

IND SAFETY REPORT: INITIAL WRITTEN REPORT

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

FAX: 301-796-9849

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

FAX: 301-796-9845

1. IND NUMBER

100947

61010

2. AGENT NAME

IMC-A12 (HuMab IGF-1R)

CCI-779 (temsirolimus, Torisel™)

3. DATE

January 7, 2011

4. SPONSOR

Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION

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8a. PROTOCOL NUMBER (AE #)

8121 (AE# 1021986)

8b. AE GRADE: AE

Grade 2: Eye disorder – Other: Periorbital hemorrhage

9. PATIENT IDENTIFICATION

CTS-000171

10. AGE

19 yrs

11. SEX

Male

12. DESCRIPTION OF ADVERSE EVENT

The patient is a 19-year-old male with metastatic Ewing sarcoma who experienced grade 2 periorbital hemorrhage while on a phase 2 trial utilizing the investigational agents IMC-A12 and temsirolimus. He began the investigational therapy on October 18, 2010, and received his last doses of IMC-A12 and temsirolimus on December 13, 2010 (Cycle 2, Day 8). On November 6, 2010 (Cycle 1, Day 20), the patient presented to the local ER with severe nausea and vomiting related to acute alcohol intoxication. He had severe periorbital hemorrhage and swelling secondary to extensive vomiting after being intoxicated. The patient was treated with IV fluids. On November 15, 2010 (Cycle 1, Day 29), he reported experiencing daily headaches primarily around his eyes which improved with Vicodin® and application of ice. The physical examination showed mild bilateral periorbital edema, but no scleral injection or petechiae around his eyes. This was thought to be most likely due to his excessive nausea and vomiting on November 6, 2010. On November 22, 2010 (Cycle 1, Day 36), the patient presented to the Infusion Center with a 2-day history of a bulging right eye and morning headaches which improved on waking up. He also complained of vision changes and scleral bleeding. His left eye remained swollen. The patient denied acute vision changes, floaters, epistaxis, gum bleeding, or easy bruising. He had subconjunctival hemorrhage on the left lateral sclera, mild bilateral periorbital edema, and a painful lateral gaze in each eye. A CT scan of the head and orbits revealed bilateral symmetric superior orbital soft tissue masses with associated proptosis which were concerning for metastatic disease. On November 24, 2010, during an oculoplastic consultation, the patient presented with bilateral proptosis, decreased extraocular motility on up-gaze, and decreased sensation along ophthalmic (V1) distribution of the trigeminal nerve bilaterally. His visual acuity was 20/60 in the right eye, improving with pinholing to 20/20, and 20/50 in the left eye, improving with pinholing to 20/20. It was suspected that his current presentation was a result of orbital hematoma that was compressing his optic nerves leading to his visual field deficit. This was thought to be less likely secondary to metastases given the fact that his symptoms were those following his alcohol intoxication and severe vomiting episode. As a result of the patient's risk of bleeding related to thrombocytopenia, surgical intervention was delayed and he was to be observed for spontaneous resolution. Week 1 of Cycle 2 was held. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drugs.

13. DOSE, ROUTE, AND SCHEDULE Cycle = 42 Days. IMC-A12: 6 mg/kg IV over 1 hour weekly
Temsirolimus: 25 mg IV over 30 minutes weekly

14. DATES OF TREATMENT

The patient began the investigational therapy on October 18, 2010, and received the last doses of IMC-A12 and temsirolimus on December 13, 2010 (Cycle 2, Day 8).

15. ACCRUAL AND IND EXPERIENCE

Number of patients enrolled in NCI-sponsored clinical trials using IMC-A12= 762, and temsirolimus = 2429. There have been no other cases of periorbital hemorrhage reported to the NCI through AdEERS as serious adverse events for either IMC-A12 or temsirolimus.

16. COMMENTS

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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