
**Gene Transfer Safety Assessment Board
Adverse Event Report
NIH Office of Biotechnology Activities
June 2012**

Protocol Number: 780

Protocol Title: Phase II Study of Adenovirus/PSA Vaccine in Men with Recurrent Prostate Cancer after Local Therapy

| DocID# | Receipt Date | Event Description |
|--------|--------------|--|
| 11428 | 03/16/2012 | Subject went to the emergency room at a local hospital and passed away. Because this event occurred while the subject was still on protocol, between the second and third injections, this event must be considered as possibly related to the vaccine. However, in the opinion of the attending physician at the emergency room, death was most likely due to either a pulmonary embolus or rupture of a great vessel such as the heart or aorta. |

Protocol Number: 793

Protocol Title: Pilot Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR ζ and 4-1 BB Signaling Domains in Patients with Chemotherapy Resistant Or Refractory CD19+ Leukemia and Lymphoma

| DocID# | Receipt Date | Event Description |
|--------|--------------|--|
| 11480 | 06/07/2012 | Subject developed a tumor lysis syndrome about two weeks after receiving the gene modified T cells. See Chimeric Antigen Receptor- Modified T Cells in Chronic Lymphocytic Leukemia, NEJM 365: 8 725-733, August 25, 2011. |

Protocol Number: 819

Protocol Title: **Registration Phase III Study of Lucanix™ (belagenpumatu cel-L) in Advanced Non-small Cell Lung Cancer: An International Multicenter, Randomized, Double-blinded, Placebo-controlled Study Of Lucanix™ Maintenance Therapy for Stages III/IV NSCLC Subjects who have Responded to or Have Stable Disease Following One Regimen of Front-line, Platinum-based Combination Chemotherapy**

| DocID# | Receipt Date | Event Description |
|--------|--------------|---|
| 11457 | 05/03/2012 | Approximately 227 days post study agent administration (gene transfer or placebo), the subject was diagnosed with leptomeningeal cancer, (when cancer cells spread from the original (primary) tumor to the meninges - thin layers of tissue that cover and protect the brain and spinal cord). In the opinion of the Investigator, the event of 'Leptomeningeal carcinomatosis' was considered severe and possibly related to the study drug. Lung cancer does spread to the meninges and this event may also be secondary to progression of disease. |
| 11458 | 05/03/2012 | Approximately 167 days post study agent administration, the subject was diagnosed with leptomeningeal cancer, (when cancer cells spread) from the original (primary) tumor to the meninges - thin layers of tissue that cover and protect the brain and spinal cord). In the opinion of the Investigator, the event of "Leptomeningeal carcinomatosis" was considered severe and possibly related to the study drug. Lung cancer does spread to the meninges and this event may also be secondary to progression of disease. |
| 11436 | 05/03/2012 | Approximately 288 days post last study agent administration (gene transfer or placebo), the subject was diagnosed with leptomeningeal cancer, (when cancer cells spread from the original (primary) tumor to the meninges thin layers of tissue that cover and protect the brain and spinal cord). In the opinion of the Investigator, the event of 'Leptomeningeal carcinomatosis' was considered severe and possibly related to the study drug. Lung cancer does spread to the meninges and this event may also be secondary to progression of disease. |

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 |
|--------|--------------|---|
| 11422 | 03/12/2012 | <p>Subject developed new onset of acute renal failure approximately one month after first dose of study agent. Subject was treated with normal saline and then admitted to the hospital for further kidney function evaluation. A possible cause of this event was initially thought to be secondary to prerenal azotemia in setting of dehydration from decreased oral intake, possibly with medication (ACE inhibitors) contributing. Subject received aggressive intravenous fluids (IVF) overnight, but creatinine failed to improve. A renal ultrasound did not demonstrate hydronephrosis or renal artery narrowing.</p> <p>The event of acute renal failure is considered possibly related to study agent, however, the subject has negative urine protein test which may rule out the study agent as a cause of this event.</p> |

Protocol Number: 848

Protocol Title: Phase 1 Study of Cellular Immunotherapy for Recurrent/Refractory Malignant Glioma Using Intratumoral Infusions of GRm13Z40-2, an Allogeneic CD8+ Cytolytic T Cell Line Genetically Modified To Express the IL13-Zetakine and HyTK and to be Resistant to Glucocorticoids, in Combination with interleukin-2

| DocID# | Receipt Date | Event Description |
|--------|--------------|---|
| 11419 | 03/08/2012 | Following the third infusion of the gene modified T cells in combination with interleukin 2, the subject was noted to have more difficulty walking with generalized weakness and an awkward gait. Subject was on steroids for his brain tumor. Because of concern about safety at home, subject was admitted for observation and further evaluation. The subject continued to receive the infusions of T cells. |

Protocol Number: 861

Protocol Title: Immunotherapy for Unresectable Pancreas Cancer: A Phase 1 Study of Intratumoral Recombinant Fowlpox PANVAC (PANVAC-F) plus Subcutaneous Recombinant Vaccinia PANVAC (PANVAC-V), PANVAC-F and Recombinant Granulocyte-Macrophage Colony Stimulating Factor (rHGM-CSF)

| DocID# | Receipt Date | Event Description |
|--------|--------------|--|
| 11448 | 05/11/2012 | Subject developed abdominal pain, nausea, vomiting, anorexia and fatigue shortly after receiving an injection of the gene transfer agent into the pancreatic tumor and intravenously. The symptoms led to prolongation of the hospitalization and then resolved. However, the subject was removed from the protocol. |
| 11453 | 05/04/2012 | Subject admitted to outside hospital about two weeks after the first dose of the gene transfer due to severe diarrhea. Medical workup showed some inflammation in the distal colon. Subject also received a biliary stent. However, over the next several months subject's condition continued to worsen, likely due to disease progression. |

Protocol Number: 940

Protocol Title: Assessment of the Safety and Feasibility of Administering T cells Expressing an anti-CD19 Chimeric Antigen Receptor to Patients with B cell Lymphoma

| DocID# | Receipt Date | Event Description |
|--------|--------------|--|
| 11406 | 02/16/2012 | Subject developed low blood pressure and confusion approximately one day after receiving the gene modified cells, requiring transfer to the intensive care unit. The subject recovered but the event is considered a dose limiting toxicity. |

Protocol Number: 947

Protocol Title: A Randomized Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of a Treatment with OncoVEXGM-CSF Compared to Subcutaneously Administered GM-CSF in Melanoma Patients with Unresectable Stage IIIb, IIIc or Stage IV Disease

| DocID# | Receipt Date | Event Description |
|--------|--------------|---|
| 11462 | 05/18/2012 | Approximately eight months after study agent dosing, the subject developed new small scalp lesions that were close to the melanoma lesions that had been injected with the gene transfer agent. Of note, the subject had also received prior radiation to the scalp. Biopsy revealed a plasmacytoma. Bone marrow biopsy revealed plasma cell dyscrasia. Serum protein electrophoresis showed a monoclonal IgA kappa spike consistent with monoclonal gammopathy of unclear etiology. The investigator and sponsor considered the causal relationship of the adverse event to the study drug as possibly related but confounded by prior local radiation to the scalp. |

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 |
|--------|--------------|---|
| 11415 | 03/05/2012 | Subject developed a fever within two hours of infusion of the cells and was hospitalized to rule out an infection. The fever resolved and subject was discharged. |

Protocol Number: 977

Protocol Title: Direct CNS Administration of a Replication Deficient Adeno-Associated Virus Gene Transfer Vector Serotype rh.10 Expressing the Human CLN2 cDNA to Children with Late Infantile Neuronal Ceroid Lipofuscinosis

| DocID# | Receipt Date | Event Description |
|--------|--------------|--|
| 11417 | 03/07/2012 | Subject developed new diffusion abnormalities on MRI near the regions of the brain in which the gene transfer agent was delivered. There were no apparent clinical effects. For a discussion of similar events on this protocol please see the presentation by the sponsor at the March 7, 2012, meeting of the Recombinant DNA Advisory Committee. http://oba.od.nih.gov/oba/RAC/meetings/mar2012/RAC_Minutes_03-12.pdf |
| 11435 | 04/02/2012 | Approximately 18 months post vector administration, diffusion changes were noted on subject's MRI. The subject was asymptomatic. The significance of these changes on imaging with no apparent clinical effect is not clear. For a discussion of similar events on this protocol please see the presentation by the Sponsor at the March 7, 2012, meeting of the Recombinant DNA Advisory Committee. http://oba.od.nih.gov/oba/RAC/meetings/mar2012/RAC_Minutes_03-12.pdf |
| 11456 | 05/04/2012 | Approximately 12 months post vector administration, diffusion changes were noted on the subject's MRI. The subject was asymptomatic. The significance of these changes on imaging with no apparent clinical effect is not clear. For a discussion of similar events on this protocol, please see a presentation by the Sponsor at the March 7, 2012, meeting of the Recombinant DNA Advisory Committee Meeting. http://oba.od.nih.gov/oba/RAC/meetings/mar2012/RAC_Minutes_03-12.pdf |
| 11418 | 03/09/2012 | Approximately 12 months post vector administration, diffusion changes noted on the subject's MRI. The subject was asymptomatic. The significance of these changes on imaging with no apparent clinical effect is not clear. For a discussion of similar events on this protocol, please see the presentation by the Sponsor at the March 7, 2012, meeting of the Recombinant DNA Advisory Committee Meeting. http://oba.od.nih.gov/oba/RAC/meetings/mar2012/RAC_Minutes_03-12.pdf |

Protocol Number: 1014

Protocol Title: Administration of Rapidly Generated Multivirus-Specific Cytotoxic T-Lymphocytes for the Prophylaxis and Treatment of EBV, CMV and Adenovirus Infection post Allogeneic Stem Cell Transplant (VIRAGE)

| DocID# | Receipt Date | Event Description |
|--------|--------------|--|
| | 01/26/2012 | <p>Subject is a pediatric patient with secondary acute myeloid leukemia (AML) developing after therapy for Ewing's sarcoma. Subject received a haploidentical transplant in the fall of 2011. The post transplant course was complicated by several episodes of fever with no cause found. In early January, subject was admitted for fever now accompanied by enlarged cervical lymph nodes and a rise in Epstein-Barr virus (EBV) DNA in peripheral blood. Subject was enrolled on protocol in January 2012 and received the multivirus T-cells with no immediate adverse side effects. At that time her EBV DNA was approximately 6000ug/10E6 cells. A computed tomography (CT) scan of the neck showed a poorly defined mass like lesion in the left retropharyngeal region, a soft tissue mass in the nasopharynx and left cervical lymphadenopathy. CT scan of the chest and abdomen showed no evidence of post-transplant lymphoproliferative disorder (PTLD). Biopsy of the nasopharynx mass and a cervical node confirmed the presence of the EBV-PTLD. By the time the biopsy report came back the fevers had resolved and subject was discharged.</p> <p>Subject was readmitted shortly after with a new high fever and skin rash. The rash was atypical for graft-versus-host disease (GVHD). A biopsy was non-diagnostic although it was reported it could be consistent with mild GVHD. Subject had no diarrhea or serum liver test (LFT) abnormalities. Subject's illness was not attributable to persistent EBV lymphoproliferative disorder since subject's EBV DNA remained within the normal range. An immune response to EBV was demonstrated. A follow-up CT scan showed a decrease in the size of the nasopharyngeal mass and resolution of the previously seen area of hypodensity in cervical retropharyngeal space. Although EBV DNA level was now 0, subject had an elevated polyoma virus (BK) level of 8800 in blood, and human herpes virus 6 in peripheral blood was also elevated at 4000. Broad spectrum antibiotics were started together with steroids, resulting in a reduction in fevers. At present the differential diagnosis is an additional viral infection or an inflammatory response during the response of EBV post-transplant lymphoproliferative disorder to multivirus T-cells. Therefore the fever and rash may be possibly related to infused cytotoxic T lymphocytes.</p> |
| | 04/13/2012 | <p>This 60+ year old subject is four years after a matched sibling non myeloablative transplant for mantle cell lymphoma. Post transplant course was complicated by persistent colitis with multiple colonoscopy and biopsies most recently in early 2012 showing cytomegalovirus colitis. Subject had failed multiple therapies including intravenous immunoglobulin separately and in combination. At the time of referral to this protocol, subject continued to have severe diarrhea, with 15-20 episodes per day of watery diarrhea with no blood. Subject is able to eat small amounts of food such as cereal and drink clear fluids and protein supplements and is on total parenteral nutrition (TPN). Subject tolerated the infusion of the gene modified T-cells and went home but one day later presented to the emergency room with a fever 102.5. As subject had a central venous catheter and history of infection/sepsis, the subject was admitted and started on antibiotics. The subject was discharged the following evening after all lab results and cultures were negative and the fever had resolved. However as it occurred around 60 hours after T-cell infusion, and therefore may also be possibly be related to the CTLs.</p> <p>The subject was readmitted several weeks later with a low grade fever. Once again, after all cultures were found to be negative and after the fever resolved, the subject was discharged within three days. There has been no evidence of graft-versus-host disease. The episode of fever in a patient with cytomegalovirus colitis on TPN has many possible etiologies but cannot exclude a possible relationship to the T-cell infusion.</p> |

Protocol Number: 1043

Protocol Title: **A Randomized Phase II Study to Assess the Activity of TroVax® (MVA-5T4) Plus Docetaxel Versus Docetaxel Alone in Subjects with Progressive Hormone Refractory Prostate Cancer**

| DocID# | Receipt Date | Event Description |
|--------|--------------|--|
| 11444 | 04/18/2012 | Approximately one week post gene transfer agent administration, the subject complained of headache, weakness, poor appetite, diarrhea and neck rash. The subject had not been feeling well for the last few days. Rash was vesicular, consistent with a herpes zoster. The white blood cell count was very low (neutropenia) likely from the chemotherapy. Subject was admitted to the hospital. |
| 11427 | 03/16/2012 | Approximately one month after the most recent study agent administration, the subject was hospitalized due to arm pain and a vesicular rash felt to be herpes zoster, extending from the shoulder to the arm (entire arm). The subject had received ten previous doses prior to developing the rash. The subject recovered. |

Protocol Number: 1051

Protocol Title: **A Phase I/II Single-Arm Open-Label Multicenter Study of VB-111 in Patients with Recurrent Glioblastoma Multiforme**

| DocID# | Receipt Date | Event Description |
|--------|--------------|--|
| 11423 | 03/12/2012 | Within one month of receiving the gene transfer agent, the subject was admitted to hospital for progressive weakness. The imaging studies and the subject's response to steroid treatments were suggestive of cerebral edema (swelling) as the cause of the weakness. This is likely due to disease-related edema but a possible relationship to the gene transfer agent cannot be excluded. The subject improved with steroid treatment and was discharged but within a month was diagnosed with disease progression. |

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 |
|--------|--------------|--|
| 11476 | 05/21/2012 | Four days after receiving gene modified cells and a week after stem cell transplant, the subject developed cardiac complications that led to his death. The case was discussed at the June 19, 2012, meeting of the NIH Recombinant DNA Advisory Committee. http://oba.od.nih.gov/oba/RAC/meetings/June2011/RAC_Minutes_06-11.pdf |
