IND SAFETY REPORT: FOLLOW-UP #1

1. IND NUMBER	2. AGENT NAME	3. DATE
137759	KW-0761 (mogamulizumab) MK-3475 (pembrolizumab)	**June 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
10106 (AE #2129377)	~~Grade 4: Hypotension~~ **Grade 4: Cardiac disorders: Apical ballooning** **Grade 4: Infusion related reaction**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
NY016-0002	71 years	Male

12. PROTOCOL SPECIFIED

Cycle = 21 days (max = 35 cycles)
KW-0761 (Mogamulizumab): 1 mg/kg IV on Days 1, 8 and 15
MK-3475 (Pembrolizumab): 200 mg IV on Day 1

Cycle 2+
KW-0761 (Mogamulizumab): 1.5 mg/kg IV on Day 1
MK-3475 (Pembrolizumab): 200 mg IV on Day 1

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on April ~~14~~**15**, 2019, and received the last doses of mogamulizumab and pembrolizumab on June 6, 2019 (Cycle 3, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 71-year-old male with diffuse large B-cell lymphoma, who experienced grade 4 ~~hypotension~~ **apical ballooning and grade 4 infusion related reaction** while on a Phase 1/2 trial utilizing the investigational agents mogamulizumab and pembrolizumab. Additional information has been requested from the investigational site.

The Initial Written Report was sent to the FDA on June 14, 2019.

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

Of note, the patient has a history of acute motor axonal neuropathy, hypothyroidism, Epstein-Barr virus-positive (EBV+) diffuse large B-cell lymphoma (EBV+ DLBCL), reactive airways, obesity, hypertension, coronary artery disease (CAD) status post 3-vessel coronary artery bypass graft, and intermittent right bundle branch block. On June 6, 2019 (Cycle 3, Day 1), the patient presented to the clinic feeling very weak, and tired, and had ongoing productive cough with clear sputum. His pre-infusion blood pressure was 88/62 mmHg. That day, he received his pembrolizumab infusion. Ten minutes into his mogamulizumab infusion, he developed what seemed like an infusion reaction with hypotension, rigors, and dyspnea. The infusion was stopped, and his blood pressure was 80/40 mmHg. Of note, per protocol, he did not receive premedication before the infusion. He was started on diphenhydramine, famotidine, methylprednisolone, albuterol, and normal saline. His symptoms improved but his blood pressure was unresponsive to fluid resuscitation

(systolic blood pressure in the 60-70s mmHg). He was placed on norepinephrine bitartrate and was transferred to the intensive care unit (ICU) for management of shock. At the ICU, he was alert and oriented and was able to speak coherently. His troponin level was 0.53 ng/ml (reference range: </= 0.02 ng/mL). On June 7, 2019, an echocardiogram showed a new left ventricular (LV) dysfunction with Takotsubo pattern with akinetic mid to apical portions of all walls and with hyperdynamic basal segments. His ejection fraction determined by 2-D echocardiogram was 37%. His troponin level was 0.64 ng/mL. A telemetry tracing showed a period of severe sinus bradycardia with short idioventricular vs. junctional escape rhythm. A chest radiograph showed pulmonary vascular congestion. It was unclear what this acute cardiac event represented. The pattern of LV wall motion abnormalities and low-level troponin suggested a stress induced cardiac myopathy; however, in the presence of known CAD and check-point inhibitor therapy, an acute myocardial infarction/ severe ischemia or myocarditis related to pembrolizumab could not be ruled out. That day, a right and left heart catheterization showed non-obstructive coronaries and grafts with apical hypokinesis on ventriculogram. Global left ventricular systolic function was moderately to severely decreased with wall motion abnormalities suggestive of Takatsubo's cardiomyopathy. There was a triple vessel native coronary disease with patent grafts (LIMA-to-LAD, RIMA-to-RPDA, radial-to-OM1; mild dilatation of the aortic root and ascending aorta). A right ventricle biopsy was negative for myocarditis, granulomas or amyloid. Cortisol levels that was measured for suspected Addisonian crisis was in normal-high range repeatedly. On June 10, 2019, an echocardiogram showed the mid to distal left ventricular wall was severely hypokinetic to akinetic and the apical cap was akinetic. There was eccentric left ventricular hypertrophy. The global left ventricle function was severely reduced to 30-35%. The left atrium was severely dilated, and the right ventricle was mildly dilated with mildly reduced function. There was a septal motion consistent with a conduction defect. There was no pericardial effusion. Additional information has been requested from the site.

15. ACCRUAL AND IND EXPERIENCE

~~Pending for 15-day report~~

Number of patients enrolled in NCI-sponsored clinical trials using mogamulizumab under NSC 791064 = 4.
Number of patients enrolled in NCI-sponsored clinical trials using pembrolizumab under NSC 776864 = 2,893.
There have been no other cases of apical ballooning reported to the NCI through CTEP-AERS as serious adverse events for mogamulizumab under NSC 791064 or for pembrolizumab under NSC 776864.
There have been no other cases of infusion related reaction reported to the NCI through CTEP-AERS as serious adverse events for mogamulizumab under NSC 791064.
There has been 1 definite case of infusion related reaction reported to the NCI through CTEP-AERS as serious adverse events for pembrolizumab under NSC 776864.

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 apical ballooning and infusion related reaction and the investigational agents mogamulizumab and pembrolizumab.

	Apical ballooning	Infusion related reaction
Mogamulizumab	Possible	Probable
Pembrolizumab	Possible	Possible
Diffuse large B-cell	Unlikely	Unlikely

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lymphoma
17. CONCOMITANT MEDICATIONS ~~Pending for 15-day report~~ **Medications taken at the time of the event were polyethylene glycol, dronabinol, amoxicillin, guaifenesin, ondansetron, magnesium oxide, methylphenidate, levothyroxine, polysaccharide iron complex, codeine-guaifenesin, potassium chloride, bupropion, diclofenac sodium, acyclovir, lorazepam, aspirin, vitamin D3, and pantoprazole.**
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.