7-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
124975	**Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)** **Nivolumab**	**December 16, 2021**

4. SPONSOR

Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION	6. PHONE NUMBER
Howard Streicher, MD – Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI	**240-276-6565**
	7. EMAIL ADDRESS **ctepsupportae@tech-res.com**

8a. PROTOCOL NUMBER (AE #)	8b. AE GRADE: AE
EA6141 (AE #2884258)	**Grade 4: Myocarditis** **Grade 4: Sinus bradycardia**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
16299	**72 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 November 10, 2021, and received the first and only doses of nivolumab and ipilimumab on that same day and the last dose of sargramostim on November 23, 2021 (Cycle 1, Day 14).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 72-year-old male with metastatic cutaneous melanoma of the right jaw who developed grade 4 myocarditis and grade 4 sinus bradycardia while on a Phase II/III trial utilizing the investigational agents nivolumab and ipilimumab in combination with GM-CSF (sargramostim, Leukine). He has a history of atrial fibrillation and hypertension. On November 28, 2021, the patient was feeling unwell at home and called emergency medical services (EMS). Upon arrival, EMS found him to be poorly responsive and bradycardic with a heart rate in the 30s and heart block on the rhythm strip. On route to the hospital the patient was given atropine and two doses of epinephrine, and a transcutaneous pacing was performed. On arrival to the emergency department (ED), he was paced at a heart rate of 70 beats per minute and had a blood pressure of 115/88 mmHg and an oxygen saturation (SPO_2) of 86-90% on 15 L non-rebreather mask (NRB). Laboratory results were significant for a troponin level of 6.7 (reference range and units: not provided). A cardiologist was consulted, and he was planned for transvenous pacing. The patient was intubated and admitted to the critical care unit for further management. On November 29, 2021, the patient was started on methylprednisolone. On November 30, 2021, a transvenous pacemaker was placed for bradycardia. On December 1, 2021, the patient was started on abatacept and was extubated. 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 = 8,636.
Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 732442 = 8,638.

7-DAY IND SAFETY REPORT

Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 720801 = 208.
There has been 1 other case of sinus bradycardia (Grade 1, unrelated) reported to the NCI through CTEP-AERS as a serious adverse event for nivolumab under NSC 748726.
There have been 2 other cases of sinus bradycardia reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 732442.
There have been no other cases of sinus bradycardia reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 720801.
Myocarditis is an expected event for the investigational agents ipilimumab and nivolumab.

Adverse Event	Grade	Attribution
Ipilimumab (NSC 732442)		
Sinus bradycardia (n=2)	**2** **1**	**1 Unlikely** **1 Unrelated**

16. ASSESSMENT

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

	Myocarditis	Sinus bradycardia
Ipilimumab	**Possible**	**Possible**
Nivolumab	**Possible**	**Possible**
Sargramostim	**Unrelated**	**Unrelated**
Melanoma	**Unrelated**	**Unrelated**

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were not provided.

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.