
**Gene Transfer Safety Assessment Board
Adverse Event Report
NIH Office of Biotechnology Activities
March 2014**

Protocol Number: 965

Protocol Title: **Adoptive Transfer Of Autologous T Cells Targeted To Prostate Specific Membrane Antigen (PSMA) For The Treatment Of Castrate Metastatic Prostate Cancer (CPMC)**

DocID#	Receipt Date	Event Description
11969	08/13/2013	Subject developed fever (approximately 104°F) several hours after T cell infusion. Subject took Tylenol and his fever resolved. Subject was admitted the next day for overnight observation. Upon admission, intravenous antibiotics were started due to the subject's neutropenia (low white blood cell count), but blood and urine cultures were found to be negative and subject's fever resolved. Subject remained afebrile and was discharged in stable condition.
11970	08/13/2013	Subject developed fever and chills several hours after T cell infusion and presented to an Urgent Care Center. Subject was admitted for further evaluation and was found to be warm to touch with diffuse redness of his body and diaphoresis (sweating). Subject was treated with Tylenol and intravenous antibiotics (Unasyn) and after fever reached 39°C it improved and he became afebrile the next day. Chest X-ray was performed and showed possible pneumonia versus partial lung collapse (atelectasis). Urinalysis was negative and cultures were taken. A single positive blood culture from his central venous catheter tested positive for coagulase negative staphylococcus, but since multiple other blood cultures from the catheter were negative it was thought to be a contaminant and antibiotics were stopped. Subject remained afebrile and was discharged two days after the admission in stable condition.

Protocol Number: 985

Protocol Title: A Phase I Trial of Precursor B Cell Acute Lymphoblastic Leukemia (B-ALL) Treated with Autologous T Cells Genetically Targeted to the B Cell Specific Antigen CD19

DocID#	Receipt Date	Event Description
12033	01/15/2014	<p>Subject developed low-grade fever on the day of the his second chimeric antigen receptor (CAR) T cell infusion and one day after his first T cell infusion. The next morning, subject developed difficult speech and a change in mental status, including loss of attention and loss of short-term memory. Neurology was consulted. A head CAT scan was normal. Subject was intubated the next day for airway protection due to his depressed neurologic status. Following intubation, subject developed hypotension (low blood pressure) that required administration of medicines that that support blood pressure (pressors).</p> <p>The following day, his blood pressure became markedly low with a systolic blood pressure in the 40's to 60's despite medical support. Tocilizumab (anti-IL6 receptor antibody) and steroids were given to terminate the action of the infused CAR T cells. An echocardiogram showed new depressed left ventricular function with an ejection fraction (EF) of 35% (normal >55%). Troponin blood test was not elevated. Despite maximum supportive care, the following day the subject developed multi-organ system failure presumably from hypoperfusion.</p> <p>The subject suffered cardiac arrest and died.</p>

Protocol Number: 1060

Protocol Title: A Phase I/II, Open Label Study of Ad-RTS-hIL-12, an Adenovirus Vector Engineered to Express hIL-12, in Combination with an Oral Activator Ligand, in Subjects with Unresectable Stage III or IV Melanoma.

Extension Study: An Open-Label Extension Study of Ad-RTS-hIL-12, an Adenovirus Vector Engineered to Express hIL-12, in Combination with an Oral Activator Ligand, in Subjects Who Completed Protocol ATI001-101 with Evidence of Ongoing Clinical Benefit" (ATI001-101-EXT)

DocID#	Receipt Date	Event Description
12022	01/02/2014	Subject was previously admitted for a change in mental status, anemia and high serum calcium levels following dosing with the gene transfer agent and activator ligand. Subject was discharged to a rehabilitation facility but returned less than a week later with decreased mental status characterized as encephalopathy. An infectious etiology was not found although subject did have slight elevations in temperature. Brain imaging did not show any acute changes and the cerebral spinal fluid was significant for increased protein and histiocytes (cells). Subject was treated with high dose steroids and his mental status improved, however upon tapering of the steroids subject developed signs of confusion again. Subject's condition improved and he was discharged to a rehabilitation facility approximately 10 days after re-admission for altered mental status. A clear etiology for the altered mental status was not found.
12019	12/26/2013	Six days after administration of the study drug and on the day of administration of the activator ligand subject was admitted to the hospital complaining of worsening ascites (fluid in the abdomen) resulting in abdominal discomfort and dyspnea (shortness of breath). Subject was also more confused than usual and found to have hyponatremia (low serum sodium). A paracentesis was performed removing more than seven liters of fluid from his abdomen, which improved his abdominal discomfort and dyspnea, but worsened the hyponatremia decreasing his serum sodium further from 120 to 111 mEq/L (normal range: 136 - 145 mEq/L). Subject was treated with normal saline intravenous fluids and sodium tablets and transferred to the intensive care unit on the next day. A rise in his creatinine (worsening kidney function) was also observed. His urine sodium was very low suggesting intravascular volume depletion likely worsened by paracentesis. His altered mental status was likely due to hyponatremia. Subject was also treated with albumin as well as additional normal saline and eventually his hyponatremia, mental status, and kidney function improved. Subject was discharged home five days after he was admitted. On follow up visit approximately one week after his discharge the subject's serum sodium and kidney function had normalized and his mental status was back to his baseline.

Protocol Number: 1101

Protocol Title: **A Randomized, Double-blind, Phase 3 Efficacy Trial of PROSTVAC ± GM-CSF in Men With Asymptomatic or Minimally Symptomatic Metastatic, Castrate-Resistant Prostate Cancer**

DocID#	Receipt Date	Event Description
12041	02/11/2014	Approximately two weeks after dose of study agent (either the fowlpox vector with the PSA antigen and co-stimulatory genes or the empty fowlpox vector), the subject was seen by a general practitioner. The subject reported symptoms of fever, nausea, vomiting and blood in his urine. Subject received a flu vaccine on the same day. The principal investigator saw the subject in an out-patient clinic the next day and laboratory tests revealed acute renal failure and severe thrombocytopenia (low platelets). Subject was also diagnosed with urinary retention. The final diagnosis was hemolytic uremic syndrome. Subject recovered.
12047	02/21/2014	Subject was admitted to hospital with a "severe systemic reaction" with lightheadedness, malaise, abdominal pain, nausea and vomiting about three days after receiving the gene transfer agent. The next day, the subject's symptoms abated and he was discharged from the hospital. As this study is blinded, it is not clear which study agent the subject received. In this study the placebo is a fowlpox vector without the PSA antigen and costimulatory molecule.

Protocol Number: 1161

Protocol Title: **A Phase I Feasibility and Safety Study of Cellular Immunotherapy for Relapsed Pediatric CD19+ Acute Lymphoblastic Leukemia Using Autologous T-cells Lentivirally Transduced to Express a CD19-Specific Chimeric Antigen Receptor**

DocID#	Receipt Date	Event Description
11987	11/12/2013	Subject was admitted to hospital with low grade fever and neutropenia (low white blood cell count) four days after receiving the chimeric antigen receptor (CAR) T cell infusion. The next day subject developed severe hypotension (low blood pressure) and was treated with intravenous fluids and a unit of packed red cells for anemia. Hypotension persisted and he was transferred to the intensive care unit and started on epinephrine, which was later switched to norepinephrine. Serum cytokine levels were measured and were found to be elevated (i.e., IL-6, IL-8, IL-10, and INFgamma). Subject was treated with Tocilizumab (anti-IL-6 receptor antibody) and his symptoms improved rapidly. Subject was discharged in stable condition one week after admission to the hospital.

Protocol Number: 1163

Protocol Title: **A Phase II, Randomized, Open Label, Parallel Arm Study to Evaluate the Safety and Efficacy of rAd-IFN/Syn3 Following Intravesical Administration in Subjects with High Grade, BCG Refractory, Relapsed or Resistant Non-Muscle Invasive Bladder Cancer (NMIBC)**

DocID#	Receipt Date	Event Description
12016	11/29/2013	One day after receiving the gene transfer agent by intravesicular administration into the bladder, the subject developed bloody diarrhea and an elevated white blood cell count (mainly neutrophils). Subject received intravenous fluids and was released within two days when the diarrhea resolved and the blood counts returned to baseline.

Protocol Number: 1167

Protocol Title: **A Phase 2b, Double-Blind, Placebo-Controlled, Multinational, Multicenter, Randomized Study Evaluating the Safety and Efficacy of Intracoronary Administration of MYDICAR® (AAV1/SERCA2a) in Subjects with Heart Failure**

DocID#	Receipt Date	Event Description
11996	11/20/2013	Subject experienced heart failure exacerbation. Subject was treated with intravenous diuretic medicine and his symptoms improved.

Protocol Number: 1189

Protocol Title: **A Phase II, Randomized, Open Label Study of Ad-RTS-hIL-12 Monotherapy or Combination with Palifosfamide-tris in Subjects with Recurrent/Metastatic Breast Cancer and Accessible Lesions**

DocID#	Receipt Date	Event Description
12035	01/22/2014	<p>Two days after intratumoral injection of the study drug, subject was found to have abnormal labs, which included low white blood cell counts. The following day, subject presented to the clinic with lethargy, headache, lightheadedness and a low blood pressure (BP) of 80/60mm Hg. Subject went to the emergency room and was treated with intravenous fluid and the BP improved. The subject additionally reported new pain in the thighs, together with shivering and vomiting. Subject was admitted to the hospital for hypotension (low blood pressure), neutropenia (low white blood cell count), vomiting, and thigh pain.</p> <p>Treatment included fluids, and medications to relieve nausea and vomiting. The subject developed a fever and antibiotics were begun. A computerized tomography (CT) of the abdomen noted previous findings of skeletal and liver metastasis with a new small pleural effusion and a small amount of fluid in the pelvis. Subject also reported new onset of back pain and reflux symptoms with continuing abdominal pain, nausea and vomiting. Antibiotics were discontinued when no clear source of infection was found. On day six of hospitalization the subject's gastrointestinal symptoms and pain improved. It was thought that the subject had a systemic cytokine response related to the study agent, but cytokine levels were not measured. Subject was also transfused with two units of packed red blood cells before being discharged from the hospital and was withdrawn from the study.</p>
