

IND SAFETY REPORT: INITIAL WRITTEN REPORT

TO: Division of Biologic Oncology Products, Center for Drug Evaluation and Research, FDA

FAX: 301-796-9849

1. IND NUMBER

7921

2. AGENT NAME

Bevacizumab (rhuMAb VEGF)

3. DATE

October 25, 2010

4. SPONSOR

Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION

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6. PHONE NUMBER

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8a. PROTOCOL NUMBER (AE #)

PBTC-022 (AE# 1470711)

8b. AE GRADE: AE

Grade 3: Osteonecrosis (avascular necrosis)

9. PATIENT IDENTIFICATION

54301

10. AGE

13 years

11. SEX

Female

12. DESCRIPTION OF ADVERSE EVENT

The patient is a 13 year-old female with pilocytic astrocytoma who experienced grade 3 avascular osteonecrosis while on a phase 2 trial utilizing the investigational agent bevacizumab in combination with irinotecan. She began her first course of treatment on February 9, 2009, and received the last dose of bevacizumab on October 4, 2010 (Cycle 18, Day 1), and the last dose of irinotecan on August 2, 2010 (Cycle 15, Day 22). In mid-September 2010, the patient started complaining of left wrist pain, and an X-ray of the wrist was read as normal. On September 20, 2010 (Cycle 17, Day 15), the patient presented to the clinic with mild swelling of the left wrist, tenderness of the left anterior aspect of the wrist, with limited range of motion, and the inability to make a fist. The same day, her dosage of bevacizumab was held, and an orthopedic consultation noted the patient to have pain with hyperextension of the wrist, while all motor functions were normal. A repeat X-ray of the left wrist showed no evidence of fracture or infection; however, osteopenia was identified. The orthopedist was unclear as to the etiology of her symptoms and recommended consultation with a rheumatologist if her symptoms did not improve. On October 4, 2010 (Cycle 18, Day 1), the patient returned to the clinic and reported that the pain had improved, although she continued to experience some discomfort. On October 12, 2010 (Cycle 18, Day 9), an MRI of the left wrist revealed Kienbock malacia (avascular necrosis of the lunate) with mild fragmentation and collapse of the lunate. The decision was that the patient's bevacizumab would be discontinued indefinitely, and a consultation with a hand surgeon was scheduled. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drug.

13. DOSE, ROUTE, AND SCHEDULE

Cycle = 4 weeks

Patients not on EIACDs (enzyme-inducing anticonvulsant drugs):

Bevacizumab: 10 mg/kg IV over 90-30 minutes on Days 1 and 15

14. DATES OF TREATMENT

The patient began the investigational therapy on February 9, 2009, and received last dose of bevacizumab on October 4, 2010 (Cycle 18, Day 1).

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using Bevacizumab = 29,191. There have been 14 other cases of reported to the NCI through AdEERS as serious adverse events for bevacizumab.

16. COMMENTS

Cycles= 4 weeks

Irinotecan: 125-150 mg/m² IV over 90 minutes every 2 weeks starting on Day 15

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).

DISCLAIMER per 21 CFR 312.32(e): THIS SAFETY REPORT DOES NOT NECESSARILY REFLECT A CONCLUSION OR ADMISSION BY THE CTEP IDB SENIOR INVESTIGATOR/SPONSOR THAT THE INVESTIGATIONAL AGENT/THERAPY CAUSED OR CONTRIBUTED TO THE ADVERSE EXPERIENCE BEING REPORTED.

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