# FOLLOW-UP IND SAFETY REPORT #1

| 1. IND NUMBER | 2. AGENT NAME | 3. DATE |
|---|---|---|
| 129803 | Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)<br>Nivolumab<br>XL184 (Cabozantinib) | **November 12, 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 Wright, MD, PhD – Associate Branch Chief, 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 |
|---|---|
| A031704 (AE #2764709) | Grade 5: ~~Death NOS~~ **Cardiac disorders: Cardiogenic shock**<br>Grade 3: Chest pain - cardiac |

| 9. PATIENT IDENTIFICATION | 10. AGE | 11. SEX |
|---|---|---|
| 9128540 | 83 years | Male |

12. PROTOCOL SPECIFIED

Cycle = 28 Days

Nivolumab (BMS-936558, MDX-1106): 480 mg IV on Day 1

XL184 (Cabozantinib): 40 mg PO QD

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on February 5, 2020, and received the last dose of ipilimumab on April 8, 2020, the last dose of nivolumab on June 15, 2021, and the last dose of cabozantinib on July 4, 2021.

14. DESCRIPTION OF ADVERSE EVENT

The patient was an 83-year-old male with metastatic clear cell renal cell adenocarcinoma who developed grade 3 cardiac chest pain and later expired on July 7, 2021, **due to cardiogenic shock** while on a Phase III trial utilizing the investigational agents ipilimumab, nivolumab, and cabozantinib. Additional information has been requested from the investigational site.

**The Initial Written Report was sent to the FDA on August 2, 2021, as a 7-day report.**

**The patient had a history of coronary heart disease, myocardial infarction status post angioplasty with stent placement, skin cancer, hypertension, atrial fibrillation, hyperlipidemia, and was a former smoker. On July 4, 2021, the patient presented to the emergency department (ED) complaining of a constant, sudden onset, left-sided chest pain, which started earlier that day. He described the pain as intense, heavy pressure localized to the midsternal region radiating to his left arm, left jaw, and left scapula, and was associated with diaphoresis, shortness of breath, and left arm numbness. He reported taking aspirin at home without relief. Upon arrival to the ED, he was alert and oriented. He had a blood pressure of 109/67 mmHg, a heart rate of 92 beats per minute, a respiratory rate of 18 breaths per minute, a temperature of 98.7 °F, and an oxygen saturation ($SpO_2$) of 98% on room air. Physical examination revealed an irregularly, irregular heart rhythm. Laboratory results were significant for a troponin I level of <0.02 ng/mL (reference range: 0.00-0.04 ng/mL). An electrocardiogram (ECG) showed atrial fibrillation, right bundle branch block (RBBB), and ST depression in the anterolateral leads with occasional premature ventricular contractions (PVCs). A chest X-ray showed an enlarged lung mass and fibrotic changes in the lungs. A CT scan of the chest with contrast showed progression of the right lower lobe mass and the smaller bilateral lung nodules, cardiomegaly, and coronary artery calcifications. There was no evidence of pulmonary embolism. He was**

**diagnosed with a non-ST elevated myocardial infarction (NSTEMI), started on intravenous fluids, nitroglycerin, acetaminophen, ondansetron, morphine, melatonin, iopamiodol, and admitted for further management. Overnight, the patient's troponin level trended up to 3.09 ng/mL and he was started on heparin. On July 5, 2021, the patient was asymptomatic, and a repeat ECG showed atrial fibrillation, RBBB, and normalization of his ST depression. An echocardiogram showed an ejection fraction (EF) of 35-40%. His troponin level was elevated to 12.62 ng/mL. That day, he was removed from the study treatment. On July 6, 2021, the patient was scheduled to undergo a left heart catherization, but the procedure was aborted due to patient feeling short of breath and being unable to tolerate lying flat. On July 7, 2021, the patient was noted to have difficulty breathing, hypoxia, and hypotension. Laboratory results were significant for a B-type natriuretic peptide level of 1,500.4 pg/mL (reference range: 0.0-100.0 pg/mL). The patient was intubated due to worsening respiratory distress and went into cardiogenic shock followed by cardiac arrest. Despite receiving cardiopulmonary resuscitation for 30 minutes, the patient did not regain a pulse and was pronounced dead. An autopsy was not performed.**

15. ACCRUAL AND IND EXPERIENCE

~~Pending Follow-up report.~~

**Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 732442 = 8,576.**
**Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 720801 = 208.**
**Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = 8,505.**
**Number of patients enrolled in NCI-sponsored clinical trials using cabozantinib under NSC 761968 = 2,329.**
**There have been no other cases of cardiogenic shock reported to the NCI through CTEP-AERS as a serious adverse event for ipilimumab under NSC 732442.**
**There have been no other cases of cardiogenic shock reported to the NCI through CTEP-AERS as a serious adverse event for ipilimumab under NSC 720801**
**There have been no other cases of cardiogenic shock reported to the NCI through CTEP-AERS as a serious adverse event for nivolumab under NSC 748726.**
**There have been no other cases of cardiogenic shock reported to the NCI through CTEP-AERS as a serious adverse event for cabozantinib under NSC 761968.**
**There have been 12 other cases of cardiac chest pain reported to the NCI through CTEP-AERS as a serious adverse event for ipilimumab under NSC 732442.**
**There have been no other cases of cardiac chest pain reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 720801**
**There have been 11 other cases of cardiac chest pain reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.**
**There have been 3 other cases of cardiac chest pain reported to the NCI through CTEP-AERS as serious adverse events for cabozantinib under NSC 761968.**

| Adverse Event | Grade | Attribution |
|---|---|---|
| ***Ipilimumab NSC (732442)*** | | |
| Chest pain - cardiac (n=12) | 5 | 5 Possible, 3 Unlikely, 4 unrelated |
| ***Nivolumab NSC (748726)*** | | |
| Chest pain - cardiac (n=11) | 5 | 2 Possible, 5 Unlikely, 4 unrelated |
| ***Cabozantinib NSC (761968)*** | | |
| Chest pain - cardiac (n=3) | 5 | 2 Possible, 1 unlikely |

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16. ASSESSMENT

~~Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship between the cardiac chest pain, and the death NOS and the investigational agents ipilimumab, nivolumab, and cabozantinib cannot be excluded. The adverse events and attributions will be reassessed when additional information becomes available.~~

**Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the cardiogenic shock, and the cardiac chest pain and the investigational agents ipilimumab, nivolumab, and cabozantinib.**

| | Cardiogenic shock | Chest pain - cardiac |
|---|---|---|
| **Ipilimumab** | **Possible** | **Possible** |
| **Nivolumab** | **Possible** | **Possible** |
| **Cabozantinib** | **Possible** | **Possible** |
| **Clear cell renal cell adenocarcinoma** | **Unlikely** | **Unlikely** |
| **CAD angina NSTEMI** | **Probable** | **Probable** |
| **Cardiomyopathy low EF** | **Definite** | **Possible** |
| **Atrial fibrillation** | **Possible** | **Possible** |
| **History of hypertension** | **Possible** | **Possible** |

17. CONCOMITANT MEDICATIONS

~~Pending Follow-up report.~~

**Medications taken at the time of the event were aspirin, metoprolol succinate, and tamsulosin.**

18. COMMENTS

~~Pending Follow-up report.~~

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.