FOLLOW-UP IND SAFETY REPORT #2

1. IND NUMBER	2. AGENT NAME	3. DATE
129803	Nivolumab XL184 (Cabozantinib)	**June 21, 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 # 2431301)	~~Grade 4: Chronic kidney disease~~ ~~Grade 4: Enterocolitis infectious~~ **Grade 4: Cardiomyopathy** Grade 3: Myocardial infarction ~~Grade 3: Heart failure~~

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
9130809	64 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 July 16, 2020, and received the last dose of nivolumab on April 27, 2021 (Cycle 11, Day 1), and the last dose of cabozantinib on May 11, 2021 (Cycle 11, Day 15).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 64-year-old male with metastatic clear cell renal cell adenocarcinoma of the left kidney who developed grade 3 myocardial infarction and **grade 4 cardiomyopathy** ~~grade 3 heart failure~~ ~~4 chronic kidney disease and grade 4 infectious enterocolitis~~ 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 June 3, 2021, as a 7-day report.
The Follow-Up Report #1 was sent to the FDA on July 6, 2021.

Follow-Up #1

The patient has a history of adrenal insufficiency, anemia, colitis, hyperlipidemia, hypertension, and hypokalemia. On May 11, 2021 (Cycle 11, Day 15), the patient's wife brought him to the emergency department (ED) for evaluation of weakness and confusion following an acute onset of nausea, vomiting, and intractable non-bloody diarrhea which started 3 days prior. Upon arrival, he had a temperature of 98.3°F, heart rate of 109 beats per minute, respiratory rate of 40 breaths per minute, blood pressure of 86/75 mmHg, and oxygen saturation (SpO_2) of 93%. On physical examination, he was alert but had altered mental status. Laboratory results revealed a white blood cell count of 11.4 x 10^3/uL (reference range: 4.0-11.0 x 10^3/uL), neutrophil count of 10.4 x 10^3/uL (reference range: 2.5-7.5 x 10^3/uL), creatinine level of 5.62 mg/dL (reference range: 0.5-1.20 mg/dL), and venous lactic acid level of 4.87 mmol/L (reference range: 0.90-1.70 mmol/L). Stool cultures were positive for *Clostridium difficile.* That day, the treating physician held the investigational agent. He was started on vancomycin and intravenous fluids and admitted for further evaluation and management. On May 12, 2021, a CT scan of the abdomen and pelvis revealed a thickening of the descending large intestine and sigmoid colon, mild reactive thickening of the

appendix, and cholelithiasis. Following fluid resuscitation, the patient symptomatically improved and his lactic acid level decreased to 1.9 mmol/L. His blood pressure improved to 111/72 mmHg, respiratory rate to 16 breaths per minute, and SpO_2 increased to 100%. Overnight on May 13, 2021, the patient reported some dyspnea while ambulating. A chest X-ray showed clear lung fields. On May 16, 2021, the patient was discharged home in stable condition on vancomycin with a plan to follow up with the treating physician in 1 week. On May 17, 2021, the patient returned to the ED with worsening dyspnea and a dry cough. Upon arrival, his respiratory rate was 24 breaths per minute, blood pressure was 142/89 mmHg, and SpO_2 was 82%. On physical examination, he had diffuse rales bilaterally. Laboratory results showed a troponin I of 12.24 and brain natriuretic peptide of 1526 (reference ranges and units: not provided). An electrocardiogram (ECG) showed normal rate and rhythm without ST elevation or depression. A chest X-ray showed mild congestive heart failure *vs.* acute interstitial edema. A pulmonary perfusion scan was negative for pulmonary embolism. He was started on high-flow nasal cannula (HFNC) with bilevel positive airway pressure (BiPAP) to achieve an SpO_2 greater than 95%. He was given aspirin and furosemide and was admitted. An echocardiogram showed mild left ventricular concentric hypertrophy, significant left ventricular systolic dysfunction, and an ejection fraction of 30-35%. He was diagnosed with non-ST elevation myocardial infarction. On May 19, 2021, cardiac catheterization was performed and revealed right posterior left ventricular branch vessel disease containing a probable ruptured plaque with 50-70% vessel stenosis, which could not be intraoperatively stented. The patient was given carvedilol. On May 20, 2021, a nuclear multigated acquisition (MUGA) scan showed an ejection fraction of 35.9%. On May 21, 2021, the patient was discharged in stable condition and planned for cardiac rehabilitation and follow-up with the oncologist. On May 25, 2021, the patient presented to the clinic for scheduled follow-up and was removed from the study treatment. On June 4, 2021, the patient returned to the clinic and reported that he has been feeling better. 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 = ~~7,590~~ **9,319**
Number of patients enrolled in NCI-sponsored clinical trials using cabozantinib under NSC 761968 = ~~2,181~~ **2,565**
There have been ~~12~~ **15** other cases of myocardial infarction reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.
~~There have been 16 other cases of heart failure reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.~~
Cardiomyopathy is an expected event for nivolumab.
There have been no other cases of cardiomyopathy reported to the NCI through CTEP-AERS as a serious adverse event for cabozantinib under NSC 761968.
There have been ~~2~~ **4** other cases of myocardial infarction reported to the NCI through CTEP-AERS as serious adverse events for cabozantinib under NSC 761968.
~~There have been 5 other cases of heart failure reported to the NCI through CTEP-AERS as serious adverse events for cabozantinib under NSC 761968.~~

Adverse Event	Grade	Attribution
Nivolumab (NSC 748726)		
Myocardial infarction (n=~~12~~ **15**)	4 3 2	1 Probable, 1 Possible, 1 Unrelated 6 Possible, 3 Unlikely, 1 Unrelated 2 Unlikely
~~Heart failure (n=16)~~	~~5~~ ~~4~~ ~~3~~ ~~2~~ ~~1~~	~~1 Unlikely~~ ~~1 Probable, 1 Possible, 1 Unlikely~~ ~~2 Probable, 2 Possible, 1 Unlikely, 2 Unrelated~~ ~~1 Possible~~ ~~2 Possible, 1 Unlikely, 1 Unrelated~~
XL184 (Cabozantinib) (NSC 761968)		
Myocardial infarction (n=~~2~~ **4**)	4 3	1 Probable 1 Probable, 2 Possible

	~~Heart failure (n=5)~~	~~4~~ ~~3~~ ~~2~~ ~~1~~	~~1 Unlikely~~ ~~1 Probable, 1 Possible~~ ~~1 Possible~~ ~~1 Possible~~	

16. ASSESSMENT

~~Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship between the chronic kidney disease and enterocolitis infectious 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 probable relationship exists between the cardiomyopathy and the investigational agent nivolumab, a possible relationship exists between the cardiomyopathy and the investigational agent cabozantinib, and** a possible relationship exists between the myocardial infarction ~~and the heart failure~~ and the investigational agents nivolumab and cabozantinib.

	Myocardial infarction	~~Heart Failure~~	**Cardiomyopathy**
Nivolumab	Possible	~~Possible~~	**Probable**
XL184 (Cabozantinib)	Possible	~~Possible~~	**Possible**
Clear cell renal cell adenocarcinoma	Unrelated	~~Unrelated~~	**Unlikely**
~~Accumulation of chemotherapeutic drug~~	~~Possible~~	~~Possible~~	-
Heart failure	Possible	~~N/A~~	**Definite**
Myocarditis	**Probable**	-	**Probable**
Atherosclerotic vascular disease	**Probable**	**-**	**N/A**

17. CONCOMITANT MEDICATIONS

~~Pending Follow-up report.~~

Medications taken at the time of the event were atorvastatin, amlodipine, spironolactone, carvedilol, losartan, omeprazole, apixaban, ondansetron, and hydrocortisone.

18. COMMENTS

~~Pending Follow-up report.~~