

---

---

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

---

---

Protocol Number: 738

Protocol Title: **A Phase I Dose Escalation Study of Intratumoral Herpes Simplex Virus-1 Mutant HSV1716 in Patients with Refractory Non-Central Nervous System (Non-CNS) Solid Tumors.**

DocID#	Receipt Date	Event Description
12053	03/04/2014	Subject had advanced rhabdomyosarcoma. About two weeks after intravenous dosing, the subject was discovered at home in cardiac arrest. The suspected cause was gastrointestinal hemorrhage likely from tumor erosion into the esophagus. A possible role for the study agent could not be definitively ruled out due to the timing of the event relative to dosing.

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
12077	04/14/2014	Subject developed neutropenic fever following chemotherapy and study drug administration. One week after T cell infusion subject started having seizures despite prophylaxis with anti-seizure medication. Subject was transferred to the intensive care unit and placed on a respirator (breathing machine) to protect the airway. Subject was suspected of having a cytokine release syndrome, which can present with seizure and was treated with high dose steroids and tocilizumab (anti-IL-6 receptor antibody). Subject's fever resolved promptly after these treatments, but subject continued to have intermittent seizures and did not improve. Subject died approximately three weeks after the study drug administration. An autopsy showed no evidence of leukemia or infection in the brain but noted some injury in the hippocampus and amygdala (parts of the brain) likely due to seizure activity. The cause of seizures remained unclear, but the role for the study drug in causing the seizures could not be ruled out.

---

Protocol Number: 1003

Protocol Title: CD19-specific T Cell Infusion in Patients with B-Lineage Lymphoid Malignancies after Allogeneic Hematopoietic Stem-Cell Transplantation

---

DocID#	Receipt Date	Event Description
12071	03/28/2014	Subject with pre-existing history of liver dysfunction from chemotherapy and fatty liver received CAR T cells and developed steroid refractory, progressive liver failure due to graft-versus-host disease. The subject was withdrawn from the study.

---

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
12068	03/21/2014	Subject had stem cell transplant, and two days later had T-cell infusion with study agent, and tolerated both treatments well. Approximately two weeks later she complained of some fatigue and loss of appetite. Later she was found to have mucosal and skin yeast infections. Subject developed a low grade fever and was hospitalized for workup and management of the fever. Subject was treated with antimicrobials and was given fluids. Subject improved and was discharged from the hospital one day after admission.

---

Protocol Number: 1057

Protocol Title: Phase I study to assess the safety and activity of enhanced TCR transduced autologous T cells against cancer-testis antigens in metastatic melanoma

---

DocID#	Receipt Date	Event Description
12061	03/14/2014	Four days after the study drug administration and approximately a week after chemotherapy subject developed fever, fatigue, and low blood cell counts. Subject was admitted to the hospital and treated with antimicrobials. The next day subject was noted to have some swelling around the eyes with rising fevers, and later developed a mild skin rash suggestive of a drug reaction. The labs also revealed mildly elevated liver enzymes. No obvious source of infection was identified. The low blood cell counts were thought to be related to chemotherapy, but the role of the study drug in causing the fever could not be ruled out.

---

---

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
12067	03/20/2014	A few days after the study drug administration and the last dose of study activator ligand, subject presented to the clinic. Subject was found to have a fever, elevated liver function tests, low white blood cell count and low absolute neutrophil count. The subject was admitted to the hospital and the adverse events resolved in a few days. The study drug and activator ligand were discontinued in response to the above adverse events.

---

Protocol Number: 1092

Protocol Title: Administration of Haploidentical Donor T Cells Gene Transduced with the Inducible Caspase-9 Suicide Gene (DOTTI)

---

DocID#	Receipt Date	Event Description
	03/13/2014	This young subject with myelodysplastic syndrome that developed after treatment for another tumor, was treated with the study drug (donor T cell infusion engineered with suicide gene) while he was having hemorrhagic cystitis (inflammation of urinary bladder) due to a viral infection, which was being treated in the hospital. He was discharged home approximately a week after the study drug administration in stable condition. Five days later he was found to have worsening hematuria (blood in urine) with blood clots, abdominal pain and vomiting. He was admitted to the hospital and treated with anti-viral medications and discharged home three days later. The next day he was readmitted to emergency room with fever, vomiting, and diarrhea and was started on antibiotics. He continued to have high fevers and developed a diffuse rash over his face, neck and trunk. He was thought to have acute graft-versus-host disease (GVHD), with rejection of donor transplanted T lymphocytes (immune cells). Subject was treated with the drug that triggers the Caspase 9 suicide gene that stops the effects of the transplanted T cells, with rapid improvement of his fever and rash. He was also found to have a respiratory viral infection and was treated with inhaled Ribavirin and discharged home with improved condition about ten days after his last admission.

---

---

Protocol Number: 1118

Protocol Title: Phase I, open label, dual cohort, triple center clinical trial evaluating the safety and efficacy of autologous T cell expressing enhanced TCRs specific for Mage-A3/6/B18 or NY-ESO-1/LAGE in patients with recurrent or treatment refractory ovarian cancer

---

DocID#	Receipt Date	Event Description
12066	03/19/2014	This subject with advanced metastatic ovarian cancer developed mild nausea, decreased appetite, and fatigue after chemotherapy and few days before the study drug administration. Later she developed neutropenia (low white blood cell count) and fever two days after the study drug administration. Her chest X-ray was abnormal suggesting a possible pneumonia, but difficult to interpret because she had metastatic disease in her chest at the area of the abnormal findings. She was treated with antibiotics and remained stable.

---

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
12049	02/21/2014	Subject experienced neutropenia (low white blood cell count) almost two months after receiving chemotherapy and T-cells. This was unexpected given the length of time between the preoperative chemotherapy and the event of neutropenia. Subject recovered after being given medicine to raise the white blood cell count. It was unclear whether this was due to the antibiotic prophylaxis given to prevent infection or the gene modified T cells.
12050	02/21/2014	Subject developed severe cytokine release syndrome a few days after study drug administration that resulted in a cardiac arrest. Subject was resuscitated and given steroids and tocilizumab (anti-IL-6 receptor antibody) and eventually recovered with aggressive resuscitation and care. At subject's three month follow-up, there was a complete remission of the leukemia.
12051	02/21/2014	Subject had a cytokine release syndrome characterized by fevers, chills and low blood pressure. Subject's low blood pressure did not respond to intravenous fluids but subject did recover after tocilizumab (anti-IL-6 receptor antibody).
12102	02/12/2014	Subject developed cytokine release syndrome manifested by fever, chills, and low blood pressure that was managed by intravenous fluids. Subject also developed mild visual hallucinations, which were associated with some small radiographic abnormalities on a brain MRI. Subject's symptoms resolved in five days and the brain imaging abnormality resolved in two weeks.

---

---

Protocol Number: 1182

Protocol Title: **Autologous Activated T-Cells Transduced with a 3rd Generation GD-2 Chimeric Antigen Receptor and iCaspase9 Safety Switch Administered to Patients with Relapsed or Refractory Neuroblastoma (GRAIN)**

---

DocID#	Receipt Date	Event Description
12076	03/26/2014	This pediatric subject with neuroblastoma developed fever and right leg pain few days after receiving the study drug. An enlarged and tender left inguinal (groin) lymph node was noted on exam. In addition, X-rays revealed two fractures of the right fibula (leg bone) secondary to osteoporosis. Subject was treated with antibiotics and pain medications were started. Orthopedics recommended splints for both legs and the subject was discharged home. Two days later, the subject was readmitted with fever and worsening pain in right knee and left groin, which was more swollen and red. Blood cultures were negative to date. A biopsy of the enlarged left inguinal lymph node was scheduled to evaluate for infection.

---

Protocol Number: 1201

Protocol Title: **A Phase I Trial of Autologous T-Lymphocytes Genetically Targeted to the B-Cell Specific Antigen CD19 in Pediatric and Young Adult Patients with Relapsed B-Cell Acute Lymphoblastic Leukemia**

---

DocID#	Receipt Date	Event Description
12103	05/14/2014	This young subject with leukemia developed fever and low blood pressure approximately two weeks after the study drug administration, which was thought to be related to a cytokine release syndrome (CRS). Subject was transferred to the intensive care unit few days later for respiratory distress (difficulty breathing) and was found to have pneumonia. Five days later, subject's breathing worsened and while being placed on a respirator (a machine to assist with breathing), subject suffered a cardiac arrest and was successfully resuscitated. Subject's hospital course was further complicated by low blood cell counts, kidney failure requiring several days of dialysis, and additional lung infections and ventilator dependence for respiration. Subject survived the above CRS event but subsequently died four months later from respiratory complications related to the multi-viral pneumonia and immunocompromised state without evidence of leukemia.

---

---

Protocol Number: 1208

Protocol Title: Pilot Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR $\zeta$  and 4-1BB Signaling Domains Coupled with Salvage Autologous Stem-Cell Transplantation (ASCT) in Multiple Myeloma Patients with Early Relapse/Progression after Initial ASCT

---

DocID#	Receipt Date	Event Description
12111	06/02/2014	Subject received autologous T cells expressing an anti-CD19 chimeric receptor two days after undergoing hematopoietic stem cell transplant. Three days after the T cell infusion, the subject developed fever, and the next day the subject developed hypotension, tachycardia, tachypnea, renal (kidney) insufficiency and mental status changes. Three days later, the subject was transferred to the medical intensive care unit and was intubated for respiratory distress. The presentation was consistent with cytokine release syndrome (CRS). Subject was treated with tocilizumab (anti-IL-6 receptor antibody) and high-dose steroids. Subject's condition improved and subject was extubated three days after intubation. However, the subject continued to have mental status changes consistent with a neurological process that could be related to the CRS, malignancy, or the T cell infusion. The cognitive disturbance was described as a frontal lobe syndrome and resolved after approximately three weeks.

---

Protocol Number: 1213

Protocol Title: Phase I/II Study of Immunotherapy for Advanced CD19+ B Cell Malignancies with Defined Subsets of Autologous T Cells Engineered to Express a CD19-Specific Chimeric Antigen Receptor

---

DocID#	Receipt Date	Event Description
12079	04/16/2014	This elderly subject with acute lymphocytic leukemia developed fever and confusion hours after receiving the study drug. Brain imaging showed no evidence of abnormalities and some cytokine levels were noted to be elevated suggesting a cytokine release syndrome related to the study agent. Subject had complete resolution of symptoms by the time of discharge from the hospital approximately two weeks after the study drug administration.
12110	06/02/2014	This subject with relapsed acute lymphocytic leukemia developed fever, low blood pressure, nausea, and diarrhea hours after administration of study agent. Subject was transferred to the intensive care unit and was suspected of having severe cytokine release syndrome. Subject was treated with tocilizumab (anti-IL-6 receptor antibody) with improvement of the fever and low blood pressure. However, over the next 48 hours subject's condition rapidly worsened with increasing fever, difficulty breathing, and kidney failure secondary to tumor lysis syndrome. Subject was placed on a ventilator (a machine that assists with breathing), but developed multi-organ failure. Subject passed away.

---