7-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
124975	**Nivolumab**	**May 5, 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
10204 (AE # 2692319)	**Grade 5: Myocarditis** **Grade 4: Myositis** **Grade 3: Cardiac troponin T increased** **Grade 3: Nervous system disorders: Myasthenia gravis** **Grade 2: Pericardial effusion**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
MA036-0013	**77 years**	**Female**

12. PROTOCOL SPECIFIED

Cycle = 4 weeks
BMS-936558 (Nivolumab, MDX-1106): 480 mg IV every 4 Weeks

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on January 07, 2021 and received the last dose of nivolumab on February 22, 2021 (Cycle 2, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient was a 77-year-old female with recurrent metastatic esophageal adenocarcinoma status post esophagectomy and chemoradiation therapy who developed grade 4 myositis, grade 3 increased cardiac troponin T, grade 3 myasthenia gravis, grade 2 pericardial effusion, and later expired from myocarditis on March 27, 2021, while on a phase I trial utilizing the investigational agent nivolumab. She had a history of hypertension, hyperlipidemia, pulmonary embolism, Crohn's disease (status post colectomy), and hypothyroidism. On February 7, 2021, the patient was hospitalized for worsening fatigue and dyspnea, underwent a video-assisted thoracoscopy (VATS) with pericardial window procedure, and was found to have left-sided hemopneumothorax. A transthoracic echocardiogram (TTE) showed re-accumulation of pericardial effusion, an ejection fraction of 55%, and a pulmonary artery systolic pressure of 24 mmHg. On March 16, 2021, she presented to the hospital for progressive weakness, nausea, dyspnea with minimal exertion, and loss of appetite over the previous 3 weeks. She also reported a loss of nearly 20% of her body weight (20 lbs.) over the past 6 months. A troponin-I test was negative. A chest x-ray showed concern for a new opacity, and she was treated with antibiotics for presumed pneumonia. That day, she changed her status to do not resuscitate/do not intubate (DNR/DNI). On March 18, 2021, following discussion with her treating physician, the patient presented to the hospital and was admitted to the neurology unit for further workup. Upon arrival, she reported having continued severe proximal muscle and neck flexion weakness, diplopia, difficulty swallowing, weak voice with slurred speech, dyspnea on exertion, productive cough, diplopia, episodic headaches, and positional vertigo. She had a blood pressure of 128/72 mmHg, a heart rate of 123 beats per minute, a respiratory rate of 16 breaths per minute and a temperature of 98.7 °F. Laboratory results were significant for a troponin level of 1405 ng/mL, N-terminal pro-brain natriuretic peptide level of 1195 pg/ml, and a creatine kinase level of 633 U/L (reference ranges: not provided). An electrocardiogram (ECG) showed sinus tachycardia, possible inferior myocardial infarction, a T wave abnormality which raised concern for anterior wall ischemia, and a prolonged QT interval vs. T-U wave fusion suggestive of myocardial disease, electrolyte imbalance, or drug effects. A chest x-ray showed bibasilar atelectasis and a similar small volume left pleural effusion. There was no evidence of

pneumothorax or pulmonary edema. She was started on intravenous immunoglobulin therapy and methylprednisolone and was subsequently transitioned to high dose prednisone. Her troponin levels initially decreased following the therapy, but later rebounded that day. Cardiology was consulted and she was given methylprednisolone 1 g IV. On March 19, 2021, an electromyography (EMG) and nerve conduction study reported concurrent immune checkpoint inhibitor myositis and myasthenia gravis; the study did not exclude concurrent myocarditis. That day, a repeat TTE showed no pericardial effusion. Also, her COVID-19 test was negative. On March 22, 2021, an ECG showed new T waves anteriorly in leads V1-V3 which raised concern for worsening myocarditis vs. cardiac ischemia. That day, her troponin levels were also noted to rise again. On March 24, 2021, a repeat echocardiogram showed an acute decrease in the ejection fraction to 40-50%, new regional wall motion abnormalities in multiple vascular distributions, and a normal right ventricular size with mildly impaired function. No pericardial effusion was noted. She was started on prednisone 1 mg/Kg daily and furosemide. Given the overall trend with rising troponins, ECG changes, and decline in left ventricular function, the differential diagnosis was broadened to include acute coronary syndrome. A coronary angiography with possible endomyocardial biopsy was recommended. The patient was transferred to cardiology for further care. On March 25, 2021, her captopril, magnesium supplement, betablockers, and statin were discontinued due to concern for myasthenia gravis flare. On March 26, 2021, the patient was taken to the cardiac catheterization lab to rule out ischemic heart disease. She acutely became hypertensive, tachycardic, and hypoxic after returning to the floor from the cardiac catheterization lab. On physical examination, she was diaphoretic and in acute distress. A repeat ECG showed sinus tachycardia with no other acute changes. There was concern for flash pulmonary edema, and she was given sublingual nitroglycerin ×2, furosemide 80 mg IV, and was placed on non-invasive ventilation (NIV). She was briefly started on a nitroglycerin drip, following which her blood pressure improved and the drip was discontinued. She remained in acute respiratory distress; the plan was to attempt to take her off NIV when she became stabilized. Her heparin drip was discontinued, and she was placed on aspirin 81 mg and mycophenolate. That day, the patient was deemed to not be a candidate for future immune checkpoint inhibitor therapies. On March 27, 2021, per the patient and her family's request, she was transitioned to comfort measures only. That day, the patient expired. An autopsy was not performed. Per the treating physician's assessment, the patient's death was due to respiratory distress caused by cardiac decompensation. 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= 7,671.
There have been 4 other cases of increased cardiac troponin T reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.
There have been 8 other cases of pericardial effusion reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726
Myocarditis, myositis and myasthenia gravis are expected events for the investigational agent nivolumab.

Adverse Event	Grade	Attribution
Nivolumab (NSC 748726)		
Cardiac Troponin T Increased (n=4)	3 1	1 Probable 3 Possible
Pericardial Effusion (n=8)	4 3 2	2 Possible 1 Probable, 1 Possible, 1 Unlikely 1 Possible, 1 Unlikely, 1 Unrelated

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16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a definite relationship exists between the myocarditis and the myositis and the investigational agent nivolumab. A probable relationship exists between the myasthenia gravis and the investigational agent nivolumab. A possible relationship exists between the increased cardiac troponin T and the pericardial effusion and the investigational agent nivolumab.

	Myocarditis	Myositis	Cardiac troponin T increased	Myasthenia gravis	Pericardial effusion
Nivolumab	**Definite**	**Definite**	**Possible**	**Probable**	**Possible**
Esophageal adenocarcinoma	**Unrelated**	**Unrelated**	**Unrelated**	**Unlikely**	**Possible**
Pre-existing pericardial effusion	**Unlikely**	**Unlikely**	**Unlikely**	**Unlikely**	**N/A**

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were acetaminophen, amlodipine-benazepril, vitamin C, vitamin D3, citalopram, vitamin B-12, docusate sodium, enoxaparin, levothyroxine, loperamide, meclizine, melatonin, multivitamins, pantoprazole and senna.

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.