AMENDMENTS AND UPDATES TO
HUMAN GENE TRANSFER PROTOCOLS
RECOMBINANT DNA ADVISORY COMMITTEE MEETING
JUNE 18-19, 1998

2-10-98 (letter date)	**9209-026 Walker**	**A Study of the Safety and Survival of the Adoptive Transfer of Genetically Marked Syngeneic Lymphocytes in HIV Infected Identical Twins** **Update** No new amendments have been made since the last update. In addition, no new subjects have been enrolled since the last update. Genetically marked lymphocytes are still detected in the circulation of all six twin recipients. The number of months since the last gene-marked cell infusion ranges from 14 to 30.
3-4-98	**9712-226 Dreicer**	**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)** **Amendment:** Four new investigators/sites have been added. 1) Allen Cohn, M.D. at the University of Colorado Health Sciences Center, Denver, Colorado; 2) Stephen K. Williamson, M.D. at the University of Kansas Medical Center, Kansas City, Kansas; 3) David A.VanEcho, M.D. at the University of Maryland School of Medicine, Baltimore, Maryland; and 4) Fred Rosen, M.D., a the University of Illinois at Chicago Hospitals & Clinics, Chicago, Illinois
3-9-98	**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** **Amendments:** Changes have been made to the protocol to modify the transduction procedure in order to avoic unnecessary manipulation of the cells. The cytokine cocktail now contains G-CSF, SCF, and MGDF. In addition, VP-16 administration will be stopped if the granulocyte count falls below

		500 and the following cycles will be reduced by 25%. The number of patients to be enrolled has been clarified to 15 over a two year period.
3-13-98	**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 RecurrentSquamous Cell Carcinoma of the Head and Neck (SCCHN)** **Amendment:** An amendment has been made to the clinical protocol to address a concern of investigators that a certain subset of typical patients with head and neck cancer were being excluded and/or withdrawn prematurely from the study. Specifically the amendments relate to: "Patients with needle inaccessible tumor in the head and neck region will now be considered on a case by case basis for enrollment providing non-treatment of these lesions is not expected to impact negatively on the patient's ability to complete the study. Additionally, if during study treatment, a patient exhibits a mixed response in the head and neck region, consisting of a PR [partial response] or stabilization of treated lesions, but appearance of new lesion(s) may be added to treatment. This may occur as long as the sum of the longest diameters of all lesions, including new lesion(s), is less than 10 cm. The number of pfu [plaque forming units] per treatment day will be increased according to the existing treatment dose table".
3-13-98	**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)** **Amendment:** Same amendment has been made to this protocol as for protocol 9709-214 (amendment dated 3-13-98).
3-16-98	**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 RecurrentSquamous Cell Carcinoma of the Head and Neck (SCCHN)** **Amendment:** Three new investigators/sites are added. 1) Sanjiv Agarwala, M.D. at the University of Pittsburgh Cancer Institute, Pittsburgh, Pennsylvania; 2) Marshall R. Posner, M.D. at the

		Dana-Farber Cancer Institute, Boston, Massachusetts; and 3) Howard S. Hochster, M.D., FACP at New York University Medical Center, New York, New York.
3-17-98	**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** **Amendment:** One new investigator/site is added. The new investigator is John A. Thompson, M.D. at the University of Washington Medical Center, Seattle, Washington.
4-8-98	**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)** **Amendment:** One new investigator/site is added. The new investigator is James N. Endicott, M.D. at the University of South Florida, Tampa, Florida.
4-14-98	**9705-190 O'Malley**	**A Double-Blind, Placebo-Controlled, Single Rising-Dose Study of the Safety and Tolerability of Formulated hIL-2 Plasmid in Patients with Squamous Cell Carcinoma of the Head and Neck (SCCHN)** **Amendment:** An amendment was made to the clinical protocol to change the dose of the third cohorts from a single to a multiple dose. This change made was from a single dose of 0.6 mg formulated plasmid to doses (0.6 mg) on days 0, 3, and 7 and then once per week for three weeks (6 doses total). This change has been made based on safety data collected by the PI. The sponsor (GenMedicine) reports that the "[m]ultiple dose exposure in the third cohort will provide additional safety and tolerability data". Change has been approved by the IBC, IRB, and FDA.
4-21-98	**9803-241 Bensinger and Parker**	**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 Myleogenous Leukemia, Chronic Lymphocytic Leukemia, Multiple Myeloma, and Non-Hodgkin's Lymphoma after HLA-Matched Sibling Allogeneic Stem Cell Transplant**

		Amendment: Four new investigators/sites are added. 1) Peggy J. Henslee-Downey, M.D. and Sunil Abhyankar, M.D. co-PIs at Richland Memorial Hospital, University of South Carolina School of Medicine; Columbia, South Carolina 2) Sergio Giralt, M.D. at the University of Texas, MD Anderson Cancer Center; Houston, Texas 3) Kenneth Cornetta, M.D. at Indiana University-Purdue University; Indianapolis, Indiana
4-27-98	**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** **Amendment:** Minor amendment has been made to clarify the exact dose of G-CSF used to treat cells *in vitro*. Change made is from units of G-CSF to ng.
4-28-98	**9409-087 Whitley**	**Retroviral-Mediated Transfer of the Iduronate-2-Sulfatase Gene into Lymphocytes for Treatment of Mild Hunter Syndrome (Mucopolysaccharidosis Type II)** **Update:** The only patient to be treated has received the last of 12 infusions (in January 1998) of genetically-correctedautologous cells. The investigator reports that routine tests do not show any signs of toxicity. In addition, the investigator states that "[a]t least one potential marker of efficacy, (i.e., quantitative urineglycosaminoglycan) failed to show any trend from the high, pathologically-elevated levels down toward the normal range.Estimates of liver volume by computerized tomography did not show a consistent trend.Additional tests to evaluate other parameter -- such as transduction frequency, survival of genetically-modified cells, etc.-- are st in progress and will be reported at [a] later date".
5-20-98	**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)** **Amendment:**

		One new investigator/site is added. The new investigator is Carol M. Bier-Laning, M.D. at the University of Texas Southwestern Medical Center at Dallas, Dallas, Texas
5-20-98	**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 RecurrentSquamous Cell Carcinoma of the Head and Neck (SCCHN)** **Amendment:** One new investigator/site is added. The new investigator is Andreas Dietz, M.D. at the University of Heidelberg, Heidelberg, Germany.