IND SAFETY REPORT: FOLLOW-UP #1

1. IND NUMBER	2. AGENT NAME	3. DATE
123618	MK-3475 (pembrolizumab) Ziv-aflibercept (VEGF-Trap, AVE 0005)	**July 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
9676 (AE #2947697)	**Grade 4: Immune system disorders: immune-mediated encephalomeningitis** ~~Grade 4: Encephalitis infection~~ ~~Grade 4: Meningitis~~

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
FL065-046	64 years	Female

12. PROTOCOL SPECIFIED

Cycle: 14 Days
MK-3475: 2 mg/kg IV over 30 minutes on Day 1
Ziv-aflibercept (VEGF-Trap, AVE 0005): 4 mg/kg IV over approximately one hour on Day 1

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on February 18, 2019 and received the last doses of pembrolizumab and ziv-aflibercept on March 18, 2019 (Cycle 3, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 64-year-old female with melanoma of the eye who experienced **grade 4 immune-mediated encephalomeningitis** ~~grade 4~~ ~~encephalitis infection and grade 4 meningitis~~ while on a Phase 1 trial utilizing the investigational agents pembrolizumab and ziv-aflibercept. Additional information has been requested from the investigational site.

The Initial Written Report was submitted to the FDA on June 28, 2019.

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

The patient has a past medical history of hypertension. On March 26, 2019 (Cycle 3, Day 9), the patient was seen in the emergency room (ER) for headache, neck pain and vomiting. She claimed to be nauseated from the pain, and she was placed on ondansetron and pain medications. That day, she was admitted and started on doxycycline and levofloxacin. On March 27, 2019, a brain MRI showed small vessel ischemic disease with no evidence of metastasis or other acute findings. On March 28, 2019, her blood cultures showed no growth. On March 29, 2019, a stroke alert was called. Her temperature was 104.5°F. A spinal tap was ordered to rule-out aseptic meningitis versus carcinomatous meningitis. A repeat blood culture was not positive for *Staphylococcus capitis.* A CT scan of the head was negative. Due to severe sepsis with lactic acidosis, tachycardia and her immunocompromised state, the treating physician suspected she had meningitis or hospital-acquired pneumonia. Her antibiotics was changed to IV vancomycin and cefepime. On March 30, 2019, her headache improved and her cerebrospinal fluid (CSF) showed no white blood cells (WBC), 11 red

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blood cells (RBC), 48 mg/dL of glucose, and 27 mg/dL of protein (reference ranges not provided). On March 31, 2019, a laboratory result showed a WBC of 7.3 ×10^3µL, hemoglobin of 11.9 g/dL, hematocrit of 36.7%, sodium of 133 mmol/L, potassium of 3.7 mmol/L, and carbon dioxide of 20 mmol/L (reference ranges not provided). That night she had difficulty breathing. On April 1, 2019, the patient continued to have an elevated temperature reaching 102.5°F. On April 3, 2019, a CT scan of the thorax, abdomen and pelvis showed new cardiomegaly with new small pericardial effusion and new small bilateral pleural effusions. On April 4, 2019, the patient continued to remain tachycardic and encephalopathic, and an electroencephalogram (EEG) showed a non-specific moderate to severe encephalopathy. On April 5, 2019, a repeat lumbar puncture showed 37 WBC and 75 RBC. She was started on solumedrol and then transitioned to a prednisolone taper over six weeks. On April 12, 2019, the patient was taken off her study therapy and was discharged to a rehabilitation facility. Additional information has been requested from the investigational site.

15. ACCRUAL AND IND EXPERIENCE

~~Pending for 15-day report.~~

Number of patients enrolled in NCI-sponsored clinical trials using pembrolizumab under NSC 776864 = 2,942.

Number of patients enrolled in NCI-sponsored clinical trials using ziv-aflibercept under NSC 724770 = 1,046.

There have been no other cases of immune mediated encephalomeningitis reported to the NCI through CTEP-AERS as serious adverse events for pembrolizumab under NSC 776864 and ziv-aflibercept under NSC 724770.

16. ASSESSMENT

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

In this case, it is felt that a definite relationship exists between the immune-mediated encephalomeningitis and the investigational agent pembrolizumab, and that there is no relationship between the immune-related encephalomeningitis and the investigational agent ziv-aflibercept.

	Encephalomeningitis
MK-3475 (Pembrolizumab)	**Definite**
Ziv-aflibercept (VEGF-Trap, AVE 0005)	**Unrelated**
Melanoma	**Unrelated**

17. CONCOMITANT MEDICATIONS

~~Pending for 15-day report.~~

Medications taken at the time of the event were acetaminophen-hydrocodone, alprazolam, amlodipine, clonidine, hydralazine, hydrocortisone, metoprolol and sodium chloride.

18. COMMENTS

~~Pending for 15-day report.~~

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.