

North Central Cancer Treatment Group

N0272: Phase I/II Trial of Imatinib Mesylate; (Gleevec; STI571) in Treatment of Recurrent Oligodendroglioma and Mixed Oligoastrocytoma

Addendum 2 – December 3, 2004

Summary

Scientific:

- This addendum is in response to the Action Letter dated October 6, 2004 from Dr. Anthony J. Murgo of the National Cancer Institute regarding the development of benign and malignant renal tumors and benign urinary bladder tumors in animals.
- As reflected in the protocol, both blood and tissue samples will be used for research testing. Therefore clarification made to the consent form reflecting the correct questions patients will answer.
- Editorial/administrative changes.

Replacement pages are included. Please incorporate into the protocol and keep this addendum with your protocol.

Title page: The title page now reflects Addendum 2 and revised NCI version date.

Page 16: Section 4.0 (Test Schedule), X's have been placed in the last column for both the Hematology and Chemistry groups for clarification.

Pages 17-18: Section 6.3 (Registration/Randomization Procedures), the permission questions which will be asked to the patient have been revised for clarification as follows:

- Patient has/has not given permission to store and use blood ~~and tissue~~ sample(s) for future research of cancer.
- **Patient has/has not given permission to store and use tissue sample for future research of cancer.**
- Patient has/has not given permission to store blood ~~and tissue~~ sample(s) for future research to learn, prevent, or treat other health problems.
- **Patient has/has not given permission to store tissue sample for future research to learn, prevent, or treat other health problems.**
- Patient has/has not given NCCTG permission to give their blood ~~and tissue~~ sample(s) to outside researchers.
- **Patient has/has not given NCCTG permission to give their tissue sample to outside researchers.**

Page 22: Footnote #1 in Section 8.2 (Dosage Modification Based on Adverse Events) has been revised for clarification as follows:

1. Adjusted to the nearest 100 mg, since imatinib is only available in 100 mg capsules. If the total daily dose is less than or equal to 400 mg, a single daily dosing schedule should be utilized. Following dose reduction, if the dose is maintained for 4 weeks without further dose reduction then subsequent dose escalation to prior levels may be considered. **Note: PK is needed after 1st dose reduction.**

Page 41: Section 15.41 (Drug Information), a new sentence has been added to the first paragraph and reads “**Benign and malignant renal tumors and benign urinary bladder tumors have also been reported in animals.**”

Appendix IA: Under section “Will any biological sample(s) be stored and used in the future by the North Central Cancer Treatment Group (NCCTG), or released to researchers outside of NCCTG for future unspecified use?” the permission questions for the tumor and blood samples on page 4 have been revised for clarification as follows:

- New question #2 has been added and reads
I permit my blood sample to be stored and used for future research of cancer
 Yes No **Please initial here:** _____ **Date:** _____
- Previous question #2 has now become question #3
- New question #4 has been added and reads
I permit my blood sample to be stored and used in future research to learn, prevent, or treat other health problems
 Yes No **Please initial here:** _____ **Date:** _____
- Previous question #3 has been deleted

Under section “How do outside researchers get the sample?” the permission questions for the tumor and blood samples on page 4 have been revised for clarification as follows:

1. I permit NCCTG to give my **blood** samples(s) to outside researchers:

Please mark one box:

Yes No **Please initial here:** _____ **Date:** _____

2. I permit NCCTG to give my **tissue** sample to outside researchers:

Please mark one box:

Yes No **Please initial here:** _____ **Date:** _____

A new paragraph has been added on page 7 under “What are the risks of the research study?” and reads “**Tumors in the urinary system or reproductive organs have also been reported in animals.**”

Appendix IB: Under section “Will any biological sample(s) be stored and used in the future by the North Central Cancer Treatment Group (NCCTG), or released to researchers outside of NCCTG for future unspecified use?” the permission questions for the tumor and blood samples on page 4 have been revised for clarification as follows:

- Question #4 has been renumbered to #1
- New question #2 has been added and reads
I permit my blood sample to be stored and used for future research of cancer
 Yes No **Please initial here:** _____ **Date:** _____
- Previous question #5 has now become question #3
- New question #4 has been added and reads
I permit my blood sample to be stored and used in future research to learn, prevent, or treat other health problems
 Yes No **Please initial here:** _____ **Date:** _____
- Previous question #6 has been deleted

Under section “How do outside researchers get the sample?” the permission questions for the tumor and blood samples on page 4 have been revised for clarification as follows:

1. I permit NCCTG to give my **blood** samples(±) to outside researchers:

Please mark one box:

Yes No **Please initial here:** _____ **Date:** _____

3. I permit NCCTG to give my **tissue sample** to outside researchers:

Please mark one box:

Yes No **Please initial here:** _____ **Date:** _____

A new paragraph has been added on page 7 under “What are the risks of the research study?” and reads “**Tumors in the urinary system or reproductive organs have also been reported in animals.**”

**ACTION LETTER**

page 1

DATE: October 6, 2004

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

SUBJECT: Gleevec[®], imatinib mesylate (STI-571) IND Safety Report

TO: Investigators using STI571, IND 61,135

The purpose of this letter is to alert investigators of the following non-clinical toxicology information provided by Novartis Pharmaceuticals Corporation relevant to STI571 studies sponsored by the National Cancer Institute (NCI), Division of Cancer Treatment and Diagnosis (DCTD). A revision to the informed consent form is **required** by CTEP.

The letter that describes the following results is attached:

As part of the continuing preclinical studies on imatinib (formerly STI571, now marketed as Glivec[®]/Gleevec[®]), Novartis completed the in-life part and the necropsy of a 2-year oral (in feed) carcinogenicity study in rats at doses of 15, 30 and 60 mg/kg. Increased incidence of palpable masses in the urogenital region led to an accelerated histopathological analysis of these organs. The target organs for neoplastic changes were kidneys in both sexes, urinary bladder and preputial gland in males, and clitoral gland in females.

A statistically significant increase in renal benign and malignant tumors and the urinary bladder benign tumors were noted only at 60 mg/kg/day, representing approximately 1.74x to 4.14x human daily exposure (based on AUC) to imatinib at the dose of 400mg/day. In addition, a statistically significant increase in benign and malignant tumors of the preputial/clitoral gland was noted at 30 and 60 mg/kg/day, representing approximately 0.5x to 1.7x human daily exposure (based on AUC) to imatinib at the dose of 400mg/day. Please see the attached Novartis notice to investigators for additional information.

In view of these important non-clinical toxicology data, CTEP is requesting that all principal investigators do the following:

- 1) Distribute this letter to all participating investigators and IRBs with a copy of the e-mail or other rapid trackable communication (e.g. fax with return requested) to **Dr. Michael Montello** at PIO@CTEP.NCI.NIH.GOV within 7 calendar days of the date of this letter. Failure to comply within the 7-day timeframe may result in the temporary suspension of the principal investigator and enrollment of patients to the study.
- 2) Amend the informed consent documents to inform patients in lay terms of the potential for carcinogenicity in organs of the urogenital region.
 - For Cooperative Group studies, the revision to the protocol and informed consent form will be made by the Cooperative Group Operations office, forwarded to CTEP for approval, and

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circulated to the Group's investigators. Please follow any instructions provided by the Cooperative Group.

- For non-Cooperative Group studies, the principal investigator is required to forward a copy of the revised protocol and informed consent form to CTEP as outlined below.
- 3) Submit all amendments to the protocol and informed consent form to NCI by 5:00 pm EST on November 8, 2004. The amendment cover letter must state "these amendments are in response to the memo from Dr. Anthony Murgo (murgoa@ctep.nci.nih.gov, phone 301-496-1196) regarding non-clinical carcinogenicity studies. Failure to comply within this timeframe may result in the temporary suspension of the principal investigator and enrollment to the study.

Please submit the amendment, the change memo, and the cover letter to Dr. Michael Montello at PIO@CTEP.NCI.NIH.GOV.

To: All Investigators in imatinib studies

DATE: 27th September 2004

Re: Investigator Notification for imatinib (formerly known as STI571)* - new animal toxicology information

Dear Doctor,

In accordance with the Good Clinical Practice and specific national regulatory requirements we wish to inform you of some preliminary findings from the two-year carcinogenicity study in rats with imatinib.

As part of the continuing preclinical studies on imatinib (formerly STI571)*, we have completed the in-life part and the necropsy of a 2-year oral (in feed) carcinogenicity study in rats at doses of 15, 30 & 60 mg/kg. Increased incidence of palpable masses in the urogenital region led to an accelerated histopathological analysis of these organs. The target organs for neoplastic changes were kidneys in both sexes, urinary bladder and preputial gland in males and clitoral gland in females.

A statistically significant increase in renal benign and malignant tumours and the urinary bladder benign tumours were noted only at 60 mg/kg/day, representing approximately 1.74x to 4.14x human daily exposure (based on AUC) to imatinib at the dose of 400mg/day. In addition, a statistically significant increase in benign and malignant tumours of the preputial/clitoral gland was noted at 30 and 60 mg/kg/day, representing approximately 0.5x to 1.7x human daily exposure (based on AUC) to imatinib at the dose of 400mg/day.

The recommended therapeutic dose for imatinib for CML and GIST patients is 400-600 mg, given once daily as a single agent. In cases of insufficient response to the initial dosing or relapse, the daily dose may be increased to 800 mg. Imatinib is also studied in other oncology indications with the same dose range. In the light of the severity of the oncology indications and the lack of adequate treatment providing long-term efficacy and safety, the data from the rat carcinogenicity study are not considered to shift the risk assessment of imatinib.

A preliminary analysis of the safety data from clinical trials and spontaneous adverse event reports did not provide evidence for an increased overall incidence of malignancies in patients treated with imatinib compared to that of the general population. No changes to the Novartis clinical trial program are foreseen.

* Marketed as Glivec® / Gleevec®

Imatinib is also under evaluation in on-going clinical trials for non-oncology indications in rheumatoid arthritis, idiopathic pulmonary fibrosis and psoriatic arthropathy / ankylosing spondylitis. In light of the life threatening nature of idiopathic pulmonary fibrosis and the absence of effective therapy for this indication Novartis sees no immediate need to halt this trial. Regarding the rheumatoid arthritis and psoriatic arthropathy / ankylosing spondylitis trials, due to the debilitating nature of these diseases together with the short exposure of 12 weeks treatment, Novartis again sees no immediate need to halt these trials.

All appropriate clinical trial related documents (e.g. Investigator's Brochure) for Novartis sponsored trials, as well as product information as part of marketing authorizations, will be amended to include these carcinogenicity findings. 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 these findings. If you are conducting a clinical trial under your own sponsorship, please amend the relevant documents for your trial according to the information contained in this notification and inform your Data Safety Monitoring Board and Health Authority. Novartis has informed Health Authorities of these findings in all countries involved in Novartis sponsored trials.

Sincerely,

Philip Bentley, Ph.D.
Vice President, acting Global Head
Preclinical Safety

Philippe Close, M.D.
Head Global Medical Safety
Clinical Safety &
Epidemiology