



DATE: March 11, 2009

FROM: L. Austin Doyle, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
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SUBJECT: CCI-779 (Temsirrolimus, Torisel[®]) and Bevacizumab (rhuMAb VEGF) IND Safety Report #2, AE# 1951869

TO: Investigators Using CCI-779 (Temsirrolimus, Torisel[®]) (NSC 683864) and Bevacizumab (rhuMAb VEGF) (NSC 704865)

L. Austin Doyle

Helen Chen

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 temsirolimus and bevacizumab.

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

- 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 IND 61010, 7921, or 11460, 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 temsirolimus and bevacizumab, there does not appear to be a change in the risk-benefit ratio for combination studies of temsirolimus and bevacizumab; 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 61-year-old male with metastatic renal cell carcinoma died while on a phase 1/2 study utilizing the investigational agent temsirolimus in combination with bevacizumab.

ADVERSE EVENTS ASSESSMENT

IND 7921	61010	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 2 Event: Gr. 5: Death not related to CTCAE term: Death, NOS Protocol: 6986
NSC 704865	683864	
Bevacizumab (rhuMAB VEGF)	CCI-779 (temsirolimus, Torisel®)	
AE: 1951869		

This report has been amended to reflect new information. Changes to the original summary are indicated by bold and italics (new information) and/or strikethrough (deleted information). If this assessment is changed further, we will notify your office. Please note that this modified report will be distributed to investigators.

The patient was a 61-year-old male with renal cell carcinoma metastatic to the lungs, bone and abdominal lymph nodes who died while on a phase 1/2 study utilizing the investigational agent temsirolimus in combination with bevacizumab. He began his first course of the investigational treatment on April 1, 2008, receiving temsirolimus 10 mg IV on Days 1, 8, 15, and 22 and bevacizumab 5 mg/kg IV on Days 1 and 15, every 28 days. The patient received his last dose of bevacizumab on June 10, 2008 (Cycle 3, Day 15), and the last dose of temsirolimus on June 17, 2008 (Cycle 3, Day 22).

The patient was initially diagnosed with renal cell carcinoma in November 2006, when he presented to the hospital with a ruptured abdominal aortic aneurysm (AAA) and was found to have a large mass in his left kidney. After a prolonged period of healing from the AAA repair, the patient underwent a left radical nephrectomy with adrenalectomy in March 2007 at which time, he was found to have metastatic disease. The patient completed 7 cycles of Sutent® (sunitinib malate) and was placed on Zometa® for significant metastatic disease in his bones. A CT scan of the chest, abdomen, and pelvis in March 2008 revealed an interval increase in the size of multiple abdominal lymph nodes, consistent with disease progression, as well as evidence of healing metastatic disease in the vertebral bodies; it also revealed a stable short segment dissection of the descending aorta. He began the investigational therapy with temsirolimus and bevacizumab on April 1, 2008.

At a follow-up appointment on April 29, 2008 (Cycle 2, Day 1), the patient reported increased sinus drainage, runny eyes and nose, a rash on his back and forearms, mild pruritus, and more recently perirectal tenderness. His performance status was 90% with him working full-time; he denied fatigue. He weighed 66.6 kg. His examination was unremarkable except for some dry areas of his skin on the left and right scapula and forearms and scattered erythema in his oropharynx. His CBC was normal. He received Cycle 2 as scheduled. On May 13, 2008 (Cycle 2, Day 15), the patient reported that over the last week he had had worsening perirectal tenderness and irritation interfering with his daily activities as well as some anorexia and weight loss. Although he was still working full-time, his performance status was down to 70%. He now weighed 62.9 kg. Physical examination at this time showed a fair amount of erythema and tenderness in the perirectal area. After some discussion, the temsirolimus was held, bevacizumab was continued per protocol, and the patient was to be reevaluated the following week.

On May 20, 2008 (Cycle 2, Day 22), the patient's now intermittent perirectal tenderness showed some improvement, but he had increasing fatigue. He was still at a performance status of 70%, now working at a sedentary position at his job. His weight was 63.0 kg. He was afebrile with a pulse rate of 136 bpm and blood pressure 110/65 mmHg. The perirectal erythema was markedly reduced as compared to the previous assessment. The patient's hemoglobin was 8 g/dL (reference range: 13.8-17.2 g/dL) with a normal WBC and platelet count. The fatigue was attributed to anemia and renal insufficiency. A CT scan of the chest, abdomen, and pelvis showed an interval decrease in the size of multiple lymph nodes within the abdomen and chest consistent with interval response to therapy; interval development of bilateral ground glass opacities and tree-in-bud opacities consistent with development of pneumonia; and lytic lesions unchanged and suggestive of metastatic disease in the right iliac bone and lateral left sixth rib. It

was decided to continue holding temsirolimus and see the patient in one week, at which time it would be decided whether he would continue the study or be taken off the protocol. On May 27, 2008 (Cycle 3, Day 1), his perirectal tenderness was improved, but he had a slight nonproductive cough without fever or dyspnea. His weight was steady at 62.9 kg, and his performance status was unchanged. The perirectal area had healed considerably and the remaining physical examination was unremarkable. His hemoglobin was 7.8 g/dL, and he received 2 units of packed red blood cells. His temsirolimus was restarted at a reduced dose with plans to withhold it altogether if there was any evidence of symptom recurrence. By June 10, 2008 (Cycle 3, Day15), the patient's hemoglobin had recovered to 10.4 g/dL.

On June 24, 2008 (Cycle 4, Day 1), the patient did not come for his scheduled visit. Documents indicate that his wife called the clinic on June 24, 2008, and informed the clinic staff that the patient had not kept the appointment due to diarrhea and significant weakness; he was also sleeping most of the time. He did not want to reschedule the appointment. With the wife's agreement, the patient was referred to hospice; however, he himself later declined hospice services. The patient expired on June 26, 2008. There is no specific information as to the circumstances surrounding his death. An autopsy was not performed.

The patient's past medical/surgical history was significant for his disease as described. Medications taken at the time of the event included A&D ointment, diphenhydramine, and Zometa®.

There have been 18 other cases of death, NOS reported to the NCI through AdEERS as serious adverse events for temsirolimus and there have been 61 other cases of death, NOS reported to the NCI through AdEERS under the bevacizumab NSC as summarized in the table below.

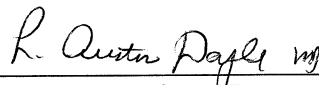
Adverse Event	Grade	Attribution
<i>Temsirolimus</i>		
Death not related to CTCAE Term: Death, NOS (n=18)	5	2 Possible, 6 Unlikely, 10 Unrelated
<i>Bevacizumab</i>		
Death not related to CTCAE Term: Death, NOS (n=61)	5	15 Possible, 35 Unlikely, 11 Unrelated

To date, a total of 18,655 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab NSC, and a total of 1,461 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus NSC.


In this case, a possible causal relationship between temsirolimus, *bevacizumab*, and the patient's death could not be excluded.

	Death not related to CTCAE Term: Death, NOS
Bevacizumab	Unrelated <i>Possible</i>
Temsirolimus	Possible
Renal cell carcinoma, clear cell adenocarcinoma	Possible

Date: 3/6/09

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

Date: 3/5/09

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

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