IND SAFETY REPORT: FOLLOW-UP#1		
1. IND NUMBER 120268	2. AGENT NAME MK-3475 (pembrolizumab) Epacadostat (INCB024360)	3. DATE **May 21, 2019**
4. SPONSOR Division of Cancer Treatment and Diagnosis, National Cancer Institute		
5. REPORTER'S NAME, TITLE, AND INSTITUTION Elad Sharon, MD, MPH – Medical Officer for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI Howard Streicher, MD – Medical Officer for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI		6. PHONE NUMBER 240-276-6565 7. EMAIL ADDRESS ctepsupportae@tech-res.com
8a. PROTOCOL NUMBER (AE #) NRG-GY016 (AE #2169620)	8b. AE GRADE: AE Grade 5: Gastrointestinal disorders: intestinal perforation unknown site Grade 4: Disseminated intravascular coagulation Grade 4: Sepsis	
9. PATIENT IDENTIFICATION NM004-GY016-00010	10. AGE 57 years	11. SEX Female
12. PROTOCOL SPECIFIED Cycle = 21 days MK-3475 (Pembrolizumab): 200 mg (fixed dose) IV Q3 Weeks Epacadostat (INCB024360): 100 mg PO BID		
13. TREATMENT RECEIVED AND DATES The patient began the investigational therapy on April 2, 2019, and received the last dose of pembrolizumab on April 2, 2019 (Cycle 1, Day 1) and the last dose of epacadostat on April 14, 2019 (Cycle 1, Day 11).		

14. DESCRIPTION OF ADVERSE EVENT

The patient was a 57-year-old female with metastatic ovarian cancer who experienced grade 4 disseminated intravascular coagulation, grade 4 sepsis, and expired on ~~April 5~~ **May 9,** 2019 from intestinal perforation at an unknown site, while on a Phase 2 trial utilizing the investigational agents pembrolizumab and epacadostat . Additional information has been requested from the investigational site.

The Initial Written Report was submitted to the FDA on May 17, 2019.

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

The patient had a history of anxiety, asthma, deep venous thrombosis, and hypertension. Of note, the patient had been diagnosed with rib cage and thoracic spine disease; she had a baseline right-sided pleural effusion. On April 15, 2019 (Cycle 1, Day 12), the patient was admitted for excruciating back pain and low oxygen saturation requiring oxygen by nasal canula. The initial X-ray showed evidence of a large right pleural effusion. An MRI of the thoracic spine showed an interval increase in vertebral thoracic metastasis T3-T6 in addition to metastasis at level T9, T12, and L2 compared to a CT scan in March 2019. Her pain was successfully managed with morphine patient-controlled analgesia (PCA) and gabapentin. Her laboratory results showed an elevated troponin level at 0.745 ng/mL (reference range: not provided) that peaked at 1.5 ng/mL. The electrocardiogram (ECG) was normal, the cardiologist felt that the troponin leak was secondary to type 2 demand ischemia in the setting of a pleural effusion and hypoxia, especially in the context of a negative CT PE and unremarkable echocardiogram. On April 16, 2019, a thoracentesis was performed. On April 17, 2019, a follow-up X-ray showed an improved right pleural effusion and lung

ventilation, but the patient continued to require oxygen. On April 18, 2019, the patient was discharged on home oxygen, in stable condition. On April 21, 2019, the patient was readmitted for uncontrolled pain and intractable nausea and vomiting. On April 22, 2019 (Cycle 1, Day 18), a head CT scan and an MRI of the brain and brain stem were negative for cranial metastasis but suspected parietal bone metastasis bilaterally. The patient was started on hydromorphone PCA and fentanyl. On April 23, 2019, the patient was removed from the investigational study. On May 2, 2019 she was readmitted for abdominal pain and intractable nausea and vomiting. A CT of the abdomen showed a large abscess and a pneumoperitoneum consistent with a bowel perforation. She developed clinical sepsis with respiratory compromise, as well as disseminated intravascular coagulation and hemoptysis. The patient declined operative management and elected to pursue comfort measures only. She rapidly deteriorated. On May 9, 2019, the patient expired. No autopsy was performed.

15. ACCRUAL AND IND EXPERIENCE

~~Pending for 15-day report~~

Number of patients enrolled in NCI-sponsored clinical trials using pembrolizumab under NSC 776864 = 2,796.

Number of patients enrolled in NCI-sponsored clinical trials using epacadostat under NSC 766086 = 42.

There have been no other cases of intestinal perforation of unknown site reported to the NCI through CTEP-AERS as serious adverse event for pembrolizumab under NSC 776864.

There have been no other cases of intestinal perforation of unknown site reported to the NCI through CTEP-AERS as serious adverse event for epacadostat under NSC 766086.

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 intestinal perforation unknown site and the investigational agents pembrolizumab and epacadostat.

	Intestinal perforation unknown site
Epacadostat	**Possible**
Pembrolizumab	**Possible**
Ovarian epithelial cancer	**Probable**
Small bowel obstruction	**Probable**

17. CONCOMITANT MEDICATIONS

~~Pending for 15-day report~~

Medications taken at the time of the event were aspirin, cetirizine, diclofenac, docusate, enoxaparin, gabapentin, hydrocodone, acetaminophen, metoprolol, montelukast, morphine, olopatadine, ondansetron, prednisone, and ranitidine.

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

IND SAFETY REPORT: FOLLOW-UP#1
OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.