# FOLLOW-UP IND SAFETY REPORT #1

| 1. IND NUMBER | 2. AGENT NAME | 3. DATE |
|---|---|---|
| 137656 | Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)<br>Nivolumab<br>XL184 (Cabozantinib) | **April 18, 2022** |

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 |
|---|---|
| 10240 (AE # 2528098) | Grade 5: Cardiac disorders: Diastolic heart failure |

| 9. PATIENT IDENTIFICATION | 10. AGE | 11. SEX |
|---|---|---|
| NY016-0013 | 70 years | Female |

12. PROTOCOL SPECIFIED

Run-in (Days -14 to -1)
XL184 (Cabozantinib): 40 mg PO QD

Cycles 1 - 4
Cycle = 42 days

XL184 (Cabozantinib): 40 mg PO QD
Nivolumab (BMS-936558, MDX-1106): 240 mg IV on Days 1, 15, and 29
Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)1 mg/kg IV on Day 1

Cycles 5+
Cycle = 28 days

XL184 (Cabozantinib): 40 mg PO QD
Nivolumab (BMS-936558, MDX-1106): 480 mg IV on Day 1

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on July ~~9~~ **8**, 2021, and received the last doses of ipilimumab and nivolumab on December 8, 2021 (Cycle 4, Day 1), and the last dose of cabozantinib on December 26, 2021 (Cycle 4, Day 19).

14. DESCRIPTION OF ADVERSE EVENT

The patient was a 70-year-old female with metastatic papillary thyroid carcinoma **(status post chemoradiotherapy and bilateral thyroidectomy)** who expired on January 22, 2022, due to diastolic heart failure while on a Phase II 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 February 15, 2022, as a 7-day report.**

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

**The patient had a history of heart base tumor (HCC; status cardiac surgery in 2009), hypertension, and hypothyroidism. Of note, she was hospitalized on December 27, 2021, for dyspnea. A CT scan of the chest showed worsening bilateral pleural effusions. On December 29, 2021, the patient underwent a right-sided tunneled pleural catheter placement procedure with drainage of 650 mL of serous fluid, following which her**

**dyspnea improved. A small 10-15% pneumothorax was noted on serial chest X-rays, which required no intervention. On December 31, 2021, she was discharged home with a plan to undergo a left-sided thoracentesis as an outpatient. On January 18, 2022, the patient was admitted to the hospital for progressively worsening dyspnea over the prior 3 days (at baseline, she required 2 L of supplemental oxygen). Laboratory results were significant for a serum calcium level of 12.6 mg/dL, a creatinine level of 1.74 mg/dL, a brain natriuretic peptide (BNP) level of 16,555, and a troponin level of 0.21 (reference range and units: not provided). A CT angiogram of the chest showed a possible pulmonary embolism (PE); bilateral pleural effusions were stable to improved. An echocardiogram showed normal left ventricular function, no pericardial effusion, and a mildly dilated/mildly hypokinetic right ventricle with mild pulmonary hypertension, which was suggestive of possible PE. She was started on a heparin drip. On January 19, 2022, a ventilation–perfusion (VQ) scan was negative for PE and the heparin drip was discontinued. On January 20, 2022, she was given zoledronic acid for hypercalcemia and the patient's respiratory status improved to require 3 L supplemental oxygen. On January 22, 2022, telemetry detected sudden bradycardia and the patient was found unresponsive and pulseless. She was resuscitated and intubated. A chest X-ray showed increased interstitial and alveolar opacities in the right lung. The patient's family decided to make her do-not-resuscitate (DNR). That day, the patient expired. 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 = 8,845.**
**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 = 9,108.**
**Number of patients enrolled in NCI-sponsored clinical trials using cabozantinib under NSC 761968 = 2,506.**
**There have been no other cases of diastolic heart failure reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 732442.**
**There have been 14 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 diastolic heart failure reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 720801.**
**There have been no other cases of heart failure reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 720801.**
**There have been no other cases of diastolic heart failure 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.**
**There have been no other cases of diastolic heart failure reported to the NCI through CTEP-AERS as serious adverse events for cabozantinib under NSC 761968.**
**There have been 6 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 |
|---|---|---|
| ***Ipilimumab (NSC 732442)*** | | |
| Heart Failure (n=14) | 5 | 2 Possible |
| | 4 | 1 Probable |
| | 3 | 2 Probable, 1 Possible, 1 Unlikely, 4 Unrelated |
| | 2 | 1 Possible |
| | 1 | 1 Possible, 1 Unrelated |

| | | |
|---|---|---|
| ***Nivolumab (NSC 748726)*** | | |
| **Heart Failure (n=16)** | **5**<br>**4**<br>**3**<br>**2**<br>**1** | **1 Unlikely**<br>**1 Probable, 1 Possible, 1 Unlikely, 1 unrelated**<br>**2 Probable, 3 Possible, 1 Unlikely, 2 Unrelated**<br>**1 Possible**<br>**2 Possible** |
| ***Cabozantinib (NSC 761968)*** | | |
| **Heart Failure (n=6)** | **4**<br>**3**<br>**2**<br>**1** | **1 Unlikely**<br>**1 Probable, 2 Possible**<br>**1 Possible**<br>**1 Possible** |

16. ASSESSMENT

~~Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship between the Diastolic heart failure 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 diastolic heart failure and the investigational agents ipilimumab, and cabozantinib. A probable relationship exists between the diastolic heart failure and the investigational agent nivolumab.**

| | **Diastolic heart failure** |
|---|---|
| **Ipilimumab** | **Possible** |
| **Nivolumab** | **Probable** |
| **Cabozantinib** | **Possible** |
| **Papillary thyroid carcinoma** | **Unlikely** |
| **Likely related to progression of disease and pulmonary hypertension** | **Possible** |

17. CONCOMITANT MEDICATIONS

~~Pending Follow-up report.~~

**Medications taken at the time of the event were not provided.**

18. COMMENTS

Pe~~nding 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.