7-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
125586	**Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)** **Nivolumab**	**May 9, 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	**240-276-6565**
	7. EMAIL ADDRESS **ctepsupportae@tech-res.com**

8a. PROTOCOL NUMBER (AE #)	8b. AE GRADE: AE
EA2174 (AE #2001839)	**Grade 5: Myasthenia gravis**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
42086	**77 years**	**Female**

12. PROTOCOL SPECIFIED

Cycle: 2 weeks (Max= 12 cycles)
BMS-936558 (Nivolumab, MDX-1106): 240 mg IV on Day 1
Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived): 1 mg/kg IV on Day 1 of Cycles 1, 4, 7, and 10

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on October 4, 2021, and received the last dose of ipilimumab on February 22, 2022, and the last dose of nivolumab on March 14, 2022 (Cycle 2, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient was a 77-year-old female with adenocarcinoma of the gastroesophageal junction, who expired on April 15, 2022, due to myasthenia gravis while on a Phase II/III trial utilizing the investigational agents ipilimumab and nivolumab. She had a history of hypertension, heart failure, and arrhythmia (possible atrial fibrillation). On April 10, 2022, the patient presented to the emergency department with complaints of left eye ptosis and dysarthria for 4 weeks associated with progressive generalized weakness. The patient reported redness around her left eye which had started 2 days prior. On arrival, she had a blood pressure of 123/67 mmHg, a heart rate of 69 beats per minute, a temperature of 35.8 °C, a respiratory rate of 18 breaths per minute, and an oxygen saturation (SpO_2) of 95% on room air. Laboratory results were significant for a troponin I of 0.456 ng/mL (reference range: 0.000-0.034 ng/mL), creatinine phosphokinase of 686 U/L (reference range: 30-135 U/L), an alanine aminotransferase of 156 Units/L (reference range: <= 35 Units/L) and an aspartate aminotransferase of 202 Units/L (reference range: 14-36 Units/L). A chest X-ray showed decreased lung volumes, bibasilar atelectasis or infiltrate, and possible pleural effusions. An electrocardiogram (ECG) showed no acute ischemic changes. A CT scan of the brain and CT arteriogram showed no acute intracranial abnormality. The patient was admitted for further evaluation and management. On April 11, 2022, an MRI of the brain showed mild generalized cerebral atrophy and mild chronic small vessel ischemia but did not reveal any acute intracranial abnormalities. On April 12, 2022, an echocardiogram showed an ejection fraction of 76 % and grade II abnormal ventricular diastolic function. A lumbar puncture was performed due to worsening slurred speech and cerebral spinal fluid analysis was unremarkable. Following a neurology consult, the patient was started on pyridostigmine every 8 hours for suspected myasthenia gravis possibly due to immunotherapy. A vasculitis panel, anti-nuclear antibody test,

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and double stranded DNA autoantibody test were negative. On April 13, 2022, the pyridostigmine was increased to every 6 hours. Pulmonary function tests (PFTs) showed a negative inspiratory force of -28 (reference range and units: not provided), and a forced vital capacity (FVC) of 0.9 mL (reference range: not provided). By April 14, 2022, the patient's left eye ptosis had improved, and her slurred speech had slightly improved. The cardiologist recommended starting her on apixaban for an episode of atrial fibrillation observed on telemetry. Repeat PFTs showed an FVC of 0.6 mL and she was initiated on intravenous immunoglobulin (IVIG) therapy for 5 days. On April 15, 2022, the patient was intubated due to respiratory insufficiency in the setting of aspiration pneumonia and possible bulbar myasthenia gravis. The patient became hypotensive and desaturated to the 50s. Following aggressive resuscitation, the patient was pronounced dead. An autopsy was not performed.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 732442= 8,606.
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= 9,175.
Myasthenia gravis is an expected event for the investigational agents ipilimumab and nivolumab.

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a probable relationship exists between the myasthenia gravis and the investigational agents ipilimumab and nivolumab.

	Myasthenia gravis
Ipilimumab	Probable
Nivolumab	Probable
Adenocarcinoma of the gastroesophageal junction	Possible
Myositis/myocarditis	Possible

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were sertraline, mirtazapine, clonazepam, cyanocobalamin, docusate sodium, metoprolol, esomeprazole magnesium, and multivitamin.

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.