FOLLOW-UP IND SAFETY REPORT #1

1. IND NUMBER	2. AGENT NAME	3. DATE
129803	Nivolumab XL184 (Cabozantinib)	**April 15, 2022**

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 John Wright, MD, PhD – Associate Branch Chief, Investigational Drug Branch, CTEP, DCTD, NCI	240-276-6565 7. EMAIL ADDRESS ctepsupportae@tech-res.com

8a. PROTOCOL NUMBER (AE #)	8b. AE GRADE: AE
A031704 (AE #2299279)	Grade 5: Death NOS ~~Grade 4: Hypoglycemia~~

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
9130919	66 years	Female (per medical records)

12. PROTOCOL SPECIFIED

Cycle = 28 Days
Nivolumab (BMS-936558, MDX-1106): 480 mg IV on Day 1
XL184 (Cabozantinib): 760 mg PO QD

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on July 23, 2020, and received the last dose of nivolumab on July 25, 2021, and the last dose of cabozantinib on August 3, 2021.

14. DESCRIPTION OF ADVERSE EVENT

The patient was a 66-year-old female with metastatic clear cell renal cell adenocarcinoma who expired on August 11, 2021, while on a Phase III trial utilizing the investigational agents nivolumab and cabozantinib. Additional information has been requested from the investigational site.

The Initial Written Report was sent to the FDA on September 8, 2021, as a 7-day report.

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

The patient had a history of cardiomyopathy requiring automatic implantable cardioverter-defibrillator (AICD), heart failure with reduced ejection fraction and diastolic dysfunction, pulmonary embolism, chronic kidney disease, anemia, hypertension, and hyperlipidemia. On August 10, 2021, the patient was brought to the emergency department (ED) via emergency medical services (EMS) with a 1-week history of vomiting, diarrhea, altered mental status, dehydration, and dyspnea on exertion. That morning, the patient was too weak to get out of bed and upon EMS arrival, she had a capillary blood glucose (CBG) level of 28 (reference range and units: not provided). She required transient bag mask ventilation and intravenous glucose administration en route to the ED. Upon arrival, she had a had a temperature of 98.8°F, blood pressure of 102/58 mmHg, heart rate of 68 beats per minute, respiratory rate of 16 breaths per minute, and an oxygen saturation (SpO_2) of 92% on a non-rebreather mask. On physical examination, she was awake and alert, but ill-appearing. Laboratory results were significant for a white blood cell (WBC) count of 11.2 (reference range: 4.5-11.0), hemoglobin level of 6.9 (reference range: 12.0-16.0), creatinine of 4.0 (reference range: 0.5-1.0), blood urea nitrogen (BUN) of 45 (reference range: 7-21), aspartate aminotransferase (AST) of 306 (reference range: 7-40), alanine aminotransferase of 72 (reference range: 7-56), and a glucose level of 185 (reference range: 70-100). A urinalysis was positive for leukocytes. She was given 0.9% sodium chloride, ondansetron, and admitted to the hospital for further evaluation and management of septic shock, encephalopathy, congestive heart failure, acute on chronic renal failure, and transaminitis. CT scans of the

chest, abdomen, and pelvis showed interval development of patchy peripheral infiltrates in the inferior right upper lobe and left lower lobe consistent with pneumonia, and fluid throughout the colon suggestive of colitis and diarrhea. A CT scan of the brain revealed mild changes of small vessel ischemic disease, but no acute intracranial process. She was started on broad spectrum antibiotics, intravenous bicarbonate, norepinephrine, steroids, and received 1 unit of packed red blood cells. That evening, laboratory tests were significant for a troponin T of 0.104 (reference range: 0.000-0.030) and a lactic acid level of 92.5 (reference range: 9.0-16.0). Despite aggressive treatment, the patient showed no signs of clinical improvement. On August 11, 2021, the patient's daughter decided to transition her to comfort care. That day, the patient expired. An autopsy was not performed. Additional information has been requested from the investigational site.

15. ACCRUAL AND IND EXPERIENCE

~~Pending Follow-up report.~~

Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = 9,091.
Number of patients enrolled in NCI-sponsored clinical trials using cabozantinib under NSC 761968 = 2,500.
There have been 131 other cases of death NOS reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.
There have been 14 other cases of sudden death NOS reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.
There have been 15 other cases of death NOS reported to the NCI through CTEP-AERS as serious adverse events for cabozantinib under NSC 761968.
There have been 4 other cases of sudden death NOS reported to the NCI through CTEP-AERS as serious adverse events for cabozantinib under 761968.

Adverse Event	Grade	Attribution
Nivolumab (NSC 748726)		
Death NOS (n=131)	5	1 Definite, 1 Probable, 45 Possible, 56 Unlikely, 28 Unrelated
Sudden Death (n=14)	5	1 Probable, 9 Possible, 4 Unlikely
Cabozantinib (NSC 761968)		
Death NOS (n=15)	5	1 Possible, 7 Unlikely, 7 Unrelated
Sudden Death (n=4)	5	3 Possible, 1 Unrelated

16. ASSESSMENT

~~Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship between the death NOS and the investigational agents 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 death NOS and the investigational agents nivolumab and cabozantinib.

	Death NOS
Nivolumab	Possible
Cabozantinib	Possible
Clear cell renal cell carcinoma	Unlikely

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	Cardiomyopathy, heart failure, reduced ejection fraction	**Probable**
	Possible colitis with dehydration	**Possible**
	Urinary tract infection	**Possible**
	Renal failure, congestive heart failure, possible sepsis, or adrenal insufficiency physiology	**Possible**

17. CONCOMITANT MEDICATIONS

~~Pending Follow-up report.~~

Medications taken at the time of the event were apixaban, magnesium oxide, metoprolol succinate, pantoprazole, vitamin B12, vitamin C, and vitamin D3.

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 AGENTTHERAPY CAUSED OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.