FOLLOW-UP IND SAFETY REPORT # 1

1. IND NUMBER	2. AGENT NAME	3. DATE
125462	Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) Nivolumab	**November 16, 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
10193 (AE #2410214)	Grade 3: Hypoxia

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
NC002-0011	75 years	Female

12. PROTOCOL SPECIFIED

Cycles 1-8
Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride): 60 mg IV on Days 1, 8 and 15
BMS-936558 (Nivolumab, MDX-1106): 240 mg IV on Days 1 and 15

Cycle 9+
Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride): 60 mg IV on Days 1 and 15
BMS-936558 (Nivolumab, MDX-1106): 480 mg IV on Day 1

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on July 14, 2021, and received the last doses of copanlisib dihydrochloride and nivolumab on August 25, 2021 (Cycle 2, Day 15).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 75-year-old female with refractory diffuse large B-cell lymphoma who experienced grade 3 hypoxia while on a Phase II trial utilizing the investigational agents copanlisib dihydrochloride and nivolumab. The patient has a history of atrial fibrillation, polyp of the colon, and is a former smoker. On September 19, 2021, the patient was brought to the emergency department (ED) by emergency medical services (EMS) for evaluation of increased confusion, falls, burning sensation with urination, and frequent drop in oxygen saturation to 85% on room air. Upon arrival, the patient was alert but lethargic and in mild distress. She had a temperature of 37.8°C, blood pressure of 121/64 mmHg, heart rate of 82 beats per minute, respiratory rate of 27 breaths per minute, and an oxygen saturation (SpO_2) of 98% on room air. On physical examination, she was slow to respond. Laboratory results were significant for partial thromboplastin time of 117.9 seconds (reference range: 23.9-30.7 seconds), urinalysis showed a trace amount of blood (reference range: negative), 1+ protein (reference range: negative), 1+ leukocyte esterase (reference range: negative), white blood cell count of 31-50/ HPF (reference range: 0/ HPF), red blood cell count of 6-10/ HPF (reference range: 0/ HPF), and 1+ bacteria/ HPF (reference range: 0/ HPF). The patient was started on empiric ceftriaxone and intravenous fluids in the ED, and initially placed on supplemental oxygen. Blood and urine cultures were obtained. An electrocardiogram (EKG) showed sinus tachycardia, inferior infarct, and anterolateral infract. A CT angiography (CTA) of the chest showed an eccentric non-occlusive thrombus within the left superior portion of the pulmonary trunk, bibasilar consolidation, and multifocal ground glass opacities were noted in the lungs, representing pulmonary infarcts *vs.* multifocal pneumonia. A CT scan of the head without contrast showed no evidence of an acute intracranial process. The patient was admitted to the in-patient unit and treatment with IV heparin and azithromycin was initiated. On September 20, 2021, an echocardiogram showed normal left ventricular systolic function with an ejection fraction of 60%, mild mitral regurgitation, and pulmonary artery pressure of 29.38 mmHg. On September 28, 2021, a chest X-ray showed extensive bilateral airspace disease and low lung volumes. On September 29, 2021, a CT scan of the chest without contrast revealed patchy bilateral pulmonary opacities, mild bilateral pleural effusions (left > right), and multilobular pneumonitis, which had

increased in severity as compared to the previous scan. A repeat urinalysis revealed a red blood cell count of 0-2, no white blood cells, and no bacteria. On October 2, 2021, a repeat CT scan of the chest without contrast revealed grossly stable left lung consolidation with decreased consolidation on the right lung and overall decreased interspersed crazy paving, suggestive of interval improvement with potential organization. Additional information has been requested from the investigational site.

The Initial Written Report was sent to the FDA on October 22, 2021, as a 15-day report.

<u>Follow-up #1</u>:
On October 2, 2021, the patient required bilevel positive airway pressure (BiPAP) with a high level of oxygen support. She was placed on a high dose of corticosteroids for pneumonitis. On October 4, 2021, a repeat chest X-ray showed an improvement in the left upper lobe consolidation and an apparent increase in the opacity at the right lung base, suggestive of worsening atelectasis *vs.* consolidation. Laboratory results were significant for a histoplasmosis yeast antibody titer of 1:32 (reference range: <1:2). The infectious disease specialist started the patient on itraconazole. During the hospitalization, the patient had one episode of hematemesis, and her IV heparin was stopped. The oxygen requirement of the patient was weaned down to 1 L by nasal cannula, and there was marked improvement in the clinical status of the patient. On October 14, 2021, the patient developed abdominal discomfort. A CT scan of the abdomen and pelvis showed a large-volume pneumoperitoneum predominantly within the upper abdomen with locules of gas adjacent to the gastric pylorus and antrum of the stomach, suggestive of perforation within the upper gastrointestinal tract due to the distribution of extraluminal gas. However, there was no discrete site of perforation noted. Following a surgical consultation, the patient was advised to be kept nil per oral, and no acute surgical intervention was recommended at that time. On October 15, 2021, the patient was transferred to another hospital for evaluation of pneumoperitoneum. Upon arrival, the patient was hemodynamically stable and was in no acute distress. On October 16, 2021, a repeat CT scan of the abdomen showed moderate pneumoperitoneum of unclear source, no evidence of bowel perforation, and no extravasation of dye into the peritoneum. Upon consultation with the surgeon, the patient declined to undergo any surgical intervention, and she was started on proton pump inhibitors. That day, she was seen by an infectious disease specialist who stopped the antibiotics as the patient was clinically stable. On October 21, 2021, the patient was discharged in a stable condition to a skilled nursing facility on trimethoprim-sulfamethoxazole prophylaxis for prevention of *Pneumocystis jirovecii* infection and a plan to taper corticosteroids. Additional information has been requested from the investigational site.

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15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using copanlisib dihydrochloride under NSC 784727 = 191.

Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = 8,407.

There have been 3 other cases of hypoxia reported to the NCI through CTEP-AERS as serious adverse events for copanlisib dihydrochloride under NSC 784727.

There have been 55 other cases of hypoxia reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.

Adverse Event	Grade	Attribution
Copanlisib dihydrochloride (NSC 784727)		
Hypoxia (n=3)	4 3	1 Possible 1 Definite, 1 Possible
Nivolumab (NSC 748726)		
Hypoxia (n=55)	5 4 3 2	1 Possible, 2 Unrelated 2 Possible, 1 Unrelated 1 Definite, 3 Probable, 14 Possible, 16 Unlikely, 4 Unrelated 3 Possible, 7 Unlikely, 1 Unrelated

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the hypoxia and the investigational agent copanlisib dihydrochloride.

A probable relationship exists between the hypoxia and the investigational agent nivolumab.

	Hypoxia
Copanlisib dihydrochloride	Possible
Nivolumab	Probable
Diffuse large B-cell lymphoma	Unlikely
Pulmonary embolism	Probable

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were alendronate, diltiazem, doxycycline hyclate, magnesium oxide, oxycodone, albuterol sulfate, docusate sodium, and solifenacin.

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.