FOLLOW-UP IND SAFETY REPORT #1

1. IND NUMBER	2. AGENT NAME	3. DATE
134416	MEDI4736 (Durvalumab)	**May 26, 2021**

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-HN004 (AE #2327633)	Grade 5: **Infections and Infestations:** Lung infection **and Sepsis** Grade 3: Thromboembolic event

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
KY002-HN004-00160	63 years	Male

12. PROTOCOL SPECIFIED
IMRT: 70 Gy (2 Gy/fx)
MEDI4736 (Durvalumab): 1500 mg IV on Week -2
MEDI4736 (Durvalumab): 1500 mg IV Q4 Weeks beginning Week 2

13. TREATMENT RECEIVED AND DATES
The patient began the investigational therapy on January 13, 2021, and received the last dose of durvalumab on March 31, 2021 (Cycle 4, Day 1), and the last dose of radiotherapy on March 17, 2021.

14. DESCRIPTION OF ADVERSE EVENT

The Initial Written Report was sent to the FDA on May 20, 2021, as a 7-day report.

Follow-up #1:

The patient was a 63-year-old male with squamous cell carcinoma of the soft palate who experienced a grade 3 thromboembolic event **(pulmonary embolism)**, and later expired on April 27, 2021 due to a lung infection **and sepsis**, while on a Phase II/III trial utilizing the investigational agent durvalumab in combination with radiotherapy. The patient had a history of coronary artery disease status post coronary artery bypass graft surgery, cerebrovascular accident with mild residual right-sided weakness, hypertension, hyperlipidemia, bowel obstruction, and smoking. On April 21, 2021 (Cycle 4, Day 22), the patient presented to the emergency department (ED) with a 1-month history of generalized weakness, an inability to walk the previous day, and swelling in his feet. Upon arrival, he was alert, oriented, and cachectic, but in no acute distress. He had a temperature of 97.9°F, blood pressure of 147/94 mmHg, heart rate of 101 beats per minute, respiratory rate of 18 breaths per minute, and an oxygen saturation (SpO_2) of 96%. Laboratory results were significant for a sodium of 129 mmol/L (reference range: 135-143 mmol/L), chloride of 91 mmol/L (reference range: 100-108 mmol/L), creatinine of 1.41 mg/dL (reference range: 0.64-1.27 mg/dL), blood urea nitrogen of 26 mg/dL (reference range: 6-20 mg/dL), troponin I of 0.05 ng/ml (reference range: 0.00-0.03 ng/ml), lactic acid of 1.87 mmol/L (reference range: 0.90-1.70 mmol/L), and D-dimer of 3.44 mcg/mL (reference range: 0.19-0.74 mcg/ml). A CT pulmonary angiogram revealed an acute on chronic pulmonary embolism involving the posterior segment of the left lower lobe pulmonary artery with complete occlusion distally and an associated pulmonary infarct involving the medial posterior left lower lobe parenchyma. An electrocardiogram showed normal sinus rhythm, left ventricular hypertrophy, ST segment depression in lead V4, and T-wave inversion in leads V5 and V6. The cardiologist attributed the findings to type II non-ST segment elevation myocardial infarction (NSTEMI) in the setting of pulmonary embolism. The patient was started on heparin, intravenous fluid hydration with normal saline, and was placed on 2L of supplemental oxygen therapy with a plan to wean oxygen as able. He was admitted to the hospital for further evaluation and

management of acute hypoxic respiratory failure. On April 22, 2021 (Cycle 4, Day 23), he was seen by a cardiologist who started the patient on carvedilol. An echocardiogram showed moderate left global hypokinesis and an ejection fraction of 42%, but no evidence of right ventricular strain. On April 23, 2021, the heparin drip was stopped, and he was started on apixaban.

Overnight on April 24, 2021, the patient had a temperature of 100.9°F and a hypotensive episode with systolic blood pressure in the 70s, which was corrected with intravenous fluids. He also became hypoxic and was placed on Ventimask®. Laboratory results were significant for a white blood cell (WBC) count of 1.7 K/mcL (reference range: 4.1-10.8 K/mcL), red blood cell count of 3.14 x 10^9/L (reference range: 4.37-5.74 x 10^9/L), and platelet count of 88 x 10^9/L (reference range: 140-370 x 10^9/L). A chest X-ray showed interval development of diffuse confluent left-sided opacities consistent with pneumonia, left-sided pleural effusion, and associated atelectasis. A CT scan of the head showed no acute intracranial process. A lower extremity doppler scan showed a left popliteal deep vein thrombosis. A urinalysis was positive for 10-14 WBCs/HPF (reference range: 0 WBCs/HPF). Blood cultures were drawn, and he was started empirically on cefepime, vancomycin, and metronidazole. On April 25, 2021, the patient's blood culture was positive for *Pseudomonas* with additional cultures pending. Apixaban was stopped and the patient was started on heparin. On April 26, 2021, the patient had an oxygen saturation in the low 90s, despite being on 5L of supplemental oxygen therapy. His platelet count dropped to 44 x 10^9/L, and he was transfused 1 unit of platelets. That day, vancomycin was stopped. Overnight on April 27, 2021, the patient decompensated with worsening hypoxia and continued desaturation episodes, requiring initiation of high-flow nasal cannula therapy (HFNC). He had shortness of breath with respiratory muscle use and was given intravenous furosemide. A chest X-ray showed near complete opacification of the left hemithorax. In view of worsening infection and respiratory failure, the patient's family decided to transition him to comfort care. That day, the patient expired. An autopsy was not performed.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using durvalumab under NSC 778709 = 915.
Lung infection **and sepsis are** ~~is an~~ expected event**s** for durvalumab.
There have been 6 other cases of thromboembolic event reported to the NCI through CTEP-AERS as serious adverse events for durvalumab under NSC 778709.

Adverse Event	Grade	Attribution
Durvalumab (NSC 778709)		
Thromboembolic event (n=6)	4 3 2	1 Unlikely 3 Possible, 1 Unrelated 1 Unrelated

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the lung infection **and sepsis**, and the thromboembolic event and the investigational agent durvalumab.

	Lung infection **and Sepsis**	Thromboembolic event
Durvalumab (MEDI4736)	Possible	Possible
Radiation	Possible	Possible
Head and neck squamous cell carcinoma	Possible	Possible

17. CONCOMITANT MEDICATIONS

Medications taken at the time of the event were sucralfate, diphenoxylate/atropine, omeprazole, and prochlorperazine.

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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.