



DATE: October 21, 2009

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SUBJECT: Bevacizumab (rhuMAb VEGF) and CCI-779 (tamsirolimus, Torisel®) NCI IND Safety Report, AE #1392926

TO: Investigators Using Bevacizumab (NSC 704865) and Tamsirolimus (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 tamsirolimus.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460 and tamsirolimus 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 tamsirolimus, there does not appear to be a change in the risk-benefit ratio for bevacizumab and tamsirolimus 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 72-year-old female with endometrioid endometrial adenocarcinoma experienced grade 5 pneumonitis/pulmonary infiltrates while on a phase 2 trial utilizing the investigational agents bevacizumab and tamsirolimus.

ADVERSE EVENTS ASSESSMENT

IND 7921 61010 NSC 704865 683864 Bevacizumab (rhuMAb VEGF) CCI-779 (temsirolimus, Torisel®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Gr. 5: Pneumonitis/pulmonary infiltrates
AE: 1392926	Protocol: GOG-0229G

The patient was a 72-year-old female with endometrioid endometrial adenocarcinoma who experienced pneumonitis/pulmonary infiltrates and subsequently expired while on a phase 2 trial utilizing the investigational agents bevacizumab and temsirolimus. She began her first course of treatment on January 8, 2009, receiving temsirolimus 25 mg/kg IV over 30 minutes on Days 1, 8, 15, and 22 and bevacizumab 10 mg/kg IV over 30-90 minutes on Days 1 and 15, every 28 days. The patient received her last dose of bevacizumab on April 2, 2009 (Cycle 4, Day 1) and her last dose of temsirolimus on April 9, 2009 (Cycle 4, Day 8).

The patient was diagnosed with endometrial adenocarcinoma in June 2007, and was status post total abdominal hysterectomy with bilateral salpingo-oophorectomy and multi-agent chemotherapy. She was in complete remission until the middle of 2008, when she was diagnosed with lung metastasis. She began the investigational therapy on January 8, 2009.

On April 16, 2009 (Cycle 4, Day 1), the patient presented to the clinic with significant dyspnea on exertion. She was sent to the emergency room and reported that she had not felt well for the last 3 days (generalized fatigue and malaise). She denied any history of cough, orthopnea, nocturnal dyspnea, hemoptysis, fever, or chills. A CT angiogram of the chest was compared to the patient's most recent study in February 2009 and revealed interval development of cystic changes and ground-glass opacification within the lungs fields consistent with interstitial pneumonitis. The differential diagnosis included a drug-related hypersensitivity pneumonitis versus bacterial or viral pneumonitis.

On April 17, 2009, the patient underwent a bronchoscopy with bronchoalveolar lavage (BAL) of the right middle lobe. The bronchoscope was introduced orally and the vocal cords, trachea, and carina all appeared normal. The mucosa was unremarkable and there were no secretions. No biopsies were obtained. She tolerated the procedure well and no complications were noticed. BAL specimens sent for routine gram stain/culture, AFB, fungus, PCP, cell count/differential and cytology yielded unremarkable results. The patient was started on IV antibiotics, initially with Avelox® and subsequently vancomycin, Zithromax®, acyclovir, cefipime (replacing Avelox®), and IV Bactrim® (which was discontinued when the BAL results were negative for *Pneumocystis carinii pneumoniae*). Despite the aggressive treatment, her hypoxemia progressively worsened. By April 20, 2009, the patient was on 100% non-rebreather mask with oxygen saturation in the 80s. She was placed in hospice care as per her wishes and after discussion with her family members. The patient expired on April 21, 2009, due to respiratory failure with pneumonitis and metastatic disease.

The patient's past medical and surgical history is significant for hypertension and hyperlipidemia. Her father had bone cancer, and her mother had stomach cancer. Medications taken at the time of the event included Vasotec®, simvastatin, sertraline, Coumadin®, Ambien®, and dexamethasone.

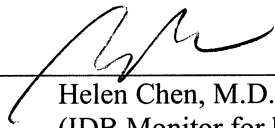
Pneumonitis is a known event for both bevacizumab and temsirolimus.

A total of 23,109 patients have been enrolled in NCI-sponsored clinical trials using bevacizumab, and 1765 patients have been enrolled using CCI-779.

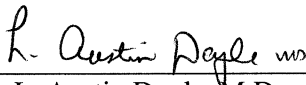
Although pneumonitis is a known event for both bevacizumab and temsirolimus, because of the unusual severity of this case, it is being reported.

	Pneumonitis
Bevacizumab (rhuMAb VEGF)	Unlikely
CCI-779 (temsirolimus, Torisel)	Possible
Endometrioid endometrial adenocarcinoma	Possible

Date: 10/22/09

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

Date: 10/23/09

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

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

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