15-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
124975	**Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)** **Nivolumab**	**June 30, 2022**

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
EA6141 (AE #2733334)	**Grade 3: Pneumonitis** **Grade 2: Arthritis**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
16327	**51 years**	**Male**

12. PROTOCOL SPECIFIED

Cycle: 21 Days (Induction Phase = 4 cycles)
Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived): 3 mg/kg IV, Day 1
BMS-936558 (Nivolumab, MDX-1106): 1 mg/kg IV, Day 1
GM-CSF (sargramostim, Leukine): 250 ug SQ, Days 1-14

Cycle: 21 Days (Maintenance Phase)
BMS-936558 (Nivolumab, MDX-1106): 3 mg/kg IV, Day 1
GM-CSF (sargramostim, Leukine): 250 ug SQ, Days 1-14

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on April 27, 2022, and received the last doses of ipilimumab, nivolumab, and sargramostim on June 1, 2022 (Cycle 2, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 51-year-old male with metastatic superficial spreading melanoma of the left flank who developed grade 2 arthritis and grade 3 pneumonitis, while on a Phase II/III trial utilizing the investigational agents ipilimumab and nivolumab in combination with sargramostim. He has a history of hypertension, meningitis, and is a smoker. On June 3, 2022, the patient presented to the clinic with arthralgias, a swollen left hand, pain over the immunotherapy injection site, low-grade fever, and a worsening productive cough, which started after receiving protocol therapy on June 1, 2022. He had a temperature of 99.6 °F, a blood pressure of 109/67 mmHg, a heart rate of 96 beats per minute, and a respiratory rate of 16 breaths per minute. Physical exam revealed a flushed face, edema and joint tenderness in left hand, and a left arm injection site that was warm, pink, and edematous. Laboratory results were significant for a white blood cell count of 11.9 K/uL (reference range: 4.5-10.0 K/uL), an absolute neutrophil count of 8.3 K/uL (reference range: 1.50-7.00 K/uL), an eosinophil percentage of 9.7% (reference range: 0.0-5.0%), an erythrocyte sedimentation rate (ESR) of 24 mm/hr (reference range: 0-20 mm/hr), a C-reactive protein (CRP) of 17.60 mg/dL (reference range: <0.80 mg/dL), and a procalcitonin level of 0.50 ng/mL (reference range: 0.00-0.09 ng/mL). A respiratory viral panel, including a COVID-19 test, was negative. A CT scan of the chest without contrast showed bilateral centrilobular micronodules suggestive of infectious bronchiolitis, aspiration, or hypersensitivity pneumonitis and new mild subcarinal lymphadenopathy. He was diagnosed with systemic inflammatory response syndrome (SIRS) and administered intravenous fluids with some improvement, but due to worsening of his symptoms he was transferred to the emergency department (ED) for further evaluation. Upon arrival, he was alert, oriented, and in no acute distress. He had a temperature of 98.7 °F,

a blood pressure of 121/88 mmHg, a heart rate of 115 beats per minute, a respiratory rate of 12 breaths per minute, and an oxygen saturation (SpO_2) of 100% on room air. Physical examination revealed bilateral upper arm erythema with slight induration, tenderness, and warmth at the site of the immunotherapy injection. An electrocardiogram (ECG) showed a normal sinus rhythm with no ischemic changes. He was started on intravenous fluids, methylprednisolone for possible immunotherapy-induced pneumonitis, ampicillin-sulbactam and doxycycline for possible pneumonia, and was admitted to the hospital for further management. Overnight, the patient's temperature reached 101.2 °F and he became tachycardic, requiring 4L of oxygen supplementation. Over the next 2 days, the patient's symptoms rapidly improved with resolution of his joint pain and rash, and he was completely weaned off oxygen. On June 5, 2022, the patient was discharged in stable condition with a plan to continue the prednisone taper and doxycycline, and to follow-up with his oncologist. On June 7, 2022, the patient was removed from the study treatment. At an oncology follow-up visit on June 10, 2022, the patient reported his symptoms had resolved and laboratory results for ESR and CRP were normal. On June 13, 2022, a repeat CT scan of the chest without contrast showed a stable right upper lobe lung nodule, mild apical paraseptal emphysema, decrease in size of the left lateral chest mass and left axillary hypermetabolic lymph node, suggestive of a positive response to the oncologic therapy. At a pulmonary follow-up visit on June 17, 2022, the patient had no complaints and was advised to continue his prednisone taper and follow-up with his 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= 8,974.
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= 9,373.
There have been 12 other cases of arthritis reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.
Pneumonitis is an expected event for ipilimumab and nivolumab.
Arthritis is an expected event for ipilimumab.

Adverse Event	Grade	Attribution
Nivolumab (NSC 748726)		
Arthritis (n=12)	3 2	6 Probable, 1 Possible 4 Probable, 1 Possible

16. ASSESSMENT

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

	Pneumonitis	Arthritis
Ipilimumab	Probable	Probable
Nivolumab	Probable	Probable
Sargramostim	Possible	Unlikely
Melanoma	Unrelated	Unrelated

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were acetaminophen, clobetasol, diphenhydramine, ergocalciferol, ibuprofen, and losartan.

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.