7-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
129803	**Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)** **Nivolumab**	**July 11, 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 #2858701)	**Grade 5: Edema cerebral**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
9140868	**59 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

The patient began the investigational therapy on May 24, 2022, and received the last doses of ipilimumab and nivolumab on June 14, 2022 (Cycle 2, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient was a 59-year-old male with clear cell renal cell adenocarcinoma with metastases to the left eye, lungs, bones, and adrenal glands who expired on June 25, 2022, due to cerebral edema while on a Phase III trial utilizing the investigational agents ipilimumab and nivolumab. The patient was a former smoker. On June 24, 2022, the patient was brought to the emergency department (ED) by emergency medical services (EMS) after being found on the floor of his home by his brother. The patient reported that he had been lying on the floor for over 24 hours after losing his balance in the bathroom and falling. He was found by EMS to be lying face down with increased erythema and open abrasions on his chest, which the patient attributed to crawling on the carpet. Upon arrival to the ED, the patient was awake and oriented, but markedly uncomfortable with tachycardia, tachypnea, hypoxemia, and had a temperature of 101 °F. On physical examination, the patient had increased work of breathing, no breath sounds in the right lower lung field with a few rales in the right mid lung field, and diminished breath sounds bilaterally. He also displayed some weakness, slowed cognition, possible confusion, and processing difficulty. Laboratory results were significant for a C-reactive protein of 19.80 mg/dL (reference range: <0.50 mg/dL), a brain natriuretic peptide (BNP) of 996 pg/mL (reference range: <100 pg/mL), a total creatine kinase of 1,730 IU/L (reference range: 30-200 IU/L), a white blood count (WBC) of 13.0 thou/cu mm (reference range: 4.5-11.0 thou/cu mm), and a troponin I of 1.860 (reference range: <0.034 ng/mL). An electrocardiogram (ECG) showed sinus tachycardia and possible left atrial enlargement. A CT scan of the brain revealed numerous new bilateral hemorrhagic masses with surrounding vasogenic edema in both the supratentorial and infratentorial brain, including a large metastatic lesion within the left cerebellum. The numerous metastases caused sulcal effacement, effacement in the basilar cisterns, and a 9 mm right-to-left shift along

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the anterior falx cerebri. A CT scan of the cervical spine revealed significant increase in size of a lytic metastatic lesion involving the odontoid process. A CT scan of the chest, abdomen, and pelvis with contrast showed a right 4th rib fracture through a metastatic lesion, near complete right lower lobe collapse, and progressive metastases involving the lung, retroperitoneum, and pelvis. The patient was given fentanyl and supplemental oxygen while in the ED. Following discussion with the patient and his family, he was transitioned to comfort care and admitted to hospice. On June 25, 2022, the patient expired. An autopsy was not performed.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = 9,409.
Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 732442 = 8,990.
Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 720801 = 208.
There have been 4 other cases of edema cerebral reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.
There have been 5 other cases of edema cerebral reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 732442.
There have been no other cases of edema cerebral reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 720801.

Adverse Event	Grade	Attribution
Nivolumab (NSC 748726)		
Edema cerebral (n= 4)	4 3	1 Unlikely 2 Possible, 1 Unlikely
Ipilimumab (NSC 732442)		
Edema cerebral (n= 5)	4 3	1 Unlikely, 1 Unrelated 2 Possible, 1 Unlikely

16. ASSESSMENT

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

	Edema cerebral
Ipilimumab	Probable
Nivolumab	Probable
Renal cell carcinoma, clear cell adenocarcinoma	Definite
New brain metastases	Definite
Rapid disease progression vs pseudo progression and edema	Definite

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were acetaminophen, amlodipine, cholecalciferol, furosemide, prochlorperazine, and topical triamcinolone.

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.