



DATE: APR 11 2011
FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# **1694292**
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 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 and 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 69-year-old female with ovarian cancer experienced **grade 5 peritoneal cavity infection** while on a phase 3 study utilizing the investigational agent bevacizumab.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF) AE: 1694292	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 5: Infection with normal ANC or grade 1 or 2 neutrophils: Peritoneal cavity Protocol: GOG-0252
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The patient was a 69-year-old female with ovarian cancer who experienced peritoneal cavity infection and subsequently expired from blood infection while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with carboplatin and paclitaxel. She began the first course of the investigational therapy on September 7, 2010, receiving carboplatin AUC 6 IP on Day 1 of Cycles 1-6, paclitaxel 80 mg/m² IV over 1 hour on Days 1, 8, and 15 of Cycles 1-6, and bevacizumab 15 mg/kg IV over 30-90 minutes on Day 1 beginning with Cycle 2, every 21 days. She received her last doses of bevacizumab and carboplatin on December 30, 2010 (Cycle 6, Day 1), and the last dose of paclitaxel on January 12, 2011 (Cycle 6, Day 14).

The patient was diagnosed with ovarian epithelial cancer in August 2010, and was status post total abdominal hysterectomy and bilateral salpingo-oophorectomy, performed on August 9, 2010. Post surgery, the patient had a bilateral pelvic fluid collection, periaortic lymphocyst, multiple intra-abdominal abscesses, and bacteremia. The patient received placement of a JP drain, and a percutaneous nephrostomy tube into her back and into the periaortic lymphocyst. Abdominal fluid cultures were positive for MRSA, *Enterococcus*, and multiresistant *Enterobacter*. The patient was treated with broad-spectrum antibiotics. She began the investigational therapy on September 7, 2010.

On January 16, 2011 (Cycle 6, Day 18), the patient was admitted to the hospital with progressive neuropathy and weakness. Spinal cord compression was ruled out by MRI, and a neurology consultation indicated that the peripheral polyneuropathy was most likely due to Taxol[®]. On January 17, 2011, an abdominal and pelvic CT scan was performed and compared with a prior CT scan; it revealed an increased quantity of air and diminished fluid collection in the left retroperitoneum, and increased fluid collection close to the infusion catheter in the right hemipelvis. The patient was started on vancomycin. On January 19, 2011, a drainage catheter was placed into the left-retroperitoneal fluid and gas collection. The fluid culture revealed moderate growth of MRSA, multiresistant *Enterobacter cloacae*, and *Enterococcus* species. The blood culture also found gram positive cocci in clusters. On January 21, 2011, the vascular access port and intraperitoneal port were surgically removed. One day later, an abdominal X-ray showed free air suspicious for a ruptured viscus, which was further evaluated by CT scan and revealed pneumoperitoneum, but no definite source of the free air. On January 24, 2011, routine drainage cultures revealed heavy growth of alpha-hemolytic *Streptococci*; anaerobic drainage culture revealed moderate growth of *Prevotella* species. On January 27, 2011, the patient made the decision to stop medical intervention. Shortly thereafter she became unresponsive. The patient was then transferred to home hospice care and died on January 29, 2011.

The patient's past medical and surgical history was significant for diabetes mellitus, hypertension, obstructive sleep apnea, sigmoid resection, bilateral hip arthroplasty, L5-S1 fusion, and appendectomy. Medications taken at the time of the event included gabapentin, loratadine, naproxen, Actos[®], simvastatin, and Ambien[®].

Infection is an expected event for bevacizumab.

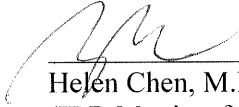
To date, a total of 31,563 patients have been enrolled in NCI-sponsored clinical trials under the

bevacizumab IND and/or NSC.

In this case, it is felt that a possible causal relationship exists between the events and the investigational therapy bevacizumab.

	Peritoneal cavity infection
Bevacizumab (rhuMAb VEGF)	Possible
Carboplatin	Possible
Paclitaxel	Possible
Ovarian epithelial cancer	Possible
Infection – Peritoneal cavity	N/A
Intraperitoneal port	Possible
Possible visceral perforation	Possible

Date: 4/8/11

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

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

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Genentech, Inc.