FOLLOW-UP IND SAFETY REPORT #1

1. IND NUMBER	2. AGENT NAME	3. DATE
134416	MEDI4736 (Durvalumab)	**May 20, 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
EA5181 (AE #2892141)	Grade 4: Stroke

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
15109	66 years	Female

12. PROTOCOL SPECIFIED
Durvalumab + Platinum Doublet + RT

13. TREATMENT RECEIVED AND DATES
The patient began the investigational therapy on March 22, 2021, and received the last doses of durvalumab, carboplatin, and paclitaxel on April 19, 2021 (Cycle 5, Day 1), and the last dose of radiotherapy on April 20, 2021 (Cycle 5, Day 2).

14. DESCRIPTION OF ADVERSE EVENT
The patient is a 66-year-old female with stage IIIB non-small cell lung cancer who experienced a grade 4 stroke while on a Phase III trial utilizing the investigational agent durvalumab in combination with carboplatin, paclitaxel, and radiotherapy. Additional information has been requested from the investigational site.

The Initial Written Report was sent to the FDA on May 12, 2021, as a 7-Day Report.

<u>Follow-Up #1:</u>
The patient has a history of vasovagal syncope, deep vein thrombosis, essential hypertension, pulmonary embolus, hyperlipidemia, melanoma, and is a former smoker. The patient was randomized to the concurrent chemoradiotherapy and durvalumab arm. On April 20, 2021 (Cycle 5, Day 2), the patient received scheduled protocol-specified radiation therapy. Later that day, she suddenly developed left-sided weakness at home. The patient was transported to the emergency department (ED) via emergency medical services (EMS). Upon arrival, the patient had left-sided hemiparesis with dense neurological deficit. A CT scan of the brain showed acute ischemia within the right posterior middle cerebral artery (MCA) territory extending to the right temporal lobe. There was no evidence of acute intracranial hemorrhage. A CT angiogram of the head and neck showed diminutive flow within the right proximal M2 segments extending to the right MCA territory, suggesting possibility of embolic phenomenon.

The patient was not a candidate for tissue plasminogen activator (tPA) therapy as she was taking apixaban. An electrocardiogram showed normal sinus rhythm. She was emergently transferred to another facility for planned neurovascular intervention and was admitted to the neurological critical care unit. Physical examination upon arrival showed right-sided gaze deviation with inability to cross the midline, left facial droop, reduced muscle strength in the left upper and lower extremities (grade 2/5), and decreased sensation to light touch on the left hemi-body. She had a temperature of 97.9°F, blood pressure of 136/83 mmHg, heart rate of 77 beats per minute, respiratory rate of 18 breaths per minute, and an oxygen saturation

(SpO_2) of 99%. Laboratory results were significant for a red blood cell count of 3.11 x 10^9/L (reference range: 3.91-5.04 x 10^9/L) and a platelet count of 153 x 10^9/L (reference range: 150-393 x 10^9/L). The patient was intubated and underwent a diagnostic cerebral angiogram and M2 segment endovascular thrombectomy. The intervention resulted in a thrombolysis in cerebral infarction (TICI) grade 2B revascularization (complete filling of all of the expected vascular territory visualized, but slower filling than normal).

On April 21, 2021, an MRI of the brain showed a large right MCA territory infarct with associated hemorrhagic conversion involving the right insula, a right cerebellar infarct with cytotoxic edema, and multiple infarcts throughout the left cerebral hemisphere consistent with embolic showering. On April 22, 2021, the patient was extubated. A CT scan of the head showed evolving edema with midline shift and intraparenchymal, subarachnoid, and intraventricular hemorrhage. That day, apixaban was held.

On April 23, 2021, the patient had a tremor in her right upper and lower extremities, increased drooling, and gaze preference with lateral eye movements towards the right. She was started on levetiracetam due to a concern for seizure. An electroencephalogram revealed no seizures or epileptiform abnormality but showed diffuse moderate encephalopathy of nonspecific etiology. A transthoracic echocardiogram showed an ejection fraction of 63% and mildly elevated right ventricular systolic pressure of 39 mmHg with no right to left shunt. Overnight on April 24, 2021, the patient stopped following commands and was re-intubated due to continued lethargy. On April 26, 2021, levetiracetam was discontinued.

On May 10, 2021, a venous duplex scan of the bilateral lower extremities showed an acute deep venous thrombosis involving the left common femoral, posterior tibial, peroneal, and gastrocnemius veins. She was started on heparin, and a follow-up CT scan of the head was stable. On May 12, 2021, the patient had episodes of lethargy, decreased responsiveness, and left gaze preference. A repeat CT scan of the head showed stable appearance of a subacute right MCA territory infarct with resolving hemorrhagic transformation and areas of gyriform hyperattenuation within the infarct, likely representing cortical laminar necrosis. Levetiracetam was resumed.

On May 13, 2021, the patient was discharged to a skilled nursing facility in stable condition on enoxaparin and atorvastatin. Additional information has been requested from the investigational site.

15. ACCRUAL AND IND EXPERIENCE

~~Pending Follow-up report.~~

Number of patients enrolled in NCI-sponsored clinical trials using durvalumab under NSC 778709 = 915. There has been 1 other case of stroke (grade 2, possible) reported to the NCI through CTEP-AERS as a serious adverse event for durvalumab under NSC 778709.

16. ASSESSMENT

~~Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship between the stroke and the investigational agent durvalumab cannot be excluded. The adverse events and attributions will be reassessed when additional information becomes available.~~

Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the stroke and the investigational agent durvalumab.

FOLLOW-UP IND SAFETY REPORT #1	
	Stroke
Durvalumab (MEDI4736)	**Possible**
Carboplatin	**Possible**
Paclitaxel	**Possible**
Radiation	**Unrelated**
Non-small cell lung cancer	**Probable**
Hypercoagulable state secondary to cancer therapy and underlying malignancy	**Probable**

17. CONCOMITANT MEDICATIONS

~~Pending Follow-up report.~~

Medications taken at the time of the event were acetaminophen, betamethasone dipropionate, calcium carbonate, citalopram, apixaban, enoxaparin, irbesartan, multivitamins, oxygen, promethazine, and sodium chloride.

18. COMMENTS

~~Pending Follow-up report.~~

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.