FOLLOW-UP IND SAFETY REPORT #1

1. IND NUMBER	2. AGENT NAME	3. DATE
17311	Nivolumab Talimogene laherparepvec (T-VEC, IMLYGIC)	**June 28, 2022**

4. SPONSOR

Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION	6. PHONE NUMBER
Howard Streicher, MD – Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI Helen Chen, MD – Associate Branch Chief, Investigational Drug Branch, CTEP, DCTD, NCI	240-276-6565 7. EMAIL ADDRESS ctepsupportae@tech-res.com

8a. PROTOCOL NUMBER (AE #)	8b. AE GRADE: AE
10057 (AE #2149339)	Grade 5: ~~Multi-organ failure~~ **Cardiac disorders: Cardiogenic shock**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
MA036-0058	79 years	Male

12. PROTOCOL SPECIFIED

Cycle 1, Cycle = 21 days
Talimogene laherparepvec: $10e^6$ pfu/mL intratumorally on Day 1
BMS-936558 (Nivolumab, MDX-1106): 3 mg/kg IV on Day 1
Cycle 2+, Cycle = 14 days
Talimogene laherparepvec: $10e^8$ pfu/mL intratumorally on Day 1
BMS-936558 (Nivolumab, MDX-1106): 3 mg/kg IV on Day 1

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on April 29, 2022, and received the first and only doses of nivolumab and talimogene laherparepvec on that same day (Cycle 1, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient was a 79-year-old male with Merkel cell tumor of the ~~hand~~ **right upper extremity with metastasis to his chest** who expired on May 5, 2022, due to ~~multi-organ failure~~ **cardiogenic shock** while on a Phase II trial utilizing the investigational agents nivolumab and talimogene laherparepvec. Additional information has been requested from the investigational site.

The Initial Written Report was sent to the FDA on May 26, 2022, as a 7-day report.

<u>Follow-up #1:</u>

The patient had a history of hypothyroidism, hypertension, and hyperglycemia. The patient's tumor in his right third finger was treated with cryotherapy and curettage in January 2018, with recurrence in June 2018. It then spread to the right sided lymph nodes for which he underwent salvage right radical axillary lymphonodectomy in November 2018, followed by adjuvant radiation therapy. The tumor then metastasized to the chest in February 2019, for which he was treated with pembrolizumab but discontinued on March 23, 2022, due to a rash. He received radiation therapy for a left chest wall lesion in October 2021, and was enrolled in the protocol therapy on April 27, 2022, with talimogene and nivolumab. Laboratory reports at enrollment were unremarkable except for a lactate dehydrogenase of 722 IU/L (reference range: 100-190 IU/L). On April 29, 2022, the patient received the first doses of the study drugs at which time he was doing well. On May 4, 2022, the patient presented to the emergency room (ER) via emergency medical services

FOLLOW-UP IND SAFETY REPORT #1

(EMS) due to complaints of increasing weakness for 3 days, which progressed to an inability to ambulate and restlessness. Upon arrival of EMS, his blood glucose was 24 mg/dL (reference range: 70-120 mg/dL), and he was given glucose. In the ER, a repeat blood glucose level was 57 mg/dL. Upon physical examination, the patient looked pale and acutely ill and was not breathing effectively. He had a rectal temperature of 34.3 °C, a blood pressure of 92/70 mmHg, a heart rate of 105 beats per minute, and a respiratory rate of 40-50 breaths per minute, and he was started on supplemental oxygen via a non-rebreather mask. New onset atrial fibrillation was also noted. Initial arterial blood gas analysis revealed severe metabolic acidosis with a pH of 6.99 (reference range: 7.35-7.45), a pCO_2 of 27 mmHg (reference range: 35-45 mmHg), a pO_2 of 360 mmHg (reference range: >=80 mmHg), and a bicarbonate of 7.9 mmol/L (reference range: 22.0–26.0 mmol/L). The patient's respiratory rate was 42 breaths per minute on 100% FiO_2 and he was temporarily placed on bilevel positive airway pressure while work up was done. Laboratory results were significant for a normal hemoglobin, hematocrit and white blood cell count with significant left shift, a platelet count of 41,000 per mcL, an INR of 3.4 (therapeutic range: 2.0-3.0), blood urea nitrogen (BUN) of 55 mg/dL (reference range: 6-26 mg/dL), creatinine of 3.85 mg/dL (reference range: 0.370-1.300 mg/dL), anion gap of 32 mmol/L (reference range: 7-23 mmol/L), CO_2 of 9 mmol/L (reference range: 21-32 mmol/L), a plasma lactic acid of 19.1 mmol/L (reference range: 0.5-2.2 mmol/L), a total bilirubin of 2.9 mg/dL (reference range: 0.0-1.0 mg/dL), alanine aminotransferase of 3,344 IU/L (reference range: 12-78 IU/L) and aspartate aminotransferase of 3,666 IU/L (reference range: 5-37 IU/L) - consistent with shock liver, C-reactive protein of 209 mg/L (reference range: 0.00-2.99 mg/L), creatine kinase of 204 IU/L (reference range: 38-183 IU/L), and a significantly elevated N-type pro B-type natriuretic peptide of 12,242 pg/mL (reference range: <=449 pg/mL) with normal troponin. His blood glucose after receiving 10 g of dextrose (D10) was 138 g/dL but had continued to dip down below 50 g/dL requiring additional doses. A COVID-19 test was negative. Urine analysis was not consistent with infection. A bedside echocardiogram showed moderate impairment of cardiac function. Preliminary blood cultures were negative. The patient was mottled with very poor intravenous access. He was started on vasopressors, stress dose steroids, and a bicarbonate drip via a left femoral central venous line. The patient was sedated and intubated to protect his airway. A chest X-ray was otherwise unremarkable. The patient was then moved to the intensive care unit where he became significantly hypotensive requiring high doses of vasopressors. No further imaging was done due to the patient's unstable condition. Despite maximal ventilator settings to compensate for his severe metabolic acidosis, the patient was in persistent and worsening metabolic acidosis and lactic acidosis. Later that night, repeat laboratory results showed a plasma lactic acid of 28.5 mmol/L, platelet count of 54,000 per mcL, INR of 4.8, blood glucose of 742 mg/dL, and an LDH greater than 1000 IU/L. During early hours of May 5, 2022, the patient's code status was changed to do not resuscitate and the patient expired. The treating physician felt that at the time of presentation, the patient likely had cardiovascular and hypovolemic shock possibly related to direct insult at the cellular level and cell death, leading to severe metabolic acidosis and significantly decreased perfusion to the kidneys, liver, and heart. An autopsy was notable for hypertensive and arteriosclerotic cardiovascular disease with hypertrophy of the heart, focal high-grade stenosis of the proximal left anterior descending coronary artery, a calcified arteriosclerotic plaque in the mid-right coronary artery, and marked arteriolonephrosclerosis. Microscopic examination of the heart revealed florid subacute myocarditis with a mixed inflammatory infiltrate comprised of polymorphonuclear leukocytes, lymphocytes, and rare eosinophils accompanied by focal necrosis of myocytes.

FOLLOW-UP IND SAFETY REPORT #1

15. ACCRUAL AND IND EXPERIENCE

~~Pending Follow-up report.~~

Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726= 9,311.
Number of patients enrolled in NCI-sponsored clinical trials using talimogene laherparepvec under NSC 785349= 115.
There have been no other cases of cardiogenic shock reported to the NCI through CTEP-AERS as a serious adverse event for nivolumab under NSC 748726.
There have been no other cases of cardiogenic shock reported to the NCI through CTEP-AERS as a serious adverse event for talimogene laherparepvec under NSC 785349.

16. ASSESSMENT

~~Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship between the multi-organ failure and the investigational agents nivolumab and talimogene laherparepvec cannot be excluded. The adverse events and attributions will be reassessed when additional information becomes available.~~

Based on the provided medical documentation and our medical and scientific knowledge, a definite relationship exists between the cardiogenic shock and the investigational agent nivolumab, and a possible relationship exists between the cardiogenic shock and the investigational agent talimogene laherparepvec.

	Cardiogenic shock
Nivolumab	**Definite**
Talimogene laherparepvec	**Possible**
Merkel cell tumor	**Unlikely**
Myocarditis	**Definite**
Cardiovascular disease	**Possible**

17. CONCOMITANT MEDICATIONS

~~Pending Follow-up report.~~

Medications taken at the time of the event included aspirin, atorvastatin, bismuth subsalicylate, ciclopirox, eye vitamin and mineral supplements, vardenafil, levothyroxine, naproxen, oxycodone/acetaminophen, verapamil, vitamin D_3, and zolpidem.

18. COMMENTS

~~Pending Follow-up report.~~