BG00001 in Prostate Cancer, RAC Submission

Scientific Abstract:

An adenoviral vector, BG00001, which carries the human interferon beta (hIFN-β) gene under the direction of the cytomegalovirus (CMV) immediate-early promoter, is being developed as a locally administered therapy for prostate cancer. The phase I study described in this submission will include adult male patients with prostate cancer that is clinically localized and resectable, but at high risk of relapse. In animal models the local production and secretion of hIFN-β protein following gene transfer demonstrates potent tumoricidal effects against both transfected and untransfected tumor cells in the vicinity of the vector injection site. Furthermore, in murine models of both murine and human cancers, local gene transfer therapy with adenoviral vectors carrying the hIFN-β gene induces an anti-tumor immune response that results in potent anti-tumor activity at distant sites. Additional data support that this activity at distant sites is not mediated by high levels of circulating IFN-β or by transduction but rather by induction of systemic immunity, which confers long lasting resistance to tumor re-challenge in mice. It is hoped that local delivery of the hIFN-β gene will have similar local and distant anti-tumor activity in humans with prostate cancer.

BG00001 is a human serotype 5 adenoviral vector from which most of the E1 and E3 genes have been deleted, and into which the hIFN-β gene has been inserted. The E1 deletion renders the vector replication-incompetent. BG00001 is derived from a Master Seed Stock of virus H5.010CMVhIFN-β, which was generated through a collaboration between Biogen, Inc. and the University of Pennsylvania. BG00001 and similar adenoviral vectors delivering the human or murine interferon-beta genes (including H5.010CMVhIFN-β have been tested by direct injection into various murine tumor models, including subcutaneous and orthotopic xenograft models with human prostate cancer cell lines. These experiments have consistently demonstrated a potent anti-tumor effect. In an orthotopic xenograft model of human prostate cancer, high intra-tumor concentrations of IFN-β (100-1000 ng/g tissue) have been achieved with little or no detectable circulating IFN-β These results suggest that gene transfer therapy with BG00001 has the potential to result in anti-tumor activity without producing the toxicities caused by high circulating concentrations of IFN-β.

A single patient with recurrent anaplastic astrocytoma has been treated with H5.010CMVhIFN-β in a phase I study. The patient received a dose of $3x10^{10}$ vector particles at each of two intra-cranial administrations, and tolerated the therapy well. More than 24 months following treatment the patient remains fully functional and free of detectable disease. An adenoviral vector carrying the hIFN-β gene has not been delivered to a patient with prostate cancer. However, both replication defective adenoviral vectors, and conditionally replication competent, cytolytic adenoviruses have been evaluated in clinical studies in prostate cancer. These agents have been generally safe and well tolerated following direct intraprostatic injection.

As described below, the lots of BG00001 to be used in the proposed study have been manufactured at BioReliance (Rockville, MD) according to cGMP. BG00001 has been evaluated in a GLP compliant toxicology and biodistribution study of direct intracerebral injection, in rhesus monkeys. This study demonstrated that intracerebral dosing of BG00001 in

rhesus monkeys was tolerated without systemic toxicity, or neurobehavioral abnormalities. The MRI and neuropathological findings were indicative of local, dose-related self-limited inflammatory changes. A GLP compliant toxicology and biodistribution study of direct intraprostatic injection of BG00001 in rhesus monkeys is ongoing, and the phase I clinical study will not be initiated until the results of this preclinical study have been reviewed.

The proposed phase I study will be performed at the University of Texas M.D. Anderson Cancer Center, under the direction of Colin P. N. Dinney, M.D. In order to enroll the required number of patients within the planned one year period, additional clinical sites will be added. When additional sites are identified the Principal Investigator's curriculum vitae, and other required information will be provided to the Recombinant DNA Advisory Committee, in accordance with NIH regulations.

The proposed phase I study is a multi-center, open label, dose escalation by cohort protocol. The primary objective is to determine the tolerability of intra-tumor injection of BG00001 in subjects with surgically resectable prostate cancer that is at high risk of recurrence. The secondary objectives are as follows: determine the maximum tolerated dose (MTD) of BG00001; assess the feasibility of using a 3-dimensional brachytherapy planning system and Transrectal Ultrasound (TRUS)-guided transperineal injection to deliver BG00001 to the prostate; assess pathological evidence of antitumor activity in resected tumor specimens; assess pathological evidence of gene transfer in resected tumor specimens; assess dissemination of BG00001 in blood, urine, and nasal secretions by PCR; measure serum and prostate tissue interferon-beta levels; measure antibodies to adenoviral vector and to human interferon-beta; measure the frequency of negative surgical margins at radical prostatectomy, following neoadjuvant treatment with BG00001, and assess clinical/biological response by PSA, physical examination, and TRUS.

A minimum of two and a maximum of 36 subjects will participate. Subjects will be ≥ 18 years of age, with a diagnosis of surgically resectable adenocarcinoma of the prostate at clinical stage T3, N0, M0; T-any, N0, M0 if Gleason score is 8-10; or T2b, N0, M0 if Gleason score is 7 and PSA greater than 10. The 1997 AJCC TNM Staging System will be used where "T'refers to Tumor Stage, "N" refers to Lymph Node Stage, and "M" indicates the presence or absence of metastatic disease.

The study uses a standard phase I, dose escalation design. Up to six cohorts of 3-6 subjects will be enrolled. A total of six subjects will be treated at the MTD, or maximum achievable dose. The starting dose will be $1x10^{10}$ vector particles (vp), and the doses will escalate approximately three fold between cohorts.

After informed consent is obtained, subjects will undergo screening and baseline evaluations, including three-dimensional brachytherapy planning using trans-rectal ultrasound (TRUS) to identify 40 target injection sites evenly distributed throughout the prostate. On Day 1 eligible subjects will be hospitalized, and undergo TRUS-guided, transperineal, intraprostatic injections using a brachytherapy template. BG00001 will be deposited at the 40 planned target sites. Subjects will remain hospitalized overnight, and a Foley catheter will remain in the urethra for 7 days, to reduce the risk of urinary obstruction due to acute prostatitis. Subjects will be evaluated as outpatients on a weekly basis, until Day 43, when they are re-admitted to the hospital for radical prostatectomy. Subjects will remain hospitalized for a minimum of 4 days (including the day of surgery). The remainder of study follow-up will be on an outpatient basis. Subjects will

follow-up on Days 60 (2 months), 120 (4 months), 183 (6 months), 274 (9 months), and 365 (12 months). After one year of follow-up subjects will be contacted annually for a total of 15 years to assess survival, and occurrence of serious adverse events (SAEs).

Safety will be monitored by periodic physical examinations, laboratory tests, and questioning about adverse events. Study-specific laboratory tests to assess safety will include anti-adenovirus and anti-interferon beta antibodies in blood, blood levels of the cytokines IL6 and IL10, and BG00001 levels in blood, urine, and nasal swabs, as measured by PCR.

If available, autopsy data will be collected. This will include the autopsy report, and PCR analysis of tissue samples from prostate and seminal vesicles (if prostatectomy was not performed), testes, lung, heart, liver, spleen, and bone marrow. Subjects will be asked to consider agreeing to an autopsy when they give consent to participate in this study. However, subjects may enroll in this study whether or not they agree to an autopsy.

Efficacy measures will include the following: pathological evidence of anti-tumor activity, pathological evidence of gene transfer in resected tumor specimens, fraction of subjects with negative surgical margins, interferon-beta level in resected prostate specimen, serum levels of interferon beta and neopterin, response rate prior to prostatectomy (as determined by TRUS, physical examination, and serum PSA concentrations).