

NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

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_1983514

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/dkf
enclosure



DATE: April 24, 2007
FROM: Anthony J. Murgo, M.D., M.S., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: STI571 (Imatinib Mesylate, Gleevec®) NCI IND Safety Report, AE# 1983514
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.

Based on CTEP's assessment of the current information in light of previous experience with AZD2171, there does not appear to be a change in the risk-benefit ratio for AZD2171 studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The attached Adverse Events Assessment describes the adverse event(s) (synopsis provided below), relevant previous experience under this IND and/or NSC, and the total number of patients enrolled in trials under this IND and/or NSC.

A 61-year-old female with gastrointestinal stromal tumor (GIST) developed grade 4 liver failure within 30 days of completing a phase 3 trial utilizing the investigational agent STI571 or placebo. The patient was unblinded after her death secondary to *Klebsiella pneumoniae* bacteremia and was found to be on the STI571 arm.

ADVERSE EVENTS ASSESSMENT

IND 61135 NSC 716051 STI571 (imatinib mesylate, Gleevec™)	ADVERSE EXPERIENCE REPORT NO. 44 IND Safety Report: Initial Event: Gr. 4: Liver dysfunction failure
AE: 1983514	Protocol: ACOSOG-Z9001

The patient was a 61-year-old female with gastrointestinal stromal tumor (GIST) who developed liver failure within 30 days of completing a phase 3 trial utilizing the investigational agent STI571 or placebo. She began her first course of treatment on February 10, 2006, receiving STI571 or placebo 400 mg PO daily, on Days 1-28, every 28 days for 1 year. She received her last dose of STI571 or placebo on February 13, 2007, approximately 1 year after starting the investigational therapy.

The patient was initially diagnosed with GIST in November 2005 and is status post exploratory laparotomy, cholecystectomy, right colectomy, and Whipple procedure surgery in November 2005. She began the investigational therapy on February 10, 2006, and completed treatment with STI571 or placebo on February 13, 2007. On March 2, 2007, the patient was admitted to the hospital for a 3-week history of increasing weakness and confusion. Her husband reported that approximately 1 week prior to admission the patient had a fever that resolved on its own, jaundice, leg itchiness, and a 10-pound weight gain primarily in her abdomen. He reported that today her weakness was more severe, and she was confused, which prompted him to bring her to the emergency room. He denied that she had a cough, headache, shortness of breath, chest pain, palpitations, nausea, vomiting, melena, diarrhea, constipation, or neurological deficits. Of note, the patient had recently had her eyebrows tattooed. Upon physical examination, the patient was groaning, unable to speak, and jaundiced, with a blood pressure of 77/55 mmHg, a pulse of 124 bpm, a temperature of 101.1°F. Her lungs were clear bilaterally to auscultation, and her abdomen was soft, nondistended, nontender, and positive for bowel sounds. Laboratory analysis indicated that she had acute liver failure, as shown in the Table below. In addition, a urine culture came back positive for abundant bacteria growth. She was given 2 L normal saline boluses for hypotension; however, her blood pressure remained low and treatment with Levophed® was initiated. She was also given Rocaphin®, lactulose, and Ativan® for agitation. The patient developed some wheezing, which resolved after one treatment with albuteral. She was admitted to the intensive care unit for acute liver failure, hepatic encephalopathy, and sepsis most likely secondary to the urinary tract infection.

Her condition continued to decline, and she developed respiratory failure secondary to fluid overload. Her IV fluids were decreased, Lasix® was administered, and she was placed on BiPaP with improvement in respiratory status. She was found to have a coagulopathy (prolonged PT and PTT, and increased INR, as shown in the Table below), which was treated with fresh frozen plasma transfusions and vitamin K to keep her INR ≤ 4. A CT scan of the head and chest X-ray from March 2, 2007, showed no apparent disease. A CT of the abdomen on March 4, 2007 was significant for ascites, mostly in the right flank and around the liver, as well as small liver size with questionable partial resection and several hypodensities. A chest X-ray on March 5, 2007 showed increased pulmonary vasculature with a right lower lobe infiltrate or atelectasis. An ultrasound also performed that day revealed decreased portal vein flow with possible obstruction. Hepatitis C antibody and monospot studies were negative. Blood cultures came back positive for *Klebsiella pneumoniae*, and she was started on additional antibiotics. She developed metabolic acidosis and was given sodium bicarbonate with resolution of acidosis, but then developed alkalosis. Because of the patient's overall worsening condition, the patient was transferred to a larger facility on March 5, 2007. She was sedated, intubated and placed on pressure controlled ventilation for transfer.

Upon admission after transfer, the patient was found to have multiorgan failure secondary to septic shock, including respiratory, liver and renal failure. The patient was obtunded and was withdrawing only to painful stimuli; she was unarousable to verbal stimuli. Treatment with lactulose continued, and sodium benzoate was added. Her chest X-ray on transfer showed diffuse bilateral infiltrates consistent with acute respiratory distress syndrome. Upon review of her abdominal CT scan, it was felt that her liver failure

was not due to biliary obstruction, and she was started on lamivudine for presumed acute hepatitis B. However, her hepatitis B profile result was HBsAb positive and HBsAg negative. Her renal failure continued to worsen, and she was started on continuous veno-venous hemodialysis. The patient was given multiple blood transfusions to treat disseminated intravascular coagulopathy, anemia and gastrointestinal bleeding. Antibiotic treatment continued for sepsis. On March 11, 2007, she rapidly decompensated, and after discussion with the family, ventilatory support was withdrawn. The patient subsequently died. No autopsy was performed. The patient was unblinded and found to be on the STI571 arm.

Pertinent laboratory values are summarized in the Table below:

	11/19/05 (Pre-study)	1/09/07	3/02/07	3/08/07
Total bilirubin, mg/dL (reference range: 0.2-1.5 mg/dL)	-	0.5	12.9	12
AST, IU/L (reference range: 0-37 IU/L)	28	94	465	420
ALT, IU/L (reference range: 0-40 IU/L)	28	105	724	760
Alkaline phosphatase, IU/L (reference range: 33-130 IU/L)	48	75	98	89
Albumin, g/dL (reference range: 3.4-5.0 g/dL)	2.2	2.9	2.6	3.0
BUN, mg/dL (reference range: 6-19 mg/dL)	-	12	16	20
Creatinine, mg/dL (reference range: 0.6-1.5 mg/dL)	0.3	0.6	1.2	0.76
Ammonia, µg/dL (reference range: 10-80 µg/dL)	-	-	-	121
PT, seconds (reference range: 11.0-12.5 seconds)	13	-	38.1	40.2
aPTT, seconds (reference range: 30-40 seconds)	32.1	-	75.5	39
INR (reference range: 1.5-2.0)	-	-	9.9	4.37

The patient's past medical history is significant for *Helicobacter pylori* positive peptic ulcer disease with upper gastrointestinal bleeding (November 2005), aspiration pneumonia involving the left lower lobe, melanoma presenting as a solitary pulmonary nodule status post lung biopsy, urinary tract infection, asthma, and chronic back pain. Medications taken at the time of the event included potassium chloride and magnesium.

There have been 10 other cases of liver dysfunction reported to the NCI as serious adverse events through AdEERS under the STI571 NSC, as summarized in the table below.

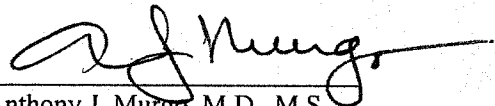
Adverse Event	Grade	Attribution
Liver dysfunction (n=10)	5	1 Possible, 4 Unlikely, 1 Unrelated
	4	2 Possible, 1 Unlikely
	3	1 Unlikely

A total of 3443 patients have been enrolled in NCI-sponsored clinical trials under NSC 716051.

In this case, a possible relationship between the liver failure and STI571 administration cannot be excluded.

	Liver dysfunction/ failure
STI571	Possible
GIST	Unlikely
Sepsis w/multi-organ failure	Possible
Urinary tract infection	Unlikely

Date: 4/25/07

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

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

cc: Clinical Safety & Epidemiology
Faith Williams
Novartis Pharmaceuticals Corporation