7-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
125462	**Nivolumab**	**November 18, 2021**

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	**240-276-6565**
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8a. PROTOCOL NUMBER (AE #)	8b. AE GRADE: AE
S1826 (AE #2600198)	**Grade 5: Death NOS**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
288036	**68 years**	**Female**

12. PROTOCOL SPECIFIED

Cycle = 28 days (max 6 cycles)

Doxorubicin hydrochloride: 25 mg/m^2 IV on Days 1 and 15
Vinblastine sulfate: 6 mg/m^2 IV on Days 1 and 15
Dacarbazine: 375 mg/m^2 IV on Days 1 and 15
Nivolumab: 240 mg IV on Days 1 and 15 [<18 years: 3 mg/kg (up to 240 mg) IV on Days 1 and 15]

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on October 29, 2021, and received the first and only doses of doxorubicin, vinblastine, dacarbazine, and nivolumab on that same day (Cycle 1, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient was a 68-year-old female with Hodgkin lymphoma who expired on November 6, 2021, due to unknown causes, while on a phase III trial utilizing the investigational agent nivolumab in combination with doxorubicin, vinblastine, and dacarbazine. She had a history of hypertension, atrial fibrillation, and peptic ulcer disease, and was a former smoker. On October 31, 2021, the patient was admitted for evaluation of aching, non-radiating anterior chest pain. An echocardiogram showed a left ventricular ejection fraction of 65%. A CT scan showed no signs of pulmonary embolism. On November 2, 2021, the patient was discharged home in stable condition. On November 5, 2021, the patient presented to the emergency department (ED) with complaints of chest tightness, dyspnea, abdominal pain, profound weakness, nausea, vomiting, and loose stools. Upon arrival, the patient appeared distressed. She had a blood pressure of 119/49 mmHg, a heart rate of 121 beats per minute, a temperature of 100.4°F, and an oxygen saturation (SpO_2) of 98%. Physical examination revealed mottling in her extremities and diffuse abdominal pain with diminished bowel sounds. Laboratory results were significant for a serum creatinine of 2.52, blood urea nitrogen of 57, serum glucose of 484, alkaline phosphatase of 217, aspartate aminotransferase of 56, alanine aminotransferase of 126, INR of 1.52, D-dimer of 16.6, pH of 7.19, PCO2 of 26, PO2 of 486, lactic acid of 13.1, and white blood cell band count of 14% (reference ranges and units: not provided). A chest X-ray showed no evidence of acute cardiopulmonary disease. A transthoracic echocardiogram revealed possible reduced left ventricular ejection fraction. She was started on IV fluids, dobutamine, epinephrine, norepinephrine, cefepime, and vancomycin and was admitted to the intensive care unit for further management. She was placed on bilevel positive airway pressure (BiPAP) and 8 L of oxygen via nasal cannula. Later that evening, the patient was intubated due to respiratory distress with tachypnea. On November 6, 2021, she had sudden onset of a wide-complex escape rhythm bradycardia with heart rate in

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the 30s. The patient was immediately administered advanced cardiovascular life support (ACLS) following which she had a restoration of spontaneous circulation. However, after the initial resuscitation the patient had a second bradycardic arrest. Per the family's request, resuscitative efforts were stopped. That day, the patient expired. An autopsy was not performed. The clinical evidence suggests possible sepsis or sepsis physiology, DIC, and circulatory failure possibly a result of an abdominal catastrophe. Additional information has been requested from the investigational site.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = 8,539.
There have been 122 other cases of death NOS reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.
There have been 13 other cases of sudden death NOS reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.

Adverse Event	Grade	Attribution
Nivolumab (NSC 748726)		
Death NOS (n=122)	5	1 Definite, 2 Probable, 42 Possible, 50 Unlikely, 27 Unrelated
Sudden Death (n=13)	5	9 Possible, 4 Unlikely

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the death NOS and the investigational agent nivolumab.

	Death NOS
Nivolumab	Possible
Dacarbazine	Possible
Doxorubicin hydrochloride	Possible
Vinblastine sulfate	Possible
Hodgkin lymphoma	Unrelated
Infection	Probable

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were atomoxetine hydrochloride, spironolactone, acetaminophen, docusate sodium, mupirocin nasal ointment, acyclovir, allopurinol, atovaquone, calcium carbonate-vitamin D, dexamethasone, fluconazole, metoprolol succinate, rosuvastatin, vitamin D3, esomeprazole, and duloxetine hydrochloride.

18. COMMENTS