SAFETY REPORTS AND ADVERSE EVENTS FOR HUMAN GENE TRANSFER PROTOCOLS RECOMBINANT DNA ADVISORY COMMITTEE MEETING MARCH 11-12, 1999

September 2, 1998 (letter date) **[received by ORDA Sept. 22, 1998]**	**9511-135 Alvarez and Curiel**	**A Phase I Study of Recombinant Adenovirus Vector-Mediated Intraperitoneal Delivery of Herpes Simplex Virus Thymidine Kinase (HSV-TK) Gene and Intravenous Ganciclovir for Previously Treated Ovarian and Extraovarian Cancer Patients** **Adverse events** 1) One patient experienced two separate incidences of partial small bowel obstruction. Both incidences occurred after the first administration of study drug and were determined by the investigator as unrelated to the investigational treatment. 2) A second patient experienced fever and abdominal pain that resulted in grade III toxicity. These events were judged to be related to tenckhoff catheter infection and not related to the study medication.
September 16, 1998	**9403-069 Walker**	**A Phase I/II Pilot Study of the Safety of the Adoptive Transfer of Syngeneic Gene-Modified Cytotoxic T-Lymphocytes in HIV-Infected Identical Twins** **Adverse event** Patient death due to complications of hepatitis C infection (cirrhosis and encephalopathy). Death was determined to be not related to study medication.
September 21, 1998	**9804-250 Swisher**	**An Efficacy Study of Ad5CMV-p53 Administered Intralesionally as an Adjunct to Radiation Therapy in Patients with Non-Small Cell Lung Cancer** **Adverse event** Patient received three injections of Ad5CMV-p53; radiation was started three days after first study drug injection. Patient experienced vomiting and poor appetite and was hospitalized for dehydration. Dehydration was considered by the investigator as possibly related to the study medication. Follow-up to this event was reported on November 5, 1998. Dehydration was resolved.
September 25, 1998	**9709-214 Breau *et al*.**	**A Phase II Multi-Center, Open Label, Randomized Study to Evaluate Effectiveness and Safety of Two Treatment Regimens of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 78 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN)** **Adverse events** 1) Follow-up to previously reported events reported on July 29, 1998 and August 18, 1998. Patient recovered from previous conditions of dehydration and gastroenteritis and went off study on July 17, 1998. On August 18, 1998 patient went into cardiac arrest and was stabilized. Patient died on August 25 due to disease progression. The investigator now considers that none of the previously reported events were related to the study medication.

		2) Patient experienced tumor breakdown approximately five days after receiving first dose of Ad5CMV-p53. Patient was treated with an antibiotic to treat wound infection and was treated with IV fluids for dehydration. Investigator considered that infection and dehydration were possibly related to the study medication.
October 19, 1998	**9209-026 Walker**	**A Study of the Safety and Survival of the Adoptive Transfer of Genetically Marked Syngeneic Lymphocytes in HIV Infected Identical Twins** **Adverse event** Patient was diagnosed with coronary artery disease requiring a bypass. Investigator considered that coronary artery disease was unrelated to gene transfer protocol.
October 27, 1998	**9209-026 Walker**	**A Study of the Safety and Survival of the Adoptive Transfer of Genetically Marked Syngeneic Lymphocytes in HIV Infected Identical Twins** **Adverse event** Diagnosis of Bowen's Disease in one individual, due to complications of AIDS; not related to gene transfer protocol.
November 9, 1998	**9709-212 Gonzalez*et al.***	**Phase I Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) with IL-2 Plasmid DNA/DMRIE/DOPE Lipid Complex (Leuvectin) as an Immunotherapeutic Regimen in Patients with Metastatic Melanoma** **Adverse event** Patient completed first (three injections of Allovectin and four of Leuvectin). Patient usually experienced some mild to moderate pain at the injection site, low grade fever, muscle pain, chills, and fatigue following the Leuvectin doses. These symptoms were resolved within 24 hours. Patient was enrolled in a second course of treatment. Following the last Leuvectin dose, the 14th injection, the patient experienced severe pain and was given IV Demerol; a CT scan was negative for internal bleeding. Pain resolved and patient was discharged; however patient returned to emergency room later that evening and was hospitalized for severe pain. Patient experienced nausea, vomiting, and a fever (40.6 C). Patient was discharged the next day with no further complications. Cultures were negative for bacterial infection. It should be noted that all injections of study drug were given with CT guidance. The investigator considered the event as definitely related to the injection procedure.
November 16, 1998	**9709-214 Breau *et al*** .	**A Phase II Multi-Center, Open Label, Randomized Study to Evaluate Effectiveness and Safety of Two Treatment Regimens of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 78 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN) Adverse event** Follow-up to an adverse event of the Ad5CMV-p53 trial that is being conducted in Europe only. This relates to the one patient who experienced dyspnea (see reports dated July 29, 1998 and August 18, 1998). The investigator now considers the dyspnea to be related to swelling around the mandibulae and that the swelling may be related to the study medication. On December 9, 1998, the sponsor reported that the investigator now considers the

		above event to be unlikely related to the study medication.
December 3, 1998	**9712-226 Dreicer *et al.***	**A Phase II, Multi-Center, Open Label, Study to Evaluate Effectiveness and Safety of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 39 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN)** **Adverse events** 1) Patient experienced fever that was resolved with IV antibiotics. Fever, due to infection t, was considered by the investigator as possibly related to the study medication. 2) Patient experienced local ulceration that exposed the carotid artery. Patient died due to "carotid artery blow out." Local ulceration was considered by the investigator as probably related to the study medication.
December 9, 1998	**9712-226 Dreicer *et al.***	**A Phase II, Multi-Center, Open Label, Study to Evaluate Effectiveness and Safety of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 39 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN)** **Adverse event** Patient experienced bleeding from tumor immediately after injection of the study medication. Bleeding was stopped with pressure, but restarted approximately five hours after Ad5CMV-p53 injection. Patient was hospitalized and received a blood transfusion. Investigator considered hemorrhage as probably related to the study medication.
January 5, 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 Ad5CMV-p53 Administered by Intra-Tumoral Injections in 78 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN)** **Adverse event** Patient has received six cycles of Ad5CMV-p53. Patient has been diagnosed with Guillain-Barr syndrome that the investigator considers as possibly related to the study mediation.
January 5, 1999	**9712-226 Dreicer *et al.***	**A Phase II, Multi-Center, Open Label, Study to Evaluate Effectiveness and Safety of Ad5CMV-p53 Administered by Intra-Tumoral Injections in 39 Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN)** **Adverse events** 1) Follow-up to event that was reported on December 9, 1998. Patient experienced a second episode of tumor hemorrhage two days after event reported on December 9. Patient was hospitalized for bleeding and also experienced a headache and neck pain. A right carotid artery angiogram and embolization were performed. Second episode of bleeding was considered by the investigator as probably related to the study medication. 2) Patient experienced an episode of unresponsiveness and bradycardia after the first course of Ad5CMV-p53. Investigator considered these events as unlikely to be due to the study medication and were "...most likely caused by manipulation of the area surrounding the carotid which may have caused stimulation of the parasympathetic nerves."

February 2. 1999	**9804-250 Swisher**	**An Efficacy Study of Ad5CMV-p53 Administered Intralesionally as an Adjunct to Radiation Therapy in Patients with Non-Small Cell Lung Cancer** **Adverse event** White patches were observed on right upper lobe of the lung on patient's CT scan done for second injection of Ad5CMV-p53. Second injection of study medication was completed. Tests are being performed to determine if infiltrate is pneumonia or pneumonitis. Investigator considered the event as possibly related to the study medication.
February 9, 1999	**9804-250 Swisher**	**An Efficacy Study of Ad5CMV-p53 Administered Intralesionally as an Adjunct to Radiation Therapy in Patients with Non-Small Cell Lung Cancer** **Adverse event** Follow-up to event reported on February 2, 1999. Patient received IV antibiotics and was discharged after symptoms improved.