

North Central Cancer Treatment Group

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

Addendum 15 – December 23, 2011

Summary

- This addendum is in response to a Request for Amendment (RA) from the National Cancer Institute (NCI) dated November 16, 2011 concerning Imatinib Mesylate (STI571). The Drug Information section and the Phase II consent form have been updated accordingly.
- Administrative changes.

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

Title page Revised to reflect Addendum 15 and updated NCI version date.

Protocol Resources

Page 2: **Sanna L. McKinzie** replaces ~~John M. (Jack) Beranek~~ as the NCCTG Research Base Protocol Specialist.

Section 15.0 Drug Information

Pages 43-46: Due to the receipt of the RA from NCI for Imatinib Mesylate, Section 15.42 has been replaced in its entirety.

Appendix IB Consent Form

Page 6: Due to the receipt of the RA from NCI for Imatinib Mesylate, the Less Likely risk section has been updated as follows:

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)
- 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 (newly added)**

- **Irritation or sores in the lining of the mouth** (*newly added*)
- **Irritation or sores in the lining of the rectum** (*newly added*)
- **Irritation or sores in the lining of the small bowel** (*newly added*)
- **Irritation or sores in the lining of the voice box** (*newly added*)
- **Irritation or sores in the lining of the throat** (*newly added*)
- **Irritation or sores in the lining of the windpipe** (*newly added*)
- 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)** (*wording expanded*)
- Fever
- Muscle cramps
- Infection somewhere in the body associated with or without dangerously low levels of a type of white blood cell (neutrophils)

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.

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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

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.

**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:

- 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)**

- 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)

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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)
- Fever
- Muscle cramps
- Infection somewhere in the body associated with or without dangerously low levels of a type of white blood cell (neutrophils)

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)

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.

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.