



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: February 15, 2008
To: NCCTG Primary Clinical Research Associates
From: Janis Wobschall
Re: N027D, "A Phase I Study of CCI-779 and Temozolomide in Combination with Radiation Therapy in Glioblastoma Multiforme"

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 rapamycin analog 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_1259970

Please note that all risks currently cited in the NCCTG consent form can not 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: January 29, 2008

FROM: Janet Dancey, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: CCI-779 (Temsirolimus, Torisel®) IND Safety Report, AE# 1259970

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 74-year-old male with mantle cell lymphoma with a history of coronary artery disease and atrial flutter expired after cardiac arrest while on a phase 1 trial utilizing the investigational agent CCI-779 in combination with rituximab.

ADVERSE EVENTS ASSESSMENT

IND 61010 NSC 683864 CCI-779 (temsirolimus, Torisel®)	ADVERSE EXPERIENCE REPORT NO. 15 IND Safety Report: Initial Event: Gr. 5: Ventricular Arrhythmia: Ventricular fibrillation
AE: 1259970	Protocol: N038H

The patient was a 74-year-old male with mantle cell lymphoma, with history of coronary artery disease, and atrial flutter, who expired while on a phase 2 trial utilizing the investigational agent CCI-779 in combination with rituximab. He began his first course of treatment on November 26, 2007, and was to receive CCI-779 25 mg IV over 30 minutes on days 1, 8, 15, and 22 every 28 days (one cycle), and rituximab 375 mg/m² IV on days 1, 8, 15, and 22 of cycles 1, 3, 5, 7, 9, and 11 only. He received his last doses of CCI-779 and rituximab on December 3, 2007 (Cycle 1, Day 8).

The patient was initially diagnosed with mantle cell non Hodgkin's lymphoma in May 2006 and was status post multiple agent chemotherapy regimens. He began investigational therapy on November 26, 2007. On that date, he was noted to have ECOG performance status of 1 and new onset of 1+ edema of his right arm and left leg without evidence of erythema or tenderness and scrotal edema. These were likely due to lymphomatous adenopathy. There were no cardiopulmonary signs or symptoms noted.

On December 10, 2007 (Cycle 1, Day 15), the patient was found unresponsive at home. According to the patient's wife, after getting up that morning he was feeling tired and while sitting on the bed, fell back onto the bed and became unresponsive. She reported that for the previous 2 to 3 days he also had pain and diarrhea, however, he did not complain of chest pain or shortness of breath, and had no recent fevers or chills. Upon the paramedics arrival, the patient was in ventricular fibrillation and was defibrillated. He received epinephrine, atropine, and amiodarone and he developed a pulse but no spontaneous respirations. He arrived at the hospital intubated, unresponsive to verbal and painful stimuli and with decorticate posturing. His heart rate was in the 70's with a wide complex rhythm noted and right bundle branch pattern on the monitor. He had brisk radial pulses, no spontaneous respiration, his blood pressure was 84/69 mmHg, and his pupils were equal and reactive to light. His O₂ saturation was 98% by pulse oximetry with bagging. He was given a 1 liter normal saline intravenous fluid bolus. A nasogastric tube was placed. A chest X-ray showed hyperinflation, chronic interstitial changes, no gross pneumothorax, and verified proper placement of endotracheal tube. He was placed on a ventilator for respiratory support and an amiodarone infusion was initiated. His EKG showed atrial fibrillation with rapid ventricular response, at a rate of 148 bpm and he received an additional bolus of amiodarone. His white cell count was 10.6×10³ cells/μL (reference range: 4.0-11.0×10³ cells/μL), hemoglobin was 11.6 g/dL (reference range: 14.0-17.5 g/dL), hematocrit was 33.3% (reference range: 41-51%), and platelets were 73×10³ cells/μL (reference range: 150-450×10³ cells/μL). Other pertinent laboratory values were: glucose 152 mg/dL (reference range: 70-110 mg/dL), BUN 14 mg/dL (reference range: 9-23 mg/dL), creatinine 1.5 mg/dL (reference range: 0.5-1.5 mg/dL), sodium 134 mmol/L (reference range: 136-146 mmol/L), potassium 4.3 mmol/L (reference range: 3.5-5.1 mmol/L), chloride 104 mmol/L (reference range: 95-114 mmol/L), bicarbonate 14.7 mmol/L (reference range: 22.0-30.0 mmol/L), magnesium 2.3 mg/dL (reference range: 1.6-2.6 mg/dL), calcium 8.3 mg/dL (reference range: 8.2-10.2 mg/dL), CK 57 U/L (reference range: 22-269 U/L), CK-MG 1.8 ng/mL (reference range: 0.6-6.3 ng/mL), CK-MB index 3.3 (reference range: 0.11-2.50), and troponin I was 0.06 ng/mL (reference range: 0-0.02 ng/mL). A CT scan of the brain showed no acute intracranial abnormalities. He was transferred to the intensive care unit with a poor prognosis. The patient arrested a second time, and was found to be in ventricular fibrillation. He was converted to wide complex tachycardia, either ventricular tachycardia or supraventricular tachycardia with aberrant conduction and with palpable carotid and femoral arterial pulses; however, the family, in accordance with the patient's wishes, decided not to proceed with further cardiac resuscitation, and the patient expired. No autopsy was performed.

The patient's past medical/surgical history was significant for coronary artery disease status post coronary artery bypass grafts and cardiac catheterizations, atrial flutter, chronic obstructive pulmonary disease, gastroesophageal reflux disease, hypercholesterolemia, and restless leg syndrome. Medications taken at the time of the event included albuterol, allopurinol, Imodium[®], Motrin[®], Digitek[®], Lipitor[®], Requip[®], Protonix[®], Atarax[®], and Advair[®].

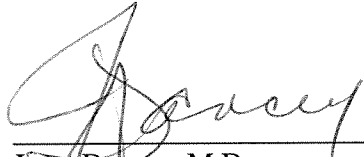
This patient with history of coronary artery disease and atrial flutter, experienced two cardiac arrests with documented ventricular fibrillation, ventricular tachycardia, and atrial fibrillation prior to his demise. There have been no other cases of ventricular fibrillation reported to the NCI as serious adverse events through AdEERS under the CCI-779 IND and NSC.

A total of 1086 patients have been enrolled in NCI-sponsored clinical trials under the CCI-779 IND and NSC.

Although it is likely that the cardiac arrhythmias are due to pre-existing coronary artery and cardiac conduction abnormalities, in this case, it is felt that a possible contribution of CCI-779 therapy to the patient's death cannot be excluded.

	Ventricular fibrillation
CCI-779	Possible
Rituximab	Possible
Mantle cell lymphoma	Possible
Albuterol	Unlikely
Digitek[®]	Unlikely
Lipitor[®]	Unlikely
Requip[®]	Unlikely
Advair[®]	Unlikely
Allopurinol	Unlikely
Coronary artery disease	Possible

Date: 1/29/08

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.