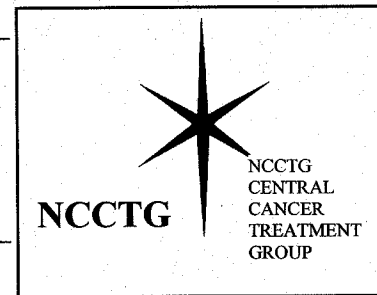

Operations Office

Telephone (507) 266-3549



Date: January 13, 2006

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_PHHO2005ES16489

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



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: December 23, 2005

FROM: Alice Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: STI571 (Imatinib) Investigator Notification: Urothelial Carcinoma
Novartis Report #PHHO2005ES16489

TO: Investigators of CTEP-sponsored trials using 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. An investigator notification, which describes urothelial carcinoma in a leukemia patient participating in a Novartis-sponsored clinical study utilizing the investigational agent STI571 (NSC 716051), 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 73-year-old male with chronic myelogenous leukemia developed urothelial carcinoma (grade III) while on a phase 3 trial using the investigational agent STI571.

There have been no other incidences of urothelial carcinoma reported to the NCI as serious adverse events under NSC 716051 (STI571).

There have been 2805 patients enrolled under NSC 716051 (STI571).

CONFIDENTIAL

00001

To: All Investigators in Imatinib (STI571) Studies*

DATE: October 31st, 2005
Re: Investigator Notification for Imatinib (STI571)
Manufacturer Case ID PHHO2005ES16489
Study CSTI571 0106

Urothelial Carcinoma

Dear Doctor,

In accordance with the Good Clinical Practice and specific national regulatory requirements, we wish to inform you of a serious, unexpected and possibly related adverse event of urothelial carcinoma that occurred in a patient enrolled in protocol CSTI571 0106. For the current case details are provided in the CIOMS I form, which contains information as reported to Novartis.

To summarize,

Initial report received 19 Oct 2005 combined with follow-up information received 26 Oct 2005

A 73-year-old male was enrolled in study protocol CSTI571 0106, a Phase III study of STI571 versus interferon-alpha combined with Cytarabine in patients with newly diagnosed, previously untreated Philadelphia chromosome positive chronic myelogenous leukaemia in chronic phase. He received his first dose of the study medication on 14 December 2000. Medical history included transurethral resection of a papilloma of the urinary bladder in 1997 and a diagnosis of prostate adenoma in 1997. The patient never smoked and had no history of professional exposure to carcinogens. During March 2005 and September 2005 the patient presented with haematuria. He was hospitalised from 25 September 2005 until 06 October 2005 to undergo surgery due to the previous diagnosis of prostate adenoma in 1997 and a suspected tumour of the urinary bladder. An open suprapubic prostatectomy plus partial cystectomy was performed on 28 September 2005. The urinary bladder biopsy diagnosed urothelial carcinoma (grade III). The study medication was temporarily interrupted from 28 Sep 2005 until 29 Sep 2005 due to the surgery. At the time of this report the patient's condition was improving. The investigator suspected a relationship between the event and the study medication, stating that the patient's previous urinary bladder papilloma was different from the present carcinoma.

00002

Sponsor's assessment:

In November 2004, confirmed by an update in June of 2005, an epidemiological analysis of second primary malignancies among patients treated with Gleevec in Novartis sponsored clinical trials was performed. The main findings of the analysis have meanwhile been published (1). The objective was to compare the incidence rates of second cancers among patients treated with Gleevec with the expected incidence based on the rates among the general population. In addition, the frequency of spontaneous reports of cancer associated with Gleevec was analyzed based on cases collected in the clinical safety database.

The comparison of the incidence rates of second cancers in Gleevec-treated patients with the incidence of cancer in general population based on Surveillance Epidemiology and End Results (SEER) registries was performed by estimating standardized incidence ratio (SIR), which is the ratio of observed to expected cases. For all malignant cancers (excluding non-melanoma skin cancer and malignancies representing progression of the underlying disease) and specifically for kidney, urinary bladder and prostate cancers, the numbers of cases diagnosed (observed) during Novartis sponsored clinical trials were similar to those expected in the general population.

The analysis of spontaneous reports on malignancies from the market experience collected in the clinical safety database revealed reporting rates of all cancers, as well as of kidney, urinary bladder and prostate cancer several times lower than the incidence rates for respective cancers in the general population.

It was concluded that:

- The incidence rate of all cancers, as well as the incidence rates of specific cancers of kidney, urinary bladder and prostate observed in Gleevec treated patients during Novartis sponsored clinical trials did not differ from the incidence rates in the general population.
- The results of analysis of the spontaneous reports on cancer from Gleevec market experience are consistent with the results from the analysis of the clinical trials data.
- The analysis of clinical safety data from clinical trials and spontaneous adverse event reports did not provide evidence for an increased overall incidence of malignancies or in the incidence of bladder, kidney or prostate tumors in patients treated with imatinib compared to that of the general population.

We ask that you please inform your Institutional Review Board or Ethics Review Board of this event, if you have such an obligation.

Yours sincerely,

Richard Pilot, MD
Director, Clinical Safety and Epidemiology
Novartis Pharmaceutical Corporation
One Health Plaza
East Hanover, NJ, 07936
United States of America

Reference:

- (1) Pilot PR, Sablinska K, Owen S, Hatfield A
Epidemiological analysis of second primary malignancies in more than 9500
patients treated with imatinib
Manuscript for publication
Leukemia 2006

Attachment: CIOMS case report

* 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.

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year	73 Years	Male	Unk	Day	Month	Year	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) Urothelial carcinoma [Transitional cell carcinoma] ([Haematuria], [Urinary bladder excision], [Prostatectomy]) Case Description: Initial report received 19 Oct 2005 combined with follow-up information received 26 Oct 2005: This patient (centre number XXX, patient number XX) was enrolled in study protocol CSTI571 0106, a Phase III study of STI571 versus interferon-alpha combined with Cytarabine in patients with newly diagnosed, previously untreated Philadelphia chromosome positive chronic myelogenous leukaemia in chronic phase. He received his first dose of the study medication on 14 Dec 2000. (continue)											<input type="checkbox"/> PATIENT DIED <input checked="" type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALISATION <input type="checkbox"/> INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) #1 IMATINIB(STI571/CGP57148B T35717+CAPS)Capsule		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S) #1 400 mg, QD	16. ROUTE(S) OF ADMINISTRATION #1 Oral	
17. INDICATION(S) FOR USE #1 Chronic myeloid leukaemia		21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
18. THERAPY DATES(from/to) #1 14-DEC-2000 00:00 / 27-SEP-2005 00:00	19. THERAPY DURATION #1 1749 days	

III. CONCOMITANT DRUG(S) AND HISTORY (Continued on Additional Information Page)

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)		
23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)		
From/To Dates	Type of History / Notes	Description
Unknown		Bladder papilloma
Unknown	Historical Condition	Papilloma excision

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER Novartis Pharma Headquarter		26. REMARKS
	24b. MFR CONTROL NO. PHHO2005ES16489	
24c. DATE RECEIVED BY MANUFACTURER 19-OCT-2005	24d. REPORT SOURCE <input checked="" type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input checked="" type="checkbox"/> HEALTH PROFESSIONAL <input type="checkbox"/> OTHER:	25b. NAME AND ADDRESS OF REPORTER
DATE OF THIS REPORT 28-OCT-2005	25a. REPORT TYPE <input checked="" type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOWUP	

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Medical history: transurethral resection of papilloma of urinary bladder in 1997 and diagnosis of prostate adenoma in 1997. The patient has never smoked and has no history of professional exposure to carcinogens. During Mar 2005 and Sep 2005 the patient presented with haematuria. He was hospitalised from 25 Sep 2005 until 06 Oct 2005 to undergo surgery due to the previous diagnosis of prostate adenoma in 1997 and suspected tumour of the urinary bladder. An open suprapubic prostatectomy plus partial cystectomy was performed on 28 Sep 2005. The urinary bladder biopsy diagnosed urothelial carcinoma (grade III). The study medication was temporarily interrupted from 28 Sep 2005 until 29 Sep 2005 due to the surgery. At the time of this report (19 Oct 2005) the patient's condition was improving. The investigator suspected a relationship between the event and the study medication, stating that the patient's previous urinary bladder papilloma was different from the present carcinoma.

Novartis Comment: Serious adverse event report (involved or prolonged inpatient hospitalisation), assessed as unexpected according to the Investigator's Brochure.

The information provided in this individual case does not warrant a change to the Investigator's Brochure. The topic will be monitored closely. Investigator causality is suspected.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
1997 to Unknown		Prostatic adenoma