7-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
125462	**Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride)** **Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)** **Nivolumab**	**March 11, 2021**

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
10145 (AE #2168935)	**Grade 4: Gastric Ulcer** **Grade 4: Pneumonitis** **Grade 4: Platelet count decreased** **Grade 3: Myocarditis**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
NCIDTC-0027	**55 years**	**Female**

12. PROTOCOL SPECIFIED

Triplet Safety Run-in: Ipilimumab (Cycles 1-4 only) + Copanlisib + Nivolumab

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on January 26, 2021, and received the first and only doses of copanlisib dihydrochloride, nivolumab, and ipilimumab that same day (Cycle 1, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 55-year-old female with a metastatic clear cell ovarian sarcoma who developed a grade 4 gastric ulcer, grade 4 pneumonitis, grade 4 platelet count decrease, and grade 3 myocarditis while on a Phase Ib trial utilizing the investigational agents copanlisib dihydrochloride, nivolumab, and ipilimumab. The last doses of each agent were given on January 26. 2021. On February 2, 2021 (Cycle 1, Day 8), the patient presented to the clinic for scheduled Week 2 protocol therapy and was found to have an elevated troponin level of 0.2 ng/mL (reference range: not provided) and an abnormal electrocardiogram (ECG). The patient reported having no symptoms. Following a cardiology consult, the patient was tested for pro B-type natriuretic peptide (proBNP) which was found to be abnormal. On February 3, 2021, she returned to the clinic for follow-up. That day, an echocardiogram showed an increase in left ventricular dilation as compared to a baseline scan performed on January 5, 2021. Of note, the patient's troponin and proBNP levels fluctuated but remained elevated over the following two weeks and her ECG continued to be abnormal, yet the patient remained asymptomatic. On February 5, 2021, a cardiac MRI demonstrated myocarditis and the patient was started on high dose steroids. On February 8, 2021, her troponin levels decreased to 0.07 ng/mL and proBNP levels decreased but remained elevated at 9,684 pg/mL (reference range: not provided). The patient's steroid dose was adjusted to 100mg daily. On February 16, 2021, a repeat echocardiogram showed improved function with an ejection fraction (EF) of 55%. On February 23, 2021, the cardiologist felt that the creatine kinase/creatine kinase-MB ratio of < 10% was stable and the patient's steroids could be safely dose reduced to 80mg. The patient reported onset of a non-pruritic rash which started a few days prior, and covered her back, chest, neck, and face. She was given a topical steroid cream. On February 26, 2021, the treating physician continued to hold the protocol agents until the myocarditis was controlled. On February 28, 2021, the patient was admitted for hypoxia. Upon arrival, her

oxygen saturation (SpO_2) was around 50% on room air, requiring initiation of supplemental oxygen through nasal cannula at 6 L/min to achieve an SpO_2 in the 80s. She was started on bilevel positive airway pressure (BiPAP) therapy, following which her SpO_2 remained in the 90s. She was started on broad spectrum antibiotics and blood cultures were drawn. Laboratory results were significant for a hemoglobin of 7.6 g/dL (reference range: not provided). A CT scan showed increased pleural effusion and a therapeutic thoracentesis was performed. That day, a repeat echocardiogram showed an EF of 55%. On March 1, 2021, the patient's condition worsened, and she was intubated for continued oxygenation. Blood cultures showed no growth. On March 2, 2021, the patient's hemoglobin level decreased to 4.8 g/dL. An ultrasound of bilateral lower extremities showed a possible thrombus in the right femoral/saphenous vein, partial occlusive thrombus to the right femoral vein, and total occlusive thrombus at the right femoral and popliteal vein. She was started on heparin and 2 units of packed red blood cells were transfused. On March 3, 2021, an esophagogastroduodenoscopy (EGD) showed an oozing ulcer at the gastric antrum, non-bleeding gastric ulcer, and clotted blood in the fundus. She was treated with coagulation spray therapy, following which her hemoglobin levels remained stable. On March 7, 2021, the patient was weaned off ventilation and initiated on high flow nasal cannula (HFNC) at 5.5 L/min. The patient's platelet count dropped to 14 x 10^9/L and her hemoglobin level decreased to 6 g/dL. Per the family's request, the patient's status was changed to do-not-resuscitate and do-not-intubate and she was transitioned to comfort care. Additional information has been requested from the investigational site.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using copanlisib dihydrochloride under NSC 784727 = 180.

Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = 7,203.

Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 732442 = 7,887.

Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 720801 = 208.

There have been no other cases of gastric ulcer reported to the NCI through CTEP-AERS as serious adverse events for copanlisib dihydrochloride under NSC 784727.

There have been two other cases of gastric ulcer reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.

There has been one other case of gastric ulcer (grade 3, possible) reported to the NCI through CTEP-AERS as a serious adverse event for ipilimumab under NSC 732442.

There have been no other cases of gastric ulcer reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 720801.

There have been no other cases of myocarditis reported to the NCI through CTEP-AERS as serious adverse events for copanlisib dihydrochloride under NSC 784727.

Myocarditis is an expected event for ipilimumab and nivolumab.

Pneumonitis is an expected event for copanlisib dihydrochloride, ipilimumab, and nivolumab.

There have been 31 other cases of platelet count decreased reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 732442.

There has been one other case of platelet count decreased (grade 4, unlikely) reported to the NCI through CTEP-AERS as a serious adverse event for ipilimumab under NSC 720801.

Platelet count decreased is an expected event for copanlisib dihydrochloride and nivolumab.

Adverse Event	Grade	Attribution
Nivolumab (NSC 748726)		
Gastric ulcer (n=2)	3 2	1 Unlikely 1 Unlikely

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Ipilimumab (NSC 732442)		
Platelet count decreased (n=31)	4 3 2	2 Probable, 5 Possible, 7 Unlikely, 1 Unrelated 1 Probable, 3 Possible, 5 Unlikely 5 Possible, 1 Unlikely, 1 Unrelated

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the myocarditis, and the pneumonitis and the investigational agents copanlisib dihydrochloride, ipilimumab, and nivolumab.

A possible relationship exists between the platelet count decreased and the investigational agent copanlisib dihydrochloride. The platelet count decreased is not related to the investigational agents ipilimumab or nivolumab.

The gastric ulcer is not related to the investigational agents copanlisib dihydrochloride, ipilimumab, or nivolumab.

	Myocarditis	Gastric ulcer	Pneumonitis	Platelet count decreased
Copanlisib dihydrochloride	Possible	Unlikely	Possible	Possible
Ipilimumab	Possible	Unrelated	Possible	Unlikely
Nivolumab	Possible	Unrelated	Possible	Unlikely
Metastatic clear cell ovarian sarcoma	Unlikely	Possible	Unrelated	Unlikely
Anticoagulation therapy	Unrelated	Unrelated	Unrelated	Possible
Continued steroid use	Unrelated	Possible	Unlikely	Possible
Prior therapy	Possible	Unlikely	Unrelated	Unlikely
Gastric ulcer	Unrelated	N/A	Unrelated	Possible
Stress	Unrelated	Possible	Unlikely	Unlikely
Environment/infection	Unlikely	Unrelated	Possible	Unlikely

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were not provided.

18. COMMENTS

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.