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

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Protocol Number: 886

Protocol Title: Phase II Study of Metastatic Cancer that Expresses NY-ESO-1 Using Lymphodepleting Conditioning Followed by Infusion of Anti-NY-ESO-1 TCR-Gene Engineered Lymphocytes

DocID#	Receipt Date	Event Description
11631	11/30/2012	Subject died within four days of receiving the gene modified T cells after developing confusion, low blood oxygen levels (hypoxemia) and renal failure shortly after receiving the cells. Autopsy results were consistent with severe infection and multi-organ failure consistent with sepsis. The chemotherapy given on this protocol and the T cells may have been contributing factors.

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
11671	12/26/2012	Subject diagnosed with metastatic squamous cell carcinoma about a year after completing the study for melanoma. Subject had a history of squamous cell carcinoma that was diagnosed five years prior to enrollment in the study, as well as a lesion diagnosed during the study that was removed.
11692	01/03/2013	Approximately two weeks after receiving the last dose of study agent for Cycle 4, elderly subject experienced a fall at home. Subject underwent MRI and had a fracture of a rib, which was painful and was noted to have slow ambulation and balance problems. Also, a melanoma lesion on lower leg had purulent drainage, odor and was felt to be infected. The lesion was cultured and reported positive for Klebsiella oxytoca and Staphylococcus aureus. Intravenous antibiotics were administered. The subject improved and was transferred to a transitional care facility on oral antibiotics. The investigator considered the event as possibly related to the gene transfer investigational agent. Approximately six months later, the subject was discontinued from the study due to progressive disease and died.

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Protocol Number: 958

Protocol Title: **A Randomized, Double Blind, Placebo Controlled, Parallel Group, Multicenter Study Of The Safety And Response Rate Of Three Subcutaneously Administered Doses Of 5 X 10e7 Pfu RO5217790 In Patients With High Grade Cervical Intraepithelial Neoplasia Grade 2 Or 3 Associated With High Risk HPV Infection**

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DocID#	Receipt Date	Event Description
11658	09/27/2012	On Study Day 8, after receiving the second injection of investigational agent, the subject experienced lymphadenopathy (swelling in lymph nodes) that was severe and probably related to study agent. Subject had painful lymph nodes in the thigh, which was the site of the first injection and in groin. On Study Day 15, the subject still had painful lymph nodes bilaterally in the groin, more on the left and also had lymph node swelling in the neck. Subject experienced pain in leg and sensitivity in jaw and gums and complained of decreased appetite and fatigue. The third injection was delayed initially and then given on Study Day 21. The event resolved on Study Day 92. The investigator considered the event of lymphadenopathy to be probably related.

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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**

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DocID#	Receipt Date	Event Description
11639	12/11/2012	Approximately 12 months after gene transfer 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. <a href="http://osp.od.nih.gov/sites/default/files/977_Crystal.pdf">http://osp.od.nih.gov/sites/default/files/977_Crystal.pdf</a>

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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
11626	11/26/2012	<p>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. <a href="http://osp.od.nih.gov/sites/default/files/1_TCRUpdate_June.pdf">http://osp.od.nih.gov/sites/default/files/1_TCRUpdate_June.pdf</a></p> <p>Cancer Regression and Neurological Toxicity Following Anti-MAGE-A3 TCR Gene Therapy Richard A. Morgan, Nachimuthu Chinnasamy, Daniel Abate-Daga, Alena Gros, Paul F. Robbins, Zhili Zheng, Mark E. Dudley, Steven A. Feldman, James C. Yang, Richard M. Sherry, Gao Q. Phan, Marybeth S. Hughes, Udai S. Kammula, Akemi D. Miller, Crystal J. Hessman, Ashley A. Stewart, Nicholas P. Restifo, Martha M. Quezado, Meghna Alimchandani, w Avi Z. Rosenberg, w Avindra Nath, z Tongguang Wang, Bibiana Bielekova, Simone C. Wuest, Nirmala Akula, y Francis J. McMahon, y Susanne Wilde, Barbara Mosetter, Dolores J. Schendel, Carolyn M. Laurecot, Steven A. Rosenberg J Immunother □ Volume 36, Number 2, February–March 2013</p> <p>Identification of a Titin-Derived HLA-A1–Presented Peptide as a Cross-Reactive Target for Engineered MAGE A3–Directed T Cells Brian J. Cameron, Andrew B. Gerry, Joseph Dukes, Jane V. Harper, Vivekanandan Kannan, Frayne C. Bianchi, Francis Grand, Joanna E. Brewer, Minnal Gupta, Gabriela Plesa, Giovanna Bossi, Annelise Vuidepot, Alex S. Powlesland, Alison Legg, Katherine J. Adams, Alan D. Bennett, Nicholas J. Pumphrey, Daniel D. Williams, Gwendolyn Binder-Scholl, Irina Kulikovskaya, Bruce L. Levine, James L. Riley, Angel Varela-Rohena, Edward A. Stadtmauer, Aaron P. Rapoport, Gerald P. Linette, Carl H. June, Namir J. Hassan, 1 Michael Kalos, Bent K. Jakobsen <a href="http://www.ScienceTranslationalMedicine.org">www.ScienceTranslationalMedicine.org</a> 7 August 2013 Vol 5 Issue 197 197ra103</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
11635	12/04/2012	<p>Event occurred in a different study not registered with NIH/OBA.</p> <p>Subject experienced elevated serum liver enzyme tests after the fourth cycle of study agent dosing. The subject did not have a fever. Subject had pain in the right upper quadrant of the abdomen. A CAT (computed tomography) scan revealed an increase in the size of the biliary ducts implying a worsening obstruction. Subject was treated with intravenous fluids and steroids. Elevations in the serum bilirubin resolved, but the liver enzyme test for ALT was still elevated at the time of this report.</p>

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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

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DocID#	Receipt Date	Event Description
11675	01/25/2013	Approximately three weeks after the last dose of study drug, the subject went to an urgent care center complaining of headache, difficulty breathing, sharp pain in the right chest area and feeling tired. A chest x-ray was obtained and reported as inconclusive. On the same day, the subject was sent to the emergency room and admitted to the hospital for an adverse event of bilateral pulmonary embolism (blood clot in the lungs). The study drug was interrupted. The investigator reported the causality as possibly related. The Medical Monitor assessed the relationship to the investigational product as not related.

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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)

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DocID#	Receipt Date	Event Description
11645	12/18/2012	Subject was on medicine to anticoagulate (prevent the blood from clotting). This medication was held prior to the fourth administration of the vector into the tumor. However, about two weeks after that dose the subject presented with a hepatic hemorrhage. The subject was hospitalized and released, but was readmitted less than a month later with the same issue. This hemorrhage resolved but subject was taken off the study. Of note, subject had considerable hepatic metastases.
11640	12/11/2012	<p>The subject received protocol specified treatment #2 intratumoral (IT) injection into the liver without complication. The subject did, however, experience increased pain during IT injection which continued after treatment completed. Therefore, the investigator increased pain medication and started the subject on medication for anxiety.</p> <p>The subject presented with progressive mental status changes (i.e., confusion and somnolence) consistent with hepatic encephalopathy. Treatment included lactulose and discontinuation of pain medication and anti-anxiety medication. The subject's condition improved progressively and the event was considered resolved.</p> <p>Although the investigator stated he could not completely rule out some contribution of investigational product to the event, he attributed the primary cause as hepatic encephalopathy and to treatment with oxycodone and lorazepam in a subject with marginal liver function. Specifically, in the investigator's opinion JX-594 treatment caused right upper quadrant pain, which then led to the increased dose of oxycodone and the addition of lorazepam and was therefore indirectly related to the event. The investigator noted that liver cancer and cirrhosis were also alternative etiologies for these events.</p>

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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

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DocID#	Receipt Date	Event Description
11641	12/11/2012	Subject had a history of relapsed diffuse large B-Cell lymphoma with extensive disease of the paraspinal tissues as well as the thoracic spine. Five days after receiving the modified T cells, the subject developed worsening back pain and a sensation of "popping" or "cracking" in the back. Because of the extensive disease, subject was admitted to the intensive care unit for closer monitoring and pain control. New imaging revealed no changes in the lesions. It was concluded that the increase in pain was related to progression of disease, but was reported because it occurred in close temporal proximity to the administration of the T cells.