15-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
129803	**XL184 (Cabozantinib)** **Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)** **Nivolumab**	**March 15, 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
A031704 (AE #2268658)	**Grade 3: Hypertension** **Grade 3: Heart failure**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
9132180	**61 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 October 07, 2020, and received the last dose of ipilimumab on December 08, 2020, the last dose of nivolumab on January 19, 2021, and the last dose of cabozantinib on February 16, 2021.

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 61-year-old male with clear cell renal cell adenocarcinoma with metastasis to the lungs and bone (left 5th and 7th ribs) who developed grade 3 hypertension and grade 3 heart failure while on a Phase III trial utilizing the investigational agents ipilimumab, nivolumab, and cabozantinib. On February 9, 2021, the patient's systolic blood pressure was elevated to the 190s and he was started on low dose lisinopril. On February 17, 2021, he presented to the emergency department (ED) with dizziness, nausea following meals, and shortness of breath when lying flat. The patient reported being exposed to a fire in his home one week prior, following which he developed a continuous frontal headache, dizziness, and an elevated blood pressure in the 160s despite taking lisinopril. In the ED, he had a blood pressure of 176/117 mmHg, heart rate of 103 beats per minute, temperature of 97.4°F, respiratory rate of 20 breaths per minute, and an oxygen saturation (SpO_2) of 99%. He was given intravenous metoprolol and oral clonidine in the ED and was admitted for further evaluation and monitoring of severe hypertension. Upon arrival, his blood pressure was 187/122 mmHg, but he was alert, oriented, and in no acute distress. Laboratory results were significant for a creatinine of 1.37 mg/dL (reference range: 0.70–1.30 mg/dL), troponin I of 0.05 ng/mL (reference range: 0.00–0.04 ng/mL), glucose of 139 mg/dL (reference range: 65-99 mg/dL) and pro-brain natriuretic peptide NT of 22,857 pg/mL (reference range <= 124 pg/mL). That day, he noted having some shortness of breath and an electrocardiogram (ECG) showed an accelerated junctional rhythm *vs.* sinus rhythm with first-degree atrioventricular block. Left ventricular hypertrophy with secondary

repolarization abnormality and low voltage in extremities were also noted. An echocardiogram revealed mild left ventricular hypertrophy with severely decreased left ventricular systolic function (left ventricular ejection fraction of 21%), severe global hypokinesis, moderate mitral valve regurgitation, mild aortic valve regurgitation, a small pericardial effusion near the right atrium, and probable grade II diastolic dysfunction. A CT scan of the head showed no acute intracranial process. A chest x-ray showed improved aeration of the right upper lobe with near complete resolution of an opacity at the right lung apex as compared to previous scans. There was also evidence of fullness of the pulmonary vasculature, interstitial edema, and bilateral small pleural effusions. The patient's lisinopril dose was increased to 20mg daily and he was started on carvedilol and enoxaparin. On February 18, 2021, in view of new onset congestive heart failure, he was started on furosemide and acetylsalicylic acid following which his blood pressure decreased to 121/80 mmHg and his shortness of breath improved. The treating physician recommended holding cabozantinib and reducing the dose of nivolumab. On February 19, 2021, he was seen by a cardiologist who cleared the patient for discharge, initiated oral furosemide, spironolactone, and carvedilol, and recommended giving sacubitril/valsartan on an outpatient basis. That day, the patient was discharged in stable condition with his blood pressure well-controlled. On February 23, 2021, the patient returned to the clinic for follow-up and stated he was asymptomatic and doing well. His nivolumab therapy was changed from 28 days to 14 days with dose reduction due to hypertensive urgency. He was advised to return for follow-up visits and ECGs on Day 1 and Day 15 of each cycle. Additional information has been requested from the site.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 732442 = 7,903.
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 = 7,241.
Number of patients enrolled in NCI-sponsored clinical trials using cabozantinib under NSC 761968 = 2,066
There have been 36 other cases of hypertension reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 732442.
There has been 1 other case of hypertension (grade 3, possible) reported to the NCI through CTEP-AERS as a serious adverse event for ipilimumab under NSC 720801.
There have been 28 other cases of hypertension reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.
There have been 11 other cases of heart failure reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 732442.
There have been no other cases of heart failure reported to the NCI through CTEP-AERS as a serious adverse event for ipilimumab under NSC 720801.
There have been 12 other cases of heart failure reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.
There have been 4 other cases of heart failure reported to the NCI through CTEP-AERS as serious adverse events for cabozantinib under NSC 761968.
Hypertension is an expected event for the investigational agent cabozantinib.

Adverse Event	Grade	Attribution
Ipilimumab NSC (732442)		

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Hypertension (n=36)	4 3 2 1	2 Unlikely 1 Probable, 3 Possible, 14 Unlikely, 6 Unrelated 3 Possible, 5 Unlikely, 1 Unrelated 1 Definite
Heart failure (n=11)	5 3 2 1	2 Possible 1 Probable, 1 Possible, 1 Unlikely, 3 Unrelated 1 Possible 1 Possible, 1 Unrelated
Nivolumab NSC (748726)		
Hypertension (n=28)	4 3 2	1 Unlikely 1 Probable, 15 Unlikely, 8 Unrelated 2 Unlikely, 1 Unrelated
Heart failure (n=12)	5 4 3 2 1	1 Unlikely 1 Possible, 1 Unlikely 1 Probable, 1 Possible, 1 Unlikely, 2 Unrelated 1 Possible 2 Possible, 1 Unrelated
Cabozantinib NSC (761968)		
Heart failure (n=4)	4 3 2 1	1 Unlikely 1 Possible 1 Possible 1 Possible

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a probable relationship exists between the heart failure and the investigational agents cabozantinib, ipilimumab, and nivolumab. A possible relationship exists between the hypertension and the investigational agent cabozantinib. The hypertension is not related to the investigational agents ipilimumab or nivolumab.

	Hypertension	Heart Failure
Ipilimumab	Unrelated	Probable
Nivolumab	Unlikely	Probable
Cabozantinib	Possible	Probable
Clear cell renal cell adenocarcinoma	Unlikely	Unlikely
Hypertension	N/A	Probable
Possible myocarditis	Unlikely	Possible

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were fluticasone propionate nasal spray, guaifenesin, lisinopril, tamsulosin, and tramadol.

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.