15-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
125462	**Nivolumab**	**July 7, 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
S1826 (AE #2785548)	**Grade 2: Nervous system disorders: Cerebellitis**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
290173	**17 years**	**Male**

12. PROTOCOL SPECIFIED

Cycle = 28 Days (max 6 cycles)

Doxorubicin hydrochloride: 25 mg/m^2 IV on Days 1 and 15
Vinblastine sulfate: 6 mg/m^2 IV on Days 1 and 15
Dacarbazine: 375 mg/m^2 IV on Days 1 and 15
Nivolumab: 240 mg IV on Days 1 and 15 [<18 years: 3 mg/kg (up to 240 mg) IV on Days 1 and 15]

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on April 27, 2022, and received the last doses of doxorubicin, vinblastine, dacarbazine, and nivolumab on May 24, 2022 (Cycle 2, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 17-year-old male with stage IIIb classical Hodgkin lymphoma who developed grade 2 cerebellitis while on a phase III trial utilizing the investigational agent nivolumab in combination with doxorubicin, vinblastine, and dacarbazine. He has a history of bone fractures (right tibia/fibula and clavicle). On May 31, 2022, at a scheduled follow-up visit with the oncologist, the patient reported a 5-day history of intermittent diffuse headaches, which were non-focal, persistent, and responded to acetaminophen. A CT scan of the head without contrast was normal. On June 1, 2022, the patient complained of worsening of his headache along with a new onset of nausea and vomiting, which started that morning. He underwent an MRI of the brain with contrast, angiography (MRA), and venography (MRV), which showed a focal hyperintense signal abnormality and a nodular, irregular, overlying leptomeningeal enhancement involving the right inferior medial cerebellar hemisphere, suggestive of acute cerebellitis. The intracranial MRA and MRV were normal. The patient was transferred to the emergency department (ED) for further evaluation. Upon arrival, he was alert, oriented, and in no acute distress. He had a temperature of 97.3 °F, a blood pressure of 117/81 mmHg, a heart rate of 80 beats per minute, a respiratory rate of 16 breaths per minute, and an oxygen saturation (SpO_2) of 97%. A neurological exam, including a fundoscopic exam, were normal. He was started methylprednisolone for possible immunotherapy-induced cerebellitis, and was transferred to another facility for further management. That day, the patient was removed from the study treatment. On June 2, 2022, the patient's symptoms had resolved. Following a neurology consult, he was discharged home in stable condition with a plan to start dexamethasone for 10 days. On June 8, 2022, at a follow-up oncology clinic visit, the patient reported having no new symptoms and was advised to continue the dexamethasone taper and follow-up in approximately 1 week. On June 13, 2022, a repeat MRI of the brain with and without contrast showed a mild interval decrease in size of the signal abnormality in the right inferior cerebellum, few small foci of microhemorrhage, and resolution of adjacent leptomeningeal

15-DAY IND SAFETY REPORT

enhancement with a small ill-defined area of enhancement at the site, suggestive of evolving cerebellitis. On June 17, 2022, at a follow-up clinic visit, the patient had no complaints and was instructed to continue his dexamethasone taper. On June 27, 2022, a PET/CT scan of the skull to middle thigh and a CT scan of the neck, chest, abdomen, and pelvis showed substantial interval decrease in size and fluorodeoxyglucose (FDG) avidity of disease sites in the neck, chest, and abdomen. There was new FDG uptake in non-enlarged submandibular lymph nodes and throughout the thyroid gland. Additional information has been requested from the investigational site.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = 9,393. There has been 1 other case of cerebellitis (grade 3, possible) 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 cerebellitis and the investigational agent nivolumab.

	Cerebellitis
Nivolumab	Probable
Dacarbazine	Unlikely
Doxorubicin hydrochloride	Unlikely
Vinblastine sulfate	Unlikely
Hodgkin lymphoma	Unlikely

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were acetaminophen, filgrastim, lactulose, lorazepam, olanzapine, ondansetron, and polyethylene glycol.

18. COMMENTS