7-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
129803	**Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)** **Nivolumab (BMS-936558, MDX-1106):**	**April 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 #2970184)	**Grade 3: Acute kidney injury**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
9129231	**63 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 March 17, 2020, and received the last doses of ipilimumab and nivolumab on April 28, 2020 (Cycle 3, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 63-year-old male with clear cell renal cell adenocarcinoma of the right kidney who experienced a grade 3 acute kidney injury while on a Phase III trial utilizing the investigational agents ipilimumab and nivolumab. He has a history of atrial fibrillation and stroke. The patient's baseline creatinine was between 1.2–1.4 mg/dL. On April 28, 2020, the patient's creatinine level was 1.54 mg/dL (reference range: 0.60–1.30 mg/dL). On May 19, 2020, the patient presented to the clinic for Cycle 4, Day 1 infusion, and was noted to have a creatinine level of 3.08 mg/dL and a potassium level of 5.7 mEq/L (reference range: 3.5–5.1 mEq/L). He was given 1 L of IV fluids and was prescribed kayexalate, which he did not take at home. A kidney ultrasound showed stable moderate to severe right kidney hydronephrosis, secondary to a mass effect from a known inferior pole (13.2 cm) renal cell carcinoma. No left kidney hydronephrosis or shadowing renal stones were noted. On May 20, 2020, the patient returned to the clinic for a follow up and was given two additional liters of IV fluids. His creatinine improved to 2.68 mg/dL and his potassium level decreased to 5.1 mEq/L. His fractional excretion of sodium was 2.7% and urine eosinophil was negative. That same day, the patient was admitted to the hospital for acute kidney injury. Per the nephrologist's assessment, the acute kidney injury was possibly related to the immune checkpoint inhibitor (ICPI) and it was recommended to hold off on ICPI; Cycle 4 immunotherapy was held. His urine microscopy showed no red blood cell or white blood cell casts. The patient's creatinine remained at 2.5 mg/dL despite good hydration. On May 21, 2020, a renal function panel showed a urea nitrogen level of 28 mg/dL (reference range: 2–25 mg/dL), a creatinine level of 2.57 mg/dL, and a glomerular filtration rate (GFR) of 25 mL/min/1.73m^2. On May 23, 2020, a renal vascular ultrasound showed no evidence of renal artery occlusive disease or renal vein thrombosis. A nuclear GFR scan showed mild asymmetry in kidney

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function; the left side provided 46% and the right side provided 54%. His home enoxaparin was adjusted for renal dosing of 1 mg/kg daily. On May 24, 2020, the patient was discharged home with a plan to follow-up with his nephrologist. On August 6, 2020, a pathology report showed grade 3 clear cell renal cell adenocarcinoma (11.5 cm) according to WHO/ISUP (World Health Organization/International Society of Urologic Pathologists) classification with tumor extension into the perinephric adipose tissue; tumor necrosis with extensive fibrosis and hyalinization was noted. A non-neoplastic renal parenchyma with subcapsular scarring, global glomerulosclerosis, and focal interstitial fibrosis/tubular atrophy was also observed. 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 = 8,113.
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 = 7,539.
Acute kidney injury is an expected event for both investigational agents ipilimumab and nivolumab. This event is being reported because of the unusual histopathology.

16. ASSESSMENT

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

	Acute Kidney Injury
Ipilimumab	**Probable**
Nivolumab	**Probable**
Renal cell carcinoma, clear cell adenocarcinoma	**Possible**
Glomerulosclerosis	**Definite**

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were baclofen, metoprolol, and enoxaparin.

18. COMMENTS