FOLLOW-UP IND SAFETY REPORT #3

1. IND NUMBER	2. AGENT NAME	3. DATE
133111	Nivolumab	**April 14, 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
E4412 (AE #2387700)	Grade 3: Respiratory, thoracic and mediastinal disorders: Obstructive Lung Disease Grade 3: Respiratory, thoracic and mediastinal disorders: Bronchiolitis Obliterans **Grade 3: Respiratory, thoracic and mediastinal disorders: Bronchiolitis Obliterans with Organizing Pneumonia**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
44150	21 years	Male

12. PROTOCOL SPECIFIED

Cycle = 21 days
Nivolumab: 360 mg IV (3mg/kg pediatric) on Day 1 (Cycles 1-34)
Brentuximab vedotin: 1.8 mg/kg IV on Day 1 (Cycles 1-16)

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on August 7, 2020, and received the last doses of nivolumab and brentuximab vedotin on October 19, 2020 (Cycle 4, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 21-year-old male with relapsed low-stage, lymphocyte-rich classical Hodgkin's lymphoma of the intrapelvic lymph nodes who experienced grade 3 obstructive lung disease**,** ~~and~~ grade 3 bronchiolitis obliterans**, and bronchiolitis obliterans with organizing pneumonia** while on a Phase I trial utilizing the investigational agent nivolumab in combination with brentuximab vedotin. He has a history of diastolic dysfunction and seasonal allergies. On October 19, 2020, he completed 4 cycles of protocol therapy. On November 6, 2020, a PET/CT scan showed stable to slightly progressed disease. On November 9, 2020, he was removed from the study treatment. On November 12, 2020, he received gemcitabine, vinorelbine, and liposomal doxorubicin. On December 2, 2020, he received a second cycle of gemcitabine and vinorelbine. He developed severe mucositis, anorexia, and weight loss each time, following which his salvage regimen was changed to etoposide, cisplatin, methylprednisolone, and cytarabine which he received from December 26, 2020 to December 30, 2020. Over the next several weeks, the patient experienced a persistent, occasionally productive cough, shortness of breath with minimal exertion, and increasing fatigue. On January 11, 2021, a COVID-19 test was negative, and a chest X-ray showed no acute cardio-pulmonary disease. On January 26, 2021, he was seen by a pulmonologist for evaluation of his symptoms at which time he was dyspneic while speaking. Decreased breath sounds with expiratory wheezes were noted on the physical examination. He had a blood pressure of 111/73 mmHg, a heart rate of 108 beats per minute, and an oxygen saturation (SpO_2) of 94%. Pulmonary function tests (PFTs) showed marked decline in forced expiratory volume (FEV1) and minimally reversible severe obstructive lung disease. He was started on prednisone 60 mg with a plan to taper in 5 days, nebulized albuterol with ipratropium, and omeprazole. Following a cardiology consult, his enalapril and carvedilol were tapered off over 2 weeks. On February 11, 2021, a CT scan of the chest with contrast showed mild central bronchiectasis with scattered mucus plugs and mild diffuse air trapping

consistent with small airway disease. On February 26, 2021, the patient underwent flexible bronchoscopy with bronchoalveolar lavage, which grew candida. He was treated with broad-spectrum antibiotics and antifungals. At a follow-up visit on April 6, 2021, the patient reported that his cough had nearly resolved, and the shortness of breath had been slowly improving, at which time he had an SpO_2 of 93%. On June 4, 2021, at a follow-up visit with the pulmonologist, he had a respiratory rate of 16 breaths per minute and an SpO_2 of 92%. Repeat PFTs showed obstruction and diminished flows but no evidence of restriction. The pulmonologist recommended continuation of therapy with bronchodilators and the VEST™. Additional information has been requested from the investigational site.

The Initial Written Report was sent to the FDA on July 9, 2021, as a 15-day report.
The Follow-Up Report #1 was sent to the FDA on January 7, 2022.
The Follow-Up Report #2 was sent to the FDA on January 20, 2022 with a date correction.

Follow-up #1:
On August 16, 2021, a follow-up CT scan of the chest with contrast showed new atelectasis of the right middle lobe and mild diffuse bronchiectasis. He was started on azithromycin 3x/week as an immunomodulator. On October 14, 2021, pulmonary function tests showed severe obstructive defect without bronchodilator response which had progressed as compared to previous studies. Lung volume measurements were consistent with air trapping. He was started on a tapering course of prednisone. On October 15, 2021, an echocardiogram showed grade 1 left ventricular dysfunction. On October 27, 2021, the patient presented to the emergency department (ED) for evaluation of worsening shortness of breath with activity. He reported having a baseline SpO_2 of 93-94% on room air. In the ED, the patient had increased respiratory effort and required supplemental oxygen for an SpO_2 of 89%. Imaging studies were negative for a pulmonary embolism. Of note, the patient does not have a family history of lung disease, or exposure to toxic substances or e-cigarettes. He was admitted for further management. On October 30, 2021, the patient was discharged on 2L of home oxygen. On November 16, 2021, a transbronchial biopsy of the right lower lobe was suggestive of bronchiolitis obliterans. Bronchioalveolar lavage cultures grew *Mycobacterim abscessus* complex. On November 24, 2021, a CT scan of the chest with contrast showed interval development of pneumomediastinum and a small amount of subcutaneous gas in the right anterior chest/abdominal wall. He received intravenous immunoglobulin (IVIG) for 5 days. On November 29, 2021, during a tele-visit with the pulmonologist, the patient reported feeling slightly better. Additional information has been requested from the investigational site.

Follow-up #3:
On March 28, 2022, at a follow-up visit, the patient was noted to have progressive respiratory decline since his previous visit. He was short of breath with minimal exertion. Pulmonary function tests (PFT) showed positive bronchodilator reversibility. A chest X-ray showed chronic middle lobe atelectasis. Lungs were hyperextended but clear. The patient had initial improvement with IVIG but has had progressive decline which was confirmed with more air trapping on PFTs and higher oxygen requirement with exertion. He was deemed not to be a suitable candidate for other immunosuppressives due to the *Mycobacterim abscessus.* He was advised to stop IVIG treatment due to progressive respiratory disease and a plan was made to refer him for lung transplantation. Additional information has been requested from the investigational site.

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15. ACCRUAL AFND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = ~~8,713~~ ~~8,036~~ **9083**.

There have been no other cases of obstructive lung disease reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.

There have been no other cases of bronchiolitis obliterans reported to the NCI through CTEP-AERS as serious adverse events for nivolumab under NSC 748726.

Bronchiolitis obliterans with organizing pneumonia is an expected event for nivolumab.

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the obstructive lung disease and bronchiolitis obliterans **and bronchiolitis obliterans with organizing pneumonia** and the investigational agent nivolumab.

This event is being reported because of the unusual severity of the event.

	Obstructive Lung Disease	Bronchiolitis Obliterans	**Bronchiolitis Obliterans with Organizing Pneumonia**
Nivolumab	Possible	Possible	**Possible**
SGN-35 (Brentuximab vedotin)	Possible	Possible	**Possible**
Hodgkin lymphoma	Unlikely	Unlikely	**Unlikely**
Off-protocol chemotherapy: Gemcitabine, Vinorelbine, Liposomal doxorubicin, Etoposide, Cisplatinum, HD Cytarabine	~~Probable~~ Possible	Possible	**Possible**
~~Obstructive physiology~~	~~Definite~~		
Bronchiolitis Obliterans	Definite	N/A	**N/A**

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were dexamethasone, polyethylene glycol, lorazepam, lidocaine-aluminum-magnesium hydroxide-simethicone-diphenhydramine mouthwash, ~~carvedilol, enalapril, oxycodone,~~ ondansetron, modafinil, ~~naloxone spray,~~ bupropion, ~~and~~ trimethoprim-sulfamethoxazole, azithromycin, ipratropium-albuterol nebulizer, montelukast, voriconazole, fluticasone propionate-salmeterol inhaler, omeprazole, and prednisone.

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.