15-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
129803	**Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived) Nivolumab**	**June 3, 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 #2323586)	**Grade 3: Hematuria**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
9135483	**62 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 April 21, 2021, and received the first and only doses of nivolumab and ipilimumab that same day (Cycle 1, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 62-year-old male with metastatic clear cell renal cell adenocarcinoma who developed grade 3 hematuria while on a phase III trial utilizing the investigational agents nivolumab and ipilimumab. The patient has a history of basal cell carcinoma, testicular cancer, and hypertension. On May 7, 2021, the patient presented to the emergency department with an acute onset of gross hematuria and right flank and suprapubic pain. A CT scan of the abdomen and pelvis with contrast showed extensive, infiltrative neoplasm throughout the right kidney with renal vein invasion, stable metastatic adenopathy throughout the retroperitoneum, and new hemorrhage throughout much of the urinary bladder. Laboratory results were significant for a white blood cell count of 11.8 K/uL (reference range: 4.0-11.0 K/uL), red blood cell count of 5.93 M/uL (reference range: 4.40-5.80 M/uL), hemoglobin of 16.7 g/dL (reference range: 13.5-17.5 g/dL), hematocrit of 50.7% (reference range: 40.0-50.0%), glucose of 112 mg/dL (reference range: 70-99 mg/dL), and calcium level of 12.5 mg/dL (reference range: 8.5-10.5 mg/dL). Overnight on May 8, 2021, he was transferred to another facility for admission and further management. Upon arrival, he had a temperature of 97.5°F, blood pressure of 177/118 mmHg, heart rate of 105 beats per minute, respiratory rate of 16 breaths per minute, and an oxygen saturation (SpO_2) of 97% on room air. He was started on intravenous fluids and continuous bladder irrigation (CBI) using a 3-way catheter with a small amount of clot retrieval. On May 9, 2021, the patient's calcium level was 10.1 mg/dL and was trending down. On May 10, 2021, the CBI catheter was clamped as all retained clots appeared to have been removed. On May 11, 2021, the patient was urinating without difficulty with his pain nearly resolved and clear bladder flushes. That day, he was discharged home in stable condition with a plan to follow up with his oncologist and urologist. On May 13, 2021, the patient received Cycle 2, Day 1 therapy, and his hematuria was back to baseline. Additional information has been requested from the investigational site.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = 7,884.
Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 732442 = 8,264.
Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 720801 = 208.
There have been 15 other cases of hematuria reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.

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There have been 6 other cases of hematuria reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 732442.
There have been no other cases of hematuria reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 720801.

Adverse Event	Grade	Attribution
Nivolumab (NSC 748726)		
Hematuria (n=15)	**3** **2**	**8 Unlikely, 5 Unrelated** **2 Unrelated**
Ipilimumab (NSC 732442)		
Hematuria (n=6)	**3** **2**	**3 Unlikely, 2 Unrelated** **1 Possible**

16. ASSESSMENT

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

	Hematuria
Ipilimumab	**Probable**
Nivolumab	**Probable**
Renal cell carcinoma, clear cell adenocarcinoma	**Possible**

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were acetaminophen, hydrochlorothiazide, senna, ondansetron, flax seed oil, and aspirin.

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.