
**Serious and Other Selected Adverse Events
Reported for Human Gene Transfer Protocols
Recombinant DNA Advisory Committee Meeting
June 2008**

Protocol Number: 366

Protocol Title: **A Phase III Multi-Center, Open-Label, Randomized Study to Compare the Overall Survival and Safety of Bi-Weekly Intratumoral Administration of RPR/INGN 201 Versus Weekly Methotrexate in 240 Patients with Refractory Squamous Cell Carcinoma of the Head and Neck (SCCHN).**

| DocID# | Receipt Date | Event Description |
|--------|--------------|---|
| 9631 | 02/28/2008 | In 2000, about a week after receiving intratumoral injection of the gene transfer agent into the neck tumor, the subject developed a serious infection that led to sepsis. A computed tomography scan of the neck showed fluid collections and pockets of air in the soft tissue of the neck due to the infection. Subject was treated with antibiotics and recovered but still had an infection of the soft tissues of the left neck. The investigator assessed the infection as possibly related to the gene transfer agent. |
| 9633 | 02/28/2008 | Subject had preexisting ulcers on neck at the site of the subject's cancer. During the gene transfer injections the ulcers initially increased in size and one was noted to develop a necrotic area without bleeding. The ulcer improved after ceasing the gene transfer injections. Subject had disease progression and was removed from the study. Approximately 3 weeks after the last dose of the gene transfer, during a dressing change, the subject had a fatal hemorrhage from the tumor site. The principal investigator noted that the bleeding may have been possibly related to necrosis caused by the gene transfer. [Event occurred 6 years ago.] |

Protocol Number: **530**

Protocol Title: **A Randomized, Phase II/III 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 |
|--------|--------------|--|
| 9561 | 02/08/2008 | Subject admitted to the hospital due to abdominal pain, nausea and vomiting following the second intratumoral injection of the study agent. The subject received supportive care and had a computed tomography scan that ruled out an injection induced hematoma (blood clot). The event resolved. Initially the principal investigator judged the event as possibly related, but after further information was obtained the principal investigator changed the assessment to probably unrelated to the gene transfer agent. |
| 9559 | 02/08/2008 | Subject developed a fever three hours after the second dose of the gene transfer. Subject was hospitalized for observation. Symptoms resolved and the subject continued on the study. The fever was possibly related to the study agent. |
| 9600 | 03/06/2008 | Nine days after the final dose of intratumoral injection of the gene transfer vector the subject was admitted for abdominal pain and vomiting. The subject responded to supportive treatment and was discharged. The subject was readmitted about a week later with similar symptoms and a computed tomography scan revealed inflammation at the head of the pancreas versus progression of disease. |
| 9656 | 04/07/2008 | About 6 weeks after the last dose of gene transfer and 4 days after starting gemcitabine, the subject was admitted with acute abdominal pain and suspected pancreatitis. Subject was treated with pain medications and quickly recovered. Of note the lipase levels remained normal and amylase was less than twice normal on one blood test. |
| 9658 | 04/07/2008 | Approximately 6 weeks after the last injection of study agent, the subject underwent a post treatment computed tomography scan that revealed a thrombosis of the superior mesenteric vein. No treatments were administered for the event. |

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)-1 α /VP16 in Patients with Intermittent Claudication.**

| DocID# | Receipt Date | Event Description |
|--------|--------------|---|
| 9735 | 05/19/2008 | Approximately 6 months after receiving either placebo or study agent this elderly subject with a family history of breast cancer and on estrogen therapy was discovered to have an early stage cancer in the left breast. The investigator concluded that the breast cancer could possibly be related to the study agent, although the principal investigator did not know whether the subject received the gene transfer agent or placebo. |

Protocol Number: 741

Protocol Title: **A Phase 2 Double-Blind, Placebo Controlled, Multi-center Adjuvant Trial of the Efficacy, Immunogenicity, and Safety of GI-4000; an Inactivated Recombinant Saccharomyces cerevisiae Expressing Mutant Ras Protein Combined with a Gemcitabine Regimen Versus a Gemcitabine Regimen with Placebo, in Patients with Post-resection R0/R1 Pancreatic Cancer with Tumor Sequence Confirmation of Ras Mutations.**

| DocID# | Receipt Date | Event Description |
|--------|--------------|--|
| 9569 | 02/19/2008 | About three weeks after the most recent dose of the gene transfer or placebo the subject developed swelling in the lower extremity and was diagnosed with a blood clot. That same day the subject underwent a CAT scan because of shortness of breath and was diagnosed with a pulmonary embolism. |
| 9620 | 03/20/2008 | The subject was enrolled in the trial for two hundred and thirty days and had eight doses of the blinded study medication (i.e. active agent or placebo). Subject developed hemolytic uremic like syndrome that led to renal failure due to small blood clots in the kidneys. It is unclear whether this was caused by the underlying pancreatic cancer, the concomitant chemotherapy or the blinded study medication. |

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 |
|--------|--------------|--|
| 9525 | 01/24/2008 | The patient expired approximately six months after the last dose of the gene transfer. No information available on cause of death. |
| 9593 | 03/05/2008 | Subject developed a fever of 102o Fahrenheit while in the period of receiving the gene transfer infections. Blood cultures obtained were positive for pseudomonas, a bacteria. Subject's port-a-cath was replaced with a peripherally inserted central catheter and antibiotics were administered. |

Protocol Number: **754**

Protocol Title: **Phase I Study Combining Replication-Competent Adenovirus-Mediated Suicide Gene Therapy with Chemoradiotherapy for the Treatment of Unresectable Non-Metastatic Pancreatic Cancer**

| DocID# | Receipt Date | Event Description |
|--------|--------------|--|
| 9613 | 03/19/2008 | Subject expired eight months after administration of the gene transfer. Subject completed gene transfer/chemoradiation course with minor complications but developed post-surgical complications. Subject died without recurrent disease. Investigator believes it is possible that the added physiological stress of the gene transfer may have contributed to post-surgical complications, which eventually led to the subject's death. |
| 8615 | 03/19/2008 | Subject expired one year after administration of the gene transfer. Subject completed gene transfer/chemoradiation course without complications but developed post-surgical complications. Following surgery, subject's condition gradually deteriorated with several hospitalizations. Subject developed ascites that did not appear to be due to the underlying pancreatic cancer or liver disease. Subject's immediate cause of death was infection but subject died without recurrent disease. |

Protocol Number: **773**

Protocol Title: **A Phase I Study of In-Situ, Neoadjuvant, Pre-Radical Prostatectomy RTVP-1 Gene Therapy in Patients with Locally Advanced Adenocarcinoma of the Prostate (Spore #: 11-01-30-15)**

| DocID# | Receipt Date | Event Description |
|--------|--------------|--|
| 9614 | 03/03/2008 | Subject admitted to the hospital due to a urinary tract infection and fever about 5 weeks after the gene transfer and 2 weeks after radical prostatectomy. |

Protocol Number: **784**

Protocol Title: **A Phase I, Open Label, Dose-Escalation, Pharmacodynamic Study of Intranodal Injection of Adenovirus-CD154 (Ad-ISF35) in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**

| DocID# | Receipt Date | Event Description |
|--------|--------------|---|
| 9766 | 06/04/2008 | Four weeks after the gene transfer the subject was admitted with pneumonia. |

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 |
|--------|--------------|--|
| 9537 | 01/30/2008 | Approximately four months after starting on the study the subject was admitted to hospital after loosing consciousness. Subject was found to have low blood counts, dehydration, acute gastrointestinal bleeding and acute renal failure. Further tests revealed an ulcer at the esophageal junction. Subject received blood transfusions for anemia and intravenous fluids. At discharge acute renal failure had resolved. It is not known if the subject was receiving the gene transfer agent or placebo. |
| 9604 | 03/14/2008 | Approximately two months after starting on the study the subject was admitted for one day after being diagnosed with pneumonia. Subject was discharged on antibiotics. |
| 9626 | 03/21/2008 | Shortly after starting on the study the subject developed shortness or breath and elevated blood liver tests. The subject's oxygenation levels were normal. At first the principal investigator felt this could be secondary to a pulmonary embolus due to the underlying cancer. However, in follow-up correspondence the investigator stated the cause of the events could not be determined and therefore they could be possibly related to the blinded study agent (i.e., active agent or placebo) or the co-administered sunitinib. The sunitinib was stopped but the study agent was continued. |
| 9670 | 04/21/2008 | This elderly subject with a history of coronary artery disease and lung metastasis received either placebo or the active study agent and Sunitinib per the study protocol. Approximately one month after beginning on the study, the subject began to complain of decreased energy, nausea, fevers and fatigue. The subject was diagnosed with a "chest infection" as an outpatient but progressed to require hospitalization for respiratory distress requiring intubation. Because the etiology of the respiratory distress was not known, the possible contribution of either sunitinib or the blinded study medication could not be ruled out initially. However, the principal investigator ultimately decided that the event was unrelated to the blinded study agent. |

Protocol Number: 788

Protocol Title: **CERE-120, an Adeno-Associated Virus-Based Vector to Deliver Human Neurturin to Parkinson's Disease Patients in a Phase II Trial**

| DocID# | Receipt Date | Event Description |
|--------|--------------|---|
| 9542 | 02/01/2008 | Approximately seven months after surgery for the study, the subject presented to the emergency room with intractable hip and back pain unresponsive to pain medications. The subject was admitted to the hospital for further treatment and treated with intravenous narcotics and physical therapy. Subject had surgery on the thoracic and lumbar spine including a laminectomy and osteotomy. The subject was subsequently discharged to a rehabilitation facility. The investigator assessed the back pain as moderate in severity and possibly (albeit unlikely) related to the clinical trial surgical procedure as well as to study drug. |
| 9568 | 02/19/2008 | Approximately 10 months after surgery for the study in which the subject received either the active agent or a placebo, the subject was diagnosed with invasive moderately differentiated adenocarcinoma of the esophagus. The investigator felt that given the possible role growth factors have in cell growth, that it was difficult to completely exclude a causal relationship between the experimental treatment and this adverse event. However, to date there is no evidence that the viral vector or the transgene product goes outside the brain, the site of the injection. Moreover, as the study is blinded it is not known whether the subject received the gene transfer agent or the placebo. |

Protocol Number: 801

Protocol Title: **A Phase II Trial Using a GM-CSF-Producing and CD40L-Expressing Bystander Cell Line (GM.CD40L) in the Formulation of Allogeneic Tumor Cell-Based Vaccines in Combination with ATRA, and Cyclophosphamide for Patients with Stage IV Adenocarcinoma of the Lung**

| DocID# | Receipt Date | Event Description |
|--------|--------------|--|
| 9563 | 02/11/2008 | Approximately 3 weeks after the fourth gene transfer vaccine and second round of the co-administered drug all-trans retinoic acid the subject, who had a history of chronic obstructive pulmonary disease, was admitted to the hospital for a two to three day history of shortness of breath. Subject was hypoxemic. Subject experienced frequent episodes rapid heart beat and an echocardiogram of the heart revealed a severe cardiomyopathy (ejection fraction 10%). The etiology of the cardiomyopathy was not known and subject died two days after being admitted. The cardiology consultant attributed the cause of death to sepsis because the subject had an increased white blood cell count on admission. The underlying COPD and supraventricular tachycardia were considered contributing factors. The principal investigator concurs with this assessment. |

Protocol Number: **840**

Protocol Title: **Phase II Study of Metastatic Melanoma Using Lymphodepleting Conditioning Followed by Infusion of Anti-MART-1 F5 TCR-Gene Engineered Lymphocyte**

| DocID# | Receipt Date | Event Description |
|--------|--------------|---|
| 9627 | 03/21/2008 | Subject developed dizziness and hearing loss about one month after receiving the gene modified T lymphocytes. She received a transtympanic steroid injection but did not completely recover. An autoimmune reaction, possibly due to the gene modified T lymphocytes, can not be ruled out as a cause of the dizziness. |