15-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
129803	**Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)** **Nivolumab**	**November 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
A031704 (AE #2724667)	**Grade 3: Neoplasms benign, malignant and unspecified (incl. cysts and polyps): Pituitary adenoma**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
9137599	**48 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 20, 2021, and received the last doses of ipilimumab and nivolumab on September 10, 2021 (Cycle 2, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 48-year-old female with clear cell renal cell carcinoma with rhabdoid features status post right radical nephrectomy (April 6, 2021), who experienced a grade 3 pituitary adenoma while on a Phase III trial utilizing the investigational agents ipilimumab and nivolumab. The patient has a history of asthma, hyperlipidemia, depression, obstructive sleep apnea, and is a current smoker. On October 14, 2021, the patient presented to the emergency department (ED) with complaints of fever with chills for 3 days, dizziness, vision abnormalities, vomiting, arthralgia, diarrhea, and cough. Upon arrival, she had a heart rate of 101 beats per minute, blood pressure of 118/68 mmHg, temperature of 99.7°F, respiratory rate of 16 breaths per minute, and an oxygen saturation (SpO_2) of 96% on room air. Laboratory results were remarkable for a serum sodium level of 126 mmol/L (reference range: 133-143 mmol/L), a serum chloride level of 96 mmol/L (reference range: 98-108 mmol/L), a serum glucose level of 132 mg/dL (reference range: 70-99 mg/dL), and a serum osmolality of 271 mOsm/kg (reference range: 278-305 mOsm/kg). A chest x-ray showed subtle central/axial interstitial thickening related to trace interstitial edema or atypical/viral infection. An MRI of the pituitary with and without contrast showed an interval increase in the size of the hypoenhancing lesion in close proximity to the left prechiasmatic optic nerve and optic chiasm involving the left aspect of the pituitary gland, suggestive of an adenoma. An interval increase in the volume of the pituitary parenchyma, suspicious for an underlying hypophysitis, was also noted. No significant mass effect or signs of cavernous sinus invasion were noted. She was started on intravenous cefepime, vancomycin, azithromycin, and normal saline due to a concern for atypical pneumonia and was admitted for further management. On October 15, 2021, the neurosurgeon felt that no acute neurosurgical intervention or

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additional imaging were required at that time. A CT scan of the chest with contrast showed no evidence of acute or active processes. Laboratory results were significant for an overnight cortisol of 24.11 and adrenocorticotropic hormone of 44.1 (reference ranges: not provided). Of note, the prolactin levels were normal. The patient remained afebrile with antibiotics. On October 17, 2021, the patient was discharged home in stable condition on azithromycin with plans to follow-up with the neurosurgeon and endocrinologist on an outpatient basis. On October 22, 2021, the patient was removed from the study treatment. 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 = 8,573.
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 = 8,494.
There have been no other cases of pituitary adenoma reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 732442.
There have been no other cases of pituitary adenoma reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 720801.
There have been no other cases of pituitary adenoma reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.

16. ASSESSMENT

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

	Pituitary Adenoma
Ipilimumab	**Possible**
Nivolumab	**Possible**
Renal Cell Carcinoma	**Possible**

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were albuterol sulfate inhaler, atorvastatin, escitalopram, lisinopril, multivitamins, probiotics, and vitamin D3.

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.