SAFETY REPORTS, ADVERSE EVENTS, AND UPDATES FOR HUMAN GENE TRANSFER PROTOCOLS RECOMBINANT DNA ADVISORY COMMITTEE MEETING MARCH 10, 1998

11-17-97 (letter date)	**9512-137 Hortobagyi *et al.***	**Phase I Study of E1A Gene Therapy for Patients with Metastatic Breast or Ovarian Cancer that Overexpresses Her-2/neu** **Adverse event:** Occurred at Virginia Mason Medical center under the direction of Dr. Paul Weiden. Patient received 7.2 mg DNA/m^2 on 10-30-97. One and a half hours after infusion of the plasmid DNA/lipid complex, patient experienced severe abdominal pain and vomiting. Patient required IV morphine to relieve the pain. Due to labored breathing, caused by the pain, oxygen was administered. Patient was admitted to the hospital for pain control; patient continued vomiting for several hours. Patient spiked a fever of 39^{O} C. Patient was released form the hospital on 10-31-97 and fully recovered on 11-2-97. **Update:** To date, 6 patients have been enrolled in the breast cancer arm of this study. This arm of the study is going to be closed by Targeted Genetics to accrual. Targeted Genetics does not intend to pursue this indication. Twelve ovarian cancer patients have been treated under this protocol. Dosing has stopped past the 7.2 mg DNA/m^2 group. Maximum tolerated dose has been determined to be 3.6 mg DNA/m^2 for this formulation of plasmid: lipid (25 mg DNA: 250 nmole lipid).
11-24-97	**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 received first dose of Ad5CMV-p53 on Sept. 8, 1997 and second dose the following day. After second injection of study drug, patient experienced fatigue, chills, and a fever of 103.5^{O} F. Two ibuprofen tablets were given and fever was reduced to 99.4^{O} F. Minimal bleeding at injection site occurred, packed with surgicel. One day after second dose, patient experienced moderate bleeding which quickly ceased. Patient received third injection of drug; moderate bleeding at injection site, packed with surgicel. Patient stayed in hospital overnight for observation. On Sept. 11, 1997 mild amount of bleeding, but no obstruction or inflammation. Temperature was normal and bleeding resolved. Patient discharged from hospital. The fever experienced by the patient was considered by the investigator as possibly related to the study drug. Patient went on to receive cycle 2 of study from October 6-8, 1997 and did not experience any complications.
11-18-97	**9703-183 Straus**	**Administration of Neomycin Resistance Gene Marked EBV Specific Cytotoxic T-Lymphocytes to Patients with Relapsed EBV-Positive Hodgkin Disease Compassionate Case** **Update:** Compassionate single patient protocol was terminated due to inability to grow out EBV-specific cytotoxic T lymphocytes (after multiple attempts) from the patient. Patient was never treated under this compassionate protocol. Patient underwent aggressive courses of chemotherapy, that as of this date have led to clinical remission.

11-26-97	**9512-137 Hortobagyi *et al.***	**Phase I Study of E1A Gene Therapy for Patients with Metastatic Breast or Ovarian Cancer that Overexpresses Her-2/neu** **Adverse event:** Patient received third infusion of lipid:DNA complex (3.6mg DNA/m^2) on November 13, 1997. Patient went back to complain of nausea, vomiting, and severe constipation; nausea and vomiting had occurred for the past 10 days. Patient was admitted to the hospital for IV fluids to control nausea and vomiting and remained in the hospital for 6 days. During this hospitalization, patient received chemotherapy and was taken off study. According to the report filed by the sponsor (Targeted Genetic): "The investigator did not believe these events were related to E1A Lipid Complex; however, the Targeted Genetics medical monitor could not rule out the possibility considering the frequency of previous reports of patients experiencing nausea and vomiting treated with E1A Lipid Complex in this trial."
1-23-98	**9609-161 Antonia**	**Treatment of Small Cell Lung Cancer in Partial Remission or at Relapse with B7-1 Gene-Modified Autologous Tumor Cells as a Vaccine with Systemic Interferon Gamma** **Update:** Protocol has been closed. Investigators were able to culture autologous tumor cells from several patients. However, they were unable to transfect the cells with their plasmid construct expressing B7-1; even though a variety of transfection techniques were tried.
1-30-98	**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:** On day 14 of third course of treatment, patient experienced bleeding from the oral cavity with decreased blood pressure and decreased hematocrit. In addition, patient had bloody emesis with clots. Patient was hospitalized and treated with promethazine and IV fluids. An electrocardiogram showed sinus rhythm, sinus tachycardia with occasional premature ventricular contractions. Hematocrit was 25-29% compared to 38% two days before start of third course. Bleeding continued for approximately 6 hours; a similar episode occurred two days prior to this event (no hospitalization was required). "This event was considered by the investigator as possibly related to [the] study medication."
2-16-98	**9701-172 Cornetta and Abonour**	**High Dose Carboplatin and Etoposide Followed by Transplantation with Peripheral Blood Stem Cells Transduced with the Multiple Drug Resistance Gene in the Treatment of Germ Cell Tumors - A Pilot Study** **Update:** To date, a total of ten patients, 15 total over two years, have been enrolled. Of the ten patients, three failed to mobilize sufficient number of CD34+ cells and therefore did not meet the eligibility requirements for the study. However, enough cells were obtained from these three patients to allow for transplantation with untransduced cells. Failure to mobilize sufficient number of cells is not unexpected given that many of the patients are heavily pre-treated. The other seven have either completed the tandem transplantation regimen (five patients) or are in the midst of the first transplant. Drug resistant transduced progenitors have been detected in the five patients that have completed the tandem transplantations. The investigators report that: "The range of gene transfer into progenitors is 10 to 27 %. Analysis for replication competent retrovirus of infused product and patients samples post-BMT have all been negative to date." In addition, the investigators report that no safety reports have been filed, no patients have dropped out of the study due to an adverse event, and all patients are still alive.