




**DATE:** October 9, 2009

**FROM:** Kevin Conlon, M.D., Investigational Drug Branch, CTEP, DCTD, NCI 

**SUBJECT:** Trastuzumab (Herceptin) NCI IND Safety Report, AE# **1353951**

**TO:** Investigators Using Trastuzumab (NSC 688097)

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 trastuzumab.

The following must be completed by all investigators using trastuzumab under NCI IND 6667.

- 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 6667 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 trastuzumab, there does not appear to be a change in the risk-benefit ratio for trastuzumab 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 transitional cell carcinoma of the urothelial tract experienced grade 5 small bowel perforation while on a phase 1/2 study using the investigational agent trastuzumab in combination with paclitaxel and radiation therapy.

## ADVERSE EVENTS ASSESSMENT

|  |   |
|--|---|
| IND <b>6667</b><br>NSC <b>688097</b><br><b>Trastuzumab (Herceptin)</b><br><br>AE: <b>1353951</b> | ADVERSE EXPERIENCE REPORT NO.<br>IND Safety Report: <b># 1</b><br>Event: <b>Gr. 5: Perforation, GI: Small Bowel NOS</b><br><br>Protocol: <b>RTOG-0524</b> |
|--|---|

The patient was a 79-year-old female with transitional cell carcinoma of the urothelial tract who experienced small bowel perforation and subsequently expired while on a phase 1/2 study using the investigational agent trastuzumab in combination with paclitaxel and radiation therapy. She began her first course of treatment on March 16, 2009, receiving trastuzumab 4 mg/kg IV over 90 minutes on Day 1 only, trastuzumab 2 mg/kg IV over 30 minutes on Days 8, 15, 22, 29, 36, and 43, paclitaxel 50 mg/m<sup>2</sup> IV over 60 minutes on Days 1, 8, 15, 22, 29, 36, and 43, and radiation therapy 1.8 Gy daily for 5 fractions/week for a total of 36 fractions (total dose=64.8 Gy). She received the last doses of trastuzumab and paclitaxel on April 27, 2009 (Cycle 1, Day 43), and the last dose of radiation therapy on April 28, 2009 (Cycle 1, Day 44).

The patient was diagnosed with urothelial bladder carcinoma in September 2007, and was status post two bladder biopsies (2008) and three transurethral resections of the bladder tumor (2007, August 2008, and December 2008). She began the investigational therapy on March 16, 2009.

On April 30, 2009 (Cycle 1, Day 46), the patient presented to the emergency room complaining of severe abdominal pain with movement or touch which rated 9 out of 10 on the pain scale. She also reported a 4-day history of generalized weakness, reduced appetite, nausea, vomiting, and dehydration since her last treatment on April 27, 2009 (Cycle 1, Day 43). She was alert but lethargic and in moderate distress. She had a temperature of 96.4°F, and physical examination revealed an abdomen that exhibited positive bowel sounds and was not rigid but diffusely tender with increased tenderness in the lower left quadrant; 2+ pitting edema of the lower extremities; and a stage 2 decubitus ulcer. An EKG showed sinus tachycardia with frequent premature ventricular complexes. Laboratory results included a sodium of 129 mEq/L (reference range: 136-145 mEq/L), BUN 40 mg/dL (reference range: 6-23 mg/dL), WBC  $1.3 \times 10^9/L$  (reference range:  $4.0-10.0 \times 10^9/L$ ), and hemoglobin 9.8 g/dL (reference range: 12.3-15.5 g/dL). The chest X-ray revealed possible free air under the diaphragm; a subsequent abdominal series revealed a pneumoperitoneum and moderate atherosclerotic calcifications. There were dilated small bowel and colonic bowel loops noted, and obstruction in the region of the splenic flexure could not be excluded. A subsequent CT scan of the abdomen indicated that there was a suggestion of free air and the presence of distal small bowel wall thickening perforation secondary to infectious, inflammatory, or ischemic etiology. It was felt that ischemia was likely due to the presence of significant atherosclerotic findings associated with the abdominal aorta. A surgical consult was obtained; the surgeon, with the agreement of the patient, elected to observe the patient closely (considering that she would not likely survive surgical intervention) and repeat a CT scan later in the day. In the meantime, the patient was admitted to the hospital, started on oxygen, IV fluids, and broad spectrum antibiotics with vancomycin, aztreonam, Flagyl<sup>®</sup>, and later Cipro<sup>®</sup>. She was removed from the study. A PICC line was placed and the patient was started on parenteral nutrition and therapy with Neupogen<sup>®</sup>. Note that she was DNR (do not resuscitate).

On May 1, 2009 (Cycle 1, Day 47), a repeat CT scan of the abdomen showed progression of massive free air with contrast extravasation versus walled-off perforation with abscess formation. Her prognosis was grave with or without surgery. On May 3, 2009, blood cultures grew gram negative rods. The patient's condition steadily deteriorated with her blood pressure dropping to the 60s/40s mmHg. She was kept comfortable until she expired on May 8, 2009. The autopsy revealed perforation of the ileum due to radiation-induced injury, and cholestyramine crystals at the site of the perforation may have acted as an irritant. Per the autopsy report, "Cholestyramine resembles Kayexalate<sup>®</sup> crystals in the colon and Kayexalate<sup>®</sup> has been associated with intestinal perforation." The pathologist could not exclude the

possibility that the bile acid binding resin reacted with the area of the radiation-induced injury to cause additional injury. There was no evidence of vascular-related ischemia.

The patient's past medical and surgical history was significant for hypertension, hypothyroidism, cerebrovascular disease, right moderate internal carotid artery stenosis, hypothermia, tachycardia, appendectomy (1956), cataract removal (2003), resection of benign bladder tumor (1975), parotid tumor resection (1975), and bladder polyp resection (1961). Her family history is significant for a father with bladder cancer. Medications taken at the time of the event included aspirin, cholestyramine, levothyroxine, Toprol<sup>®</sup> XL, Caduet<sup>®</sup>, and Lomotil<sup>®</sup>.

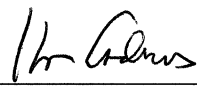
There have been no other cases of small bowel perforation previously reported to the NCI as serious adverse events through AdEERS under the trastuzumab NSC and/or IND.

There have been 17,063 patients enrolled in NCI-sponsored clinical trials under this IND and/or NSC.

In this case, it is felt that a relationship between trastuzumab and the event is possible. The autopsy supports the role of radiation as a causal factor for this event.

|  | <b>Small Bowel Perforation</b> |
|--|--------------------------------|
| <b>Trastuzumab</b>   | Possible                       |
| <b>Radiation</b>   | Probable                       |
| <b>Paclitaxel</b>  | Possible                       |
| <b>Transitional cell carcinoma of the urothelial tract</b> | Possible                       |
| <b>Aspirin</b>   | Possible                       |
| <b>Caduet<sup>®</sup></b>                                  | Possible                       |
| <b>Levothyroxine</b>                                       | Possible                       |
| <b>Toprol<sup>®</sup> XL</b>                               | Possible                       |

Date: 8 October 2009

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

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

cc: Shelley Coleman  
[onc\\_drug.safety@gene.com](mailto:onc_drug.safety@gene.com)  
Genentech, Inc.