IND SAFETY REPORT: FOLLOW UP#1

1. IND NUMBER	2. AGENT NAME	3. DATE
10200	Ipilimumab (BMS-734016; MDX-010 Transfectoma derived) Bevacizumab (rhuMAb VEGF)	**June 12, 2019**

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
E3612 (AE #2178734)	Grade 5: Cardiac arrest

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
36158	88 years	Female

12. PROTOCOL SPECIFIED

Induction (Cycle = 21 days)
Ipilimumab: 3 mg/kg IV on Day 1 of Cycles 1-4
Bevacizumab: 15 mg/kg IV on Day 1 of Cycles 1-4
Maintenance (Cycle = 21 days)
Bevacizumab: 15 mg/kg IV on Day 1 of each cycle beginning on Cycle 5
Ipilimumab: 3 mg/kg IV on Day 1 of every fourth cycle beginning on Cycle 8

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on November 16, 2016, and received the last dose of ipilimumab on January 19, 2017 (Cycle 4, Day 1) and the last dose of bevacizumab on December 9, 2016 (Cycle 2, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient was an 88-year-old female with metastatic melanoma who expired due to cardiac arrest on March 14, 2017 while on a Phase 2 trial utilizing the investigational agents ipilimumab and bevacizumab. Of note, the patient had a history of hypertension. On December 9, 2016 (Cycle 2, Day 1), the investigational agent bevacizumab was discontinued due to hypertension. On January 22, 2017 (Cycle 4, Day 4), the patient was admitted to a local hospital with a transient ischemic attack and lung infection. She was started on antibiotics and transferred to a rehabilitation facility due to left-sided stroke with resultant mild hemiparesis on the right side, aphasia, and considerable functional decline. Of note, the patient also had bilateral wounds in her lower extremities that required negative-pressure wound therapy while in rehabilitation. On February 4, 2017, the patient called her treating physician to express her desire to stop the investigational agent due to her deteriorating health status. On March 9, 2017, the patient returned to the treating physician's office for an end-of-treatment visit. The patient was in good spirits and had extensive family support. On March 10, 2017, the patient was found at her house unresponsive in her own vomit. She was transported to the local emergency department where she was admitted for comfort measures only, per her do not resuscitate (DNR) order included in her Living Will. That day, the patient expired of cardiac arrest per the death note of the treating physician. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the investigational agents.

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The Initial Written Report was sent to the FDA on April 26, 2017.

Follow-up #1:

On January 22, 2017, upon arrival to the emergency room the patient was in atrial fibrillation with a rapid ventricular response. She was started on IV nicardipine with no change in her atrial fibrillation with rapid ventricular response. Her nicardipine was changed to diltiazem and she was admitted to the hospital.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 732442 = ~~4,768~~ **6,538**, and under NSC 720801 = 208.

Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab under NSC 704865 = ~~43,007~~ **43,730**.

There have been ~~9~~ **13** other cases of cardiac arrest reported to the NCI through CTEP-AERS as a serious adverse events for ipilimumab under NSC 732442, and **none** under NSC 720801.

There have been 19 other cases of cardiac arrest reported to the NCI through CTEP-AERS as serious adverse events for bevacizumab under NSC 704865.

Adverse Event	Grade	Attribution
Ipilimumab (NSC 732442)		
Cardiac arrest (n = ~~9~~ **13**)	4 5	1 Possible, ~~1~~ **2** Unlikely ~~3~~ **4** Possible, ~~1~~ **2** Unlikely, ~~3~~ **4** Unrelated

Adverse Event	Grade	Attribution
Bevacizumab (NSC 704865)		
Cardiac arrest (n = 19)	4 5	~~5~~ **4** Possible, 7 Unlikely, 1 Unrelated ~~2~~ **3** Possible, 3 Unlikely, 1 Unrelated

16. ASSESSMENT

In this case, it is felt that a possible relationship exists between the cardiac arrest and the investigational agent bevacizumab and a~~n unlikely~~ **possible** relationship exists between cardiac arrest and the investigational agent ipilimumab.

	Cardiac arrest
Ipilimumab	~~Unlikely~~ **Possible**
Bevacizumab	Possible
Melanoma	Unlikely
Atrial fibrillation, rapid ventricular response, cardiovascular disease	**Probable**
Uncontrolled hypertension	~~Definite~~ **Possible**

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17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event are amlodipine, labetalol, losartan-hydrochlorothiazide, omeprazole, pantoprazole, loratadine, sucralfate, escitalopram, tramadol, acetaminophen-hydrocodone, methocarbamol, alprazolam, levothyroxine, aspirin, multivitamins, and glucosamine.

18. COMMENTS

AT THIS TIME, NO OTHER INFORMATION IS AVAILABLE. IF UPON FURTHER INVESTIGATION RELEVANT INFORMATION BECOMES AVAILABLE, THEN A FOLLOW-UP REPORT WILL BE SUBMITTED IN ACCORDANCE WITH 21CFR 312.32(d)(2).

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.