



DATE: July 13, 2010

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

SUBJECT: Bevacizumab (rhuMAb VEGF) and CCI-779 (temsirolimus, Torisel™) NCI IND Safety Report, AE#1671222

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 temsirolimus.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460, and temsirolimus under NCI IND 61010:

- 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 INDs 7921, 11460, and/or 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 temsirolimus, there does not appear to be a change in the risk-benefit ratio for bevacizumab and temsirolimus 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 Assessments describe 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 74-year-old female with renal cell carcinoma experienced grade 3 rectal pain and a grade 3 anal fistula while on a phase 2 trial utilizing the investigational agents bevacizumab and temsirolimus in combination with sorafenib.

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. 3: Pain: Rectum Gr. 3: Fistula, GI: Anus |
| AE: 1671222 | | Protocol: E2804 |

The patient is a 74-year-old female with metastatic renal cell carcinoma who experienced rectal pain and an anal fistula while on a phase 2 trial utilizing the investigational agents bevacizumab and temsirolimus in combination with sorafenib. The patient was not enrolled on an arm that contained sorafenib. The patient began her first course of the investigational therapy on September 18, 2009, receiving bevacizumab 10 mg/kg IV over 30-90 min on Days 1 and 15, and temsirolimus 25 mg IV over 30 min on Days 1, 8, 15, and 22, every 28 days. She received her last dose of bevacizumab on December 30, 2009 (Cycle 4, Day 15), and her last dose of temsirolimus on January 13, 2010 (Cycle 5, Day 1).

The patient was diagnosed with metastatic renal cell adenocarcinoma in September 2006, and is status post a right radical nephrectomy in September 2006, and wedge resection of the right lower lung lobe due to metastatic disease in August 2009. She began the investigational therapy on September 18, 2009, and was removed from the protocol on February 9, 2010 (Cycle 6, Day 10).

On February 24, 2010, the patient presented to the emergency room and was admitted with rectal pain and fecal incontinence with bloody diarrhea. The rectal examination performed by the consulting surgeon was significant for a deep anterior midline fissure/fistula with an opening about the size of the anus itself just below the anus, and it was leaking stool. There was bridging tissue between this fistulous opening and the anus itself. It was felt that this was not a rectovaginal fistula, but rather an unusually complicated perineal fistula. At this time, an examination under anesthesia was recommended over surgical intervention, but because of her cardiac history, it was felt that the patient could not safely be placed under anesthesia without further cardiac work-up. The surgeon recommended therapy with nifedipine ointment, Analpram® rectal lotion, and daily sitz bath after bowel movements. On February 25, 2010, the patient reported having less rectal pain, and she was discharged home with follow-up instructions.

At her follow-up visit on March 29, 2010, the patient stated that she had less bleeding and pain. Her anal examination revealed a non-tender anterior anal ulceration, which appeared to be healing. She was advised to continue with the conservative management, and return for a follow-up visit in 4 months.

The patient's past medical/surgical history is significant for accelerated hypertension in 2002, atrial flutter in 2006, appendectomy, cholecystectomy, sinus surgery, hernia repair in 2006, and vein stripping in 2006. Medications taken at the time of the event included EMLA®, MVI®, Probiotic Complex®, citalopram, Lasix®, Bystolic®, Cozaar®, Norvasc®, Marinol®, Reglan®, albuterol, Atrovent®, Arixtra®, prednisone, Procrit®, lactulose, Phenergan®, Xopenex®, and hydrocortisone acetate.

There have been 34 other cases of rectal pain reported to the NCI as serious adverse events through ADEERS under the bevacizumab NSC and/or IND as summarized in the table below. Gastrointestinal fistulas are expected events for bevacizumab. There have been 8 other cases of rectal pain and 3 other cases of gastrointestinal fistula (anal, colonic, and rectal) reported to the NCI as serious adverse events through ADEERS under the temsirolimus NSC and/or IND as summarized in the table below.


| Adverse Event | Grade | Attribution |
|--------------------------------|-------|--|
| Bevacizumab | | |
| Rectal pain (n=34) | 4 | 2 Unrelated, 1 Unlikely, 1 Possible |
| | 3 | 13 Unrelated, 7 Unlikely, 3 Possible, 3 Probable |
| | 2 | 1 Unrelated, 2 Unlikely, 1 Possible |
| Temsirolimus | | |
| Rectal pain (n=8) | 3 | 2 Unrelated, 1 Unlikely, 1 Probable |
| | 2 | 2 Unlikely, 2 Possible |
| Gastrointestinal fistula (n=3) | 3 | 1 Possible, 1 Probable |
| | 2 | 1 Possible |

To date, a total of 27,206 patients have been enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC, and 2,134 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

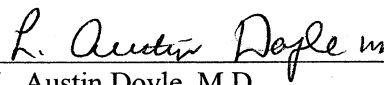
In this case, it is felt that a possible causal relationship exists between the events and both investigational agents.

| | Rectal Pain | Anal Fistula |
|-----------------------------|-------------|--------------|
| Bevacizumab | Possible | Possible |
| Temsirolimus | Possible | Possible |
| Renal cell carcinoma | Possible | Unrelated |

Date: 7/13/10

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

Date: 7/15/10

Signature: 
L. Austin Doyle, M.D.
(IDB Monitor for temsirolimus)

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

cc: Arthur Cannon
Safety Contact: onc_drug.safety@gene.com
Genentech, Inc.

cc: Rafael E. Curiel, Ph.D.
Wyeth GSSE Triage: WASDTRI@wyeth.com
Wyeth Pharmaceuticals, Inc.