15-DAY IND SAFETY REPORT

1. IND NUMBER	2. AGENT NAME	3. DATE
131657	**Atezolizumab (MPDL3280A)**	**December 10, 2020**

4. SPONSOR

Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION	6. PHONE NUMBER
Elad Sharon, MD, MPH – Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI	**240-276-6565**
	7. EMAIL ADDRESS **ctepsupportae@tech-res.com**

8a. PROTOCOL NUMBER (AE #)	8b. AE GRADE: AE
A021502 (AE #2015409)	**Grade 3: Vascular disorder: Cerebral venous thrombosis**

9. PATIENT IDENTIFICATION	10. AGE	11. SEX
9124284	**58 years**	**Male**

12. PROTOCOL SPECIFIED

Cycles 1-12
Cycle = 14 Days
Oxaliplatin (Eloxatin): 85 mg/m^2 IV over 2 hours on Day 1
Leucovorin calcium: 400 mg/m^2 IV over 2 hours on Day 1
5-Fluorouracil (5-FU): 400 mg/m^2 IV (bolus) on Day 1 followed by 2400 mg/m^2 IV over 46 hours Days 1-3
Atezolizumab (MPDL3280A): 840 mg IV on Day 1

Cycles 13-25
Cycle = 14 Days
Atezolizumab (MPDL3280A): 840 mg IV on Day 1

13. TREATMENT RECEIVED AND DATES

The patient began the investigational therapy on May 7, 2019, and received the last dose of atezolizumab on June 5, 2019 (unconfirmed by site).

14. DESCRIPTION OF EVENT

The patient is a 58-year-old male with adenocarcinoma of the colon who experienced grade 3 cerebral venous thrombosis while on a Phase III trial utilizing the investigational agent atezolizumab. He is status post right hemicolectomy (in March of 2019). He had been receiving standard chemotherapy combined with immunotherapy on the current protocol. The patient had a right chest port that was removed in early June 2019 due to infection. On June 18, 2019 (Cycle 3, Day 16), the patient presented to the emergency room (ER) with worsening headache for the previous 4 to 5 weeks, despite receiving narcotics for it. He denied nausea, vomiting, chest pain, arm and leg weakness, and any fall injury. An MRI of the brain showed a dural venous sinus thrombosis involving the right transverse and sigmoid sinuses with thrombus extending slightly into the superior sagittal sinus. There was also thrombosis within the visualized proximal jugular vein. An extensive opacification of the right mastoid air cells with fluid signal, likely secondary to the dural venous sinus thrombosis, was also noted. He was started on enoxaparin and admitted to the hospital. The study drug was put on hold. No hypercoagulable workup was recommended. On June 20, 2019, the patient was discharged home in stable condition on enoxaparin and was provided with coordination of care, along with an explained follow-up and treatment plan. Of note, the patient reported improvement of symptoms associated with the cerebral venous thrombosis, but continued changes in visual acuity and darkening of his vision. On July 23, 2019, he was found to have disc edema on exam by an ophthalmologist and was followed. On November 14, 2019, he was found to have bilateral disc edema with significant visual field loss. He was

started on acetazolamide 3000 mg daily. On December 11, 2019, the patient presented to the ophthalmologist with gradual darkening of his vision. A workup showed intracranial hypertension with papilledema and visual loss secondary to the thrombosis of the transverse sinus. Subsequently, he presented to an urgent care and underwent a ventriculoperitoneal (VP) shunt placement with strata valve set to 1.5. He was restarted on anticoagulation per neurology. On January 10, 2020, an eye exam revealed a visual acuity of 20/50+1 in the right eye and 20/40-3 in the left eye and a bilateral optic disc pallor was noted. His vision was stable and his difficulty with different lighting conditions was attributed to optic neuropathy. On January 22, 2020, the patient was removed from protocol therapy secondary to the VP shunt and an interruption of >42 days of therapy. On January 28, 2020, the patient presented to the clinic for a one-month follow-up and stated that his vision had improved since his surgery. On March 19, 2020, at a follow-up visit with neuro-ophthalmology, the patient had improved visual acuity and stable visual fields. A follow-up was scheduled for five months after the visit. The treating physicians felt that the cerebral venous thrombosis was possibly related to the study drug. Additional information has been requested from the investigational site.

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using atezolizumab under NSC 783608 = 1,991. There have been no other cases of cerebral venous thrombosis reported to the NCI through CTEP-AERS as serious adverse events for atezolizumab under NSC 783608.

16. ASSESSMENT

Based on the provided medical documentation and our medical and scientific knowledge, a possible relationship exists between the cerebral venous thrombosis and the investigational agent atezolizumab.

	Cerebral venous thrombosis
Atezolizumab	Possible
Adenocarcinoma of the colon	Possible
Central line placement and infection	Possible
Thromboembolic event	Possible

17. CONCOMITANT MEDICATIONS

Medications taken at the time of event were acetaminophen, gabapentin, ibuprofen, and sildenafil.

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.