15-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
129803	**Nivolumab**	**April 1, 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**
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8a. PROTOCOL NUMBER (AE #)	8b. AE GRADE: AE
EA8143 (AE #2808782)	**Grade 3: Myelitis**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
38789	**56 years**	**Male**

12. PROTOCOL SPECIFIED

Nivolumab dosing per protocol + Partial or radical nephrectomy followed by Nivolumab dosing per protocol

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on May 3, 2021, and received the last dose of nivolumab on February 14, 2022.

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 56-year-old male with renal cell carcinoma, status post right radical nephrectomy (May 2021) who developed grade 3 myelitis while on a Phase III trial utilizing the investigational agent nivolumab. He has a history of vitamin B12 deficiency, gastroesophageal reflux disease, depression, obstructive sleep apnea, and post-traumatic stress disorder. On March 11, 2022, the patient presented to the emergency department (ED) with complaints of dizziness, numbness of the arms and hands, and fatigue during the previous week. Upon arrival, he had a blood pressure of 132/83 mmHg, heart rate of 81 beats per minute, respiratory rate of 18 breaths per minute and an oxygen saturation of 99% on room air. Physical examination revealed mild instability on tandem gait and swaying on Romberg's test. An MRI of the brain showed no acute intracranial hemorrhage, mass effect, or abnormal enhancement. Laboratory results revealed a vitamin B12 level of 219 (reference range and units: not provided). The patient was started on vitamin B12 injections and admitted to the inpatient unit for further management. On March 12, 2022, an MRI of the cervical spine with contrast revealed a small enhancing cord lesion at C3-C4, C6 and possibly at C2 level, representing areas of acute myelitis or possibly active demyelinating plaques. Following a neurology consult, a lumbar puncture and cerebrospinal fluid (CSF) analysis was ordered. CSF analysis revealed a protein level of 76 mg/dL (reference range: 15-45 mg/dL), glucose level of 55 mg/dL (reference range: 40-80 mg/dL), lymphocyte count of 144/ cubic mm (reference range: not provided), nucleated cell count of 147/ cubic mm (reference range: not provided), and was negative for infectious workup, which was most consistent with transverse myelitis. The patient was started on IV methylprednisolone for three days. On March 13, 2022, following a transfusion medicine consult, the patient was scheduled for therapeutic plasma exchanges every other day for five treatment sessions. On March 15, 2022, the patient received his first treatment session of plasmapheresis. On March 17, 2022, the patient received his second treatment session of plasmapheresis, which he tolerated well. On March 21, 2022, he received his fourth treatment session of plasmapheresis. Over the course of hospitalization, the patient showed improvement in his initial symptoms of dizziness, numbness of the arms and hands, and fatigue. On March 23, 2022, he received his fifth treatment session of plasmapheresis. He reported feeling better and had no new complaints. That day,

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the patient was discharged home in stable condition with plans to follow-up with the neurologist on an outpatient basis. Additional information has been requested from the investigational site.

15. ACCRUAL AFND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = 8,922. There have been no other cases of myelitis reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a probable relationship exists between the myelitis and the investigational agent nivolumab.

	Myelitis
Nivolumab	Probable
Renal cell carcinoma	Unlikely

17. CONCOMITANT MEDICATIONS

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

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.