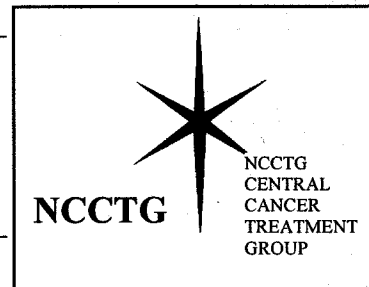

Operations Office

Telephone (507) 266-3549



Date: March 18, 2005

To: NCCTG Primary Clinical Research Associates

From: Lori K. Kelly
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_1090301

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 Lori K. Kelly at 507/266-3549.

lkk
enclosure



DATE: February 18, 2005
FROM: Alice Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: STI-571 IND Safety Report, AE# 1090301
TO: Investigators Using STI571, IND 61135

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 (IND 61135).

Please complete the following:

- 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 STI571 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 is attached:

A 17-year-old male with acute lymphoblastic leukemia experienced grade 4 DIC, grade 4 infection with grade 3 or 4 neutrophils, and grade 4 hemorrhage with grade 3 or 4 thrombocytopenia after receiving two courses of STI571 in combination with methotrexate, cytarabine, and leucovorin.

Infection and hemorrhage are known toxicities of STI571. There have been three cases of DIC reported to the NCI as serious adverse events under this IND, one considered possibly related and two considered unlikely related to STI571.

There have been 2106 patients enrolled in NCI-sponsored clinical trials under this IND.

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ADVERSE EVENTS ASSESSMENT

IND 61135 NSC 716051 STI571 (imatinib, Gleevec®)	ADVERSE EXPERIENCE REPORT NO. 27 IND Safety Report: Event: Gr. 4: DIC Gr. 4 Infection with grade 3 or 4 neutropenia Gr. 3: Hemorrhage with grade 3 or 4 thrombocytopenia Protocol: AALL0031
AE: 1090301	

The patient is a 17-year-old male with acute lymphoblastic leukemia who developed an infection and subsequent disseminated intravascular coagulation (DIC) while on a pilot study using the investigational agent STI571. He began his first course of treatment on November 10, 2004. He began cycle 2 of therapy on December 7, 2004 receiving methotrexate 500 mg/m² intravenously (IV) over 30 minutes followed by methotrexate 4500 mg/m² IV over 23.5 hours on day 1; methotrexate 12 mg intrathecally (IT) on day 1; cytarabine 3 g/m²/dose IV on days 2 and 3 (hour 24, 36, 48, and 60); and STI571 340 mg/m² orally on days 1-21. He also received leucovorin rescue beginning at hour 36, with the last dose administered on December 11, 2004. He began G-CSF 5 µg/kg/day subcutaneously at least 24 hours after the completion of the cytarabine daily for 10 days or until his ANC > 1.5 K/µL; his last dose administered was on December 22, 2004.

The patient was diagnosed with B-progenitor acute lymphoblastic leukemia in October of 2004. He had been recently hospitalized from December 7, 2004 to December 11, 2004 for the initiation of consolidation therapy. On December 19, 2004, the patient presented to his local emergency room (ER) with a fever to 103.8° F, uncontrollable rigors, and complaints of emesis. Blood cultures were obtained, and he was started on antibiotics, as well as antiemetics. The patient also developed hypotension while in the ER, with blood pressures of 80s/30s mm Hg, for which he received intravenous fluids. He was transferred to a larger facility for further treatment. On arrival, his white blood cell count was 0.3 K/µL (reference range: 4.0-11.0 K/µL), hemoglobin level was 5.9 g/dL (reference range: 13.5-17.7 g/dL), and platelet count was 2 K/µL (reference range: 150-400 K/µL). Other significant laboratory values included a PT of 18.4 seconds (reference range: 9.8-12.8 seconds), a PTT of 56.8 seconds (reference range: 24-38 seconds), and a fibrinogen level of 469 mg/dL (reference range: 210-439 mg/dL). He was transfused with packed red blood cells and platelets. Despite hydration, he remained hypotensive and was transferred to the PICU on December

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20, 2004. There he received pressors, additional units of packed red blood cells and platelets, and continued on antibiotics for documented *E. coli* sepsis. His coagulation studies remained elevated, and a D-dimer result on December 21, 2004 was 1000-2000 ng/mL (reference range: <250 ng/mL). The patient also had an ophthalmology consult for a subconjunctival hemorrhage, felt to be due to the thrombocytopenia. The patient recovered and was discharged on December 25, 2004, to receive IV antibiotics at home in order to complete a 10-day course. Of note, the patient continues on his G-CSF and STI571, which was withheld for 5 days due to the patient's *E. coli* sepsis.

Laboratory results are presented in the table below:

	11/4/04	11/18/04	12/20/04	12/21/04	12/23/04	12/25/04
WBC (K/ μ L) (reference range: 4.0-11.0 K/ μ L)			0.3	0.5	5.1	11.2
Hemoglobin (g/dL) (reference range: 13.5-17.7 g/dL)			5.9	10.4	10.2	10.4
Platelets (K/ μ L) (reference range: 150-400 K/ μ L)		150	2	23	71	146
INR (reference range: 0.9-1.1)	1		1.6	1.3	1.2	1.3
PT (seconds) (reference range: 9.8-12.8 seconds)	11.1		18.4	14.4	13.3	15
PTT (seconds) (reference range: 24-38 seconds)	31.9		56.8	69.3	38.0	43.5
D-dimer (ng/mL) (< 250 ng/mL)			250	1000-2000	500-1000	500-1000
Fibrinogen (mg/dL) (reference range: 210-439 mg/dL)			469	663	621	444

The patient's past medical history is significant for events related to his leukemia and seasonal allergies. Medications at the time of the event included G-CSF, Bactrim DS, lorazepam, and Zofran[®] as needed for nausea.

Infection and hemorrhage are known toxicities of STI571. There have been three cases of DIC reported to the NCI as serious adverse events under this IND, one considered possibly related and two considered unlikely related to STI571.

In this case, it is felt that the study drug, cytarabine, methotrexate, and the disease all possibly contributed to the event of DIC. It is felt that the cytarabine and methotrexate probably contributed

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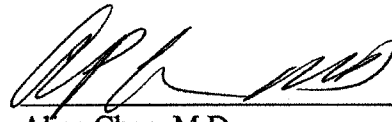
to the infection and ocular hemorrhage; however, the patient's underlying disease and study drug could not be excluded from possibly contributing to these events. There have been 2,106 patients enrolled in NCI-sponsored clinical trials under this IND.

	DIC	Infection with grade 3 or 4 neutrophils	Hemorrhage with grade 3 or 4 thrombocytopenia
Cytarabine	Possible	Probable	Probable
G-CSF	Unrelated	Unrelated	Unrelated
Leucovorin	Unrelated	Unrelated	Unrelated
Methotrexate	Possible	Probable	Probable
STI571	Possible	Possible	Possible
Acute lymphoblastic leukemia	Possible	Possible	Possible
Zofran®	Unrelated	Unlikely	Unlikely

Date:

2/18/05

Signature:



Alice Chen, M.D.
(IDB Monitor for STI571)

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

cc: Faith Williams
Novartis Pharmaceuticals Corporation

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