7-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
129803	**Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)** **Nivolumab (BMS-936558, MDX-1106)**	**July 8, 2022**

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
A031704 (AE #2217814) **A031704 (AE #2240757)**	**Grade 5: Respiratory failure** **Grade 4: Respiratory failure**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
9140398	**58 years**	**Male**

12. PROTOCOL SPECIFIED

Induction Therapy
Cycle = 21 Days (max 4 cycles)
Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived): 1 mg/kg IV on Day 1
Nivolumab (BMS-936558, MDX-1106): 3 mg/kg IV on Day 1

13. TREATMENT RECEIVED AND DATES

AE #2217814

The patient began the investigational therapy on March 31, 2022, and received the last doses of nivolumab and ipilimumab on June 9, 2022 (Cycle 4, Day 1).

AE #2240757

The patient began the investigational therapy on March 31, 2022, and received the last doses of ipilimumab and nivolumab on May 19, 2022 (Cycle 3, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient was a 58-year-old male with clear cell renal cell adenocarcinoma metastatic to the lungs who expired on June 21, 2022, due to respiratory failure while on a phase III trial utilizing the investigational agents nivolumab and ipilimumab. He had a history of coronary artery disease, non-ST-elevation myocardial infarction status post drug-eluting stent placement, type 2 diabetes mellitus, hyperlipidemia, hypertension, chronic respiratory failure on 3-4 L of home oxygen supplementation and was a former smoker. Of note, the patient complained of intermittent vertigo and nausea after receiving scheduled Cycle 3, Day 1 protocol therapy on May 19, 2022, for which he was treated with scopolamine transdermal patch. On May 23, 2022, he was brought to the emergency department (ED) by emergency medical services (EMS) with complaints of increased confusion. His wife reported that he was in a normal state of health that morning, but had profoundly altered mental status later that day, along with slurred, garbled, and nonsensical speech. Upon arrival to the ED, he was awake, but confused, and in no acute distress. He had a temperature of 99.7°F, a blood pressure of 106/80 mmHg, a heart rate of 79 beats per minute, a respiratory rate of 23 breaths per minute, and an oxygen saturation (SpO_2) of 97% on nasal cannula. Laboratory results were significant for a blood glucose level of 46 mg/dL (reference range: 70-100 mg/dL), a hemoglobin level of 9.6 gm/dL (reference range: 13.8-17.3 gm/dL), a sodium level of 133 mmol/L (reference range: 136-145 mmol/L), a potassium level of 5.3 mmol/L (reference range: 3.5-5 mmol/L), a chloride level of 92 mmol/L (reference range: 96-110 mmol/L), and a creatinine level of 1.72 mg/dL (reference range: 0.66-1.25 mg/dL). A CT scan of head showed no evidence of recent intracranial hemorrhage, acute infarction, or mass. The patient was started on IV dextrose and droperidol. A lumbar puncture showed clear and

colorless cerebrospinal fluid (CSF), a red blood cell count of 76/cmm (reference range: 0-5 /cmm), a CSF glucose level of 51 mg/dL (reference range: not provided), a CSF protein level of 62 mg/dL (reference range: 12-45 mg/dL), and a lymphocyte count of 72% (reference range: 40-80%). A CSF polymerase chain reaction (PCR) was negative for *herpes simplex virus*, *enterovirus*, and *varicella zoster virus*. Overnight on May 24, 2022, the patient was placed on bilevel positive airway pressure (BiPAP) and admitted to the medical intensive care unit (MICU) for altered mental status and hypercapnic respiratory failure. An MRI of the head with and without contrast showed no acute intracranial abnormality. A chest X-ray showed pulmonary metastatic disease and increasing airspace opacities in the right lower lung, suggestive of worsening lymphangitic carcinomatosis *vs.* pneumonia. Later that day, the patient was found without his BiPAP for an unknown amount of time. Venous blood gas analysis showed a respiratory acidosis with a pH of 7.25 (reference range: 7.31-7.41) and partial pressure of carbon dioxide (pCO_2) of 82 mmHg (reference range: 41-51 mmHg). He was started on methylprednisolone and azithromycin. On May 26, 2022, the patient had significant improvement in his mental and respiratory status and was transferred out of the MICU. On May 27, 2022, the patient was discharged home in stable condition. On June 9, 2022, the patient received scheduled Cycle 4, Day 1 protocol therapy. On June 17, 2022, the patient was brought to the ED by EMS for evaluation of altered mental status. The patient's wife reported that he also had purple knees, a flushed face, and his eyes were rolling back into his head. Upon arrival, the patient was unresponsive and was placed on BiPAP to achieve an SpO_2 of 96%. On physical examination, there were disseminated rhonchi throughout both lung fields and pitting edema in his lower extremities. Laboratory results were significant for a potassium level of 6.2 mmol/L (reference range: 3.5-5.0 mmol/L) and a lactic acid level of 4.4 mmol/L (reference range: ≤ 2.0 mmol/L). An electrocardiogram showed sinus rhythm with borderline left axis deviation, right bundle branch block, and moderate t-wave abnormality, suggesting possibility of anterolateral ischemia. A CT scan of the chest showed enlarging bilateral pleural effusions (right > left), superimposed ground-glass opacities and small nodular opacities in the middle and right lower lobe, and progressive pulmonary metastatic disease with lymphangitic carcinomatosis and mediastinal/hilar adenopathy. The patient was started on ondansetron, lorazepam, and ipratropium bromide/albuterol, and was admitted to the MICU for management of acute encephalopathy and acute-on-chronic respiratory failure. A transthoracic echocardiogram showed right ventricular dilation and dysfunction with an ejection fraction of 40-45%. The patient was started on furosemide, azithromycin, ceftriaxone, and methylprednisolone. During the hospitalization, the patient's N-terminal pro-brain natriuretic peptide (NT-proBNP) was significantly elevated to 31,400 (reference range and units: not provided). The patient's condition continued to decline with worsening hypoxic respiratory failure despite maximal medical therapy. On July 19, 2022, a CT pulmonary angiogram showed no evidence of pulmonary embolism but demonstrated widespread metastatic disease throughout the chest and mediastinum. On June 20, 2022, following a discussion with patient's family, he was transitioned to comfort care measures. On June 21, 2022, the patient expired. An autopsy was not performed.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 732442 = 8,983.

Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 720801 = 208.

Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = 9,393.

Respiratory failure is an expected event for ipilimumab.

There have been 73 other cases of respiratory failure reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.

Adverse Event	Grade	Attribution
***Nivolumab* (NSC 748726)**		
Respiratory failure (n=73)	5 4	2 Probable, 19 Possible, 9 Unlikely, 7 Unrelated 3 Probable, 10 Possible, 16 Unlikely, 7 Unrelated

16. ASSESSMENT

AE #2217814

Based on the provided medical documentation and our medical and scientific knowledge, a possible

relationship exists between the respiratory failure and the investigational agents ipilimumab and nivolumab.

	Respiratory failure
Ipilimumab	**Possible**
Nivolumab	**Possible**
Renal cell carcinoma, clear cell adenocarcinoma	**Probable**
Acute on chronic respiratory failure	**Definite**
Right-sided congestive heart failure	**Probable**

AE #2240757

Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the respiratory failure and the investigational agents ipilimumab and nivolumab.

	Respiratory failure
Ipilimumab	**Possible**
Nivolumab	**Possible**
Renal cell carcinoma, clear cell adenocarcinoma	**Possible**
Non-compliance with oxygen	**Probable**
Scopolamine	**Possible**

17. CONCOMITANT MEDICATIONS

AE #2217814

Medications taken during the time of the event were aspirin, acetaminophen, atorvastatin, benzonatate, doxylamine-dextromethorphan-acetaminophen, hydromorphone, ipratropium-albuterol, lancets, magnesium sulfate, metformin, metoprolol, omeprazole, prochlorperazine, and ramelteon.

AE #2240757

Medications taken during the time of the event were aspirin, atorvastatin, benzonatate, dextromethorphan, gabapentin, glipizide, guaifenesin-codeine syrup, hydromorphone, losartan, metformin, metoprolol, magnesium, olanzapine, omeprazole, ramelteon, and scopolamine transdermal patch.

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.