Non-Technical Abstract

Prostate cancer is the second leading cause of cancer death in men in the United States, with about 40,000 deaths per year, comparable to the annual death rate from breast cancer in women. The incidence of this cancer has increased dramatically over the past 25 years, and this has been attributed in part to improvements in screening for elevated prostate-specific antigen (PSA). While elevated PSA levels are sometimes a natural phenomena of aging, or of other physiological states, they continue to be the most useful marker for prostate cancer.

If prostate cancer is caught early it can often be cured; in some cases the disease will continue to spread throughout the body. Metastatic prostate cancer is initially treated with androgen deprivation, which achieves stabilization or regression of disease in more than 80% of patients. However, despite androgen deprivation and secondary hormonal manipulations, all patients ultimately develop hormone-refractory prostate cancer (HRPC). Although symptomatic improvement and control of metastatic disease is obtained in most patients after androgen ablation, disease progression occurs at a median of 12 to 18 months.

The perception that prostate cancer is resistant to chemotherapy has been changing. This is the result of several reported trials investigating a variety of single agents or combination chemotherapy indicating some clinical efficacy. In men with HRPC, objective measurable responses, palliation of bone pain, and reductions in serum PSA have been produced with combinations of estramustine and vinblastine, paclitaxel, etoposide, or docetaxel (Taxotere™). More recently, the FDA approved the combination of mitoxantrone and prednisone based solely on its superior palliative effects as compared to steroids alone. However, chemotherapy with cytotoxic agents has not extended the median survival of approximately 10-12 months for patients with hormone-refractory metastatic prostate cancer. New therapeutic modalities are therefore actively being sought for these patients with hormone-refractory disease.

The trial proposed here is based on a new approach to treatment of prostate cancer. Specifically it is aimed at patients in whom the cancer has spread, and is based on the use of a genetically engineered virus which is injected into the bloodstream to destroy the metastatic cancer cells as identified by the presence of PSA on their surface.

The technology begins with the common cold virus known as adenovirus. Calydon has altered this virus by injecting it with promoter and enhancer elements cloned from the human PSA gene. As a result of this engineering, Calydon's new therapeutic, CV787, reproduces only in prostate cancer cells (or those cells containing PSA) causing cancer cell death. Conversely, CV787 affects a minute number of cells that do not contain PSA (10,000:1) thus limiting the death of non-cancerous cells.

In our laboratory, CV787 has been shown to be effective against human prostate tumors. However, total eradication of human LNCaP xenografts in our animal model required as high as one third of the lethal dose of virus alone. Therefore, strategies to improve the efficacy of this form of treatment are desirable. In efforts to augment the cytotoxic activity of CV787, we have investigated in preclinical studies a combination CV787 plus an anti-cancer agent, Taxotere™. Previous studies have demonstrated that tumors were eliminated within 6 weeks by a single intravenous administration of CV787 at a dose of $1x10^{11}$ particles per animal. However, in combination with a single dose of docetaxel, CV787 doses as low as $1x10^{8}$ particles per animal produced complete elimination of tumors within 4 weeks. Thus, the addition of a single dose of docetaxel reduced the dose of CV787 required for complete remission 1000-fold, while maintaining an acceptable side effect profile. As a result, the curative therapeutic index was increased 1000-fold in this preclinical model.

The first human study, a phase 1-2, open-label, dose finding safety study of intravenous CV787 adenovirus in patients with hormone refractory metastatic prostate cancer was initiated in 2000 at three academic hospitals throughout the US. To date, a total of ten patients in four cohorts have received one intravenous injection of CV787 at escalating doses from $1x10^{10}$ to $3x10^{11}$ virus particles.

No significant adverse events and/or dose-limiting toxicities have been observed in these patients. Therefore the maximum tolerated and clinically safe dose has not yet been defined.

The proposed clinical study CV787-2001 is a "Randomized, Placebo Controlled Phase 2 Study of an Intravenous Injection of CV787, a Prostate-Specific Antigen Oncolytic Adenovirus, Plus Weekly Docetaxel in Patients with Metastatic Hormone Refractory Prostate Cancer" and will use a clinically safe and tolerable CV787 dose that is currently being established in the ongoing CV787-9902 phase 1-2 study.

The objectives of the clinical study are:

1. Compare the antitumor activity of CV787 plus weekly docetaxel versus placebo (saline) plus weekly docetaxel, as measured by PSA response in patients with Metastatic Hormone Refractory Prostate Cancer.
2. Compare the pain response and palliation of metastatic bone pain (McGill scale and analgesics usage) in these two treatment arms in this patient population.
3. Compare the antitumor activity of this regimen as measured by objective response (CT/pelvic scan) and evaluable disease (bonescan) in these two treatment arms in this patient population.
4. Evaluate the quantitative and qualitative toxicities in these two treatment arms in this patient population.

This is a randomized, double-blind, placebo-controlled multi-center study and approximately 60 patients with Metastatic Hormone Refractory Prostate Cancer will be enrolled. The assignment ratio will be 2:1 (40 patients CV787 plus Docetaxel : 20 patients Placebo plus Docetaxel). Patients are randomized into one of the following two treatment arms:

Arm I: Patients receive CV787 administered as a single intravenous infusion over 10 minutes plus 36 mg/m^2 docetaxel IV over 60 minutes on day 1, followed by weekly docetaxel (36 mg/m^2) for a total of 6 consecutive weeks, followed by 2 weeks without treatment (8 week cycle). The maximum tolerated and clinically safe CV787 dose to be used in this study is currently being determined in the ongoing study CV787-9902.

Arm II: Patients receive placebo (saline) administered as a single intravenous infusion over 10 minutes plus 36 mg/m^2 docetaxel IV over 60 minutes on day 1, followed by weekly docetaxel (36 mg/m^2) for a total of 6 consecutive weeks, followed by 2 weeks without treatment (8 week cycle).

Patients in both Arm I and II receive treatment with dexamethasone as docetaxel pretreatment; a single dose of dexamethasone (not to exceed 10mg/week) will be administered immediately before treatment. The dexamethasone dose will be standardized for the study based on a consensus of the clinical investigators.

CV787 (or placebo) treatment is only administered once (day 1); treatment with docetaxel continues in both arms for at least 3 cycles (24 weeks) in the absence of disease progression or unacceptable toxicity. Patients are followed up to 18 months post-treatment.

Once the first ten patients in the study have received their first month of study treatment, the adverse events observed in those patients will be analyzed by a safety monitoring board. If unacceptable toxicity attributed to either CV787 or the combination of CV787 plus docetaxel has been observed in this group, recruitment will be halted and the protocol may either be modified (e.g., CV787 dose reduced) or discontinued.

The endpoints for each patient are PSA reduction, pain control, safety and survival. An endpoint for patients with measurable disease will be objective response. This study is not designed to have the power to detect differences between the treatment groups. The control arm, placebo plus docetaxel, is present to provide a reference enhancing the reliability of the data collected on the experimental arm, IV injection of CV787 plus docetaxel. The primary analysis will include all randomized and treated patients (an intent to treat analysis).