SAFETY REPORTS AND ADVERSE EVENTS FOR HUMAN GENE TRANSFER PROTOCOLS RECOMBINANT DNA ADVISORY COMMITTEE MEETING JUNE 18-19, 1998

3-6-98 (letter date)	**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)** **Two adverse events:**One patient experienced chills, fever (39 C), and vomiting same day that first dose ($4x10^{10}$) of Ad5CMV-p53 was administered. Investigator considered fever and chills to be probably related to the study medication. Vomiting was considered by the investigator as unlikely to be related to the study medication. Second event was reported as a follow-up to an adverse event that was originally reported on 1-30-98. Patient experienced a second episode of bleeding from the oral cavity with decreased hematocrit (23% to 19%). Patient received two units packed red cells and one unit of frozen plasma. Patient underwent an embolization of the right ligula facial artery trunk. Bleeding stopped after embolization.
3-6-98	**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** **One adverse event:**This event was originally reported by the investigator as not related the study medication; however, the investigator has changed his decision to "possibly related" to the E1A Lipid Complex. Patient received all scheduled infusions of 3.2 mg E1A Lipid Complex (1.8 mg DNA/m^2 dose group) for first and second cycles without incident. In addition, patient did not experience any complications after first round of third cycle. Patient complained of nausea two days before the scheduled start of the second infusion of the third cycle. Nausea was resolved with IV medications and patient received the second infusion. Three days after the infusion, patient returned to the hospital with protracted nausea, vomiting and abdominal pain. Patient was hospitalized for IV hydration, pain control, and nausea management. The patient, at this time, was taken off study. A CT scan during this hospitalization showed a large bowel obstruction and was diagnosed with a left lower extremity deep vein thrombosis. Patient underwent surgery to remove the bowel obstruction. During this surgery, significant abdominal fibrosis was noted. Due to the occurrence of similar fibrosis with other patients on this study, the principal investigator changed his opinion regarding the relatedness of this event to the study medication.
5-15-98	**9212-035 Wilson, Simon, and McCoy**	**Gene Therapy of Cystic Fibrosis Lung Disease Using E1 Deleted Adenoviruses: A Phase I Trial** **Adverse event:** Patient remained hospitalized throughout this event. Due to extended hospitalization, this event is considered to be adverse. Patient # 11 received 2.1×10^{11} particles (in 7 ml) to the right lower lobe. Within the first 24 hours after virus instillation, patient experienced myalgia and flu-like symptoms (including headache and fever). Maximum temperature over this period was 101.2 F. In addition, pulmonary function tests, performed one day after gene transfer, showed a decrease (compared to measurements 14 days prior to gene

transfer) in both expiratory volume (from 60% to 51% of predicted) and vital capacity (from 67% to 57% of predicted). On the second day after gene transfer, patient still had a maximum temperature of 102.2 F, even with the use of Tylenol. However, measurements of pulmonary function performed two days after gene transfer were slightly elevated: expiratory volume was 56% of predicted and vital capacity was 60% of predicted. Patient experienced coughing with deep inspiration and chest X-rays revealed a small infiltrate in the region where the gene transfer was performed.

On the third day after gene transfer, a bronchoscopy was performed to re-examine the airways and to obtain samples to test for gene transfer (no results of the tests for gene transfer were submitted). In addition, patient continued to have thin secretions, that were present on the day of vector instillation, bilaterally. After bronchoscopy, patient complained of continued occipital headache, first experienced two days after gene transfer. Patient also experienced right-sided pleuritic chest pain and demonstrated inspiratory crackles over the right lower lung field. An X-ray revealed an extension of the infiltrate observed the previous day and some consolidation within the lateral basal segment of the right lower lobe. Patient no longer was running a fever, although Tylenol was still being taken.

On the fourth day after gene transfer, patient still experienced a headache in addition mild nausea. Pulmonary tests showed an expiratory volume of 58% of predicted and a vital capacity of 61% of predicted. Chest X-ray continued to show some consolidation within the lateral basal segment of the right lower lobe as observed on the third day.

On the fifth day after gene transfer, an X-ray indicated a reduction in the size of the lung infiltrate. In addition, nausea was improved and patient was discharged. Follow-up nine days after gene transfer, indicated that infiltrate had resolved and no crackles were detected. (No mention of the results of any pulmonary function tests performed nine days after gene transfer.)

In consultation with the FDA, the investigators treated the next patient at the same, instead of escalating the, dose.