SAFETY REPORTS AND ADVERSE EVENTS FOR HUMAN GENE TRANSFER PROTOCOLS RECOMBINANT DNA ADVISORY COMMITTEE MEETING MARCH 8-10, 2000

ID#	OBA Date	Protocol	Event Description	#Events
510	1/14/00	**C95-084** **Sponsor: Schering**	**A Phase I Study in Patients with Peritoneal Carcinomatosis Using SCH 58500 (rAd/p53) Administered by Single Intraperitoneal Instillation.** **Follow Up1; Event: Anaphylactic Reaction.** **Patient is a 40+ yo F with diagnosis of ovarian cancer and advanced peritoneal involvement. Patient had received 2 previous cycles of Adp53 with concurrent chemo (taxol + carboplatin); no complications were noted. For the 3rd cycle, the patient was hospitalized. After receiving 2 doses of Adp53, the patient developed fever, nausea, vomiting, malaise; dosing was interrupted. A 3rd dose was administered later that day followed by chemo (carboplatin). Itching at IV site noted. Within 8 minutes of receiving the chemo, the patient experienced lightheadedness and became agitated; BP fell to: 37/23 with a HR of 140. Chemo was interrupted and 500 ml IV saline was administered. Chemo was resumed within 10 min and was successfully completed. The patient was subsequently treated with IV Dexamethasone and Benadryl. BP increased to 121/64 within a matter of hours. The patient was discharged within four days of the treatment. The PI initially reported the event (anaphylaxis) as possibly associated with Adp53. On Follow-Up 1 (F/U1), the sponsor considers anaphylaxis as possibly associated with chemo and unlikely to be associated with Adp53.**	1
509	1/11/00	**9412-097** **Venook**	**Gene Therapy of Primary and Metastatic Malignant Tumors of the Liver Using ACN53 Via Hepatic Artery Infusion: A Phase I Study.** **Follow Up2; Events: 1. Myocardial Ischemia, 2. Premature atrial contractions; 3. Dyspnea.** **Patient is a 60+ yo F w/ metastatic colorectal cancer to liver under treatment w/ Adp53. Pt received Adp53 dose on 2/18/98 and 12 min into infusion, developed premature atrial contractions and dyspnea that resolved immediately following O_2 administration. Pain, nausea, vomiting and fever management was started on 2/18/98. ECG was performed on 2/19/98 -- normal sinus rhythm; but cannot**	3

			rule out anterior infarction. Pt was placed on IV fluids (Mg, KCl, PO4) for hypo- [magnesmia, kalemia, phosphatemia] on 2/19/98. Pt underwent surgical placement of hepatic arterial pump on 2/20/98 for Adp53 treatment -- no cardiac abnormalities noted during procedure. IV fluids were discontinued by 2/22/98. F/U1: Repeat ECG on 10/02/98 noted normal sinus rhythm w/ abnormalities indicative of possible anterior ischemia. PI initially considered ischemia possibly related to IND product but changed causality to "unrelated" after pt had undergone surgery on 2/20/99 w/o complications. On F/U2, sponsor considered the ischemia noted 2/19/98 and 2/20/98 to be "possibly associated" w/ IND product [Adp53].	
174	2/9/00	**9508-117** **Mitsuyasu**	**A Phase I Trial of Autologous CD34+ Hematopoietic Progenitor Cells Transduced with an Anti-HIV-1 Ribozyme.** **Initial; Events: 1. Fever, 2. L Hip pain, 3. Skin rash.** **Patient is a 55+ yo M. He received a) ribozyme transduced CD34+ cells on 2/23/98 and b) RevM10-transduced autologous HSC (bone marrow) from a 1/11/00 aspirate. The patient developed progressive L flank, L hip pain, tachycardia, fever (102.8 F), and skin rash. Patient was admitted for evaluation on 1/30/00. Blood, urine and chest X-ray were within normal limits. No evidence of deep vein thrombosis. Pain was ascribed to myositis (pt has history of Reiter syndrome). Fever abated spontaneously w/o antibiotics. Rash thought to be eosinophilic folliculitis, Rx: steroid cream. Pt was discharged on 2/1/00. Causalities: 1. Fever: 2ndry to URI; 2. L hip pain: 2ndry to gluteus myositis; 3. Eosinophilic folliculitis.**	3
512	1/18/00	**9705-189** **Belani**	**Phase I Study of Percutaneous Injections of Adenovirus p53 Construct (Adeno-p53) for Hepatocellular Carcinoma.** **Follow Up1. Event: Medically Significant LFT increase.** ***Report filed by Sponsor upon receipt of data from PI.*** **Pt is a 65+ yo M. Pt LFTs (ALT & AST) elevated on 8/31/99. He received second dose of treatment (Adp53) on 9/1/99 after which AST levels declined. PI considered elevation of AST as possibly related to IND drug and possibly related to hepatocellular cancer.**	1
69	1/5/00	**9712-223** **Bowman**	**Phase I Study of Chemokine and Cytokine Gene Modified Allogeneic Neuroblastoma Cells for Treatment of Relapsed/Refractory Neuroblastoma Using a Retroviral Vector.**	**1**

			Initial. Events: L. periorbital edema, hospitalization for IV antibiotics to treat possible cellulitis. **Pt is a child w/ recurrent neuroblastoma (stage II); Intervention: immunotherapy (SC injection of retrovirally transduced cells). Pt experienced L periorbital edema w/o pain, fever or conjunctival swelling. Transient diplopia noted. Swelling peaked at 96 hrs post-admin and gradually resolved. Event "inflammation of tumor nidus" considered possibly associated with IND product.**	
70	**1/5/00**	**9712-223** **Bowman**	**Initial. Events: Abdominal pain, constipation (gr 3) and abdominal pain (gr 2).** **Pt is a child w/ history of metastatic neuroblastoma and hip athralagias. Intervention: immunotherapy (SC inj of retrovirally transduced cells). Pt hospitalized for treatment of constipation - resolved; transient abdominal pain continues. Differential Diagnosis: constipation (vs.) peptic ulcer disease (vs.) rectal tear (vs.) vaccine effect. Causality deemed possibly associated w/ IND product.**	**2**
1	**2/8/00**	**9712-226** **Sponsor: Aventis**	**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).** **Follow Up Report re: (SCCHN) Pt that died from local ulceration leading to event of carotid "blow-out."** **Causality of event was changed from "Probably Related to IND" product to Unrelated. Causality now attributed to "Respiratory Compromise due to chronic secretions secondary to progressive disease." Confirmation of causality has been requested.**	**0**
152	**1/21/00**	**9802-233** **Sponsor: Vical**	**Phase II Study of Direct Gene Transfer of HLA-B7 Plasmid DNA/DMRIE/DOPE Lipid Complex (Allovectin-7) as an Immunotherapeutic Agent in Patients with Stage III or IV Melanoma with No Treatment Alternatives.** **Follow Up2; Autopsy. Event: Severe ascites.** **Pt undergoing treatment for metastatic melanoma developed severe ascites and severe GI bleed first documented 7/15/99. Events occurred 15-d post admin of**	**0**

			immunotherapeutic liposome: HLA-B7 & beta-2 microglobulin genes as DNA-lipid complex. Bleeding was attributed to NSAID use and resolved. Pt re-hospitalized on 8/2/99 for recurrent abdominal ascites and pain. Fluid was negative for infectious agents but positive for reactive cells. Pt was discharged 8/7/99 under pain management for colorectal melanoma mass -- SAE ongoing. Pt removed from study 8/31/99 due to disease progression; lesions present in lungs, mass in colorectal area and ascites. Pt expired; autopsy indicated cause of death to be multifactorial: metastatic melanoma, hypoperfusion due to heart failure, hypoxia due to anemia and pulmonary insufficiency. Emphysema, bronchial mucous obstruction, lung atlectasis and ascites attributed to pulmonary insufficiency. Cause of event "ascites" deemed by investigator to be possibly associated with IND drug; sponsor states that causality is unlikely to be associated with IND drug.	
171	**1/28/00**	**9804-243** **Crystal** **Sponsor: GenVec**	**Phase I Study of Direct Administration of a replication Deficient Adenovirus vector (Ad_{GV}VEGF121.10) Containing the VEGF121 cDNA to the Ischemic Lower Limb of Individuals with Peripheral Vascular Disease.** **Initial; Event: Diagnosis of Bladder Cancer (Medically Significant)** **Pt is a 65+ yo M w/ hist of coronary artery disease, hypercholesterolemia, hypertension, asthma, cerebral vascular disease, arthritis & gout. Pt treated for peripheral vascular disease using AdVEGF. 7 MOs post AdVEGF treatment, patient undergoes lithotripsy for kidney stones and is diagnosed w/ bladder cancer. Pt underwent surgery for removal of early stage cancer and is considered recovered. PI attributed causality to IND drug "unknown". The sponsor considers the relationship to the IND drug (AdVEGF) as "unknown."**	**1**
71	**1/31/00**	**9804-249** **Junghans**	**Phase I Study of T Cells Modified with Chimeric AntiCEA Immunoglobulin-T Cell Receptors (IgTCR) in Adenocarcinoma.** **Follow Up: Autopsy. Event: Death.** **Pt was a 70+ yo M w/ history of myocardial infarctions followed by CABG in 1976. Diagnosed w/ rectal cancer in 1994, metastasized to lungs and liver in 1996. Intervention: Reinfusion of retrovirally transduced autologous lymphocytes expressing CEA antibody (ex-vivo immunotherapy); enrolled in 1998. On 2/1/99, pt admitted for dose 5 of experimental therapy; noted decreased**	**0**

			appetite, dyspnea, and episodes of mild chest pain. On day of admission pt presented w/ low O_2 saturation and several hrs post treatment, experienced substernal chest pain that resolved. Some T-wave changes (by EKG), heart enzymes not elevated. Discharged; found dead at home. Causality of the initial event (death) was originally deemed "unrelated" and subsequently changed by the PI to "possibly related" by virtue of temporal association. Direct cause and effect cannot be substantiated on known or described mechanistic grounds.	
64	**1/20/00**	**9901-280** **Sponsor: Schering**	**A Phase II/III Trial of Chemotherapy Alone Versus Chemotherapy Plus SCH 58500 in Newly Diagnosed Stage III Ovarian and Primary Peritoneal Cancer Patients with ≥0.5 cm and ≤2 cm Residual Disease Following Surgery** **Initial; Event: Tachyarrythmia.** **Patient is a 50+ yo F w/ history of cardiac palpitations and tachycardia. Pt was treated w/ chemo and Adp53 via IP port. Pt experienced pain and tachycardia dyspnea and fever (40 C) 1 hr post Adp53 administration. Causality (by CCU diagnosis) was attributed to cardiac electrophysiolgical abnormality possibly exacerbated by fever from Adp53 administration.**	1
65	2/2/00	**9901-280** **Sponsor: Schering**	**Follow Up1: Refer to ID #64 (above)** **Fever abated 1/12/00; pt discharged 1/13/00. Investigator considers the supraventricular tachycardia related to underlying congenital cardiac electrophysiology and possibly exacerbated by catecholamine release from fever due to IND product administration.**	0
172	1/13/00	**9901-280** **Sponsor: Schering**	**Initial; Events: 1. Neutropenia, 2. Sepsis, 3. Death.** **55+ yo F w/ history of Stage III ovarian ca. Pt treated w/ Adp53 via IP admin from 4/5 to 7/2/99. After completing Adp53 therapy, pt was placed on chemo (topotecan & etoposide) from 9/99 to 12/99 via IP admin. Pt developed fever, chills, neutropenia on 12/26/99, and was hospitalized on 12/28/99 for pelvic abscess. Blood, sputum and abscess cultures were positive for Methicillin sensitive. Staph. aureus. Pt was improving w/ antibiotic therapy. PI reported that Staph colonization at catheter, or fistula in combination with neutropenia may have led to sepsis. Sudden cardiovascular collapse occurred. The pt expired from a**	3

			large pulmonary embolus (per autopsy). PI considered sepsis as unrelated to IND drug, but possibly associated w/ chemo. Cause of death was attributed to an embolism; unrelated to the IND product.	
173	1/13/00	**9901-280** **Sponsor: Schering**	**Follow Up2: (No Antecedents submitted to OBA)** **Events: 1. Neutropenia, 2. Leukopenia** **Patient is a 50+ yo F diagnosed w/ stage III ovarian cancer that spread to the peritoneal cavity . Patient was treated w/ Adp53 from 10/11/99 to 10/15/99. Pt also received chemo (taxol + carboplatin) on 9/17/99 (dose 1) and 10/11/99 (dose 2). Pt developed nausea, vomiting, diarrhea on 10/17/99. Pt hospitalized on 10/17/99 for dehydration, nausea, vomiting and neutropenia. Leukopenia was also noted. Pt was rehydrated and treated w/ Diflucan. Condition resolved and pt was discharged on 10/20/99. Pt received dose #3 chemo and Adp53 from 11/1/99 to 11/5/99. PI attributed neutropenia as possibly associated w/ Adp53. Sponsor attributes neutropenia to chemo whereas leukopenia is possibly related to IND product.**	2
511	1/4/00	**9902-285** **Grandis**	**A Phase I Trial of Intratumoral Antisense EGFR DNA and DC-Chol Liposomes in Advanced Oral Squamous Cell Carcinoma.** **Initial; Event: Cellulitis requiring hospitalization.** **Patient is a 45+ yo M diagnosed with oral squamous cell carcinoma. Pt was treated w/ antisense EGFR DNA-liposome (by intratumoral injection). Prior therapy included chemo and radiation. Pt admitted to hospital on 12/23/99 for cellulitis of the face (an identical event occurred 12/18/99). Pt was treated w/ IV antibiotics and discharged 12/23/99. Causalities provided by investigator: IND drug: "possible association;" Non-IND drug: also a "possible association"; Underlying Disease: "probable association."**	1
68	2/9/00	**9902-287** **Schiller**	**Phase I Pilot Trial of Adenovirus p53 in Bronchioloalveolar Cell Lung Carcinoma (BAC) Administered by Bronchoalveolar Lavage.** **Initial. Events: 1. Hypoxia (gr 4), 2. Death.** **Patient is a 50+ yo M w/ advanced bronchioalveolar**	2

			carcinoma (BAC). Pt developed increasing dyspnea 3-4 days post Adp53 administration. Pt died from progressive respiratory insufficiency over several weeks. Investigator's differential diagnosis: Progressive lung cancer (vs.) acute pneumonitis (vs.) ARDS-like syndrome. Causality: Death probably due to BAC w/ possible association to concurrent inflammation due to Adp53 administration.	
394	2/9/00	**9902-287** **Schiller**	**Initial; Event: Bronchospasm.** **65+ yo M w/ hist of bronchioalveolar carcinoma; undergoing chemo (taxol - most recent dose 7/99) and having prior surgery for complete resection of right lower / right middle (RL/RM) lung lobes (5/96). Pt developed bronchospasm following first dose of IND product (Adp53); Event trt'd with steroidal anti-inflammatory and antibiotic. Pt pre-medicated prior to receiving second dose of Adp53 on 8/17/99. Spasm did not recur. Event , bronchospasm [allergic/hypersensitive reaction] was deemed as "probably associated" w/ IND product.**	**1**
395	**2/9/00**	**9902-287** **Schiller**	**F/U1(?); Event Hyperalkalemia; [see ID #394 above].** **No details provided, blood chemistry result -- no further information provided. Event deemed "unrelated".**	**1**
513	**2/2/00**	**9902-287** **Schiller**	**Initial; Events: 1. Fatigue (gr 2) and Bronchial mucous (gr 1).** **Patient is a 50+ yo F w/ history of metastatic bronchioalveolar lung carcinoma (BAC). Priors include: chemo & radiation therapy. Pt treated w/ Adp53 on 3/9/99 complained of fatigue and thick bronchial mucous 2-days following administration (by bronchioalveolar lavage -- BAL) of IND product. Bronchial mucous resolved w/o treatment; fatigue was not treated and was ongoing. Investigator listed causality as "probably associated" w/ IND drug for both events.**	**2**
514	**2/2/00**	**9902-287** **Schiller**	**Initial; Events: 1. Bronchial mucous; 2. Anemia (gr 2); 3. Increased hepatic Alkphos (gr 1).** **[see ID #513 above]**	**3**

			Pt (ID #513) was treated w/ 2nd cycle Adp53 (by BAL administration) and redeveloped bronchial mucous (again, self resolving). On same day of IND drug administration, pt was shown to have elevated levels of hepatic Alkaline Phosphatase and low hemoglobin. A F/U1 on 4/14/99 indicated no definite causality for low Hematocrit values or elevated Alk Phos (although bone metastasis is suspected). Investigator listed both events as "possibly associated" with IND product.	
515	**2/2/00**	**9902-287** **Schiller**	**Initial; Event: Bronchopulmonary Fistula. [see ID #513 & #514]** **Pt (ID #513) admitted to hospital for O_2 admin and possible chest tube placement. Pt had elevated WBC count and low grade fever. CT scan indicated bronchopulmonary fistula in RL lobe (area previously treated w/ IND product). 3rd cycle IND treatment was withheld. SAE is ongoing. Investigator deemed causality of fistula as "possibly associated" to IND product although association to disease progression is "probable".**	**1**
66	**1/21/00**	**9910-350** **Alberts *et al.*** **Sponsor: Targeted Genetics**	**A Phase I Dose Escalation Study of Intraperitoneal E1A-Lipid Complex (1:3) with Combination Chemotherapy in Women with Epithelial Ovarian Cancer** **Initial; Event: Hypotension.** **Patient is a 65+ yo F under treatment for Ovarian cancer w/ hist of cardiovascular disease and hypertension. Allergic to PCN and codeine, and exhibits a type 1 hypersensitivity to Taxol, requiring steroid pre-loading. 4 hrs post-admin of E1a DNA-Liposome, pt complained of nausea, dizziness, dyspnea & chest pain. Later complained of abdominal pain & cramping. BP: 88/50. Pt admitted for IV hydration. BP normalized w/in 30 min. Causality of hypotension deemed possibly associated with IND product.**	**1**
67	**1/28/00**	**9910-350** **Alberts *et al.*** **Sponsor: Targeted Genetics**	**Follow Up1: [see ID #66 above].** **Pt temperature spiked to 39.5 C for 8-24 hrs post E1a-liposome admin. Pt defervesced on day-2 and received Taxol and Carboplatin on d-2 & d-3 w/o incident. Symptomatology (nausea, vomiting, pain and fever) is expected. Event hypotension considered unexpected w/ subsequent amendment of investigator brochure. Event causality considered "probable".**	**0**

			TOTAL EVENTS REPORTED:	**30**