

SECTION 1 SCIENTIFIC ABSTRACT

External beam radiation therapy (EBRT) is an appropriate treatment option for the management of clinical stage II prostate cancer. While prolonged survival is common, disease control following EBRT varies considerably with pre-treatment risk factors, method of delivery, and radiation dose. In patients with favorable risk factors (Stage T1 - T2a, Gleason score ≤ 6 , PSA ≤ 10 ng/ml), conventional dose (70 - 75 Gy) EBRT results in excellent long-term cancer-free survival ($\geq 80\%$). In contrast, disease control in intermediate (Stage T2b or Gleason score = 7 or PSA 10 - 20 ng/ml) and high (Stage T2c or Gleason score ≥ 8 or PSA > 20 ng/ml) risk patients is considerably less (25% - 70%) using the same criteria. A significant fraction of intermediate-to-high risk patients treated with conventional dose radiotherapy will develop recurrent disease within 10 years.

Unfortunately, patients with locally recurrent prostate cancer have no therapeutic options that have a high degree of efficacy in eradicating tumor with a reasonable degree of safety. The risks associated with salvage radical prostatectomy and cryotherapy are high, the merit of salvage brachytherapy has not been established, and androgen deprivation therapy is not curative. More effective treatments for this group of patients are badly needed.

The scientific rationale for this Phase I/II study derives from the extensive preclinical and clinical work conducted in Drs. Freytag's and Kim's laboratories during the past 10 years. Our research program has developed a novel, gene therapy-based approach for the treatment of cancer. A replication-competent adenovirus is used to deliver a cytosine deaminase (CD)/herpes simplex virus thymidine kinase (HSV-1 TK) fusion gene to tumors. Our preclinical studies have demonstrated that the replication-competent adenovirus itself has potent anti-tumor activity by replicating in and preferentially destroying human cancer cells. The therapeutic effect of the replication-competent adenovirus can be enhanced significantly by invoking two suicide gene systems (CD/5-FC and HSV-1 TK/GCV), which render malignant cells sensitive to specific pharmacological agents and, importantly, sensitizes them to radiation.

The safety and efficacy of our gene therapy-based approach using the replication-competent Ad5-CD/TK rep adenovirus has been evaluated in two Phase I clinical trials without (BB-IND 8436, RAC 9906-321) and with (BB-IND 9852, RAC 0104-464) conventional dose three-dimensional (3D) conformal radiation therapy (CRT). There were no dose-limiting toxicities and no treatment-related serious adverse events. Bladder and bowel toxicities were similar to that expected for conventional dose 3D-CRT alone. Tumor destruction in post-treatment prostate biopsies was demonstrated. The mean PSA half-life of patients administered greater than one week of prodrug therapy was significantly shorter than that of patients receiving prodrugs for only one week (0.6 vs. 2.0 months; $p < 0.02$), and markedly shorter than that reported previously for patients treated with conventional dose 3D-CRT alone (2.4 months). The results demonstrate that replication-competent adenovirus-mediated double suicide gene therapy can be combined safely with conventional dose 3D-CRT in patients with

intermediate-to-high risk prostate cancer and that the therapy is showing signs of activity.

The primary objective of this Phase I/II study is to determine the dose-dependent toxicity and therapeutic efficacy of replication-competent adenovirus-mediated double suicide gene therapy in combination with salvage intensity modulated radiation therapy (IMRT) in patients with locally recurrent prostate cancer after definitive radiation therapy. A second-generation adenovirus (Ad5-yCD/*mutTK*_{SR39}*rep*-ADP) containing a more catalytically active yeast cytosine deaminase (yCD)/mutant SR39 herpes simplex virus thymidine kinase (*mutTK*_{SR39}) fusion gene and the Ad5 ADP gene will be used. Three cohorts of three patients will receive a single intraprostatic injection of adenovirus (10^{12} vp) along with three weeks of 5-FC + vGCV prodrug therapy and an escalating dose (20, 26, 30 Gy) of IMRT. The primary endpoint will be toxicity at 90 days. If there are no toxicity concerns, a Phase II trial will be conducted in which patients will receive a single intraprostatic injection of Ad5-yCD/*mutTK*_{SR39}*rep*-ADP (10^{12} vp) along with three weeks of 5-FC + vGCV prodrug therapy and the maximum tolerated dose (MTD) of IMRT. The primary endpoint will be local tumor control as determined by prostate biopsy status at two years. Other endpoints will be acute (≤ 90 days) and late (> 90 days) toxicity, and freedom from biochemical or clinical failure.