7-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
124975	**Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived) Nivolumab**	**April 5, 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
EA6141 (AE #2162782)	**Grade 5: Hepatic failure**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
16306	**72 years**	**Male**

12. PROTOCOL SPECIFIED

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

Cycle: 21 Days (Maintenance Phase)
BMS-936558 (Nivolumab, MDX-1106): 3 mg/kg IV, Day 1

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on December 29, 2021, and received the last doses of ipilimumab and nivolumab on March 2, 2020 (Cycle 4, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient was a 72-year-old male with malignant melanoma of the neck metastatic to the cerebrum, liver, spleen, and lung, who expired on March 22, 2022, due to hepatic failure while on a Phase II/III trial utilizing the investigational agents ipilimumab and nivolumab. He had a history of hypertension, diabetes mellitus, benign prostatic hyperplasia, and nonspecific elevation of levels of transaminases or lactate dehydrogenase. On December 23, 2021, prior to initiation of the protocol therapy, his hepatitis B surface antigen and hepatitis C antibody tests were nonreactive. On March 2, 2022, laboratory results were notable for an aspartate aminotransferase (AST) level of 43 IU/L (reference range: 10- 40 IU/L), an alanine aminotransferase (ALT) level of 49 IU/L (reference range: 6 - 40 IU/L), and a lactate dehydrogenase level of 246 IU/L (reference range: 51 – 238 IU/L). On March 16, 2022, his restaging CT scan showed evidence of improvement with respect to measurable disease in the lower lobe of the right lung and the right hilum, as well as the left retroperitoneum. On March 21, 2022, the patient presented to the emergency department (ED) with altered mental status, shortness of breath, and fatigue. The patient's wife presented with the patient. Per his wife, the patient had been fatigued for approximately 5 days prior, had a very slow gait, and was confused the day before. She reported that she noticed blood in the patient's stool, his abdomen appeared slightly more distended, and that he appeared jaundiced on the day prior to the presentation. On arrival, he had a temperature of 93.92 °F, a heart rate of 98 beats per minute, a blood pressure of 75/52 mmHg, a respiratory rate of 21 breaths per minute, and an oxygen saturation (SpO_2) of 98% on room air. An electrocardiogram was normal. Laboratory results were significant for a serum AST level of 1,024 IU/L, an ALT level of 643 IU/L, a total blood bilirubin level of 7.5 mg/dL (reference range: 0.2 – 1.2 mg/dL), an alkaline phosphatase level of 256 IU/L (reference range: 40 – 150 IU/L), an international normalized ratio (INR) of 4.3 (reference range: 0.9 – 1.1), a serum albumin level of 2.3 g/dL (reference range: 3.5 – 5.0 g/dL),

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a blood ammonia level of 3.04 (reference range and units: not provided), and a creatinine level of 2.19 mg/dL (reference range: 0.70 – 1.20 mg/dL). He was started on IV fluids, norepinephrine, cefepime, vancomycin and IV steroids. A CT scan of the abdomen and pelvis with IV contrast showed no intrahepatic or extrahepatic biliary dilation, but portal hypertension with a recanalized paraumbilical vein was noted. A CT scan of the head without IV contrast showed no acute intracranial changes. He was admitted for further management. Per the treating physician, the patient's clinical decline over the past few days was likely related to a fulminant autoimmune hepatitis attributable to ipilimumab and nivolumab. Despite aggressive measures, the patient remained hypotensive and clinically deteriorated. The patient's family decided to transition him to comfort care. On March 22, 2022, 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 ipilimumab under NSC 732442= 8,824.
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= 9,068.
There have been 8 other cases of hepatic failure reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 732442.
There have been no other cases of hepatic failure reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 720801.
There have been 9 other cases of hepatic failure reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.
Note: This form of acute hepatic failure is rarely seen.

Adverse Event	Grade	Attribution
Ipilimumab **(NSC 732442)**		
Hepatic Failure (n=8)	5 4 3	1 Unlikely 2 Probable, 1 Unlikely 1 Probable, 2 Possible, 1 Unlikely
Nivolumab **(NSC 748726)**		
Hepatic Failure (n=9)	5 4 3	1 Unlikely 1 Probable 1 Definite, 1 Probable, 4 Possible, 1 Unlikely

16. ASSESSMENT

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

	Hepatic failure
Ipilimumab	Probable
Nivolumab	Probable
Melanoma	Possible

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were amlodipine, lisinopril, metformin, multivitamin, prochlorperazine, sildenafil citrate, tamsulosin, and trazodone.

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.