A Phase III Randomized, Open-Label Study of Docetaxel in Combination with CG1940 and CG8711 versus Docetaxel and Prednisone in Taxane-Naïve Patients with Metastatic Hormone-Refractory Prostate Cancer With Pain.

Scientific Abstract

INTRODUCTION

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 2005, the estimated incidence and mortality rates in the U.S.A. are 232,090 new cases and 30,350 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. Treatment of metastatic prostate cancer is focused on palliation of disease-related morbidity (primarily palliation of bone pain that occurs secondary to bony metastatic disease) and prolongation of patient survival. Primary treatment of systemic (metastatic) prostate cancer is hormonal ablation with either orchiectomy or medical castration (luteinizing hormone releasing hormone (LHRH) agonist/antagonist given alone or in combination with an antiandrogen agent). Hormonal ablation provides excellent disease control. However, virtually all patients develop progressive prostate cancer that is hormone refractory. Two treatments approved for metastatic prostate cancer are Taxotere® (docetaxel) and Novatrone® (mitoxantrone). In a phase 3 trial, the combination of mitoxantrone and prednisone demonstrated a significant increase in bone pain palliation compared to prednisone alone. (Tannock et al, JCO, 1996, 14:1756-1764). No significant improvement in survival was demonstrated for mitoxantrone/prednisone compared to prednisone alone. Docetaxel was approved for the treatment of metastatic hormone refractory prostate cancer (HRPC) based on the results of a phase 3 trial in which the combination of docetaxel and daily prednisone demonstrated a survival advantage of 2.4 months (p=0.009) over HRPC patients treated with mitoxantrone and daily prednisone. (Tannock et al, NEJM, 2004, 351:1502-1512). No curative systemic therapy exists for metastatic disease.

Immunotherapy with earlier versions of granulocyte-macrophage colony-stimulating factor (GM-CSF) secreting tumor cell vaccines have demonstrated a good safety profile and some anti-tumor activity in phase 2 studies. In order to improve the clinical efficacy of docetaxel as a single treatment regimen used to treat HRPC, CG1940 and CG8711, a prostate cancer specific GM-CSF secreting tumor cell vaccine, is administered in combination with docetaxel. In preclinical animal models, the addition of docetaxel to GM-CSF secreting vaccine cells demonstrated a synergistic anti-tumor effect (prolonged survival) compared to either agent alone. The best survival was seen when animals were treated with chemotherapy prior to receiving immune therapy. In addition to increased animal survival, administration of docetaxel prolonged the survival of activated immune cells (antigen-specific T cells), resulting in increased numbers of tumor-specific T cells in the spleen and lymph nodes for nearly two weeks post-treatment. The mechanism of the synergy between the vaccine and chemotherapy is unknown.

OBJECTIVES:
This phase 3, randomized, open-label study will be conducted in patients with metastatic hormone-refractory prostate cancer who have disease progression despite hormone ablative therapy and have symptomatic disease (primarily metastatic disease related bone pain). The study will compare a regimen of CG1940 and CG8711 plus docetaxel chemotherapy to docetaxel chemotherapy alone. 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 time to radiologic disease progression and the time to pain progression.

PATIENT POPULATION:
This study will enroll approximately 600 eligible patients with hormone-refractory prostate cancer with pain requiring narcotic analgesia. Patients must be taxane-naïve and have had no more than one prior systemic chemotherapy treatment. Eligible patients will have an ECOG performance status of ≤ 2 (performance status of 3 allowed if due to bone pain) and detectable metastases by bone scan, CT scan, or MRI. Patients are required to have moderate or severe cancer related pain and be taking ketorlac, opioids, and/or acetaminophen/opioid combination analgesic medications.

STUDY DESIGN:
This is a phase 3, randomized, open-label study in taxane-naïve patients with metastatic hormone-refractory prostate cancer comparing docetaxel in combination with CG1940 and CG8711 to docetaxel and prednisone.

TREATMENT PLAN AND SCHEDULE:
All patients will be randomly assigned to one of two treatment arms. Randomization is stratified based on ECOG performance status, Gleason score and alkaline phosphatase. Patients will be randomized 1:1 to one of the following 2 treatment groups:

Arm 1 (Chemotherapy plus Vaccine): Patients randomized to Arm 1 will receive treatment cycles of docetaxel and vaccine every 21 days for 10 cycles. At the completion of 10 cycles of combination therapy with vaccine and docetaxel, patients will receive maintenance vaccinations of CG1940 and CG8711 every 28 days until death or until they require new systemic therapy for prostate cancer.

Arm 2 **(Chemotherapy Only):** Patients randomized to Arm 2 will receive docetaxel q 3 weeks and prednisone daily for 10 cycles (27 weeks).

DOSE:
Arm 1(Chemotherapy plus Vaccine): Patients randomized to Arm 1 will receive treatment cycles of docetaxel and vaccine every 21 days. Docetaxel (75 mg/m^2) will be administered on Day 1 of each cycle. At treatment cycle 1, patients will receive a prime vaccination of 5×10^8 cells consisting of equal amounts of CG1940 and CG8711, followed on subsequent cycles by boost vaccinations of 3×10^8 cells consisting of equal amounts of CG1940 and CG8711. All vaccinations will be administered on Day 3 of

each treatment cycle. Treatment cycles will be repeated for 10 cycles (27 weeks of treatment). Dexamethasone premedication (4mg x 3 doses) will be administered at 12 hours, 3 hours and 1 hour prior to docetaxel administration. At the completion of 10 cycles of combination therapy, patients will receive maintenance vaccinations of 3×10^8 cells consisting of equal amounts of CG1940 and CG8711 alone, every 28 days until death, or until they require new systemic therapy for prostate cancer.

Arm 2 **(Chemotherapy Only):** Patients randomized to Arm 2 will receive docetaxel (75 mg/m^2) and prednisone (10 mg a day) every 21 days for 10 cycles (27 weeks). Dexamethasone premedication (4mg x 3 doses) will be administered at 12 hours, 3 hours and 1 hour prior to docetaxel administration.

ADVERSE EVENT REPORTING PERIOD

Treatment is defined as starting with receipt of the first study drug during the initial 10 cycle treatment period and ending 28 days after day 1 of the last administration of study drug (including maintenance vaccine), or upon receipt of new systemic therapy for prostate cancer. During treatment, adverse events will be assessed at each clinic visit and all adverse events will be reported.

Following treatment, patients are followed quarterly for life during which time all adverse events will be assessed and only adverse events and serious adverse event considered by the investigator to be related to study drug treatment will be reported, regardless of receipt of any other therapies for prostate cancer. In the quarterly follow-up, all randomized patients will be followed for potential long-term effects of therapy (hematologic disorders, neurologic disorders, new or secondary malignancies or autoimmune disease) regardless of potential relationship to study drug. If any of these are identified, the patient may be requested to return to the clinic for additional testing.

SAFETY ASSESSMENTS:

Safety will be monitored by physical examinations, hematology, serum chemistry, anti-nuclear antibody, and adverse events. The principal investigator is responsible for evaluating all adverse events, obtaining supporting documents, and determining that documentation of the event is accurate. The principal investigator is responsible for determining the severity and relationship of the adverse event to study drug(s). All adverse events are recorded on Case Report Forms. The severity of the adverse event is categorized by toxicity grade according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0 (CTCAE) [available at http://ctep.cancer.gov/. Safety data, including laboratory results and all adverse events, will be presented to an Independent Data Monitoring Committee (ICMC) every six months during the study. The IDMC will review the data provided to them and make a recommendation to the sponsor to either continue the trial or suspend enrollment pending further evaluation.

PRODUCTS:

Vaccine (CG1940 and CG8711)

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.

Docetaxel

Docetaxel is commercially available.

Docetaxel is an antineoplastic agent belonging to the taxoid family that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel is approved for treatment of several cancers including breast cancer, non-small cell lung cancer, and prostate cancer. In prostate cancer, docetaxel in combination with prednisone is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.