IND SAFETY REPORT: FOLLOW-UP #1		
1. IND NUMBER 117467	2. AGENT NAME Blinatumomab (AMG 103) Nivolumab (BMS-936558, MDX-1106)	3. DATE **November 22, 2019**
4. SPONSOR Division of Cancer Treatment and Diagnosis, National Cancer Institute		
5. REPORTER'S NAME, TITLE, AND INSTITUTION Elad Sharon, MD, MPH - Medical Officer for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI Howard Streicher, MD – Medical Officer for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI		6. PHONE NUMBER 240-276-6565 7. EMAIL ADDRESS ctepsupportae@tech-res.com
8a. PROTOCOL NUMBER (AE #) 10030 (AE #2801846)	8b. AE GRADE: AE Grade 4: Pneumonitis	
9. PATIENT IDENTIFICATION MA036-0008	10. AGE 57 years	11. SEX Male

Cycle = 42 days (given up to 1 year)

Cycle 1
Blinatumomab (AMG 103): 9 ug/day IV continuous infusion on Days 1-7 and then 28 ug/day IV continuous infusion on Days 8-28
BMS-936558 (Nivolumab, MDX-1106): 240 mg IV over 60 minutes on Day 11 and then every two Weeks

Cycles 2-5
Blinatumomab (AMG 103): 28 ug/day IV continuous infusion on Days 1-28
BMS-936558 (Nivolumab, MDX-1106): 240 mg IV over 60 minutes every two Weeks

Cycles 6+
BMS-936558 (Nivolumab, MDX-1106): 240 mg IV over 60 minutes every two Weeks

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on July 25, 2018, and received the last dose of blinatumomab on December 10, 2018 (Cycle 4, Day 6), and the last dose of nivolumab o~~f~~**n** December 5, 2018 (Cycle 4, Day 1).

14. DESCRIPTION OF ADVERSE EVENT

The patient is a 57-year-old male with precursor B-lymphoblastic leukemia (B-precursor ALL) who experienced grade 4 pneumonitis while on a Phase I trial utilizing the investigational agents blinatumomab and nivolumab. Additional information has been requested from the investigational site.

The Initial Written Report was sent to the FDA on November 15, 2019.

<u>Follow-up #1:</u>

On December 11, 2018 (Cycle 4, Day 7), the patient was removed from the study treatment due to a pulmonary embolus and right internal jugular thrombus. Of note, the patient also had a relapse of extramedullary Philadelphia chromosome–positive (Ph+) precursor B-cell acute lymphocytic leukemia (ALL). On January 18, 2019, the patient was admitted for confirmed influenza A and was treated with oseltamivir for 5 days. On February 6, 2019, he was readmitted for persistent influenza A and was treated with zanamivir and levofloxacin. A chest CT scan showed diffuse patchy consolidations concerning for influenza *vs.* bacterial superinfection. On February 8, 2019, the patient was discharged home and he continued to have persistent cough and fatigue. On February 27, 2019, a PET scan showed persistent ground glass opacities and scattered consolidated opacities suspicious for organizing pneumonia *vs.* drug toxicity *vs.* atypical infection. He was started on prednisone 20 mg, which was decreased to 10 mg one week

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later. On March 4, 2019, the patient presented to the clinic with a fever of 101.9°F. He had an O_2 saturation of 89% on room air and 92-93% on 2L nasal cannula. He was admitted and started on doxycycline and cefepime. A chest X-ray showed diffuse bilateral patchy opacities. On March 5, 2019, a repeat chest CT scan showed extensive consolidative and ground glass opacities in a bronchovascular distribution increased relative to his previous CT scan. On March 7, 2019, the patient was started on high flow oxygen via nasal cannula (HFNC) due to increased oxygen requirements. His infectious workup was unrevealing and the etiology was thought to be due to nivolumab-induced pneumonitis. He was started on methylprednisolone. On March 9, 2019, the patient had worsening cough and hypoxia. His arterial blood gases showed a pH of 7.42, PCO_2 of 35, and PO_2 of 117. A chest X-ray showed worsening multifocal bilateral opacities, particularly on the left, with dense opacification of the entire lower lung field with evident air bronchograms consistent with adult respiratory distress syndrome (ARDS) of unclear etiology. The patient was started on furosemide and was transferred to the medical intensive care unit and intubated. On March 12, 2019, he was started on etanercept. On March 14, 2019, a repeat chest CT remained unchanged. On March 15, 2019, he was extubated and placed on HFNC. On March 16, 2019, the patient required increased ventilatory support with low grade fevers. He improved with Bilevel Positive Airway Pressure (BiPAP) and diuresis. A repeat chest X-ray was stable with persistent bilateral opacities. His procalcitonin was elevated at 1.71 ng/mL (reference range: not provided) and he was started on empiric coverage with vancomycin and cefepime. On March 17, 2019, he was weaned to nasal cannula and he was subsequently stable on 6L. On March 26, 2019, he was started on a steroid taper with plan for a slow 10 mg decrease per week. On April 9, 2019, he was discharged home. On October 2, 2019, following pulmonary evaluation, the patient remained on oxygen with interstitial lung abnormalities, likely a consequence from immune checkpoint inhibitor therapy and acute lung injury from influenza, which was felt to be chronic.

15. ACCRUAL AND IND EXPERIENCE

~~Pending for 15-day report.~~

Number of patients enrolled in NCI-sponsored clinical trials using blinatumomab under NSC 765986 = 1,720.

Number of patients enrolled in NCI-sponsored clinical trials using nivolumab under NSC 748726 = 4,989.

Pneumonitis is an expected event for blinatumomab and nivolumab.

16. ASSESSMENT

~~Based on the information provided, a causal relationship cannot be ruled out.~~

In this case, it is felt that a possible relationship exists between the pneumonitis and the investigational agents blinatumomab and nivolumab.

	Pneumonitis
Blinatumomab	**Possible**
Nivolumab	**Possible**
Precursor B-lymphoblastic leukemia (B Precursor ALL)	**Unrelated**

17. CONCOMITANT MEDICATIONS

~~Pending for 15-day report.~~

Medications taken at the time of the event were calcium carbonate, carboxymethylcellulose, cholecalciferol, folic acid, multivitamin, prednisone, ursodiol, albuterol, apixaban, benzonatate, dextromethorphan-guaifenesin, ergocalciferol, guaifenesin-codeine, ondansetron, and prochlorperazine.

18. COMMENTS

~~Pending for 15-day report.~~

AT THIS TIME, NO OTHER INFORMATION IS AVAILABLE. IF UPON FURTHER INVESTIGATION RELEVANT INFORMATION BECOMES AVAILABLE, THEN A FOLLOW-UP REPORT WILL BE SUBMITTED IN ACCORDANCE WITH 21CFR 312.32(d)(2).

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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.