# 15-DAY IND SAFETY REPORT

| 1. IND NUMBER | 2. AGENT NAME | 3. DATE |
|---|---|---|
| **126461** | **Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived)**<br>**Nivolumab** | **March 3, 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 |
|---|---|
| **NRG-BN007 (AE #2427414)** | **Grade 3: Rhabdomyolysis** |

| 9. PATIENT IDENTIFICATION | 10. AGE | 11. SEX |
|---|---|---|
| **MN031-BN007-00223** | **75 years** | **Male** |

12. PROTOCOL SPECIFIED

**RT + Ipilimumab + Nivolumab**

13. TREATMENT RECEIVED AND DATES

**The patient began the investigational therapy on October 25, 2021, received the last dose of radiation on December 6, 2021, and the last doses of ipilimumab and nivolumab on January 17, 2022.**

14. DESCRIPTION OF ADVERSE EVENT

**The patient is a 75-year-old male with glioblastoma multiforme who developed grade 3 rhabdomyolysis while on a Phase II/III trial utilizing the investigational agents ipilimumab and nivolumab in combination with radiation. The patient has a history of deep venous thrombosis, Hageman factor deficiency, hematoma of lower limb, hypercholesterolemia, hypertension, post-phlebitic syndrome, and seizures. On January 28, 2022, the patient presented to the clinic complaining of a 4-day history of weakness, difficulty with finding words, and aphasia. The patient reported a transient improvement of symptoms 2 days after onset. Laboratory results were significant for glucose of 162 mg/dL (reference range: 70-99 mg/dL) and creatinine of 1.15 mg/dL (reference range: 0.66-1.25 mg/dL). Of note, he tested positive for COVID-19 on January 9, 2022, though he is fully vaccinated against COVID-19. On January 31, 2022, the patient presented to the emergency department (ED) for further evaluation of the generalized weakness and worsening aphasia, at which time he reported dark urine for the previous 2 days, and urinary incontinence. Upon presentation, he had a blood pressure of 70/18 mmHg, heart rate of 72 beats per minute, temperature of 85.3°F, respiratory rate of 16 breaths per minute, and an oxygen saturation of 90%. Repeat laboratory results were significant for a creatinine of 5.95 mg/dL, aspartate aminotransferase of 47 U/L (reference range: 0-45 U/L), lactic acid of 12.2 mmol/L (reference range: 0.7-2.0 mmol/L), an anion gap of 16 mmol/L (reference range: 3-14 mmol/L), and a creatine kinase of 832 U/L (reference range: 30-300 U/L). A CT scan of the chest revealed new peripheral ground-glass opacities with superimposed tree-in-bud nodularity in the right upper lobe. An Electroencephalogram (EEG) showed no evidence of epileptic activity. He was given ceftriaxone, azithromycin, intravenous fluids, heparin, and pressors and was admitted to the medical intensive care unit (MICU). The patient was later transitioned to a 5-day course of piperacillin-tazobactam due to concern for lower extremity/intraperitoneal infection. On February 2, 2022, he developed hematuria. Repeat laboratory results were significant for a creatinine kinase of 4,204 U/L (reference range: 30-300 U/L). On February 7, 2022, he developed urinary retention, was catheterized, and was placed on**

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**continuous bladder irrigation. That day, he was transferred out of the MICU. On February 10, a cystoscopy was performed that revealed bladder perforation. On February 13, 2022, his hematuria stabilized. On February 14, 2022, he was transitioned from heparin to apixaban. On February 15, 2022, he was discharged home in stable condition with a plan to follow-up with his physician. Additional information has been requested from the investigational site.**

15. ACCRUAL AND IND EXPERIENCE

**Number of patients enrolled in NCI-sponsored clinical trials using ipilimumab under NSC 732442 = 8,763.**
**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 = 8,912.**
**There has been one other case (grade 3, unlikely) of rhabdomyolysis reported to the NCI through CTEP-AERS as a serious adverse event for ipilimumab under NSC 732442.**
**There have been no other cases of rhabdomyolysis reported to the NCI through CTEP-AERS as serious adverse events for ipilimumab under NSC 720801.**
**There has been one other case (grade 3, unlikely) of rhabdomyolysis reported to the NCI through CTEP-AERS as a serious adverse event for nivolumab under NSC 748726.**

16. ASSESSMENT

**Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the rhabdomyolysis and the investigational agents ipilimumab and nivolumab.**

| | Rhabdomyolysis |
|---|---|
| **Ipilimumab** | **Possible** |
| **Nivolumab** | **Possible** |
| **Radiation** | **Unlikely** |
| **Glioblastoma multiforme** | **Unrelated** |
| **Sepsis** | **Probable** |

17. CONCOMITANT MEDICATIONS

**Medications taken at the time of the event were cholecalciferol, dutasteride, famotidine, levetiracetam, lisinopril, and multivitamins with minerals.**

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.**