SAFETY REPORTS AND ADVERSE EVENTS FOR HUMAN GENE TRANSFER PROTOCOLS RECOMBINANT DNA ADVISORY COMMITTEE MEETING DECEMBER 8-10, 1999

August 11, 1999(Letter date)	**9701-173 Croop**	**A Pilot Study of Dose Intensified Procarbazine, CCNU, Vincristine (PCV) for Poor Prognosis Pediatric and Adult Brain Tumors Utilizing Fibronectin-Assisted, Retroviral-Mediated Modification of CD34+ Peripheral Blood Cells with O^6-Methylguanine DNA Methyltransferase** **Adverse event:** A patient with pontine glioma experienced vomiting (grade III), abdominal pain (grade III), and constipation (grade III). Patient was hospitalized and treated for the above symptoms. A follow-up report indicated that the vomiting, abdominal pain, and constipation were resolved. The investigator considered the vomiting, abdominal pain, and constipation as known side effects of intensive chemotherapy and radiation therapy.
August 13, 1999	**9804-246 Yoo *et al.***	**A Multicenter Phase II Study of E1A Lipid Complex for the Intratumoral Treatment of Patients with Recurrent Head and Neck Squamous Cell Carcinoma** **Adverse events:** 1) Patient death due to disease progression. Patient didn't return for follow-up after last administration of study medication. An autopsy was not performed. 2) Patient experienced shortness of breath, headache, dizziness, and a 104 F fever following the sixth administration of E1A-lipid complex (30 mg total). Patient was hospitalized, treated with antibiotics, and released two days later. Investigator determined that event was possibly related to the E1A-lipid complex.
August 30, 1999	**9804-250 Swisher**	**An Efficacy Study of Adenoviral Vector Expressing Wildtype p53 (Ad5CMV-p53) Administered Intralesionally as an Adjunct to Radiation Therapy in Patients with Non-Small Cell Lung Cancer** **Adverse event:** Patient received $3x10^{12}$ pfu of Ad5CMV-p53. During post treatment biopsy (next day after vector administration), patient experienced shortness of breath, coughing, atrial fibrillation, and hemoptosis; procedure was terminated. Patient was placed on oxygen, intubated, and admitted to intensive care. The event, respiratory distress, was considered by the investigator as possibly related to Ad5CMV-p53.
September 9, 1999	**9804-250 Swisher**	**An Efficacy Study of Adenoviral Vector Expressing Wildtype p53 (Ad5CMV-p53) Administered Intralesionally as an Adjunct to Radiation Therapy in Patients with Non-Small Cell Lung Cancer** **Correction of August 30 report:**

		Dose of adenovirus vector for adverse event reported on August 30, 1999 was given as plaque forming units. The dose administered was $3x10^{12}$ viral particles. In addition, administration of radiation was initially reported (on August 30) as being started and completed two-weeks prior to Ad5CMV-p53 administration. However, radiation was started two weeks prior to Ad5 administration, and was ongoing at the time of the adverse event.
September 9, 1999	**9806-260 Hersh**	**Phase I Study of HLA-B7/ b 2M Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) by Direct Gene Transfer with Concurrent Low Dose Subcutaneous IL-2 Protein Therapy as an Immunotherapeutic Regimen in Malignant Meloma** **Adverse event:** Patient death associated with the injection procedure. Autopsy indicated a puncture of the pericardial sac and pulmonic trunk; plasmid/lipid complex were administered to the left side anterior mediastinal lymph node. This was the second injection to the same node.
September 14, 1999	**9802-233 Dreicer *et al.***	**Phase II Study of Direct Gene Transfer of HLA-B7/ b 2M Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Immunotherapeutic Agent in Patients with Stage III or IV Melanoma with no Treatment Alternatives** >** **Adverse event:** >Ascites fluid and abdominal pain occurred in a patient in the second course of six weekly injections of DNA/lipid complex. Second course of injections were completed. Patient was hospitalized two weeks after last administration of DNA/lipid for gastrointestinal bleeding and severe ascites. Patient complained of fatigue, dizziness, melena, and left lower quadrant pain. Hemoglobin was 7.9. Packed blood cells and plasma were administered. Paracentesis was performed. Gastric biopsy suggested *H. pylori* infection. Course of antibiotics was started. Patient was discharged; diagnosis of gastritis and upper gastrointestinal bleeding secondary to non-steroidal anti-inflammatory drug use, unlikely to be related to DNA/lipid complex. Approximately two weeks later, patient was hospitalized again due to intense abdominal pain and ascites. Paracentesis was performed again; ascites cultures were negative for bacterial infection. Patient was discharged after pain was controlled. Patient was withdrawn from the study due to progressive disease. PI feels that ascites is possibly related to the DNA/lipid complex. Sponsor's, Vical, opinion is that the event is most likely related to the underlying disease.
September 20, 1999	**9512-139 Batshaw**	**A Phase I Study of Adenoviral Vector Mediated Gene Transfer to Liver in Adults with Partial Ornithine Transcarbamylase Deficiency** **Adverse event:** Patient death due to adult respiratory distress syndrome, multiple organ failure, and disseminated intravascular coagulation. Within 12 hours of receiving the intrahepatic adenoviral vector administration, patient experienced fever, nausea, and back pain. The following morning after vector administration, patient experienced elevated ammonia levels and jaundice. During days 2-4 after vector injection, patient

		experienced disseminated intravascular coagulation, adult respiratory distress syndrome, and kidney and liver failure. Patient died four days after vector administration. A more detailed report of this event is included in the meeting material; presentations relating to this event were made at the December 8-10, 1999 meeting.
September 21, 1999	**9804-250 Swisher**	**An Efficacy Study of Adenoviral Vector Expressing Wildtype p53 (Ad5CMV-p53) Administered Intralesionally as an Adjunct to Radiation Therapy in Patients with Non-Small Cell Lung Cancer** **Follow-up to August 30, 1999 report:** During hospitalization following shortness of breath, etc. during biopsy, laboratory tests (ECG and cardiac enzymes) indicated that patient experienced an acute myocardial infarct. No indication was given as to the possible relationship between the vector and the infarct. Patient was discharged approximately one week following infarct.
September 27, 1999	**9804-250 Swisher**	**An Efficacy Study of Adenoviral Vector Expressing Wildtype p53 (Ad5CMV-p53) Administered Intralesionally as an Adjunct to Radiation Therapy in Patients with Non-Small Cell Lung Cancer** **Adverse event:** Patient that experienced an adverse event on August 30 experienced another adverse event. Shortly, a few hours, after receiving the third dose of Ad5CMV-p53 ($3x10^{12}$ viral particles), the patient developed acute respiratory distress and atrial fibrillation. Patient was hospitalized, with a diagnosis of "...exacerbation of congestive heart failure." Congestive heart failure resolved and patient was discharged three days after event. Patient has a history of congestive heart failure, atrial fibrillation, asthma, hypertension, and aortic insufficiency. Patient normally takes a morning dose of furosemide; however on the day of Ad5 administration, the patient skips the morning dose. "The treating physician considers it possible that this [lack of morning dose] could contribute to the respiratory problems..."
October 5, 1999	**9701-173 Croop**	**A Pilot Study of Dose Intensified Procarbazine, CCNU, Vincristine (PCV) for Poor Prognosis Pediatric and Adult Brain Tumors Utilizing Fibronectin-Assisted, Retroviral-Mediated Modification of CD34+ Peripheral Blood Cells with O^6-Methyguanine DNA Methyltransferase** **Adverse event:** Patient death due to progressive disease.
October 8, 1999	**9706-196 Smith and Dinauer**	**Fibronectin-Assisted, Retroviral-Mediated Transduction of CD34+ Peripheral Blood Cells with gp91 phox in Patients with X-Linked Chronic Granulomatous Disease: A Phase I Study** **Adverse event:** Patient underwent treatment for kidney stones, a long-standing condition. Kidney stones were determined to be unlikely to be related to the study medication.

October 22, 1999	**9706-196 Smith and Dinauer**	**Fibronectin-Assisted, Retrovira-Mediated Transduction of CD34+ Peripheral Blood Cells with gp91 phox in Patients with X-Linked Chronic Granulomatous Disease: A Phase I Study** **Adverse events:** Two different patients were notified that their peripheral blood tested positive for antibodies to Hepatitis C. Antibodies to HCV were considered to be a pre-existing condition.
October 25, 1999	**9709-214 Breau *et al.***	**A Phase II, Multi-Center, Open Label, Randomized Study to Evaluate Effectiveness and Safety of Two Treatment Regimens of Ad5VMV-p53 Administered by Intra-Tumoral Injections in 78 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN)** **Follow-up:** Follow-up to an event that occurred in the related trial that is being conducted in Europe. Event was initially reported on July 29, 1998 and subsequent follow-ups on August 18, 1998, and November 16, 1998.The causality of the dyspnea as not related to the study medication has been confirmed; swelling was confirmed to be possibly related to the study medication.
October 25, 1999	**9803-241 Bensinger *et al.***	**A Phase I/II Outpatient, Multicenter, Intrapatient, Multiple Dose Escalation Study of Herpes Simplex Virus Thymidine Kinase (HSV-TK) Transduced Mononuclear Cells in Subjects with Persistent or Relapsed Chronic Mylegenous Leukemia, Chronic Lymphocytic Leukemia, Multiple Myeloma, and Non-Hodgkin's Lymphoma after HLA-Matched Sibling Allogeneic Stem Cell Transplant** **Adverse event:** Patient experienced respiratory insufficiency, hypotension, and leukemoid reaction after the fourth infusion of transduced cells. Patient was hospitalized three hours after infusion. Antibiotics were administered, patient was intubated for respiratory insufficiency. Fluids and medication for hypotension were administered. The following day, chest X-rays revealed a pattern of "...diffuse alveolar infiltrate consistent with edema, leukostatis, or infection." Cultures for bacterial infection were negative. Patient stabilized the next day and was extubated. Patient was discharged later that week.
November 3, 1999	**9903-299 Isner**	**A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalating Study of Intramuscular Vascular Endothelial Growth Factor-2 (VEGF-2) Gene Therapy in Patients with Moderate-Risk Critical Limb Ischemia** **Adverse event:** Patient complained, at four week post-treatment follow-up visit, of increased rest pain and rusty colored sputum. Patient was referred to a pulmonologist, had chest X-ray taken and was started on antibiotics and continuous oxygen due to shortness of breath. Patient had a history of pneumonia and pulmonary fibrosis and used oxygen at night. A few days later, patient was bed-ridden, started vomiting, and was discovered a few hours later by their spouse as not breathing. Patient was resuscitated by paramedics, transported to the hospital where the patient died several hours later. Patient was cremated the next day, no autopsy was performed.

		The PI and sponsor do not consider that the death was associated with the administration of the study medication.
November 5, 1999	**9902-294 Isner**	**A Multicenter, Open-Label, Dose-Escalating study of Intramyocardial Vascular Endothelial Growth Factor 2 (VEGF2) Gene Therapy in Refractory Patients with Stable Exertional Angina Who Are Not Candidates for Revascularization Procedures** **Adverse event:** Submission of complete patient's records for event that was initially reported to ORDA on the annual data reporting form for the gene transfer relational database. Patient death, less than 24 hours after administration of the study medication. Preliminary autopsy findings were presented. The sponsor, in consultation with the physicians associated with the treatment of this individual, pathologists, and outside experts has not found a reason "...to implicate the procedure for this death, and no reason to implicate the administration of the [plasmid vector]." The sponsor continues to state: "While the preliminary autopsy report leads to no definitive diagnosis, the adrenalcortical atrophy coupled with the patient's significant coronary arterial disease may have compromised the patient's ability to respond to a cardiovascular crisis. In conclusion, there is no definitive reason for the unfortunate death of this patient."
November 8, 1999 (received by ORDA)	**9804-249 Junghans**	**Phase I Study of T Cells Modified with Chimeric AntiCEA Immunoglobulin-T Cell Receptors (IgTCR) in Adenocarcinoma** **Adverse events:** These events were reported to ORDA on November 8, 1999. Reports on four different patients were received. 1) Patient with metastatic colon cancer remained hospitalized after third course of treatment ($1x10^{10}$ cells) due to gastrointestinal bleeding. Patient remained hospitalized, refused the use of heroic measures (was given morphine IV for pain control), and died four days after administration of third dose. Request was made for an autopsy, but was denied by the family. Investigator considers that the GI bleed and death are possibly related to the study medication. Investigator believes that a more likely explanation is that the GI bleed and death were due to disease progression. 2) Patient experienced atrial flutter five days after first dose ($1x10^{10}$ cells) of modified T cells. Relatedness to study drug was considered by the investigator as possibly related, but remote. Approximately two hours after receiving second dose ($1x10^{11}$ cells) of cells, patient experienced mild chest pain. EKG showed evidence of potential reversible ischemia, Myocardial Infarction was ruled out; patient was discharged. Two days after administration of the second dose, patient was due to receive an out-patient transfusion of red cells. Patient did not keep the appointment for the transfusion. Patient was found dead at their home. Request for an autopsy was granted by sibling. Autopsy results were not provided. The investigator feels that the death is possibly related to the study medication, due to

	the temporal association of the event with the infusion of modified cells. It should be noted that the patient had a history of ischemic heart disease (two MIs, followed by bypass surgery) and that the EKG after the second infusion indicated a decreased ejection fraction. 3) Patient underwent three infusions of modified cells. Patient experienced progressive liver failure. Patient died at home, no autopsy was performed. Investigator strongly believes that death was due to progressive liver disease and should be considered to be unrelated to the study medication. 4) Patient experienced rigors, chills, and a fever after the first infusion of modified cells. Fever persisted for 36 hours. “Patient developed raid supra ventricular tachycardia with hemodynamic compromise,” during this febrile period. This event was judged as grade IV. An echocardiogram did not indicate any cardiac abnormalities. Patient was treated with beta blockers, tachycardia was resolved and patient was discharged from the hospital. Investigator considers that the cardiac event was remotely related to study drug, but was probably related to the fever. Fever is a known complication of IL2 and T cell treatment. In addition, patient experienced grade II diarrhea and cramping that the investigator felt was possibly to probably related to T cell administration.