arm: The dose of CG 1940 and CG8711 will consist of a prime vaccination containing an equal amount of CG1940 and CG8711 to deliver a total of 5×10^8 cells. Boost vaccinations will consist of equal amounts of CG1940 and CG8711 to deliver a total of 3×10^8 cells.

Chemotherapy arm: For every 21-day treatment cycle, patients will receive prednisone 10 mg daily and docetaxel at 75 mg/m^2 by intravenous infusion on Day 1.

ADVERSE EVENT REPORTING PERIOD:

The treatment period is defined as starting with the first treatment and ending 4 weeks after the last treatment. 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 treatment. Adverse events will be assessed and all adverse events that may be related to treatment will be reported. If any related adverse events are reported in patients who received CG1940 and CG8711 that might be indicative of long-term effects of gene therapy (e.g., new malignancies or autoimmune disease), the patient may be requested to return to the clinic for additional tests. Patients will be followed long-term for survival.

SAFETY ASSESSMENTS:

Safety will be monitored by physical examinations, hematology, serum chemistry, anti-nuclear antibody, and adverse events.

PRODUCT:

The vaccine is composed of two cell-lines: CG1940 (PC-3) and CG8711 (LNCaP). CG1940 and CG8711 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. AAV has a simple genome organization comprised of three major components: (1) two regulatory (*rep*) and structural (*cap*) genes required for viral replication and virus production; (2) inverted

terminal DNA repeats flanking the viral genome, necessary for viral genome replication, packaging, and integration. The recombinant AAV vector was derived by deleting the *rep* and *cap* genes, and replacing them with the GM-CSF gene and the genetic control elements needed for its expression. The vector can integrate, but in the absence of *rep* and *cap* genes, is unable to replicate on subsequent helper virus infection. The *ex vivo* transduction with rAAV encoding for hgGM-CSF resulted in integration of the transgene sequence into the host genome and expression of GM-CSF from the transduced cells. The cloned GM-CSF-transduced cells are grown in suspension, frozen and lethally irradiated to arrest cell growth