IND SAFETY REPORT: FOLLOW-UP #1

1. IND NUMBER	2. AGENT NAME	3. DATE
133687	MEDI4736 (durvalumab) Tremelimumab (CP-675,206)	**April 25, 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 #2647448)	Grade 5: Encephalitis infection

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
KY010-0089	81 years	Male

12. PROTOCOL SPECIFIED

Cycle = 28 days
RT:8 GY BID x 3 fractions QOD/total dose = 24 GY, Cycle 1 only
Cycles 1-4
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 December 3, 2018, and received the last doses of durvalumab and tremelimumab on January 29, 2019 (Cycle 3, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient was an 81-year-old male with non-small cell lung cancer who expired on March 31, 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 April 17, 2019.

<u>Follow-up report #1:</u>

On February 9, 2019 (Cycle 3, Day 12), the patient was admitted to the hospital with diarrhea attributed to immunotherapy-induced colitis. A stool culture for C. *difficle* and a stool GI panel were negative. On February 11, 2019, his diarrhea improved, and he was discharged home on prednisone taper. On March 11, 2019, the patient returned to the oncology clinic for evaluation prior to his Cycle 4 therapy. He had recurrence of his diarrhea with associated nausea, poor appetite, and generalized weakness. Laboratory reports showed a sodium of 124 mmol/L (reference range: 136-145 mmol/L) and a phosphate of 1.9 mg/ dL (reference range: 2.5-4.5 mg/dL). He was reinitiated on high dose prednisone with a plan for IV fluid hydration in a hospital close to home, and his treatment was held. On March 14, 2019, he presented to the ER with worsening generalized weakness and decreased oral intake. He reported falling twice at home at night in his bathroom while standing. He denied loss of consciousness, light-headedness, room-spinning, palpitations, or vision changes during the falls. Since restarting the high-dose prednisone, he noted

improvement in his diarrhea. Laboratory reports were concerning for a sodium level of 129 mmol/L, and a phosphorus level of 1.6 mg/dL. Given his lung cancer, the treating team felt that paraneoplastic syndrome such as a syndrome of inappropriate antidiuretic hormone (SIADH) secretion was a possible cause of the patient's hyponatremia and could have contributed to his weakness and confusion. He was clinically dehydrated with a plasma osmolality of 268 mOsm/kg (reference range: 280-301 mOsm/kg. He was started on IV fluids to slowly correct his hyponatremia. On March 15, 2019, he was readmitted for weakness caused by hyponatremia. On March 16, 2019, the patient had a fever of 38.8^{0}C, and was started on vancomycin. The blood culture remained negative. A CT scan of the chest, abdomen, and pelvis did not show any significant acute abnormalities. On March 17, 2019, he had an acute neurological decline and reportedly had one sided weakness *vs* seizure-like episodes. He continued to have a high-grade fever, and due to concerns for CNS infection, his antibiotics regimen was switched to vancomycin, cefepime, and ampicillin. On March 18, 2019, an MRI of the brain showed abnormal signal and mild swelling in the medial right temporal lobe, right thalamus, right insular cortex, and portions of the right lateral ventricle near the foramen of Monro. The patient was subsequently started on acyclovir. He later became hypotensive and a vasopressor was started. On March 19, 2019, a cerebrospinal fluid (CSF) analysis was positive for herpes simplex virus (HSV). The treating team assessed acute HSV encephalitis with a plan to discontinue the antibiotics, but to continue with acyclovir. On March 27, 2019, following the treating team's discussion with the patient, including HSV encephalitis and underlying life-limiting prognosis of his metastatic adenocarcinoma of the lungs, the patient and his family requested a home hospice evaluation. The patient was discharged to hospice care with encephalitis infection. On March 31, 2019, the patient refused further treatment and expired subsequently.

15. ACCRUAL AND IND EXPERIENCE

~~Pending for 15-day report~~

Number of patients enrolled in NCI-sponsored clinical trials using durvalumab under NSC 778709 = 448.
Number of patients enrolled in NCI-sponsored clinical trials using tremelimumb under NSC 744483 = 170.
There has been 1 other case of encephalitis infection (grade 4, unlikely) reported to the NCI through CTEP-AERS as a serious adverse event for durvalumab under NSC 778709.
There has been 1 other case of encephalitis infection (grade 4, unlikely) reported to the NCI through CTEP-AERS as a serious adverse event for tremelimumb under NSC 744483.

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 encephalitis infection and the investigational agents durvalumab and tremelimumab.

	Encephalitis infection
Durvalumab	**Possible**
Tremelimumab	**Possible**
Radiation	**Unrelated**
Non-small cell lung cancer	**Unrelated**

17. CONCOMITANT MEDICATIONS

~~Pending for 15-day report~~

Medications taken at the time of the event were calcium, fluticasone, triamcinolone, losartan, acetyl salicylic

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acid, chlopidogrel, simvastatin, ranitidine, zinc, enoxaparin, famotidine, and nystatin.
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.