7-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
126146	**Nivolumab**	**April 8, 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
EA3161 (AE #2477496)	**Grade 4: Multi-organ failure** **Grade 4: Cardiac disorders: Takotsubo cardiomyopathy**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
13104	**59 years**	**Male**

12. PROTOCOL SPECIFIED

Cisplatin: 40 mg/m^2 IV QW for 7 weeks
RT: 70 Gy in 35 fractions over 7 weeks (2 Gy/day on Days 1-5 each week)

Maintenance (Cycle= 28 days, maximum 12 cycles)
Nivolumab (BMS-936558, MDX-1106): 480 mg IV on day 1

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on October 12, 2020, and received the last dose of nivolumab on March 11, 2021 (Cycle 5, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 59-year-old male with advanced oropharyngeal squamous cell carcinoma (SCC) involving the left base of his tongue status post chemotherapy and radiation therapy (November 2020), who developed grade 4 Takotsubo cardiomyopathy and grade 4 multi-organ failure while on a phase II/III trial utilizing the investigational agent nivolumab. He has a history of odynophagia and is a former smoker. On March 16, 2021, the patient presented to the emergency room (ER) with spontaneous bleeding from his oropharynx in the setting of SCC. Due to excessive bleeding, he was electively intubated, and his oropharynx was packed with gauze soaked in tranexamic acid before being transferred to another medical facility. At that time, a CT angiography of the head and neck showed patent carotid, vertebral and cerebral arteries. He received 2 units of packed red blood cells. Upon arrival, he was hypotensive and required vasopressors. He was admitted to the intensive care unit (ICU) for management of acute hypoxemia and shock. On March 17, 2021, the patient underwent a direct laryngoscopy, for a biopsy and exploration of the left hypopharyngeal base of the tongue wound, and control of hemorrhage. An echocardiogram showed a left ventricular ejection fraction of <20%, with severely decreased systolic function; apical ballooning pattern was consistent with Takotsubo cardiomyopathy *vs.* ischemia of the left anterior descending artery. He was started on a high dose of IV steroids. Biopsy of the left base of tongue ulcer showed no invasive carcinoma. Blood cultures were obtained and, due to concern for pre-septal abscess, he was started on antibiotics. On March 18, 2021, the patient was noted to have seizure-like activity lasting approximately 35 seconds and was given 2 mg of midazolam. He experienced a second similar episode prior to levetiracetam load. The patient was on IV sedation; ketamine, dexmedetomidine, fentanyl and midazolam were included. On March 19, 2021, per the ICU physician's assessment the patient was considered to have septic shock versus cardiogenic shock, and stress induced takotsubo cardiomyopathy. Clinically, he was improving, and his vasopressors and steroids were discontinued. He was extubated and started on non-invasive ventilation. On March 20, 2021, a chest X-ray showed increased haziness on the right side with opacification of the right lower lung suggesting the possibility of aspiration. That day, the patient was re-intubated due to respiratory failure and increased work of breathing. A repeat chest x-ray continued to show right lower and medial infiltrate, suggestive of possible aspiration pneumonia. The patient's acute kidney injury improved with diuresis. On March 21, 2021, antibiotics were recommended for aspiration pneumonia and Takotsubo cardiomyopathy

was managed with diuretics. Cultures showed no growth at Day 5. On March 22, 2021, the patient was extubated and placed on 3 L of oxygen per minute via nasal cannula. On March 23, 2021, he was moved out of the ICU. On March 24, 2021, it was recommended to continue with captopril and diuretics as needed. On March 25, 2021, an echocardiogram showed an ejection fraction of 20-24% that has slightly improved form prior. Takotsubo cardiomyopathy pattern was noted, very suspicious for noncompaction syndrome. No significant valvular abnormalities were observed. That day, the patient was found to have a deep vein thrombosis of the right internal subclavian and axillary veins and was started on apixaban in addition to captopril and spironolactone. On March 26, 2021, patient was started on carvedilol and continued captopril and spironolactone. The patient completed ampicillin/sulbactam for aspiration pneumonia and blood cultures were negative to date. On March 27, 2021, patient was euvolemic and a cardiac MRI was recommended as an outpatient. During the hospital stay, the patient's condition improved. On March 31, 2021, the patient was discharged home in a stable condition. 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= 7,539.
There have been 11 other cases of multi-organ failure reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.
There have been no other cases of Takotsubo cardiomyopathy reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.

Adverse Event	Grade	Attribution
Nivolumab (NSC 748726)		
Multi-organ failure (n = 11)	5 4	2 Probable, 5 Possible, 2 Unlikely, 1 Unrelated 1 Unlikely

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the multi-organ failure and the investigational agent nivolumab. A probable relationship exists between the Takotsubo cardiomyopathy and the investigational agent and nivolumab.

	Multi-organ failure	Takotsubo cardiomyopathy
Nivolumab	Possible	Probable
Head and neck squamous cell carcinoma	Unlikely	Unlikely
Heart failure Takotsubo cardiomyopathy	Probable	N/A

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were amoxicillin, acetylsalicylic acid, docusate sodium, fentanyl, ibuprofen, atorvastatin, loratadine, polyethylene glycol, liquid nutrition, omeprazole, oxycodone, senna, and ondansetron.

18. COMMENTS

<u>DISCLAIMER per 21 CFR 312.32(e)</u>: 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.