

North Central Cancer Treatment Group

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

Addendum 4 – December 23, 2005

**Summary**

- Study 3 is being newly added in order to collect pilot data on recurrent patients that have had >2 prior therapies that have not been traditionally eligible for recurrent glioma trials.
- Alfred F. Furth, M.S. replaces Matthew J. Maurer, M.S. as statistician.
- Clarification has been made to the required characteristics for Studies 1, 2, and 3 to reflect that the patient must have failed surgery/radiotherapy and TMZ or nitrosourea based therapy.
- The pregnancy test is only needed at baseline. Therefore, the test schedule and consent forms have been revised.
- Section 10.3 (Adverse Event [AE] Reporting and Monitoring) has been revised to reflect a change in the NCCTG routine adverse event reporting requirements.
- Editorial/administrative changes.

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

Title page: Now reflects Addendum 4 and revised NCI version date. Alfred F. Furth, M.S. has replaced Matthew J. Maurer, M.S. as statistician.

Page 2: The fax number for the NCCTG Research Base Quality Control Specialist has been revised to read 507/~~284-1902~~ **266-7240**.

The name of the NCCTG Research Base Protocol Development Coordinator has been changed from Lori ~~Kelly~~ to **Bratvold**.

The NCCTG Research Base Protocol Administration Specialist is newly added.

Page 5: Study 3 has been newly added to the Schema in order to collect pilot data on recurrent patients that have had >2 prior therapies.

Pages 5-61: Due to the addition of Study 3 to the Schema, the entire protocol has been repaginated.

Page 13: New Section 2.13 (Goals) has been added to reflect the addition of Study 3 as follows and all remaining sections have been renumbered:

**Study 3: To acquire pilot data on a patient group not traditionally eligible for recurrent oligodendroglioma and mixed oligoastrocytoma clinical trials (those having >2 prior chemotherapy regimens or 2 prior chemotherapy regimens for recurrent/progressive disease). The pilot data will be compared with the traditional recurrent oligodendroglioma and mixed oligoastrocytoma patients for planning of eligibility in future trials.**

Sections 2.14, 2.15, and 2.16 (Goals) have been revised to include study 3 as follows:

Studies 1 ~~and~~ 2, **and 3**:

Page 14: Sections 2.24 and 2.25 (Goals) have been newly added to reflect the addition of Study 3.

Section 3.0 (Patient Eligibility) has been revised to reflect the addition of Study 3 as follows:

3.1 Required Characteristics for Study 1

3.11 Currently on anticonvulsants which can induce cytochrome p450 (phenytoin, carbamazepine, barbiturates, primidone and if unsure contact study chair).

**3.12 ≤2 prior chemotherapy regimens (with maximum of 1 prior chemotherapy regimen for recurrent disease).**

3.2 Required Characteristics for Study 2

3.21 On or off anticonvulsants.

**3.22 ≤2 prior chemotherapy regimens (with maximum of 1 prior chemotherapy regimen for recurrent disease).**

3.3 Required Characteristics for Study 3

**3.31 On or off anticonvulsants.**

**3.32 >2 chemotherapy regimens or 2 prior chemotherapy regimens for progressive/recurrent disease.**

Due to new Section 3.3 being added, all remaining sections have been renumbered.

Page 15: Section 3.4, previously Section 3.3, the heading has been revised to include Study 3 as follows:

Required Characteristics for ~~Both~~ Studies 1, ~~and~~ 2, **and 3**

Page 15: Section 3.47 has been revised for clarification as follows:

~~Prior surgery, radiotherapy (RT), temozolomide, nitrosourea based therapy, or temozolomide chemotherapy regimen failed~~ **Must have failed surgery/radiotherapy (RT) and Temozolomide or nitrosourea based therapy.**

Page 16: Previous Section 3.39i has been deleted as follows:

~~≤2 prior chemotherapy regimens.~~

Section 3.5, previously Section 3.4, the heading has been revised to include Study 3 as follows:

Contraindications for ~~Both~~ Studies 1, ~~and 2,~~ **and 3**

Page 17: Section 4.0 (Test Schedule), the “X” has been removed from the column “≤7 days before each cycle” for the serum pregnancy test as the pregnancy test is only needed at baseline.

Section 4.0 (Test Schedule), footnote #2 has been revised to reflect that the serum pregnancy test is only needed at baseline as follows:

For women of childbearing potential only. Must be done ≤7 days prior to registration; ~~and every four weeks during treatment.~~

Section 4.0 (Test Schedule), footnote #6 is newly added for clarification that the pharmacologic studies/laboratory correlates are for Studies 1 and 2 only.

Page 18: Section 5.1 (Grouping Factor) has been revised to reflect the addition of Study 3 as follows:

2-EIAC vs. 2-Non EIAC vs. 1 **vs. 3-EIAC vs. 3-Non EIAC** (see Appendix IIIB for list of EIAC and non-EIAC agents).

Section 6.12 (Registration/Randomization Procedures), the heading has been revised to reflect the addition of Study 3 as follows:

6.12 Studies 1, ~~and 2,~~ **and 3**

Page 18: Section 6.13 (Registration/Randomization Procedures), the opening paragraph has been revised for clarification as follows:

Randomization Center will register patients separately to the translational research component of this study (**Studies 1 and 2 patients only**) (see Section 14.0).

Page 19: Section 7.1 (Protocol Treatment), the first sentence has been revised to reflect the addition of Study 3 as follows:

Studies 1, ~~and 2,~~ **and 3**: Cycles will be defined...

Page 21: Section 7.3 (Protocol Treatment) has been revised to reflect the addition of Study 3 as follows:

7.3 Treatment Schedule for **Studyies 2 and 3**

\*Studyies 2 and 3: Arms A and D will not open until a dose level has been established in Study 1

**Studyies 2 and 3**

<b>Arm</b>	<b>Dose</b>	<b>Route</b>	<b>Day</b>	<b>Retreatment</b>
<b>A and D</b> (EIACs*)	Not yet open to patient accrual	P.O.	Twice daily	Every 28 days (continuous without break)
<b>B and E</b> (non -EIACs*)	Imatinib 300 mg	P.O.	Twice daily	Every 28 days (continuous without break)

Page 23: Section 8.2 (Dosage Modification Based on Adverse Events), the heading has been revised to reflect the addition of Study 3 as follows:

**Studyies 1, ~~and 2,~~ and 3**

Page 24: Section 9.1 (Ancillary Treatment), the fourth sentence has been revised due to the addition of Study 3 as follows:

If patients are not receiving EIACs (Arms **B and E**), and it is necessary to switch anticonvulsant medications, they should be placed on another non-EIAC if at all possible.

Page 28: Section 10.22 (Adverse Event (AE) Reporting and Monitoring), the first paragraph has been revised for clarification as this reporting affects both studies 2 and 3 as follows:

**Studyies 2 and 3**: Phase 2 and 3 Trials....

Pages 29-30: Sections 10.312 and 10.313 have been revised to reflect a change in the NCCTG routine adverse event reporting requirements as follows:

10.312 Grade 3, ~~and 4, and 5~~ AEs ~~and deaths within 30 days of the patient's last treatment~~, regardless of attribution to the study treatment or procedure, ~~with the exception of signs or symptoms definitely related to the patient's disease or disease progression.~~

**10.313 Grade 5 AEs (Deaths)**

**10.3131 Any death within 30 days after the patient's last study treatment regardless of relationship to study treatment or procedure.**

10.3132 ~~10.313~~ Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

Page 32: Section 12.0 (Descriptive Factors), the heading has been revised to reflect the addition of Study 3 as follows:

Descriptive Factors (for ~~both~~ studies 1, 2, and 3)

Page 33: Section 13.2 (Treatment/Follow-up Decision at Evaluation of Patient), the heading has been revised to reflect the addition of Study 3 as follows:

**Studies 2 and 3**

Section 14.0 (Translational Research), the heading has been revised for clarification as follows:

Translational Research and Pharmacologic Studies on Tissue Specimens – **Studies 1 and 2** (Optional but strongly encouraged due to nature of this investigation)

Page 46: Section 16.1 (Statistical Considerations & Methodology) has been revised to reflect the addition of Study 3 as follows:

Overview: This ~~study~~ **protocol** consists of ~~two~~ **three** clinical trials in patients with oligodendroglioma or mixed oligoastrocytoma. Study 1 is a phase I trial designed to establish the maximum-tolerated dose (MTD) of imatinib when given to patients who are receiving enzyme-induced anticonvulsants (EIACs). Study 2 is a single-stage, phase II trial designed to assess (a) the ability of imatinib to extend progression-free survival in oligodendroglioma and mixed oligoastrocytoma, as measured by 6-month progression-free survival from study registration, (b) the toxicities associated with this agent, and (c) associations between clinical variables, 1p/19q alterations, and various parameters related to  $\alpha$ PDGFR gene amplification. It uses a single-stage, Simon MinMax phase II design with an interim analysis. **Study 3 is a pilot study designed to obtain data with respect to survival, progression-free survival, response rate, and toxicity associated with Imatinib in patients with >2 prior chemotherapy regimens (any combination adjuvant + recurrence) or 2 regimens given for recurrent/progressive disease.** ~~Studies 2 and 3~~ will initially open to patients not on EIACs and will open to patients on EIACs after the conclusion of Study 1.

Page 46: Previous Section 16.11 (Study 1) has now become Section 16.2 due to the inclusion of Study 3.

Previous Section 16.12 (Study 2) has now become Section 16.3 due to the inclusion of Study 3.

Page 47: Previous Section 16.2 (Study Design) has now become Section 16.35 due to the inclusion of Study 3.

Page 49: Previous Section 16.3 (Analysis Plans) has now become Section 16.36 due to the inclusion of Study 3 and has been revised as follows:

Analysis Plans: All evaluable patients (see Section ~~16.21~~ **16.351**) will be used for these analyses.

Previous Section 16.32 (Secondary Efficacy Analyses) has now become Section 16.362 due to the inclusion of Study 3.

Page 50: New Section 16.37 (Adverse Event Monitoring) has been added due to the inclusion of Study 3.

Pages 51-52: New Section 16.4 (Study 3) has been added to reflect the inclusion of Study 3.

Page 52: Previous Section 16.34 (Translational Research Endpoints) has now become Section 16.5 due to the inclusion of Study 3 and has been revised as follows:

Translational Research Endpoints (**Studies 1 and 2**): Exploratory...

Page 51: Previous Section 16.4 (Toxicity Monitoring) has been deleted and has been replaced with New Section 16.37 (Adverse Event Monitoring) due to the inclusion of Study 3.

Page 52: Previous Section 16.5 (Routine Monitoring) has now become Section 16.6 due to the inclusion of Study 3.

Previous Section 16.6 (Clinical Data Update System [CDUS]) has now become Section 16.7 due to the inclusion of Study 3.

Previous Section 16.7 (Subset Analyses for Women and Minorities) has now become Section 16.8 due to the inclusion of Study 3.

Page 53: Section 16.83, previously Section 16.73, a new last sentence has been added to reflect the inclusion of Study 3 as follows:

Since (a) women typically comprise 40% of this patient population and (b) racial/ethnic minorities have constituted about 7% of patients enrolled in prior NCCTG trials, the number of women and minorities that will enroll in this trial is expected to be about 27 and 5, respectively. The expected accrual by gender and racial/ethnic group is summarized in the following table. **Total sample size by study is 24 expected for Study 1, 43 for Study 2, and 20 for Study 3 for a total sample size of 87.**

Page 53: The following revisions have been made to the Ethnic table in Section 16.83 due to the inclusion of Study 3 as follows:

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	10	31	0	41
Not Hispanic or Latino	2327	6039	0	8366
Unknown	0	0	0	0
<b>Ethnic Category: Total of all subjects*</b>	<b>2427</b>	<b>6340</b>	<b>0</b>	<b>8767</b>
Racial Category				
American Indian or Alaskan Native	0	1	0	1
Asian	0	0	0	0
Black or African American	1	2	0	3
Native Hawaiian or other Pacific Islander	0	0	0	0
White	2326	6037	0	8364
More than one race	0	0	0	0
Unknown	0	0	0	0
<b>Racial Category: Total of all subjects*</b>	<b>2427</b>	<b>6340</b>	<b>0</b>	<b>8767</b>

Page 56: Footnote #5 has been revised as follows due to the inclusion of Study 3:

Post treatment samples to be drawn in Section 14.0 (Studies 1 and 2 only)

Appendix IA: The second row of the table on page 2 has been revised to delete the repeat pregnancy test as follows as this is not needed:

Pregnancy test (if applicable; ~~and repeated every 4 weeks~~)

Per Addendum 2, “Tumors in the urinary system or reproductive organs have also been reported in animals” was added to the “What are the risks of the study?” section on page 7 for imatinib. At that time, this was not added to the correct location. It should have been added after the “Interaction between imatinib and anti-seizure medicines” section and has now been relocated.

Appendix IB: The second row of the table on page 2 has been revised to delete the repeat pregnancy test as follows as this is not needed:

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