7-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
113916	**Bevacizumab (rhuMAb VEGF)** **Osimertinib (AZD9291)**	**April 28, 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
EA5182 (AE # 2892939)	**Grade 5: Sepsis** **Grade 4: Lung infection** **Grade 4: Intracranial hemorrhage**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
25022	**79 years**	**Male**

12. PROTOCOL SPECIFIED

Bevacizumab + Osimertinib

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on September 15, 2021, and received the last dose of bevacizumab on March 14, 2022 (Cycle 9, Day 1) and the last dose of osimertinib on March 27, 2022 (Cycle 9, Day 14).

14. DESCRIPTION OF ADVERSE EVENT

The patient was a 79-year-old male with stage IV non-small cell lung cancer who experienced a grade 4 intracranial hemorrhage and a grade 4 lung infection and later expired on April 1, 2022, due to sepsis while on a Phase III trial utilizing the investigational agents osimertinib and bevacizumab. He had a history of hypertension, hyperlipidemia, glaucoma, sleep apnea, and atrial fibrillation for which he was on anticoagulation. On March 27, 2022, the patient's wife found him on the floor of his home with altered mental status and difficulty moving his right side. He was brought to the emergency department (ED) and upon arrival, he had a blood pressure of 180/88 mmHg to 214/112 mmHg, a heart rate of 62 – 70 beats per minute, a respiratory rate of 22 – 24 breaths per minute, and an oxygen saturation (SpO_2) 99 – 100% on room air. On physical examination, the patient was unable to speak and had right-sided hemiplegia. The patient was intubated and sedated. Laboratory results were significant for a red blood cell count (RBC) of 3.69 M/µL (reference range: 4.70 – 6.10 M/µL), a platelet count of 63 K/µL (reference range: 130 – 400 K/µL), a prothrombin time of 18.2 seconds (reference range: 10.2 – 12.9 sec), an international normalized ratio (INR) of 1.5 (reference range: not provided), a blood glucose level of 265 mg/dL (reference range: 70 – 90 mg/dL), a blood urea nitrogen (BUN) of 34 mg/dL (reference range: 7 – 18 mg/dL), a creatinine level of 2.35 mg/dL (reference range: 0.7 – 1.3 mg/dL). A chest X-ray showed a persistent rounded opacity in the right lateral lower lung field with linear atelectasis in the left lower lung field. A CT scan of the head without contrast showed a large intraparenchymal hemorrhage involving the left basal ganglia with mild to moderate surrounding vasogenic edema and old right frontal cortical infarcts. That evening, the patient was transferred via helicopter to a medical facility with neurosurgical capabilities. En route, he developed left anisocoria, bradycardia, and severe hypertension, requiring fentanyl, midazolam, 250 mL of 3% NaCl, and levetiracetam. Upon arrival, he was coughing and was admitted to the intensive care unit (ICU). He remained intubated, mechanically ventilated, and was on a hypertonic saline drip. A nasal screening for methicillin-resistant *Staphylococcus aureus* (MRSA) was positive. An MRI of the brain with and without contrast showed redemonstration of a large area of acute intraparenchymal hemorrhage involving the left frontal lobe and insular cortex with adjacent edema and associated mass effect/effacement on the left lateral ventricle. An electrocardiogram showed sinus bradycardia, an incomplete right bundle branch block, and a

prolonged QT interval. On March 29, 2022, blood cultures showed gram-positive rods for which he was started on antibiotics. Overnight, he received a unit of platelets. On March 31, 2022, a chest X-ray showed worsening of the infiltrates in the bilateral lungs with pleural parenchymal changes and effusion on the left side. On April 1, 2022, a CT scan of the head without contrast showed slight improvement in the persistent left-sided intraparenchymal hemorrhage. That evening, the patient's family decided to transition him to comfort care. He was extubated and expired shortly after. An autopsy was not performed. Additional information has been requested from the investigational site.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using osimertinib under NSC 781254 = 192.
Number of patients enrolled in NCI-sponsored clinical trials using bevacizumab under NSC 704865 = 44,399.
There have been 3 other cases of sepsis reported to the NCI through CTEP-AERS as serious adverse events for osimertinib under NSC 781254.
There have been 7 other cases of lung infection reported to the NCI through CTEP-AERS as serious adverse events for osimertinib under NSC 781254.
There has been no other case of intracranial hemorrhage reported to the NCI through CTEP-AERS as a serious adverse event for osimertinib under NSC 781254.
There has been no other case of intracranial hemorrhage reported to the NCI through CTEP-AERS as a serious adverse event for bevacizumab under NSC 704865.
Infection/sepsis and intracranial hemorrhage are expected events for the investigational agent bevacizumab.

Adverse Event	Grade	Attribution
Osimertinib (NSC 781254)		
Sepsis (n=3)	4 3	1 Unlikely, 1 Unrelated 1 Unrelated
Lung infection (n=7)	5 3	2 Unrelated 2 Unlikely, 3 Unrelated

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the sepsis and the lung infection and the investigational agent bevacizumab. A probable relationship exists between the intracranial hemorrhage and the investigational agent bevacizumab. The sepsis, lung infection, and the intracranial hemorrhage are not related to the investigational agent osimertinib.

Note: The inciting event in this case was the intracranial hemorrhage that led to fatal complications of lung infection and sepsis.

	Sepsis	Intracranial hemorrhage	Lung infection
Bevacizumab	**Possible**	**Probable**	**Possible**
Osimertinib	**Unlikely**	**Unlikely**	**Unlikely**
Non-small cell lung cancer	**Unlikely**	**Unlikely**	**Unlikely**
Rivaroxaban therapy for atrial fibrillation	**Unlikely**	**Definite**	**Unlikely**
Chronic thrombocytopenia	**Unlikely**	**Probable**	**Unlikely**
Nosocomial risk factors - intubation, central lines, urinary catheter	**Probable**	**Unlikely**	**Probable**

17. CONCOMITANT MEDICATIONS

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Medications taken at the time of the event were acetaminophen, azilsartan medoxomil, dapagliflozin, fluticasone-umeclidin-vilanter, lantanoprost, rivaroxaban, amlodipine, amiodarone, atorvastatin, brimonidine, metoprolol, multivitamin, and vitamin D3.
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.