




DATE: October 28, 2009
FROM: Kevin Conlon, M.D., Investigational Drug Branch, CTEP, DCTD, NCI 
SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE # **1202538**
TO: Investigators Using Bevacizumab (NSC 704865)

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 agent bevacizumab.

The following must be completed by all investigators using 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 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 bevacizumab, there does not appear to be a change in the risk-benefit ratio for bevacizumab 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 NSC, and the total number of patients enrolled in trials under these INDs and/or NSC.

A 56-year-old female with ovarian cancer experienced grade 4 ischemic colitis while on a phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with carboplatin and paclitaxel.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 4: Colitis
AE: 1202538	Protocol: GOG-0218

The patient is a 56-year-old female with ovarian epithelial cancer who experienced ischemic colitis while on a phase 3 study using the investigational agent bevacizumab/placebo in combination with paclitaxel and carboplatin. She began her first course of treatment on March 23, 2009, receiving paclitaxel 175 mg/m² IV over 3 hours on Day 1 × 6 cycles, carboplatin AUC 6 IV over 30 minutes on Day 1 × 6 cycles, and bevacizumab or placebo 15 mg/kg IV on Day 1 starting with Cycle 2 × 5 cycles. She received the last doses of bevacizumab/placebo, paclitaxel, and carboplatin on May 13, 2009 (Cycle 3, Day 1).

The patient was diagnosed with stage IIIC ovarian cancer in March 2009 and is status post hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and peritoneal sampling. She began the investigational therapy on March 23, 2009.

On May 17, 2009 (Cycle 3, Day 5), the patient developed acute lower abdominal pain and a gastrointestinal hemorrhage. She stated that she had lost approximately 500 grams of blood. When she presented to the hospital the following day, she had slight abdominal tenderness, but did not present with bleeding. Vital signs upon arrival were stable, and an X-ray of the abdomen was negative. The patient was admitted to the hospital. A CT scan of the abdomen revealed a continuous and diffuse hypertrophy of the bowel wall from the rectum to the descending colon consistent with ischemic colitis. There were no signs of tumor metastasis. A sigmoidoscopy revealed a longitudinal ulcer from the sigmoid colon to the upper rectum and girdle ulceration from the sigmoid to the proximal colon consistent with severe ischemic colitis. Biopsies of the ulcer and two polyps were taken and revealed ischemic colitis in the colon and low-grade tubular adenoma in the rectum. The patient was placed on IV antibiotics and IV fluids, and was placed on oral intake restrictions. Laboratory results showed: WBC 9200/μl (reference range: 3500-8500/μl), ANC 8234 mm³ (reference range: 1575-4675 mm³), LDH 541 U/L (reference range: 100-190 U/L), AST 46 IU/L (reference range: 11-29 IU/L), ALT 57 IU/L (reference range: 7-27 IU/L), and C-reactive protein 4.73 peaking to 12.14 (reference range: 0.00-0.20). On May 20, 2009 (Cycle 3, Day 8), the patient was removed from the protocol.

On May 25, 2009, a colonoscopy showed evidence of improved ischemic colitis since the previous study. The patient's IV fluids were stopped, oral intake was resumed, and she was switched to oral antibiotics. Her abdominal tenderness resolved as did her fever, her stool normalized, and her appetite returned. During the course of this hospitalization, the patient developed a fever of over 39.8°C along with an absolute neutrophil count of 324 mm³ and was given G-CSF. On June 12, 2009, she was discharged from the hospital, having had no further bleeding episodes. A repeat colonoscopy on June 30, 2009 revealed no bleeding or stenosis and an improvement in the ulcer from the previous study. A follow-up colonoscopy on September 25, 2009, showed that the ischemic colitis was completely resolved without sequelae.

The patient's past medical history is significant for appendicitis, bilateral cataracts, hepatitis B carrier, and anemia. Medications at the time of the event onset were not recorded.

While colitis in general is a known event for bevacizumab, there have only been 4 other cases of ischemic colitis previously reported to the NCI as serious adverse events through AdEERS under the bevacizumab NSC. The incidences of ischemic colitis are shown in the table below:

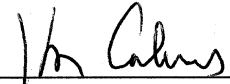
Adverse Event	Grade	Attribution
Ischemic colitis (n = 4)	4	3 possible
	3	1 possible

There have been 23,583 patients enrolled in NCI-sponsored clinical trials under this NSC.

In this case, a possible causal relationship between bevacizumab and the ischemic colitis exists.

	Ischemic colitis
Bevacizumab	Possible
Carboplatin	Possible
Paclitaxel	Possible
Ovarian epithelial cancer	Possible

Date: 29 October 2009

Signature: 
 Kevin Conlon, M.D.
 (IDB Monitor for bevacizumab)

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

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 Genentech, Inc.