

NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: May 11, 2007

To: NCCTG Primary Clinical Research Associates

From: Janis Wobschall
Protocol Development Coordinator

Re: N0572, A Phase I/II Study of Sorafenib and CCI-779 in Patients with Recurrent Glioblastoma

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with CCI-779 for a study where the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) is distributing this agent. You may have also received this communication directly from DCTD.

AE_1926581

Please note that all risks currently cited in the NCCTG consent form cannot be omitted; it is at the discretion of your local IRB as to whether they wish to add risks based on the enclosed information. If a determination has been made by the NCCTG Research Base that a protocol amendment is necessary, you will receive the NCI-approved protocol addendum at a later date; for purposes of cross-reference, this communication will cite the adverse event noted above.

Please submit this adverse event to your Institutional Review Board.

If you have any questions concerning this communication, please contact Janis Wobschall at wobschall.janis@mayo.edu or 507/284-4852.

JW/df
enclosure



DATE: March 23, 2007
FROM: Janet Dancey, M.D., Investigational Drug Branch, CTEP, DCTD, NC
SUBJECT: CCI-779 (Temsirrolimus, Torisel®) IND Safety Report, AE# 1926581
TO: Investigators Using CTEP-supplied Investigational 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 agent CCI-779.

The following must be completed by all investigators using CCI-779 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 IND 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.

CTEP's evaluation of this IND Safety Report in light of previous experience with CCI-779 does not require a change in the clinical protocols for this agent at this time. The risk benefit ratio has not been altered based on CTEP's assessment.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The Adverse Events Assessment that describes the following adverse event(s), previous experience under this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC is attached:

A 69-year-old male with glioblastoma multiforme experienced grade 3 lower extremity muscle weakness and fatal abdominal sepsis while on a phase 1 trial utilizing the investigational agent CCI-779 in combination with temozolomide and radiation therapy.

ADVERSE EVENTS ASSESSMENT

| | |
|---|---|
| IND 61010 NSC 683864 CCI-779 (temsirolimus, Torisel®) | ADVERSE EXPERIENCE REPORT NO. 13 IND Safety Report: Initial Event: Gr. 5: Infection with normal ANC or grade 1 or 2 neutrophils: Abdomen Gr. 3: Muscle weakness: extremity-lower |
| AE: 1926581 | Protocol: N027D |

The patient was a 69-year-old male with glioblastoma multiforme who experienced lower extremity muscle weakness and ultimately died of abdominal sepsis, while on a phase 1 trial utilizing the investigational agent CCI-779 in combination with temozolomide and radiation therapy. He began his first course of treatment on January 24, 2007 and was to receive CCI-779 75 mg IV over 30 minutes weekly, 7-10 days prior to receiving radiation therapy 200 cGy daily × 5, and temozolomide 75 mg/m² PO daily for 6 weeks. He received his first and only dose of CCI-779 on January 24, 2007 (Cycle 1, Day 1). Neither temozolomide nor radiation therapy were administered.

The patient was initially diagnosed with a possible brain tumor in December 2006, after presenting with right leg weakness, numbness, and gait problems. He was status post stereotactic biopsy surgery performed on January 8, 2007, confirming glioblastoma multiforme. During this hospitalization, he was also found to have recurrent atrial fibrillation with rapid ventricular response (status post CABG in June 2005); impaired fasting glucose levels with an elevated HbA1c suggesting long-standing hyperglycemia and felt to be exacerbated by corticosteroid use; and hyperthyroidism, with a low TSH level likely from dexamethasone use.

The patient began the investigational therapy on January 24, 2007. On January 30, 2007 (Cycle 1, Day 7), he was admitted to the hospital for a 5-day history of progressively worsening mental status changes, worsening lower extremity weakness, fatigue, two-day history of abdominal pain and one-day history of dysphagia. Upon physical examination, the patient was found to have a distended abdomen and lesions in the oropharynx, which cultured positive for herpes simplex virus type 1. A head CT scan showed no significant changes in tumor mass and no signs of intracranial hemorrhage. An abdominal X-ray showed a large, gas-containing structure in the left upper quadrant. A CT scan of the abdomen and pelvis on January 31, 2007, showed pre-retroperitoneal air dissecting along the entire retroperitoneum into the left iliac fossa, around the left kidney, and into the lower mediastinum, as well as within the gastrosplenic ligament. Findings were most consistent with a perforated viscus, likely arising from the posterior wall of the stomach. The patient also underwent a lumbar puncture on January 31, 2007; cerebrospinal fluid cytology was negative for malignancy. He was treated with steroids, acyclovir, antimicrobial agents, sedatives, and analgesics. His atrial fibrillation was controlled with Toprol XL® and diltiazem.

On the afternoon of January 31, 2007, the patient was transferred to a larger facility for surgical management, where he underwent an emergency transperitoneal exploration of the retroperitoneum with debridement, drain placement, and open abdominal packing. During surgery, the patient was found to have retroperitoneal abscess with purulent necrosis; although such findings are consistent with a perforated viscus, perforation was found, and the source of the contamination could not be determined. Necrotizing pancreatitis was considered unlikely because of the patient's normal pancreatic enzyme levels. Blood cultures were positive for *Escherichia coli*. After surgery, the patient returned to the ICU where he remained intubated and continued on corticosteroids, acyclovir, antimicrobial agents, sedatives, and analgesics. The patient's condition deteriorated over the next few days. Due to his poor prognosis, the family decided to continue with comfort care only. On February 2, 2007 (Cycle 1, Day 10), the patient was extubated and all IV medications with the exception of analgesics and sedatives were withdrawn. The patient expired on February 5, 2007. No autopsy was performed.

The patient's past medical/surgical history was significant for coronary artery disease status post 3-vessel CABG in June 2005, hyperlipidemia, hypertension, paroxysmal atrial fibrillation with rapid ventricular response, hyperglycemia, osteoarthritis, colon polyps, gout and gastroesophageal reflux disease. Medications taken at the time of the event included Vytorin®, allopurinol, Hyzaar®, Toprol-XL®, dexamethasone, omeprazole, diltiazem HCl SR, aspirin, Tylenol®, fluconazole, Hadad Solution®, and multivitamins.

There have been no other cases of abdominal infection and seven other cases of muscle weakness reported to the NCI as serious adverse events through AdEERS under the CCI-779 IND and NSC, which are summarized in the table below.

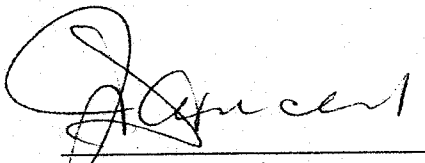
| Adverse Event | Grade | Attribution |
|----------------------------------|-------------|---|
| Abdominal Infection/Sepsis (n=0) | - | - |
| Muscle weakness (n=7) | 4 3 2 | 1 Unlikely 2 Possible, 2 Unlikely, 1 Unrelated 1 Possible |

A total of 839 patients have been enrolled in NCI-sponsored clinical trials under the CCI-779 IND and NSC.

In this case, it is felt that intra-abdominal sepsis, with abscess and purulent necrosis, is the cause of death and also contributed to the patient's muscle weakness. The patient was on dexamethasone and aspirin, which could have contributed to the risk of gastrointestinal perforation and the presentation is most consistent with perforated viscus; however, no perforation was identified. Normal pancreatic enzymes and operative findings do not support the diagnosis of necrotizing pancreatitis as a cause of retroperitoneal abscess with necrosis. A possible contribution of CCI-779 therapy to the events cannot be excluded.

| | Infection with normal ANC or grade 1 or 2 neutrophils: Abdomen | Muscle weakness: lower extremity |
|-------------------------|--|----------------------------------|
| CCI-779 | Possible | Possible |
| Temozolomide | Unrelated | Unrelated |
| Glioblastoma multiforme | Unlikely | Probable |
| Dexamethasone | Probable | Probable |
| Intra-abdominal sepsis | N/A | Possible |

Date: 3/27/07

Signature: 

Janet Dancey, M.D.
(IDB Monitor for CCI-779)

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

cc: Mark S. Gelder, M.D.
Wyeth Pharmaceuticals, Inc.