15-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
129803	**Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)** **Nivolumab** **XL184 (Cabozantinib)**	**October 15, 2021**

4. SPONSOR	
Division of Cancer Treatment and Diagnosis, National Cancer Institute	
5. REPORTER'S NAME, TITLE, AND INSTITUTION	6. PHONE NUMBER
Howard Streicher, MD – Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI	**240-276-6565**
	7. EMAIL ADDRESS **ctepsupportae@tech-res.com**

8a. PROTOCOL NUMBER (AE #)	8b. AE GRADE: AE
A031704 (AE #2101848)	**Grade 3: Reversible posterior leukoencephalopathy syndrome** **Grade 3: Vasculitis**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
9137553	**60 years**	**Female**

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 August 17, 2021, and received the first and only doses of ipilimumab and nivolumab on that same day (Cycle 1, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 60-year-old female with metastatic clear cell renal cell adenocarcinoma who experienced a grade 3 vasculitis and grade 3 reversible posterior leukoencephalopathy syndrome while on a Phase III trial utilizing the investigational agents ipilimumab and nivolumab. The patient has a history of hypertension, prediabetes, depression/anxiety, pulmonary embolism status post thrombectomy (on apixaban), and COVID-19 infection. Of note, the patient was undergoing treatment for grade 3 small vessel leukocytoclastic vasculitis after receiving the first doses of the investigational agents. On September 27, 2021, the patient presented to the emergency department (ED) for altered mental status. The patient's husband reported that she was having a difficult time sleeping for several days despite taking zolpidem. The patient was in her usual state of health the previous night except for some head and back pain. On arrival, the patient was in atrial fibrillation (Afib) with a heart rate of 110 beats per minute, a blood pressure of 166/109 mmHg and an oxygen saturation (SpO_2) of 98% on 2 L of oxygen *via* nasal cannula. Laboratory results were remarkable for a white blood cell count of 10.2 K/µL, a serum sodium level of 134 mEq/L, a serum chloride level of 97 mmol/L, a serum bicarbonate level of 19 mEq/L, a blood total bilirubin of 1.59 mg/L, and an alkaline phosphatase level of 181 U/L (reference ranges: not provided). A chest x-ray showed no acute cardiopulmonary disease. A CT scan of the head without contrast showed no acute intracranial hemorrhage. Ill-defined hypoattenuation of the bilateral occipital white matter, likely representing edema which can be seen with posterior reversible encephalopathy syndrome (PRES), was noted. While in the ED, she experienced an episode of seizure and was given 1 mg of lorazepam. Following

a neurology consult, she was given a loading dose of levetiracetam, and was started on Ceribell® monitoring. The patient was also given several pushes of labetalol and was admitted to the intensive care unit (ICU). On September 28, 2021, her electroencephalogram (EEG) study was moderate-severely abnormal. That day, the patient was intubated due to altered mental status. On September 29, 2021, MRI of the brain with and without contrast findings were most consistent with PRES. On October 4, 2021, her mental status improved, and she was transferred out of the ICU. On October 5, 2021, she was started on oral prednisone with a plan to taper every 7 days. On October 7, 2021, the patient was discharged home with a plan to follow-up with her oncologist. 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 = 8,535.
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 = 8,414.
There have been 2 other cases of reversible posterior leukoencephalopathy syndrome reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 732442.
There have been no other cases of vasculitis reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 732442.
There have been no other cases of reversible posterior leukoencephalopathy syndrome and vasculitis reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 720801.
There have been no other cases of vasculitis reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.
Reversible posterior leukoencephalopathy syndrome is an expected event for the investigational agent nivolumab.

Adverse Event	Grade	Attribution
Ipilimumab NSC (732442)		
Reversible posterior leukoencephalopathy syndrome (n=2)	3 2	1 Unlikely 1 Unrelated

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the reversible posterior leukoencephalopathy syndrome and the investigational agents ipilimumab and nivolumab. A definite relationship exists between vasculitis and the investigational agents ipilimumab and nivolumab. The event seizure is not related to the investigational agents ipilimumab and nivolumab.

	Reversible posterior leukoencephalopathy syndrome	Vasculitis
Ipilimumab	Possible	Definite
Nivolumab	Possible	Definite
Renal cell carcinoma, clear cell adenocarcinoma	Possible	Unrelated
Leukocytoclastic vasculitis	Unrelated	Probable

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	Reversible posterior leukoencephalopathy syndrome	**N/A**	**Probable**

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were acetaminophen, amlodipine, apixaban, atorvastatin, docusate sodium, ferrous sulfate, hydrochlorothiazide, hydrocodone-acetaminophen, melatonin, metoprolol succinate, omeprazole, polyethylene glycol, prednisone, prochlorperazine, sulfamethoxazole-trimethoprim, trazodone, triamcinolone 0.1% ointment, and zolpidem.

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.