# 7-DAY IND SAFETY REPORT

| 1. IND NUMBER | 2. AGENT NAME | 3. DATE |
|---|---|---|
| **125462** | **Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride)**<br>**Nivolumab** | **March 23, 2021** |

4. SPONSOR

**Division of Cancer Treatment and Diagnosis, National Cancer Institute**

| 5. REPORTER'S NAME, TITLE, AND INSTITUTION | 6. PHONE NUMBER |
|---|---|
| **Howard Streicher, MD – Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI**<br><br>**John T. Sandlund, MD – Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI** | **240-276-6565**<br>7. EMAIL ADDRESS<br>**ctepsupportae@tech-res.com** |

| 8a. PROTOCOL NUMBER (AE #) | 8b. AE GRADE: AE |
|---|---|
| **10193 (AE #2161660)** | **Grade 5: Cardiac arrest** |

| 9. PATIENT IDENTIFICATION | 10. AGE | 11. SEX |
|---|---|---|
| **AL002-0009** | **74 years** | **Male** |

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 February 25, 2021, and received the first and only dose of nivolumab that same day (Cycle 1, Day 1), and the last dose of copanlisib dihydrochloride on March 2, 2021 (Cycle 1, Day 6) (unconfirmed).**

14. DESCRIPTION OF ADVERSE EVENT

**The patient was a 74-year-old male with diffuse large B-cell lymphoma who expired on March 4, 2021, due to cardiac arrest while on a Phase II trial utilizing the investigational agents copanlisib and nivolumab. The patient had a history of arthritis, atrial fibrillation, chronic obstructive pulmonary disease, diabetes mellitus, gastro-esophageal reflux disease, hyperlipidemia, hypertension, peptic ulcer disease, smoking, and sleep apnea. On February 25, 2021, routine screening blood work prior to his Cycle 1, Day 1 therapy showed a blood glucose of 207 mg/dL and an elevated troponin I (high sensitivity) of 22 ng/mL; and a troponin I of 32 ng/dL a few hours later (reference ranges: not provided). On March 4, 2021, the patient presented to the clinic for repeat blood work following which he collapsed. At that time, his blood glucose was 350 mg/dL and a COVID-19 test was negative. Cardiopulmonary resuscitation (CPR) was initiated, and the patient was given epinephrine x5 and bicarbonate x2. The patient was found to be in pulseless electrical activity (PEA) and did not achieve return of circulation despite defibrillation. The patient was intubated despite initial difficulty visualizing the airway due to bloody secretions. He was then transported to the emergency department (ED) by emergency medical services. CPR was continued upon arrival and he was given 3 more doses of epinephrine and one dose of calcium. A bedside ultrasound confirmed cardiac standstill with persistent PEA. The patient was pronounced dead in the ED. An autopsy was not performed.**

15. ACCRUAL AND IND EXPERIENCE

**Number of patients enrolled in NCI-sponsored clinical trials using copanlisib dihydrochloride under NSC 784727=182.**
**Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726=7,289.**
**There have been no other cases of cardiac arrest reported to the NCI through CTEP-AERS as serious adverse events for copanlisib dihydrochloride under NSC 784727.**
**There have been 11 other cases of cardiac arrest reported to the NCI through CTEP-AERS as serious**

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**adverse events for nivolumab under NSC 748726.**

| Adverse Event | Grade | Attribution |
|---|---|---|
| ***Nivolumab (NSC 748726)*** | | |
| **Cardiac arrest (n=11)** | **4**<br>**5** | **1 Possible, 1 Unlikely**<br>**5 Possible, 1 Unlikely, 3 Unrelated** |

16. ASSESSMENT

**Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the cardiac arrest and the investigational agents copanlisib dihydrochloride and nivolumab.**

| | Cardiac arrest |
|---|---|
| **Copanlisib dihydrochloride** | **Possible** |
| **Nivolumab** | **Possible** |
| **Diffuse large B-cell lymphoma** | **Unlikely** |
| **Medical history of atrial fibrillation** | **Probable** |
| **Pulseless electrical activity, sudden death, possible pulmonary embolism** | **Possible** |

17. CONCOMITANT MEDICATIONS

**Medications taken at the time of the event were allopurinol, sucralfate, cetirizine, cilostazol, fluticasone, linaclotide, metoprolol, montelukast, omeprazole, oxycodone, topiramate, and topical triamcinolone.**

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.**