

North Central Cancer Treatment Group

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

Addendum 8 – July 20, 2007

Summary

To date, we have accrued a total of 6 patients and observed 2 clinically relevant DLTs at dose level 1 (1000 mg/D). According to the cohort-of-3 algorithm, the next 3 patients would be placed on study at dose level -1 (800 mg/D). However, PK results from 2 of the patients at dose level 1 show serum concentrations below that necessary to inhibit PDGFR and a prior study by the NABTC indicated low serum concentrations from EIAC patients administered 1200 mg/day. Thus, it is unlikely that therapeutic serum concentrations of imatinib will be reached at 800 mg/day.

Based on all the information we have, we will add a 3rd cohort of 3 patients at dose level 1 for further DLT evaluation. If ≥ 2 DLTs are observed in this cohort, we will close the Phase I study for EIAC patients, as doses at 800 mg/day in these patients will be considered highly unlikely to be efficacious due to inadequate serum levels.

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

Title page: Revised to reflect Addendum 8 and updated NCI version date.

Section 7.0 Protocol Treatment

Pages 19-20: Due to adding a 3rd cohort of 3 patients for further DLT evaluation, Section 7.212 has been revised as follows:

7.212 The **original study designed called for the** first of cohort patients ~~will~~ **to** be treated at dose level 1 (1000mg/D, divided into b.i.d dosing p.o.). If 1 DLT **occurred** in the first 3 patients at dose level 1, an additional cohort of 3 patients ~~will were~~ **to** be enrolled at dose level 1. If DLT ~~is was~~ not observed in the first 3 patients at dose level 1 OR only 1 DLT ~~is was~~ observed in the first 6 patients at dose level 1, the next three patients ~~will would~~ **be** entered at dose level 2. If dose level 1 yielded ~~sed~~ ≥ 2 DLTs (in either the first cohort of 3 patients or 2 cohorts of 3 patients), a daily dose of 800 mg ~~will would~~ **be** evaluated ~~as stated in Section 7.213.~~

~~If 2 DLTs are observed on dose level 1, 6~~ **Six** patients ~~will would~~ **be** entered on dose level -1 (800 mg/D). If 0 or 1 DLTs ~~are were~~ observed in the 6 patients on dose level -1, then dose level -1 ~~will would~~ **be** used as the dose for the EIAC patients on study 2. If 2 or more DLTs were observed on dose level -1, the non-EIAC dose (600 mg/D) ~~will would~~ **be** used as dose for the EIAC patients in Study 2.

Page 20:

Due to adding a 3rd cohort of 3 patients for further DLT evaluation, Section 7.2121 has been revised as follows:

- 7.2121 To date, we have accrued a total of 6 patients and observed ~~3~~ **2 clinically relevant DLTs** at dose level 1 (1000 mg/D). According to the cohort-of-3 algorithm, ~~we are to put the next the next 3 patients would be placed on study on~~ at dose level -1 (800 mg/D). However, ~~we have~~ PK results from 2 of the patients at dose level 1 ~~that indicate borderline concentration levels for~~ **showed serum concentrations below that necessary to inhibiting PDGFR and PDGF-dependent signaling events; and a prior study by the NABTC indicated low serum concentrations from E1AC patients administered 1200 mg/day.** Thus, a lower dose level might not work. Results from dose finding studies of imatinib (STI-571) in recurrent malignant glioma patients receiving E1ACs suggest ~~no DLTs at dose level 1200 mg/D~~ **it is unlikely that therapeutic serum concentrations of imatinib will be reached at 800 mg/day (59).**

Based on all the information we have, we will add a 3rd cohort of 3 patients at dose level 1 for further DLT evaluation. If ≥ 2 DLTs are observed in this cohort, ~~we will evaluate DLT at dose level -1 (800 mg/D) as stated in Section 7.213~~ **we will close the Phase I study for E1AC patients, as doses at 800 mg/day in these patients will be considered highly unlikely to be efficacious due to inadequate serum levels.** If ~~no~~ 1 DLTs ~~are~~ **is** observed, we will add a 4th cohort of 3 patients to dose level 1 to evaluate for DLT. If ≥ 1 DLTs ~~are~~ **is** observed in the 4th cohort at dose level 1, a DLT rate of $\geq 33\%$ ($4+/12$) will have been observed and ~~we will evaluate DLT at dose level -1 (800 mg/D) as stated in Section 7.213~~ **the Phase I study for E1AC patients will be closed.** If no DLTs are observed **in the 4th cohort**, as stated in Section 7.213, dose level 2 (1200 mg/D) will be evaluated and additional dose escalation above 1200 mg/D will be pursued conditional on ~~number~~ **frequency** of DLTs at 1200 mg/D. ~~At dose level -1 (800 mg/D), either following the 3rd cohort or the 4th cohort of 3 patients, if a DLT rate of $\leq 33\%$ is observed, we will define an MTD of 800 mg/D. At dose level 2 (1200 mg/D), dose escalation would continue if DLT is not observed in the first 3 patients OR only 1 DLT is observed in the first 6 patients as stated in Section 7.213~~ **At dose level 2 (1200 mg/D), dose escalation would continue if DLT is not observed in the first 3 patients OR only 1 DLT is observed in the first 6 patients as stated in Section 7.213.** All dose escalation decisions will also include a review and discussion of AEs and available PK results by the discussion team and where appropriate, with NCI.

Section 10.0 Adverse Event (AE) Reporting and Monitoring

Page 29:

The Other Grade 4 or 5 Events section of Section 10.23 has been revised to reflect current electronic procedures as follows:

<p>Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report</p>	<p>Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form within 5 working days of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form.</p> <p>If an AdeERS report has been submitted, this form does not need to be submitted.</p> <p>Submit the Non-AER form electronically via the NCCTG Remote Data Entry System within 5 working days of the date the CRA is aware of the event(s) necessitating the form.</p> <p><i>Fax or mail to the NCCTG SAE Coordinator, NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax (507)284-9628.</i></p>
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Section 14.0 Translational Research and Pharmacologic Studies on Tissue Specimens

Pages 34-40:

The following revisions have been made this section to reflect current specimen submission procedures:

14.11 Methods

The NCCTG Operations Office will accession the specimens and tissues will be ~~Tissues will be logged and distributed under the direction of to the~~ Tissue Acquisition and Cellular/Molecular Analysis (TACMA)/NCCTG Biospecimens Resource **core laboratory, Stable 13-10, Mayo Clinic Rochester, for immunohistochemical staining.** The antibodies for these proteins are commercially available and conditions for their use have been published (29,15,26,6,43,44). The conditions for staining of the slides for this study will be developed and then applied in ~~the~~ **this** core tissue processing laboratory of the Mayo Clinic Cancer Center, and interpreted in consultation with Drs. Bernd Scheithauer, Caterina Giannini, and Dr. Joseph Parisi. This study is not powered based on the expected results of the translational investigations, but descriptive correlations between the expression of the proteins, specific genetic mutations, and clinical endpoints will be made

14.121 Within 30 days of registration submit the sample to the NCCTG Operations Office at the following address:

NCCTG Operations Office
 ATTN: NCCTG ~~Research Coordinator~~ **PC Office**
 RO_FF_03_24-CC/NW Clinic
 200 First Street, SW
 Rochester, MN 55905

- Page 37: 14.41 Blood for lymphocytes and buffy coat preparation will also be obtained whenever possible for correlative gene studies. This blood will be drawn before the first treatment with imatinib. For these studies, 5 ml of blood in NaHeparin will be drawn (for EBV cell line immortalization) and 20ml of blood in EDTA (for buffy coat leukocyte preparation) will be drawn. Blood should be mailed **the same day it is drawn** per kit instructions provided in the kit (see Section 14.42) to Mayo Central Laboratory for Clinical Trials (MCLCT), ~~as soon as is practical following procurement of the sample.~~ The studies will be performed in the laboratory of Dr. Robert Jenkins.
- 14.42 Kits for shipment of the blood samples will be supplied through MCLCT. Participating institutions may obtain kits by faxing the MCLCT Fax Supply Order Form (found in the Forms Packet) to 1-877-486-0338. Allow at least two weeks to receive the kits. ~~MCLCT will not be able to forward kits to you by express mail.~~ **Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. NCCTG will not cover the cost for rush delivery of kits.**

Page 40: 14.59c Summary of Specimen Processing

Mail according to the following schedule. Kits, where indicated, are provided as indicated from Mayo Clinical Laboratories Clinical Trials Facility (MCLCT). Participating institutions may obtain kits by faxing the MCLCT Fax Supply Order Form (found in the Forms Packet) to 1-877-486-0338. Allow at least two weeks to receive the kits. ~~MCLCT will not be able to forward kits to you by express mail.~~ **Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. NCCTG will not cover the cost for rush delivery of kits.**

Page 40: The following revision has been made to the table in Section 14.6:

Peripheral Blood Lymphocytes	Correlative Gene Studies	14.4	Before first treatment of Imatinib	Samples may be sent Monday through Thursday. Samples should be shipped after the blood draw per kit instructions to MCLCT.
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