Serious and Other Selected Adverse Events
Reported for Human Gene Transfer Protocols
Recombinant DNA Advisory Commitee Meeting
March 2008

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
9399	12/03/2007	The subject received the initial injection of TNFerade via endoscopic ultrasound administration and was discharged in stable condition. The next morning, the subject was somnolent upon arrival to clinic and was hospitalized for further evaluation. Hospital notes indicate the subject was able to answer "yes" and "no" questions, appeared jaundiced and had a fever of 100.2 F. Labs showed elevated liver enzymes and bilirubin as well as a low potassium level. Subject was discharged from the hospital with a diagnosis of cholangitis. Although at the time of admission, the principal investigator could not rule out a role for the TNFerade given the temporal relationship, after the diagnosis was established the principal investigator concluded that the event was not related to the study agent.
9410	12/10/2007	The subject received first injection of TNFerade via endoscopic ultrasound administration. Three days later, the subject was hospitalized for lethargy and was diagnosed with cholangitis. Subject was discharged from the hospital. About two weeks after receiving the second dose of the TNFerade, the subject experienced rectal bleeding and was seen by a physician. Subject had an endoscopy and colonoscopy without identification of a source for the bleeding. The subject's hematocrit (red blood cell count) was measured and noted to be just below normal. Additonal laboratry work showed no evidence of coagulation problems (i.e. abnormal clotting). However, that evening the subject died from a large gastrointestinal bleed that was likely due to disease progression resulting in gastric wall penetration by the tumor and not related to the study agent.
9400	12/03/2007	Approximately 11 weeks after the last dose of study agent, the subject was seen in a hospital emergency room complaining of dizziness and feeling faint. Subject was hospitalized with a diagnosis of dehydration. The subject's dehydration led to orthostatic hypotension (i.e. a significant drop in blood pressure that occurred when the subject rose from a lying position to a standing position). A computed tomography scan (CAT) of the head was negative for any significant pathology but a CAT scan of the lungs showed either a right lower lobe pneumonia versus partial collapse of part of the lung (atelectasis). The event resolved within one day.

Protocol Number: **552**

Protocol Title: **A Phase I/II Study of An Antitumor Vaccination using α(1, 3) Galactosyltransferase Expressing Allogeneic Tumor Cells in Patients with Refractory or Recurrent Non-Small Cell Lung Cancer.**

DocID#	Receipt Date	Event Description
9535	01/29/2008	About two weeks after starting the gene transfer cancer vaccine, which subject received by intradermal injection, the subject complained of increased fatigue and pink tinged sputum with increased non-productive cough and a couple of days of low grade fever. Computed tomography (CAT) scan revealed possible progression of cancer with increased consolidation/atelectasis (partial collapse) of the left lower lobe of the lung and a pleural effusion(fluid around the lung) that was found to contain cancer cells. A bronchoscopy also revealed extrinsic partial compression of the left lower lobe bronchus likely indicative of a mass compressing the airway. The subject was given vaccination number two without problem but three days after the second dose was admitted to local hospital for increasing shortness of breath and was found to have low blood oxygen levels. During that admission, the subject was diagnosed with multiple pulmonary emboli. Subject was treated with antibiotics, steroids and anticoagulants and was discharged with home oxygen therapy.

Protocol Number: **647**

Protocol Title: **A Phase I Dose-Escalation Trial of JX-594 (GM-CSF Recombinant Vaccinia Virus) Administered by Intratumoral Injection in Patients with Superficial Injectable Tumors.**

DocID#	Receipt Date	Event Description
9348	10/31/2007	This serious adverse event occurred on a non-US trial that enrolls subject with hepatocellular carcinoma or hepatic metastases. The study agent is injected directly into the liver tumor. The subject was treated with study agent in hospital and then as an outpatient The subject experienced anorexia (loss of appetite) and right upper quadrant abdominal pain one week after the last dose and went to the emergency room. The subject was then admitted for pain control and nutrition support. The anorexia and the right upper quadrant abdominal pain improved significantly two days after admission and treatment. The subject was kept in the hospital for further nutritional support and for treatment of swelling in both legs. These events were likely related to underlying disease progression but could also be related to the investigational agent.

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
9352	11/01/2007	Subject had been receiving regularly scheduled injections of the study agent for three months. The day of dosing subject developed increased shortness of breath leading to hospitalization. Subject had a history of lung metastases and a computed tomography (CAT) scan showed increased consolidation (dense, white appearance) compared to previous chest x-rays. This change was attributed to progression of disease or an inflammatory process. Subject was treated with antibiotics and steroids and was discharged about a week later. Approximately two months after discharge repeat imaging appeared to show a regression of lung lesions compared to the CAT scan done during the hospitalization. The etiology of this event could be progression of disease or involve an inflammatory reaction related to the study agent.

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
9359	11/07/2007	An elderly subject with a history of coronary artery disease presented with unstable angina (chest pain) 82 days after receiving the gene transfer injections. An angiogram of the coronary vessels revealed a critical blockage of the left coronary artery requiring a stent. The subject was discharged in stable condition.
9360	11/07/2007	Five days after being discharged from a previous admission for unstable angina and stent placement the subject was readmitted for observation due to feeling faint and diaphoretic while driving. Serial troponin-T levels, a blood test for heart injury, remained low. The adenosine-single photon emission computed tomography (SPECT) stress test showed no adenosine-induced myocardial ischemia. Subject was discharged and subject's diabetes medications were adjusted.

Protocol Number: **665**

Protocol Title: **A Phase II study of the Efficacy, Safety and Immunogenicity of ONCOVEX GM-CSF in Patients with Inoperable Malignant Melanoma.**

DocID#	Receipt Date	Event Description
9454	08/01/2007	Shortly after receiving a second dose of the gene transfer, the subject was hospitalized with shortness of breath and hypoxia (low oxygen level). Subject did not improve despite aggressive care in the intensive care unit. The cause of death was respiratory failure as a result of progression of pulmonary metastases, however, the principle investigator noted that the possibility that the gene transfer contributed to the progression of disease could not be ruled out.

Protocol Number: **705**

Protocol Title: **A Phase I/II Study of Repeat Intra-Articular Administration of tgAAC94, a Recombinant Adeno-Associated Vector Containing the TNFR:Fc Fusion Gene, in Inflammatory Arthritis Subjects with and without Concurrent TNF antagonists.**

DocID#	Receipt Date	Event Description
9428	12/07/2007	Subject died approximately 3 weeks after receiving second dose of gene transfer. Subject had multiorgan failure and final autopsy results showed evidence of dessiminated histoplasmosis infection. This adverse event was reviewed at following RAC meetings: September 17, 2007, December 3, 2007 and January 14, 2008.

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
9430	12/14/2007	About a week after the subject received his first and only injection of OncoVEX-GM-CSF, the subject was diagnosed with ascites (fluid in the abdomen). The patient was hospitalized about a week later and the fluid was drained. Studies of the fluid did not reveal cancer cells. However, the medical monitor for the study noted that this does not necessarily mean the ascites is not related to the cancer. Nonetheless, given the timing of this event and the severity of the event, a possible relationship to the gene transfer can not be ruled out.

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
9364	11/09/2007	Two days after the last dose of the TNFerade, the subject was admitted to the hospital for possible pneumonia. While initially a relationship to the TNFerade could not be ruled out when further information was obtained the event was determined to be unrelated to the gene transfer.

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
9344	10/29/2007	Subject was receiving treatment for pseudomonas bacteremia (bacteria in the blood) the day of the final injection of TNFerade. Due to a fever, the subject was monitored and after negative cultures were obtained the subject was given the TNFerade and then treated with other protocol specified chemotherapy. Two days after administration of the study agent swelling was noted at the site of the subject's central intravenous line. The line was removed after a Doppler revealed a blood clot in the left arm. Subject was treated with Lovenox. The investigator judged the event as possibly related to TNFerade, unrelated to the administration procedure and probably unrelated to underlying disease.
9402	12/03/2007	Subject admitted to the hospital with a fever approximately 10 days after injection of the last scheduled dose of the gene transfer and was found to have bacteremia (bacteria in the blood). Subject was also diagnosed with pneumonia and during the hospitalization required a stay in the intensive care unit due symptoms of respiratory distress and low blood pressure. While initially the principal investigator could not rule out a possible role for the gene transfer, after more information was obtained the principal investigator concluded that the event was not related to the gene transfer.
9485	01/07/2008	About five months after the last dose of the TNFerade the subject was taken to a local emergency room due to purulent discharge from the tracheostomy site and mild mental status changes. The subject became febrile while in the emergency room and also experienced some drops in blood pressure. The subject was treated with oxygen and admitted to the intensive care unit for ventilator assisted breathing. Pneumonia was considered the most likely diagnosis. The investigator judged the event as possibly related to TNFerade, unrelated to the administration procedure and probably unrelated to underlying disease.

Protocol Number: **759**

Protocol Title: **Phase II Study of Metastatic Cancer That Overexpresses p53 Using Lymphodepleting Conditioning Followed by Infusion of Anti-p53 TCR-Gene Engineered Lymphocytes**

DocID#	Receipt Date	Event Description
9573	02/22/2008	Approximately three months after receiving the last dose of the gene modified T lymphocytes the subject developed a lymphoma. Biopsy samples were analyzed by polymerase chain reaction amplification for two distinct regions of the p53 t-cell receptor (TCR) retroviral vector. While T-cells in the blood and a small number of T cells that infiltrated the tumor contained the p53 TCR insert, there was no p53 TCR insert in the B cell lymphoma. The conclusion was that this was a secondary malignancy that was unrelated to the gene transfer vector.

Protocol Number: **785**

Protocol Title: **TRIST (TroVax Renal Immunotherapy Survival Trial) An International, randomized, double-blind, placebo controlled, parallel group study to investigate whether TroVax added to first-line standard of care therapy, prolongs the survival of patients with locally advanced or metastatic clear cell renal adenocarcinoma**

DocID#	Receipt Date	Event Description
9426	12/12/2007	The subject was admitted to the hospital with complaints of dizziness, fatigue, confusion and jaundice approximately 5 weeks after the first dose of the gene transfer vaccine and sunitinib. A computed tomography scan was reported to be normal. The principal investigator considered these events to be possibly related to the gene transfer vaccine and sunitinib, but also commented that the possible cause of this event could be hepatic encephalopathy (a potentially-reversible neuropsychiatric abnormality in the setting of liver failure). After additional information was obtained the principal investigator concluded that this event was unrelated to the gene transfer and was most probably related to progression of the subject's cancer.
9431	12/14/2007	Subject was admitted to hospital with symptomatic anemia (low blood count) about 2 months after starting on the study and received a transfusion. At the time the initial report was received a relationship to the gene transfer agent could not be ruled out. In follow-up reports the investigator determined that the event was not related to the gene transfer.

Protocol Number: **845**

Protocol Title: **A Phase I/II Study of Active Immunotherapy with CEA(6D) VRP Vaccine (AVX701) in Patients with Advanced or Metastatic Malignancies Expressing CEA**

DocID#	Receipt Date	Event Description
9549	02/04/2008	Subject received first gene transfer vaccine and three weeks later developed new symptoms of headaches, confusion, inappropriate behavior and falling at home. The subject was involved in a motor vehicle accident and went to the hospital. A computed tomography of the brain showed three brain metastases with a large one in the left parietal lobe and midline shift and surrounding edema. The subject was transported to home but due to confusion was admitted to the hospital for emergent treatment with steroids and brain radiation. Subject was discharged to hospice. While the principle investigator initially felt these events were possibly related to study agent in follow-up the events was attributed to underlying disease and not to the study agent