7-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
129803	**Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)** **Nivolumab**	**December 15, 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 #2337769)	**Grade 5: Infections and infestations: COVID-19**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
9138133	**61 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 September 29, 2021, and received the last doses of ipilimumab and nivolumab on October 22, 2021.

14. DESCRIPTION OF ADVERSE EVENT

The patient was a 61-year-old female with clear cell renal cell adenocarcinoma with metastasis to the lungs, who expired on November 27, 2021, due to COVID-19 while on a Phase III trial utilizing the investigational agents ipilimumab and nivolumab. On October 29, 2021, the patient presented to the emergency department (ED) complaining of shortness of breath and cough of 4 hours duration with a reported oxygen saturation of 58% on 3 L of home oxygen. Upon arrival, she had a blood pressure of 98/62 mmHg, a temperature of 37°C, a heart rate of 98 beats per minute, a respiratory rate of 16 breaths per minute, and an oxygen saturation of 98% on room air. Laboratory results were significant for an anion gap of 9 mmol/L (reference range: 10-20 mmol/L) and an N-terminal Pro-B-type natriuretic peptide of 981 pg/mL (reference range: 0-125 pg/mL). A COVID-19 test was positive. Of note, she was not vaccinated for COVID 19. A chest X-ray was significant for a mildly enlarged heart and slightly increasing small to moderate left-sided pleural effusion. A CT angiogram of the chest with contrast revealed no evidence of pulmonary embolism. No abnormal findings were noted on the electrocardiogram. While in the ED, she was placed on supplemental oxygen via high-flow nasal cannula for hypoxic respiratory failure and was started on heparin, enoxaparin, dexamethasone, azithromycin, ceftriaxone, ondansetron, and mupirocin. A left thoracentesis was performed draining 800 mL of lightly blood-tinged fluid. She was admitted into the intensive care unit (ICU) for further management. On November 1, 2021, she was intubated. During her course in the ICU, she completed a 5-day course of remdesivir and was also treated with antibiotics, vitamins, and high-dose steroids for COVID-19 pneumonia. She could not be weaned off the ventilator, and a tracheostomy was performed. On November 13, 2021, a percutaneous endoscopic gastrostomy was performed due to failure to thrive. On November 25, 2021, a repeat chest X-ray revealed worsening

moderate left pleural effusion with atelectasis of the left lower lobe. Throughout the hospital course, the patient's condition continued to decline with worsening oxygen requirements, recurrence of pleural effusion, and persistent fever despite antibiotic treatment. On November 27, 2021, per the family's request, she was transferred to hospice care for comfort measures. That day, 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 = 8,656.
Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 732442 = 8,434.
Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 720801 = 208.
There have been 5 other cases of COVID-19 reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 732442.
There have been no other cases of COVID-19 reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 720801.
There have been 14 other cases of COVID-19 reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.

Adverse Event	Grade	Attribution
Nivolumab (NSC 748726)		
COVID-19 (n=14)	5 4 3 2 1	2 Possible, 3 Unlikely, 1 Unrelated 1 Unlikely, 1 Unrelated 2 Unlikely, 1 Unrelated 2 Unlikely 1 Unlikely
Ipilimumab (NSC 732442)		
COVID-19 (n=5)	4 3 2 1	1 Unlikely, 1 Unrelated 1 Unrelated 1 Unlikely 1 Unlikely

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the COVID-19 and the investigational agents ipilimumab and nivolumab.

	COVID-19
Ipilimumab	Possible
Nivolumab	Possible
Renal cell carcinoma, clear cell adenocarcinoma	Possible

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were docusate sodium, diltiazem, and oxycodone.

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.