
**Gene Transfer Safety Assessment Board
Adverse Event Report
NIH Office of Biotechnology Activities
September 2013**

Protocol Number: 799

Protocol Title: **A Safety and Efficacy Trial of Vaccine Boosting with Lethally Irradiated Allogeneic Pancreatic Tumor Cells Transfected with the GM-CSF Gene for the Treatment of Pancreatic Adenocarcinoma**

DocID#	Receipt Date	Event Description
11797	06/27/2013	Subject has been receiving the gene transfer vaccine since 2003 and had received twelve doses prior to the event. Shortly after the most recent vaccine, subject became lightheaded and dizzy. The subject recovered. No etiology for these symptoms were found, however, it was noted that when subject's systolic blood pressure is < 110 systolic he feels lightheaded.

Protocol Number: 846

Protocol Title: **A Phase I, Open-Label, Dose Ranging Study to Assess the Safety and Distribution of Single or Multiple Doses of VB-111 in Patients with Advanced Metastatic Cancer**

DocID#	Receipt Date	Event Description
11785	05/29/2013	Subject became dizzy and the subject's blood pressure dropped below 70mm/Hg systolic within eight hours of receiving third dose. The subject received the first two doses without any low blood pressure or other complication. The subject recovered.

Protocol Number: 901

Protocol Title: **Adoptive Transfer of MART-1 F5 TCR Engineered Peripheral Blood Mononuclear Cells (PBMC) after a Nonmyeloablative Conditioning Regimen, with Administration of MART-126-35-Pulsed Dendritic Cells and Interleukin-2, in Patients with Advanced Melanoma**

DocID#	Receipt Date	Event Description
11791	06/12/2013	Subject developed a cough and chest x-ray showed patchy infiltrates during the course of chemotherapy and MART-1 DCs cell infusion. Subject also developed a blood clot during this time. These symptoms progressed and subject was admitted to the intensive care unit with increasing difficulty breathing about ten days after receiving the cells. Subject developed acute anemia and suffered a cardiopulmonary arrest and later died, after a decision was made to provide comfort care only. Autopsy revealed progressive disease and a retroperitoneal bleed, likely in part due to the anticoagulation medication given for the clot.

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
11780	05/15/2013	Subject was infused with study drug one day after receiving cyclophosphamide. Subject had no adverse symptoms and was discharged home. Subject experienced chills, fever and flu-like symptoms after arriving home. Subject reported to an urgent care center with mild fever and moderate low blood pressure (BP), and was treated with intravenous fluids and antibiotics. The low blood pressure responded to fluids but fever increased to moderate overnight despite anti-inflammatory medication. Subject was admitted to the hospital. Fever in the absence of neutropenia (low white blood cell count) and low blood pressure are expected side effects of T cell infusion and are related to treatment with autologous T cells, which can precipitate a cytokine release syndrome consistent with these symptoms.

Protocol Number: 1019

Protocol Title: **A Phase IIA Open-Label Study to Assess the Safety and Efficacy of a Single or Multiple Intravenous (IV) Dose of VB- 111 in subjects with Advanced Differentiated Thyroid Cancer (DTC)**

DocID#	Receipt Date	Event Description
11813	07/17/2013	Several days after the first dose of the study agent, the subject was admitted after experiencing an increase in cough and an episode of hemoptysis that resolved without intervention. Subject also had an increase in the size of the thyroid mass as noted on imaging. Subject recovered from the acute event but developed progressive disease and died several months later.

Protocol Number: 1037

Protocol Title: Phase I/II Study of Metastatic Melanoma Using Lymphodepleting Conditioning Followed by Infusion of Tumor Infiltrating Lymphocytes Genetically Engineered to Express IL-12

DocID#	Receipt Date	Event Description
11828	08/09/2013	<p>Six months after receiving the gene modified cells, the subject returned with complaints of increased shortness of breath with exertion and fatigue. Lab tests revealed decreased hemoglobin and elevated creatinine (a blood test that measures kidney function). Subject was treated with packed red blood cells and nephrology was consulted. Subject was admitted to the hospital and kidney ultrasound revealed moderate bilateral renal sinus lipomatosis. No other abnormalities were found. In addition, subject was noted to have elevated blood pressure, 160s to 170s systolic over 80s to 90s diastolic, and was treated with Losartan. Due to a worsening creatinine (peaked to 3.37 [NL 0.6-1.5]). Subject underwent a kidney biopsy, revealing thrombotic microangiopathy. Subject's creatinine began to trend downward and subject was discharged home. In addition, mild hypoxia (low blood oxygen levels) was documented on this admission.</p> <p>Subject returned three months later for complaints of severe dyspnea on exertion and fatigue, which were partially disabling and subject was admitted for evaluation. A pulmonary function test revealed severe gas transfer abnormality with a DLCO of 25% predicted. Subject was placed on oxygen with improvement of symptoms. Transthoracic echocardiogram showed decreased left ventricular ejection fraction with no evidence of pulmonary hypertension, confirmed by right heart catheterization. A ventilation perfusion scan showed low probability of pulmonary embolus (clot). Bilateral lower extremity duplex ultrasound showed no evidence of deep vein thrombosis (clot). Subject underwent a video assisted thoracic surgery for lung wedge biopsy. Final pathology report from the lung biopsy is pending; however, preliminary review suggests an interstitial pneumonitis. Subject was discharged with home oxygen with plans to return in one month for evaluation of clinical symptoms and treatment response.</p> <p>About two months later, repeat pulmonary function testing showed significant improvement but the subject still required supplemental oxygen. Subject's creatinine stabilized but did not return to normal. Subject will continue to be followed.</p>
11831	08/15/2013	<p>Subject, who had a history of liver metastases and increased liver enzymes after receiving anti-PD-L1, developed significant elevations in liver enzymes about ten days after receiving the IL-12 modified T cells. The AST and ALT peaked above 5000 approximately and the bilirubin reached 10.6. Subject was treated with an anti-IL12 (ustekinumab) agent injection, campath, steroids and plasmapheresis. Subject recovered and at follow-up about one month later all liver enzyme tests had normalized. The liver biopsy revealed signs of hepatocyte damage and macrophage infiltration.</p>

Protocol Number: 1056

Protocol Title: A Phase I, Dual, Cohort, Two Site, Clinical Trial Evaluating the Safety and Activity of Redirected Autologous T-cell Expressing a High Affinity TCR Specific for MAGE-A 3/6 or NYESO-1 Administered Post ASCT in Patients With Advanced Myeloma

DocID#	Receipt Date	Event Description
11787	06/05/2013	<p>About one month after bone marrow transplant and gene-modified T-cell infusion, the subject developed life-threatening low platelets, which the investigator deemed immune-mediated (post-transplant idiopathic thrombocytopenic purpura or immune mediated thrombocytopenia) and related to the T-cells. Subject received platelet transfusions and intravenous immune globulin.</p>

Protocol Number: 1089

Protocol Title: Phase I Trial of Attenuated Vaccinia Virus (GL-ONC1) Delivered Intravenously with Concurrent Cisplatin and Radiotherapy in Patients with Locoregionally Advanced Head and Neck Carcinoma

DocID#	Receipt Date	Event Description
11837	08/01/2013	On the same day that the subject received the second dose of study drug, he experienced weakness, chills and vomiting. Subject went to hospital via ambulance and was admitted for vomiting and acute kidney failure. Upon assessment, laboratory tests showed elevated creatinine suggesting acute renal failure. The investigator determined that the subject had a myocardial infarction, which was the cause of acute renal failure. Cardiac enzymes were elevated. In the opinion of the investigator, the event of myocardial infarction with acute renal failure and emesis was considered severe and possibly related to the study medication. However, because subject had cardiac risk factors, including age, smoking and hypertension, the investigator eventually changed the attribution to unrelated.

Protocol Number: 1108

Protocol Title: A Phase 2b Randomized Open-Label Trial of JX-594 (vaccinia GM-CSF/TK-deactivated virus) Plus Best Supportive Care Versus Best Supportive Care In Patients With Advanced Hepatocellular Carcinoma Who Have Failed Sorafenib Treatment (TRAVERSE)

DocID#	Receipt Date	Event Description
11808	07/03/2013	<p>About three hours post intravenous infusion of study drug, subject developed life-threatening respiratory distress requiring intubation and was admitted to the hospital. A bronchoscopy showed a left pulmonary metastasis occluding the left mainstem bronchus. This was treated by interventional pulmonology with restoration of bronchial patency and re-expansion of the left lung. Subject was transferred to intensive care unit. Over the latter course of the night, the subject's oxygenation worsened and a second flexible bronchoscopy operation was done for bronchial dilation, excision of tumor, biopsy, and release of stenosis from the tumor. Subject was taken off the study.</p> <p>The event respiratory distress (Common Toxicity Grade 4) was reported by the investigator as probably related to the study drug and study procedure.</p>
11773	05/06/2013	<p>Approximately three days after receiving the study dose, subject was found to have a low serum hemoglobin and was admitted to hospital for severe anemia (low red blood cell counts). After transfusion with two units of red blood cells, the event was considered resolved and the subject was discharged.</p> <p>Ultrasonography, complete blood count and vital signs did not reveal an etiology for the anemia. The investigator believed the decrease in hemoglobin was secondary to post treatment JX-594 inflammation and suppression of bone marrow in conjunction with possible hemodilution rather than bleeding. Suspected alternative cause for the event was reported as possible internal tumor bleeding after the intratumoral injection of JX594. However, no active bleeding was revealed using ultrasonography.</p>
11818	07/24/2013	<p>Subject developed severe hypotension down to approximately 70/40mm/Hg and shortness of breath about six hours after receiving the second intratumoral dose of the gene transfer agent. The subject also developed a fever. Subject required intravenous vasopressor medication to raise the blood pressure. Subject recovered and was discharged.</p>
11807	07/01/2013	<p>Subject with extensive cardiac disease. Subject developed an acute episode of heart failure requiring admission to the intensive care unit (ICU). Unfortunately, while in the ICU subject developed a number of complications, including hospital acquired pneumonia, sepsis and acute renal failure. Subject was discharged to hospice care.</p>
11783	05/24/2013	<p>Subject developed anemia (Common Terminology Criteria for Adverse Event Grade 3) after the third intratumoral dose. The subject was hospitalized for the fourth intratumoral dose of study drug. Subject's fourth intratumoral injection was completed without complications. Subject was treated with Fentanyl. On the same day, subject experienced low systolic blood pressure with recovery following treatment with intravenous normal saline and albumin. The investigator stopped the subject's opioid analgesic and propranolol. Subject again developed low blood pressure and decreased urine output. Subject was pre-treated with norepinephrine to support blood pressure with improved urine output.</p> <p>An electrocardiogram showed normal sinus rhythm and an echocardiogram revealed normal cardiac function without wall motion abnormality suggestive of underlying cardiac disease. Subject received intravenous diuretic and anti-anxiety medication to control insomnia and agitation. Thereafter, subject continued to receive vasopressor support intermittently.</p> <p>The hypotension completely resolved and the subject was discharged from the hospital.</p>

11806	07/03/2013	Subject developed altered mental status changes with no other neurological findings about 25 days after the last dose of the study agent. Subject was diagnosed with hepatic encephalopathy and did not improve. Palliative care was provided and subject died about a week later. Subject had very advanced disease with multiple liver tumors.
11799	06/27/2013	Subject had very low blood pressures (down as low as approximately 70's/40's) for more than 24 hours following dosing with study agent and required almost seven liters of intravenous fluids. Notably, on the morning of dosing, blood pressure medications were given for the subject's underlying diagnosis of high blood pressure and the baseline systolic blood pressure was just below 100. Subject recovered and subsequently received an intratumoral injection of the study agent without any further problems with low blood pressure. Subject's blood pressure medications were held before this last injection.
11810	07/05/2013	On the same day as the intratumoral dosing of study agent, subject developed low blood pressure and rigors. The site reported that the subject started to experience low blood pressure but systolic blood pressure remained above 100mm/Hg. The subject was subsequently admitted to the hospital for further observation and blood pressure dropped to about about 70/40mm/Hg. Vasopressor (medications that raise blood pressure) treatment was not required and there was no evidence of bleeding as the reason for the drop in blood pressure. Treatment for the events included albumin 25% intravenously, and intravenous fluids. Additional treatment included acetaminophen for fever, and midazolam, fentanyl, and dimenhydrinate for rigors and nausea.
11814	07/18/2013	Subject developed nausea and vomiting eight days after the last dose of study drug. Two days later, due to decreased ability to eat or drink without vomiting, the subject was admitted to the hospital. He was also noted to have weakness and confusion at the time of admission. According to the principal investigator (PI), treatment of underlying diabetes had become problematic because nausea and vomiting led to decreased oral intake. Per the PI, confusion may have been due to the subject's low blood sugar or due to underlying liver disease. In addition, the PI attributed weakness to vomiting and diabetes. Magnetic resonance imaging demonstrated a new tumor (unspecified location). The subject remained on study.
11815	07/19/2013	On the first day of study agent dosing, the subject 's hospitalization was prolonged due to severe low blood pressure (hypotension). Prior to administration of study agent, the subject was given intravenous fluids and received acetaminophen for premedication per protocol. Intravenous norepinephrine was started the next day when blood pressures dropped into the 80's/60's mm/Hg. Thereafter, the subject's systolic blood pressure improved and the subject was discharged on the next day. The event of hypotension was considered resolved. No action was taken with study agent due to the event.

Protocol Number: 1147

Protocol Title: Phase I Study of T Cells Expressing an Anti-CD19 Chimeric Receptor in Children and Young Adults with B Cell Malignancies

DocID#	Receipt Date	Event Description
11805	07/02/2013	<p>Five days after the subject received the anti-CD19 T cells, he developed fevers and blood tests showed a rising C-reactive protein (CRP). Subject developed a widened pulse pressure (the differential between systolic and diastolic blood pressures) concerning for cytokine release syndrome (CRS).</p> <p>Subject was closely monitored and remained febrile but with adequate blood pressures. He had episodes of hypotension (low blood pressure) that improved with normal saline fluid boluses. On Day +8 after the CAR T cells were administered, the decision was made to transfer the subject to the intensive care unit (ICU) for supportive care after his low blood pressure did not respond to repeated fluid boluses.</p> <p>While in the ICU the subject received normal saline boluses and a vasopressor medicine infusion was initiated for blood pressure support. Tocilizumab (an antibody against IL-6 receptor) was also initiated on Day +8 after CAR T-cells per established protocol, once the patient failed intravenous fluid therapy for his hypotension. His fever curve immediately improved and over the next 36 hours, the subject was completely weaned off of the vasopressor medicine.</p> <p>Two days after receiving tocilizumab, subject developed visual hallucinations (mostly visualizing family members not present). At first, he was aware that he was hallucinating but then was not aware: serum IL-6 levels increased dramatically during this time. . By the twelfth day after the CAR T-cell administered, the hallucinations had completely resolved. Subject was transferred from the ICU to the inpatient unit and had complete resolution of cytokine release syndrome and neurological symptoms.</p>

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
11804	07/02/2013	<p>Five days after T cell infusion, subject experienced severe hypotension (low blood pressure) and fever requiring intensive care unit (ICU) admission and medications to support the subject's blood pressure. No infection was identified as a source of the subject's symptoms. Studies showed that 30% of the T-cells in the subject's bone marrow aspirate were gene modified. Because no infectious etiology was found to explain the fever and low blood pressure, and the positive response to the experimental therapy, including persistence of the subject's CAR+ T-cells in the marrow, the investigator concluded that the T cells were probably responsible for this event. Subject is recovering.</p>
