IND SAFETY REPORT: FOLLOW-UP #2

1. IND NUMBER	2. AGENT NAME	3. DATE
133687	MEDI4736 (durvalumab) Tremelimumab (CP-675,206)	**April 8, 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
10021 (AE #2646219)	~~Grade 5: Cardiac arrest~~ ~~Grade 5: Death NOS~~ **Grade 5: Sudden death NOS**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
CA011-092	62 years	Male

12. PROTOCOL SPECIFIED

Cycle = 28 days
Cycles 1-4
RT:0.5 GY BID x 2 days/total dose = 2 GY in 4 fractions
MEDI4736 (durvalumab): 1500 mg IV over 1 hour on Day 1
Tremelimumab (CP-675,206): 75 mg IV over 1 hour on Day 1
Cycles 5-13
MEDI4736 (durvalumab): 1500 mg IV over 1 hour on Day 1

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on January 2, 2019, and received the last doses of durvalumab and tremelimumab on January 30, 2019 (Cycle 2, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient was a 62-year-old male with non-small cell lung cancer who expired on February 4, 2019, while on a Phase 2 trial utilizing the investigational agents durvalumab and tremelimumab.
Additional information has been requested from the investigational site.

The Initial Written Report was submitted to the FDA on February 14, 2019.
The Follow-up Report #1 was submitted to the FDA on March 25, 2019.

<u>Follow-up report #2:</u>

On December 28, 2018, during a routine baseline office visit, the patient had a temperature of 36° C, a heart rate of 94 beats per minute, a respiratory rate of 18 breaths per minute, blood pressure of 149/78 mmHg, and an SpO_2 of 94%. **A CT scan of the chest showed no significant interval change in right apical ill-defined, infiltrative mass with similar appearance of surrounding fibrotic changes, likely post radiation fibrosis; surrounding ground-glass and consolidative opacities/nodules in the right upper, middle, and lower lobes, some of which are new or enlarging and others of which are unchanged or have resolved; focal consolidation in the left lower lobe; interval increase in left apical consolidative opacities; no significant interval change in trace pleural effusion and borderline enlarged mediastinal lymphadenopathy. A CT scan of the abdomen and**

pelvis showed no evidence of metastatic disease in the abdomen and pelvis. An MRI of the brain showed punctate foci of diffusion restriction within the right lentiform nucleus compatible with acute lacunar infarcts and no evidence of intracranial metastatic disease. On January 2, 2019 (Cycle 1, Day 1), the patient began the investigational therapy with low dose of radiotherapy. Of note, he had a history of diabetes and hypertension. On January 30, 2019 (Cycle 2, Day 1), the patient presented to the oncology clinic with numbness in the left hand and the toes of his feet, flu-like symptoms of cough for one week and muscle weakness/body pain for the last few days. **His laboratory tests including blood chemistry, liver function tests and complete blood counts were normal except for a glucose level of 267 mg/dL (reference range not provided).** He had a blood pressure of 140/70 mmHg, temperature of 36°C, heart rate of 96 beats per minute, respiratory rate of 16 breaths per minute and an SpO_2 of 94%. The treating physician felt that the patient's symptoms were unrelated to treatment and the investigational agents were administered. On February 4, 2019, the patient was brought to the emergency department (ED), where he was found to be completely unresponsive and limp. Per the patient's family, the patient was feeling weak for approximately 1 week after the last infusion of the investigational agents. The patient was gradually deteriorating, and over the last 2 days, he was unable to get out of bed. On that afternoon, his symptoms significantly worsened. In the ED, the patient was found to be pulseless and cardiopulmonary resuscitation (CPR) was initiated. They were unable to obtain vital signs. **No other lab tests or scans were performed at the ED.** He was unable to be revived and was pronounced dead. An autopsy was not performed.

15. ACCRUAL AND IND EXPERIENCE

~~Pending for 15-day report~~

Number of patients enrolled in NCI-sponsored clinical trials using durvalumab under NSC 778709 = 289.
Number of patients enrolled in NCI-sponsored clinical trials using tremelimumb under NSC 744483 = 163.
There have been 2 other cases of death NOS reported to the NCI through CTEP-AERS as serious adverse events for durvalumab under NSC 778709.
There have been no other cases of sudden death reported to the NCI through CTEP-AERS as serious adverse events for durvalumab under NSC 778709.
There have been 2 other cases of death NOS reported to the NCI through CTEP-AERS as serious adverse events for tremelimumb under NSC 744483.
There have been no other cases of sudden death reported to the NCI through CTEP-AERS as serious adverse events for tremelimumb under NSC 744483.

Durvalumab (NSC# 778709)		
Death NOS (n = 2)	5	1 Possible, 1 Unrelated
Tremelimumab (NSC# 744483)		
Death NOS (n = 2)	5	1 Possible, 1 Unrelated

16. ASSESSMENT

~~Based on the information provided, a causal relationship cannot be ruled out.~~

In this case, it is felt that a possible relationship exists between the ~~death~~ **sudden death** and the investigational agents durvalumab and tremelimumab.

	~~Death NOS~~ **Sudden death NOS**
Durvalumab	Possible
Tremelimumab	Possible
Non-small cell lung cancer	Possible

17. CONCOMITANT MEDICATIONS

~~Pending for 15-day report~~

Medications taken at the time of the event were acetaminophen, amlodipine, aspirin, clobetasol topical, hydrochlorothiazide-olmesartan, loratadine, and metformin.

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.