



DATE: AUG 09 2011

FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 1258239

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 79-year-old female with stage IIIC metastatic serous ovarian cancer experienced grade 4 cerebellar syndrome and grade 4 ataxia while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with paclitaxel and carboplatin.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab(rhuMAb VEGF) AE: 1258239	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 4: Cerebellar syndrome Gr. 4: Ataxia Protocol: GOG-0252
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The patient is a 79-year-old female with stage IIIC metastatic serous ovarian cancer who experienced cerebellar syndrome and ataxia while on a phase 3 trial utilizing the investigational agent bevacizumab in combination with paclitaxel and carboplatin. The planned protocol therapy the patient was assigned to was as follows:

Cycle = 3 weeks:

Phase A (Cycles = 1-6):

Paclitaxel: 80 mg/m² IV over 1 hr on Days 1, 8 & 15.

Carboplatin: AUC 6 IP on Day 1

Bevacizumab: 15 mg/kg IV over 30-90 min on Day 1, beginning with Cycle 2.

Phase B: (Cycles 7-22):

Bevacizumab: 15 mg/kg IV over 30-90 min on Day 1.

The patient was diagnosed with stage IIIC metastatic serous ovarian cancer in July 2010 and underwent debulking surgery in September 2010. The patient began the investigational agent on November 4, 2010, and received the last dose of bevacizumab on June 16, 2011 (Cycle 11, Day 1), the last dose of carboplatin on March 3, 2011 (Cycle 6, Day 1), and the last dose of dose of paclitaxel on March 10, 2011 (Cycle 6, Day 8).

On July 2, 2011 (Cycle 11, Day 17), the patient presented to the emergency room (ER) with complaints of uncontrolled tremors involving her extremities which decreased at rest and prevented her from walking due to an unsteady gait, nystagmus, nausea, and increased mid abdominal pain. Her physical examination was within normal limits and blood pressure was 117/72 mmHg. The patient's KUB, CT scan of the head, CT scan of the abdomen/pelvis, and laboratory results showed no evidence of infarction, infection, obstruction, or tumor. She was started on IV fluids and Zofran[®], and was later sent home.

On July 3, 2011 (Cycle 11, Day 18), the patient presented to the ER of another hospital with worsening symptoms. Her neurological examination revealed ataxia with positive a Romberg sign. The patient's cardiac markers, ECG, and electrolytes were normal. She was admitted for observation and further evaluation of her symptoms, and was started on IV fluids. Differential diagnosis included vitamin deficiency, paraneoplastic syndrome, side effect of bevacizumab, or Parkinsonian tremors. The neurologist felt that the patient's history and physical examination were most consistent with a cerebellar syndrome, more precisely truncal ataxia with severe ataxic gait. The combination of little objective appendicular involvement along, with what appeared to be extraocular movement irregularity (which was felt to be opsoclonus), suggested the possibility of a paraneoplastic cerebellar degeneration associated with ovarian cancer although it is difficult to confirm as the patient remained free of evidence of tumor. Laboratory workup for paraneoplastic syndrome revealed negative autoantibodies with the exception of positive glutamic acid decarboxylase antibodies, which may be associated with multifocal neurological manifestations.

On July 5, 2011, a brain MRI revealed minimal chronic patchy white matter changes and mild diffuse cerebral volume loss; however, there was no abnormal enhancement to represent metastatic disease

specifically in the cerebellum. There was no MRI of the brain performed prior to that time. Ativan[®], which had been given previously, was continued on an as-needed basis. On July 7, 2011, the patient was started on IV immunoglobulin G to treat the suspected paraneoplastic syndrome manifesting as opsoclonus.

On July 11, 2011, the patient developed altered mental status after receiving Ativan[®] and Dilaudid[®]. She was transferred to the ICU. The patient followed commands but did not speak. Her BP was 171/93 mmHg, pulse was 118 beats per minute, RR was 27 breaths per minute, and her oxygen saturation was 95% on room air. Ativan[®] and Dilaudid[®] were held, and neurochecks every 4 hours were recommended. The patient's mental status improved slightly in the ICU since the medication adjustment, and she later reached what was felt to be her baseline mental function. On July 19, 2011, the patient was discharged to hospice. Additional information regarding the patient's status is not available at this time.

The patient's past medical/surgical history is significant for duodenal ulcer, diabetes mellitus, cerebrovascular accident, non-ischemic heart disease, colon polyp, gastroesophageal reflux disease, hyperlipidemia, physiologic vaginal drainage, esophagogastroduodenoscopy (October 2010), wound seroma, large hiatal hernia, remote seizure disorder, right hip arthroplasty, and intraperitoneal chemotherapy port insertion with cystoscopy (September 2010). Medications taken at the time of the event included aspirin, dexlansoprazole, Dexalone[®], oxycodone-acetaminophen, magnesium gluconate, ondansetron, and Compazine[®].

There have been 37 other cases of ataxia and no other cases of cerebellar syndrome reported to the NCI through AdEERS as serious adverse events for bevacizumab as summarized in the table below:

Adverse Event	Grade	Attribution
Ataxia (n=37)	4	1 Unrelated
	3	7 Unrelated, 11 Unlikely, 14 Possible
	2	1 Unrelated, 2 Unlikely, 1 Possible

There have been 33,935 patients enrolled in NCI-sponsored clinical trials under the bevacizumab INDs and/or NSC.

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

	Cerebellar syndrome	Ataxia
Bevacizumab	Possible	Possible
Carboplatin	unlikely	unlikely
Paclitaxel	unlikely	unlikely
Ovarian epithelial cancer	Possible	Possible

Date:

8/3/11

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.