7-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
125586	**Nivolumab**	**December 22, 2021**

4. SPONSOR

Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION	6. PHONE NUMBER
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8a. PROTOCOL NUMBER (AE #)	8b. AE GRADE: AE
EA2165 (AE #2594900)	**Grade 5: Pneumonitis** **Grade 4: Myocardial infarction**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
52357	**71 years**	**Female**

12. PROTOCOL SPECIFIED

BMS-936558 (Nivolumab, MDX-1106): 480 mg IV Q28D
Prior to addendum #1 activation:
BMS-936558 (Nivolumab, MDX-1106): 240 mg IV Q14D

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on July 19, 2021, and received the last dose of nivolumab on November 8, 2021 (Cycle 5, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient was a 71-year-old female with squamous cell carcinoma of the anal canal, who experienced a grade 4 myocardial infarction and later expired on December 4, 2021, due to pneumonitis while on a phase III trial utilizing the investigational agent nivolumab. She had a history of right breast cancer status post lumpectomy (1997) with chemotherapy and radiation therapy, hypertension, hyperlipidemia, and hypothyroidism. On November 21, 2021, the patient was brought to the emergency department (ED) by emergency medical services for progressively worsening shortness of breath. She reported fever, productive cough, diaphoresis, weakness, and fatigue. She denied any chest pain, abdominal pain, dark tarry stool, hematochezia, or hematemesis. Upon arrival, she had a blood pressure of 117/80 mmHg, a heart rate of 89 beats per minute, a respiratory rate of 31 breaths per minute, and an oxygen saturation (SpO_2) of 75%. An electrocardiogram showed non-ST elevated myocardial infarction with a left bundle branch block. Laboratory results were remarkable for a red blood cell (RBC) count of 2.79 M/µL, a hemoglobin (Hgb) level of 10.4 g/dL, a B-type natriuretic peptide (BNP) level of 383 pg/mL, a high-sensitivity troponin I level of 835 pg/mL, a blood lactate level of 5.7 mmol/L, an arterial pH of 7.456, a PCO_2 of 24.1 mmHg, an HCO_3 level of 17.0 meq/L, and an arterial PO_2 of 71.7% (reference ranges: not provided). A COVID-19 test was negative. A chest X-ray showed bilateral coarse reticular opacities suggestive of underlying pulmonary fibrosis with possible superimposed infection and/or edema. An echocardiogram showed normal left ventricular systolic function with an ejection fraction of 55-60%, moderately dilated right ventricular cavity with a mild to moderately reduced systolic function, and a mild tricuspid valve regurgitation. A CT angiogram of the chest without contrast showed no evidence of pulmonary embolism, but showed extensive patchy ground-glass opacities bilaterally. Blood cultures were obtained. She was started on IV fluids, antibiotics, and oxygen via high-flow nasal cannula (HFNC), and was admitted to the intensive care unit (ICU) for further management. On November 23, 2021, her troponin I level was 4,831 pg/mL. On November 25, 2021, the patient was afebrile, hemodynamically stable, and on 6 L of oxygen via nasal cannula (NC). However, she started to desaturate and was placed back on HFNC. On November 30, 2021, a repeat echocardiogram without contrast showed a low normal left ventricular systolic function with an ejection fraction of 50%. There was severe hypokinesis of the apical septal and apical inferior segments. On December 1, 2021, the patient complained of chest pain radiating to the back and shoulder. On December 2, 2021, the patient was more dyspneic at rest. She was unresponsive to high-dose IV steroids and was given one dose of infliximab. On December 3, 2021, a repeat chest X-ray showed significant interval worsening of

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extensive bilateral infiltrates. She was on HFNC with a Fraction of inspired Oxygen (FiO_2) of 100%. Blood cultures were negative to date. Repeat laboratory results were significant for an RBC count of 2.38 M/µL, a Hgb level of 8.7 g/dL, a BNP level of 1,465.0 pg/mL, a D-dimer level of 2,460, and a creatinine level 0.5 mg/dL. That day, per the patient's wish, her code status was changed to Do Not Resuscitate/Do-Not-Intubate (DNR/DNI). Her condition continued to deteriorate, and she wished to transition to comfort care. On December 4, 2021, the patient expired. An autopsy was not performed. 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 = 8,670.
Pneumonitis is an expected event for the investigational agent nivolumab.
There have been 13 other cases of myocardial infarction reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.

Adverse Event	Grade	Attribution
Nivolumab (NSC 748726)		
Myocardial infarction (n = 13)	4 3 2	1 possible, 1 unrelated 5 possible, 3 unlikely, 1 unrelated 2 unlikely

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a probable relationship exists between the pneumonitis and myocardial infarction and the investigational agent nivolumab.

	Pneumonitis	Myocardial infarction
Nivolumab	Probable	Probable
Anal cancer	Unrelated	Unlikely

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were fluoxetine, acetylsalicylic acid, atorvastatin, cefuroxime, levothyroxine, lisinopril, magnesium, meloxicam, pantoprazole, triamterene-hydrochlorothiazide, and valacyclovir.

18. COMMENTS

DISCLAIMER per 21 CFR 312.32(e): THIS SAFETY REPORT DOES NOT NECESSARILY REFLECT A CONCLUSION OR ADMISSION BY THE CTEP IDB MEDICAL OFFICER/SPONSOR THAT THE INVESTIGATIONAL AGENT/THERAPY CAUSED OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.