

NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: December 15 2006

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_1619905

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: December 11, 2006

FROM: A. Dimitrios Colevas, M.D., Investigational Drug Branch, CTEP, DCTD, NCI *Agut for DC*

SUBJECT: STI571 (Imatinib Mesylate, Gleevec™) NCI IND Safety Report, AE# 1619905

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.

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 is attached:

An 82-year-old male with Merkel cell carcinoma experienced a grade 3 seizure followed by sudden death while on a phase 2 trial using the investigational agent STI571.

ADVERSE EVENTS ASSESSMENT

IND 61135 NSC 716051 STI571 (imatinib mesylate, Gleevec™)	ADVERSE EXPERIENCE REPORT NO. 39 IND Safety Report: Initial Event: Gr. 5: Sudden death Gr. 3: Seizure
AE: 1619905	Protocol: S0331

The patient was an 82-year-old male with advanced Merkel cell carcinoma who experienced a seizure followed by sudden death while on a phase 2 trial using the investigational agent STI571. He began his first course of treatment on October 3, 2006, receiving STI571 400 mg PO daily for 28 days, every 28 days. He received his last dose of STI571 on October 19, 2006 (Cycle 1, Day 17).

The patient was initially diagnosed with Merkel cell carcinoma in May 2004 and is status post adjuvant radiation therapy and concurrent chemotherapy with subsequent courses of radiation therapy for recurrences. He began treatment with STI571 on October 3, 2006 and received 6800 mg total (17 doses). He presented to the clinic on October 20, 2006 with a 2-day history of nausea and vomiting. He received IV fluids and antiemetics. The patient had discontinued his OxyContin® on October 18, 2006 and was told to discontinue STI571 at that time. On October 22, 2006, the patient presented to the emergency room with continued intractable nausea, vomiting, and dehydration and was admitted to the hospital for treatment. A physical examination was remarkable for a pulse of 123 beats per minute and a blood pressure of 167/98 mmHg. An ECG confirmed sinus tachycardia with fusion complexes and an inferior infarct of undetermined age. He was treated with IV fluids, antiemetics, antibiotics for leg lesions, and Vicodin®, with some improvement over the next day. Of note, a CT scan of the abdomen and pelvis performed on September 28, 2006 showed no evidence of bowel obstruction.

On the morning of October 24, 2006, the patient got up to the bedside commode, became very confused, and according to his nurse had hallucinations. As his nurse was putting him back to bed, he had an apparent seizure and then became unresponsive. He was successfully resuscitated twice before being transferred to the intensive care unit where he again needed to be resuscitated. This time resuscitative efforts were unsuccessful, and the patient expired. No autopsy was performed.

Pertinent laboratory values are provided in the table below:

	9/28/06 Baseline	10/20/06 C1, D18	10/22/06 Admission C1, D20
White blood cells count ($10^3/mm^3$) (reference ranges: 4.0 – 10.0 $\times 10^3/mm^3$)	6.6	9.3	11.4
Hemoglobin (g/dL) (reference range: 13-17 g/dL)	10.5	10.3	10.1
Calcium, mg/dL (reference range: 8.5-10.5 mg/dL)	8.7	8.7	8.7
Potassium, mmol/L (reference range: 3.5-5.1 mmol/L)	4.5	3.9	3.2

The patient's past medical/surgical history is significant for coronary artery disease status post bypass graft in 1969, hypercholesterolemia, hypertension, and stroke in 1988. Medications taken at the time of the events included Vicodin®, Phenergan®, Lipitor®, aspirin, and Norvasc®.

There have been 3 other cases of sudden death, 2 other cases of death of unknown etiology, and 28 other cases of seizures reported to the NCI as serious adverse events through AdEERS under NSC 716051, which are summarized in the table below.

Adverse Event	Grade	Attribution
Sudden Death (n=3)	5	1 Possible, 1 Unlikely, 1 Unrelated
Death of unknown etiology (n=2)	5	1 Possible, 1 Unlikely
Seizure (n=28)	4	7 Unlikely
	3	10 Unlikely, 6 Unrelated
	2	5 Unlikely

There have been 3,260 patients enrolled in NCI-sponsored clinical trials under the STI571 NSC.

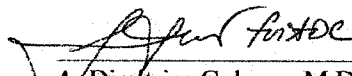
In this case, it is felt that a possible relationship between the events and STI571 cannot be excluded.

	Sudden Death	Seizure
STI571	Possible	Possible
Merkel Cell Tumor	Possible	Possible
Oxycontin	Possible	Unlikely
History of coronary artery disease	Possible	Possible

Date:

12/11/06

Signature:


A. Dimitrios Colevas, 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