

NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: September 22, 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_1620411

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 507/284-4852.

JW/dd
enclosure



DATE: July 6, 2006

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

SUBJECT: CCI-779 (Rapamycin Analog, Temozolomide) and Bryostatins-1 IND Safety Report,
AE# 1620411

TO: Investigators Using CCI-779, IND 61010 and Bryostatins-1, IND 42780

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 (IND 61010) and Bryostatins-1 (IND 42780).

The following must be completed by all investigators using CCI-779 under NCI IND 61010 and Bryostatins-1 under NCI IND 42780:

- 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.

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 and Bryostatins-1 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 events, previous experience under this IND, and the total number of patients enrolled in trials under this IND is attached:

A 63-year-old male with renal cell carcinoma with metastasis to the lungs and liver experienced a grade 4 pulmonary embolism and left ventricular systolic dysfunction while on a phase 1 trial using the investigational agent CCI-779 in combination with Bryostatins-1.

ADVERSE EVENTS ASSESSMENT

IND 61010 and 42780 NSC 683864 and 339555 CCI-779 (rapamycin analog) and Bryostatatin-1 AE: 1620411	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: Initial Event: Gr: 4 Thrombosis Gr: 4 Left ventricular systolic dysfunction Protocol: 5785
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The patient is a 63-year-old male with stage IV renal cell carcinoma with metastasis to the lungs and liver who experienced a pulmonary embolism and left ventricular systolic dysfunction while on a phase 1 trial using the investigational agent CCI-779 in combination with Bryostatatin-1. He began his first course of therapy on January 19, 2006, receiving CCI-779 15 mg IV over 30 minutes and Bryostatatin-1 20 mcg/m² IV over 1 hour weekly for three weeks each cycle (Cycle = 4 weeks). He received the last doses of CCI-779 and Bryostatatin-1 on April 27, 2006 (Cycle 4, Day 15).

The patient was initially diagnosed with renal cell carcinoma in December 2003 and is status post chemoembolization and systemic therapy with interferon and gemcitabine. He began the investigational therapy on January 19, 2006. The patient presented to the clinic on May 11, 2006 (Cycle 4, Day 29), with a one week history of increasing shortness of breath, dyspnea on exertion, orthopnea, a non-productive cough, bilateral lower extremity edema, and loss of appetite. He was noted to be hypoxic with an oxygen saturation of 83% on room air and was hospitalized for further evaluation and treatment. Upon admission, he was noted to be in no acute distress with a blood pressure of 164/98 mmHg and an oxygen saturation of 96% on 5L of oxygen. Physical examination revealed increased jugular venous distention, inspiratory crackles at the lung bases with dullness to percussion, and 2+ pitting edema of bilateral lower extremities. An EKG demonstrated sinus rhythm with 80 bpm, minor criteria for left ventricular hypertrophy, and non-specific ST-T wave changes in the inferior leads (findings not different from the baseline evaluation on January 16, 2006). A CT scan of the chest revealed a non-obstructing thrombus in the right descending pulmonary artery, moderate sized bilateral pleural effusions, ground glass opacities throughout the right lung, and pulmonary nodules consistent with metastatic disease. A lower extremity venous Doppler study detected a deep venous thrombosis in the right leg, and an echocardiogram showed mild hypertrophy with moderate to severe global hypokinesis of the left ventricle with an ejection fraction of 30-35%. Troponin I level was elevated at 0.06 ng/ml (reference range < 0.06 ng/ml) and B type natriuretic peptide was 2041 pg/ml (values > 100 pg/ml are considered positive). The patient was treated with an ACE inhibitor, a beta blocker, and anticoagulation therapy. His symptoms improved and a repeat chest x-ray on May 14, 2006, revealed mild improvement in the pulmonary vascular congestion. The patient was discharged on May 16, 2006, with home oxygen administration. He was discontinued from protocol participation.

The patient's past medical history is significant for coronary artery disease with a myocardial infarction, a coronary artery bypass graft (2003), type II diabetes mellitus, chronic constipation, hypertension, obesity, and herpes zoster. Medications taken at the time of the event included Ativan®, Compazine®, Tylenol®, Senokot®, metoprolol, glyburide, gemfibrozil, and multivitamin supplements.

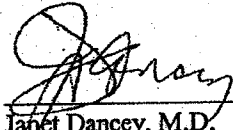
There have been 20 other incidences of thrombosis and 6 other incidences of left ventricular systolic dysfunction reported to the NCI as serious adverse events under IND 42780. There have been 26 other incidences of thrombosis and 4 other incidences of left ventricular systolic dysfunction reported to the NCI as serious adverse events under IND 61010. The attributions are summarized in the following table:

Agent	Adverse Event	Grade	Attribution
Bryostatin-1 (IND 42780)	Thrombosis (n=20)	5	2 Unlikely
		4	3 Unlikely
		3	11 Unlikely, 4 Unrelated
	Left ventricular systolic dysfunction (n=6)	5	1 Unlikely, 3 Unrelated
3		1 Unlikely, 1 Unrelated	
CCI-779 (IND 61010)	Thrombosis (n=26)	5	1 Unlikely
		4	12 Unlikely, 2 Unrelated
		3	7 Unlikely, 4 Unrelated
	Left ventricular systolic dysfunction (n=4)	3	2 Unlikely, 1 Unrelated
		2	1 Unlikely

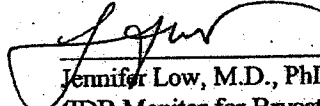
In this case, it is felt that a possible relationship between the left ventricular systolic dysfunction and CCI-779 in combination with Bryostatin-1 cannot be excluded. There have been 1292 patients enrolled in NCI-sponsored clinical trials under IND 42780 and 649 patients enrolled in NCI-sponsored clinical trials under IND 61010.

	Thrombosis	Left ventricular systolic dysfunction
Bryostatin-1	Unlikely	Possible
CCI-779	Unlikely	Possible
Renal cell carcinoma	Possible	Unlikely
History of CAD	Unlikely	Probable

Date: 7/10/06

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

Date: 7/7/06

Signature: 
Jennifer Low, M.D., PhD
(IDB Monitor for Bryostatin)

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

cc: Laurence Moore, M.D., Ph.D.
Wyeth Pharmaceuticals, Inc.