

## IND SAFETY REPORT: FOLLOW-UP #1

1. IND NUMBER 133687	2. AGENT NAME MEDI4736 (durvalumab) Tremelimumab (CP-675,206)	3. DATE <b>March 25, 2019</b>
4. SPONSOR Division of Cancer Treatment and Diagnosis, National Cancer Institute		
5. REPORTER'S NAME, TITLE, AND INSTITUTION Helen Chen, MD – Associate Branch Chief for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI		6. PHONE NUMBER 240-276-6565
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8a. PROTOCOL NUMBER (AE #) 10021 (AE #2646219)	8b. AE GRADE: AE <del>Grade 5: Cardiac arrest</del> <b>Grade 5: Death NOS</b>	
9. PATIENT IDENTIFICATION CA011-092	10. AGE 62 years	11. SEX 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.  <b>The Initial Written Report was submitted to the FDA on February 14, 2019.</b>  <b><u>Follow-up #1:</u></b> <b>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<sub>2</sub> of 94%. 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. 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<sub>2</sub> 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. He was unable to be revived and was pronounced dead. An autopsy was not performed.</b>		

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 tremelimumab 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 tremelimumab under NSC 744483.**

**There have been no other cases of sudden death reported to the NCI through CTEP-AERS as serious adverse events for tremelimumab under NSC 744483.**

<b><i>Durvalumab (NSC# 778709)</i></b>		
<b>Death NOS (n = 2)</b>	<b>5</b>	<b>1 Possible, 1 Unrelated</b>
<b><i>Tremelimumab (NSC# 744483)</i></b>		
<b>Death NOS (n = 2)</b>	<b>5</b>	<b>1 Possible, 1 Unrelated</b>

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 and the investigational agents durvalumab and tremelimumab.**

	<b>Death NOS</b>
<b>Durvalumab</b>	<b>Possible</b>
<b>Tremelimumab</b>	<b>Possible</b>
<b>Non-small cell lung cancer</b>	<b>Possible</b>

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

~~Pending for 15-day report~~

AT THIS TIME, NO OTHER INFORMATION IS AVAILABLE. 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.