



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: February 29, 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_1717970_F1

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: February 19, 2008

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

SUBJECT: CCI-779 (Temsirrolimus, Torisel®) IND Safety Report, AE# 1717970 – ***Follow-up #1***

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 51-year-old male with chronic myelogenous leukemia experienced pericardial effusion ,left ventricular diastolic dysfunction, and pleural effusion ***and subsequently expired of disease progression*** while on a phase 1 trial utilizing the investigational agent CCI-779 in combination with imatinib mesylate.

The attached Adverse Events Assessment has been amended to reflect additional information. Changes to the attached report are indicated by bold and italics (new information) and/or strikethrough (deleted information).

ADVERSE EVENTS ASSESSMENT

IND 61010 NSC 683864 CCI-779 (temsirrolimus, Torisel®)	ADVERSE EXPERIENCE REPORT NO. #15 IND Safety Report: <i>Follow-up #1</i> Event: Gr. 4: Pericardial effusion Gr. 3: Left ventricular diastolic dysfunction Gr. 3: Pleural effusion Gr 5: Death: Disease progression
AE: 1717970	Protocol: 6619

This report has been amended to reflect new information. Changes to the original summary are indicated by bold and italics (new information) and/or strikethrough (deleted information). If this assessment is changed further, we will notify your office. Please note that this modified report will be distributed to investigators.

The patient was a 51-year-old male with Philadelphia chromosome positive chronic myelogenous leukemia (CML) in blast transformation (BT), who experienced pericardial effusion, left ventricular diastolic dysfunction, and pleural effusion while on a phase 1 trial utilizing the investigational agent CCI-779 in combination with imatinib mesylate. He began his first course of treatment on October 23, 2007, and was to receive CCI-779 25 mg IV over 30 minutes weekly, and imatinib mesylate 400 mg PO daily, every 28 days. He received the last dose of CCI-779 on November 6, 2007 (Cycle 1, Day 15), and the last dose of imatinib mesylate on November 11, 2007 (Cycle 1, Day 20).

The patient was initially diagnosed with a Philadelphia chromosome-positive CML in accelerated phase in April 2006, treated with imatinib mesylate 400 mg PO daily. He was diagnosed with CML-BT in September 2007 and treated with imatinib mesylate 600 mg PO daily without response. Prior to enrolling on study, he was known to require platelet and blood transfusions. He began the investigational therapy with CCI-779 and imatinib mesylate on October 23, 2007.

On October 25, 2007, the patient presented to the hospital complaining of fever, chills, nausea, mucositis, sore throat, fatigue, and blood-stained nasal drip after sneezing. On physical examinations, temperature was 39°C, blood pressure was 109/60 mmHg, and pulse was 116 bpm. An ulcer over the tongue was noted. Laboratory values were remarkable for hemoglobin of 9.1 g/dL (reference range 13.2-16.7 g/dL), platelet count of 6×10^3 cells/ μ L (reference range: $140-380 \times 10^3$ cells/ μ L), and white blood cell count of 22.8×10^3 cells/ μ L (reference range: $4.0-10.8 \times 10^3$ cells/ μ L), with 38% blasts and 1% neutrophils. Anemia and thrombocytopenia are known adverse events of imatinib, CCI-779, and CML-BT. He was diagnosed with neutropenic fever, possibly related to infection or CML-BT. Blood cultures were negative and no source of infection was identified. He was treated with antibiotics, antifungals, acyclovir, blood product support, and continued on imatinib mesylate. On October 29, 2007, he was afebrile, his chest was clear, his blood pressure was 115/70 mmHg and his pulse was 92 bpm. He received week 2 of CCI-779 treatment on October 30, 2007, and became febrile two hours after the infusion. The following day his vital signs were stable, and his oxygen saturation was 98% on room air; however, the fever persisted (temperature of 36.9°C to maximum of 39°C over the preceding 2 days). He received 6 units of platelets and was continued on antibiotics. He received week 3 of CCI-779 treatment on November 6, 2007. He had a low grade fever prior to receiving treatment which persisted afterwards and he was changed from oral to intravenous acyclovir and started on additional intravenous antibiotics, meropenem and amikacin. His blood pressure and pulse were stable. His oxygen saturation on November 8, 2007 was 89% on room air and he was started on 2L of oxygen by mask. A chest X-ray done on November 8, 2007 revealed left pleural effusion and slight cardiomegaly. He continued to receive platelet transfusions and packed red blood cells as needed.

On November 11, 2007, the patient had persistent fever, increased cough, dyspnea at rest, facial edema without limb edema, pleuritic chest pain, and weight gain of 67 to 68.4 kg over a 1-week period. Physical examination showed puffy face without ankle or limb edema, no elevation of jugular-venous pulse,

normal heart sounds, crepitus over both lung bases. He was placed on oxygen and diuresed with furosemide. Electrocardiogram showed ST elevation over II, V2-V5 (1mm in V4 and V5), with normal cardiac enzymes. WBC was 4.7×10^3 cells/ μ L, 4% neutrophils and 46% blasts. An echocardiogram performed on November 12, 2007, was significant for a small rim of pericardial effusion with maximum thickness of <0.5 cm and a normal left ventricular (LV) ejection fraction of 60% without wall motion abnormalities. His condition worsened with increased dyspnea and rising white blood cell and blast counts. CT thorax on November 13 2007 showed moderate, bilateral effusions with atelectasis of the lung bases, 1.8 cm thick pericardial effusion and borderline heart size. Patchy opacities were noted in both lungs. On November 16, 2007, the patient was tachypneic at rest, blood pressure was 110/70 mmHg, pulse was 120 bpm, JVP was not elevated, breath sounds were diminished at both lung bases and edema was noted at the patient's back. Oxygen saturation was 94% on 3 L of oxygen,. Echocardiogram showed pericardial effusion of maximum thickness 1.1 cm, LV ejection fraction of 60% with no evidence of cardiac tamponade. WBC had risen from nadir of 4.2 to 76×10^3 cells/ μ L with 65% blasts. On November 16, 2007, the patient was removed from the protocol and was started on ARA-C[®], asparaginase, hydroxyurea. On November 19, 2007, a CT pulmonary angiogram showed large pericardial effusion 2.3 cm thick, moderate bilateral pleural effusions with compressive collapse of the lower lobes and lingular segment and multiple bilateral pulmonary nodules (largest diameter 2.6 cm), consistent with leukemic involvement but did not show pulmonary embolus. His echocardiogram showed increased pericardial effusion and right ventricular diastolic collapse consistent with pericardial tamponade. He underwent pericardiocentesis with 400 mL of straw-colored, slightly blood tinged pericardial fluid removed. Fluid analyses for malignant cells or infection were unremarkable. After the procedure his blood pressure was 128/85 mmHg, his oxygen saturation was 98% on 100% oxygen, and his echocardiogram was significant for no reaccumulation of pericardial fluid, good left ventricular function, and normal right ventricular filling. Laboratory tests of liver enzymes, creatinine were not indicative of significant hepatic or renal dysfunction. On November 21, 2007, he underwent pleurocentesis with insertion of bilateral pig-tail drains. No malignant cells, acid alcohol fast bacilli, or organisms were found on pleural fluid cytology. On November 22, 2007, his chest X-ray showed small pleural effusions and the patient reported feeling improved, less short of breath, and tired. He continued to receive antibiotics, blood products and oxygen as needed.

On December 7, 2007 his left pleural pigtail drain was removed. His right pleural pigtail drain remained in place with continued output. He continued to have a productive cough with yellow sputum. He remained febrile with temperatures up to 39.9° C. Blood cultures were positive for gram-positive *cocci*. His liver function tests were progressively worsening. He was started on vancomycin and ciprofloxacin. On December 11, 2007, the right pleural pigtail drain was removed. A CT scan on December 15, 2007 showed splenomegaly with multiple hypodense lesions, probably due to leukemic/lymphomatous infiltration that had increased in number and size, patchy consolidations in both lungs and two more hypodense areas in the right base abutting the right heart border (consistent with necrotic lesions, early abscess or loculated effusion). The patient's condition continued to deteriorate and on December 20, 2007, CT chest showed progressive pulmonary lesions, however effusions were not worse. He was changed to comfort care. He expired the following day of presumed complication of leukemia.

The patient's past medical/surgical history is significant for hepatomegaly and inguinal hernia. Medications taken at the time of the event included multiple antibiotics, antifungal and antiviral drugs, Senokot[®], lactulose, Dologesic[®], furosemide, aplopurinol, Maxolon[®], CaltrateV, Slow-K[®], phensedyl, and chlorhexidine mouth wash.

There have been two other cases of pericardial effusion, one other case of left ventricular diastolic dysfunction, and six other cases of pleural effusion 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
Pericardial effusion (n=2)	3	2 Unrelated
Left ventricular diastolic dysfunction (n=1)	3	1 Unlikely
Pleural effusion (n=6)	3 2	4 Unlikely 2 Unlikely

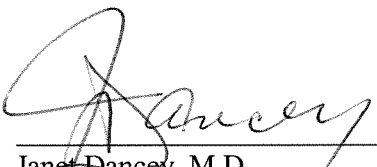
A total of 1070 patients have been enrolled in NCI-sponsored clinical trials under the CCI-779 IND and NSC.

Pericardial and pleural effusions are considered to be rare adverse events associated with imatinib or acute leukemia but are not known adverse events associated with CCI-779. The patient's prior tolerance of imatinib without the complication, suggests additional and/or alternated causative factors. Both underlying CML and CCI-779 may have contributed to the occurrences of the effusions. LV diastolic dysfunction was due to the accumulation of pericardial fluid causing tamponade although contribution of CCI-779 cannot be excluded.

	Pericardial effusion	Left ventricular diastolic dysfunction	Pleural effusion	Death: Disease progression
CCI-779	Possible	Possible	Possible	<i>Unrelated</i>
Imatinib mesylate	Probable	Possible	Probable	<i>Unrelated</i>
Chronic myelogenous leukemia	Unlikely	Unlikely	Possible	<i>Definite</i>
Pericardial effusion with tamponade	N/A	Definite	Unrelated	<i>N/A</i>

Date: 2/19/2008

Signature:


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

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

cc: Rafael Curiel, PhD
 Elizabeth Watts
 Wyeth Pharmaceuticals, Inc.