

IND SAFETY REPORT: INITIAL WRITTEN REPORT

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

FAX: 301-796-9845

FAX: 301-796-9849

1. IND NUMBER 70116 7921	2. AGENT NAME CC-5013 (lenalidomide, Revlimid®) Bevacizumab (rhuMAB VEGF)	3. DATE September 20, 2010
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4. SPONSOR
Division of Cancer Treatment and Diagnosis, National Cancer Institute

5. REPORTER'S NAME, TITLE, AND INSTITUTION Howard Streicher, MD-Senior Investigator for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI Helen Chen, MD-Associate Branch Chief for Investigational Therapeutics 3, Investigational Drug Branch, CTEP, DCTD, NCI	6. PHONE NUMBER 301-496-1196
	7. FAX NUMBER 301-402-0428

8a. PROTOCOL NUMBER (AE #) 8217 (AE# 1963940)	8b. AE GRADE: AE Grade 2: Osteonecrosis (avascular necrosis)
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9. PATIENT IDENTIFICATION 1010022	10. AGE 63 years	11. SEX Male
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12. DESCRIPTION OF ADVERSE EVENT
The patient is a 63-year-old male with prostate cancer who experienced grade 2 osteonecrosis while on a phase 2 study utilizing the investigational agents CC-5013 and bevacizumab in combination with docetaxel and prednisone. He began the investigational therapy on July 21, 2010, and received his last dose of CC-5013 on August 22, 2010 (Cycle 2, Day 14), the last doses of bevacizumab and docetaxel on August 9, 2010 (Cycle 2, Day 1), and the last dose of prednisone on August 30, 2010 (Cycle 2, Day 22). The patient had baseline moderate periodontitis, but osseous structures of the maxillofacial region and mandible were unremarkable on the CT scan. On August 30, 2010 (Cycle 2, Day 22), the patient presented to the clinic with jaw discomfort for dental consultation. A diagnosis of left lingual mandibular ridge osteonecrosis was made by the dentist. Additional information has been requested from the investigational site. There is a reasonable possibility that the experience may have been caused by the drugs. This report is being filed due to an increased frequency of this event in patients undergoing this combination of drugs. The follow-up report will include adverse events #1735101 and #1755517.

13. DOSE, ROUTE, AND SCHEDULE:
Cycle = 21 days
CC-5013: 25 mg PO daily on Days 1-14
Bevacizumab: 15 mg/kg IV over 30-90 minutes on Day 1

14. DATES OF TREATMENT
The patient began the investigational therapy on July 21, 2010, and received his last dose of CC-5013 on August 22, 2010 (Cycle 2, Day 14), and the last dose of bevacizumab on August 9, 2010 (Cycle 2, Day 1).

15. ACCRUAL AND IND EXPERIENCE
Number of patients enrolled in NCI-sponsored clinical trials using CC-5013 = 2240 and bevacizumab = 28700. There have been 3 other cases of osteonecrosis reported to the NCI through AdEERS as serious adverse events for CC-5013 and 13 other cases of osteonecrosis reported to the NCI through AdEERS as serious adverse events for bevacizumab.

16. COMMENTS: **Also administered on this protocol:**
Docetaxel: 75 mg/m² IV over 60 minutes on Day 1
Prednisone: 5 mg PO twice daily

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.