

A PHASE I/II TRIAL OF INTRAPROSTATIC INJECTION OF CG7870 FOLLOWED BY THREE-DIMENSIONAL CONFORMAL RADIATION THERAPY (3D-CRT) IN PATIENTS WITH CLINICALLY LOCALIZED INTERMEDIATE-RISK PROSTATE CANCER

Scientific Abstract

Prostate cancer is the most common type of cancer and the second leading cause of cancer death in men in the United States. The incidence has increased dramatically over the past 25 years, due in part to improved detection of subclinical carcinomas during transurethral resections of the prostate, but also to improvements in screening for elevated prostate-specific antigen (PSA). PSA is a prostate-derived serine protease. Normal prostate cells produce PSA but little is released into the bloodstream. In contrast, nearly all prostate cancers produce or release a significantly higher level of PSA. No other cells within vital organs of the body express PSA. As a result, PSA has become the most widely used cancer marker. PSA levels have been shown to increase with increasing age and have been correlated with the development of benign prostatic hypertrophy and with prostate cancer.

Treatment for early stage (T1, T2) prostate carcinoma in which disease is clinically confined to the prostate has generally consisted of either radical prostatectomy or radiation therapy (external beam radiation or brachytherapy). These therapies provide an excellent chance of long-term disease-free survival in men with very good prognosis (low-risk) tumors, but they all show substantially less efficacy in men with higher-risk prostate carcinoma. Intermediate-risk prostate cancer patients need improved treatment options. Following standard three-dimensional conformal radiotherapy, local and distant cancer relapse occurs in many cases. Approximately 20% of patients will relapse within 5 years or less, and many of these will relapse in the radiation field. The prostate-specific survival at 5 years post-treatment is approximately 94%. In addition, for the best cancer control results to be obtained, radiotherapy must be used at the highest cumulative doses that are feasible clinically. At these doses, radiation-induced toxicities are common; these include rectal complications (eg, bleeding, fibrosis) and lower urinary tract toxicities (eg, strictures, hematuria). Therefore, novel treatment approaches are needed that result in better cancer control and/or reduced toxicities.

Several attempts have been made to exploit the cell-killing properties of replication-competent adenoviruses in the treatment of cancer. CG7060 (formerly CN706) was a first generation virus constructed to result in the preferential replication of CG7060 in PSA-producing prostate cancer cells. CG7870, the virus used in this study, is a second-generation virus with much more specificity than CG7060 for PSA-producing cells.

OBJECTIVES

The primary objectives of this study are to determine: 1) the maximum-tolerated dose (MTD) or maximum feasible dose (MFD) of CG7870 administered intraprostatically when combined with three-dimensional conformal radiation therapy (3D-CRT) in the treatment of patients with clinically-localized intermediate-risk prostate cancer, and 2) the safety and feasibility of intraprostatic CG7870 when combined with 3D-CRT in patients with clinically-localized intermediate-risk prostate cancer. The secondary objective is to determine the proportion of patients with PSA < 0.5 ng/mL at 18 months after initiation of treatment.

PATIENT POPULATION

Approximately 26 patients with histologically proven, localized adenocarcinoma of the prostate, who are eligible for 3D-CRT and who are at intermediate-risk for biochemical (PSA) failure following irradiation.

STUDY DESIGN

Phase I/II, multicenter, open-label dose-escalation study.

TREATMENT PLAN, DOSE, AND SCHEDULE

Using transrectal ultrasound (TRUS) guidance with a 22 gauge TRUS needle, 0.67 mL of CG7870 will be administered into each of six intraprostatic sites. For each injection site, the needle will be passed initially to the deepest margin of the prostate. As the needle is gradually withdrawn the treatment volume will slowly be injected, thus resulting in uniform virus distribution along the needle pass. The standard sextant biopsy pattern will be used. Institutional guidelines for TRUS guidance will be followed.

Phase I of the trial will have 2 treatment cohorts. *Cohort 1:* Two to 6 patients will receive treatment with CG7870 consisting of a single dose of 1×10^{12} viral particles on Day 1. 3D-CRT will commence 3 days following treatment with CG7870 on study Day 4. *Cohort 2:* Two to 6 patients will receive treatment with CG7870 consisting of 2×10^{12} viral particles administered in divided doses of 1×10^{12} viral particles on study Days 1 and 22. 3D-CRT will commence 3 days following treatment with CG7870 on study Day 4.

For all cohorts the dose of 3D-CRT will be 7380 cGy to the planning target volume (PTV) (ie, standard radiotherapy for this patient population). Patients will be treated with 180 cGy daily, 5 days a week, for 41 treatments.

Phase II: After the completion of Phase I, additional patients will be added in Phase II of the trial for a total of 20 patients to be treated at the dose level and treatment regimen established as the MTD or MFD in Phase I. If two patients in the first cohort experience a DLT, the study will be halted without Phase II expansion.

Patients will be actively involved in the study for approximately 18 months. During the treatment phase, they will be seen daily for 5 consecutive working days after CG7870 administration then weekly for 9 weeks. During the follow-up phase, patients will be seen at Months 3, 4, 6, 9, 15, and 18 after CG7870 administration. After this, patients will be asked to enroll in a separate, long-term follow-up study.

ENDPOINTS

Primary endpoints are safety evaluation by adverse event monitoring, physical examination including ECOG performance status, and standard testing for laboratory toxicity. Secondary endpoints are rate of PSA decline; PSA nadir; proportion of patients with PSA < 0.5 ng/mL at 9, 12, and 18 months after treatment initiation; time to biochemical PSA failure; time to clinical disease progression; CG7870 pharmacokinetics; immune response to CG7870; and rate of cancer positive sextant biopsies at 18 months after treatment initiation.

PRODUCT

CG7870 is an attenuated, replication-competent adenovirus, genetically modified by the addition of the human prostate-specific enhancer/promoter and the rat probasin promoter with preservation of the E3 viral genome, to replicate preferentially in cells producing PSA.