

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 ($> 80\%$). 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. This poorer outcome highlights the need for better radiation regimens for intermediate-to-high risk patients.

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/TKrep 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 test the hypothesis that replication-competent adenovirus-mediated double suicide gene therapy when combined with conventional dose CRT (called trimodal therapy) is superior to CRT alone in patients with newly diagnosed, intermediate-to-high risk prostate cancer. 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. An abbreviated Phase I study (6 patients) will be conducted to assess the dose-dependent toxicity of Ad5-yCD/*mutTK_{SR39}rep*-ADP when combined with 5-fluorocytosine (5-FC) and valganciclovir (vGCV) prodrug therapy and conventional dose CRT. Two cohorts of three patients will receive a single intraprostatic injection of the Ad5-yCD/*mutTK_{SR39}rep*-ADP adenovirus at two dose levels (10^{11} and 10^{12} vp), followed by three weeks of 5-FC + vGCV prodrug therapy and 74 Gy CRT. The primary endpoint is acute toxicity through Day 90. If there are no toxicity concerns, a randomized, prospective, two-arm Phase II study (130 patients) will be conducted in which patients will receive either a single intraprostatic injection of Ad5-yCD/*mutTK_{SR39}rep*-ADP (10^{12} vp or MTD) along with three weeks of 5-FC + vGCV prodrug therapy and 74 Gy CRT (Arm 1) or 74 Gy CRT alone (Arm 2). 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, early tumor control at six months and one year, and freedom from biochemical or clinical failure.