

# NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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**Date:** May 11, 2007  
**To:** NCCTG Primary Clinical Research Associates  
**From:** Janis Wobschall  
Protocol Development Coordinator  
**Re:** N0272, Phase II Trial of STI-571 in Treatment of Recurrent Oligodendroglioma and Mixed Oligoastrocytoma

The purpose of this memorandum is to provide investigators with a recent report of an adverse event that has occurred in association with STI-571 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\_1198038**

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](mailto:wobschall.janis@mayo.edu) or 507/284-4852

JW/dkf  
enclosure



DATE: April 2, 2007 *ajm*  
FROM: Anthony J. Murgo, M.D., Investigational Drug Branch, CTEP, DCTD, NCI  
SUBJECT: STI571 (Imatinib Mesylate, Gleevec®) NCI IND Safety Report, AB# 1198038  
TO: Investigators Using CTEP-supplied Investigational STI571 (NSC 716051)

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 STI571.

The following must be completed by all investigators using STI571 under NCI IND 61135:

- 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 61135, 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 STI571 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 the CTEP 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, 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 23-year-old female with Philadelphia chromosome positive acute lymphoblastic leukemia experienced grade 4 left ventricular dysfunction and died from a presumed ventricular arrhythmia while on a phase 2 trial utilizing the investigational agent STI571 in combination with chemotherapy.

**ADVERSE EVENTS ASSESSMENT**

IND 61135	ADVERSE EXPERIENCE REPORT NO. 43
NSC 716051	IND Safety Report: Initial
STI571 (imatinib mesylate, Gleevec™)	Event: Gr. 5: Ventricular arrhythmia NOS
	Gr. 4: Cardiac left ventricular function
AE: 1198038	Protocol: CALGB-10001

The patient was a 23-year-old female with Philadelphia chromosome positive acute lymphoblastic leukemia (ALL) who experienced left ventricular dysfunction and died from a presumed ventricular arrhythmia while on a phase 2 trial utilizing the investigational agent STI571 in combination with chemotherapy. The patient began Course I of therapy as part of another CALGB protocol on October 11, 2006, which consisted of a first induction therapy with daunorubicin, vincristine, prednisone and 1 week of STI571 (seven daily doses), as well as a second induction therapy of high dose Ara-C, mitoxantrone, and STI571 (30 daily doses). During Course I (induction therapy), she received a total dose of 294 mg of daunorubicin, 130 mg of mitoxantrone, and 14,800 mg of STI571. The patient began STI571 therapy on protocol CALGB-10001 on December 19, 2006 (Course II, Day 1), receiving STI571 400 mg PO twice daily for 28 days. She received her last dose of STI571 on January 9, 2007 (Course II, Day 22), receiving a total of 17600 mg during Course II.

The patient was initially diagnosed with ALL in October 2006 and was status post double induction therapy, including daunorubicin, mitoxantrone, Ara-C, and STI571. Although she was responding to treatment as evidenced by bone marrow biopsy, which showed a complete and cytogenetic remission, she was removed from the study when she was found to have the Philadelphia chromosome. Consequently, the patient began therapy on CALGB-10001 with STI571 on December 19, 2006. On January 4, 2007 (Day 17), the patient reported nausea and vomiting, which required IV hydration administered at the treatment facility on January 4 to 6, 2007. On January 8, 2007 (Day 21), she also developed persistent chills, sore throat, shortness of breath and cough, which was severe at times. A chest X-ray that day showed bilateral pleural effusions with atelectasis but no consolidation. She was started on moxifloxacin for presumed pneumonia.

On January 9, 2007 (Day 22), the patient was reevaluated. She reported persistent nausea and vomiting, as well as abdominal pain. Because of the grade 3 nausea and vomiting, STI571 was discontinued. Due to a history of intussusception, a CT scan of the chest, abdomen, and pelvis was scheduled. The patient was admitted to the hospital later that day, where a physical examination revealed a temperature of 36.7°C, blood pressure of 98/57 mmHg, heart rate of 112 bpm, and respiratory rate of 16 breaths per minute. In general, the patient was in no acute distress, with decreased breath sounds at the lung bases and soft, mild epigastric and right lower quadrant tenderness noted. A bone marrow biopsy performed on January 10, 2007 showed that the patient continued to be in complete remission. A CT scan of the chest, abdomen, and pelvis that day revealed no bowel obstruction, no pulmonary embolism, a thickening of the right colon, an increase in pleural effusions, no change in the hepatic lobe lesion, and cardiomegaly. An emergent echocardiogram indicated severe biventricular failure. Her left ventricular ejection fraction (LVEF) was 20%, and her heart rate was 119 bpm. Her previous echocardiograms from October 11, 2006, and October 30, 2006, reported LVEF's of 60% and 50%, respectively, with normal biventricular function. She also underwent a thoracentesis on January 10, 2007, with the removal of 650 cc of fluid, which resulted in some improvement of her pulmonary function.

On January 11, 2007 (Day 24), the patient was removed from the protocol. That morning, she was initially breathing comfortably on room air; however, she then developed increased shortness of breath requiring a non-rebreather mask with 100% oxygen and also developed hypotension with systolic blood pressures in the 80s. She had received one dose of Coreg® prior to this episode, which was subsequently discontinued. She was treated with diuretics, but her condition did not improve, and she was transferred to the cardiac care unit on January 12, 2007 for closer cardiac management. Upon admission to the cardiac service, the patient's physical examination revealed a temperature of 37.7° C, pulse between 110 and 130 bpm, blood pressure 73 to 103 mmHg systolic and 50 to 70 mmHg diastolic, S1 and S2 murmurs

with audible tachycardia and 8 cm of jugular distension. Her lungs were clear to auscultation bilaterally, and she had 1+ distal pulses in her extremities, which were not edematous. The patient was started on IV milrinone lactate, but remained hypotensive and tachycardic. Of note, the patient had a several month history of tachycardia with heart rates between 110 and 120 bpm reported. The milrinone was discontinued on January 16, 2007, due to patient's refusal to have the necessary laboratory testing and weight measurements required for safe administration. Treatment was complicated by the patient's noncompliance and inconsistent behavior. On January 16, 2007, while talking to a healthcare provider, she fell to the floor and exhibited twitching activity, which was presumed to be a seizure. Neurology was consulted, and after further discussion with the patient, an EEG and a head CT scan were performed. It was determined that the patient had a psychogenic event and not a neurological event. No evidence of epileptiform activity or CNS abnormality was found. Meetings were held with the patient and her family, and the patient consented to treatment with digoxin and spironolactone, both of which could be given orally and required laboratory testing only once daily. She responded to treatment, and her systolic blood pressure returned to baseline measurements between 86 and 92 mmHg. The nursing staff continued to have concern and frustration due to compliance issues with the patient. A psychiatric consult suggested a tentative diagnosis of adjustment disorder with depressed mood, but determined that the patient did have the capacity to make decisions in regard to her care. On January 19, 2007, a physical examination and laboratory testing were unchanged except for a rise in her anion gap. The patient was alert and oriented and denied discomfort, but did complain of fatigue that she related to lack of sleep on the previous night. She refused arterial blood gas testing. Later in the day, she again refused arterial blood gas testing, but consented to venous electrolyte testing. Later that evening, the patient had removed her telemetry monitors. At approximately 9:50 pm (21:50), she was found unresponsive. Resuscitation efforts were unsuccessful, and the patient expired from a presumed cardiac arrhythmia. Per the family's wishes, an autopsy was not performed.

Pertinent laboratory values are as follows:

	12/19/06 Course II, Day 1 (post induction)	1/09/07 Course II, Day 22, Hospital admission	1/11/07 Course 2, Day 24	1/19/07 (19:20)
WBC (reference ranges: 4.8-10.8×10 <sup>3</sup> /μL)	4.7	5.0	3.7	5.3
Hgb (reference range: 14.0-17.5 g/dL)	10.7	9.4	9.1	10.2
Platelets (reference range: 150-400×10 <sup>3</sup> /μL)	272	80	79	92
Carboxyhemoglobin (reference range: 0.0-1.4%)	-	-	0.6	0.4
Methemoglobin (reference range: 0.0-1.4%)	-	-	0.0	0.8
Sodium (reference range: 132-146 mmol/L)	142	145	142	136
Potassium (reference range: 3.5-5.5 mmol/L)	4.0	3.4	3.6	5.4
Magnesium (reference range: 1.3-2.1 mEq/L)	-	1.5	1.4	1.7 (07:05)
Calcium (reference range: 8.6-10.2 mg/dL)	9.0	7.8	7.7	9.0
Albumin (reference range: 3.2-4.8 g/dL)	4.2	3.2	3.1	-
Anion Gap (reference range: 7-16)	9	9	6	26
PCO2 (reference range: 35-45 mmHg)	-	-	36	-
PO2 (reference range: 80-100 mmHg)	-	-	86	-
PT (reference range: 11.0-12.5 sec)	-	-	18.7	-
INR (reference range: 0.75-1.19)	-	-	1.5	-

The patient's past medical/surgical history is significant for vacuum assisted vaginal delivery in January 2006 and intussusception during induction therapy. Medications taken at the time of the event included Prilosec®, Ativan®, Kytril®, oxycodone and moxifloxacin, which she started on January 8, 2007.

There have been four other incidences of ventricular arrhythmia and no other incidences of left ventricular function reported to the NCI as serious adverse events through AdEERS under the STI571 IND and NSC, which are summarized in the table below.

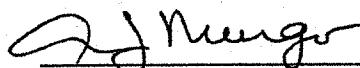
Event	Grade	Attribution
Ventricular arrhythmia (n = 4)	4 3	1 Possible, 1 Possible, 2 Unlikely

A total of 3,301 patients have been enrolled in NCI-sponsored clinical trials under the STI571 NSC.

In this case, it is felt that a possible relationship between the events and STI571 therapy cannot be excluded.

	Ventricular arrhythmia NOS	Cardiac left ventricular function
STI571	Possible	Possible
ALL	Unrelated	Unrelated
Daunorubicin	Possible	Probable
Mitoxantone	Possible	Probable
Cardiomyopathy	Probable	N/A

Date: 4-3-07

Signature:   
 Anthony J. Murgo, M.D.  
 (IDB Monitor for STI571)

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

cc: Clinical Safety & Epidemiology  
 Faith Williams  
 Novartis Pharmaceuticals Corporation