



DATE: APR 05 2011

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SUBJECT: CC-5013 (Lenalidomide, Revlimid®) and Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE # 1963940, 1605554, 1755517, 1735101, and 1889339

TO: Investigators Using Lenalidomide (NSC 703813) and Bevacizumab (NSC 704865)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agents lenalidomide and bevacizumab.

The following must be completed by all investigators using lenalidomide under NCI IND 70116 and bevacizumab under NCI IND 7921 and 11460:

- Send a copy of this letter to your Institutional Review Board (IRB) of record according to your policies and procedures.
- File a copy of the IND Safety Report in your protocol file.

If your study is not covered under IND 7921, 11460, and/or 70116, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with lenalidomide and bevacizumab, there does not appear to be a change in the risk-benefit ratio for lenalidomide and bevacizumab studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The attached Adverse Events Assessment describes the adverse event(s) (synopsis provided below), relevant previous experience under these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

AE # 1963940 (Patient 1)

A 63-year-old male with prostate cancer experienced grade 2 osteonecrosis while on a phase 2 study using the investigational agents lenalidomide and bevacizumab in combination with docetaxel and prednisone.

AE # 1605554 (Patient 2)

A 65-year-old male with prostate cancer experienced grade 2 osteonecrosis while on a

phase 2 study using the investigational agents lenalidomide and bevacizumab in combination with docetaxel and prednisone.

AE # 1755517 (Patient 3)

A 56-year-old male with prostate cancer experienced grade 2 osteonecrosis while on a phase 2 study using the investigational agents lenalidomide and bevacizumab in combination with docetaxel and prednisone.

AE # 1735101 (Patient 4)

A 73-year-old male with prostate cancer experienced grade 2 osteonecrosis while on a phase 2 study using the investigational agents lenalidomide and bevacizumab in combination with docetaxel and prednisone.

AE # 1889339 (Patient 5)

A 73-year-old male with prostate cancer experienced grade 2 osteonecrosis while on a phase 2 study using the investigational agents lenalidomide and bevacizumab in combination with docetaxel and prednisone.

ADVERSE EVENTS ASSESSMENT

IND 70116	7921	ADVERSE EXPERIENCE REPORT NO.
NSC 703813	704865	IND Safety Report: #1
CC-5013 (Lenalidomide, Revlimid®)	Bevacizumab (rhuMab VEGF)	Event: Gr. 2: Osteonecrosis (avascular necrosis)
AEs: 1963940, 1605554, 1755517, 1735101, and 1889339		Protocol: 8217

Five cases of osteonecrosis of the jaw have been reported to the NCI as serious adverse events under INDs 70116 and 7921 on protocol 8217, “**A Phase 2 Trial of Bevacizumab, Lenalidomide, Docetaxel, and Prednisone (ART-P) for Treatment of Metastatic Castrate-Resistant Prostate Cancer**”. The protocol regimen includes lenalidomide 15 or 25 mg PO once daily on Days 1-14; bevacizumab 15 mg/kg IV over 30-90 minutes on Day 1; docetaxel 75 mg/m² IV over 60 minutes on Day 1; and prednisone 5 mg PO twice daily, every 21 days. These cases are briefly summarized below.

AE # 1963940 (Patient 1): The patient is a 63-year-old male with prostate cancer who experienced osteonecrosis while on a phase 2 study using the investigational agents. He began the first course of the investigational therapy on July 21, 2010. The patient received his last dose of lenalidomide on August 22, 2010 (Cycle 2, Day 14), his last doses of bevacizumab and docetaxel on August 9, 2010 (Cycle 2, Day 1), and his last dose of prednisone on August 30, 2010 (Cycle 3, Day 1).

The patient was diagnosed with prostate cancer in March 2009 and is status post surgery and hormonal therapy. At a baseline dental evaluation on July 19, 2010, the patient had active moderate periodontitis, but osseous structures of the maxillofacial region and mandible were unremarkable on the CT scan. He began the investigational treatment on July 21, 2010.

On August 30, 2010 (Cycle 2, Day 22), the patient presented to the clinic for dental consultation with jaw discomfort. The patient stated that he had had tenderness of the L mandible treated with antibiotics for 10 days, and pain had been mostly resolved. Oral examination revealed that the bone located in the lingual posterior mandibular ridge area was exposed. The patient denied prior history of or current use of Zometa® or bisphosphonates. The radiographic exam did not show radiolucency or osteolytic lesion. A diagnosis of left lingual mandibular ridge osteonecrosis was made by the dentist. The patient was instructed to continue his antibiotics and initiate oral chlorhexidine rinses.

The patient’s past medical/surgical history is significant for hypertension, diabetes mellitus, inflammatory bowel disease, cerebrovascular accident, and osteoarthritis. The patient has a history of smoking cigars and chewing tobacco on a daily basis. Medications taken at the time of the event included amoxicillin, Decadron®, dexamethasone, Neulasta®, and Lovenox®.

AE # 1605554 (Patient 2): The patient is a 65-year-old male with prostate cancer who experienced osteonecrosis while on a phase 2 study using the investigational agents. He began the first course of the investigational therapy on May 5, 2010. He received his last dose of lenalidomide on August 10, 2010 (Cycle 5, Day 14), his last doses of bevacizumab and docetaxel on July 28, 2010 (Cycle 5, Day 1), and his last dose of prednisone on August 15, 2010 (Cycle 5, Day 19).

The patient was diagnosed with prostate cancer in October 2005. He is status post surgery, hormonal therapy, and radiation therapy. He began the investigational treatment on May 5, 2010.

On August 4, 2010 (Cycle 5, Day 8), the patient was evaluated by a dentist per protocol schema. He was noted to have osteonecrosis of the jaw, but no evidence of infection was found. Zometa® was discontinued. The patient was treated with chlorhexidine mouth rinses.

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The patient's past medical/surgical history is significant for anemia, inflammatory bowel disease, and renal impairment. Medications taken at the time of the event included Lisinopril[®], amlodipine, and morphine.

AE # 1755517 (Patient 3): The patient is a 56-year-old male with prostate cancer who experienced osteonecrosis while on a phase 2 study using the investigational agents. He began the first course of the investigational therapy on December 22, 2009. He received his last dose of lenalidomide on June 14, 2010 (Cycle 8, Day 14), his last doses of bevacizumab and docetaxel on June 1, 2010 (Cycle 8, Day 1), and his last dose of prednisone on June 21, 2010 (Cycle 8, Day 21).

The patient was diagnosed with prostate cancer in February 2009. He is status post surgery, hormonal therapy, and radiation therapy. The baseline dental consultation revealed a significant periodontal concern on tooth #18 and a recent root canal on tooth #31; chlorhexidine mouth rinse was provided to the patient. He began the investigational treatment on December 22, 2009.

On June 1, 2010 (Cycle 8, Day 1), the patient presented to the clinic with a new lesion in his lower jaw. He had been on Zometa[®] infusion once a month since February 2010. During a dental consultation on June 4, 2010, a new area of bone exposure at the lingual posterior of tooth #31 was found, consistent with ONJ, but no obvious bony changes were seen from dental radiographs. The recommendation was to hold Zometa[®].

The patient's past medical/surgical history is significant for anemia, coronary artery disease, and inflammatory bowel disease. Medications taken at the time of the event include Norvasc[®], OxyContin[®], oxycodone, Lexapro[®], Protonix[®], Neurontin[®], Ativan[®], Restoril[®], vitamin D, Zometa[®], calcium, and Lupron[®].

AE # 1735101 (Patient 4): The patient is a 73-year-old male with prostate cancer who experienced osteonecrosis while on a phase 2 study using the investigational agents. He began the first course of the investigational therapy on August 31, 2009. He received his last dose of lenalidomide on March 1, 2010 (Cycle 9, Day 14), his last doses of bevacizumab and docetaxel on February 16, 2010 (Cycle 9, Day 1), and his last dose of prednisone on March 7, 2010 (Cycle 9, Day 21).

The patient was diagnosed with prostate cancer in May 2002. He is status post surgery, hormonal therapy, and radiation therapy. His baseline mandible CT did not show any abnormalities. He began the investigational treatment on August 31, 2009.

On February 16, 2010 (Cycle 9, Day 1), the patient presented to the clinic for a follow-up dental consultation. The patient stated that he began to feel roughness on the back of both tongue sides of his jaw right after his last chemotherapy. Oral examination revealed two areas of exposed bone, both of which were located in the posterior lingual aspect of jaw bone, but no localized swelling or inflammation was noted. Beginning stage of jaw bone osteonecrosis was indicated. The patient was to continue chlorhexidine rinses and Biotene[®] products.

The patient's past medical/surgical history is significant for psoriasis, coronary artery disease, allergic rhinitis, obstructive sleep apnea, degenerative joint disease, back pain, hypercholesterolemia, dermatitis, herpes simplex virus zoster, right-sided hearing loss, coronary stent placement, prostatectomy, nasal septoplasty and polypectomy, angioplasty of left leg artery, and right inguinal hernia repair. Medications taken at the time of the event included Lupron[®], Zometa[®], oxycodone, OxyContin[®], metoprolol, lotrel, Levaquin[®], clindamycin, fexofenadine, Advair[®], Atrovent[®], Flonase[®], vitamin D, aspirin, ranitidine, temazepam, halobetasol propionate, hydrocortisone, fluocinonide, valerate, ultimate eye support, docusate sodium sennoside, and Miralax[®].

AE # 1889339 (Patient 5): The patient is a 73-year-old male with prostate cancer who experienced osteonecrosis while on a phase 2 study using the investigational agents. He began the first course of the investigational therapy on March 1, 2010. He received his last dose of lenalidomide on July 20, 2010 (Cycle 7, Day 14), his last doses of bevacizumab and docetaxel on July 7, 2010 (Cycle 7, Day 1), and his last dose of prednisone on July 25, 2010 (Cycle 7, Day 19).

The patient was diagnosed with prostate cancer in December 2005. He is status post surgery, radiation therapy, and hormonal therapy. The patient has baseline grade 1 osteonecrosis of the jaw. His baseline mandible CT scan revealed: destructive osteolytic lesion in the right mandible and associated bone osteosclerosis; and diffuse heterogeneity and sclerosis throughout the mandible, as well as the rest of the visualized bones, compatible with metastatic disease. He began the investigational treatment on March 1, 2010.

On July 13, 2010, the patient was admitted to the hospital for neutropenic fever, worsening right jaw pain, and mucositis. He had been found to have bilateral osteonecrosis of the jaw. Mandible CT performed on July 2, 2010 did not show significant differences from the previous tests. The patient was evaluated by dental surgery and it was felt that the jaw symptoms were likely due to inflammation and unlikely due to infection. Grade 2 osteonecrosis of the jaw was diagnosed.

The patient's past medical/surgical history is significant for chronic obstructive airways disease, hepatic disorder, osteoarthritis, renal impairment, and peripheral neuropathy. Medications taken at the time of the event included Lovenox[®], cyclobenzaprine, Colace[®], senna, and oxycodone.

Summary and CTEP assessment:

There have been a total of 8 out of 28 patients (29%) on this protocol reported to have ONJ. Four patients were being treated with bisphosphonates, 2 had past treatment, and 1 had not been treated in the past with bisphosphonate. In the currently study, patients have had baseline and periodic dental evaluation as well as referral for symptoms.

An apparent increase in ONJ incidence (18.3%) has been reported in a study utilizing similar investigational drug regimen including thalidomide (rather than lenalidomide), bevacizumab, docetaxel and prednisone for the treatment of metastatic castrate-resistant prostate cancer (Aragon-Ching, *et al*, 2009).

An increased rate of ONJ with or without Zometa[®] has not been reported for single agent lenalidomide, bevacizumab or other combinations of these 4 drugs. Both prednisone and bisphosphonates have a well established relationship to ONJ. The incidence of ONJ with either of these treatments may be in the range of 5%. Patients being treated with any combination of the study drugs especially those receiving steroids and bisphosphonates should be evaluated as clinically appropriate for evidence of ONJ.

There have been 3 other cases of osteonecrosis reported to the NCI as a serious adverse event through AdEERS under the lenalidomide NSC and/or IND and 13 other cases of osteonecrosis reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND as summarized in the table below:

Adverse Event	Grade	Attribution
Lenalidomide (NSC 703813)		
Osteonecrosis (n=3)	2	1 Possible, 2 Unlikely
Bevacizumab (NSC 704865)		
Osteonecrosis (n=13)	4	1 Probable
	3	3 Possible, 1 Unrelated
	2	6 Possible, 1 Unrelated
	1	1 Probable

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To date, a total of 31,454 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC, and 2,514 patients have been enrolled in NCI-sponsored clinical trials under the lenalidomide IND and/or NSC.


In these cases, it is felt that the combination of bevacizumab, lenalidomide, docetaxel, and prednisone with the use of bisphosphonates in these patients with prostate cancer is associated with an increased risk of osteonecrosis.

	Osteonecrosis
Lenalidomide	Possible
Bevacizumab	Possible
Docetaxel	Possible
Prednisone	Probable
Zometa	Probable
Prostate cancer	Unlikely


Reference:

1. Jeanny B. Aragon-Ching, Yang-Min Ning, Clara C. Chen, Lea Latham, Jean-Pierre Guadagnini, James L. Gulley, Philip M. Arlen, John J. Wright, Howard Parnes, William D. Figg, and William L. Dahut. Higher incidence of osteonecrosis of the jaw (ONJ) in patients with metastatic castration resistant prostate cancer treated with anti-angiogenic agents. *Cancer Invest.* 2009, 27(2), 221–226.

Date: 3/24/11

Signature: 
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If this assessment is changed, we will notify your office.

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