

SECTION 1 SCIENTIFIC ABSTRACT

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States (U.S.) representing 5% of all cancer deaths. The American Cancer Society estimates that pancreatic cancer will claim 31,800 lives in the U.S. in 2005. Although these statistics demonstrate the significance of pancreatic cancer as a health problem, none is more chilling than the fact that the annual incidence to mortality ratio is almost one. The need for better treatments can't be overstated.

The scientific rationale for this Phase I study derives from the extensive preclinical and clinical work conducted in Drs. Freytag's and Kim's laboratories during the past 12 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 has been evaluated in three Phase I clinical trials of prostate cancer without (BB-IND 8436, RAC 9906-321) and with (BB-IND 9852, RAC 0104-464; BB-IND 11253, RAC 0307-590) conformal radiotherapy (CRT). When combining the results of these three Phase I trials, there have been no dose-limiting toxicities (DLTs) and no treatment-related serious adverse events (SAEs). Over 90% of the adverse events have been mild (grade 1) to moderate (grade 2). Evidence of therapeutic gene expression and tumor destruction was demonstrated in post-treatment biopsies. Post-treatment PSA and prostate biopsies have generated provocative results suggesting that the oncolytic adenoviral and suicide gene therapies may have provided a therapeutic benefit beyond that expected for radiotherapy alone. The results demonstrate that replication-competent adenovirus-mediated double suicide gene therapy can be combined safely with conformal radiotherapy and that the investigational therapy may benefit select patient groups.

We now plan to evaluate the safety and potential efficacy of our multi-modal approach in other cancers. The primary purpose of this Phase I study is to determine the safety of combining replication-competent adenovirus-mediated suicide gene therapy with neoadjuvant chemoradiotherapy in subjects with potentially resectable pancreatic cancer. Nine to 18 subjects (3 cohorts of 3 - 6 subjects each) with potentially resectable pancreatic cancer will receive a single intratumoral injection of the Ad5-yCD/*mutTK_{SR39rep}*-ADP adenovirus at three dose levels (10^{10} , 10^{11} , 10^{12} vp) under endoscopic ultrasound (EUS)-guidance. Beginning three days later, subjects will be administered 3 weeks (15 days) of 5-FC and vGCV prodrug therapy concomitant with a 5.6 week (28 day) course of capecitabine chemotherapy and 50.4 Gy conformal radiotherapy. Within two weeks after completion of the chemoradiation course, subjects

will be re-staged and will undergo surgery if the primary tumor is deemed resectable.

The primary endpoint is toxicity at 6 weeks. Secondary endpoints are: 1) toxicity at 3 months, 2) tumor (radiological) response, 3) time to disease progression, 4) survival, 5) histopathological evidence of tumor destruction, 6) immunohistochemical evidence of adenoviral replication, 7) persistence of Ad5-yCD/*mutTK_{SR39}rep*-ADP adenoviral DNA in blood, and 8) evidence of therapeutic gene expression *in vivo* as determined by positron emission tomography (PET).