

North Central Cancer Treatment Group

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

For any communications regarding this protocol,
please call the protocol resource person on the following page.

Study Chairs: Kurt A. Jaeckle, MD (Research Base)*
Mayo Clinic
200 First Street, SW
Rochester, MN 55905
507/284-1370
507/284-5280 (FAX)
jaeckle.kurt@mayo.edu
Patrick J. Flynn, MD (NCCTG)

Study Co-chairs: Robert Jenkins, MD, Ph.D. (Research Base)
Bernd Scheithauer, M.D. (Pathology - Mayo)

Statistician: S. Keith Anderson, M.S. (507-284-8803)

DCTD Supplied Investigational Agents: Imatinib (Gleevec; STI571) (NSC 716051)

*Investigator having NCI responsibility for this protocol.

<u>Document History</u>	<u>Effective Date</u>	<u>Document History</u>	<u>Effective Date</u>
Activation	June 20, 2003	Addendum 14	April 15, 2011
Addendum 1	December 3, 2004	Addendum 15	December 23, 2011
Addendum 2	December 3, 2004		
Addendum 3	July 8, 2005		
Addendum 4	December 23, 2005		
Addendum 5	October 6, 2006		
Addendum 6	January 19, 2007		
Addendum 7	July 20, 2007		
Addendum 8	July 20, 2007		
Addendum 9	September 14, 2007		
Addendum 10	May 8, 2009		
Addendum 11	July 24, 2009		
Addendum 12	September 11, 2009		
Addendum 13	April 16, 2010		

<u>Study Participants</u>	<u>Date Activated</u>
Entire NCCTG	June 20, 2003

NCI Version Date: December 8, 2011

Protocol Resource

	Questions:	Contact Name:
Add 4,13	Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events	Carla Hilton NCCTG <i>Research Base</i> Quality Assurance Specialist Phone: 507/284-1370 Fax: 507/284-1902 e-mail: hilton.carla@mayo.edu
Add 1 Add 10	Drug administration, infusion pumps, nursing guidelines	Marcia Salayi, R.N. NCCTG <i>Research Base</i> Nurse Phone: 507/284-2459 Wanda DeKrey, R.N., OCN NCCTG Member Nurse Phone: 701/777-4862
Add 14	Forms completion and submission	Carlene Dillavou NCCTG Member Clinical Research Associate Phone: 515/244-7586 Fax: 515/244-3037 e-mail: cdillavou@iora.org
Add 1,4,5, 10,11, 14,15	Protocol document, consent form, Regulatory issues	Sanna L. McKinzie NCCTG <i>Research Base</i> Research Protocol Specialist Phone: 507/538-6646 Fax: 507/284-5280 e-mail: mckinzie.sanna@mayo.edu
Add 6,10	Paraffin-embedded Tissue Pathology	Helen J. Tollefson NCCTG <i>Research Base</i> Pathology Coordinator Phone: 507/266-0724 Fax: 507/284-9628 E-mail: tollefson.helen@mayo.edu
Add 6,10 Add 4,7,14	Non-paraffin Biospecimens	Roxann Neumann, RN, BSN, CCRP NCCTG Biospecimen Resource Manager Phone: 507/538-0602 Fax: 507/284-8105 Email: neumann.roxann@mayo.edu

* No waivers of eligibility per NCI

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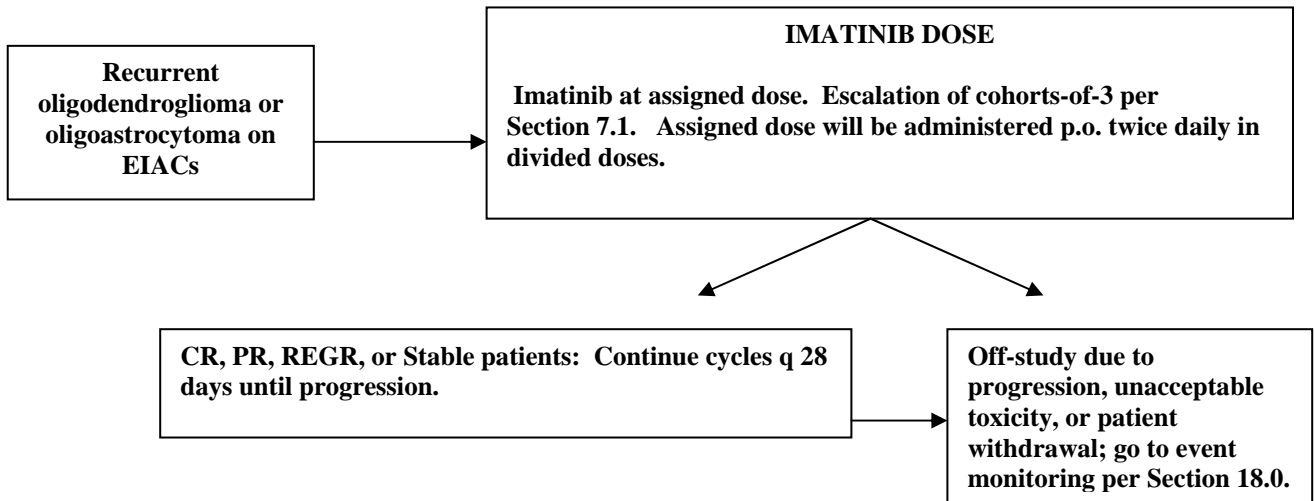
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SCHEMA

Study 1 only: Prior to discussing protocol entry with the patient, call the Random Center (507/284-4130) for dose level and to ensure that a place on the protocol is open to the patient

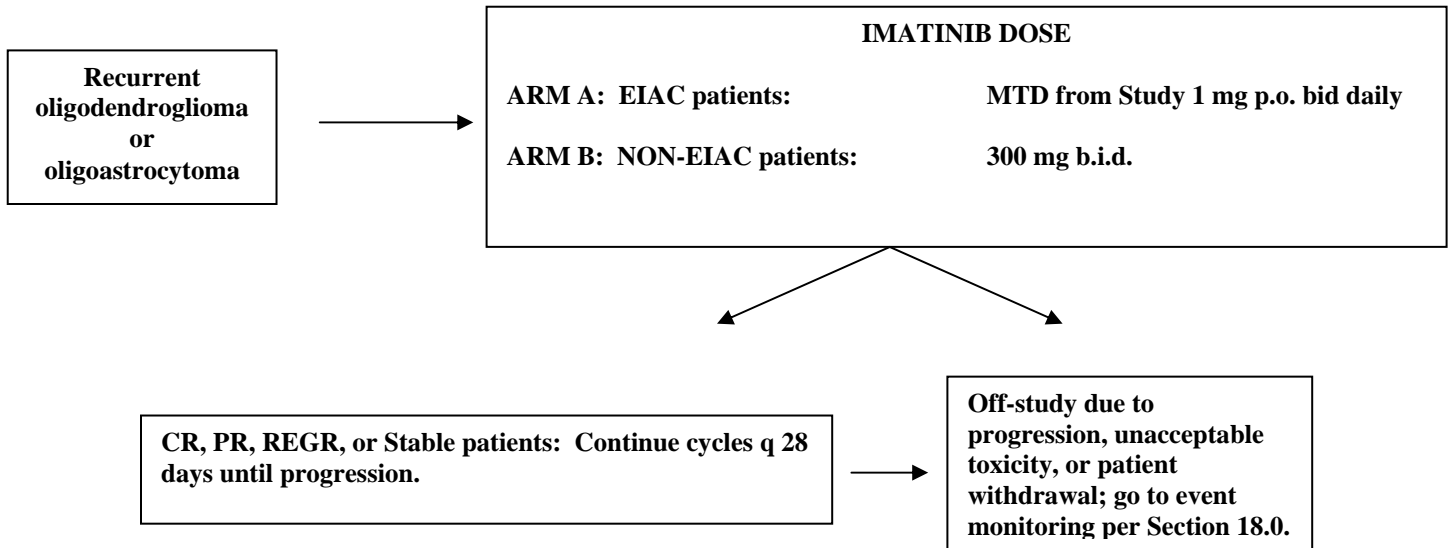
Study 1

Phase I trial in recurrent glioma patients on enzyme-inducing anticonvulsants



Study 2

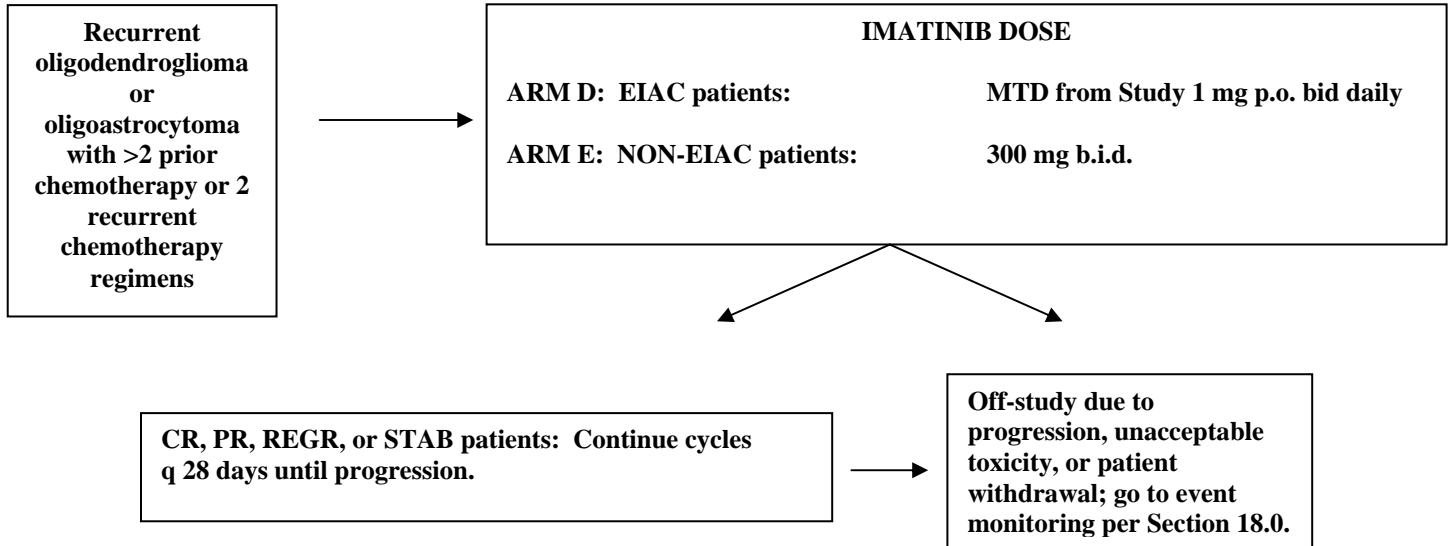
Phase II trial in recurrent glioma patients on or off enzyme-inducing anticonvulsants



Study 3

Add 4

Phase II trial in recurrent glioma patients on or off enzyme-inducing anticonvulsants having >2 prior chemotherapy regimens or 2 prior chemotherapy regimens for recurrent/progressive disease



Key: EIAC = p 450 microsomal enzyme-inducing anticonvulsants; CR = complete response; PR = partial response; REGR = regression

Generic name:	Imatinib (STI 571)
Brand name:	Gleevec
Mayo abbreviation:	STI571

1.0 Background

1.1 Introduction

Although oligodendrogliomas represent only 5-10% of gliomas, they are of particular interest due to their chemosensitivity to alkylating chemotherapy regimens, such as procarbazine, CCNU, and vincristine (1). Oligodendrogliomas with genetic alterations in chromosomes 1p or 19q appear more responsive to such therapy (2,3), but unfortunately, almost all patients still have recurrence after an initial response. Although 70% of patients with anaplastic oligodendrogliomas respond to initial chemotherapy, only 20% remain progression free for 2 years (4).

At recurrence, salvage treatment produces response rates of approximately 40%, but of relatively short duration, with overall median time to progression (TTP) of 6.7 mo., and median overall survival of 10 months (5). There is no consensus on a standard therapy for patients with recurrent disease. Salvage therapy has typically included nitrosoureas, temozolomide, platinum-based therapies, or others, but to date, there is no conclusive evidence that any therapeutic strategy has produced durable patient benefit in recurrent oligodendrogliomas. Newer therapeutic approaches are clearly needed.

Recent investigations have identified genetic markers of potential prognostic significance in gliomas including oligodendrogliomas, including 1p/19q, p53, and PTEN/MMAC mutations; EGFR and PDGFR amplification, and MIB-1 expression. There is potential for newer therapeutic agents, and in particular signal transduction inhibitors, to target these molecular alterations. There is increasing evidence that activation of certain tyrosine kinases may play a role in the pathogenesis of several tumors, including oligodendrogliomas. Preliminary data suggests that platelet-derived growth factor receptor-alpha (α PDGFR) overexpression may correlate with progression of oligodendrogliomas (6). Agents which block this signaling pathway would potentially have therapeutic promise in oligodendroglioma treatment. Imatinib (Gleevec; STI571; CGP57148B), a derivative of the 2-phenylaminopyrimidine series of protein tyrosine kinase (TK) inhibitors, has been shown to be a potent inhibitor of signaling by the platelet-derived growth factor receptor kinase, as well as the c-kit and bcr-abl kinases (7,8,9). This agent is also capable of inhibiting the proliferation in vitro and in vivo of the U343 and U87 glioma cell lines, both of which express PDGF receptors (10).

It is our hypothesis that inhibition of tyrosine kinases including the α PDGFR kinase, by imatinib will arrest the growth of recurrent, progressive oligodendrogliomas. To test this hypothesis, we propose a Phase II trial of imatinib in recurrent oligodendroglioma patients that will incorporate key translational studies. These studies will include: 1) correlation of α PDGFR gene amplification, chromosomal 1p and 19q alterations, and clinical outcome endpoints, and 2) pharmacokinetic studies of steady state levels of the parent compound imatinib and N-desmethyl derivative in patients receiving enzyme inducing anticonvulsants (EIA) and those not receiving EIA. Attempts will be made to relate these steady state levels to clinical outcome measures.

The genetic studies will evaluate the frequency of amplification of the α PDGFR gene, and determine if gene amplification is associated with the absence of LOH of chromosomes 1p or 19q. Studies will attempt to demonstrate that amplification of the α PDGFR gene is correlated with overexpression of the receptor protein, and evaluate whether overexpression is observed in tumors that lack gene amplification. The tumors will also be studied for expression of other potential targets of STI571 (β PDGFR and ckit), and perform a preliminary investigation which correlates receptor overexpression of α PDGFR gene amplification with levels of additional activated downstream effectors (Erk1/2, AFX, and p27^{kip1}). The laboratory correlates of this study may provide a set of molecular phenotypic markers that can be used to identify subsets of oligodendroglioma patients that might preferentially respond to imatinib.

Quality of Life: For purposes of assessing Quality of Life (QOL) in this study, we plan to utilize the Linear Analogue Self Assessment (LASA) questionnaire (Appendix VII).

1.2 Rationale for Translational Studies:

1.21 Platelet derived growth factor (PDGF) and pathogenesis of oligodendroglioma

Platelet-derived growth factor (PDGF) has mitogenic and chemotactic properties which affect cells including central nervous system glia (11). It is likely that signals generated by receptor-alpha (α PDGFR) contribute to the pathogenicity of oligodendrogliomas. α PDGFR is a transmembrane receptor tyrosine kinase that is activated by binding of PDGF or other specific ligands to the ectodomain. This results in activation of the receptor kinase, autophosphorylation, and stimulation of downstream signal transduction pathways that promote cell proliferation and survival. Recent work in our Mayo laboratories has documented amplification of the α PDGFR gene in 4/41 anaplastic oligodendrogliomas and in one oligoastrocytoma, but in none of 167 grade 3 and 4 astrocytomas (12). The frequency of gene amplification in oligodendroglioma exceeds that reported previously in high grade astrocytic tumors (13,14). Expression of the α PDGFR and β PDGFR and PDGF B chain has been reported in 17 of 17 oligodendrogliomas, and in the PDGF A chain in 16 of these 17 tumors (15). These results implicate a potential autocrine loop stimulated by interaction of PDGF and its receptor (15). Overexpression of the alpha receptor subunit in malignant gliomas, coupled with constitutive expression of PDGF A and B ligands in the higher grade tumors may result in tumor progression (16,17). Oligodendrogliomas with a high level of PDGF B chain demonstrate high proliferative activity (18). In another study, 86% of oligodendrogliomas expressed components of the GRO1 - PDGF pathway (GRO1 protein, its receptor CXCR2, PDGF a chain, PDGF α receptor); in contrast, no diffuse astrocytomas and 18% of glioblastomas showed similar expression. Intact function of this pathway was a requirement of proliferation of the oligodendroglioma cells (6).

In contrast, amplification of the epidermal growth factor receptor (EGFR) gene, which is found in as many as 40% of grade IV astrocytomas, is rarely seen in oligodendrogliomas (19,20). Studies have shown that amplification of the gene for either EGFR or α PDGFR in the grade IV astrocytomas results in overexpression of the corresponding receptor (21). By analogy, amplification of the α PDGFR genes in anaplastic oligodendroglioma is likely to result in receptor overexpression, but this has yet to be confirmed. Since most oligodendrogliomas express α PDGFRs, it is likely that there is autocrine stimulation due to the coexpression of the receptor ligands PDGF or EDGE-A (6,15). The fact that signals promote the growth and survival of oligodendroglioma cells is consistent with the critical role that this receptor plays in the regulation of oligodendroglial cell proliferation during development (22,23). α PDGFR can signal multiple downstream effectors including Ras and phosphatidylinositol-3-kinase (PI3K) which in turn stimulate effectors which induce mitogenesis and/or inhibition of apoptosis (24,25). Activation of these downstream effectors may contribute to the aggressive phenotype of recurrent or progressive oligodendrogliomas. Signaling through the Ras pathway can also induce phosphorylation and activation of Erk (or MAPK). This pathway links receptor tyrosine kinase activation to downstream serine/threonine phosphorylation events regulating cellular differentiation and proliferation. Anaplastic progression from low grade to anaplastic oligodendrogliomas is associated with an increase in cells expressing active Erk/MAPK (26).

A downstream target of the PI3K pathway is the AKT kinase, which promotes cell proliferation and resistance to apoptosis (25,27). One mechanism by which AKT promotes cell proliferation is suppression of the cyclin-dependent kinase inhibitor, p27^{kip1} (28). Cavalla et al have recently reported that patients with oligodendrogliomas that express low levels of p27^{kip1} have a poorer prognosis than patients whose tumors express high levels (29).

AKT appears to inhibit p27^{kip1} expression through the phosphorylation and inactivation of the AFX transcription factor, a member of the forkhead family of transcription factors that also includes FKHR and FKHR-L1 (28,30,31). The fact that decreased expression of p27^{kip1} contributes to the growth of oligodendrogliomas is consistent with the developmental biologic observation which shows correlation of increased p27^{kip1} expression with differentiation and growth arrest of oligodendroglial cells (23). These observations suggest that in a subset of oligodendrogliomas, signals generated by the α PDGFR promotes the growth and survival of the tumor cells through the constitutive activation of Ras, PI3K and other downstream effectors.

There is little data relating amplification of α PDGFR gene amplification or activation of the downstream effectors in oligodendrogliomas with clinical tumor responsiveness or prognosis. About 70% of oligodendrogliomas exhibit loss of heterozygosity (LOH) of chromosomes 1p and 19q (32,20,2). This strongly suggests that mutation of as yet unidentified tumor suppressor genes located on these chromosomes contribute to the pathogenesis of oligodendrogliomas. In addition, the LOH of the chromosome 1p markers is strongly associated with improved prognosis and increased sensitivity of the tumor to standard chemotherapeutic agents (12,1). Interestingly, LOH of chromosome 1p was seen in only 1/6 of the oligodendroglial tumors with amplification of the α PDGFR gene (12). This observation raises the possibility that tumors with amplification of the α PDGFR gene are less likely to have the chromosome 1p deletion and therefore will be less likely to respond to standard chemotherapy. If so, then assays for constitutive activation of the downstream effectors of the α PDGFR may also correlate with resistance to standard therapies. Conversely, α PDGFR amplification or activation of the effectors may identify a subset of tumors more likely to respond to inhibitors of α PDGFR signaling.

1.22 Rationale for imatinib in human recurrent oligodendrogliomas

Imatinib is a derivative of the 2-phenylaminopyrimidine series of protein tyrosine kinase (TK) inhibitors. Imatinib inhibits Abl tyrosine kinases including c-Abl, v-Abl and TEL-Abl tyrosine kinases (8,9). Imatinib also inhibits activation of stem cell factor (SCF) – dependent c-kit autophosphorylation in myeloid (M07e) and SCLC H526 cell lines with an IC50 of 0.1 μ M (33,34). Imatinib also inhibits PDGF receptor associated tyrosine kinases and proliferation of glioblastoma cell lines U343 and U87, which show expression of PDGF receptor (10). Anti-tumor effect has been also shown following administration of imatinib in nude mice U343 and U8 glioblastoma xenografts which expressed the PDGF receptor (10).

Imatinib-mediated apoptosis has been shown to correlate with inhibition of stat-5 and MAPK activation, without prevention of activation of jak / stat pathways (interferon α , IL 3/GM-CSF) (7). Inhibition of BCR/ABL kinase activity with imatinib also results in an increase in p27^{kip1} via PI3K. Normally, BCR/ABL suppresses p27 (Kip1) protein through this mechanism, leading to accelerated entry into S-phase, which may be blocked by imatinib (35).

Based on the mechanisms of action of imatinib, and these preliminary observations in oligodendrogliomas that implicate the role of the receptors and downstream signaling pathways, we feel that there is strong evidence supporting a clinical study of imatinib in treatment of recurrent oligodendroglioma patients.

1.23 Rationale for different dosing schemes for patients receiving or not receiving anticonvulsants

Oligodendroglioma patients frequently have seizures as a clinical manifestation of their disease, and may be receiving enzyme-inducing anticonvulsant therapy (EIAC), such as phenobarbital, carbamazepine, and phenytoin. Induction of metabolism of chemotherapeutic agents via co-administration of anticonvulsants has now been shown to affect the maximum tolerated dose (MTD) of such agents, which potentially in turn might influence outcome if the response is dose dependent. Several chemotherapeutic agents which of interest in the treatment of gliomas are partially metabolized via the P450 microsomal enzyme system, including, but not limited to, irinotecan, taxanes, OSI-774, ZD1839, and imatinib. These enzyme-inducing anticonvulsants induce P450 cytochrome enzymes such as CYP3A4. Imatinib is primarily metabolized via the CYP3A4 cytochrome P450 enzyme, and to lesser extent, CYP1A2, CYP2D6, CYP2C9, and CYP 2C19 (36). Genetic variations in enzyme level in different patients, independent of EIAC administration, may also result in variations in serum levels after drug administration. As a result, it is necessary to evaluate the effect of (EIAC) on serum levels of imatinib and its major active metabolite, the N-desmethyl piperazine derivative. There are to date few studies which have correlated the steady state levels of imatinib and its metabolites with clinical endpoints, or with molecular surrogate markers of biologic effect in patients with gliomas.

1.3 Pharmacology and Drug activity

1.31 Pharmacokinetics and Metabolism

Imatinib inhibits the bcr-abl, c-kit and PDGF tyrosine kinases, but does not significantly inhibit the EGF receptor, the VEGF receptors Flt-1 and Kdr, Src, cMet kinases, or serine-threonine kinases. (33,37). There is evidence that imatinib inhibits PDGF receptor autophosphorylation, TEL-PDFG receptor, c-fos transcript expression, and PDGF-mediated mitogen activated protein (MAP) kinase. Observed IC₅₀ values have ranged from 0.1-1 μ M (38).

Imatinib is well absorbed after oral administration. In leukemia (CML) patients, mean maximum plasma concentrations (C_{max}) following continuous single daily oral doses ranged from 71.5 (25 mg) and 3395.0 ng/ml (600 mg) on Day 1; at steady state, levels were between 179.3 (25 mg) and 3925.0 ng/ml (600 mg). C_{max} is observed within 2-4 hours of dosing. The terminal half-life ($t_{1/2}$) of imatinib is 10-23 hours, and at steady state there is a 2-3 fold accumulation. Mean bioavailability for the capsule form is 98%. Following oral dosing in healthy individuals, the elimination half-lives of imatinib and N-desmethyl metabolite were approximately 18 and 40 hours, respectively. Mean imatinib AUC increased proportionally with increasing dosage in dose ranges of 25-1000 mg. There was no significant change in the pharmacokinetics of imatinib with repeated dosing, and accumulation is 1.5-2.5 fold at steady state with daily dosing. Imatinib is approximately 95% protein bound, mostly to

albumin and α 1-acid glycoprotein. The increase in mean plasma AUC values is proportional to the administered dose up to 600 mg/day. The mean plasma AUC₍₀₋₂₄₎ at steady state following a continuous once daily oral dose of 600 mg is 59535 ng/h/mls, and increases in mean plasma AUC are noted to be proportional to administered dose to this level. The plasma AUC for the metabolite is 15% of that of imatinib. The pharmacokinetic data suggest that once daily dosing is reasonable. Data also suggests that calculation of dosing based on body surface area is not necessary, as adjustment for body size did not affect inter-patient AUC variation in a significant way.

Imatinib is primarily metabolized in the liver via the cytochrome p450 microsomal enzyme CYP3A4. Other enzymes, including CYP1A2, CYP2D6, CYP2C9, and CYP2C19, also provide minor metabolism. In humans, the N-demethylated piperazine derivative (CGP 74588) is the main circulating active metabolite, which is similar in potency to imatinib. The mean T_{1/2} of the metabolite ranges from 14-31 hours and from 15-58 hours on Day 1 and at steady state, respectively. There is a 4-7 fold accumulation of metabolite at steady state following once daily dosing. After hepatic metabolism, the primary route of excretion is gastroenteric. After oral administration of 14C-labelled imatinib, approximately 81% was eliminated within 7 days, in feces (68% of dose) and urine (13%). Approximately 25% of the dose was parent drug (5% urine, 20% feces). Studies showed that clearance of imatinib in a 50 year old patient weighing 50 kg was expected to be 8 L/h, while for a 50 year old patient weighing 100 kg the clearance increased to 14 L/h. It was not felt that interpatient variability of clearance warrants initial dose adjustment based on body weight or age but that dose adjustment would be made based on observed toxicity. To date, there have not been pharmacokinetic studies in patients with hepatic or renal disease, or pediatric patients. However, imatinib and its metabolites are not significantly excreted via the kidney.

1.32 Drug interactions and co-administration of EIACs and other compounds affecting the cytochrome p450 enzyme CYP3A4

Imatinib metabolism is influenced by concomitant administration of CYP3A4 inhibitors or CYP3A4 substrates. There was a significant increase in exposure to imatinib (mean C_{max} and AUC increased by 26% and 40%, respectively) in healthy subjects when ketoconazole (a CYP3A4 inhibitor) was administered with imatinib, and induction by enzyme inducing anticonvulsants, including phenytoin, phenobarbital, and carbamazepine is likely. An ongoing dose escalation study in patients with recurrent glioma receiving EIACs is being conducted by the North American Brain Tumor Consortium (NABTC), but data are currently not yet available; the preliminary MTD for patients not on EIACs with recurrent gliomas is 600 mg/D (personal communication, Patrick Y. Wen, MD).

A patient on chronic therapy with phenytoin given 350 mg/D of imatinib had an AUC₀₋₂₄ of about one fifth of the typical AUC₀₋₂₄ of 20 µg•h/mL. Human liver microsome studies demonstrated that imatinib is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with K_i values of 27, 7.5, and 8 µM, respectively. Imatinib is likely to increase the blood level of drugs that are substrates of CYP2C9, CYP2D6 and CYP3A4/5.

Other inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin) may decrease metabolism and increase imatinib concentrations. Conversely, medications that induce CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St. John's Wort) may increase metabolism and decrease imatinib plasma concentrations.

Imatinib can also increase levels of simvastatin, cyclosporine, pimozide, triazolobenzodiazepines, dihydropyridine calcium channel blockers and certain HMG-CoA reductase inhibitors. Because warfarin metabolized by CYP2C9, close follow-up of prothrombin time and INR is warranted, with consideration given to alternative anticoagulant therapy.

Further information regarding imatinib can be obtained in the Investigator's Brochure and prescribing information.

1.33 Preclinical studies

1.331 In vitro studies

Imatinib mesylate inhibits protein-tyrosine kinases including the Bcr-Abl tyrosine kinase, which is associated with the Philadelphia chromosome in chronic myeloid leukemia (CML). In Bcr-Abl-positive cell lines and leukemic cells from patients with Ph + CML, inhibition of proliferation and induction of apoptosis has been observed. Inhibition of colony formation from peripheral blood and bone marrow cells from CML patients have also been noted. Imatinib also inhibits receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-Kit, and also inhibits PDGF- and SCF-mediated cellular events.

1.332 Animal models

Imatinib has shown inhibition of tumor growth of Bcr-Abl transfected murine myeloid cells and Bcr-Abl positive leukemia lines that were derived from CML patients.

1.333 Clinical Phase I and II Studies

Three single-arm studies have been conducted in patients with Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase after failure of interferon-alpha (IFN), in accelerated phase disease, or in blast crisis. Hematologic responses

occurred in 88% (84.9-90.6, 95% C.I) of chronic phase patients, in 63% (56.5-69.2) of accelerated phase patients, and in 26% (20.9-31.9) of patients in blast crisis. Cytogenetic responses were noted in 9% (45.1-53.8), 21% (16.2-27.1), 13.5% (9.6-18.2), respectively. Although hematologic response rates were similar for patients receiving 600 mg and 400 mg, in chronic phase patients, major cytogenetic responses were more frequent at the higher dose (24% and 16%, respectively). The median time to hematologic response was 1 month. Response duration data were not complete due to short follow-up. Efficacy results were similar in men and women and in patients younger and older than age 65. (39,40,8,9).

A recent trial of imatinib in patients with gastrointestinal stromal tumors has been reported showing efficacy (41). An ongoing trial of imatinib in patients with recurrent glioma is being conducted by the NABTC, with separate dose escalation studies of patients receiving and not receiving EIACs. At the time of this writing, data is not yet available regarding this study.

Add 1 **2.0 Goals**

2.1 Objectives

2.11 Study 1: To identify the maximum-tolerated dose of imatinib in patients with recurrent oligodendrogliomas and mixed oligoastrocytomas that are currently on enzyme inducing anticonvulsant therapy.

2.12 Study 2: To assess the efficacy of imatinib in patients with recurrent oligodendrogliomas and mixed oligoastrocytomas (with pathologic evidence of oligodendrogliomatous component) as measured by progression-free survival, response, and overall survival.

Add 4 2.13 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.

Add 4 2.14 Studies 1, 2, and 3: To examine the toxicity and safety of imatinib in patients with recurrent oligodendrogliomas and mixed oligoastrocytomas (with pathologic evidence of oligodendrogliomatous component).

Add 4 2.15 Studies 1, 2, and 3: To perform a preliminary correlative study of 1p/19q alterations, α PDGFR gene amplification and levels of related downstream signaling elements in tumor tissue, with clinical study endpoints.

Add 4 2.16 Studies 1, 2, and 3: To perform a descriptive correlative analysis of steady state pharmacokinetic data regarding imatinib and active metabolites with the study endpoints.

2.2 Study Endpoints

2.21 Study 1: The primary endpoint of this study is dose-limiting toxicity for patients receiving EIACs.

- 2.22 Study 2: The primary endpoint of this study is progression-free survival at 6 months. All patients meeting the eligibility criteria who have signed a consent form and have received at least one dose of imatinib will be considered evaluable (intent to treat analysis, ITT). An eligible patient will be classified as a treatment “success” for the primary endpoint if he/she is alive and progression-free 183 days after study registration.
- 2.23 Study 2: The secondary endpoints include: 1) confirmed response, i.e., an objective status of CR, PR, or REGR on 2 successive evaluations at least 4 weeks apart after start of study treatment; 2) percentage of patients progression-free 12 and 18 months after start of study treatment (PFS12, PFS18); 3) progression-free survival; 4) overall time to death; and 5) quality of life. All time points will be defined as the interval from the date of study entry until the time of the particular endpoint.
- Add 4 2.24 Study 3: The primary endpoint of this study is progression-free survival at 6 months. All patients meeting the eligibility criteria who have signed a consent form and have received at least one dose of Imatinib will be considered evaluable (intent to treat analysis, ITT). An eligible patient will be classified as a treatment “success” for the primary endpoint if he/she is alive and progression-free 183 days after study registration.
- Add 4 2.25 Study 3: The secondary endpoints include: 1) confirmed response, i.e., an objective status of CR, PR, or REGR on 2 successive evaluations at least 4 weeks apart after start of study treatment; 2) percentage of patients progression-free 12 and 18 months after start of study treatment (PFS12, PFS18); 3) progression-free survival; 4) overall time to death; and 5) quality of life. All time points will be defined as the interval from the date of study entry until the time of the particular endpoint.
- Add 1 **3.0 Patient Eligibility**
- Study 1 only: Prior to discussing protocol entry with the patient, call the Random Center (507/284-4130) for dose level and to ensure that a place on the protocol is open to the patient**
- 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).
- Add 4 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.
- Add 4 3.22 ≤ 2 prior chemotherapy regimens (with maximum of 1 prior chemotherapy regimen for recurrent disease).
- 3.3 Required Characteristics for Study 3
- Add 4 3.31 On or off anticonvulsants.
- Add 4 3.32 > 2 chemotherapy regimens or 2 prior chemotherapy regimens for progressive/recurrent disease.

Add 4	3.4	Required Characteristics for Studies 1, 2, and 3
Add 4	3.41	Age ≥ 18 years.
Add 1,4	3.42	Histological confirmation of a grade 2-4 oligodendroglioma, or mixed oligoastrocytoma grade 2-4 containing oligodendrogliomatous component on central pathology review prior to study registration, and a diagnosis of recurrence. Tissues from all available prior surgeries should be sent, in particular those from time of initial diagnosis.
Add 4	3.43	Measurable or evaluable disease by MRI or CT scan.
Add 4	3.44	Fixed dose of corticosteroids (or no corticosteroids) for at least 1 week prior to the pre-study baseline scan.
Add 4	3.45	Patients undergoing surgery for initial or progressive disease, must be at least 2 weeks from the date of surgery, must have recovered from the effects of their surgery, and must have unequivocal tumor growth on the pre-study baseline neuroimaging study as compared to the first post-operative scan, unless there is a separate lesion or residual disease compatible with tumor that is not within the surgical bed.
Add 4	3.46	Unequivocal evidence of tumor progression by MRI or CT scan performed ≤ 21 days prior to study registration.
Add 1,4	3.47	Must have failed surgery/radiotherapy (RT) and Temozolomide or nitrosourea based therapy.
Add 1,4	3.48	≥ 12 weeks since the completion of RT.
Add 1,4	3.49a	The following laboratory values obtained ≤ 21 days prior to registration: <ul style="list-style-type: none"> • ANC $\geq 1500/\text{mm}^3$ • PLT $\geq 100,000/\text{mm}^3$ • Hgb ≥ 9 g/dL
Add 1,4	3.49b	The following laboratory values obtained ≤ 7 days prior to registration: <ul style="list-style-type: none"> • Total bilirubin ≤ 1.5 mg/dL • SGOT (AST) ≤ 3 x Upper limit of normal (ULN) • Creatinine ≤ 2.0 mg/dL
Add 1,4	3.49c	ECOG performance status (PS) of 0, 1, or 2.
Add 1,4	3.49d	≥ 6 weeks since the last day of nitrosourea-based chemotherapy prior to study entry.
Add 1,4	3.49e	≥ 4 weeks from any investigational agents prior to study entry.
Add 1,4	3.49f	≥ 4 weeks from other chemotherapy prior to study entry.
Add 1,4	3.49g	≥ 2 weeks from vincristine and biologic non-cytotoxic agents, e.g., tamoxifen, thalidomide, cis-retinoic acid, interferon, etc, prior to study entry.

- Add 1,4 3.49h Patients or designated individual(s) with durable medical power of attorney for the patient must be able to provide informed, written consent, and complete any required study questionnaire(s) within the specifications of this study.
- Add 1,4
- Add 4 3.5 Contraindications for Studies 1, 2, and 3
- Add 4 3.51 Receiving warfarin or heparin (see Section 9.5 for low dose warfarin).
- Add 4 3.52 Received prior stereotactic radiosurgery, interstitial brachytherapy, or interstitial chemotherapy including BCNU wafers unless there is a separate lesion on MRI, which is not part of the previous treatment field.
- Add 4 3.53 Active uncontrolled infection.
- Add 4 3.54 History of myocardial infarction ≤ 6 months or congestive heart failure (CHF) requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias. Patients must have a New York Heart Association (NYHA) of Class II or less. (NYHA Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities. Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion. Class III: patients with marked limitation of activity; they are comfortable only at rest. Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest).
- Add 4 3.55 Other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the interpretation of potential drug-induced toxicities.
- Add 4 3.56 Women of child-bearing potential, pregnant or nursing. The effects of imatinib on the developing fetus or nursing newborn are unknown, and potentially may be harmful. Such patients must have a negative pregnancy test (b-HCG) ≤ 7 days prior to study registration.
- Add 4 3.57 Men or women of childbearing potential, not willing to employ adequate contraception (condoms, diaphragm, birth control pills, injections, intrauterine device [IUD], surgical sterilization, subcutaneous implants, or abstinence, etc.). The efficacy of oral contraceptives may be decreased in patients who receive p450-inducing anticonvulsants. For these patients, use of a second mode of contraception is recommended. Patients of childbearing potential must utilize effective contraception and avoid becoming pregnant or fathering a child for 6 months after completing study drug.
- Add 4 3.58 Other active malignancy, besides skin carcinomas (must not be melanoma).
- Add 4 3.59a Concomitant serious immunocompromised status (other than that related to concomitant steroids). Patients that are HIV positive are eligible, provided that there is no other reason for exclusion, based on the eligibility as outlined elsewhere in this section.
- Add 1,4 3.59b Significant intratumoral hemorrhage on baseline MRI or CT, or other history of significant intratumoral hemorrhage.

4.0 Test Schedule

	Tests and procedures	Prior to study entry	≤21 days prior to Registration	≤7 days prior to Registration	Every other week	≤7 days before each cycle	≤7 days before 3 rd cycle and ≤7 days before every other subsequent cycle ³	At PROG, withdrawal, or removal due to adverse events
Add 1	Pathology Review	X ⁴						
	History and exam, wt, PS		X				X	X
	Height		X					
	Neuro history and exam		X				X	X
	Linear Analogue Self Assessment (LASA)		X				X	
Add 2	Hematology CBC and differential		X		X			X
Add 2	Chemistry SGOT [AST], alk phos, T. bili, creatinine, Ca, phos, glucose, sodium, potassium, chloride, magnesium, albumin			X		X		X
	Head MRI or CT with contrast ¹		X				X	X
	Chest x-ray		X					
	ECG		X				As clinically indicated	
	Recording of steroid dose		X				X	
	Anticonvulsant level		X				X	
Add 4	Serum pregnancy test ²			X				
Add 4	Pharmacologic Studies/Laboratory Correlates ⁶	See Section 14.0 for details regarding the time points for obtaining samples.						

1. MRI required with exception of patients who cannot undergo such testing or if pacemaker present. MRI strongly preferred. Use same method throughout study.
2. For women of childbearing potential only. Must be done ≤7 days prior to registration.
3. Cycle is defined as 4 weeks of treatment.
4. If materials have been previously submitted to Drs. B. Scheithauer, C. Giannini, and J. Parisi for a consult review or to a cooperative group pathologist for central pathology review for another cooperative group protocol, fax a copy of this review to the NCCTG pathology data monitor (507/284-1902) to verify eligibility for this study. Then follow the pathology material procedures found in **Section 17**.
5. Following progression, withdrawal, or removal due to adverse events, go to event monitoring until death (See Section 18.0 for details).
6. Studies 1 and 2 only.

5.0 Grouping Factor:

Add 1,4 5.1 Study: 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).

6.0 Registration/Randomization Procedures

Add 1 6.1 Registration procedures

6.11 Study 1

6.111 Prior to discussing protocol entry with the patient, call the Randomization Center (507/284-4130) for dose level and to insure that a place on the protocol is open to the patient.

Add 4 6.12 Studies 1, 2, and 3

6.121 To register a patient, call (507/284-4130) or fax (507/284-0885) a completed eligibility checklist to the Randomization Center between 8 a.m. and 4:30 p.m. central time Monday through Friday.

Add 4 6.13 Randomization Center will register patients separately to the translational research component of this study (Studies 1 and 2 patients only) (see Section 14.0).

- Patient has/has not given permission to give blood sample for research testing.
- Patient has/has not given permission to give tissue sample for research testing.

6.2 IRB approval(s) is required for each treating site. A signed Cancer Trials Support Unit (CTSUS) IRB Certification Form is to be on file at the CTSU Regulatory Office (fax 215-569-0206). This form can be found at the following Web site: www.ctsu.org/rss2_page.asp. Guidelines can be found under Quick Fact Sheets.

Add 5 In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the CTSU Regulatory Office (fax 215-569-0206). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

Add 5 When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the CTSU is no longer necessary.

6.3 At the time of registration/randomization, Randomization Center personnel will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information. (USA institutions only)

Add 2 At the time of registration/randomization, the following will also be recorded:

- Patient has/has not given permission to store and use blood sample 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 sample 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 sample to outside researchers.
- Patient has/has not given NCCTG permission to give their tissue sample to outside researchers.

- 6.4 Treatment on this protocol must commence at the accruing membership under the supervision of a NCCTG member physician.
- 6.5 Treatment cannot begin prior to registration and must begin ≤ 7 days after registration.
- 6.6 Pretreatment tests/procedures must be completed within the guidelines specified on the test schedule.
- 6.7 All required baseline symptoms must be documented and graded on the on-study form.
- 6.8 Study drug availability checked.

7.0 Protocol Treatment

Add 1

7.1 Treatment Plan - Definition of Cycles

Add 4

Studies 1, 2, and 3: Cycles will be defined as a period of 4 weeks of imatinib treatment. Patients will be treated directly with a second 4-week cycle with no interruption of treatment between cycles. During the week prior to the third, and every other subsequent cycle, patients will undergo clinical and radiographic evaluations as listed in Section 4.0. If there are no severe toxicities or significant clinical or radiographic deterioration, patients will continue on therapy. Treatment will continue indefinitely in the absence of unacceptable toxicities or tumor progression.

7.2 Treatment Schedule for Study 1

Arm	Dose	Route	Day	Retreatment
EIACs*	Imatinib Call Random Center for assigned dose level	P.O.	Divided and administered twice daily per Cohort Dose Level	Every 28 days (continuous without break)

*EIACs are defined in Appendix IIIb.

7.21 Study 1 Dose Escalation Scheme

7.211 Patients will be treated according to a dose escalation cohorts-of-3 design.

Add 5,8

7.212 The original study designed called for the first cohort of patients 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 were to be enrolled at dose level 1. If DLT was not observed in the first 3 patients at dose level 1 OR only 1 DLT was observed in the first 6 patients at dose level 1, the next three patients would be entered at dose level 2. If dose level 1 yielded ≥ 2 DLTs (in either the first cohort of 3 patients or 2 cohorts of 3 patients), a daily dose of 800 mg would be evaluated.

- Add 5,8 Six patients would be entered on dose level -1 (800 mg/D). If 0 or 1 DLTs were observed in the 6 patients on dose level -1, then dose level -1 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) would be used as dose for the EIAC patients in Study 2.
- Add 5,8,11 7.2121 To date (as of Addendum 5), 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 showed 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 (59).
- Add 11 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. If no DLTs are observed in the 3rd 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 frequency of DLTs at 1200 mg/D. If 1 DLT is observed, we will add a 4th cohort of 3 patients to dose level 1 to evaluate for DLT. If ≥ 1 DLT is observed in the 4th cohort at dose level 1, a DLT rate of $\geq 33\%$ (4+/12) will have been observed and the Phase I study for EIAC 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 frequency of DLTs at 1200 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. 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.
- Add 11 To date (as of Addendum 11), we have accrued the third cohort of 3 for a total of 9 patients and observed 2 clinically relevant DLTs at dose level 1 (1000 mg/D). No patients experienced DLT in the most recent cohort of 3. In the above paragraph, there was inadvertently no provision for 0 DLTs in this third cohort of 3. The intent was to escalate to dose level 2 and continue this study per Section 7.213. **Addendum 11 reopens Study 1 (Arm C) to accrual and continue dose escalation per Section 7.213.**
- Add 5 7.213 For dose level 2 and subsequent levels (see Section 7.214), a cohort of 3 patients will initially be entered at the dose level.
- 7.2131 If 1 DLT occurs in the first cohort of 3 patients at a dose level, an additional cohort of 3 patients will be enrolled at that dose level.
- 7.2132 If DLT is not observed in the first 3 patients at the dose level OR 1 DLT is observed in the first 6 patients at the dose level, the next three patients will be entered at the next higher dose level (see Section 7.214).

7.2133 If the dose level yields 2 DLTs (in either 1 cohort of 3 patients or 2 cohorts of 3 patients), then the previous dose level will be defined to be the MTD and the EIAC dose for study 2. If only 3 patients had been treated at the previous dose level (MTD), then an additional cohort of 3 patients will be treated at the previous dose level (MTD) to ensure 2 cohorts of 3 patients at the MTD.

7.2134 If <2 of 6 patients at dose level 5 experience DLT, the dose of 1800g/D will be used for the EIAC patients in Study 2.

Add 5

7.214 Dose Levels

Cohort Dose Level	Imatinib Daily Total Dose
-1	800
1*	1000
2	1200
3	1400
4	1600
5	1800

*Starting dose.

MTD will be defined as the highest safely tolerated dose level where, at most, 1 of 6 patients experiences DLT with the next higher dose having at least 2 patients out of 6 who experience DLT.

Add 5,13

7.215 Adverse events are to be assessed using CTC v2.0. The dose limiting toxicity (DLT) will be defined as adverse events considered clinically relevant after review by the study team (PI and Statistician) and fitting the following criteria:

Toxicity (CTC v2.0)	DLT
Hematologic	Grade 5 or grade 4 or off study due to hematologic toxicities precluding additional treatment with attribution to study treatment of possible, probable, or definite
Non-Hematologic	≥Grade 3 with attribution to study treatment of possible, probable, or definite, with the exception of controllable nausea or vomiting.
Hematologic or Non-Hematologic	Toxicity causes treatment to be held for 4 consecutive weeks, causing patient to be discontinued from study

- 7.216 Other considerations: In the event there are severe late toxicities and/or significant toxicity patterns, which although may not be a DLT as defined in the above table, a decision on dose de-escalation can still be made based on the observed toxicities by the study team (principal investigator[s] and study statistician).

Add 1,4 7.3 Treatment Schedule for Studies 2 and 3

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

Studies 2 and 3

Arm	Dose	Route	Day	Retreatment
Add 4 A and D (EIACs*)	Not yet open to patient accrual	P.O.	Twice daily	Every 28 days (continuous without break)
Add 4 B and E (non -EIACs*)	Imatinib 300 mg	P.O.	Twice daily	Every 28 days (continuous without break)

*EIACs are defined in Appendix IIIB.

- 7.4 Therapy should be initiated by an NCCTG physician who is experienced in the chemotherapeutic treatment of patients with central nervous neoplasms. The prescribed dose is given twice daily. Drug should be given with a meal and a large glass (>8 ounces) of water. Treatment should be continued as long as the patient continues to show evidence of benefit, in the opinion of the treating physician, or meets off study criteria as defined in this protocol. Dose alterations should be performed as stated in Section 8.0 according to the development of hematologic or non-hematologic toxicities as rated utilizing the National Cancer Institute Clinical Toxicity Criteria Scale, Version 2.0 at http://ctep.info.nih.gov/CTC3/ctc_ind_term.htm.
- 7.5 When it has been determined that a patient's malignant disease is stable or objective tumor regression has been observed and the patient is tolerating therapy without excessive toxicity at a stable dose level, the drug(s) may be sent with the patient for administration by the patient's local physician. In this case, a written statement outlining drug dosage, method of administration, follow-up tests required, and telephone number to call to discuss any questions with the responsible investigator must be sent with the patient to provide necessary information to the local physician. The local physician will be required to supervise the administration of investigational drugs as stipulated in the protocol and provide written documentation that the drug was administered. The physician must have the patient utilize the 'pill diary' (see Appendix V) for this purpose which is collected every other cycle at the time of return assessments. In addition, patients must return partially empty or empty pill containers at the time of assessment (every other cycle) for a pill count by the treating physician, and this information documented in the record. For this protocol, the patient must return to a NCCTG institution for evaluation at least every other cycle (8 weeks).
- 7.6 Patients can be instructed in administration techniques and granted treatment independence (self-administration of this oral agent, with proper documentation in the pill diary of such administration) after proper education and approval by the study nursing staff.

Add 1

8.0 Dosage Modification Based on Adverse Events – Strictly follow the modifications in this table until individual treatment tolerance can be ascertained. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

8.1 Study 1: Patients who experience DLT but have no progressive disease will be eligible for retreatment at the lower dose level as shown in 7.124.

8.2 Studies 1, 2, and 3

Add 1,4,13

ALERT: ADR reporting may be required for some adverse events (See Section 10)
AT ANY TIME DURING CONTINUOUS TREATMENT

→ → Use Common Toxicity Criteria (CTC) Version 2.0 unless otherwise specified ← ←

CTC V2.0 CATEGORY	ADVERSE EVENT	DOSAGE CHANGE ³
Blood/Bone Marrow	ANC 750 – 999 or PLTS 50,000 - <100,000	Hold Rx until ANC ≥1000 and PLTS ≥100,000 then ↓ 25%, ^{1,2}
	ANC <750 or PLTS <50,000	Hold Rx until ANC ≥1000 and PLTS ≥100,000 then ↓ 50%, ^{1,2}
Any nonhematologic	Grade 2	For symptomatic grade 2 adverse event, except nausea/vomiting (unless patients are on optimal antiemetic therapy), the dose may be held until recovery to grade 0-1, then ↓ 25% ^{1,2} , at the investigator’s discretion.
	Grade 3	Hold Rx until grade 0-2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) then ↓ 25% ^{1,2} .
	Grade 4	Hold Rx until grade 0-2 (or within 1 grade of starting values for pre-existing laboratory abnormalities) then ↓ 50% ^{1,2} .

Add 9

Add 2

- Adjusted to the nearest 100 mg, since imatinib is only available in 100 mg tablets. 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.
- If any patient has an adverse event that requires treatment to be held for 4 consecutive weeks, the patient will be discontinued from the study unless the investigator feels that the patient may benefit from continued treatment. Such continued treatment must be discussed with the study chair(s) before continuation of treatment and the reasons for continuation under these circumstances documented in the case report form.
- Patients will be allowed two dose reductions. If any patient has further adverse events that would require further reduction, the patient will be discontinued from the study unless the investigator feels that the patient may benefit from continued treatment. Such continued treatment must be discussed with the study chair(s) before continuation of treatment and the reasons for continuation under these circumstances documented in the case report form.
- The appearance of any other symptoms that, in the opinion of the investigator are drug-related or are hazardous to the patient’s well being, is sufficient justification to modify the dosage or discontinue the drug.

- 8.3 There should not be dose reductions below 300 mg per day, since doses below this dose are not assumed to be active. If a dose reduction below 300 mg appears necessary, the patients will be removed from study due to toxicity.
- 8.4 If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

Add 5

9.0 Ancillary Treatment

9.1 Anticonvulsants

Anticonvulsants should be used as clinically indicated. Patients that enter the trial on EIACs must remain on EIACs for the duration of imatinib treatment. If it is necessary to discontinue an EIAC in such patients, a replacement EIAC should be used. 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. Patients who require a change to an EIAC for clinical reasons may continue on protocol treatment, but must undergo an adjustment of their imatinib dosage to the dosage utilized for EIAC patients, as indicated in Section 7.2. The change in EIAC and study dosage should be clearly indicated in the patient records. Questions regarding anticonvulsant use and changes should be directed to the study chairperson.

Add 4

9.2 Steroids

Steroids can be adjusted to control symptoms of raised intracranial pressure, neurologic decline and headache, or as clinically indicated otherwise such as in antiemetic use but should be used at the smallest dose clinically possible and attempts made to taper if clinically warranted. Dosages of steroids and changes with dates of change should always be referred to in clinical notes and the case report forms.

9.3 Antiemetics

The use of antiemetics will be left to the investigators' discretion. The agent, dose, and dates should be recorded in the case report form and clinical recorded.

9.4 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (42) Update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: Evidence-Based, Clinical Practice Guidelines. J Clin Oncol 18(20): 3558-3585, 2000.

9.5 Anticoagulants

Patients needing anticoagulation with warfarin may continue treatment with imatinib, but close monitoring of the INR should be performed due to potential interactions with increases in INR and prothrombin time. Therapeutic doses of warfarin are not permitted. Low dose warfarin (e.g., 1 mg daily and heparin) may be used as clinically warranted provided that coagulation studies and platelet counts are adequate and closely monitored. Alternative antiplatelet agents should be considered and are allowed.

9.6 Other Medications

Other medications utilized for supportive and comfort care are permitted. Agents which are metabolized via p450 microsomal enzymes or serve as substrates for microsomal enzymes should in particular be avoided.

Acetaminophen should be limited to 500 mg per day due to potential interaction with imatinib and hepatic toxicity.

All concomitant medications must be recorded. The agent, dose, and dates should be recorded in the case report form and clinical recorded.

9.7 Concomitant antineoplastic therapy

No other investigational or non-investigational therapy designed to treat the brain malignancy (including surgery, chemotherapy, radiation, biologic agents, immunotherapy, or hormonal therapy) is allowed during the study period. If such agents are utilized this will constitute a major protocol violation.

Add 5

9.8 Signs and symptoms of congestive heart failure (CHF). All patients on and off therapy who develop signs and symptoms suggestive of CHF should be thoroughly evaluated and closely monitored and supported as clinically dictated. Preliminary data suggest that a combination of carvedilol and angiotensin converting enzyme inhibitors are useful treatments of CHF in this setting.

Add
1,3,13

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 The NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) will be utilized for expedited AE reporting. The CTCAE is identified and located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTC. Next, determine whether the event is expected or unexpected (see Section 10.12) and if the adverse event is related to the medical treatment or procedure (see Section 10.13). With this information, determine whether an adverse event must be reported as an expedited report (see Section 10.2). **Important:** All AEs reported via expedited mechanisms must also be reported via the routine data reporting

mechanisms defined by the protocol (see Sections 10.3 and 18.0).

Expedited adverse event reporting requires submission of an electronic Adverse Event Expedited Reporting System (AdeERS) report(s). Other expedited reporting requirements and systems may also apply. Expedited and routine reports are to be completed within the timeframes and via the mechanisms specified in Section 10.2 and 10.3. All expedited AE reports must also be sent to the local Institutional Review Board (IRB) according to local IRB's policies and procedures.

Add 13

Effective with Addendum 13, Expedited AdeERS reporting for this protocol has been updated by the NCI/CTEP to use CTCAE v4.0. Therefore;

- 1) Events requiring expedited reporting through AdeERS must be reported through the AdeERS system in CTCAE v4.0.
- 2) The events reported via AdeERS must ALSO be reported through routine reporting (i.e., Case Report Forms) using CTC v2.0.
- 3) Routine data collection via Case Report Forms, including the "Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form", will remain using CTC v2.0 for this study.

Add 3,5

10.12 Expected vs. Unexpected Events

Agent(s) under a CTEP IND:

- Expected AEs for expedited reporting purposes are listed on the CTEP Agent Specific Adverse Event List (ASAEL), a component of the Comprehensive Adverse Events and Potential Risks List (CAEPR). Refer to Section 15.0 to locate the CAEPR for the CTEP IND agent(s).
- Unexpected AEs are those not listed in the ASAEL.

Add 3

10.13 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the investigational agent(s).

Probable - The adverse event *is likely related* to the investigational agent(s).

Possible - The adverse event *may be related* to the investigational agent(s).

Unlikely - The adverse event *is doubtfully related* to the investigational agent(s).

Unrelated - The adverse event *is clearly NOT related* to the investigational agent(s).

10.2 Expedited Reporting Requirements

Add 1,3

10.21 Study 1: Phase 1 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days¹ of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days
Possible Probable Definite	Not Required	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days	24-Hour; 3 Calendar Days	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days
<p>¹ Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under an IND require reporting as follows: AdEERS 24-hour notification followed by complete report within 3 calendar days for:</p> <ul style="list-style-type: none"> • Grade 3 unexpected events with hospitalization or prolongation of hospitalization • Grade 4 unexpected events • Grade 5 expected events and unexpected events <p>² Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.</p> <p>Please see additional instructions and/or exceptions below under section entitled "Additional Instructions or Exceptions." March 2005</p>								

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

Add 13

- Expedited AE reporting timelines defined:
 - "24 hours; 3 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
 - "7 calendar days" - A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE v4.0 grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disability/incapacity, congenital anomaly, or birth defect must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- SECONDARY MALIGNANCIES (defined as "cancer caused by treatment for a previous malignancy," e.g., treatment with radiation or chemotherapy) are to be reported through AdEERS, as noted in Section 10.22. Secondary malignancies are not considered metastasis of the initial neoplasm. Secondary malignancy is unrelated to the first cancer that was treated, and may occur months or even years after initial treatment.

Add 14

Note: Second Primary malignancy (malignancy not due to prior treatment) should not be reported through AdEERS.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase I Trials Utilizing an Agent Under a CTEP IND:

Add 14

- In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP web site and will NO LONGER be accepted.
- Refer to Section 10.23 of this protocol for additional expedited reporting requirements.

Add
1,3,4

10.22 Studies 2 and 3: Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days¹ of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 ²	Grades 4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days
Possible Probable Definite	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days	7 Calendar Days

¹ Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:
 AdEERS 24-hour notification followed by complete report within 3 calendar days for:
 • Grade 4 and Grade 5 unexpected events
 AdEERS 7 calendar day report:
 • Grade 3 unexpected events with hospitalization or prolongation of hospitalization
 • Grade 5 expected events

² Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see additional instructions and/or exceptions below under section entitled “Additional Instructions or Exceptions.”
 March 2005

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

Add 13

- Expedited AE reporting timelines defined:
 - “24 hours; 3 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
 - “7 calendar days” - A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE v4.0 grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disability/incapacity, congenital anomaly, or birth defect must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- SECONDARY MALIGNANCIES (defined as “cancer caused by treatment for a previous malignancy,” e.g., treatment with radiation or chemotherapy) are to be reported through AdEERS, as noted in Section 10.22. Secondary malignancies are not considered metastasis of the initial neoplasm. Secondary malignancy is unrelated to the first cancer that was treated, and may occur months or even years after initial treatment.

Add 14

Note: Second Primary malignancy (malignancy not due to prior treatment) should not be reported through AdEERS.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND:

Add 14

- In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report **MUST** be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP web site and will **NO LONGER** be accepted.
- Refer to Section 10.23 of this protocol for additional expedited reporting requirements.

Add 3,8,13

10.23 Other Required Expedited Reporting

Add 14

EVENT TYPE	REPORTING PROCEDURE
Secondary AML/MDS	<p>Reporting for this event required during and after completion of study treatment via AdEERS.</p> <p>AdEERS will only accept CTCAE v4.0 for this study. Report these events using “Neoplasms benign, malignant and unspecified (incl. cysts and polyps)” and including all appropriate adverse event: -Leukemia secondary to oncology chemotherapy OR -Myelodysplastic syndrome OR -Treatment related secondary malignancy</p>
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	<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>You must use CTC v2.0 for data submission with this form. The events reported on this form must also appear on the Case Report Forms (i.e., routine data) for this study.</p>

Add 1,3,5,13

10.3 All adverse events (AE) must be graded and submitted for eventual CDUS quarterly reports. AEs of particular pertinence for this trial, to also be graded at each evaluation and at pretreatment baseline and follow-up evaluations per Common Toxicity Criteria (CTC) Version 2.0 grading include:

Category (CTC v2.0)	Adverse Event/Symptoms	Baseline	Each evaluation
Cardiovascular (General)	Cardiac left ventricular failure	X	X
	Edema	X	X
Dermatology/Skin	Rash/desquamation	X	X
Gastrointestinal	Nausea	X	X
	Stomatitis/pharyngitis	X	X
	Number of stools/day	X	
	Diarrhea – patients without colostomy		X
	Diarrhea – patients with colostomy		X
	Vomiting	X	X
Infection/Febrile Neutropenia	Infection with grade 3 or 4 neutropenia		X
	Infection without neutropenia		X
Metabolic/Laboratory	Hyperglycemia	X	X
	SGOT (AST)	X	X
	Creatinine	X	X
Neurology	Depressed level of consciousness	X	X
	Neuropathy-motor	X	X
	Neuropathy-sensory	X	X
Hemorrhage	Hemorrhage – Other Specify site,	X	X

Add 13

10.31 Submit to the NCCTG Research Base via the Nadir/AE Log the following AEs using CTC v2.0 experienced by a patient and not specified in Section 10.3:

10.311 Grade 1 & 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

Add 4

10.312 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

Add 4

10.313 Grade 5 AEs (Deaths)

3.3131 Any death within 30 days of the patient’s last study treatment, regardless of relationship to the study treatment or procedure.

3.3132 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.

10.32 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation

11.1 Response criteria: The neurologic examination and the MRI and/or CT at each evaluation will be scored as follows:

11.11

NEURO EXAM STATUS (compared to pre-Rx exam)	
Better:	must be on stable or decreasing dose of steroids.
Same:	failure to qualify for better or worse.
Worse:	includes patients requiring increasing steroid dose to remain stable.

11.12 MRI AND/OR CT ASSESSMENT (compared to pretreatment scan for bidimensionally measurable disease):

CR =	total disappearance of all tumor with patient off corticosteroids or only on adrenal replacement maintenance.
PR =	≥50% reduction in product of perpendicular diameters of contrast enhancement or mass with no new lesions with the patient being on stable or decreased steroid dose.
STAB =	failure to qualify for CR, PR, REGR, or PROG.
PROG =	>25% increase in product of perpendicular diameters of contrast enhancement or mass or appearance of new lesions.

11.13 MRI AND/OR CT ASSESSMENT (compared to pretreatment scan) for evaluable disease (i.e., contrast enhancing mass on MRI and/or CT that is not bidimensionally measurable but clearly evaluable for response to therapy.

CR =	total disappearance of all tumor with patient off corticosteroids or only on adrenal replacement maintenance.
REGR =	unequivocal reduction in size of contrast-enhancement or decrease in mass effect as agreed upon independently by primary physician and quality control physicians; no new lesions. Patient should be on stable or decreased steroid dose.
STAB =	failure to qualify for CR, PR, or PROG.
PROG =	unequivocal increase in size of contrast enhancement or increase in mass effect as agreed upon independently by primary physician and quality control physicians: appearance of new lesions.

11.14 Objective Status: Scored as follows for cycles with and without MRI and/or CT.

11.141 Cycle with MRI and/or CT

NEURO STATUS	MRI and/or CT Status				
	CR	PR	REGR	STAB	PROG
Better					UNKN*
Same	CR	PR	REGR	STAB	PROG
Worse	UNKN*				

* Set the Objective Status equal to unknown. Treat one more cycle and evaluate according to the table below:

NEURO STATUS	MRI and/or CT Status				
	CR	PR	REGR	STAB	PROG
Better					PROG
Same	CR	PR	REGR	STAB	
Worse					

11.142 Cycle without MRI or CT

NEURO STATUS	OBJECTIVE STATUS
Better	Last cycle status
Same	
Worse	Obtain MRI and/or CT – refer to MRI and/or CT Table

11.15 Survival and Time to Progression Definitions

Survival and time to progression endpoints will be defined as the time interval from the date of study registration to the particular endpoint.

Add 4

12.0 Descriptive Factors (for Studies 1, 2, and 3)

- 12.1 Age: (Years) <40 vs. 40-60 vs. >60.
- 12.2 ECOG Performance Score (PS): 0 vs. 1 vs. 2.
- 12.3 Prior nitrosoureas: Yes vs. no.
- 12.4 Interval since end of RT (months).
- 12.5 Corticosteroid therapy at study entry: Yes vs. no.
- 12.6 Extent of primary resection: None vs. biopsy vs. subtotal resection vs. gross total resection.
- 12.7 Histologic type of primary tumor: Oligodendroglioma vs. oligoastrocytoma.
- 12.8 Histologic grade of primary tumor: 2 vs. 3 vs. 4.
- 12.9a Extent of resection at recurrence: None vs. biopsy vs. subtotal resection vs. gross total resection.
- 12.9b Histologic type of recurrent tumor: Oligodendroglioma vs. oligoastrocytoma vs. missing.
- 12.9c Histologic grade of recurrent tumor: 2 vs. 3 vs. 4 vs. missing.
- 12.9d Family history of brain tumor: Yes vs. no.
If yes, check all that apply:
- Father
 Mother
 Brother/Sister
 Child
 Other (list: _____)
- 12.9e Is this patient receiving any agents listed in Appendix IIIA? If so, record.
- 12.9f Number of prior chemotherapy regimens.

Add 1

Add 1

13.0 Treatment/Follow-up Decision at Evaluation of Patient

13.1 Study 1

- 13.11 Patients will be eligible for retreatment at the same dose level if they are not a PROG and have acceptable toxicity.
- 13.12 Patients who have not progressed but have experienced unacceptable toxicity will be eligible for retreatment at a lower dose (see Section 8.1).
- 13.13 Patients who have progressed or who refuse further treatment will go to the event-monitoring phase. Further treatment with chemotherapy or radiotherapy may be used at the discretion of the primary physician.
- 13.14 If a patient fails to complete the initial course of therapy (defined as drug administration and the scheduled evaluation ≤ 7 days before 3rd cycle) for reasons other than toxicity, the patient will be regarded as inevaluable for DLT and will be replaced; however, all toxicity information will be utilized in the analysis. For these instances, a specific notation will be made for review by the Cancer Center Clinical Research Administrative Subcommittee (CCCRAS).

Add 4

13.2 Studies 2 and 3

- 13.21 Patients who are CR, PR, REGR, or STAB will continue treatment per protocol.
- 13.22 Patients who develop progressive disease while receiving therapy will go to the event-monitoring phase.
- 13.23 Patients who go off protocol treatment for reasons other than PROG will go to the event-monitoring phase per Section 18.0.
- 13.24 If a patient refuses or does not receive treatment or a treatment assignment (and is classified as a cancel), it is not necessary to provide follow-up information. On-study material is to be submitted.

Add 1,4

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

Add 10

14.1 These studies will be performed on tissues obtained from prior surgeries. Tissues from the initial diagnosis and any recurrent procedure should be sent, if available. Formalin fixed paraffin embedded (FFPE) tumor tissues will be used for study of expression of potential targets of imatinib and downstream effectors or markers of signaling, as follows:

- Imatinib inhibition targets: α PDGFR, β PDGFR, and c-kit.
- Markers of autocrine signaling by α PDGFR: PDGF-A and PDGF-B.

- Potential downstream effectors or markers of PDGF signaling:

Ras pathway – Phosphorylated and total Erk1/2
 PI3K pathway – Phosphorylated and total AFX; total p27^{Kip1}
 Cell proliferation and control – Ki67 (MIB-1); p53

14.11 Methods

Add 8

The NCCTG Operations Office will accession the specimens and tissues will be distributed to the Tissue Acquisition and Cellular/Molecular Analysis (TACMA)/NCCTG Biospecimens Resource core laboratory, Stabile 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 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.

14.12 Shipping Instructions

Add
1,5,6,8,10

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

NCCTG Operations Office
 ATTN: NCCTG PC Office (Study N0272)
 RO_FF_03_24-CC/NW Clinic
 200 First Street, SW
 Rochester, MN 55905

Add 1,6

14.122 The NCCTG Pathology Coordinator will forward the material to TACMA/NCCTG Biospecimens Resource lab, Stabile 13-10, Mayo Clinic Rochester.

Add 1,10

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. H&E slides will be labeled 1. 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. NOTE: If sending slides, do not bake or place coverslips on the slides.

Add 1

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.

14.2 Frozen tumor tissues: Immunoblot studies of expression of related proteins.

14.21 These studies will be performed when frozen tissues are available from prior therapeutic or diagnostic surgeries.

- 14.22 Kinase targets of imatinib: α PDGFR, β PDGFR, and c-kit. Spontaneous or autocrine activation of these proteins will be detected by immunoblots of total cell lysates and immunoprecipitates of the relevant receptors for phosphotyrosine.
- 14.23 Activation of downstream signal transduction molecules (total and/or phosphorylated), to include one or more markers in the following pathways:
- Ras pathway – Shc and Erk1/2
 - PI3K pathway – AKT, AFX, mTOR, and BAD
 - Cell cycle proteins – Rb and cell cycle regulators p16^{ink4a}, p21^{waf1}, p27^{kip1}

Add 6

14.24 Acquisition and Shipping Instructions:

Add 12

Tissue should be plunged until frozen in liquid nitrogen and kept frozen at temperatures between -20°C and -80° C until mailed. Samples should be shipped on enough dry ice to ensure safe transport while frozen. Samples may be sent Monday through Thursday and should be sent in batches whenever possible. Send samples to Biospecimens Accessioning and Processing (BAP) Laboratory/NCCTG Biospecimens Resource at the Mayo Clinic at the following address:

BAP/NCCTG Biospecimens Resource
 ATTN: BAP Supervisor
 Stabile 13-10A
 221 4th Avenue SW
 Rochester, MN 55905
 Phone: 507-538-7062

Add 10

NOTE: Do not expose tissue to be frozen to formalin preservative

Add 6

- 14.25 Methods: The BAP Laboratory will accession the specimens and the tissues will be sent to and distributed to the TACMA/NCCTG Biospecimens Resource, Stabile 13-10, Mayo Clinic Rochester. Assays will be performed in the appropriate Mayo laboratories responsible for conducting these analyses. Controls will include unstimulated or growth factor-stimulated glioma cell lines and in non-malignant brain tissues (resected from patients without brain tumors to control seizures). As this is a pilot study of a limited number of tumors to characterize the status of the selected proteins by immunoblot, a descriptive analysis of the results is not planned.

14.3 Gene studies:

- 14.31 These studies will be performed on tissues obtained from prior surgeries. Tissues from all available prior surgeries should be sent, in particular, those from the time of initial diagnosis.
- 14.32 Fluorescence *in situ* hybridization (FISH): 1p and 19q; PDGFRA and PDGFRB; PTEN

Add 10

These studies will be performed using FFPE tissues that were sent and distributed in Section 14.1 to TACMA/NCCTG Biospecimens Resource. These studies will be performed by Dr. Robert Jenkins at Mayo Clinic, who has

considerable experience with these assays and techniques. These are pilot studies and a descriptive analysis is primarily planned. However, attempts will be made to statistically correlate data with clinical endpoints.

Add 10

Fluorescence in situ hybridization will be performed as described by Smith (45). Briefly, FFPE tumor blocks will be selected based upon tumor content, including the highest-grade component and representation of the predominant morphology of the individual cases. Twenty (20) five-micron sections will be prepared from each block. The first section will be stained with H&E, and the regions representing tumor and normal tissue delineated. FISH analyses will be performed using sections immediately adjacent to the H&E-stained slide in order to minimize the effects of tumor heterogeneity.

A PDGFRA locus-specific bacterial artificial chromosome (BAC) has been isolated from the RPCI-11 Human BAC Library (Research Genetics) using the primers AGGGCTGAGCCTAATCCTCT (bases 187-206, sense) and CTGGGTCTGGCACATAGATG (bases 512-493, antisense) (45). FISH probes used for analysis of chromosome 1 and 19 deletion have been selected based upon their localization to regions of common allelic loss in diffuse gliomas, and have been previously described (45,46).

For FISH analyses, tumor sections are deparaffinized, dehydrated, microwave treated in citrate buffer (pH 6.0) for 10 minutes, digested in pepsin solution (4 mg/mL in 0.9% NaCl, pH 1.5) for 15 minutes at 37°C, rinsed in 2X SSC at room temperature for 5 minutes, and air dried (47). Dual-probe hybridizations for PDGFRA gene analyses are performed using a digoxigenin-labeled locus-specific PDGFRA probe and a SpectrumGreen(SG)-labeled chromosome 4 (48) centromere probe (CEP4, Vysis, Downers Grove, IL). Dual probe hybridizations for the analysis of chromosomes 1 and 19 are performed using a digoxigenin-labeled locus-specific 1p or 19q probe and a SpectrumGreen(SG)-labeled probe mapped to 1q or 19p, respectively. Probes and target DNA are denatured simultaneously in an 80°C oven for 5 minutes, followed by overnight incubation at 37°C. Slides are then washed in 1.5 M urea/0.1X SSC at 45°C for 10 minutes (x3) and in 2X SSC at room temperature for 2 minutes. After washing, the digoxigenin-labeled probes are detected using a rhodamine detection kit (Oncor, Gaithersburg, MD). Nuclei are counterstained with 4,6-diamidino-2-phenylindole and the antifade compound p-phenylenediamine. A Zeiss Axioplan microscope equipped with a triple-pass filter (DAPI/Green/Orange; Vysis, Downers Grove, IL) is used to assess the number of FISH signals for each probe. Approximately 300 non-overlapping nuclei are enumerated per hybridization.

14.33 Mailing instructions

Add 1,10

Studies will be performed on tissues provided and mailed as specified in Section 14.12; no additional tissues necessary. The block/slides must be appropriately packed to prevent damage (e.g. slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, NCCTG patient ID number and patient initials.

14.4 Gene Studies - Lymphocytes and peripheral blood leukocytes

- Add
1,6,8,10,13
- 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 Biospecimen Accessioning and Processing (BAP). The studies will be performed in the laboratory of Dr. Robert Jenkins.
- Add
6,8,10,12,13
- 14.42 Kits for shipment of the blood samples will be supplied through BAP. Participating institutions may obtain kits by completing and faxing the BAP Fax Supply Order Form (found in the Forms Packet) to the fax number on the form. Allow at least two weeks to receive the kits. 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.**
- 14.43 ALL sections of the form/specimen collection labels must be completed.
- 14.44 Mailing Instructions
- Add 6,11
- NOTE: Because there are charges for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Unused kits should be discarded at the site. Samples may be sent Monday through Thursday.
- Add 6,10,13
- Samples should be shipped after the blood draw per kit instructions to BAP.

14.5 Pharmacokinetic Analyses

14.51 HPLC Analysis

Samples will be analyzed by high performance liquid chromatography. 1 ml of plasma will be placed into a 15 ml Corex Centrifuge II. 10 microliters of internal standard will be added to each sample, and the samples will be vortexed vigorously. 5 ml of acetonitrile will be added to each sample, and the samples again vortexed vigorously. Samples will be centrifuged at 48,000 x g in a Sorvall RC 5 centrifuge. The resulting supernatants will be transferred to 13 x 100 mm, borosilicate glass centrifuge tubes and evaporated to dryness under a stream of nitrogen. Dried residues will be re-suspended in 125 microliters of mobile phase, transferred to HPLC autosampler microvial inserts, and 100 microliters will be injected onto the HPLC system. The HPLC system will consist of a Hewlett-

Packard 1100 Autosampler and a Waters 510-pump fitted with a lichrosphere 100 RP8 (5 micron, 125 mm x 4mm i.d.) column. The mobile phase, consisting of acetonitrile: 0.05 M sodium phosphate + 0.2 % triethylamine will be pumped at 1 ml per minute. Column eluate will be monitored at 251 nm, and detector signal will be processed with Chrom Perfect software (Justice Innovations, Sunnyvale, CA) so as to integrate the area under each eluted peak.

Concentrations of imatinib in plasma will be determined by calculating the ratio of the area of the peak in each sample to that of the respective internal standard peak in that sample and comparing that ratio to a concomitantly performed standard curve. Quality-control samples representing the lower third, middle third, and upper third of the standard curve will be included with each set of samples analyzed.

14.52 Pharmacokinetic Analysis

Concentration x time data will be analyzed with both compartmental and non-compartmental methods. Non-compartmental analyses for day 1 data will utilize the La Grange function as implemented by the program, Lagran. In addition, compartmental models will be fit to the data from day 1 and all subsequent days. This will be done with the program ADAPT. Model discrimination will be based on Akaike's Information Criterion. It is also likely that all data will be analyzed in a population pharmacokinetic manner with the program, WinNonMix.

14.53 Sample acquisition, schedules and mailing information.

14.54 If an institution is not able to accomplish this portion of the study, it does not cause the patient to be ineligible.

14.55 Sampling for PK studies should be performed according to the following schedule. All samples should be taken at trough; thus, the patient should not take their imatinib on the morning of the day of sample draw. They should then receive the dose after the sample has been obtained.

14.56 Schedule

Day	Draw Sample
0 (pre treatment)	X
28	X
56	X
84	X
At trough (see Section 14.55) following first dose reduction only	X

14.57 Patient dosing prior to PK sample draw: the patient should not take their dose on the day of sample until after the sample has been drawn (trough level). Patients should be at least 10 hours from the time of their last dose of imatinib when the sample is drawn.

14.58 Blood samples (1 tube) will be obtained in 5 ml, green-top (heparin) vacutainer tubes.

14.59a Sample Acquisition

If using a heparin lock or central venous catheter or port, at each sampling time, one ml of blood will be withdrawn and discarded to assure that the solution used to maintain catheter patency does not dilute the sample. Even if a patient has a central venous catheter, it is preferable for day 1 pharmacokinetic samples to be withdrawn through a peripheral heparin lock, but if the patient objects or has problems with peripheral venous access, the central venous catheter may be used. However, if the central venous catheter is used, sufficient blood should be withdrawn before each pharmacokinetic sample to assure that the solution used to maintain catheter patency does not dilute the pharmacokinetic sample.

14.59b Sample Processing:

Add 10

Specimen acquisition should be logged on the study kit requisition form. ALL sections of the form/specimen collection labels must be completed. Sample requisition forms should clearly indicate the last time of imatinib ingestion and the time at which the sample was obtained. Immediately after being obtained, blood samples should be gently inverted several times and placed onto wet ice. As soon as possible after acquisition, samples should be centrifuged at 1200 x g for at least 10 minutes to separate red blood cells from plasma. Plasma should be decanted into polypropylene, screw-cap tubes (e.g., Sarstedt No. 60.542) that are provided in the kit and clearly labeled with information corresponding to that on the vacutainer. Within 4 hours of being obtained, samples should be frozen at -20° C and stored at that temperature until shipment.

Add
6,10,13

Samples should be sent per kit instructions provided in the kit to BAP as they are obtained, e.g., as soon as is practical following procurement of the sample. (≤8 hours after collection)

Add
6,10,11,12,13

Kits for shipment of the blood samples will be supplied through BAP. Because there are charges for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Unused kits should be discarded at the site. Participating institutions may obtain kits by completing and faxing the BAP Fax Supply Order Form (found in the Forms Packet) to the fax number on the form. Allow at least two weeks to receive the kits. BAP 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.**

Add
6,13

Copies of the complete pharmacokinetic sample acquisition sheet should accompany each sample. Samples are to be packed in dry ice in styrofoam containers with enough dry ice to ensure that samples will not thaw within a 48-hour period. Samples may be sent Monday through Thursday. Samples should be shipped per kit instructions to BAP Receiving.

Add 6

Samples will be forwarded to the BAP Laboratory/NCCTG Biospecimens Resource for storage and later be distributed from BAP/NCCTG Biospecimens Resource to Dr. Merrill Egorin at the University of Pittsburgh for pharmacokinetic analysis.

14.59c Summary of Specimen Processing

Add
8,10,13

Mail according to the following schedule. Kits, where indicated, are provided as indicated from Biospecimen Accessioning and Processing (BAP). Participating institutions may obtain kits by faxing the BAP Fax Supply Order Form (found in the Forms Packet) to the fax number on the form. Allow at least two weeks to receive the kits. 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.**

Add 1,10

14.6 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 FFPE tissue blocks not required for the 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.

Add
1,5,6,9,
10

Add 6

Add
6,8,13

Add
1,6,13

TISSUE OBTAINED	TRANSLATIONAL STUDY	DETAILS IN SECTION	WHEN TO OBTAIN/DRAW:	MAILING INSTRUCTIONS
Paraffin Tissues	Imatinib inhibition targets; downstream signaling pathway studies; FISH 1p/19q and PTEN analyses	14.1; 14.3	Evaluate availability of prior surgical specimens at study entry; obtain and mail within 1 month of on study date	To: NCCTG Operations Office ATTN: NCCTG PC Office (Study N0272) RO_FF_03_24-CC/NW Clinic 200 First Street, SW Rochester, MN 55905
Frozen Tissues	Activation target molecules and downstream signaling activation	14.2	Evaluate availability of prior surgical specimens at study entry; obtain and mail within 1 month of on study date	On dry ice, per section 14.2 instructions to: BAP Laboratory/NCCTG Biospecimens Resource ATTN: BAP Supervisor Stabile 13-10A 221 4 th Avenue SW Rochester, MN 55905 (507-538-7062)
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 BAP.
Blood for Pharmacokinetic analyses	Imatinib steady state pharmacokinetics	14.5	According to schedule in Section 14.56	Samples may be sent Monday through Thursday. Samples should be shipped per kit instructions to BAP.

15.0 Drug Information

Add 9 15.1 Imatinib mesylate (Gleevec, Novartis; STI571; NSC 716051) is 4-[(4-Methyl-1-piperazinyl) methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate. Imatinib (STI571) is available in very dark yellow to brownish orange, round, biconvex tablets with NVR on one side and SA and a score on the other. They contain 100 mg imatinib with microcrystalline cellulose, crospovidone, hypomellose, colloidal silicone dioxide, and magnesium stearate. Each bottle contains 100 tablets.

The Food and Drug Administration has approved imatinib as indicated for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy, and for gastrointestinal stromal tumors (GIST). There are no controlled trials demonstrating a clinical benefit as measured by improvement in disease-related symptoms or survival.

15.2 Preparation and storage

Add 9 **Storage:** Store tablets at room temperature not to exceed 30° (86°F) in the original package.

Add 9 **Stability:** Shelf life testing of the intact bottles is on-going. Current data support a shelf life of five years.

Add 9

15.3 Drug Administration

Add 1
Add 5 Imatinib should be given as two divided doses. 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.

15.4 Reported Adverse Events and Potential Risks

15.41 Animal toxicology studies

The LD 10 occurred at an intravenous dose of 100mg/kg in male rats. However, oral doses of 600mg/kg in rats were well-tolerated, without demonstrable organ system toxicity. In rat and canine studies with repeated dosing over 13 weeks, no effect levels (NOEL) were less than 6mg/kg in the rat and 3 mg/kg in the dog. Dose-related vomiting occurred in dogs at >30mg/kg, and diarrhea was observed at all doses. Mild decrease in leukocytes and erythrocytes, and effects on testis, thymus and gastrointestinal tract were noted. Hepatic toxicity, with increases in transaminases and alkaline phosphatase were observed, and occasional biliary fibrosis, which was more prominent in the canine models. Renal toxicity was observed in the rat model, including transitional epithelial hyperplasia, without observable decreases in renal function. Benign and malignant renal tumors and benign urinary bladder tumors have also been reported in animals.

Add 2

Imatinib has teratogenic potential in rats at doses of 100 mg/kg or more. Doses of 60 mg / kg produced decreases in testicular and epididymal weights, and reduction in the percentage of motile sperm in rats. No effects on mating or fertility in female rats was observed.

There is no data to date supporting a mutagenic or carcinogenic effect of imatinib.

Add 13 15.42 **Comprehensive Adverse Events and Potential Risks list (CAEPR) For Imatinib mesylate (STI571, Gleevec[®], NSC 716051)**

Add 15 The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 5169 patients. Below is the CAEPR for imatinib mesylate (STI571).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, November 9, 2011¹

Adverse Events with Possible Relationship to Imatinib Mesylate (STI571) (CTCAE 4.0 Term) [n= 5169]			Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASael)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			<i>Anemia (Gr 3)</i>
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	
	Pericardial effusion		<i>Pericardial effusion (Gr 2)</i>
GASTROINTESTINAL DISORDERS			
Abdominal pain			<i>Abdominal pain (Gr 3)</i>
	Anal mucositis		<i>Anal mucositis (Gr 2)</i>
	Ascites		<i>Ascites (Gr 2)</i>
	Constipation		<i>Constipation (Gr 3)</i>
Diarrhea			<i>Diarrhea (Gr 3)</i>
	Dyspepsia		<i>Dyspepsia (Gr 3)</i>
	Flatulence		<i>Flatulence (Gr 2)</i>
	Gastrointestinal hemorrhage ²		<i>Gastrointestinal hemorrhage² (Gr 3)</i>
	Mucositis oral		<i>Mucositis oral (Gr 2)</i>
Nausea			<i>Nausea (Gr 3)</i>
	Rectal mucositis		<i>Rectal mucositis (Gr 2)</i>
	Small intestinal mucositis		<i>Small intestinal mucositis (Gr 2)</i>
Vomiting			<i>Vomiting (Gr 3)</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
	Edema face		
Edema limbs			<i>Edema limbs (Gr 2)</i>
Fatigue			<i>Fatigue (Gr 3)</i>
	Fever		<i>Fever (Gr 3)</i>
	General disorders and administration site conditions - Other (superficial edema)		<i>General disorders and administration site conditions - Other (superficial edema) (Gr 2)</i>

INFECTIONS AND INFESTATIONS		
	Infection ³	<i>Infection³ (Gr 4)</i>
INVESTIGATIONS		
	Alanine aminotransferase increased	<i>Alanine aminotransferase increased (Gr 4)</i>
	Alkaline phosphatase increased	<i>Alkaline phosphatase increased (Gr 2)</i>
	Aspartate aminotransferase increased	<i>Aspartate aminotransferase increased (Gr 3)</i>
	Blood bilirubin increased	<i>Blood bilirubin increased (Gr 4)</i>
	Creatinine increased	
	Lymphocyte count decreased	
Neutrophil count decreased		<i>Neutrophil count decreased (Gr 4)</i>
	Platelet count decreased	<i>Platelet count decreased (Gr 3)</i>
	Weight gain	<i>Weight gain (Gr 2)</i>
White blood cell decreased		<i>White blood cell decreased (Gr 4)</i>
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	<i>Anorexia (Gr 3)</i>
	Dehydration	<i>Dehydration (Gr 3)</i>
	Hypokalemia	<i>Hypokalemia (Gr 3)</i>
	Hyponatremia	<i>Hyponatremia (Gr 3)</i>
	Hypophosphatemia	<i>Hypophosphatemia (Gr 3)</i>
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	<i>Arthralgia (Gr 2)</i>
	Arthritis	<i>Arthritis (Gr 2)</i>
	Musculoskeletal and connective tissue disorder - Other (muscle cramps)	<i>Musculoskeletal and connective tissue disorder - Other (muscle cramps) (Gr 2)</i>
Myalgia		<i>Myalgia (Gr 2)</i>
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	<i>Headache (Gr 3)</i>
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
	Laryngeal mucositis	<i>Laryngeal mucositis (Gr 2)</i>
	Pharyngeal mucositis	<i>Pharyngeal mucositis (Gr 2)</i>
	Pleural effusion	<i>Pleural effusion (Gr 3)</i>
	Pleuritic pain	
	Tracheal mucositis	<i>Tracheal mucositis (Gr 2)</i>
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Erythema multiforme	<i>Erythema multiforme (Gr 2)</i>
	Hyperhidrosis	
	Pruritus	<i>Pruritus (Gr 2)</i>
Rash maculo-papular		<i>Rash maculo-papular (Gr 3)</i>
	Skin hyperpigmentation	<i>Skin hyperpigmentation (Gr 2)</i>
	Skin hypopigmentation	<i>Skin hypopigmentation (Gr 2)</i>
VASCULAR DISORDERS		
	Vascular disorders - Other (Intra-tumoral hemorrhage)	<i>Vascular disorders - Other (Intra-tumoral hemorrhage) (Gr 2)</i>
	Vascular disorders - Other (Hemorrhage with thrombocytopenia)	<i>Vascular disorders - Other (Hemorrhage with thrombocytopenia) (Gr 2)</i>

¹This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

²Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

³Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

⁴Gastrointestinal ulcer includes Anal ulcer, Colonic ulcer, Duodenal ulcer, Esophageal ulcer, Gastric ulcer, Ileal ulcer, Jejunal ulcer, Rectal ulcer, and Small intestine ulcer under the GASTROINTESTINAL DISORDERS SOC.

⁵Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

Also reported on Imatinib Mesylate (STI571) trials but with the relationship to Imatinib Mesylate (STI571) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia

CARDIAC DISORDERS - Cardiac arrest; Heart failure; Myocardial infarction; Ventricular arrhythmia

ENDOCRINE DISORDERS - Hypothyroidism

EYE DISORDERS - Blurred vision; Conjunctivitis; Papilledema; Photophobia; Watery eyes

GASTROINTESTINAL DISORDERS - Abdominal distension; Duodenal perforation; Esophageal fistula; Esophagitis; Gastritis; Gastrointestinal ulcer⁴; Ileus; Pancreatitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; General disorders and administration site conditions - Other (Guillain-Barre syndrome); Non-cardiac chest pain

HEPATOBIILIARY DISORDERS - Hepatic failure

IMMUNE SYSTEM DISORDERS - Allergic reaction; Autoimmune disorder

INVESTIGATIONS - CPK increased; GGT increased; Lipase increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypomagnesemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Avascular necrosis; Back pain; Bone pain; Generalized muscle weakness; Pain in extremity

NERVOUS SYSTEM DISORDERS - Depressed level of consciousness; Dysgeusia; Encephalopathy; Hydrocephalus; Intracranial hemorrhage; Ischemia cerebrovascular; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Tremor

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia

RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Proteinuria; Renal and urinary disorders - Other (kidney stones)

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Hypoxia; Pharyngolaryngeal pain; Pneumonitis; Pulmonary hypertension; Respiratory hemorrhage⁵; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Purpura

VASCULAR DISORDERS - Hypotension; Thromboembolic event; Vasculitis

Note: Imatinib Mesylate (STI571) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

15.5 Drug procurement:

Any questions that arise should be directed to the Mayo Investigational Pharmacist at (507) 266-4971.

Imatinib is an investigational drug supplied by the NCI. Drug is obtained from the Drug Management and Authorization Section, NCI (FAX 301-480-4612) using NIH form 986. Imatinib is being evaluated by the NCI under a CRADA with Novartis, Inc.

NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 and a CV. If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. Drug may be requested by completing a Clinical Drug Request (NIH-986) and mailing it to the Drug Management and Authorization Section, PMB, DCTD, NCI, 9000 Rockville Pike, EPN Room 7149, Bethesda MD, 20892-7422, or faxing it to (301) 480-4612. For questions call (301) 496-5725.

Add 1

15.6 Nursing guidelines:

- 15.61 This drug is a local irritant. Impress on patient the importance of taking capsule with a large glass of water (250 ml) and with a low fat meal. Caffeine and grapefruit juice should be avoided for one hour before and after taking the drug. Advise patient to report any GI symptoms such as dyspepsia or stomach upset. Patients should remain upright for one hour after taking drug. Check with patient on follow-up to assure patient is compliant.
- 15.62 Although this drug was found to be teratogenic in mice, no conclusive studies have been done in humans. Counsel patient/partner in the use of reliable birth control. Assess their understanding of the importance of adequate birth control. Ensure that new mothers are not breast-feeding.
- 15.63 During the pharmacokinetic periods of the study, anticonvulsant medications should be held constant. New agents which act as substrates for p450 enzymes, in particular CYP 3A4, or induce these enzymes, are to be avoided unless absolutely clinically necessary. All such medications, doses, and dates and schedule should be recorded. If concomitant medications are taken or doses of such are changed, care should be taken. Drugs with narrow therapeutic index (theophylline, digoxin, etc.) in particular should be carefully monitored.
- 15.64 Evaluate hepatic and renal function prior to initiation of therapy and periodically thereafter. Closely observe those patients with a history of pre-existing mild renal impairment or hepatic insufficiency. Encourage hydration.

Fatigue has been the most common complaint. Monitor HGB. Instruct patient to report to health care team if fatigue persists. Advise patient in energy saving lifestyle.

- 15.65 Nausea (42%) and vomiting (20%) can occur. Advise patient to report occurrence and offer antiemetic per MDs order.
- 15.66 Monitor CBC. Neutropenia and thrombocytopenia occur at the frequency related to the stage of disease being treated and also occur at a higher frequency with higher doses. Although a CVA would be extremely rare, instruct patient to report any one-sided weakness, slurred speech, diaphoresis, or confusion to health care team immediately. Report signs and symptoms to treating MD immediately for consideration of dose reduction or interruption. The median duration of neutropenia is 2-3 weeks and thrombocytopenia is 3-4 weeks. Instruct patient to avoid aspirin.
- 15.67 Instruct patient to report any easy bruising, unusual bleeding, epistaxis. If patient experiences epistaxis that is unable to be controlled by application of ice packs and keeping their head back, they need to report to the ER.
- 15.69a Patients should be cautioned to avoid any acetaminophen-containing products due to drug interaction. Advise patient to review product packages to determine components of products such as non-prescription medications and herbal products.
- 15.69b Instruct patient to report any edema, especially in lower peripheral and periorbital areas. Advise patients to weigh themselves weekly and to report weight gain to the health care team. Advise physician of any weight gain 5# from baseline weight or if edema persists or worsens.
- 15.69c Monitor pulmonary function. Instruct patient to report any respiratory changes such as dyspnea, shortness of breath, cough, or chest pain to the health care team. Local or general fluid retention can appear as pleural effusion, CHF, and pulmonary edema. These events are dose related and are more common in the blast crisis and at doses of 600 mg/day and in the elderly.
- 15.69d Transient joint pain, muscle pain and cramping are generally mild in severity. Again, caution patient against use of acetaminophen. Instruct patient to report any persistent muscle pain or muscle weakness.
- 15.69e Patients may have an increased susceptibility to infection. The degree of immunosuppression may be greater if corticosteroids are used. Instruct patient in infection preventive measures. Monitor CBC closely.
- 15.69f Advise patient of potential decreased libido and sexual performance. Patients and their partners may wish to discuss intimacy issues.

- 15.69g Headache may occur. Acetaminophen may be used, but must be **limited to 500mg/day**. If headache persists, or patient exhibits other neurologic symptoms with the headache, report to MD for consideration of steroid therapy.
- 15.69h Hemorrhagic events including bleeding into the GI system or tumor sites have occurred in 5% of patients previously tested. Instruct patients to report any tarry stools, vomiting coffee ground material, or severe bad pain immediately.
- 15.69i Instruct patient to report any nocturia, polyuria, or diaphoresis to the health care team.

16.0 Statistical Considerations & Methodology

Add 1,4

16.1 Overview: This protocol consists of 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 α 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.

Add 4

16.2 Study 1

Add 4

16.21 Study Design: The cohort-of-3 design described in Section 7.12 will be used to assess acute toxicity of imatinib in patients receiving EIACs.

Add 4

16.22 Sample Size: A minimum of 9 and a maximum of 30 patients will enter Study 1 unless undue toxicity or other factors affect patient accrual.

Add 4

16.23 Study Duration: It is expected to take about 5 months to accrue and evaluate each cohort of 3. Study 1 could take from 15 to 50 months to accrue, but is expected to take about 30 months to complete.

Add 4

16.24 Analysis Plans:

- Toxicity and translational variables will be analyzed primarily in a descriptive fashion. Since the small sample size associated with phase I studies restricts the generalizability of complex statistical procedures that are implemented, any notable statistical result is viewed as an impetus for further study in phase II trials rather than a definitive finding in and of itself.
- Response: Objective responses, as defined in Section 11.14, will be summarized by simple descriptive summary statistics delineating complete and partial responses as well as stable and progressive disease. Exploratory analysis of the relationship between response and clinical endpoints may be performed in conjunction with the data from Study 2.

- Add 5 16.25 Data and Safety Monitoring:
- 16.251 The principal investigator and study statistician will review this study twice a year to identify adverse event problems that might develop. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this study at least twice a year, based on reports provided by the MCCC Statistical Office.
- 16.252 Adverse Event Stopping Rules: Study 1 is a Phase I study and has strict accrual rules based on the cohorts-of-three study design. This is used to monitor acute adverse events and dose escalate or de-escalate based on the predefined rules found in Section 7.21.
- Add 1,4 16.3 Study 2
- Add 4 16.31 Primary Endpoint: Decisions regarding early reporting and therapeutic activity will be based on the primary endpoint of progression-free survival at 6 months (i.e., 183 days) after study registration.
- Add 1 Note: To obtain realistic estimates of the 6-month progression-free survival-after-study-entry distribution under the null hypothesis, we examined the patients who were enrolled in the three most recent NCCTG phase-II and phase-I/II trials in recurrent glioma (95-72-53, 96-72-51, and 98-72-54). There were 37 phase II patients with initial histology type of oligodendroglioma or mixed oligoastrocytoma. Two patients were excluded as they received radiation therapy less than 12 weeks prior to entering the study (see Section 3.37). Of the remaining 35 patients, 9 (25.7%) were alive and progression-free at 6 months after going on study.
- Add 1,4 16.32 Sample Size: A total of 43 patients (39 evaluable + 4 additional patients to compensate for losses due to ineligibility, cancellation, or major protocol violations) will be enrolled to the phase II component unless undue toxicity is encountered. Patients will be accrued in one stage. Patients enrolled in Study 1 at the dose level determined for the phase II component will be included in the efficacy parameters. This study was originally designed to prevent a potential imbalance of patients not on EIACs as compared to historical data, by placing a maximum of 20 patients not on EIACs (Arm B) to be accrued. However, the use of EIACs in this disease setting has decreased over time. Therefore, we have removed the maximum number of patients not on EIACs (Arm B) to be accrued. Maximum sample size will remain the same. We may adjust the decision rules at the end of the study if the proportion of patients receiving EIACs accrued is much larger or smaller than the proportion of patients that were receiving EIACs at baseline in the historical database.
- Add 5
- Add 1,4 16.33 Accrual Rate: In recent NCCTG recurrent glioma phase-II studies (96-72-51 and 98-72-54) the oligodendroglioma and mixed oligoastrocytoma accrual rate was 35 patients in approximately 36 months, with 3 patients on EIAC. This projects to an accrual rate of 12 per year, with 1-2 patients on EIAC. We expect the accrual rate to be slightly higher for this study because imatinib is an attractive, oral drug. Thus, the NCCTG accrual rate into the trial is expected to be about 16 patients per year, with 13 or 14 per year entering the EIAC group and 2 or 3 patients per year entering the non-EIAC group.
- Add 1,4 16.34 Study Duration: At the time of Addendum 1, about 8 patients have been accrued to Study 2 on arm B. Study 1 is expected to take about 30 months. In this time, about 7 patients not on EIACs are expected to be accrued to arm B. With the 6 patients from the MTD of Study 1, it is expected that about 22 additional patients will be required for accrual to Study 2 following the close of Study 1. If the accrual rate is 16/year, it will take about 17 months to enroll the remaining 22

patients, and the final analysis for Study 2 can be done about 23 months after the close of Study 1. The interim analysis for Study 2 is expected to take place approximately 8 months after the close of Study 1 (2 months to accrue 2 additional patients + 6 months to follow them).

- Add 4 16.35 Study Design:
- Add 1,4 16.351 Definition of Success: For design purposes, an eligible patient who signs the consent form and begins study therapy will be considered evaluable for assessment of treatment efficacy. To be classified as a success, a patient must be alive and progression-free 183 days after registration to study. Patients who die within 6 months after study registration will be considered to have failed.
- Add 4 16.352 Decision Rule:
- Add 1,4 16.3521 The single-stage 0.08-level procedure to be used tests the null hypothesis that the true success (i.e., patient is alive 183 days after registration) probability is $\leq 25\%$ versus the alternative hypothesis that it is $>25\%$.
- Add 1,4 16.3522 With a sample size of 39 patients, this procedure has 90% power to detect a true success probability of 45%.
- Add 1,4 16.3523 Imatinib will be considered active in this population if at least 14 of the 39 patients are classified as successes. Otherwise, it will be considered inactive.
- Add 4 16.353 Interim Analysis: An interim analysis will be performed to permit the decision regarding activity to be reported early if there is strong evidence that imatinib is inactive.
- Add 1,4 16.3531 The interim analysis will be performed when the first 23 eligible patients have been followed for at least 6 months after entering the study. The regimen will be considered inactive in this population if 5 or fewer of the first 23 patients are classified as successes. This allows the decision regarding inactive treatment to be reported early.
- Add 4 16.3532 If the interim analysis concludes that imatinib is inactive, accrual into the study may be terminated. However, adverse event rates, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be considered in any decision regarding early termination or reporting of this trial.
- Add 1,4 16.354 Other Considerations: If more than 39 evaluable patients are accrued, decisions regarding early reporting and therapeutic activity will be based on the first 39 only. All evaluable patients will be used for the analyses described in Section 16.3, however.

- Add 1,4 16.355 Power: The decision rules to be used for the interim and final analyses are based on a Simon MinMax design for testing $H_0: p \leq 25\%$ with an overall significance level of 0.08 and power of 0.90 for detecting a true success probability of 45% (49). The probability of early reporting at the interim analysis and the power to detect various values of the true success probability are summarized in the following table for 5 likely values of the population success rate:
- Add 1

If the true 'success' proportion is...	.25	.30	.35	.40	.45
...then the probability of declaring the regimen active is ...	0.08	0.26	0.51	0.75	0.90
...the probability of reporting after the interim analysis is ...	0.47	0.27	0.13	0.05	0.02

- Add 4 16.36 Analysis Plans: All evaluable patients (see Section 16.351) will be used for these analyses.
- Add 4 16.361 Primary Efficacy Analyses:
- Add 1,4 16.3611 6 month progression-free survival is defined as a patient being alive and progression-free 183 days after the date of registration.
- Add 4 16.3612 The proportion of successes will be estimated using the Binomial point estimator (number of successes divided by the total number of evaluable patients) and the Binomial 90% confidence interval estimated using the Duffy-Santner (50) algorithm, since accrual may not be completed before the interim analysis is performed.
- Add 4 16.362 Secondary Efficacy Analyses:
- Add 4 16.3621 Progression-free survival is defined to be the length of time from study registration to a) date of disease progression (defined in Section 11.0) or b) last follow-up. If a patient dies without documentation of disease progression, the patient will be considered to have had tumor progression at the time of death.
- Add 1,4 16.3622 Survival is defined as the length of time from date of registration to a) date of death due to any cause or b) last follow-up.
- Add 1,4 16.3623 Kaplan-Meier survival curves and logrank tests (51) will be used to estimate and compare the equality of the survival and progression-time distributions of (a) the imatinib patients, (b) comparable recurrent oligodendromas and mixed oligoastrocytomas in the NCCTG historical database, and (c) imatinib patient subsets defined by disease and/or key 1p/19q alteration or α PDGFR gene variables (see Section 16.34).

- Add 1,4 16.3624 Linear Analogue Self Assessment (LASA) items have been validated as general measures of global QOL dimensional constructs in numerous settings (52,53,54,55,56). A series of five LASA items have been constructed and validated at Mayo for use in cancer patients (57). LASA scores and their relationship(s) with clinical endpoints will be examined. Due to the small sample size these analyses will be primarily exploratory in nature.
- Add 4 16.363 Toxicity: The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns.
- Add 5 16.37 Data & Safety Monitoring
- 16.371 Prior to Addendum 5, A Simon Optimal design was used to monitor for unacceptable Adverse Events (AEs) (defined as grade 4+ non-hematologic or grade 5 hematologic adverse events that are life threatening or caused permanent morbidity or death, and were attributed as possibly, probably or definitely related to treatment). The stopping rules were if 1 or more out of the first 8 patients or 2 or more out of the 23 patients analyzed at the interim analysis had unacceptable AEs (UAEs), the treatment was to be considered to have a high rate of UAEs and the study team would review the data to determine if action is necessary. Accrual was to continue until official notice of study suspension was provided from NCCTG. After review of the data, it became clear that an approximate 10% unacceptable AE rate was too stringent for this regimen.
- Add 13 16.3711 As of May 25, 2006, 18 patients have been accrued to Study 2 and have received and been evaluated for at least 1 cycle of treatment. The study team (PI and statistician) carefully reviewed the grade 4 and 5 AEs in these 18 patients. Per CTC v.2.0, sixteen grade 4+ AEs were identified, of which only 7 had an attribution of at least possibly related to treatment. These 7 treatment-related AEs were observed in 4 patients. The table below outlines the UAE analysis for the sixteen grade 4+ AEs. Only one had a UAE, patient EX1641's grade 4 hemorrhage was treatment related and life threatening.

Add 13

Patient	Adverse Event*	Grade	Relationship	Grade 4+ AE Comments
EX1641	Seizure	4	Possible	
	Hemorrhage	4	Definite	Life threatening UAE
EX1387	Thrombosis	4	Possible	Not life threatening or causing permanent morbidity – not a UAE
	Vomiting	4	Possible	Not life threatening or causing permanent morbidity – not a UAE
	Seizure	4	Unlikely	Not related to study treatment
EX6904	Seizure	4	Unlikely	
	Hyponatremia	4	Unlikely	
	Neuro-Motor	4	Possible	Related to treatment but it is not life threatening or causing permanent morbidity. Not a UAE.
	Hemorrhage	4	Unlikely	
EX7659	Personality Change	4	Not related	
EX7854	Fatigue	4	Possible	Not life threatening or causing permanent morbidity.
EX100694	Dyspnea	4	Not related	
	Hyperuricemia	4	Not related	
	Speech	4	Not related	
	Thrombocytopenia	4	Probable	Not life threatening or causing permanent morbidity – Not a UAE
	Constitutional Symptoms	5	Not related	

*CTC v2.0

16.372 As of Addendum 5, the new safety monitoring plan will be the principal investigator and study statistician will formally review Study 2 for N0272 at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing during preparation of our twice yearly NCCTG meeting reports. However, we receive SAEs report soon after the patient has a serious AE so as to monitor the study continuously. The MCCC DSMB is responsible for formally reviewing accrual and safety data for this study at least twice a year, based on reports provided by the MCCC Statistical Office.

16.373 Definition of unacceptable AE: grade 4+ non-hematologic or grade 5+ hematologic AE that is possibly, probably or definitely related to treatment and life-threatening or causing permanent morbidity or death.

16.374 Adverse Event Stopping Rule: As of May 25, 2006, 1 of the 18 patients (6%) accrued to Study 2 have had UAEs. We plan to continue to accrue patients to this study as long as the UAE rate remains below 25%. If the UAE rate exceeds 25%, accrual to Study 2 will be temporarily suspended and the study team will review the study to determine the appropriate action. Currently 6% of patients accrued to this study have had UAEs during their treatment. We note that we will review all grade 4+ adverse events regardless of attribution to protect against the unlikely event of misattribution to the emergence of previously unrecognized AEs. The study team may also suspend accrual if unexpected AEs arise even if the UAE rate is less than 25%.

Add 4

16.4 Study 3

- 16.41 Current eligibility criteria for recurrent oligodendroglioma and oligoastrocytoma studies exclude patients with > 2 prior chemotherapy or 2 recurrent chemotherapy regimens. The goal of this study is to gather pilot data that may lead to changes to our standard eligibility criteria.
- 16.42 Accrual and sample size: We plan to accrue to Study 3 for the duration of Study 2. The belief is that between 10 and 20 patients will be accrued during this time period.
- 16.43 Power: We will not be doing any formal tests of significance in this study and thus have not determined power.
- 16.44 Analysis plan:
- 16.441 The 6-month progression-free survival percentage for all patients enrolled in Study 3, will be estimated as the number of evaluable patients still alive and progression free at 26 weeks divided by the total number of evaluable patients followed for at least 26 weeks. We will also generate 95% binomial confidence intervals.
- 16.442 The overall survival distribution will be estimated using the method of Kaplan-Meier. (Survival time is defined to be the length of time from start of study therapy to death due to any cause or until last follow-up.)
- 16.443 The progression-free survival distribution will be estimated using the Kaplan-Meier method. (Progression-free survival is defined as the time from start of study therapy to documentation of disease progression. Patients who die without documentation of progression will be considered to have had tumor progression at the time of death unless there is documented evidence that no progression occurred before death. Patients who fail to return for evaluation after beginning therapy will be censored for progression on their last evaluation date. Patients who experience major treatment violations will be censored for progression on the date the treatment violation occurred.)
- 16.444 Toxicity: The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns.
- 16.445 All endpoints (with special attention to progression-free survival rates at 6 months) will be computed and compared (if enough patients are available for a meaningful comparison) between the patients enrolled into Study 3 and the following:
- Patients enrolled in Study 2.
 - A historical database of recurrent oligodendroglioma and mixed oligoastrocytoma patients enrolled to NCCTG recurrent glioma protocols 797251, 867202, 867253, 887251, 897251, 897252, 917251, 927251, 937251, 957253, 967251, 987254, and N0272.

16.446 Linear Analogue Self Assessment (LASA) items have been validated as general measures of global QOL dimensional constructs in numerous settings (52,53,54,55,56). A series of five LASA items have been constructed and validated at Mayo for use in cancer patients (57). LASA scores and their relationship(s) with clinical endpoints will be examined. Due to the small sample size these analyses will be primarily exploratory in nature.

Add 5

16.45 Data & Safety Monitoring:

16.451 The principal investigator and the study statistician will formally review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing during preparation of our twice yearly NCCTG meetings reports. However, we receive SAEs report soon after the patient has a serious AE so as to monitor the study continuously. The MCCC DSMB is responsible for formally reviewing accrual and safety data for this study at least twice a year, based on reports provided by the MCCC Statistical Office.

16.452 Definition of unacceptable AE: grade 4+ non-hematologic or grade 5+ hematologic AE that is possibly, probably or definitely related to treatment and is life threatening or causing permanent morbidity or death.

16.453 Adverse Event Stopping Rules: Based on experience with this regimen, we expect 25% of patients to experience UAEs. If at any time 4 of the initial 15 patients or 25% of all patients (i.e., when accrual is greater than 15 patients), have experienced UAEs, accrual to Study 3 will be temporarily suspended to allow for a full review of the data. After consideration by the study team (i.e., study chair, statistician, NCCTG operations office, etc.) and consultation with representatives at the Clinical Trials Evaluation Program (CTEP), a decision will be made as to whether and how the study will proceed and appropriate modifications will be made to the AE stopping rules. The study team may also suspend accrual if unexpected AEs arise even if the UAE rate is less than 25%.

Add 5

Add 4

16.5 Translational Research Endpoints (Studies 1 and 2): Exploratory analyses will be performed to generate hypotheses for more extensive future research. Laboratory correlates such as 1p/19q status, α PDGFR amplification, and other downstream effectors will be correlated with survival, progression-time, and response. Spearman rank correlation coefficients will be calculated to assess the strength of linear associations between pairs of continuous variables. Whenever testing is deemed appropriate, nonparametric chi-squared and Wilcoxon tests will be used to compare distributions between/among subsets. Based on previous participation rates, about 48 patients should participate in the optional translational research component, though this may be higher or lower depending on the number of patient required to complete Study 1.

- Add 4 16.6 **Routine Monitoring:** This study will be monitored by the Mayo Clinic Cancer Center Data Safety Monitoring Board. In addition, efficacy, toxicity, and administrative information for this trial will be reviewed by the study team twice per year in conjunction with production of the semiannual NCCTG Group Meeting reports. The study team will monitor the trial for evidence of severe adverse effects and feasibility problems.
- Add 4 16.7 **Clinical Data Update System (CDUS):** This study will be monitored by CDUS. Cumulative complete CDUS data will be electronically submitted quarterly to the Clinical Trials Evaluation Program (CTEP) until all patients are off-study at which time a final report is submitted. Quarterly reports are due January 31, April 30, July 31, and October 31.
- Add 4 16.8 **Subset Analyses for Women and Minorities:**
- 16.81 This study will be available to all eligible patients, regardless of race, ethnic origin, and gender.
- 16.82 There is no information currently available regarding differential effects of this regimen in subsets defined by race or gender, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will look for differences in treatment effect based on gender and racial groupings, the sample size is not increased to provide additional power for subset analyses.
- 16.83 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 30 maximum for Study 1, 43 for Study 2, and 20 for Study 3 for a total sample size of 93.

Add 4,5

Add 4,5

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	1	3	0	4
Not Hispanic or Latino	36	53	0	89
Unknown	0	0	0	0
Ethnic Category: Total of all subjects*	37	56	0	93
Racial Category				
American Indian or Alaskan Native	0	1	0	1
Asian	0	0	0	0
Black or African American	2	1	0	3
Native Hawaiian or other Pacific Islander	0	0	0	0
White	35	54	0	89
More than one race	0	0	0	0
Unknown	0	0	0	0
Racial Category: Total of all subjects*	37	56	0	93

Ethnic Categories: **Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

Not Hispanic or Latino

Racial Categories: **American Indian or Alaskan Native** – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Add 1 **17.0 Pathology Considerations**

17.1 Central pathology review is mandatory prior to study entry to confirm eligibility, and should be initiated as soon after surgery as possible. Central pathology review will be performed by Drs. Bernd Scheithauer, Caterina Giannini, and Joseph Parisi, Mayo-Rochester.

Add 6 **A call needs to be made to the NCCTG pathology coordinator (507/266-0724 or 507/266-8919) prior to forwarding the following material:**

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

17.2 All materials for pre-entry review will be sent directly to NCCTG Operations Office at the following address:

Add 5,6,9
 NCCTG Operations Office
 ATTN: NCCTG PC Office (Study N0272)
 RO_FF_03_24-CC/NW Clinic
 200 First Street, SW
 Rochester, MN 55905

Add 5
 If materials have been previously submitted to Drs. Scheithauer, Giannini, and Parisi for a consult review or to a cooperative group pathologist for central pathology review for another cooperative group protocol, fax a copy of this review to the NCCTG pathology coordinator (507/284-9628) to verify oligodendroglioma or mixed oligoastrocytoma with an oligodendrogliomatous component.

- 17.3 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.
- 17.4 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.
- 17.5 If the patient does not enter the study, all slides and forms will be returned to the submitting institution.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Add 5

Forms	Active-Monitoring Phase (Compliance with Test Schedule)				Event-Monitoring Phase ² (Completion of Active-Monitoring Phase)		At Each Occurrence		
	Prior to Study Entry	Initial Material ≤2 weeks after registration	Follow-up material		Post treatment Q 3 ₂ mos. ²	Death	ADR/AER	New Primary	Grade 4 or 5 Non-AER Reportable Events/Hospitalization
Pathology Material ¹	X								
Linear Analogue Self Assessment (LASA)		X	X						
On-Study Form		X							
OP and Path Reports		X							
Measurement Form		X	X	X					
Specimen Submission Form for: Paraffin Blocks PB Mono-nuclear cells Frozen Tissue ⁴ Blood for PK ⁵		X	X						
Event-Monitoring Form				X	X	X		X	
Evaluation/Treatment Form			X	X					
Nadir/Adverse Event Form			X ³	X					
End of Active Treatment Form				X					
Concurrent Treatment Log		X	X	X					
ADR/AER (See Section 10.0)							X		
Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form									X
CTEP Report Variables Form		X							

Add 1

Add 1

Add 1,6

Add 1

Add 14

See following page for footnotes

- Add 1 1. See Section's 14.0 and 17.0.
2. Patients will be followed until death.
- Add 1 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.
- Add 1 4. Only institutions who have the capability
- Add 1,4 5. Post treatment samples to be drawn in Section 14.0 (Studies 1 and 2 only)

19.0 Budget

19.1 Costs charged to patient: Routine clinical care.

19.2 Tests to be research funded: Research lab assays.

20.0 References

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**Appendix IA
PHASE I
INFORMED CONSENT DOCUMENT**

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

PARTICIPANTS:

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

Why is this research study being done?

- ◆ To test the safety of Imatinib at different dose levels and to see what effects (good and bad) it has on you and your brain cancer
- ◆ To find the highest doses of Imatinib that can be given without causing bad side effects

How many people will take part in the study?

Add 5

The plan is to have about 93 people take part in this study.

What will happen in the study?

The highest safe doses will be found by increasing the doses of imatinib treatments in successive groups of patients until at least some patients have bothersome side effects. The doses a patient receives will depend on when they enter the study.

You will receive imatinib by mouth every day as long as you do not have any bad side effects. Imatinib should be taken with meals and water while in a sitting position. You will not need to be in the hospital for this treatment alone. During treatment your doctor may change the amount of imatinib you are taking, and how often you take it, depending on your side effects. You will receive the drug twice or once a day, depending on the dose. You will be treated in *treatment cycles*, and each cycle will last four (4) weeks. You will not stop taking the imatinib between treatment cycles.

Before and during treatment you will have physical examinations, neurological examinations, and blood tests at different times to see if imatinib is causing any side effects. An MRI or CT scan of the brain will be taken every 2 cycles (every 8 weeks). An ECG (a reading of the electrical activity of your heart) will be done before you start the study and may be done again later in the study. A chest x-ray will also be done before you start the study.

You will be asked to fill out questionnaires that look at changes in your daily life and feelings of well-being. These will be given to you before the study starts, before the start of the 3rd cycle and every 8 weeks after that. It will take you about 15-20 minutes to complete the questionnaire.

If you have recently had surgery for treatment of your brain tumor, you must have recovered from that surgery before starting this study. Additional surgery will not be done for this study.

On pages 3 and 4 of this consent form you will be asked to allow the use of your blood for research studies of imatinib. You will also be asked to allow the use of your tumor tissue that was taken from your prior surgery. If you agree, blood samples for research purposes would be taken before treatment on week 1 of the first cycle (3-4 tablespoons) and during week 4 of cycles 1, 2, and 3 (1-2 tablespoons each time). In addition, if your dose needs to be decreased during this study, blood will be again drawn 3 weeks after the dose has been decreased. This extra blood draw will only happen the first time that your drug dosage is decreased (1-2 tablespoons). It will not happen again later if your dose has to be reduced again. These blood samples would be used to find out how much imatinib is in your blood and what effects it has on your blood. Researchers would also study your stored tumor tissue to learn about ways that imatinib might work on your tumor. These studies are optional and you and/or your health plan would not have to pay the costs of these tests done for research only.

This table shows what will happen before, during, and at the end of the study:

Add 4

Before the study starts (within 21 days)	<ul style="list-style-type: none"> • Routine blood tests • Neurological and physical exams • MRI or CT of the brain • Chest x-ray • ECG
Before the study starts (within 7 days)	<ul style="list-style-type: none"> • Pregnancy test (if applicable) • Routine blood tests
Week 1 (Before study drug)	<ul style="list-style-type: none"> • Research blood tests (optional; explained below on page 4)
Week 2 (All cycles)	<ul style="list-style-type: none"> • Routine blood tests
Week 4 (Cycle 1,2 and 3 only)	<ul style="list-style-type: none"> • Research blood tests (optional; explained below on page 4)
3-4 weeks after a change in your imatinib dose (only after the first dose change)	<ul style="list-style-type: none"> • Research blood tests (optional; explained below on page 4)
Week 4 (All cycles)	<ul style="list-style-type: none"> • Routine blood tests
Week before cycle 3 and week before every other cycle after that	<ul style="list-style-type: none"> • Routine blood tests • Neurological and physical exams • MRI or CT of the brain • ECG (if necessary)
Within 1 week of when you end the study	<ul style="list-style-type: none"> • Routine blood tests • Neurological and physical exams • MRI or CT of the brain
Every 3 months after that	<ul style="list-style-type: none"> • Follow-up

The optional research studies involve genetic tests on your tumor tissue and blood cells. Because the genetic tests in this study would not be used for your regular medical care, you would not be told what your tests show. The test findings would not be put in your medical record.

How long will I be in the study?

You will be in the study as long as your disease does not get worse, or until you have side effects that are unacceptable. How long you are in the study will depend on how you do with this drug and how your cancer acts. Even if you stop taking the study drug, we will still want to stay in contact with you.

Are there reasons I might leave the study early?

Taking part in this research study is your decision. You may decide to stop at any time. You should tell the study doctor if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the investigators may stop you from taking part in this study at any time if it is in your best interest, if you do not follow the study rules, or if the study is stopped. You will be told of important new findings or any changes in the study or procedures that may affect you.

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?

Another part of this research study is using a small sample of your tumor tissue that has already been obtained from your prior surgeries to be stored for research studies on the effects of imatinib, or for future research studies of brain tumors. This is optional. You do not have to participate in this part of the study. The sample may be stored for a long time, even after your death. You have a say in how your stored sample is used in future research. You can still take part in the treatment study without giving your sample. There is one exception to use of your sample without your permission. This is when government rules say your sample may be used without identifying you, even with a code. At all other times:

- you can let NCCTG use your sample without asking you anymore;
- you can say no to having your sample used by NCCTG.

Your sample will be stored safely at NCCTG and will be given a code (rather than your name) when it is used in research. This code will allow your sample to be used without anyone knowing that it is your sample just by looking at the label.

There is a very small chance that there may be some profit from the use of your sample. If that would happen, NCCTG would decide if you would share in any profits.

Sometimes tissue is used for genetic research (research about diseases that are passed on in families). Even if your tissue is used for genetic research, the findings will not be linked with your medical records and they will not be given to people outside of the research process.

You are also being asked to participate in 2 research studies that requires extra blood samples. In the first, we would measure the levels of imatinib and its breakdown products in your blood. This would require a blood sample (about 1-2 tablespoons) taken before you start the first dose of imatinib, and the same amount would be drawn again at the end of the first, second, and third cycle of treatment. In addition, if your doctor has to change your dose later, the same amount (1-2 tablespoons) would be drawn again

about 3 – 4 weeks after the first dose change. It would not happen again later if your dose has to be reduced again. The second study would require a small amount of blood (2-3 tablespoons) to be taken only once, before you start the first dose of imatinib. This would be used for genetic studies done on your blood to compare with studies done on your tumor tissue.

Please read the following statements and mark your choice:

- Add 2 1. I permit my tissue sample to be stored and used for future research of cancer:
 Yes No Please initial here:_____ Date:_____
- Add 2 2. I permit my blood sample to be stored and used for future research of cancer:
 Yes No Please initial here:_____ Date:_____
- Add 2 3. I permit my tissue sample to be stored and used in future research to learn, prevent, or treat other health problems:
 Yes No Please initial here:_____ Date:_____
- Add 2 4. 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:_____

If you want your sample destroyed at any time, write to the Secretary of the _____ Institutional Review Board _____. NCCTG has the right to end storage of the sample without telling you.

The sample will be the property of NCCTG. Outside researchers may one day ask for a part of your sample for studies now or future studies.

How do outside researchers get the sample?

Researchers from universities, hospitals, and other health organizations do research using blood and tumor tissues. They may call NCCTG and ask for samples for their studies. NCCTG looks at the way that these studies will be done, and decides if any of the samples can be used. NCCTG sends the blood and tumor tissue samples and some information about you to the researcher. NCCTG will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your sample to be given to outside researchers, it will be given to them with a code number. If researchers outside NCCTG use the sample for future research, they will decide if you will be contacted and if so, they would have to contact you through the researchers at NCCTG.

- Add 2 1. I permit NCCTG to give my left over blood sample to outside researchers:
Please mark one box:
 Yes No Please initial here:_____ Date:_____
- Add 2 2. I permit NCCTG to give my left over tissue sample to outside researchers:
Please mark one box:
 Yes No Please initial here:_____ Date:_____

What are the risks of the study?

While you are taking part in this study, you are at risk for side effects. You should talk to your study doctor and/or your medical doctor about these side effects. There also may be other side effects that are not known. Other drugs may be given to lessen side effects. Many side effects go away shortly after the imatinib is stopped, but in some cases side effects can be serious, long lasting, or may never go away. The side effects can be mild or can lead to death.

Risks from a blood draw:

Having your blood drawn may cause some pain and a small risk of bleeding, bruising, or infection at the needle site.

Risks from MRI or CT scans:

Rarely, allergic reactions to the contrast (dye) material injected into the vein for your scan can happen, causing rash, itching, or in severe cases, trouble breathing or a lowering of your blood pressure. If you have had an allergy to contrast material used for MRI or CT scans done in the past you should tell your doctor.

Risks from imatinib:**Likely (events occurring greater than 20% of the time)**Add
5,7,12,13

- Decrease of the total number of white blood cells (leukocytes)
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Lowering in a part of the red blood cells (hemoglobin) that carries oxygen in the body leading to an increased risk of anemia, which may require you to have a blood transfusion
- Fatigue (feeling tired, lethargy, malaise)
- Rash/flaking or shedding of the outer layer of skin
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Nausea; the urge to vomit
- Vomiting
- Diarrhea
- Belly pain
- Swelling in your arms and legs
- Muscle pain

Less Likely (events occurring less than or equal to 20% of the time)Add
5,7,12,13

- Build-up of fluid around your heart and/or infection in the lining around your heart
- Chills, shivering
- Increased sweating
- Weight gain
- Hair loss or thinning
- Darkening or lightening of the skin
- Itching
- Severe reaction of the skin and gut lining that may include rash, shedding, or death of skin tissue and could cause you to be hospitalized for treatment (necrosis)

- Loss of appetite
- Build up of fluid in the belly/abdomen (Ascites)
- Constipation
- Loss of body fluids (dehydration – which may require fluids into a vein)
- Excess passing of gas (Flatulence)
- Heartburn or indigestion
- Irritation or sores somewhere in the digestive tract
- Bleeding in some organ(s) of the digestive tract
- Bleeding within a tumor
- Swelling of the head and neck area
- Swelling of the outer layers of an organ
- Abnormal liver or bone enzyme level (alkaline phosphatase)
- Increased level of a liver enzyme (ALT/SGPT)
- Increased level of a liver enzyme (AST/SGOT)
- Elevation of a liver pigment (bilirubin) in the blood indicative of liver dysfunction
- Increased blood level of creatinine, as substance normally eliminated by the kidneys into the urine
- Decreased blood phosphate level
- Decreased blood potassium level
- Decreased blood sodium level
- Arthritis/joint swelling (damage to your joints)
- Dizziness (sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking)
- Head pain/Headache
- Cough
- Excess fluid that accumulates in the pleural cavity, the fluid-filled space that surrounds the lungs
- Pain in the lining of the chest cavity and lungs
- Shortness of breath
- Joint pain
- Decreased number of a type of white blood cell (lymphocyte)
- Decreased number of blood cells (platelets) that help to clot blood (may increase risk of bleeding)
- Fever
- Muscle cramps
- Infection somewhere in the body associated with or without dangerously low levels of a type of white blood cell (neutrophils)

Add
1,5,7,
12,

Rare but Serious (events occurring less than 2-3% of the time)

- Decrease in the heart's ability to pump blood during the "active" phase of the heartbeat (systole)

Add 7

NOTE: STI571 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Add 12

As with any medication, allergic reactions are a possibility.

Add 2 Risks to an unborn child:

There is not enough medical information to know what the risks might be to a breast-fed infant or to an unborn child of a man or woman who takes part in this study. Men who are able to father a child and women who can become pregnant must use one of these birth control plans during this study: condoms, diaphragm, birth control pills, injections, intrauterine device (IUD), surgical sterilization, under the skin implants, abstinence. Another choice is for your sexual partner to use one of these birth control plans. If you are using birth control pills you must use a second form of birth control because the imatinib may make the birth control pills less effective. You must keep using birth control for 6 months after stopping the imatinib. Breast-feeding mothers must stop breast-feeding to take part in this study. Women who can become pregnant must have a pregnancy test before taking part in this study. For the pregnancy test, blood will be taken from a vein in your arm with a needle within 7 days before you enter the study. You will be told if you are pregnant or not. If you are pregnant, you will not be able to take part in the study. If you become pregnant while on the study you will be taken off the study.

Are there benefits to taking part in this study?

This drug may not make your health better. The benefit of imatinib to patients with brain tumors is unknown. This study is to see if imatinib can help make the tumor smaller or can stop the tumor from growing. No help can be promised by taking part in this study.

What other choices do I have if I don't take part in this study?

You do not have to be in this study to receive treatment for your brain tumor. Your other choices include 1) standard treatments, such as alternative radiation, chemotherapy or other agents that might be available to you, 2) other research treatments, or 3) supportive care, in which no treatment specifically for the cancer is given, but you receive the best possible care to make you as comfortable as possible during the course of the disease. You should talk to your doctor about each of your choices before you decide if you will take part in this study.

What are the costs of tests and procedures?

The National Cancer Institute will give you the imatinib free-of-charge for this study. Every effort will be made to provide enough study drug free-of-charge for everyone in the study. If imatinib becomes FDA approved as it is used in this study you may be asked to buy the rest of the doses of the drug. If this happens your doctor will talk to you about what to do. You and/or your health plan may also have to pay for other drugs or treatment that are given to help control side effects as well as the cost of tests or exams to evaluate possible side effects.

You will not need to pay for any tests and exams that are done just for this research study. These tests and exams are the optional research studies on your tumor tissues and on your blood cells, and the tests to measure the amount of imatinib that is in your blood. However, you and/or your health plan will need to pay for all other tests and exams that you would normally have as part of your regular medical care. This includes regular blood tests, visits to the doctor, care for illnesses that develop during treatment, and for routine MRI or CT scans. Before you take part in this study, you should call your health insurer to find out if the cost of these routine tests and/or procedures will be paid for by the plan. Some health insurers will not pay for these costs. You will have to pay for any costs not covered by your health insurer.

How long will my doctors or their assistants involved in this study keep in contact with me after I stop the drug?

Your doctors and their assistants will attempt to keep contact with you to find out how you are doing, and any major side effects you develop, as long as you are alive or until they are unable to find you in order to contact you.

Who can answer my questions?

You may talk to Dr. (_____), telephone (_____), at any time about any question you have on this study.

You can get information about policies, the conduct of the study, or the rights of research subjects from (_____)

Where can I get more information about clinical trials?

You may call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the NCI Web site: <http://www.cancer.gov/>

What happens if I am injured because I took part in this study?

You will not get free medical care or money for any bad side effects from taking part in this study. Medical services will be given at the usual charge.

What are my rights if I take part in this study?

You do not have to take part in this study, but if you do, you can stop at any time. Your medical care now or in the future will not be affected if you take part in this study or not.

You do not give up any of your rights by taking part in this study.

What about confidentiality?

Data from this study may be written up. Your name and other identifying data will not be given outside of NCCTG without written permission unless the law allows it. Your medical record will be used by the researchers in this study. Your medical records may also be looked at by representatives of the NCCTG, the National Cancer Institute, Novartis, and/or the Food and Drug Administration as stated in federal rules, or to the Office for Human Research Protections.

I have had an opportunity to have my questions answered. I have been given a copy of this form. I agree to participate in this study.

(Date) (Printed Name of Participant)

(Signed Name of Participant)

(Date) (Printed Name of Individual Obtaining Consent)

(Signed Name of Individual Obtaining Consent)

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. Sections “What Are The Risks Of The Study” or “What Other Choices Do I Have If I Don’t Take Part In This study?” should always be tried to be used in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.

**INFORMED CONSENT DOCUMENT
PHASE II**

Add 1 **TITLE:** N0272, Phase I/II Trial of Imatinib Mesylate; (Gleevec; STI571) in Treatment of Recurrent Oligodendroglioma and Mixed Oligoastrocytoma

PARTICIPANTS:

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

Why is this study being done?

This study is being done

- ◆ To find out how well the investigational drug imatinib works on your brain tumor. Imatinib has been approved by the Food and Drug Administration for treatment of certain leukemias and a kind of digestive tumor called GIST (gastrointestinal stromal tumor). This study is being done to see if imatinib also works on your type of tumor.
- ◆ To find out what effects (good and bad) imatinib has on you and your tumor
- ◆ To compare your response to imatinib with laboratory studies of your blood cells, and studies of tumor tissue that was taken from you in prior surgery. This part of the study is optional.

How many people will take part in the study?

Add 1,5 The plan is to have about 93 people take part in this study.

What will happen in the study?

You will receive imatinib by mouth every day as long as you do not have any bad side effects. Imatinib should be taken with meals and water while in a sitting position. You will not need to be in the hospital for this treatment alone. During treatment your doctor may change the amount of imatinib you are taking, and how often you take it, depending on your side effects. You will receive the drug twice or once a day, depending on the dose. You will be treated in *treatment cycles*, and each cycle will last four (4) weeks. You will not stop taking the imatinib between treatment cycles.

Before and during treatment you will have physical examinations, neurological examinations, and blood tests at different times to see if imatinib is causing any side effects. An MRI or CT scan of the brain will be taken every 2 cycles (every 8 weeks). An ECG (a reading of the electrical activity of your heart) will be done before you start the study and may be done again later in the study. A chest x-ray will also be done before you start the study.

You will be asked to fill out questionnaires that look at changes in your daily life and feelings of well-being. These will be given to you before the study starts, before the start of the 3rd cycle and every 8 weeks after that. It will take you about 15-20 minutes to complete the questionnaire.

If you have recently had surgery for treatment of your brain tumor, you must have recovered from that surgery before starting this study. Additional surgery will not be done for this study.

On pages 3 and 4 of this consent form you will be asked to allow the use of your blood for research studies of imatinib. You will also be asked to allow the use of your tumor tissue that was taken from your prior surgery. If you agree, blood samples for research purposes would be taken before treatment on week 1 of the first cycle (3-4 tablespoons) and during week 4 of cycles 1, 2, and 3 (1-2 tablespoons each time). In addition, if your dose needs to be decreased during this study, blood will be again drawn 3 weeks after the dose has been decreased. This extra blood draw will only happen the first time that your drug dosage is decreased (1-2 tablespoons). It will not happen again later if your dose has to be reduced again. These blood samples would be used to find out how much imatinib is in your blood and what effects it has on your blood. Researchers would also study your stored tumor tissue to learn about ways that imatinib might work on your tumor. These studies are optional and you and/or your health plan would not have to pay the costs of these tests done for research only.

This table shows what will happen before, during, and at the end of the study:

Add 4

Before the study starts (within 21 days)	<ul style="list-style-type: none"> • Routine blood tests • Neurological and physical exams • MRI or CT of the brain • Chest x-ray • ECG
Before the study starts (within 7 days)	<ul style="list-style-type: none"> • Pregnancy test (if applicable) • Routine blood tests
Week 1 (Before study drug)	<ul style="list-style-type: none"> • Research blood tests (optional; explained below on page 4)
Week 2 (All cycles)	<ul style="list-style-type: none"> • Routine blood tests
Week 4 (Cycle 1,2 and 3 only)	<ul style="list-style-type: none"> • Research blood tests (optional; explained below on page 4)
3-4 weeks after a change in your imatinib dose (only after the first dose change)	<ul style="list-style-type: none"> • Research blood tests (optional; explained below on page 4)
Week 4 (All cycles)	<ul style="list-style-type: none"> • Routine blood tests
Week before cycle 3 and week before every other cycle after that	<ul style="list-style-type: none"> • Routine blood tests • Neurological and physical exams • MRI or CT of the brain • ECG (if necessary)
Within 1 week of when you end the study	<ul style="list-style-type: none"> • Routine blood tests • Neurological and physical exams • MRI or CT of the brain
Every 3 months after that	<ul style="list-style-type: none"> • Follow-up

The optional research studies involve genetic tests on your tumor tissue and blood cells. Because the genetic tests in this study would not be used for your regular medical care, you would not be told what your tests show. The test findings would not be put in your medical record.

How long will I be in the study?

You will be in the study as long as your disease does not get worse, or until you have side effects that are unacceptable. How long you are in the study will depend on how you do with this drug and how your cancer acts. Even if you stop taking the study drug, we will still want to stay in contact with you.

Are there reasons I might leave the study early?

Taking part in this research study is your decision. You may decide to stop at any time. You should tell the study doctor if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the investigators may stop you from taking part in this study at any time if it is in your best interest, if you do not follow the study rules, or if the study is stopped. You will be told of important new findings or any changes in the study or procedures that may affect you.

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?

Another part of this research study is using a small sample of your tumor tissue that has already been obtained from your prior surgeries to be stored for research studies on the effects of imatinib, or for future research studies of brain tumors. This is optional. You do not have to participate in this part of the study. The sample may be stored for a long time, even after your death. You have a say in how your stored sample is used in future research. You can still take part in the treatment study without giving your sample. There is one exception to use of your sample without your permission. This is when government rules say your sample may be used without identifying you, even with a code. At all other times:

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Sometimes tissue is used for genetic research (research about diseases that are passed on in families). Even if your tissue is used for genetic research, the findings will not be linked with your medical records and they will not be given to people outside of the research process.

You are also being asked to participate in 2 research studies that requires extra blood samples. In the first, we would measure the levels of imatinib and its breakdown products in your blood. This would require a blood sample (about 1-2 tablespoons) taken before you start the first dose of imatinib, and the same amount would be drawn again at the end of the first, second, and third cycle of treatment. In addition, if

your doctor has to change your dose later, the same amount (1-2 tablespoons) would be drawn again about 3 – 4 weeks after the first dose change. It would not happen again later if your dose has to be reduced again. The second study would require a small amount of blood (2-3 tablespoons) to be taken only once, before you start the first dose of imatinib. This would be used for genetic studies done on your blood to compare with studies done on your tumor tissue.

Please read the following statements and mark your choice:

- Add 2 1. I permit my tissue sample to be stored and used for future research of cancer:
 Yes No Please initial here: _____ Date: _____
- Add 2 2. I permit my blood sample to be stored and used for future research of cancer:
 Yes No Please initial here: _____ Date: _____
- Add 2 3. I permit my tissue sample to be stored and used in future research to learn, prevent, or treat other health problems:
 Yes No Please initial here: _____ Date: _____
- Add 2 4. 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: _____

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- Add 2 1. I permit NCCTG to give my left over blood sample to outside researchers:
Please mark one box:
 Yes No Please initial here: _____ Date: _____
- Add 2 2. I permit NCCTG to give my left over tissue sample to outside researchers:
Please mark one box:
 Yes No Please initial here: _____ Date: _____

What are the risks of the study?

While you are taking part in this study, you are at risk for side effects. You should talk to your study doctor and/or your medical doctor about these side effects. There also may be other side effects that are not known. Other drugs may be given to lessen side effects. Many side effects go away shortly after the imatinib is stopped, but in some cases side effects can be serious, long lasting, or may never go away. The side effects can be mild or can lead to death.

Risks from a blood draw:

Having your blood drawn may cause some pain and a small risk of bleeding, bruising, or infection at the needle site.

Risks from MRI or CT scans:

Rarely, allergic reactions to the contrast (dye) material injected into the vein for your scan can happen, causing rash, itching, or in severe cases, trouble breathing or a lowering of your blood pressure. If you have had an allergy to contrast material used for MRI or CT scans done in the past you should tell your doctor.

Risks from imatinib:**Likely (events occurring greater than 20% of the time)**

- Decrease of the total number of white blood cells (leukocytes)
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Lowering in a part of the red blood cells (hemoglobin) that carries oxygen in the body leading to an increased risk of anemia, which may require you to have a blood transfusion
- Fatigue (feeling tired, lethargy, malaise)
- Rash/flaking or shedding of the outer layer of skin
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Nausea; the urge to vomit
- Vomiting
- Diarrhea
- Belly pain
- Swelling in your arms and legs
- Muscle pain

Less Likely (events occurring less than or equal to 20% of the time)

- Build-up of fluid around your heart and/or infection in the lining around your heart
- Chills, shivering
- Increased sweating
- Weight gain
- Hair loss or thinning
- Darkening or lightening of the skin
- Itching
- Severe reaction of the skin and gut lining that may include rash, shedding, or death of skin tissue and could cause you to be hospitalized for treatment (necrosis)

Add
5,7,12,13Add
5,7,12,13,
15

- Loss of appetite
- Build up of fluid in the belly/abdomen (Ascites)
- Constipation
- Loss of body fluids (dehydration – which may require fluids into a vein)
- Excess passing of gas (Flatulence)
- Heartburn or indigestion
- Irritation or sores somewhere in the digestive tract
- Irritation or sores in the lining of the anus
- Irritation or sores in the lining of the mouth
- Irritation or sores in the lining of the rectum
- Irritation or sores in the lining of the small bowel
- Irritation or sores in the lining of the voice box
- Irritation or sores in the lining of the throat
- Irritation or sores in the lining of the windpipe
- Bleeding in some organ(s) of the digestive tract
- Bleeding within a tumor
- Swelling of the head and neck area
- Swelling of the outer layers of an organ
- Abnormal liver or bone enzyme level (alkaline phosphatase)
- Increased level of a liver enzyme (ALT/SGPT)
- Increased level of a liver enzyme (AST/SGOT)
- Elevation of a liver pigment (bilirubin) in the blood indicative of liver dysfunction
- Increased blood level of creatinine, as substance normally eliminated by the kidneys into the urine
- Decreased blood phosphate level
- Decreased blood potassium level
- Decreased blood sodium level
- Arthritis/joint swelling (damage to your joints)
- Dizziness (sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking)
- Head pain/Headache
- Cough
- Excess fluid that accumulates in the pleural cavity, the fluid-filled space that surrounds the lungs
- Pain in the lining of the chest cavity and lungs
- Shortness of breath
- Joint pain
- Decreased number of a type of white blood cell (lymphocyte)
- Bleeding with a decreased number of blood cells (platelets) that help to clot blood (may increase risk of bleeding)
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Rare but Serious (events occurring less than 2-3% of the time)

- Decrease in the heart's ability to pump blood during the "active" phase of the heartbeat (systole)

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Add 12

As with any medication, allergic reactions are a possibility.

Risks to an unborn child:

There is not enough medical information to know what the risks might be to a breast-fed infant or to an unborn child of a man or woman who takes part in this study. Men who are able to father a child and women who can become pregnant must use one of these birth control plans during this study: condoms, diaphragm, birth control pills, injections, intrauterine device (IUD), surgical sterilization, under the skin implants, abstinence. Another choice is for your sexual partner to use one of these birth control plans. If you are using birth control pills you must use a second form of birth control because the imatinib may make the birth control pills less effective. You must keep using birth control for 6 months after stopping the imatinib. Breast-feeding mothers must stop breast-feeding to take part in this study. Women who can become pregnant must have a pregnancy test before taking part in this study. For the pregnancy test, blood will be taken from a vein in your arm with a needle within 7 days before you enter the study. You will be told if you are pregnant or not. If you are pregnant, you will not be able to take part in the study. If you become pregnant while on the study you will be taken off the study.

Are there benefits to taking part in this study?

This drug may not make your health better. The benefit of imatinib to patients with brain tumors is unknown. This study is to see if imatinib can help make the tumor smaller or can stop the tumor from growing. No help can be promised by taking part in this study.

What other choices do I have if I don't take part in this study?

You do not have to be in this study to receive treatment for your brain tumor. Your other choices include 1) standard treatments, such as alternative radiation, chemotherapy or other agents that might be available to you, 2) other research treatments, or 3) supportive care, in which no treatment specifically for the cancer is given, but you receive the best possible care to make you as comfortable as possible during the course of the disease. You should talk to your doctor about each of your choices before you decide if you will take part in this study.

What are the costs of tests and procedures?

The National Cancer Institute will give you the imatinib free-of-charge for this study. Every effort will be made to provide enough study drug free-of-charge for everyone in the study. If imatinib becomes FDA approved as it is used in this study you may be asked to buy the rest of the doses of the drug. If this happens your doctor will talk to you about what to do. You and/or your health plan may also have to pay for other drugs or treatment that are given to help control side effects as well as the cost of tests or exams to evaluate possible side effects.

You will not need to pay for any tests and exams that are done just for this research study. These tests and exams are the optional research studies on your tumor tissues and on your blood cells, and the tests to measure the amount of imatinib that is in your blood. However, you and/or your health plan will need to pay for all other tests and exams that you would normally have as part of your regular medical care. This includes regular blood tests, visits to the doctor, care for illnesses that develop during treatment, and for routine MRI or CT scans. Before you take part in this study, you should call your health insurer to find out if the cost of these routine tests and/or procedures will be paid for by the plan. Some health insurers will not pay for these costs. You will have to pay for any costs not covered by your health insurer.

How long will my doctors or their assistants involved in this study keep in contact with me after I stop the drug?

Your doctors and their assistants will attempt to keep contact with you to find out how you are doing, and any major side effects you develop, as long as you are alive or until they are unable to find you in order to contact you.

Who can answer my questions?

You may talk to Dr. (_____), telephone (_____), at any time about any question you have on this study.

You can get information about policies, the conduct of the study, or the rights of research subjects from (_____)

Where can I get more information about clinical trials?

You may call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the NCI Web site: <http://www.cancer.gov/>

What happens if I am injured because I took part in this study?

You will not get free medical care or money for any bad side effects from taking part in this study. Medical services will be given at the usual charge.

What are my rights if I take part in this study?

You do not have to take part in this study, but if you do, you can stop at any time. Your medical care now or in the future will not be affected if you take part in this study or not.

You do not give up any of your rights by taking part in this study.

What about confidentiality?

Data from this study may be written up. Your name and other identifying data will not be given outside of NCCTG without written permission unless the law allows it. Your medical record will be used by the researchers in this study. Your medical records may also be looked at by representatives of the NCCTG, the National Cancer Institute, Novartis, and/or the Food and Drug Administration as stated in federal rules, or to the Office for Human Research Protections.

I have had an opportunity to have my questions answered. I have been given a copy of this form. I agree to participate in this study.

(Date) (Printed Name of Participant)

(Signed Name of Participant)

(Date) (Printed Name of Individual Obtaining Consent)

(Signed Name of Individual Obtaining Consent)

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. Sections “What Are The Risks Of The Study” or “What Other Choices Do I Have If I Don’t Take Part In This study?” should always be tried to be used in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.

APPENDIX II
ECOG PERFORMANCE STATUS

<u>ECOG scale</u>		<u>Karnofsky score</u>
0	Asymptomatic and fully active	100%
1	Symptomatic; fully ambulatory; restricted in physically strenuous activity	80-90%
2	Symptomatic; ambulatory; capable of self-care; more than 50% of waking hours are spent out of bed	60-70%
3	Symptomatic; limited self-care; spends more than 50% of time in bed, but not bedridden	40-50%
4	Completely disabled; no self-care; bedridden	20-30%

Appendix IIIA

Drugs known to be metabolized by CYP450 Isoenzymes 2D6 and 3A4

CYP2D6	
Substrates	
Amitriptyline (hydroxylation)	Methamphetamine
Amphetamine	Metoclopramide
Betaxolol	Metoprolol
Bisoprolol	Mexiteline
Brofaromine	Mianserin
Buturolool	Meperidine
Bupropion	Methadone Mirtazapine (hydroxylation)
Captopril	Molindone
Carvedilol	Morphine
Cevimeline	Nortriptyline (hydroxylation)
Chlorpheniramine	Olanzapine (minor, hydroxymethylation)
Chlorpromazine	Ondansetron
Cinnartzine	Orphenadrine
Clomipramine (hydroxylation)	Oxycodone
Clozapine (minor pathway)	Papaverine
Codeine (hydroxylation, o-demethylation)	Paroxetine (minor pathway)
Cyclobenzaprine (hydroxylation)	Penbutolol
Cyclophosphamide	Pentazocine
Debrisoquin	Perhexiline
Delavirdine	Perphenazine
Desipramine	Phenformin
Dexfenfluramine	Pindolol
Dextromethorphan (o-demethylation)	Promethazine
Dihydrocodeine	Propafenone
Diphenhydramine	Propranolol
Dolasetron	Quetiapine
Donepezil	Remoxipride
Doxepin	Risperidone
Encainide	Ritonavir (minor)
Fenfluramine	Ropivacaine
Flecainide	Selegiline
Fluoxetine (minor pathway)	Sertindole
Fluphenazine	Sertraline (minor pathway)
Halofantrine	Sparteine
Haloperidol (minor pathway)	Tamoxifen
Hydrocodone	Thioridazine
Hydrocortisone	Tiagabine
Hydroxyamphetamine	Timolol
Imipramine (hydroxylation)	Tolterodine
Labetalol	Tramadol
Loratadine	Trazodone
Maprotiline	Trimipramine
m-Chlorophenylpiperazine (m-CPP)	Tropisetron
	Venlafaxine (o-desmethylation)
	Yohimbine

Inhibitors	
Amiodarone	Methadone
Celecoxib	Mibefradil
Chloroquine	Moclobemide
Chlorpromazine	Nortioxetine
Cimetidine	Paroxetine
Citalopram	Perphenazine
Clomipramine	Propafenone
Codeine	Quinacrine
Delavirdine	Quinidine
Desipramine	Ranitidine
Dextropropoxyphene	Risperidone (weak)
Diltiazem	Ritonavir
Doxorubicin	Sertindole
Entacapone (high dose)	Sertraline (weak)
Fluoxetine	Thioridazine
Fluphenazine	Valproic acid
Fluvoxamine	Venlafaxine (weak)
Haloperidol	Vinblastine
Labetalol	Vincristine
Lobeline	Vinorelbine
Lomustine	Yohimbine

CYP3A3/4	
	Substrates
Acetaminophen	Chlorpromazine
Afentanil	Cimetidine
Alosetron	Cisapride
Alprazolam	Citalopram
Amiodarone	Clarithromycin
Amitriptyline (minor)	Clindamycin
Amlodipine	Clomipramine
Anastrozole	Clozapine
Androsterone	Cocaine
Antipyrine	Codeine (demethylation)
Astemizole	Cortisol
Atorvastatin	Cortisone
Benzphetamine	Cyclobenzaprine (demethylation)
Bepidil	Cyclophosphamide
Bexarotene	Cyclosporine
Bromazepam	Dapsone
Bromocriptine	Dehydroepiandrosterone
Budesonide	Delavirdine
Bupropion (minor)	Desmethyldiazepam
Buspirone	Dexamethasone
Busulfan	Dextromethorphan (minor, N-demethylation)
Caffeine	Diazepam (minor; hydroxylation, N-demethylation)
Cannabinoids	
Carbamazepine	
Cevimeline	Nefazodone
Cerivastatin	Neofinavir

CYP3A3/4

Digitoxin	Nevirapine
Diltiazem	Nicardipine
Disopyramide	Nifedipine
Docetaxel	Niludipine
Dolasetron	Nimodipine
Donepezil	Nisoldipine
Doxorubicin	Nitrendipine
Doxycycline	Omeprazole (sulfonation)
Dronabinol	Ondansetron
Enalapril	Oral contraceptives
Erythromycin	Orphenadrine
Estradiol	Paclitaxel
Ethinyl estradiol	Pantoprazole
Ethosuximide	Pimozide
Etoposide	Pioglitazone
Exemestane	Pravastatin
Dofetilide (minor)	Prednisone
Felodipine	Progesterone
Fentanyl	Proguanil
Fexofenadine	Propafenone
Finasteride	Quercetin
Fluoxetine	Quetiapine
Flutamide	Quinidine
Glyburide	Quinine
Granisetron	Repaglinide
Halofantrine	Retinoic acid
Hydrocortisone	Rifampin
Hydroxyarginine	Risperidone
Ifosfamide	Ritonavir
Imipramine	Salmeterol
Indinavir	Saquinavir
Lisdipine	Sertindole
Litraconazole	Sertraline
Ketoconazole	Sibutramine
Lansoprazole (minor)	Sildenafil citrate
Letrozole	Simvastatin
Levobupivacaine	Siroliimus
Lidocaine	Sufentanil
Loratadine	Tacrolimus
Losartan	Tamoxifen
Lovastatin	Temazepam
Methadone	Teniposide
Mibefradil	Terfenadine
Miconazole	Testosterone
Midazolam	Tetrahydrocannabinol
Mifepristone	Theophylline
Mirtazapine (N-demethylation)	Tiagabine
Montelukast	Tolterodine
Navelbine	Vincristine
	Warfarin (R-warfarin)
Toremifene	Yohimbine
Trazodone	Zaleplon (minor pathway)
Tretinoin	Zatoestron

CYP3A3/4	
Triazolam	Zileuton
Troglitazone	Ziprasidone
Troleandomycin	Zolpidem
Venlafaxine (N-demethylation)	Zonisamide
Verapamil	
Vinblastine	
Inducers	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Ethosuximide	Progesterone
Glucocorticoids	Rifabutin
Griseofulvin	Rifampin
Nafcillin	Rofecoxib (mild)
Nelfinavir	St John's wort
Nevirapine	Sulfadimidine
Oxcarbazepine	Sulfipyrazone
Phenobarbital	Troglitazone
Phenylbutazone	
Inhibitors	
Amiodarone	Ketoconazole
Anastrozole	Metronidazole
Azithromycin	Mibefradil
Cannabinoids	Miconazole (moderate)
Cimetidine	Nefazodone
Clarithromycin	Nelfinavir
Clotrimazole	Nevirapine
Cyclosporine	Norfloxacin
Danazol	Norfluoxetine
Delavirdine	Omeprazole (weak)
Dexamethasone	Oxiconazole
Diethyldithiocarbamate	Paroxetine (weak)
Diltiazem	Propoxyphene
Dirithromycin	Quinidine
Disulfiram	Quinine
Entacapone (high dose)	Quinupristin and dalbopristin
Erythromycin	Ranitidine
Ethinyl estradiol	Ritonavir
Fluconazole (weak)	Saquinavir
Fluoxetine	Sertindole
Fluvoxamine	Sertraline
Gestodene	Troglitazone
Grapefruit juice	Troleandomycin
Indinavir	Valproic acid (weak)
Isoniazid	Verapamil
Itraconazole	Zafirlukast
	Zileuton

Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In : Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 8th ed. Hudson, OH; LexiComp Inc. 2000: 1364-1371

APPENDIX III B
ENZYME AND NON -INDUCING ANTICONVULSANT AGENTS

EIACs:	NON-EIAC:
ANTICONVULSANTS WHICH INDUCE CYP3A4	ANTICONVULSANTS NOT INDUCING CYP3A4
Phenytoin	Clonazepam
Fosphenytoin	Topiramate
Phenobarbital	Valproic acid
Carbamazepine	Lamotrigine
Oxcarbazepine	Levetiracetam
Primidone	Zonisamide
	Tiagabine
	Gabapentin

(Lacy et al, 1999)

Appendix IV

Cooperative Research and Development Agreement (CRADA)

The agent (hereinafter referred to as Agent), imatinib [STI-571, (Gleevec)], used in this protocol is provided to the NCI under a Cooperative Research and Development Agreement (CRADA) between Novartis Pharmaceuticals (hereinafter referred to as Collaborator(s)) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and should be maintained as such by the investigators.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different CTAs or CRADAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data.):
 - a. NCI must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.
 - b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
 - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. The NCI encourages investigators to make data from clinical trials fully available to Collaborator(s) for review at the appropriate time (see #5). The NCI expects that clinical trial data developed under a CTA or CRADA will be made available exclusively to Collaborator(s), and not to other parties.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for cooperative group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) must be in accordance with the guidelines and policies of the responsible Data Monitoring Committ(DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to Collaborator(s) intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator(s) for courtesy review following submission, but prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Room 7111
Bethesda, Maryland 20892
FAX 301-402-1584

The Regulatory Affairs Branch will then distribute them to Collaborator(s).

PLACE LABEL HERE

Protocol # N0272

NORTH CENTRAL CANCER TREATMENT GROUP

Patient ID # _____ Initials: _____

Appendix V

Local ID # _____ Institution L F M

PILL DIARY

PILL DIARY

INSTRUCTIONS FOR THE PATIENTS: This is a monthly calendar on which you are to record the number of pills you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the pills, mark this on the calendar on the day you note the effect. **Bring the bottle(s) with the unused pills and your calendars with you each time you have an appointment.** If you have any questions contact: _____

Telephone: _____ Your next appointment is: _____

Special Instructions: _____

*** It is very important to record exact time pills were taken.**

MONTH: _____ YEAR: _____			MONTH OF VISIT PILL DIARY REFERS TO: (Example: Reg, Rand, Month 3, etc.) _____			
SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
<input type="text"/> Time Taken: * _____	<input type="text"/> Time Taken: * _____	<input type="text"/> Time Taken: * _____	<input type="text"/> Time Taken: * _____	<input type="text"/> Time Taken: * _____	<input type="text"/> Time Taken: * _____	<input type="text"/> Time Taken: * _____
<input type="text"/> Time Taken: * _____	<input type="text"/> Time Taken: * _____	<input type="text"/> Time Taken: * _____	<input type="text"/> Time Taken: * _____	<input type="text"/> Time Taken: * _____	<input type="text"/> Time Taken: * _____	<input type="text"/> Time Taken: * _____
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COMMENTS: _____

NORTH CENTRAL CANCER TREATMENT GROUP

Linear Analogue Self Assessment (LASA)

Directions: Please circle the **one** number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today.**

How would you describe:

1. your overall Quality of Life?

0	1	2	3	4	5	6	7	8	9	10	
As bad as											As good as
it can be											it can be

2. your overall mental (intellectual) well being?

0	1	2	3	4	5	6	7	8	9	10	
As bad as											As good as
it can be											it can be

3. your overall physical well being?

0	1	2	3	4	5	6	7	8	9	10	
As bad as											As good as
it can be											it can be

4. your overall emotional well being?

0	1	2	3	4	5	6	7	8	9	10	
As bad as											As good as
it can be											it can be

5. your level of social activity?

0	1	2	3	4	5	6	7	8	9	10	
As bad as											As good as
it can be											it can be

6. your overall spiritual well being?

0	1	2	3	4	5	6	7	8	9	10	
As bad as											As good as
it can be											it can be

7. the frequency of your pain?

0	1	2	3	4	5	6	7	8	9	10	
No pain											Constant pain

8. the severity of your pain, on the average?

0	1	2	3	4	5	6	7	8	9	10	
No pain											Pain as bad as
											you can imagine

9. your level of fatigue, on the average?

0	1	2	3	4	5	6	7	8	9	10	
No fatigue											Constant tiredness

10. your level of support from friends and family?

0	1	2	3	4	5	6	7	8	9	10	
No support											Highest level of
											support