



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: October 27, 2006

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_1607354

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: October 18, 2006
FROM: Janet Dancey, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: CCI-779 (Temsirrolimus, Torisel®) IND Safety Report, AE# 1607354
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.

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 the total number of patients enrolled in trials under this IND is attached:

An 80-year-old male with non-Hodgkin's lymphoma experienced grade 3 esophagitis, and subsequently presented with hemoptysis and progressive respiratory distress leading to death while on a phase 2 trial utilizing the investigational agent CCI-779.

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Page 1 of 1

* 00003

ADVERSE EVENTS ASSESSMENT

IND 61010 NSC 683864 CCI-779 (temsirolimus, Torisel®)	ADVERSE EXPERIENCE REPORT NO. 12 IND Safety Report: Initial Event: Gr. 5: Death NOS Gr. 3: Esophagitis
AE: 1607354	Protocol: 6199

The patient was an 80-year-old male with non-Hodgkin's lymphoma who experienced esophagitis and expired while on a phase 2 trial utilizing the investigational agent CCI-779. He began his first course of treatment on August 16, 2006, receiving CCI-779 25 mg IV over 30 minutes weekly, every 28 days. He received the last dose of CCI-779 on September 13, 2006 (Cycle 1, Week 4) after a 7-day delay due to hospitalization for esophagitis and dehydration.

The patient was initially diagnosed with large B cell non-Hodgkin's lymphoma in September 2005 following biopsy of a mediastinal mass and was status post radiation therapy (for laryngeal cancer in 2001 and for non-Hodgkin's lymphoma to the mediastinum and a right pericardial mass in early 2006), and multiple agent systemic chemotherapy. He began the investigational therapy on August 16, 2006 and received three doses as scheduled. The patient developed esophagitis and dehydration secondary to poor oral intake and was admitted to the hospital on September 5, 2006 (Cycle 1, Day 21). During physical examination, the patient stated that he had a sore throat and had been unable to eat for 4-5 days; he also stated that he was able to drink only small amounts of fluid. His Day 22 dose of CCI-779 was withheld, and he was treated with IV fluids and Tylenol® with codeine elixir. The patient's condition improved over the next 48 hours, and he was discharged in stable condition on September 7, 2006 with instructions to supplement his diet with a nutritional energy drink daily x 3. The patient received his Cycle 1, Week 4 dose of CCI-779 on September 13, 2006 after a 7-day delay.

On September 17, 2006, the patient presented to the ER with hemoptysis and was admitted to the hospital. Pertinent laboratory values are summarized in the table below. Of note, the patient was taking daily Coumadin®, which was regulated by his cardiologist for a history of heart valve replacement.

	8/16/06 Baseline	9/01/06 Start of Symptoms	9/05/06 First Hospitalization	9/07/06 First Discharge	9/17/06 Second Hospitalization	9/25/06 Most Recent Values
WBC, ×10 ³ /μL (reference range: 3.5-11×10 ³ /μL)	-	3.9	3.8	2.6	4.3	-
HCT, % (reference range: 38.9-50.5%)	-	34.8	33.6	33.8	22.7	32.0
Platelets, ×10 ³ /μL (reference range: 150-450×10 ³ /μL)	100	50	32	64	63	59
PT, seconds (reference range for anticoagulant therapy: 11.5-25 seconds)	-	23.1	32.2	21.4	34.9	14.1
PTT, seconds (reference range for anticoagulant therapy: 36-85 seconds)	-	-	-	56.0	61.9	68.5
INR (reference range for prosthetic valve prophylaxis: 2.5-3.5)	-	2.28	3.1	1.9	3.5	1.1

A chest X-ray performed that day revealed a lobulated mass of the right middle lobe, new interlobal septal thickening in the lung bases (suggestive of mild interstitial edema), and small bilateral effusions. Urine, feces, and blood cultures were negative. CT scan of the chest with contrast performed September 20, 2006 should moderate size right and small to moderate left pleural effusions, multifocal scattered areas of air space disease and interstitial opacities likely representing pulmonary hemorrhage, possibly superimposed pulmonary edema, focal consolidation/fibrosis in the right perihilar area and moderate centrilobular emphysema. On September 22, 2006, a bronchoscopy was performed and revealed edema throughout the right and left tracheobronchial tree with diffuse edema and mild narrowing of the larynx.

CONFIDENTIAL

AE #1607354

Page 1 of 2

• 00001

Bleeding was induced by the procedure in the right tracheobronchial trial but resolve spontaneously during the procedure. A source of the hemoptysis was not found. Additionally, a bronchoalveolar lavage (BAL) was performed in the lingula and sent for routine cytology and bacterial, viral, AFB and fungal analyses. A chest X-ray on September 23, 2006 showed dramatic worsening, with extensive, severe bilateral edema present, some pleural fluid and/or thickening bilaterally, greater on the right. An EKG performed that day demonstrated normal sinus rhythm, low voltage QRS, non-specific T wave abnormality, and long QTc interval of 462 msec. EKG suggested pulmonary disease versus pericardial effusion versus a normal variant. The patient's condition continued to worsen, and he expired on September 26, 2006. Of note, blood and pleural fluid cultures were negative; however, the cytology report indicated that both pleural fluid and left lingula BAL specimens contained "reactive" mesothelial cells. Gram stain of the BAL specimen showed moderate WBCs, predominately mononuclear, many RBCs, many gram positive cocci in pairs, rare gram positive bacilli and few yeast. Cultures from the BAL came back positive for moderate *Candida tropicalis* and few *Candida (Torulopsis) glabrata* and > 100,000 CFU/ml normal respiratory flora after the patient had expired. BAL was negative for *Pneumocystis carinii*, *aspergillus*, parainfluenza types 1, 2, and 3, cytomegalovirus (CMV) and acid fast bacilli (AFB). Blood culture for CMV was also negative. An autopsy was performed the next day. Preliminary autopsy observations of the lungs included a right middle lobe, with a 5 cm firm, ill-defined, subpleural lesion; a firm 2 cm area of consolidation in the left upper lobe; diffuse congestion; and bilateral pleural effusions. Final autopsy results are pending.

The patient's past medical/surgical history is significant for laryngeal cancer (T3N0 squamous cell cancer with papillomatous cancer *in situ*) diagnosed in January 2001 status post radiation therapy, colon cancer diagnosed in 2003 status post surgical resection, left hand squamous cell carcinoma (in 2004 and 2005), diabetes mellitus type 2 diagnosed in 1980, hypertension, hyperthyroidism, gastric ulceration, gastroesophageal reflux disease (GERD), small hiatal hernia, left lens implant, and aortic valve replacement (requiring anticoagulation prophylaxis). Medications taken at the time of the event included Coumadin®, Synthroid®, glyburide, atenolol, and Norvasc®.

There have been two other cases of esophagitis and 9 other cases of death NOS reported to the NCI as a serious adverse events through AdEERS under the CCI-779 NSC, which are summarized in the table below.

Adverse Event	Grade	Attribution
Esophagitis (n=2)	3	1 Possible, 1 Unlikely
Death NOS (n=9)	5	2 Unlikely, 7 Unrelated

There have been a total of 703 patients enrolled in NCI-sponsored clinical trials under the CCI-779 NSC.

In this case, it is felt that a possible relationship exists between the events and CCI-779 therapy.

	Esophagitis	Death NOS
CCI-779	Possible	Possible
Non-Hodgkin's lymphoma	Unlikely	Possible
GERD	Possible	Unrelated
Pulmonary Hemorrhage	Unrelated	Possible

Date:

Oct 18/06

Signature:

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

CONFIDENTIAL
Page 2 of 2

AE #1607354

* 00002