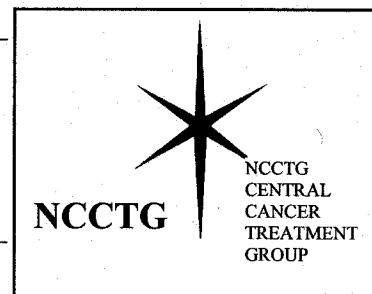

Operations Office

Telephone (507) 266-3549



Date: November 25, 2005

To: NCCTG Primary Clinical Research Associates

From: Lori K. Bratvold
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_1318064

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. Bratvold at 507/266-3549.

lkb
enclosure



DATE: November 9, 2005
FROM: Alice Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: STI571 IND Safety Report, AE# 1318064
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, previous experience under this IND, and the total number of patients enrolled in trials under this IND is attached:

A 15-year-old male with acute lymphoblastic leukemia experienced grade 4 motor neuropathy, grade 3 sensory neuropathy, grade 3 cranial neuropathy, grade 2 mood alteration and grade 2 leukoencephalopathy while on a pilot study using the investigational agent STI571 in combination with chemotherapy.

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ADVERSE EVENTS ASSESSMENT

IND 61135 NSC 716051 STI571 (imatinib mesylate, Gleevec™)	ADVERSE EXPERIENCE REPORT NO. 33 IND Safety Report: Initial Event: Gr: 4 Neuropathy: motor Gr: 3 Neuropathy: sensory Gr: 3 Neuropathy: cranial Gr: 2 Mood alteration-anxiety/agitation Gr: 2 Leukoencephalopathy Protocol: AALL0031
AE: 1318064	

The patient is a 15-year-old male with acute lymphoblastic leukemia (ALL) who experienced unusually serious motor neuropathy, sensory neuropathy, and cranial neuropathy, as well as anxiety/agitation and leukoencephalopathy while on a pilot trial using the investigational agent STI571 in combination with chemotherapy. He began his first course of treatment (Consolidation Block 1) on July 19, 2005 receiving STI571 340 mg/m² PO daily in combination with etoposide, ifosfamide, MESNA, G-CSF, and triple IT therapy consisting of methotrexate, hydrocortisone and cytarabine. He began Cycle 4 (Intensification Block 1) therapy on September 20, 2005 and was to receive STI571 340 mg/m² PO daily for 63 days; methotrexate 5 g/m² IV over 24 hours on Days 1 and 15; leucovorin 75 mg/m² IV at hour 36 then 15 mg/m² IV or PO every 6 hours x 6 doses on Days 2, 3, 16, and 17; triple IT therapy (methotrexate 15 mg, hydrocortisone 15 mg, cytarabine 30 mg) on Days 1 and 22; etoposide 100 mg/m²/day IV on Days 22-26; cyclophosphamide 300 mg/m²/day IV on days 22-26; MESNA 150 mg/m²/day IV on Days 22-26; G-CSF 5 µg/kg SC on Days 27-36 or until ANC > 1500 post nadir; cytarabine 3 g/m² IV every 12 hours on Days 43 and 44; and L-asparaginase 6000 IU/m² IM on Day 44. The patient received the last dose of STI571 on October 13, 2005 (Cycle 4, Day 24). Of note, the patient did not receive the scheduled Day 22 triple IT therapy due to low blood cell counts.

The patient was initially diagnosed with ALL in June 2005 and was status post a multiple systemic chemotherapy regimen, which he received at that time. He began treatment on protocol AALL0031 on July 19, 2005. On October 14, 2005, the patient began to notice left-sided weakness that progressively worsened throughout the day. He presented to the Emergency Room that evening with new onset left hemiplegia of his face, arm and leg with numbness and sensory loss, left-sided tongue weakness and left-sided neglect. Chemotherapy, including STI571, was withheld. A cranial CT scan with angiography showed no evidence of an acute hemorrhage, abnormal blood flow, carotid occlusion or dissection. An MRI/MRA of the brain revealed an acute deep white matter abnormality, which was asymmetric with right greater than left, and considered likely reflective of methotrexate leukoencephalopathy. A lumbar puncture produced cerebral spinal fluid with 1 white blood cell and 1 red blood cell with normal protein and glucose levels. Cerebrospinal fluid cultures were negative for fungal and bacterial organisms, and PCR testing for enterovirus, herpes simplex virus, varicella zoster virus, adenovirus, JC virus, and human herpes simplex 6 virus were negative. A viral culture and mycobacteria culture remain pending. The patient was treated with supportive care, and his neurological status and blood pressure was monitored closely for clinical signs of increased intracranial pressure, as well as decreased blood pressure to ensure adequate brain perfusion. He remained afebrile, and his strength and cranial nerve abnormalities improved quickly over his hospital stay. The patient was discharged to home on October 19, 2005, with a nearly normalized neurological exam. The patient was restarted on chemotherapy, including the investigational agent, on October 25, 2005. When he was evaluated in the clinic on October 28, 2005, his neurological exam demonstrated only a slightly weakened left grip with a normal gait.

The patient has no significant past medical history. Medications taken at the time of the event included Septra® and Zofran®.

There have been no other incidences of leukoencephalopathy reported to the NCI as serious adverse events under this IND. The one incidence of cranial neuropathy was reported as unlikely. The timing of these neurotoxicities in relation to the administration of STI571 raises the question of possible relationship between

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AE #1318064

the two. I have discussed the toxicities with the PI, Dr. Kirk Schultz. A teleconference had also been held between member of CTEP and the investigators. Because of the recent addition of continuous administration of MTX and TIT, the symptoms were felt to be secondary to HD methotrexate. However, the contribution of STI571 to these toxicities in the setting of HD MTX could not be ruled out. The other incidences of neuropathy and mood alteration reported to the NCI as serious adverse events under this IND are presented in the table below.

Neuropathy: motor (n = 5)	4 Unlikely, 1 Unrelated
Neuropathy: sensory (n = 2)	2 Unrelated
Neuropathy: cranial (n = 1)	1 Unlikely
Hemiparesis/Hemiplegia/Weakness (n = 6)	3 Unlikely, 3 Unrelated
Mood Alteration (n = 5)	1 Possible, 4 Unlikely

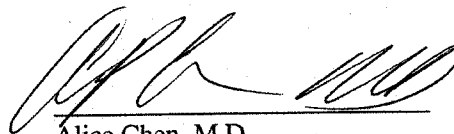
In this case, it is felt that a possible relationship between the events and STI571 cannot be excluded. There have been 2275 patients enrolled in NCI-sponsored clinical trials under this IND.

	Neuropathy: motor	Neuropathy: sensory	Neuropathy: cranial	Mood Alteration: anxiety/agitation	Leukoencephalopathy
STI571	Possible	Possible	Possible	Possible	Possible
Cytarabine	Unlikely	Unlikely	Unlikely	Unlikely	Unlikely
Leucovorin	Unrelated	Unrelated	Unrelated	Unrelated	Unrelated
Methotrexate	Probable	Probable	Probable	Probable	Probable
ALL	Unrelated	Unrelated	Unrelated	Unrelated	Unrelated

Date:

11/14/05

Signature:



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

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

cc: Clinical Safety & Epidemiology
Faith Williams
Norvartis Pharmaceuticals Corporation