



DATE: May 19, 2009

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SUBJECT: Bevacizumab (rhuMAb VEGF) and CCI-779 (temsirolimus, Torisel®) NCI IND Safety Report, AE# **1360351**

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 67-year-old female with stage IV malignant melanoma experienced grade 2 reversible posterior leukoencephalopathy syndrome (RPLS) while on a phase 2 trial utilizing the investigational agent temsirolimus in combination with bevacizumab.

ADVERSE EVENTS ASSESSMENT

IND 7921	61010	ADVERSE EXPERIENCE REPORT NO.
NSC 704865	683864	IND Safety Report: #1
Bevacizumab (rhuMAb VEGF)	CCI-779 (temsirolimus, Torisel®)	Gr. 2: Neurology: Reversible posterior leukoencephalopathy syndrome (RPLS)
AE: 1360351		Protocol: 7190

The patient is a 67-year-old female with stage IV malignant melanoma with metastases to the inguinal and periaortic lymph nodes who experienced reversible posterior leukoencephalopathy syndrome (RPLS) while on a phase 2 trial utilizing the investigational agent temsirolimus in combination with bevacizumab. She began the first course of the investigational therapy on December 15, 2008, receiving temsirolimus 25 mg IV over 30 minutes on Days 1 and 8, and bevacizumab 10 mg/kg IV over 90 minutes on Day 8, every 14 days. The patient received her last doses of both temsirolimus, at a reduced dose of 20 mg, and bevacizumab on February 2, 2009 (Cycle 4, Day 8).

The patient was diagnosed in April 2008, with stage IIIA malignant melanoma and is status post wide excision of the right lower extremity melanoma with positive sentinel lymph node biopsy of the right inguinal nodes. She began the investigational therapy on December 15, 2008.

On February 2, 2009, the patient presented to the clinic for her scheduled dosing with temsirolimus and bevacizumab. She was doing well after the infusions and was on her way home when she suddenly developed a severe mid-epigastric pain which she initially described as sharp and persistent with a sense of nausea. She returned to the clinic at which time her blood pressure was 198/90 mmHg and increased to 211/100 mmHg with the pain. Note that the patient's anti-hypertensive medications were discontinued because of low blood pressures at the start of therapy. The patient denied chest pain, dyspnea, numbness or tingling in her feet, or radiation of the pain to her back or legs. She was started on IV fluids and given IV Dilaudid® after which the patient's blood pressure decreased to 176/84 mmHg. She was admitted to the hospital for further evaluation of her abdominal pain, and continued on IV pain management. The laboratory report was unremarkable. A CT scan of the abdomen revealed mild thickening of the gallbladder wall with mild pericholecystic fluid collection and mild common bile duct dilation. An ultrasound of the abdomen was negative for gallstones within the common bile duct. The patient's abdominal pain resolved, and she was able to tolerate food.

On February 4, 2009, as part of a scheduled restaging evaluation, an MRI of the brain with and without contrast revealed findings within the bilateral cerebral and cerebellar hemispheres that were compatible with RPLS, which was thought to be related to medication or her recent hypertensive episode. There was no evidence of intracranial metastatic disease. The patient did not have any significant neurological symptoms that were associated with the syndrome, such as seizures, visual deficits, or severe persistent headache. The MRI findings were discussed with a neurologist, and it was felt that the patient was stable for discharge as long as she did not have any of the clinical symptoms mentioned above. On February 5, 2009, the patient was discharged in stable condition on lisinopril.

On February 9, 2009, the patient was seen for a follow-up neurology consultation. She denied any neurological symptoms. It was suggested that the abnormal findings could be related to either of the investigational agents since the syndrome has been reported several times with bevacizumab and sirolimus, an active metabolite of temsirolimus. The neurologist also felt that her underlying hypertension may have predisposed her to RPLS. It was recommended that if the protocol allowed, a dose reduction of both investigational agents be implemented as well as maintenance of anti-hypertensive therapy. On February 22, 2009, a follow-up MRI of the brain with and without contrast showed interval resolution of the previously described cortical and subcortical bilateral cerebral and cerebellar hemispheric lesions, consistent with resolved RPLS. Although the patient was scheduled for investigational treatment the following day, treatment was again held due to elevated blood pressures in the clinic (178/88 mmHg) as well as at home, and another anti-hypertensive was added.

At a follow-up visit on March 2, 2009, the patient complained of some memory loss. Her blood pressures were still not well controlled according to her blood pressure log, and her medications were adjusted. The investigational therapy was held again. She was seen by neuro-oncology for her memory problems on March 11, 2009, who determined that her symptoms were neither due to the investigational agent nor to RPLS. She was recommended to under a neuro-psychiatric evaluation. Her clinic visit later that day revealed persistent hypertension (146/80 mmHg), prompting further medication adjustment. She was scheduled for a staging CT scan that day and instructed to return in one week for follow-up.

The patient's past medical/surgical history is significant for hypertension, chronic obstructive pulmonary disease, anxiety, depression, myopia, multiple urinary tract infections, Rocky Mountain Spotted Fever, *Clostridium difficile* colitis in January 2009, skin nodules in the right groin, appendectomy, tonsillectomy and adenoidectomy, total abdominal hysterectomy, closed reduction of bilateral wrists, right lower extremity edema, bilateral cataract surgery, colonoscopy and excision of 1 polyp, spinal disk problems in 2004 and 2005, and D&C following miscarriages × 3, alcohol abuse ending in 2004, and a 40 pack-year smoking history. Medications taken at the time of the event included Spiriva[®], Advair Diskus[®], Klonopin[®], oxycodone, fentanyl, Flomax[®], multivitamin, Singulair[®], Protonix[®], Phenergan[®], Compazine[®], stomatitis mouthwash, Cymbalta[®], and vancomycin.

There have been no other cases of RPLS reported to the NCI as serious adverse events through AdEERS under the temsirolimus NSC and/or IND and 13 other cases of RPLS reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND as summarized in the table below.

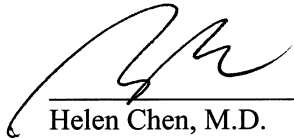
Adverse Event	Grade	Attribution
<i>Bevacizumab</i>		
RPLS (n=13)	4	2 Probable, 1 Possible 1 Unlikely
	3	1 Definite, 2 Probable, 2 Possible
	2	1 Definite, 1 Probable, 1 Possible
	1	1 Possible

To date, a total of 21,347 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC and 1,587 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

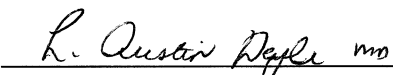
In this case, it is felt that a probable causal relationship exists between the event and the investigational agents.

	RPLS
Bevacizumab (rhuMAb VEGF)	Probable
CCI-779 (temsirolimus, Torisel[®])	Probable
Melanoma	Unlikely

Date: 5/27/09

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

Date: 5/27/09

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

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

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