SAFETY REPORTS, ADVERSE EVENTS, AND UPDATES FOR HUMAN GENE TRANSFER PROTOCOLS RECOMBINANT DNA ADVISORY COMMITTEE MEETING DECEMBER 15-16, 1997

9-10-97 (letter date)	**9611-169 Hersh ,*et al.***	**Phase I/II Trial of Interleukin-2 DNA/DMRIE/DOPE Lipid Complex as an Immunotherapeutic Agent in Cancer by Direct Gene Transfer** **One adverse event.** Patient experienced severe rigors after the fourth dose of the plasmid DNA/DMRIE/DOPE complex (Leuvectin). The first three injections of Leuvectin were in the anterior peritoneum of the lower left quadrant of the pelvis. The fourth injection was into a liver lesion.During the injection, the patient became "warm all over." Immediately after the injection, the patient developed severe rigors and within two hours developed a fever of 38C.Patient was admitted to the hospital for observation and was discharged the next day.After administration of Tylenol and two doses of Ceftazidine, the patient's temperature returned to normal. The PI, Dr. Rubin, has determined that this adverse event is probably related to Leuvectin and is not likely related to the injection procedure.Since this adverse event, the patient has received two additional injections without incident.
9-16-97	**9608-157 Maria, *et al.***	**Prospective, Open-Label, Parallel-Group, Randomized, Multicenter Trial Comparing the Effficacy of Surgery, Radiation, and Injection of Murine Cells Producing Herpes Simplex Thymidine Kinase Vector Followed by Intravenous Ganciclovir Against the Efficacy of Surgery and Radiation in the Treatment of Newly Diagnosed, Previously Untreated Glioblastoma** **Adverse event.** Patient was enrolled in the gene therapy treatment arm of this protocol.Patient was found to have, approximately 3 months after injection of 6.5 ml of murine cells following surgical resection, " a space-occupying cystic encapsulation of the surgical cavity and severe perifocal edema." Treatment consisted of the implantation of a reservoir to allow for repeated aspiration of the cyst.The aspirate was negative for the presence of tumor cells. The PI, Dr. Westphal of the Klinikum Eppendorf in Hamburg, "assessed this event as possibly related to the therapy, relating it to both the study medication and the surgical procedure categories (stating that it was a local inflammatory response after implantation of xenografts)." In a follow-up report, not provided as of 9-19-97 to ORDA, it was reported that this patient died from an infection after the reservoir was implanted.The death is not considered by the PI to be likely related to the study medication.
10-2-97	**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 was enrolled in the third cohort of this protocol. Patient received first infusion of lipid complex (7.2 mg DNA/m^2) and experienced a fever of 101C 12 hours after infusion.Four days after infusion, patient was admitted to the hospital due to dehydration (patient had been unable to eat or drink since infusion without nausea and vomiting).Patient has been taken off the study.

		The PI "noted that these events may have been due to the [patient's] disease as [the patient] had extensive tumor burden in [the] abdomen, but [the PI] could not rule out study drug due to the acute onset of these events after drug administration."
10-22-97	**9701-172 Cornetta and Abonour**	**High Dose Carboplatin and Etoposide Followed by Transplantation with Perpheral Blood Stem Cells Transduced with the Multiple Drug Resistance Gene in the Treatment of Germ Cell Tumors - A Pilot Study** **Update.** Six patients were treated between 6/4/97 and 9/24/97. Two of the patients failed to mobilize adequate CD34 cells for transduction and are off study. For one patient, only 1 x 10^6 cells/kg body weight were collected and transduced. The transduced cells were not infused (protocol requires 2 x 10^6 cells/kg).The transduction efficiency will still be determined for these cells. Two of the three patients for which adequate numbers of cell were collected have received infused transduced cells. Gene transduction efficiencies for these two patients based upon PCR analysis of colonies was 11% and 22%. The third patient will receive transduced cells in early November.
10-23-97	**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 in third cohort experienced severe abdominal pain and nausea 40 minutes aftrer receiving their first infusion of DNA/lipid complex (7.2 mg DNA/m^2). Patient became hypotensive and vomited one hour after the infusion. Patient was admitted to the hospital for IV morphine for pain control followed by patient-controlled analgesia. Twelve hours after infusion, patient developed a fever of 102 ^{o} F. Fever was resolved with Tylenol. Three days after infusion patient had a fever of 101 ^{o} F; pain had subsided and patient was no longer on analgesics. Blood cultures were negative and patient was released from the hospital, after being afebrile for 24 hours, four days after infusion. The PI, Dr. Weiden, believes that the fever, abdominal pain, and nausea are probably related to the study drug. The sponsor, Targeted Genetics Corporation, is currently evaluating whether the maximum tolerated dose is 7.2 mg DNA/m^2.