



NCCTG

NORTH CENTRAL CANCER TREATMENT GROUP

Date: February 9, 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_1386905

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



National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: February 5, 2007

FROM: A. Dimitrios Colevas, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: STI571 (Imatinib Mesylate, Gleevec®) NCI IND Safety Report, AE# 1386905

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, 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 74-year-old male with a gastrointestinal stromal tumor died from a brain hemorrhage while on a phase 2 trial utilizing the investigational agent STI571.

ADVERSE EVENTS ASSESSMENT

| | |
|---|---|
| IND 61135 NSC 716051 STI571 (imatinib mesylate, Gleevec™) | ADVERSE EXPERIENCE REPORT NO. 41 IND Safety Report: Event: Gr. 5: Hemorrhage, CNS |
| AE: 1386905 | Protocol: RTOG S-0132 |

The patient was a 74-year-old male with gastrointestinal stromal tumor (GIST) who died from a brain hemorrhage while on a phase 2 trial utilizing the investigational agent STI571. He began his first course of treatment on December 3, 2004, receiving STI571 600 mg PO daily for 8 weeks pre-operatively, and then resumed therapy within 2-4 weeks after surgery for up to 24 months. His therapy was placed on hold from January to March 2006 secondary to a fall resulting in a head injury and then resumed at a reduced dose of 200 mg daily due to complaints of dyspepsia, nausea, and vomiting. He received the last dose of STI571 on January 5, 2007 (Cycle 20, Day 22).

The patient was initially diagnosed with GIST in October 2004 and began treatment with STI571 on December 3, 2004. In March 2005, he had a partial gastrectomy and omental biopsy and then continued treatment with STI571 per protocol. In January 2006, the patient sustained a head injury after becoming dizzy and falling into a television set where he hit the right side of his head. A CT scan of the head revealed a hemorrhage within the inferior verian region, and an MRI confirmed the hemorrhage within the cerebellar vermis at the midline and also showed a small subacute hemorrhage within the left occipital lobe, along with a subacute intraventricular hemorrhage seen within the dependent portion of the bilateral occipital horns. An intracranial MRA showed no evidence of intracranial aneurysm or hemodynamically significant intracranial stenosis. The patient was treated conservatively, without surgical intervention. STI571 therapy was withheld until March 2006 and then resumed at a reduced dose.

On January 6, 2007, the patient called 9-1-1 because he was not feeling well and thought he was having a stroke. The patient was found at home by paramedics, unresponsive, with the phone in his lap and no evidence of trauma. When the patient arrived in the emergency department, he was still unresponsive and hypertensive with a systolic blood pressure in the 230s mmHg. He was intubated and given labetalol. An emergency CT scan of the brain revealed a massive posterior fossa hemorrhagic stroke involving the brain stem and the cerebellum bilaterally. He was evaluated by neurosurgery and was not considered to be a surgical candidate due to the severity of the brain stem herniation and likeliness of impending death. Upon physical examination, the patient was found to have fixed dilated pupils, no corneal reflex, a slight gag reflex, and extensor posturing to painful stimuli. There were no signs of external trauma. Vital signs were grossly unstable. Per the family's wishes, care was continued until the patient fulfilled full brain death criteria. On January 8, 2007, a brain flow study showed no perfusion above the base of the skull or uptake in the brain, and brain death was determined. No autopsy was performed.

The patient's past medical history is significant for intracranial hemorrhage in January 2006 and benign prostatic hypertrophy. Prior to the event, he did not have a history of hypertension or any other risk factors for hemorrhagic stroke. Medications taken at the time of the event included vitamin and mineral supplements.

There have been 35 other cases of CNS hemorrhage reported to the NCI as serious adverse events through AdEERS under the STI571 NSC, as summarized in the table below.

| Adverse Event | Grade | Attribution |
|-----------------------|-------|-------------------------------------|
| CNS Hemorrhage (n=35) | 5 | 4 Possible, 2 Unlikely |
| | 4 | 1 Probable, 12 Possible, 2 Unlikely |
| | 3 | 6 Possible, 5 Unlikely, 1 Unrelated |
| | 1 | 2 Possible |

A total of 3289 patients have been enrolled in NCI-sponsored clinical trials under NSC 716051.

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

| | CNS Hemorrhage |
|------------------------|-----------------------|
| STI571 | Possible |
| Surgery | Unrelated |
| GIST | Unlikely |
| Prior CNS Bleed | Possible |

Date:

2/6/07

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