DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: 6/9/11

FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
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SUBJECT: Bevacizumab (rhuMAb VEGF) and CCI-779 (temsirolimus, Torisel®) NCI IND Safety Report, AE# **1860656**

TO: Investigators Using Bevacizumab (NSC 704865) and CCI-779 (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 CCI-779.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460 and CCI-779 under NCI IND 61010:

- 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 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 CCI-779, there does not appear to be a change in the risk-benefit ratio for bevacizumab and CCI-779 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 ovarian cancer expired from respiratory failure while on a phase 2 trial utilizing the investigational agents bevacizumab and CCI-779.

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. 5: Respiratory failure**
AE: **1860656**		Protocol: **8233**

The patient was a 67-year-old female with ovarian cancer who expired from respiratory failure while on a phase 2 trial utilizing the investigational agents bevacizumab and CCI-779. The planned protocol therapy the patient was assigned to was as follows:

Cycle= 28 days:
CCI-779 (Temsirolimus): 25 mg IV on days 1, 8, 15, 22
Bevacizumab: 10 mg/ kg IV over 30-90 min on days 1 and 15

The patient was diagnosed with high-grade clear cell carcinoma of the ovary in March 2010. She was status post cytoreductive surgery and multiple-agent systemic chemotherapy. The patient was taken off the chemotherapy on February 14, 2011, due to the progression of her cancer. In March 2011, the patient was diagnosed with upper respiratory tract infection and she was treated with antibiotics. Her respiratory cultures revealed *Candida albicans* in moderate numbers, *Fusarium* species, and mixed anaerobic flora. The patient was treated with vitamin K for her high INR, which was caused by using Coumadin® for anticoagulation treatment. She began her first course of the investigational therapy on April 15, 2011, and she received the only doses of bevacizumab and CCI-779 on that day.

On April 21, 2011 (Cycle 1, Day 7), the patient presented to the hospital with a 2-day-history of nausea, vomiting, and diarrhea. She was afebrile, vomited only after eating, and had no chest pain. Physical exam revealed mild thrush on her tonsils. The patient was also dehydrated, weak, and unable to ambulate. She was admitted for further evaluation. The patient was made *n.p.o.*; she was given IV hydration, Zofran® for her nausea and vomiting, and nystatin solution for her thrush. A head CT scan revealed mild parenchymal volume loss and nonacute ischemic change, but no evidence of intracranial hemorrhage or mass. The laboratory tests revealed an INR of 12.9 (reference range: 0.9-1.3) and PT of 60.6 sec (reference range: 10.9-12.9 sec); the patient was given vitamin K for the high INR. DIC associated with malignancy was suspected. On April 22, 2011, her nausea, vomiting, and diarrhea had resolved, but the patient developed a fever of 101.2 °F; she had a cough and coarse breath sounds. Her O_2 saturation dropped to 85% (reference range 95%-100%) and she was given nasal cannula oxygen supplement. A chest X-ray showed new linear opacities overlying the left lower lung zone, likely due to atelectasis, but pneumonia could not be ruled out. A prominent right hilum was seen correlating with the right hilar lymphadenopathy seen on the prior chest CT. Laboratory results showed a D-dimer of 693 ng/mL (reference range: 0-230 ng/mL). On April 23, 2011, the patient was evaluated for chest pain and desaturation. She was started on Lasix® and DuoNeb® for rales and rhonchi that were heard on exam. She was also treated with Lovenox® for suspected pulmonary emboli and Levaquin® due to her history of recent pneumonia. Her INR level dropped to 3.6. On April 24, 2011, the patient decompensated with regards to her respiratory status and her O_2 saturation was 87% on 5 liters nasal cannula; therefore, she required a non-rebreather mask. Her urine culture results showed positive lactobacilli and azithromycin was then started. Her INR was found to be rising again to the level of 7.4. On April 25, 2011, the patient appeared to be confused and she continued to have a persistent cough. She was showing signs of rapid deterioration. The patient was made to proceed with comfort measures only. On April 26, 2011, she was discharged to an in-patient hospice care, and she expired on the day of her arrival. Her sputum culture results showed a large number of *Staphylococcus aureus*, but her blood cultures were negative.

The patient's past medical/surgical history was significant for pulmonary embolus, bladder surgery, bilateral tubal ligation, and Port-A-Cath placement. Medications taken at the time of the event included Coumadin®, iron, and multivitamin.

There have been 28 other cases of respiratory failure reported to the NCI through AdEERS as a serious adverse event for bevacizumab, and 5 other cases of respiratory failure reported to the NCI through AdEERS as serious adverse events for CCI-779.

Adverse Event	Grade	Attribution
Bevacizumab		
Respiratory failure (n=28)	5 4 3	3 Unrelated, 5 Unlikely, 7 Possible 5 Unrelated, 2 Unlikely, 3 Possible 1 Unrelated, 2 Unlikely
CCI-779		
Respiratory failure (n=5)	5	2 Unrelated, 3 Unlikely

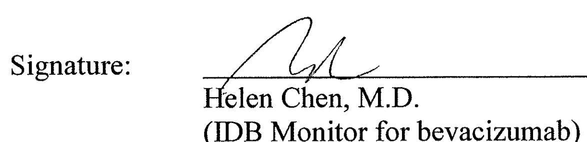
To date, a total of 32,949 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC, and 2,730 patients have been enrolled in NCI-sponsored clinical trials under the CCI-779 IND and/or NSC.

In this case, it is felt that a possible causal relationship exists between the event and the investigational agents, bevacizumab and CCI-779.

	Respiratory failure
Bevacizumab	Possible
CCI-779	Possible
Ovarian cancer	Definite

Date: 6/11/11

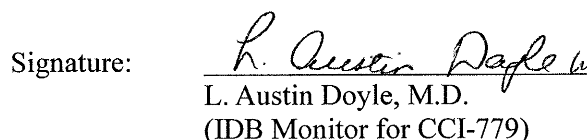
Signature:



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

Date: 6/9/11

Signature:



L. Austin Doyle, M.D.
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If this assessment is changed, we will notify your office.

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