IND SAFETY REPORT: FOLLOW-UP # 1

1. IND NUMBER	2. AGENT NAME	3. DATE
133434	MK-3475 (pembrolizumab) Entinostat (MS-275, SNDX-275)	**August 20, 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
10009 (AE #2419922)	Grade 5: Multi-organ failure

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
CT018-0010	77 years	Male

12. PROTOCOL SPECIFIED

Cycle: 21 Days
Cycle 1
MS-275 (SNDX-275, entinostat): 8 mg PO on Days 1, 8, & 15
Cycles 2-18
MS-275 (SNDX-275, entinostat): 8 mg PO on Days 1, 8, & 15
MK-3475 (pembrolizumab): 200 mg IV over 30 minutes on Day 1

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on April 25, 2019 and received the last dose of pembrolizumab on July 22, 2019 (Cycle 5, Day 1) and the last dose of entinostat on July 29, 2019 (Cycle 5, Day 8).

14. DESCRIPTION OF ADVERSE EVENT

The patient was a 77-year-old male with myelodysplastic syndrome who expired on August 1, 2019 due to multi-organ failure while on a Phase 1 trial utilizing the investigational agents pembrolizumab and entinostat. Additional information has been requested from the investigational site.

The Initial Written Report was sent to the FDA on August 8, 2019.

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Of note, the patient had a past history of transfusion dependent anemia and thrombocytopenia. On July 8, 2019, the patient had increased his home furosemide from 20 mg to 40 mg for worsening lower extremity edema. On July 31, 2019, the patient presented to the oncology clinic with complaints of weakness and pleuritic pain. He had worsening fatigue for the prior 1-2 weeks with associated decreased appetite due to chronic epigastric pain and substernal pain with deep breaths/coughs. He had a blood pressure of 93/61 mmHg, temperature of 97.7°C, heart rate of 117 beats per minute, respiratory rate of 15 breaths per minute and an SpO_2 of 97%. A laboratory result showed a white blood cell count of 17.5 K/µL (reference range: 4–10 K/µL), a creatinine of 1.48 mg/dL (reference range: 0.40–1.30 mg/dL), alkaline phosphatase of 135 U/L (reference range: 9-122 U/L), alanine aminotransferase (ALT) of 181 (reference range: 6-34 U/L), aspartate aminotransferase (AST) of 159 (reference range: 11-33 U/L), bilirubin of 2.7 mg/dL (reference range: <1.2 mg/dL), and a troponin of 0.16 ng/mL (reference range: <0.01 ng/mL). A chest X-ray showed bibasilar plate like atelectasis, small bilateral pleural effusion, and a retrocardiac opacity which could represent

atelectasis/aspiration/pneumonia. A transthoracic echo cardiogram showed severely decreased left ventricular ejection fraction, severely decreased right ventricular systolic function, mild mitral regurgitation, severe tricuspid regurgitation, and severe global hypokinesis. He was started on vancomycin and piperacillin/tazobactam. He was admitted to the medical intensive care unit (MICU) and was given 1L normal saline over 2 hours. Cardiology was consulted due to concern for cardiogenic shock and the patient was started on norepinephrine. Hematology was consulted and the patient was given one dose of 60 mg prednisone due to concern for immune mediated myocarditis. He remained hypotensive despite the up titration of norepinephrine and developed a worsening respiratory status. His liver function tests and creatinine worsened indicating multiorgan failure. An arterial line was attempted unsuccessfully. He developed atrial fibrillation with rapid ventricular rate and was started on amiodarone and continuous positive airway pressure (CPAP) which he was unable to tolerate. The patient was DNR and was transitioned to comfort measures only. He was started on morphine drip for pain. On the morning of August 1, 2019, the patient expired. An autopsy was not done.

15. ACCRUAL AND IND EXPERIENCE

~~Pending for 15-day report.~~

Number of patients enrolled in NCI-sponsored clinical trials using pembrolizumab under NSC 776864= 3,077.

Number of patients enrolled in NCI-sponsored clinical trials using pembrolizumab under NSC 706995= 1,528.

There have been 6 other cases of multi-organ failure reported to the NCI through CTEP-AERS as serious adverse events for entinostat under NSC 706995.

There have been no other cases of multi-organ failure reported to the NCI through CTEP-AERS as serious adverse event for pembrolizumab under NSC 776864.

Adverse Event	Grade	Attribution
Entinostat (NSC #706995)		
Multi-organ failure (n=6)	**5**	**1 Possible, 3 Unlikely, 2 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 multi-organ failure and the investigational agent pembrolizumab and an unlikely relationship exists between the multi-organ failure and the investigational agent entinostat.

	Multi-organ failure
Entinostat	**Unlikely**
Pembrolizumab	**Possible**
Myelodysplastic syndrome	**Possible**
Sepsis	**Probable**

17. CONCOMITANT MEDICATIONS

~~Pending for 15-day report.~~

Medications taken at the time of the event were ascorbic acid, bacitracin, clotrimazole-betamethasone,

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docusate sodium, furosemide, lidocaine-prilocaine, loperamide, ondansetron, and zolpidem.
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.