Serious and Other Selected Adverse Events
Reported for Human Gene Transfer Protocols
Recombinant DNA Advisory Commitee Meeting
December 2007

Protocol Number: **530**

Protocol Title: **A Randomized, Phase II, Study of TNFerade™ Biologic with 5-FU and Radiation Therapy for First-Line Treatment of Unresectable Locally Advanced Pancreatic Cancer.**

DocID#	Receipt Date	Event Description
9289	09/24/2007	About seven hours after the first dose of the gene transfer via percutaneous injection the subject experienced abdominal pain and vomiting. The subject was hospitalized and given supportive care. A CAT scan did not reveal any new pathology. The study agent was discontinued.
9270	09/12/2007	Subject received second dose of the gene transfer agent by percutanous intratumoral injection. Approximately 30 minutes after the dose the subject reported abdominal pain and was treated with anxiolytics and analgesics. Subject then experienced hypotension, fever and chills and was hospitalized. Labs obtained were notable for an elevation in blood liver tests but these blood tests were noted to have been elevated prior to the dose. A CAT scan done during the hospitalization did not reveal any new findings when compared to one done less than a month prior. Abdominal pain and hypotension resolved and the subject was discharged after 2 days. Subject resumed the chemotherapy and radiation that was part of the study.
9275	09/14/2007	The subject received the first injection of the gene transfer agent by endoscopic ultrasound guided administration into the pancreatic tumor. One day later, the subject was hospitalized for lethargy that resolved seven days later. The last dose of the gene transfer agent was administered six days later. About two weeks after the last dose, the subject experienced rectal bleeding and was seen by a physician two days later. The following day, the subject was evaluated again for rectal bleeding. The investigator was subsequently notified that subject passed away at home that night. The investigator judged the event as probably unrelated to the gene transfer, unrelated to the administration procedure and possibly related to underlying disease.
9293	09/26/2007	About one month after the final injection of the gene transfer agent the subject was admitted to the hospital due to generalized weakness and dehydration. Subject was found to have a urinary tract infection and after appropriate treatment recovered and was discharged. The Investigator felt the event was probably related to underlying disease but possibly related to the gene transfer agent and/or the chemotherapy and radiation being received.
9295	09/26/2007	Shortly following the second precutaneous injection of the gene transfer agent the subject developed a temperature to 101.5 degrees Farenheit, nausea and chills. The subject was admitted overnight to the hospital. Pain resolved and subject was discharged the next day. The investigator concluded that the symptoms were probably related to the gene transfer agent and/or the underlying disease but unrelated to the administration procedure.

Protocol Number: **563**

Protocol Title: **Administration of Peripheral Blood T-Cells and EBV Specific CTLs Transduced to Express GD-2 Specific Chimeric T Cell Receptors to Patients with Neuroblastoma.**

DocID#	Receipt Date	Event Description
e-Filed	08/22/2007	After two weeks after receiving the gene modified T cells the subject was admitted to the hospital for a fever. The evaluation did not reveal an infectious cause for the fever but radiologic studies showed necrosis of metastatic disease in the liver and abdomen. A biopsy confirmed necrotic tumor with infiltration of T cells. The fever was possibly due to an infection or due to the infused T cells causing destruction of the tumor.

Protocol Number: **585**

Protocol Title: **A Phase I Study of Sequential Vaccinations with Fowlpox-CEA(6D)-TRICOM (B7.1/ICAM/LFA3) and Vaccinia-CEA(6D)-TRICOM, in Combination with GM-CSF and Interferon-Alfa-2B in Patients with CEA Expressing Carcinomas.**

DocID#	Receipt Date	Event Description
9248	08/24/2007	This subject had known metastases to the liver, lung and bone. The subject tolerated the first cycle of the protocol which consisted of the gene transfer vaccine with interferon-α-2b and GM-CSF with minimal complaints. The subject arrived to clinic for cycle 2 with complaints of fatigue and dyspnea which required increased use of supplemental oxygen at home. Initial evaluation revealed anemia (low red blood count) and a transfusion was done. The subject was further evaluated and it was felt that it was appropriate to proceed with treatment. Treatment consisted of the gene transfer vaccine along with GM-CSF and interferon-α-2b. The subject completed the week of treatment in stable condition. Approximately one week after starting cycle 2 the subject was transported to a local emergency room with complaints of progressive dyspnea. The subject had hypoxemia and the chest x-ray revealed an opaque consolidation in the entire left lung field. Liver function tests and enzymes were elevated as was the D-Dimer and a brain natriuretic peptide was also elevated. The subject expired during this admission and no autopsy was performed.
9249	08/24/2007	Subject was on the second cycle of gene transfer when subject began to notice mild left-sided numbness on upper lip that was only noticeable when drinking beverages. Approximately three weeks later, the subject developed increased fatigue, dyspnea and cough and was diagnosed with a pleural effusion (fluid around the lung). The pleural fluid was negative for tumor cells. The principle investigator assessed the pulmonary symptoms as possibly related to the gene transfer or the GM-CSF.

Protocol Number: **653**

Protocol Title: **A Phase III Randomized, Open-Label Study of CG1940 and CG8711 Versus Docetaxel and Prednisone in Patients with Metastatic Hormone-Refractory Prostate Cancer Who are Chemotherapy-Naïve**

DocID#	Receipt Date	Event Description
9285	09/21/2007	Subject hospitalized about one week after injection of first dose of gene transfer cancer vaccine for persistent fever. Subject also noted to have an injection site reaction that consisted of erythematous skin on lower extremity. Subject's fever resolved two days after being admitted.

Protocol Number: **661**

Protocol Title: **A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Dose-Selection Study of Ad2/Hypoxia Inducible Factor (HIF)-1α/VP16 in Patients with Intermittent Claudication.**

DocID#	Receipt Date	Event Description
9339	10/26/2007	Subject had a history of prostate cancer treated by radical prostatectomy in the early 1990's. Subject entered the study approximately 15 years later and at the time of enrollment had a prostate specific blood (PSA) test of 2.7. PSA right after radical prostatectomy was <0.1 and then had risen to 1.4 two years prior to enrollment and to 2.0 two years prior to enrollment. Subject was diagnosed with prostate cancer almost a year after receiving the gene transfer agent. This prostate cancer was felt to be a possibly related to either the gene transfer or the original prostate cancer.

Protocol Number: **674**

Protocol Title: **A Phase I Study of ADV-TK + Valacyclovir Gene Therapy in Combination with Standard Radiation Therapy for Malignant Gliomas.**

DocID#	Receipt Date	Event Description
9326	10/15/2007	Subject underwent resection of large glioblastoma that pre-operatively showed evidence of subfalcine herniation on MRI. The subject received the gene transfer during the surgery. The subject recovered from surgery and was conversant and ambulatory. Two days after surgery the subject was started on the valacyclovir per the protocol. A post-operative MRI showed the resection of the tumor and some relief of the mass effect. A wean of steroids were begun. Four days after surgery the subject had a sudden deterioration in neurologic status with headache and decreased responsiveness. Emergent head CAT scan showed generalized edema without evidence for a significant offending clot. Subject also developed hyponatremia. Subject's neurologic status continued to decline despite medical treatment and five days after the surgery the subject died. Autopsy showed brain edema bilaterally within the tumor cavity with typical postoperative changes. The investigator noted that large glioblastoma multiforme (GBM) tumors often have a complicated treatment course that included brain swelling. Death from the disease is the expected outcome from most GBM patients. The level and rapidity of swelling observed in this patient is not common, but not totally unexpected. Initially, it was not possible to ascertain whether the event was exclusively related to the underlying disease or if there was any relation to the gene transfer. Histological exam confirmed generalized edema of brain and residual tumor. There were macrophages but few T- lymphocytes to indicate an immune response against the tumor. Immunostain for adenoviral antigen was negative. Special stains for bacterial (gram) and fungal (GMS) elements were negative. Therefore, the conclusion was that this was unrelated to the gene transfer.

Protocol Number: **747**

Protocol Title: **Targeted Delivery of OncoVEX GM-CSF by Endoscopic Ultrasound (EUS)-Guided Fine Needle Injection (FNI) in Patients with Irresectable Pancreatic Cancer: A Pilot Experiment on Safety and Proof of Concept**

DocID#	Receipt Date	Event Description
9298	10/01/2007	Two days after receiving the gene transfer agent by injection into the pancreatic lesion, the subject started experiencing abdominal pain, loss of appetite and weight loss. The subject was admitted to the hospital and diagnosed with dehydration. Upon discharge from the hospital it was decided to withdraw subject from the trial. In the opinion of the investigator, the event was severe in intensity and possibly related to the gene transfer.

Protocol Number: **749**

Protocol Title: **A Phase I/II Safety, Tolerability and "Proof of Concept" Study of Radiotherapy, Cetuximab, and Intratumoral injections of TNFerade Biologic AdgvEGR.TNF.11D for Elderly or Frail or Intermediate Stage Patients with Head and Neck Cancer (The TNF-ELF Trial)**

DocID#	Receipt Date	Event Description
9316	10/09/2007	Four days after second dose of the gene transfer administered percutaneously into the tumor, the subject was found at home "stuperous" and diaphoretic. Subject had not felt well and taken a number of sedatives. The subject was found unconscious by a family member and taken by ambulance to hospital where subject was admitted to the Intensive Care Unit and diagnosed with respiratory distress and found to have acute renal failure. Subject may have suffered a cardiac event as subject's blood troponin level was elevated and the electrocardiogram was abnormal. Subject also had transient elevation in blood liver tests that were felt to be secondary to low blood pressure during the event.

Protocol Number: **750**

Protocol Title: **A Phase I/II Safety, Tolerability, and 'Proof of Concept' Study of TNFerade™ in Combination with Concomitant Radiotherapy, Fluorouracil, and Hydroxyurea (TNF-FHX) for Patients with Unresectable Recurrent Head and Neck Cancer.**

DocID#	Receipt Date	Event Description
9317	10/09/2007	Subject admitted for likely aspiration pneumonia about one week after the second injection of the gene transfer vector. Subject also diagnosed with mucositis. Subject remained on study and received the third dose of gene transfer.

DocID#	Receipt Date	Event Description
9354	11/01/2007	Subject admitted with complaints of weakness and blood in the stool approximately 10 days after receiving first dose of gene transfer and beginning interferon-alfa. The workup revealed an upper gastrointestinal bleed, severe anemia (low red blood count) and a urinary tract infection. Subject recovered and was discharged but continued to complain of weakness.
9197	07/30/2007	Approximately 7 weeks after starting the study in which the gene transfer vaccine is administered at set intervals, the subject developed mental status changes and headaches and was admitted to the hospital. The cause of the subject's symptoms was not determined. Steroids and mannitol were administered. Symptoms resolved and subject was discharged. Although brain metastases were originally suspected, imaging failed to show metastases.
9355	11/01/2007	Subject was admitted to hospital with upper gastrointestinal bleed and discovered to have metastatic cancer in the duodenum. Subject had prolonged hospital course and although the bleeding resolved subject died a month after being admitted to the hospital.
9207	08/06/2007	One day after the initial gene transfer dose and sunitinib, the subject experienced a fever of unknown etiology and was hospitalized. No action was taken with the study treatments. The investigator considered the event to be possibly related to the gene transfer.
9218	08/09/2007	Subject was receiving the gene transfer agent and interleukin-2 (IL-2) for four months. Subject had episodes of tachycardia (increased heart rate) and local injection site reactions. One day after an episode of tachycardia the subject had a stroke. Initially, the etiology of the stroke was thought to possibly be related to the gene transfer, the IL-2 or the subject's pre-existing medical conditions which included cardiovascular disease. However, the principle investigator subsequently deemed the event to be unrelated to the gene transfer and possibly related to the IL-2.
9265	10/31/2007	Six days after receiving study agent subject reported return of "confusion." Subject reported having the same symptoms a month prior. Symptoms resulted in a prolongation of hospitalization. The precise etiology of the symptoms is unknown at the time of report. The subject was treated with steroids and mannitol pending a CAT scan or MRI of the brain. The MRI revealed no brain metastases and the confusion resolved.
9301	10/01/2007	Almost three months after starting to receive a series of gene transfer vaccines, subject was admitted with dyspnea, throat pain and weakness. Subject was diagnosed with pleuritis (inflammation of the lining of the lung) that was thought to be related to lung metastases. However, the investigator reported that it was possibly related to the gene transfer agent.
9328	10/15/2007	About 2 months after receiving first dose of the gene transfer agent and interferon-alpha , the subject developed severe nausea and was diagnosed with a fracture of femur at site of known metastatic disease. Subject was admitted to the hospital. The event was deemed possibly related to the gene transfer.

DocID#	Receipt Date	Event Description
9198	07/31/2007	One day after surgery for intracerebral gene transfer subject had an apparent siezure. Imaging revealed a small hemorrhagic infarct of caudate nucleus and edema around the surgical tracts. Antiepileptic medication was started and subject was transferred to a rehabilitation hospital before being discharged approximately 2 weeks later.
9200	07/31/2007	Seven weeks after sugary for intracranial delivery of gene transfer, while at a rehabilitation hospital, the 70+ year old subject experienced a witnessed cardiac arrest. Resuscitation efforts were initiated that revealed ventricular fibrillation which progressed to pulse less electrical activity. Subject had a history of renal failure during a hospitalization after the surgery but electrolytes were recorded as normal in the week prior to event. The Principal Investigator assessed the cardiorespiratory arrest as secondary to a postoperative myocardial infarction and as severe and possibly related to the surgical procedure but not related to the gene transfer.
9201	07/31/2007	Subject had surgery to receive intracerebral delivery of gene transfer. The post-operative course was complicated by possible seizure for which subject received antiepileptic medication. Approximately 2 weeks later, the subject was readmitted to hospital with cognitive decline and difficulties with activities of daily living. Subject was treated with steroids and improved. Imaging revealed edema along the surgical tract.
9204	08/01/2007	Subject underwent surgery to receive the gene transfer agent. The surgery was without complication. Starting on post-operative day one, the subject experienced "sundowning" described as transient, mild, disorientation thought to be related to anesthesia, the unfamiliar environment and narcotic pain medications. By post-operative day four the subject was alert and oriented. Subject also had some worsening of Parkinson's symptoms on post-operative day one that had resolved by post-operative day four. The subject was discharged home without problems. On a follow-up visit on post-operative day twelve, subject had complete resolution of symptoms. The investigator assessed the sundowning as mild in severity and possibly related to the surgical procedure and/or the gene transfer.