



**DATE:** June 26, 2009

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**SUBJECT:** Bevacizumab (rhuMAB VEGF) and CCI-779 (temsirolimus, Torisel<sup>®</sup>) NCI IND Safety Report, AE# **1994045**

**TO:** Investigators Using Bevacizumab (NSC 704865) and Temsirolimus (NSC 683864)

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 bevacizumab and temsirolimus.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460 and temsirolimus under NCI IND 61010:

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

If your study is not covered under INDs 7921, 11460, and 61010, 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 bevacizumab and temsirolimus, there does not appear to be a change in the risk-benefit ratio for bevacizumab and temsirolimus 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.

A 50-year-old male with renal cell carcinoma experienced **grade 2 osteonecrosis** while on a phase 2 study using the investigational agents bevacizumab and temsirolimus.

## ADVERSE EVENTS ASSESSMENT

IND <b>7921</b> <b>61010</b> NSC <b>704865</b> <b>683864</b> <b>Bevacizumab</b> <b>CCI-779</b> <b>(rhuMab VEGF)</b> <b>(temsirolimus,</b> <b>Torisel®)</b>  AE: <b>1994045</b>	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: <b>#1</b> <b>Gr. 2:    Osteonecrosis</b>  Protocol: <b>E2804</b>
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The patient is a 50-year-old male with renal cell carcinoma who experienced osteonecrosis while on a phase 2 trial utilizing the investigational agents bevacizumab and temsirolimus. He began the first course of the investigational therapy on July 15, 2008, receiving bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, and temsirolimus 25 mg IV over 30 minutes on Days 1, 8, 15, and 22, every 28 days. The patient received his last doses of bevacizumab and temsirolimus on March 16, 2009 (Cycle 9, Day 15).

The patient was initially diagnosed with T3, N0, M1, stage IV metastatic clear cell renal carcinoma with metastasis to the lung in June 2008, and is status post left-sided nephrectomy, adrenalectomy with periaortic lymph node dissection, and a partial left 11<sup>th</sup> rib resection in June 2008. He began the investigational therapy on July 15, 2008 and later had a dose reduction of temsirolimus to 15 mg weekly due to hand and foot syndrome.

On March 16, 2009 (Cycle 9, Day 15), the patient presented to the clinic complaining of difficulty eating and tender sore throat; the left side of his neck was swollen, and he had been taking Vicodin® to manage his pain. The patient was given a prescription for amoxicillin and proceeded with therapy.

On March 19, 2009 (Cycle 9, Day 18), the patient called the clinic to report something hard and sharp rubbing on his tongue, stating that he could see something white sticking out, and he was instructed to come into the clinic the next day. On March 20, 2009 (Cycle 9, Day 19), examination revealed a painful round area around 1 cm on his inner left lower jaw that was white and sharp to touch. The patient's bilateral neck swelling was stable. The patient was referred to an oral surgeon to be evaluated for osteonecrosis of his jaw. It was noted that he had not been on bisphosphonates. The oral surgeon planned to clean the bone and trim it down.

During a follow-up visit on March 30, 2009 (Cycle 9, Day 29), examination demonstrated that the exposed bone in the lower mandible had sloughed off, and the gum was healing over it. It also showed a small ulcer in the left lower mandible between the two last molars. The patient was doing well overall, with improved eating and oral pain. The patient declined to follow-up with the oral surgeon at that time and agreed to close clinic follow-up with the oncologist. It was decided that bevacizumab would not be restarted at that time, but rather that the patient would continue on temsirolimus only.

The patient's past medical/surgical history is significant for peripheral vascular disease, s/p stent placement in the left internal iliac artery, and mild renal impairment. Medications taken at the time of the event included Compazine®, Ativan®, lisinopril, Dilaudid®, amoxicillin, paroxitene, magic mouthwash, Vicodin®, Niaspan®, and Advair®.

There have been 10 other cases of osteonecrosis reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND, and no other case of osteonecrosis reported to the NCI as serious adverse events through AdEERS under the temsirolimus NSC and/or IND as summarized in the table below.


Adverse Event	Grade	Attribution
<i>Bevacizumab</i>		
Osteonecrosis (n=10)	4	1 Probable, 1 Possible
	3	2 Possible, 1 Unrelated
	2	3 Possible, 1 Unlikely, 1 Unrelated

To date, a total of 21,442 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC, and 1,678 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

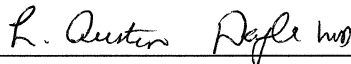
In this case, it is felt that a probable relationship exists between the event and bevacizumab, and that a possible causal relationship exists between the event and temsirolimus.

	Osteonecrosis
<b>Bevacizumab (rhuMab VEGF)</b>	Probable
<b>CCI-779 (temsirolimus, Torisel®)</b>	Possible
<b>Renal cell carcinoma, clear cell adenocarcinoma</b>	Unlikely

Date: 6/29/09

Signature:   
 Helen Chen, M.D.  
 (IDB Monitor for bevacizumab)

Date: 7/8/09

Signature:   
 L. Austin Doyle, M.D.  
 (IDB Monitor for temsirolimus)

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

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