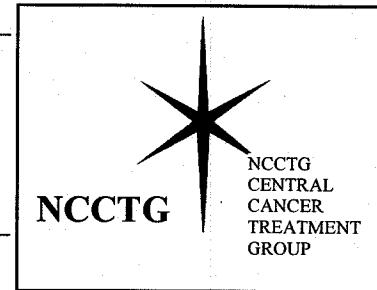


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**Operations Office**

Telephone (507) 266-3549

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**Date:** January 7, 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\_06Dec2004

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



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health  
National Cancer Institute  
Bethesda, Maryland 20892

**DATE:** December 6, 2004

**FROM:** Anthony J. Murgo, M.D., M.S., Associate Chief for Developmental Chemotherapy,  
Investigational Drug Branch, CTEP, DCTD, NCI *ajm*

**SUBJECT:** Imatinib (STI571) Investigator Notification: Fatal Pneumonitis

**TO:** Investigators Using STI571, IND 61,135

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. An investigator notification, which describes fatal pneumonitis in a patient participating in a Novartis-sponsored clinical study utilizing the investigational agent STI571 (IND 61135), was recently distributed to investigators.

Please complete the following:

- Send a copy of this letter to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of this letter 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 "Dear Doctor" letter that describes the following adverse event is attached:

A 65-year-old male with metastatic prostate cancer experienced fatal pneumonitis during the course of a clinical study of STI571 in combination with docetaxel. The event was considered possibly related to STI571.

While pneumonitis is an established but rare adverse event with STI571 treatment and listed in the Investigator's Brochure (IB), a fatal outcome is not expected. There have been a total of 27 incidences of pneumonitis reported to the NCI as serious adverse events under IND 61135, five of which have been fatal. These events are summarized in the table below.

**CONFIDENTIAL**

ADEERS REPORT NUMBER	ADVERSE EVENT	IND AGENT ATTRIBUTION	CONCOMITANT MEDICATIONS ATTRIBUTION	DISEASE ATTRIBUTION	OTHER CAUSES ATTRIBUTION
1752452	Pneumonitis	Possible	Probable Dexamethasone		
1585853	Pneumonitis	Unlikely			Probable Pneumonia  Probable Aspiration  Possible History of COPD
1935057	Pneumonitis	Unlikely		Possible Leiomyosarcoma	Probable Aspiration caused by enteral feedings
1333876	Pneumonitis	Unrelated			Definite Aspiration pneumonia
1346986	Pneumonitis	Unrelated		Possible Gastric Cancer	Possible Fentanyl Patch  Possible Pneumonia, Aspiration

Regarding AdeERS Report #1752452, the patient was a 40-year-old male with an astrocytoma who died from pneumonitis while on a phase 1/2 trial using STI571. The patient had completed 7 weeks of STI571 400 mg twice daily and was also receiving dexamethasone. He was admitted directly to the intensive care unit after a several-day history of dyspnea. Despite aggressive medical treatment, the patient did not respond. Of note, sputum cultures were positive for *Pneumocystis carinii*, and the patient was started on high dose Septra during his hospital course. Nevertheless, the patient expired 5 days after admission. An autopsy was not performed. Although steroids are known to predispose to opportunistic infections, including *Pneumocystis carinii*, a possible causal relationship to STI571 could not be excluded.

As of October 31, 2004, a total of 2066 patients have been entered on clinical trials under IND 61135.

**CONFIDENTIAL**

To: All Investigators in STI 571 Studies\*

DATE: 23 November 2003

Re: Investigator Notification for STI 571: Fatal pneumonitis PHHO2004US16008

Dear Doctor,

In accordance with the Good Clinical Practice and specific national regulatory requirements we wish to inform you of a serious, unexpected, possibly related adverse report of fatal pneumonitis that occurred in a patient being treated with STI571 in combination with docetaxel for prostate cancer during the course of a clinical study.

For the current case, details of the adverse event are provided in the attached CIOMS form, which contains the available information as reported to Novartis. To summarize briefly, a 65 year old male patient enrolled in a randomized double-blind trial of docetaxel and imatinib versus docetaxel and placebo in metastatic androgen-independent prostate cancer with bone metastases received his first dose of the study medication on 16 Aug 2004. On 25 Oct 2004 he was admitted to the intensive care unit in acute respiratory distress. Chest X-ray showed bilateral diffuse patchy infiltrates. An echocardiogram showed no mitral valve prolapse or aortic stenosis. Overall ejection fraction was 70% and there was significant tricuspid regurgitation with a peak velocity tricuspid regurgitation jet suggesting at least moderate pulmonary hypertension. Findings were not suggestive of congestive heart failure. He was treated with diuretics, broad spectrum antibiotics and high-dose steroids for possible pneumonitis. He deteriorated and was intubated on 27 Oct 2004 and a left-sided chest tube was placed on 30 Oct 2004 for a small to moderate sized left apical pneumothorax as a result of a central line placement. On 30 Oct 2004 pneumothorax had markedly decreased. Attempts to obtain sputum specimens for cultures were not successful and blood cultures reported no growth. He continued to require high levels of positive end-expiratory pressure and fraction of inspired oxygen of 70-100% to maintain oxygen saturation. Urine output responded to diuretics. Open lung biopsy was considered, but declined. Respiratory status continued to decline and the family decided that he should be made 'do not resuscitate'. The patient died on 31 Oct 2004 and the family refused an autopsy. The investigator suspected a relationship between pneumonitis / pulmonary infiltrates and the study medication.

Pneumonitis belongs to the established but rare adverse reactions to treatment with imatinib listed in the Investigator's brochure but not a fatal outcome of such a condition. There have been 3 previous patients from clinical trials with pneumonitis suspected to be related to Glivec who died but in all of these cases infections/septicaemia which are listed in the Investigator's brochure were involved in the fatal outcome. In addition Novartis has received 3 spontaneous reports of pneumonitis with a fatal outcome.

We will keep you informed if further medically significant information becomes available that is relevant to this event or if any additional action is necessary. We ask that you please inform your Institutional Review Board or Ethics Review Board of this event, if you have such an obligation.

Sincerely,

W.H. Aellig

Walter Aellig MD  
Clinical Safety and Epidemiology  
Novartis Pharma Basel

Attachment: CIOMS case report

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\* Novartis Investigator Notification: International Guidelines for Good Clinical Practice as well as specific health authority regulations require that clinical investigators be informed of any adverse drug reaction which is serious (according to specific regulatory criteria), unexpected (i.e. not specifically mentioned in the Investigator's Brochure) and which has a 'reasonable possibility' (in the opinion of the reporter and/or the Company) of being related to the study medication. While Novartis tries to obtain all meaningful information as soon as possible, we are required to communicate all available information within a specified time of its receipt. Since initial data is frequently incomplete, further information must be sent in the form of follow-up reports. Where they have such an obligation, investigators are expected to inform institutional review boards/ethics committees, of each investigator notification. Should Novartis believe that a change in protocol or other action needs to be taken on the basis of clinical reports or other available data; the company will communicate such changes to involved investigators.