

North Central Cancer Treatment Group

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

Addendum 1 – December 3, 2004

Summary

Scientific:

- The objectives for this study have been revised to further clarify the endpoints with the inclusion of the Phase I portion of the study.
- Tissues from all available prior surgeries should be sent, in particular those from time of initial diagnosis to be eligible for study entry.
- A new dose level for the enzyme-inducing anticonvulsants group has been established.
- Additional risk information has been added in the consent form regarding interactions between imatinib and anti-seizure medicines.
- Osteonecrosis has been added as a risk to both Section 15 and the consent form for imatinib.

Editorial:

- The title of the study has been revised to include Phase I.
- Update to contact person for protocol document, consent form, and regulatory issues.
- Update to NCCTG member nurse for drug administration, infusion pumps, and nursing guidelines issues.
- Clarification made in the test schedule to reflect appropriate tests performed “≤7 days before each cycle” and “≤7 days before 3rd cycle and ≤7 days before every other subsequent cycle.”
- Correction has been made to the Adverse Event (AE) Reporting and Monitoring section to reflect the appropriate CTEP websites and 24 hour electronic notification.
- Correction to mailing address for pretreatment and follow-up PK kits.
- Editorial correction to section numbering in Section 18.0 Records and Data Collection Procedures).

A replacement protocol is provided. Please replace the current copy with the one attached. Please keep this addendum with your protocol

Title page: The title page now reflects Addendum 1.

The title of the study has been revised to reflect the Phase I portion of the study.

Page 2: Protocol Resource: Lori Kelly has replaced Linda S. Long as the contact person for protocol document, consent form, and regulatory issues.

Protocol Resource: Beverly Kowbel, R.N. has replaced Gwen Finck, R.N. as the contact person for drug administration, infusion pumps, nursing guidelines issues.

Page 3: The Index page has been revised as follows:
Appendix I – A Phase I consent form has been added (Appendix IA). The Phase II consent form has been renumbered as Appendix IB..

Page 4: The Schema has been rewritten to include the Phase I portion of this study.

Pages 12 and 13: Section 2.0 (Goals) has been expanded to add a Phase I component to the study.

- Pages 13-15: Section 3.0 (Patient Eligibility) has been revised to reflect the inclusion of the Phase I portion of the study and all remaining sections have been renumbered.
- Page 13: Section 3.32 (previously Section 3.11) (Patient Eligibility), the last sentence has been added as follows:
Tissues from all available prior surgeries should be sent, in particular those from time of initial diagnosis.
- Page 13: Previous Section 3.18 (Patient Eligibility) has been deleted as follows:
~~Must have received ≤ 2 total prior chemotherapy regimens, and ≤ 1 for relapsing disease.~~
- Page 14: Section 3.39i (Patient Eligibility) has been added as follows:
 ≤ 2 prior chemotherapy regimens.
- Page 14: Section 3.41 (previously Section 3.21) (Patient Eligibility) has been revised due to adverse events occurring, as follows:
Receiving warfarin ~~therapy~~ or heparin (see Section 9.5 for low dose warfarin).
- Page 15: Section 3.49b (Patient Eligibility) has been added due to adverse events occurring, as follows:
Significant Intratumoral hemorrhage on baseline MRI or CT, or other history of significant intratumoral hemorrhage.
- Page 16: Section 4.0 (Test Schedule), the 6th and 7th column headings have been revised as follows:
~~Week ≤ 7 days~~ before each cycle
~~Week ≤ 7 days~~ before 3rd cycle and ~~week ≤ 7 days~~ before every other subsequent cycle
- Page 17: Section 5.0 (Grouping Factor:) has been revised as follows:
~~*Arm A will not open until a dose level has been established and approved by NCI~~
- 5.1 **Study: 2-EIAC vs. 2-Non EIAC vs. 1 Enzyme inducing anticonvulsant therapy (EIAC): Yes vs. no.** (See Appendix IIIB for list of EIAC and non-EIAC agents.)
- Page 17: Section 6.1 (Registration/Randomization Procedures) has been revised to include registration procedures for the Phase I portion of this study.
- Page 18-21: Section 7.0 (Protocol Treatment) has been expanded and renumbered to include the Phase I portion of this study.
- Pages 22 and 23: Section 8.0 (Dosage Modification Based on Adverse Events) has been revised to include the Phase I portion of this study.

- Pages 25-27: Section 10.0 (Adverse Event (AE) Reporting and Monitoring) has been revised to reflect the current CTEP reporting websites and 24 hour electronic notification rather than telephone notification.
- Pages 26-27: Sections 10.2 and 10.3 (Adverse Event [AE] Reporting and Monitoring) have been revised to include the Phase I procedures.
- Page 28: Section 10.4 (Adverse Event [AE] Reporting and Monitoring) has been added.
- Page 31: Section 12.9f (Descriptive Factors) has been added as follows:
Number of prior chemotherapy regimens.
- Page 32: Section 13.0 (Treatment/Follow-up Decision at Evaluation of Patient) has been revised to include the Phase I portion of this study.
- Page 32: Section 14.1 (Translational Research and Pharmacologic Studies on Tissue Specimens), the first paragraph has been revised as follows:
These studies will be performed on tissues obtained from prior surgeries. Tissues from **the initial diagnosis and any recurrent procedure** ~~all available prior surgeries~~ should be sent; ~~in particular those from the time of initial diagnosis~~, if available. Paraffin embedded fixed tumor tissues will be used for study of expression of potential targets of imatinib and downstream effectors or markers of signaling, **as follows:**
- Section numbers 14.11, 14.12, and 14.13 have been deleted and replaced with bullets and all remaining sections have been renumbered.
- Page 33: Section 14.12, previous Section 14.15 (Translational Research and Pharmacologic Studies on Tissue Specimens) has been revised to reflect current mailing address as follows:
- 14.121 ~~Samples should be shipped to TACMA/NCCTG Biospecimens Resource~~
Within 30 days of registration submit the sample to the NCCTG Operations Office at the following address:
- ~~TACMA/NCCTG Biospecimens Resource~~ **Operations Office**
~~Guggenheim 1036 Plummer 4~~
200 First Street, SW
Rochester, MN 55905
ATTN: Helen Tollefson, Pathology Coordinator
- 14.122 **The NCCTG Pathology Corrdinator will forward the material to TACMA/NCCTG Biospecimens Resource lab.**
- Page 33: Sections 14.13 and 14.14 (Translational Research and Pharmacologic Studies on Tissue Specimens – Gene Studies – Lymphocytes and peripheral blood leukocytes) have been added as follows:
- 14.13 If sending of the block is not allowable based on the referring institutional policy, please submit 20 unstained slides and 1 H&E.**

Remaining tissue will be stored in the NCCTG Operations Office for future research studies. The institutional pathologist must be informed that the blocks may be depleted. The Operations Office will inform the institution if a block is depleted. The blocks will be returned promptly to the institutional pathology upon request at any time.

14.14 Although post-treatment biopsies are not routinely planned, if clinically indicated, post-treatment samples will be obtained and analyzed also, and should be sent as in Section 17.2.

Page 35: Section 14.33 (Translational Research and Pharmacologic Studies on Tissue Specimens – Gene Studies – Lymphocytes and peripheral blood leukocytes), reference to Section 14.1 has been revised to reflect Section 14.12.

Page 36: Section 14.41 (Translational Research and Pharmacologic Studies on Tissue Specimens -- Gene Studies - Lymphocytes and peripheral blood leukocytes): The name of the biospecimens resource for mailing is more clearly identified:

14.41 Blood for lymphocytes and buffy coat preparation will also be obtained whenever possible ... will be drawn. Blood should be mailed per kit instructions to the **TACMA/NCCTG Biospecimens Resource** in the provided kit as soon as is practical following procurement of the sample. The studies will be performed in the laboratory of Dr. Robert Jenkins.

Page 39: Section 14.6 has been added and the table previously located in Section 14.59c is now located in Section 14.6.

Page 39: The table in Section 14.6 (Translational Research and Pharmacologic Studies on Tissue Specimens) has been revised as follows:

The last column (Mailing Instructions) of the first row now reads:

To: **NCCTG Biospecimens Resource Operations Office, Guggenheim 4036 Plummer 4**, 200 First Street, SW, Rochester, MN, **ATTN: Helen Tollefson, Pathology Coordinator, (800-826-5561 507-266-0724)**

The words “in batches” have been deleted from the last column of the last row.

- Page 40: Section 15.3 (Drug Information) has been revised as follows:
Imatinib should be given ~~in a single daily dose of 600 mg~~ **as two divided doses**. ~~If significant immediate side effects occur (e.g., nausea, other gastrointestinal symptoms), at the discretion of the treating physician the daily dose may be given as two divided doses at 300 mg every 12 hours by mouth.~~ Imatinib potentially causes dyspepsia and gastric irritation, and it is recommended that administration of the drug occur with water (>8 ounces) and food. Imatinib should be taken in a sitting position.
- Page 42: Section 15.42 (Drug Information), the last paragraph has been revised as follows:
.....venous thrombosis, **osteonecrosis**, and laryngeal stridor/edema.
- Pages 43 and 44: Section 15.6 (Drug Information), the nursing guidelines have been revised to reflect the most current information.
- Pages 45-51: Section 16.0 (Statistical Considerations & Methodology) has been extensively revised to include the phase I portion of this study.
- Page 52: Section 17.0 (Pathology Considerations) has been expanded for clarification of tissue submissions.
- Page 53: Section 18.1 (Records and Data Collection Procedures), the following revisions have been made to the table:
- “Specimen Submission Form” has been added to the submission timetable to be submitted prior to study entry.
 - The first column under “Follow-up Material” has been deleted as follows:
~~Week before 3rd cycle and week before every other subsequent cycle~~
 - “At PROG², withdrawal, or removal due to adverse events” column has been moved to the “Active-Monitoring Phase” section.
 - “ADR/AER” column has been moved to the “At Each Occurrence” section.
 - “Linear Analogue Self Assessment (LASA),” an X has been placed in the column “At each evaluation.”
 - Reference to footnote #3 has been added to the “X” under the “At each evaluation” column for the “Nadir/Adverse Event Form.”

Page 54:

Section 18.1 (Records and Data Collection Procedures), footnotes have been revised as follows:

1. ~~See Sections 14.0 and 17.0. Pathology materials need to be centrally reviewed prior to study entry. A call needs to be made to the NCCTG pathology coordinator (507/266-0724) prior to forwarding the following material:~~

- ~~• Pathology reporting form – Brain (complete Section I only)~~
- ~~• Operative report~~
- ~~• Pathology report~~
- ~~• ALL (not selective) diagnostic slides and blocks from the primary diagnosis and any recurrent biopsies (H & E stained and smears, if available)~~

~~After the pathology materials have been reviewed, a call will be made to the institution notifying them of Dr. Scheithauer, Giannini, or Parisi's review. A copy of the Pathology Reporting Form will be faxed to the randomizing member and eligible patients can be registered. The NCCTG pathology eligibility document form will be given to the Randomization Center.~~

~~One or two slides will be identified by the reviewing neuropathologist for inclusion in the pathology files for this study. These slides are being stored for quality assurance purposes only and no future research will be conducted on them. All remaining slides will be returned to the submitting institution.~~

~~If the patient does not enter the study, all slides, blocks, and forms will be returned to the submitting institution.~~

~~If patient permission is obtained per the Informed Consent, blood samples, tissue sections, and block materials needed for study, and frozen tissues will be kept in storage for use in this study or additional approved research purposes under the supervision of the director of the NCCTG Biospecimens Resource. All paraffin tissues not required for such study will be returned to the participating investigator or institution. Frozen tissues and blood samples and derivatives will not be returned to the participating investigator or institution.~~

Footnotes 3, 4, and 5 have been added as follows:

3. **The Nadir/Adverse Event Form from the evaluation ≤ 7 days before cycle 3 (Section 4.0) for Study I patients only must be faxed within 10 days of the evaluation to 507/266-7240 (Butch Kvittem) for determination of DLT.**
4. **Only institutions who have the capability.**
5. **Post treatment samples to be drawn in Section 14.0.**

- Page 58: Section 20.0 (References), reference #49 has been revised as follows:
~~Fleming TR: (1982). One sample multiple testing procedures for phase II clinical trials. Biometrics 43:143-151.~~ **Simon R: Optimal two-stage designs for phase II clinical trials. Controlled Clinical Trials 10:1-10, 1989.**
- Appendix IA: The Phase I consent form has been added.
- Appendix I: Previous Appendix I has been relabeled Appendix IB and includes the heading **“Phase II.”**
- Appendix IA (Page 7 or 9): “Injury to your bones” has been added as an additional side effect under the “Rare” category.
- Appendix IB (Page 1 of 9): The section titled “How many people will take part in the study?” has been revised to reflect 67 patients rather than 50.
- Appendix IB (Page 7 of 9): “Injury to your bones” has been added as an additional side effect under the “Rare” category.
- Appendix IB (Page 7 of 9): A new paragraph has been added after "Rare" risks of Imatinib and before "Risks to an unborn child":

Interaction between imatinib and anti-seizure medicines:

Imatinib may interact with certain anti-seizure and other medicines that you are taking. Your doctor will need to check for this and adjust your seizure medicines while you are receiving imatinib. There is a chance that the blood levels of your anti-seizure medicine will be lowered while you are on treatment with imatinib. This could cause occasional or frequent seizures if your anti-seizure dosage is not adjusted while taking the imatinib. You should tell your doctor if you are currently taking any anti-seizure medicines.