RADIATION THERAPY ONCOLOGY GROUP

RTOG S-0132

A PHASE II TRIAL OF NEOADJUVANT/ADJUVANT STI-571 *(GLEEVEC NSC #716051)* FOR PRIMARY AND RECURRENT OPERABLE MALIGNANT GIST EXPRESSING THE KIT RECEPTOR TYROSINE KINASE *(CD117)* *[ACRIN 6665]*

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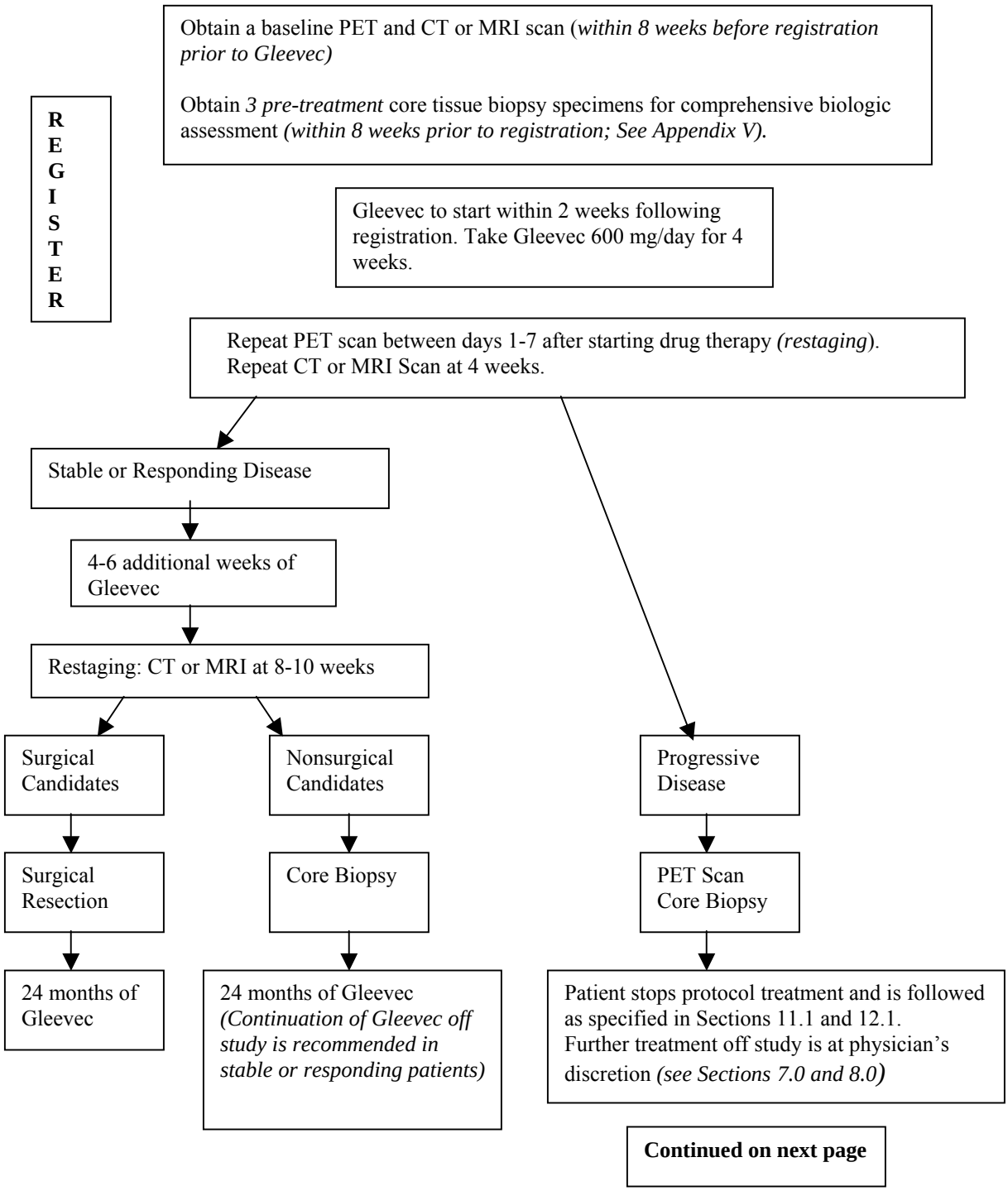
SCHEMA *(4/5/04)*



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<u>Eligibility</u>: *(See Section 3.0 for details)**[4/5/04]***

- Biopsy-proven diagnosis of either potentially resectable primary *(≥ 5 cm)* or potentially resectable recurrent *(local or metastatic [≥ 2 cm])* GIST. Primary must be visceral, intraabdominal, or pelvic in origin;
- Immunohistochemical documentation of KIT *(CD117)* expression in tumor *(either from initial core specimen or from original tumor block, if recurrent);*
- Must agree to have three core tissue biopsies performed within 8 weeks prior to registration *(see Sections 3.1 and 12.1);*
- Zubrod 0-2;
- WBC ≥ 3,000/µl; ANC ≥ 1500/µl; platelets ≥ 100,000/µl; bilirubin ≤ 1.5 x institutional ULN; ALT/AST ≤ 2.5 x institutional ULN; creatinine ≤ 1.5 x institutional ULN;
- No chemotherapy, radiation therapy, biologic therapy, prior Gleevec, or other investigational drug within 28 days of study entry;
- No NYHA Class III or IV cardiac disease;
- No pregnant or nursing women;
- Any prior malignancy is allowed as long as the patient is disease- free from that malignancy;
- No uncontrollable hyperglycemia;
- No patients with any known or suspected hypersensitivity to one of the components of the study drug;
- Patient must have a medical and surgical oncologist;
- Patient must be able to lie still in PET scanner for 60-120 minutes;
- Age ≥ 18 years.
- Gleevec to start within 2 weeks following registration.
- Study-specific signed informed consent.
- Institution able to meet PET imaging guidelines.

Required Sample Size: 63

RTOG Institution # _____

RTOG S-0132 ***(ACRIN 6665)*** **ELIGIBILITY CHECKLIST** ***(4/5/04)***

Case # _____ *(page 1 of 3)*

_____ 1. What is the Zubrod performance status *(0-2)*?

_____(N) 2. Does the patient have uncontrollable hyperglycemia?

_____(N) 3. Does the patient have class III or IV cardiac disease?

_____(N) 4. Is the patient taking > 1 mg of coumadin per day?

_____(N) 5. Has the patient had prior radiation, chemotherapy, or biologic therapy, Gleevec, or any other investigational drug within 28 days of study entry?

_____(Y) 6. Is there a biopsy-proven diagnosis of malignant GIST?

_____(Y)/NA 7. If primary GIST, is the tumor ≥ 5 cm in at least one dimension?

_____(Y)/NA 8. If recurrent GIST, is the tumor ≥ 2 cm in at least one dimension?

_____(Y) 9. Is the primary visceral, intraabdominal, or pelvic in origin?

_____(Y) 10. Is the primary tumor *(CD117)* kit positive according to Section 3.1.1 of the protocol?

_____(Y) 11. Is the WBC ≥ 3,000 µl?

_____(Y) 12. Is the ANC ≥ 1,500 µl?

_____(Y) 13. Are the platelets ≥ 100,000 ml?

_____(Y) 14. Is the bilirubin ≤ 1.5 x institutional upper limits of normal *(ULN)*?

_____(Y) 15. Is the AST/ALT ≤ 2.5x institutional ULN?

_____(Y) 16. Is creatinine ≤ 1.5 x institutional ULN?

_____(Y/N) 17. Were the three core biopsies done within 8 weeks prior to registration?

_____(Y) 18. Was the pre-treatment PET scan done at an ACRIN certified institution?

_____(Y) 19. Does the patient have an identified medical oncologist and surgical oncologist?

_____(Y) 20. Is the tumor considered to be potentially operable?

_____(Y) 21. Was a serum pregnancy test done within 7 days of study entry and was it negative *(only if applicable)*?

(Continued on next page)

_____(Y)/NA 22. Have both the male and female patients *(of reproductive potential)* agreed to use effective contraceptive methods throughout the study and 3 months post study drug?

_____(Y) 23. Is the patient disease-free from any prior malignancy?

_____(Y) 24. Can the patient lie still for 60-120 minutes in the PET scanner?

_____ (Y) 25. Is the patient at least 18 years of age?

_____(N) 26. Does the patient have severe and/or uncontrolled concurrent medical disease?

_____(N) 27. Does the patient have any known or suspected hypersensitivity to one of the components of the study drug?

The following questions will be asked at Study Registration:

_____ 1. Name of institutional person registering this case?

_____(Y) 2. Has the Eligibility Checklist *(above)* been completed?

_____(Y) 3. Is the patient eligible for this study?

_____ 4. Date the study-specific Consent Form was signed? *(must be prior to study entry)*

_____ 5. Patient's Initials (Last, First)

_____ 6. Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Ethnic Category *(Hispanic or Latino, Not Hispanic or Latino, Unknown)*

_____ 10. Race

_____ 11. Gender

_____ 12. Patient's Country of Residence

_____ 13. Zip Code

_____ 14. Patient's Insurance Status

_____(N/Y) 15. Will any component of the patient's care be given at a military or VA facility?

(Continued on next page)

RTOG Institution # _____

RTOG S-0132 ***(ACRIN 6665)*** **ELIGIBILITY CHECKLIST*4/5/04)***

Case # _____ *(page 3 of 3)*

_____ 16. Medical Oncologist

_____ 17. Surgical Oncologist

_____ 18. PET Institution

_____(N/Y) 19. Tissue/Blood kept for cancer research?

_____(N/Y) 20. Tissue/Blood kept for medical research?

_____(N/Y) 21. Allow contact for future research?

_____ 22. Treatment Start Date

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Malignant Gastrointestinal Stromal Tumor *(GIST)*

In the past, mesenchymal tumors of the gastrointestinal tract were classified as leiomyomas or leiomyosarcomas, but evidence that has accumulated over the past fifteen years supports the view that these tumors are a distinct clinicopathologic entity.[1] Now classified as "gastrointestinal stromal tumors" *(GISTs),* these neoplasms are thought to arise from the interstitial cells of Cajal *(ICC)* within the GI tract, or at least to share a common stem cell ancestor with this cell type.[2] The interstitial cells of Cajal play an important role in gut motility by regulating slow-wave contractions that propagate the contents of the GI tract. They are unusual cells in that they exhibit both smooth muscle and neural differentiation, as determined by immunohistochemistry and electron microscopy; they also express the hematopoietic progenitor cell marker CD34 as well as the c-kit tyrosine kinase.[3] Correspondingly, GISTs often express muscle actins and S-100 *(a neural marker),* and are positive for CD34 and c-kit in 72% and up to 100% of cases, respectively.[4] Importantly, leiomyomas and leiomyosarcomas do not express CD34 and c-kit. The most common site of presentation for GISTs is the stomach *(70%),* although they also arise in the small bowel, and rarely in the esophagus and large intestine.[1] They tend to occur most commonly in the middle-aged or elderly *(ages 50-60 years),* and they are more frequent in men. The most common presenting symptom is vague abdominal pain, though they can also cause upper GI bleeding and nausea. A large portion of patients with GISTs *(30%)* are asymptomatic.

Predicting a GIST's likelihood of metastasizing or recurring following complete resection is difficult. There are morphologic features that do portend for more aggressive behavior, with size being one of the most important prognosticators for both recurrence and metastasis. Specifically, Suster and colleagues have reported that the presence of two or more of the following within a single lesion suggests a malignant process and predicts for sarcoma-like behavior: size > 5 cm. in diameter, infiltration of adjacent structures, presence of tumor necrosis, increased nuclear: cytoplasmic ratio, mitotic rates > 1 per 10 HPF, and infiltration of overlying mucosa by tumor.[4] Modern surgeons have quoted recurrence rates between 40 and 90%, and at least one group has stated that there is a need for an effective adjuvant therapy to prevent both local and distant recurrence.[5]

Until recently, there has been no effective therapy for advanced, unresectable GISTs. Attempts to treat with standard sarcoma therapy have been futile. Mayo Clinic investigators recently reported a phase II trial of dacarbazine, mitomycin, doxorubicin, and cisplatin, with growth factor support, in treatment of patients with advanced malignant GISTs and leiomyosarcomas.[6] The objective response rate for the leiomyosarcomas was 67%, but only a solitary response *(4% total patients)* was seen in the GIST population *(in a patient with a colonic primary).*

However, a new agent, STI-571 (*Gleevec*), has shown promise in the metastatic setting, and it is a logical choice for neoadjuvant or adjuvant use.

A recent multinational trial sponsored by Novartis has been carried out using Gleevec in patients with incurable GIST. Patients were randomized between doses of 400 mg or 600 mg per day for planned treatment of up to 24 months. Preliminary analysis suggests a significant classic response rate, and the overwhelming majority of symptomatic patients reported clinical improvement on the study *(Blanke CD, vonMehren M, Joensuu H, et. al. Evaluation of the safety and efficacy of an oral molecularly-targeted therapy, STI-571, in patients with unresectable or metastatic gastrointestinal stromal tumors [GISTS] expressing c-kit [CD117]. Abstract, ASCO, 2001).*

Other evidence of efficacy in these patients was seen with positron emission tomography *(PET)* using a radiolabeled glucose analog, F18-fluoro-2-deoxy-D-glucose *([FDG], Van den Abbeele et al, Abstract, ASCO 2001).* Most GIST tumors demonstrated high glycolytic activity at baseline prior to Gleevec therapy with a mean standardized uptake value *(SUV)* of 5.2 *(range 1.5 to 13.4)*, and an average tumor-to-background ratio *(TBR)* of 4.5 *(range 1.3 to 11.7).* The highest glycolytic activity was usually seen at the periphery of the tumor masses, while the centers of these masses were relatively photopenic. Sites of disease defined by CT at baseline correlated with areas of abnormal glycolytic activity on PET, but PET provided additional information regarding the extent of disease. Following the initiation of Gleevec oral therapy, 80% of patients *(20/25)* demonstrated response based on qualitative evaluation of the PET images. Only one patient exhibited primary resistance to Gleevec with tumor progression. A significant decrease in SUV *(52%)* and TBR *(57%)* could be observed as early as 24 hours following the oral administration of a single dose of Gleevec. This early response was sustained and continued to improve up to 7 months

following initiation of therapy. With the exception of one patient who demonstrated repeated hyperinsulinemic states, the qualitative evaluation of response to treatment was confirmed by TBR measurements. The maximum response seen was a decrease of approximately 95% in both SUV and TBR at 6 months.

In summary, Gleevec appears to be effective in treatment of patients with advanced GIST. The metastatic disease trial incorporated biologic endpoints *(as well as clinical),* but the amount of tumor tissue obtained on that study was minimal. A neoadjuvant trial would allow investigators access to large quantities of fresh tumor, which is critical to understanding how this form of targeted, molecular therapy works in vivo. In addition, there is a distinct possibility based on the metastatic disease trial that Gleevec treatment will decrease recurrence in fully resected patients.

1.2 c-kit and Malignant Transformation

c-kit, a 145 kD transmembrane glycoprotein, is the normal cellular homologue of the viral oncoprotein v-kit and a member of the receptor tyrosine kinase subclass III family that includes receptors for PDGF, M-CSF and flt3 ligand.[7-9] All members of this family have an extracellular domain containing five immunoglobulin-like domains, a single transmembrane domain, and a cytoplasmic domain with a split kinase domain and hydrophilic kinase insert sequence.[10] The juxtamembrane and kinase domains of these receptors are strongly conserved.[11]

The c-kit gene product is expressed by hematopoietic progenitor cells, mast cells, germ cells, interstitial cells of Cajal, and certain human tumors.[12-16] Studies of mice with inactivating mutations of c-kit or its ligand, Steel factor *(SLF),* have demonstrated that normal functional activity of the c-kit gene product is absolutely essential for maintenance of normal hematopoiesis, melanogenesis, gametogenesis, development of ICC, and mast cell growth and differentiation.[13, 17-19]

In addition to its importance in normal cellular physiology, c-kit has also been thought to play a role in the biology of certain human cancers, including germ cell tumors, mast cell tumors, small cell lung cancer, melanoma, breast cancer, neuroblastoma, and GISTs.[20-26] Two general mechanisms of c-kit involvement in the development or maintenance of the malignant phenotype have been described: 1) acquisition of c-kit mutations resulting in ligand-independent activation; and 2) tumor cell expression of c-kit with autocrine and/or paracrine stimulation of the receptor by SLF.[16,22-24,27-31]

Activating mutations of c-kit have been described in cases of human mast cell disorders, seminoma, and GISTs.[32,23,24,33,34] Two classes of c-kit activating mutations have been described: 1) mutation of the conserved juxtamembrane domain; and 2) mutation of the kinase domain. The former has been described in GISTs. A variety of different types of juxtamembrane mutations have been reported, including in-frame deletions and insertions, as well as point mutations.[35] Mutations in this region lead to ligand-independent dimerization of the receptor. Structural alterations of the juxtamembrane domain may be a common pathway for activation of type III receptor tyrosine kinases as similar mutations have been described for flk2/flt3 and PDGFR.[36-38]

c-kit mutations in GIST lead to ligand-independent activation of c-kit tyrosine kinase activity and promote tumor growth in vitro. In the case of GISTs, the presence of a c-kit mutation is more common in malignant neoplasms. Investigators at the Armed Forces Institute of Pathology looked at 43 benign and malignant GISTs and found c-kit mutations occurred predominantly in the malignant GISTs with high mitotic activity.[32] Overall, half of the malignant GISTs and only 1/19 of the benign tumors showed c-kit mutations. c-kit mutations were not detected in any leiomyomas or leiomyosarcomas. In a series of 124 cases of GIST recently reported by Taniguchi and colleagues, mutations of c-kit exon 11 *(juxtamembrane domain)* were found in 57% of the tumors and correlated with 0% x 10 year long-term survival.[39]

1.3 STI-571 *(GLEEVEC)*

STI-571 or Gleevec *(formerly known as CGP 57148B),* is a 2-phenylaminopyrimidine derivative, that acts as a selective inhibitor of the c-abl, bcr-abl, and platelet-derived growth factor receptor *(PDGFR)* tyrosine kinases.[40,41] Bcr-abl is the causative molecular abnormality in chronic myelogenous leukemia *(CML),* and its kinase activity is essential to its transforming capabilities. A recently reported phase I trial of Gleevec in CML patients who failed interferon therapy demonstrated marked clinical efficacy.[42] All patients treated at doses greater than 140 mg per day had a hematologic response, and 96% treated at 300 mg or greater experienced complete hematologic responses lasting 4 weeks or greater. More interestingly, several patients

treated at 300 mg or greater experienced cytogenetic responses and even complete cytogenetic remissions, proven by FISH analysis. Side effects of therapy were minimal *(a small percent of patients treated at greater than 300 mg per day experienced myelosuppression, but that was possibly a result of successful treatment of the CML).* This compound represents the first example of successful drug development based on a tumor's specific molecular abnormality.

Based on the strong homology between the kinase domains of PDGFR and c-kit, it has been speculated that Gleevec could also potently inhibit the kinase activity of c-kit. Using biochemical and cell based assays of receptor activation, signal transduction, proliferation and apoptosis, Oregon Health Sciences University investigators found that Gleevec inhibits the Steel-factor *(SLF)*-dependent activation of a human myeloid leukemia cell line which expresses wild type c-kit receptor.[43] The IC_{50} for these effects is approximately 100 nM, which is similar to that required for inhibition of bcr-abl and PDGFR. They also performed similar studies using a mast cell leukemia cell line, HMC-1, which expresses an activated form of c-kit. This factor-independent cell line was originally derived from a patient with mast cell leukemia and contains an activating juxtamembrane V560G mutation. This mutation is similar to that found in GISTs. Similar to results with cells expressing wild type receptor, doses of 50 nM-10 μM Gleevec inhibit HMC-1 cellular proliferation. HMC-1 cells appear to be strongly dependent upon the activity of the mutant receptor to prevent apoptosis, as evidenced by the fact that 85-95% of cells exposed to 0.1-10 ?M Gleevec for 48 hours will undergo programmed cell death. The IC_{50} for induction of apoptosis is approximately 50 nM. Thus, Gleevec can inhibit the kinase activity of the mutant c-kit polypeptide expressed by HMC-1 cells. The authors concluded the ability of Gleevec to inhibit this mutant form of c-kit was similar to that seen using wild type c-kit as a target. They also felt Gleevec is a potent inhibitor of c-kit kinase activity and may be useful in the treatment of tumors that are partially or completely dependent upon c-kit for proliferation and/or avoidance of apoptosis.

A single patient with metastatic GIST was treated on a pilot proof-of-concept protocol at the University Hospital of Helsinki, Finland with a once-daily dose of 400 mg of Gleevec. This patient's tumor had previously been documented to harbor an activating mutation in c-kit. An objective response to treatment was noted and has remained stable with continued therapy for 8 months. To date, the patient has experienced only the following minor adverse events related to Gleevec administration: transient nausea, loose stools, muscle cramps, upper abdominal pain and flatulence all of which were of Grade 1 severity.

Between July 3, 2000 and November 1, 2000, 53 patients with unresectable or metastatic GIST have been treated on a Phase II multicenter international clinical trial at Dana-Farber Cancer Institute, Oregon Health Sciences University, Fox Chase Cancer Center and University Hospital of Helsinki, Finland. This trial randomized patients between two different dose levels of Gleevec *(400 mg p.o. once daily vs. 600 mg p.o. once daily).* Preliminary results indicate that the induction of major clinical objective responses is in the range of at least 50%. The overwhelming majority of symptomatic patients reported clinical improvement. Other evidence of efficacy was seen with nearly 90% of patients having documented PET scan response to Gleevec. Only 2 patients of 53 have had progression of disease, with the remainder showing stable disease or evolving minor responses. Since response may evolve over several weeks to months, these preliminary data may underestimate the actual benefit of this agent in these patients with a previously untreatable and fatal malignancy. Further follow-up is required to assess the durability of these responses and the clinical benefit of Gleevec in patients with advanced unresectable or metastatic GIST.

Overall safety and tolerability of Gleevec from this trial has been quite favorable and similar across both doses tested *(400 or 600 mg p.o. daily).* Grade 1-2 toxicities have been predictable based on the prior experience in CML patients and have included periorbital edema, headache, fatigue, diarrhea, peripheral edema, rash, and nausea without emesis. Transient Grade 4 neutropenia has occurred in 2 patients, neither of whom experienced any clinically significant sequelae *(one of these patients also had concurrent rash and eosinophilia strongly suggestive of drug hypersensitivity reaction).* Transient Grade 3-4 hepatic dysfunction has occurred in two patients with increases in serum bilirubin and transaminase levels.

There have been three patients with significant gastrointestinal bleeding, likely related to Gleevec dosing. The onset of GI bleeding has been rapid *(within 1 to 3 weeks after initiation of Gleevec administration).* There has been no obvious effect of dose on this clinically significant serious adverse effect. The bleeding may be due to tumor necrosis and disruption of tumor-related vasculature, since in at least one patient the density characteristics of the tumors were noted to change *(becoming significantly more hypodense on CT scan)* within 2 weeks of beginning Gleevec by daily administration. One patient required embolization

under radiology guidance to control a point of bleeding associated with necrotic tumor, while another patient required emergent surgical intervention to resect a site of tumor-associated bleeding. The GI bleeding can occur as intraperitoneal or retroperitoneal bleeding as well. Any drop in hemoglobin or signs or symptoms of GI bleeding *(lightheadedness, melena, hematochezia, abdominal distention or tenderness, etc.)* should be quickly and diligently evaluated in GIST patients receiving Gleevec. Re-challenge of patients with lower dose Gleevec has been tolerated in these patients after resolution of the initial GI bleeding episode and has permitted chronic dosing with this agent under close supervision of the medical and surgical team. Because of this risk of GI bleeding, it is required that all patients have a dedicated team of medical oncologist and surgeon who know the patient prior to initiation of Gleevec.

1.4 Rationale for Study Design

Gleevec appears to be effective in the treatment of patients with advanced GIST. The current trials for metastatic and unresectable malignant GIST have incorporated both clinical and biological endpoints but the amount of tumor tissue obtained and available for analysis remains minimal at this time. Important scientific questions can be asked as correlative studies within this proposed clinical trial. For example, molecular phenotypes of patients who respond to Gleevec vs. those who do not is largely unknown. A carefully designed neoadjuvant/adjuvant trial for operable and potentially resectable patients with malignant primary or recurrent GIST would provide tissue pre and post drug delivery and enable each patient's tissue evaluation to serve as its own control. The investigators would then have access to large quantities of paraffin-embedded and snap frozen tumor for laboratory testing to further the understanding on how this form of targeted molecular therapy works in vivo. Since it is very likely that these high risk patients would recur even after successful tumor removal, Gleevec therapy used as an adjuvant before and after tumor debulking may decrease recurrence rates and result in improved survival in this phase II trial design. Additionally, metabolic changes in the tumor in response to Gleevec therapy, as defined by PET and FDG-PET, appear to occur very rapidly, and may precede significant changes in size as defined by conventional anatomic modalities. Therefore, non-invasive imaging studies that allow measurement of regional tumor metabolism on the *in-situ* tumor prior to and during the drug administration could provide useful information regarding assessment of therapeutic response. Glucose transporters play a major role in FDG uptake and GLUT 4 is overexpressed in gastrointestinal tumors. *(Nogushi Y, et. al., Expression of glucose transporters and insulin resistance in human GI cancer. Abstract, Proc. Annual Mtg., AACR 36:A1218, 1995)* Hence, the availability of tissue pre and post therapy will help elucidate the relationship between FDG uptake and glucose transporter expression in GIST at baseline, and after therapy.[44-52]

2.0 OBJECTIVES

Biological Objectives

2.1 Provide a comprehensive correlative evaluation of the biological effects of Gleevec on malignant GIST by comparison of pre and post drug administration tissue samples from individual patients. Methodology will include:

2.1.1 Mutational analysis of c-kit by high throughput PCR-based assay of tumor DNA both pre and post Gleevec neoadjuvant therapy.

2.1.2 Evaluation of tyrosine phosphorylation and c-kit activation in tumor samples pre and post Gleevec neoadjuvant therapy.

2.1.3 Evaluation of tyrosine phosphorylation of intermediate signaling molecules within the activation pathways of the c-kit receptor pre and post Gleevec neoadjuvant therapy.

2.1.4 Analysis patterns of global gene expression pre and post Gleevec neoadjuvant therapy with correlation to response and mutational status.

2.1.5 Evaluation of expression and mutation patterns of putative GIST tumor suppressor genes, oncogenes, and proliferation markers with correlation to response and c-kit mutational analysis.

2.1.6 Correlation of glucose transporter expression with PET SUV and TBR pre-and post Gleevec neoadjuvant therapy.

Clinical Objectives

2.2 Determine the percentage of resected patients that remain progression free during follow-up.

2.3 Determine the objective response rate in GIST patients treated with Gleevec before resection.

2.4 Verify the safety of Gleevec in this patient population specifically related to post-surgical complications.

2.5 Measure tumor changes by PET qualitatively and semi-quantitatively with SUV and TBR during the first week of neoadjuvant treatment and prior to surgery (*at week 4 in patients with progressive disease, at week 8 to 10 in patients with stable or responding disease*), and correlate the findings with size changes as defined by conventional cross-sectional imaging scans. PET scanning is mandatory for all patients (See

Appendix VIII). PET scans may be obtained at affiliated, accredited institutions if the institution enrolling the patients does not have such capability. ***(10/10/03)***

2.6 Determine if the percent decline in SUV and TBR is an earlier, or more accurate predictor of subsequent disease recurrence compared with response assessed by conventional cross-sectional imaging scans.

3.0 PATIENT SELECTION *(10/10/03)*

3.1 Conditions for Patient Eligibility *(4/5/04)*

3.1.1 Patients must have a biopsy-proven diagnosis of malignant GIST, either potentially resectable primary *(≥ 5 cm)* or potentially resectable locally recurrent or metastatic *(≥ 2 cm)* disease. The primary must be of visceral, intra-abdominal or pelvic origin. All patients must have three core tissue biopsies performed within 8 weeks prior to registration. (See Appendix V). All patients must have immunohistochemical documentation of KIT *(CD117)* expression in the tumor, as assessed using DAKO antibody A4502 *(see Appendix IV).* Staining may be surface membrane and/or cytoplasmic. Endogenous mast cells present in the tissue should serve as a benchmark for strong staining. The antibody should be titered such that there is no staining of epithelial cells or fibroblasts in control tissues *(e.g. colon, skin).*

3.1.2 Patients with either primary or recurrent GIST must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension: a primary GIST of ≥ 5 cm in at least one dimension *(longest diameter recorded)* or a recurrent GIST of ≥ 2 cm in at least one dimension with conventional techniques *(see RECIST Section 11.2).*

3.1.3 Patient must have an identified team *(medical and surgical oncologist)* to provide care.

3.1.4 Patient must have Zubrod performance status 0-2.

3.1.5 Patient must have normal organ and marrow function as defined below:

- leukocytes ≥ 3,000/µl
- ANC ≥ 1500/µl
- platelets ≥ 100,000/ml
- bilirubin ≤ 1.5xULN per institution
- ALT/AST ≤ 2.5xULN per institution
- creatinine ≤ 1.5xULN per institution

3.1.6 Study-specific signed informed consent.

3.1.7 Institution must have attenuation-corrected dedicated PET imaging with F-18-FDG available for use, and qualify for participation in the trial through certification by ACRIN (See Appendix XI for instructions on how to register with ACRIN as a participating study site. A completed application must be approved and on file with ACRIN in order to participate). PET imaging must meet the criteria and be done in accordance with Section 11.6.1 and Appendices VII and VIII in order to calculate pre and post-treatment SUVs and TBRs. An institution that does not have its own PET imaging capability may meet this eligibility criterion by referral of the patient for PET imaging to another site that has been certified by ACRIN and is capable of performing the PET studies required by this protocol.

3.1.8 Patients must be able to lie still in the PET scanner for approximately 60-120 minutes.

3.1.9 Three PET scans will be required: the first at baseline prior to Gleevec therapy, the second within week 1 *(as early as 24 hours or up to 7 days)* following initiation of Gleevec therapy, and the third just prior to surgery.

3.1.10 Any prior malignancy is allowed as long as the patient is disease-free from that malignancy.

3.1.11 Age ≥ 18.

3.1.12 Gleevec to start within 2 weeks following registration.

3.1.13 All lab tests, and imaging studies done within timeframes specified within Section 4.0.

3.2 Conditions for Patient Ineligibility *(4/5/04)*

3.2.1 Chemotherapy, radiation therapy, biologic therapy, prior Gleevec, or any other investigational drug for any reason within 28 days prior to study entry.

3.2.2 Class III or IV cardiac disease as defined by NY Heart Association *(see Appendix II).*

3.2.3 Pregnant or nursing women because Gleevec may be harmful to the developing fetus and newborn. Women/men of reproductive potential must agree to use an effective contraceptive method. Women of reproductive potential must have a negative serum pregnancy test within 7 days prior to study entry and treatment start *(repeat if necessary).* Post-menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential. Women who have had tubal ligations will not be considered to have reproductive potential. Male and female patients of reproductive potential must agree to employ an effective barrier method of birth control throughout the study and for three months following discontinuation of study drug.

3.2.4 Patients with medical or psychological conditions that, in the opinion of the investigator, make the patient unable to tolerate or complete the treatment, or to grant reliable informed consent.

3.2.5 Patients taking therapeutic doses of coumadin *(warfarin)* for anticoagulation at the time of registration. Patients requiring therapeutic anticoagulation may use low-molecular weight heparin *(e.g. Lovenox)* or other agents, and mini-dose coumadin *(1 mg p.o. every day)* as prophylaxis is allowed.

3.2.6 Patients with severe and/or uncontrolled concurrent medical disease (e.g., uncontrolled chronic renal or liver disease, or active uncontrolled infection).

3.2.7 No uncontrollable hyperglycemia.

3.2.8 Patients with any known or suspected hypersensitivity to one of the components of the study drug.

4.0 PRETREATMENT EVALUATIONS *(10/10/03)*

4.1 Complete history, physical and evaluation of Zubrod performance status.

4.2 Pathological *(biopsy)* diagnosis of primary or recurrent malignant GIST within eight weeks prior to study entry. *(Note: Recurrent GIST diagnosis by IHC may be made on the basis of tissue block from the original tumor instead of using the pre-treatment biopsy).*

4.3 Immunohistochemical documentation of KIT *(CD117)* expression in tumor documented by DAKO antibody staining *(See Appendix IV). (In recurrent tumors, this may be obtained from the original tumor block, if available).* Obtain 3 core biopsies *(for the biological objectives in Section 2.0)* within 8 weeks prior to registration.

One paraffin block of tumor *(or ten unheated, unstained slides)* prepared from a core specimen pre-drug must be submitted to the RTOG Tissue Bank at LDS Hospital *(see Appendix V*). Also snap frozen tumor tissue taken from at least 2 core biopsies pre-drug must be submitted to the RTOG Tissue Bank at LDS Hospital *(See Appendix V).*

4.4 Laboratory Studies: CBC/differential, bilirubin, creatinine, ALT/AST, alkaline phosphatase, LDH, glucose within four weeks prior to registration. *(See Section 11.1)*

4.5 Serum pregnancy test, when applicable, must be done within 7 days prior to study entry and treatment start *(repeat if necessary).*

4.6 CT or MRI Scans for disease assessment within 8 weeks prior to registration. All disease assessment must be performed using the same assessment technique *(either CT or MRI [See Section 11.1]).*

4.7 Initial PET scanning within 8 weeks before registration prior to initiation of drug therapy. *(See Section 11.6, Appendix VII, VIII).*

5.0 REGISTRATION PROCEDURES *(4/5/04)*

5.1 Patients can be registered only after the pretreatment evaluations that are required prior to registration are completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at *(215)* 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit. **Note**: After completing the RTOG portion of the registration, sites will be asked to repeat some demographic information for the ACRIN portion of the registration.

5.2 Registration, ECOG Investigators (*10/10/03*)

5.2.1 *Submitting Regulatory Documents*

Before an ECOG Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19102
FAX: (215) 569-0206

5.2.2 *Required Protocol Specific Regulatory Documents*

1. CTSU Regulatory Transmittal Form.
2. Copy of IRB Informed Consent Document.
   Note: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form.

Or

B. HHS 310 Form.

Or

C. IRB Approval Letter

Note: The above submissions must include the following details:

- Indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB.
- Full protocol title and number.
- Version Date
- Type of review (full board vs. expedited).
- Date of review.
- Signature of IRB official.

5.2.3 The CTSU encourages you to link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed http://www.ctsu.org/rss2.0_page.asp.

If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com. Monday through Friday, 9:00am - 6:00pm. Patients must not start protocol treatment prior to registration.

5.2.4 Treatment should start as soon as possible following patient registration.

5.2.5 ***(4/5/04)*** Institutions may begin to register eligible patients to this study by completing the checklist via the ECOG web page by using the Web-based Patient Registration Program (http://webreg.ecog.org). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG Coordinating Center at *(617)* 632-2022. Please note that a password is required to use this program. The following information will be requested: Protocol Number; Investigator Identification (including institution and/or affiliate name and investigator's name); Patient Identification (including patient's initials, chart number, social security number and demographics (sex, birth date, race, nine-digit zip code and method of payment)); Eligibility Verification. Patients must meet all of the eligibility requirements listed in Section 3.0 and have completed the necessary pretreatment evaluations as listed in Section 4.0. After completing the checklist on the web, the investigator will call the Central Randomization Desk at the ECOG Coordinating Center to provide the Transaction ID # at (617) 632-2022, Monday-Friday, between the hours of 9:00 am and 4:30 pm ET. ECOG members should not call the RTOG directly.

The ECOG Randomization Desk will complete the randomization process and call the institution back to relay the treatment assignment for the patient. The ECOG Coordinating Center will forward a confirmation of treatment assignment to the ECOG participating institution.

6.0 RADIATION THERAPY

Not applicable to this study.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the medical oncology quality control guidelines stated in the RTOG Procedures Manual.

7.1 Treatment *(4/5/04)*

Patients will start taking Gleevec within two weeks following registration. If, at four weeks after initiation of Gleevec therapy, there is CT or MRI confirmation of disease progression, then the patient stops protocol treatment and should be considered for surgery. If, at 8 to 10 weeks after initiation of Gleevec therapy, there is CT or MRI confirmation of disease progression, then the patient stops protocol treatment and should be considered for surgery. Patients stop protocol treatment if their disease progresses at any time and are followed as specified in Sections 11.1 and 12.1. Further treatment off study is at physician's discretion.

Because of the potential for local irritation, the capsules should be taken all at once during a meal and with a large glass of water *(8oz)* to minimize the chance of irritating the esophageal and/or gastric mucosa. The eight week interval was felt to be adequate to evaluate drug response by both non-invasive imaging and by molecular analysis. In the initial metastatic GIST pilot study, responses were identified in some patients as early as 4 weeks and in the majority of responders by 8 weeks. For the purpose of this neoadjuvant/adjuvant

study, two months of drug therapy should provide for an adequate trial to evaluate the stated objectives in Section 2.0.

Patients will stop taking Gleevec the night before surgery. All post-operative patients *(who did not have progressive disease prior to surgery)* will resume drug as soon as they are able to take oral medications *(within 2 to 4 weeks post-operative).* Patients will remain on Gleevec for an additional 24 months unless tumor recurs or progresses, they experience intolerable toxicity, or the physician or patient desires the patient to be removed from the study. Patients are removed from protocol treatment if their disease progresses at any time.

If gross tumor is left behind, the patient will remain on study and continue on Gleevec *(see Section 8.2 for details).* Nonsurgical candidates will have a core biopsy and will remain on Gleevec for an additional 24 months unless the patient progresses, they experience intolerable toxicity, or the physician or patient desires the patient to be removed from the study. Continuation of Gleevec off study is recommended in stable or responding patients who continue to show benefit even after the study-defined 24 month dose.

7.2 Study Agent STI-571 *(Gleevec) (NSC-716051) (IND 61, 135)*

7.2.1 *Chemistry*

Chemical Name:
4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3][4-(3-pyridinyl)-2-pyrimidinyl1]amino]-phenyl]benzamide methanesulfonate;
Molecular Formula: $C_{30}H_{35}N_7SO_4$ M.W.: 589.7
CAS Registry Number: 220127-57-1
Gleevec is freely soluble in water and aqueous buffers ≤ pH 5.0 but is less soluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is soluble in 1,2-propylene glycol, PEG 400, ethanol and methanol, but is poorly soluble in less polar solvents such as acetone and toluene. Description: Gleevec is a white to slightly yellowish crystalline powder.

7.2.2 *Mechanism of Action*

Gleevec is a selective inhibitor of certain protein-tyrosine kinases. Gleevec inhibits the Abl tyrosine kinase as well as the KIT and PDGF-R RTKs. The compound specifically inhibits proliferation of v-Abl and BCR-Abl expressing cells, suggesting that it is not a general antimitotic agent. In colony formation assays using ex-vivo peripheral blood and bone marrow samples from patients with chronic myeloid leukemia *(CML),* Gleevec shows selective inhibition of BCR-Abl positive colonies. In addition, Gleevec is a potent inhibitor of receptors involved in both PDGF and SCF-mediated biochemical events *(i.e. inhibiting both PDGF-R and KIT).* In contrast, it does not affect signal transduction mediated by other stimuli including epidermal growth factor *(EGF),* insulin and phorbol esters. *In vivo*, the compound shows anti-tumor activity as a single agent in animal models at well-tolerated doses.

7.2.3 *Side Effects and Toxicites*

In in-vitro human liver microsomal studies, Gleevec appeared to be a competitive inhibitor of CYP2C9, CYP2D6 and CYP3A4/5, suggesting that Gleevec could reduce the clearance of co-administered drugs whose metabolism is dependent on these P450 cytochrome isoenzymes. Co-administration of erythromycin, cyclosporin, ketoconazole or high doses of acetaminophen *(more than 2 grams per day)* could reduce clearance and increase systemic exposure to Gleevec *(see Appendix VI).*

Gleevec causes abortions and is potentially teratogenic at high doses in rabbits and rats. The compound is therefore not suitable for administration to pregnant women, and conception while on therapy should be avoided. In women of childbearing potential, contraception should continue for three months after the last dose of Gleevec to allow the complete clearance of drug and its principle metabolites from the body. Since interactions with the metabolism of oral contraceptives cannot be excluded at present, a barrier method of contraception must be used. Gleevec should not be administered to patients who are breastfeeding.

Gleevec was clastogenic according to the results of one of the genotoxicity tests performed. These effects were seen only at toxic concentrations and all other tests were negative; therefore, Gleevec is not considered to present a genotoxic hazard.

Although there is no suggestion from available animal toxicology studies that Gleevec enters the mammalian testis, this possibility cannot be excluded. Rats had reduced testis and epididymus weights and decreased sperm motility. Therefore, male patients must use an effective method of contraception

while being treated with Gleevec and should continue contraception for three months after receiving the last dose.

Physicians and patients should be cautioned about concomitant use of acetaminophen (*Tylenol™ or Percocet™ or other analgesic combination tablets containing acetaminophen*). One fatal case of hepatic failure is described in the Investigators' Brochure and Package Insert in a patient treated with Gleevec while receiving Tylenol. Patients should not receive more than 4000 mg total daily dose of acetaminophen while on treatment.

Grapefruit and grapefruit juice inhibit cytochrome p450 3A4, and should be avoided. Also, some dietary supplements *(also called "alternative therapy" or "natural medicines")* can induce/inhibit cytochrome P450 isoenzymes *(e.g. St John's wort induces CYP3A4 metabolism*); use of these alternative therapies should be discouraged.

STI-571 Gleevec: Agent Specific Adverse Event List *(5/10/04)*

Category	**Adverse Events**
Cardiovascular *(General)*	Edema; pleurisy
Constitutional Symptoms	Weight gain, fever, insomnia, conjunctivitis, increased tear production, infection, fatigue, weakness, night sweats, pneumonitis/pulmonary infiltrates, nasopharyngitis, dry mouth, cough, shortness of breath, osteonecrosis (avascular necrosis);
Dermatology/Skin	Rash/desquamation *(usually mild),* dermatitis, eczema, petechiae, hair loss; pigmentation changes, e.g., vitiligo, hypopigmentation;
Gastrointestinal	Diarrhea, dyspepsia/heartburn, flatulence, nausea, vomiting, anorexia, constipation;
Hemorrhage	Melena/GI bleeding, decreased platelet count, decreased WBC count, decreased RBC count, nose bleeds, DIC;
Hepatic	Elevations in bilirubin; elevations in AST *(serum glutamic oxaloacetic transminase)*; ALT *(serum glutamic pyruvic transaminase);*
Pain	Abdominal pain or cramping, arthralgia *(joint pain*); headache, myalgia *(muscle pain).*
Renal	Increase in renal function tests, decrease in electrolyte levels;
Neurological	Headache, dizziness, taste disturbance, numbness of hands and feet.

7.2.4 *Pharmaceutical Data*

7.2.4.1 How supplied: Gleevec is available in hard gelatin capsules which contain a common dry powder blend filled in capsule shells of size 1 *(100 mg dosage strength).*

7.2.4.2 Storage: The capsules should be stored at room temperature not to exceed 25°C *(77°).*

7.2.4.3 Route of Administration: Oral. Should be taken with a meal to minimize GI irritation.

7.2.5 *Supply*

Gleevec will be supplied by the NCI for this study. Gleevec has been approved for CML patients who cannot tolerate or fail IFN and for patients with metastatic unresectable GIST.

Drug Ordering: 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 Clinical Drug Request *(NIH-986)* and mailing it to the Drug Management and Authorization Section, PMB, DCTD, NCI, 9900 Rockville Pike, EPN Room 7149, Bethesda, MD 20892-7422 or faxing it to 301-480-4612. For questions call 301-496-5725.

Drug Returns: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug *(e.g. sealed vials remaining when expired vials are recalled by the PMB),* investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page *(http://ctepcancer.nih.gov)* or by calling the PMB at 301-496-5725. ***(10/10/03)***

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page *(http://ctep.cancer.gov)* or by calling the PMB at 301-496-5725. ***(10/10/03)***

Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 301-496-5725 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time.

7.3 Dose Modifications

Toxicities that can be directly attributable to chemotherapy will be scored using the NCI Common Toxicity Criteria, Version 2.0. For treatment or dose modification-related questions, please contact either Dr. Blanke, Dr. Demetri, or Dr. vonMehren.

7.3.1 *Dose modifications for non-hematologic toxicity*:

7.3.1.1 *Grade 2*: If the patient experiences a clinically significant Grade 2 non-hematologic toxicity, study drug must be withheld until the toxicity has resolved to ≤ Grade 1. Gleevec may then be resumed at the same daily dose. If any Grade 2 toxicity recurs, Gleevec must be withheld until toxicity has resolved to ≤ Grade 1, and the dose of Gleevec must be reduced to 400 mg per day. If any Grade 2 toxicity recurs at this lower dose, Gleevec must be further reduced to 200 mg per day. If any Grade 2 toxicity recurs at this dose, discontinue drug. When Gleevec doses are reduced, they will not be re-escalated to the original dose. ***(10/10/03)***

7.3.1.2 *Grade 3 or 4*

If the patient experiences Grade 3 or 4 toxicity, study drug must be withheld until toxicity has resolved to ≤ Grade 1 and the daily dose must be reduced to 400 mg per day. If any Grade 3 or 4 toxicity recurs, Gleevec must be withheld until the toxicity has resolved to ≤ Grade 1 and the daily dose must be reduced again to 200 mg per day. If any Grade 3 or 4 toxicity recurs, discontinue drug. When Gleevec doses are reduced, they will not be re-escalated to the original dose.

7.3.2 *Dose modifications for hematologic toxicity*:

7.3.2.1 Grade 1 or 2:

No dose modification or reduction will be performed for Grade 1 or 2 hematological toxicity.

7.3.2.2 Grade 3 or 4 ***(10/10/03)***:

If the patient experiences a Grade 3 or 4 hematological toxicity, defined as an ANC < 1,000/ul, or a platelet count of < 50,000/μl, Gleevec must be withheld until the toxicity has resolved to ≤ Grade 1. ANC will take precedence over a WBC count in determining the degree of neutropenia *(doses should not be interrupted for a patient with a WBC < 2,000/μl).* Once the toxicity resolves to ≤ Grade 1, Gleevec may be resumed at the same dose. If any Grade 3 or 4 toxicity recurs, Gleevec must be withheld; when toxicity has resolved to ≤ Grade 1, Gleevec should be restarted at 400 mg/day. If any Grade 3 or 4 toxicity recurs, then Gleevec must be withheld until toxicity has resolved to ≤ Grade 1 and Gleevec may be restarted at a dose of 200 mg per day. If any Grade 3 or 4 toxicity recurs at this dose, then discontinue drug. No dose reduction will be made for Grade 3 or 4 anemia. The patient may be transfused.

7.3.3 If drug is held for toxicity until resolution to a lower grade, the missed doses will not be made up. When Gleevec doses are reduced, they will not be re-escalated to the original dose.

7.3.4 Drug will be stopped the night before surgery and at 24 months after surgery.

7.4 Adverse Drug Reaction Reporting

7.4.1 This study will utilize the CTC version 2.0 for toxicity and Adverse Event reporting. A copy of the CTC version 2.0 can be downloaded from the CTEP home page ***(http://ctep.cancer.gov).*** All appropriate treatment areas should have access to a copy of the CTC version 2.0. See Appendix III for protocol reporting guidelines. ***(10/10/03)***

7.4.2 This study will be monitored by the Clinical Data Update System *(CDUS)* version 1.0. Complete cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

7.4.3 Within 24 hours of discovery, any Grade 4 unexpected AE should be telephoned to RTOG HQ DM and to the study chairman. The report should be sent to RTOG within 10 working days. Any death, regardless of cause, which occurs during protocol treatment must be reported to RTOG Headquarters by telephone within 24 hours of discovery.

7.4.4 *Reporting*

7.4.4.1 Expedited Reporting for Phase II Studies *(including hospitalization defined in bullet 1 below):*

UNEXPECTED EVENTS		EXPECTED EVENTS	
Grades 2 – 3 Attribution Possible, Probable, or Definite	**Grades 4 and 5 Regardless of Attribution**	**Grades 1 - 3**	**Grades 4 and 5 Regardless of Attribution**
Expedited report within 10 working days. *(Grade 1 - Adverse Event Expedited Reporting NOT required.)*	Report by phone to IDB within 24 hours. Expedited report to follow within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent *(possible, probable, or definite)* should be reported within 10 working days.	Adverse Event Expedited Reporting NOT required.	Expedited report required within 10 working days. This includes all deaths within 30 days of the last dose of treatment with an investigational agent regardless of attribution. Any late death attributed to the agent *(possible, probable, or definite)* should be reported within 10 working days. Grade 4 myelosuppression or other Grade 4 events that do not require expedited reporting will be specified in the protocol.
Note 1	Telephone number available 24 hours daily: *(301)* 230-2330 *(Recorder after hours).*		
Note 2	See the DCTD/NCI Common Toxicity Criteria		
Note 3	Report to: *Investigational Drug Branch, Post Office Box 30012, Bethesda, Maryland 20824. Also report to RTOG Headquarters.*		
Note 4	A list of agent specific expected adverse events can be found in the protocol document or consent form.		
Note 5	**Reactions judged *definitely* not treatment-related should not be reported.** However, a report should be submitted if there is reasonable suspicion of drug effect.		

- For **Hospitalization** only – Any medical event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization *(or prolongation of existing hospitalization)* must be reported regardless of expected or unexpected and attribution.

- Expedited reports are to be submitted using AdEERS or the paper templates available at http://ctep.info.nih.gov. The NCI Guidelines for expedited adverse reporting are also available at this site.

7.4.5 Adverse Event Reporting for ECOG Investigators *(10/10/03)*

All ECOG Investigators are responsible for reporting adverse events according to the NCI guidelines. ECOG participants should employ definitions of adverse events as provided by the RTOG reporting guidelines in section 7.4. Both 24 hour and written/electronic adverse reports should be made directly to the Radiation Therapy Oncology Group according to the instructions in that section.

PLEASE NOTE:

- This study used AdEERS for adverse event reporting. The AdEERS application can be found at **http://ctep.cancer.gov/reporting/adeers.html.**

- An adverse event is considered unexpected, for expedited reporting purposes only, when either the type or the severity of the event is not listed in the current NCI Agent Specific Adverse Event List. To view the most up-to-date list, please go to the Adverse Event - AdEERS link on the ECOG webpage (www.ecog.org).

7.4.5.1 Reporting of AML/MDS ***(10/28/04)***

	NCI/CTEP Secondary AML/MDS Report Form[1]
AML/MDS	X

[1]To be completed within 30 days of diagnosis of AML/MDS that has occurred during or after protocol treatment. A copy is to be sent to ECOG and RTOG accompanied by copies of the pathology report (and when available, a copy of the cytogenetic report). ECOG will forward copies to the NCI.

ECOG Telephone Number: (617) 632-3610
ECOG Fax Number: (617) 632-2990
ECOG Mailing Address:
ECOG Coordinating Center
FSTRF
ATTN: Adverse Event
900 Commonwealth Avenue
Boston, MA 02215

NCI Fax Number: (301) 230-0159
NCI Mailing Address:
Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824

RTOG Headquarters:
Tele: 215/574-3214
Fax: 215/928-0153
RTOG Mailing Address:
RTOG Headquarters
ATTN: ADR
1818 Market Street, Suite 1600
Philadelphia, PA 19103

7.5 Clinical Trials Agreement

The agent *(hereinafter referred to as Agent),* Gleevec, used in this protocol is provided to the NCI under a CTA between Novartis Pharmaceuticals Corporation (*hereinafter referred to as Collaborator)* and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines apply to the use of the Agent in this study:

a. Agent may not be used outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agent are confidential and proprietary to Collaborator and should be maintained as such by the investigators.

b. The NCI encourages investigators to make data from clinical trials fully available to Collaborator for review at the appropriate time *(see item d).* The NCI expects that clinical trial data developed under a CTA will be made available exclusively to Collaborator, and not to other parties.

c. 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.

d. Any data provided to Collaborator*(s)* must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee *(DMC),* if there is a DMC for this clinical trial.

e. Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator for advisory review and comment prior to submission for publication. Collaborator 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 intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator 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 718
Bethesda, Maryland 20892
FAX 301-402-1584

The Regulatory Affairs Branch will then distribute them to Collaborator.

8.0 SURGERY *(10/10/03)*

8.1 Biopsy

Initially, in all patients an attempt will be made to obtain at least 3 core needle biopsies as previously described (see *Sections 3.1.1, 4.2, 4.3 Appendix V*). The core specimens will be obtained with the use of ultrasound, CT scan, or endoscopic guidance to assure adequate specimen retrieval in a non-necrotic area of tumor. The site investigator, surgeon, medical oncologist, or designated institutional study research coordinator should be present at the time of the core biopsies to insure that the sample obtained is adequate and that it is handled properly. The core specimens should be directed to the primary tumor *(in the case of primary GIST)* or toward the most viable area of tumor *recurrence (in the case of recurrent GIST).* The three or more directed core specimens should not impose any excessive risk to the patient *(tumor spillage, bleeding, etc.)* and yet provide adequate tissue *(approximately 2-4 mg)* for the proposed laboratory evaluation. At least 2 of the core specimens should be immediately snap frozen in liquid nitrogen and one should be either fixed in paraffin block or processed as 10 unheated, unstained slides and submitted to the RTOG Tissue Bank at LDS Hospital. *(See Appendix V)*

8.2 Surgery *(4/5/04)*

Patients will stop Gleevec the night before surgery and undergo standard surgical resection with the objective of surgical debulking and attempt to remove all gross disease, if possible, whether primary or intra-abdominal metastatic disease. If the patient progresses at week 4 or week 8 prior to surgery, the patient stops protocol treatment. The patient is followed as specified in Sections 11.1 and 12.1, and further treatment off study is at physician's discretion. However, a core biopsy is recommended with the objective of obtaining at least 3 specimens *(one paraffin and 2 frozen core specimens; See Appendix V).* If, at the time of surgical exploration, the tumor is substantially widespread as in recurrent GIST, then the surgeon should attempt to debulk disease especially in light of symptoms relating to obstruction or bleeding. Liver metastases may be managed by ablative techniques (RFA). Core biopsy tissue should still be obtained in these patients even if they only have RFA as a surgical procedure.

If gross tumor is left behind, the patient will remain on study and continue on Gleevec unless they had previously demonstrated disease progression on Gleevec prior to surgery, demonstrate disease progression on Gleevec in postoperative follow-up, they experience intolerable toxicity, or the physician or patient desires the patient to be removed from the study. When feasible, the specimen should be oriented by the surgeon to indicate by suture or staple right, left, or caudal position.

A portion of tumor tissue removed at the time of surgery will be submitted for paraffin block; additional non-necrotic tissue will be snap frozen *(Appendix V).* Tissue will be submitted to the RTOG Tissue Bank at LDS Hospital.

9.0 OTHER THERAPY

9.1 Cytokines

Ctyokines *(G-CSF or GM-CSF)* may not be used to support blood counts for patients in this study. Use of epoetin alfa *(EPO)* is allowed at the discretion of the treating investigator for hemoglobin ≤ 12 gm/dl and must be reported on the data forms.

10.0 PATHOLOGY

10.1 Assessment of Biopsy or Operative Specimens *(10/28/04)*

The core specimens (both frozen and paraffin) taken pre-treatment by CT or ultrasound-guided core techniques and the specimens obtained from post-treatment *(Gleevec)* surgical material will be utilized to perform the following correlative studies outlined in the primary objectives *(Section 2.1). (See Appendix V for details on tissue procurement and handling instructions).*

Tumor tissue pre-Gleevec and intraoperatively after 8 to 10 weeks of neoadjuvant Gleevec *(4 weeks in patients with progressive disease)* will be collected on each patient and sent under specified conditions with a copy of the patient consent and accompanied by the RTOG Pathology Submission Form to the RTOG Tissue Bank:

LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
***(801)* 408-5626**
FAX *(801) 408-5020*
holly.goold@ihc.com

If the patient progresses at 4 or 8 to 10 weeks and is not a candidate for surgical resection, three or more core biopsies are strongly recommended *(see Appendix V)* before the patient is removed from protocol treatment.

10.1.1 RTOG will reimburse pathologists from submitting institutions $100 per case if proper materials are submitted. RTOG Administration will prepare the proper paperwork and send a check to your institution after confirmation from LDS that they have received the appropriate number of slides/blocks.

10.2 Correlative Studies

Biologic studies will be performed on paraffin sections as well as tissue that was "snap" frozen. Specimens will be shipped to the various testing laboratories from the RTOG Tissue Bank when requested.

10.2.1 KIT mutational analyses: KIT genomic mutations will be determined using genomic DNAs isolated from paraffin sections. *(Heinrich)*

10.2.1.1 PCR will be performed to produce amplicons of exons 9, 11, 13 and 17. Mutational analysis will be performed using a high throughput PCR-based assay on a Transgenomics WAVE D-HPLC system. All mutations will be confirmed by cycle sequencing the relevant exons with incorporation of ABI BigDye terminators, and the sequences will then be analyzed using an ABI 377 automated sequencer. All mutations will be confirmed by a sequencing of a second independent amplification.

10.2.1.2 Where possible, DNA from normal tissue contained in the biopsy will be analyzed to demonstrate that any identified mutations are somatic mutations and not germline mutations or novel polymorphisms. These genomic data will be validated, by independently performed sequencing of the entire 2.9 kb cDNA coding sequence in a subset of GISTS where frozen specimens are available.[33]

10.2.1.3 Fisher's exact test will be performed to assess whether tumor responses are equal between groups of patients with various mutations.

10.2.2 Evaluation of tyrosine phosphorylation and c-kit activation in tumor samples. *(J. Fletcher)*

10.2.2.1 Snap frozen tumor specimens are ground to powder over liquid nitrogen, then resuspended in lysis buffer *(1% Nonidet P-40, 50 mmol/L Tris, pH 8.0, 100 mmol/L sodium fluoride, 30 mmol/L sodium pyrophosphate, 2 mmol/L sodium molybdate, 5 mmol/L ethylenediaminetetraacetic acid, 2 mmol/L sodium vanadate, 10 μg/ml phenylmethylsulfonyl fluoride).* The lysates are rocked for 30 minutes at 4°C, then centrifuged to remove insoluble material. Supernatant protein concentrations are determined using the BioRad MMT assay, and KIT will be immunoprecipitated from 500 ug of lysate, using a polyclonal antibody C-19 *(Santa Cruz Biotechnology, Santa Cruz, CA)* and sepharose protein-A beads *(Zymed Laboratories, South San Francisco, CA).*[10] The immunoprecipitates are separated by

gel electrophoresis and blotted to polyvinylidene difluoride membranes *(Millipore, Bedford, MA),* then stained with PY99 phosphotryosine monoclonal antibody *(Santa Cruz)* with chemilluminescence detection. The blots are then stripped and restained with a combination of polyclonal antibodies to KIT *(Dako)* and PI3-*K (p85) (Upstate Biotechnology).* This approach demonstrates total KIT, and also provides complementary evidence of KIT activation as revealed by PI3-K co-immunoprecipitation. PI3-K associates with KIT in a phosphorylation dependent manner; hence, complexing with KIT provides functional evidence for KIT phosphorylation. Positive and negative controls for KIT tyrosine phosphorylation will be the KIT-positive cell line EWS794, with and without stimulation by the KIT ligand *(SCF),* respectively.

10.2.3 Evaluation of tyrosine phosphorylation of intermediate signaling molecules following the pathways of c-kit activation. *(J. Fletcher)*

10.2.3.1 All frozen tumors will be snap-frozen and held in the liquid phase of liquid nitrogen prior to shipping.

10.2.3.2 KIT Signaling Analyses: These studies will characterize activation as manifested by tyrosine phosphorylation of KIT and signaling intermediates, including MAPK, STAT1, STAT3,and AKT. Western blotting analyses of MAPK, AKT, STAT1, STAT3, will utilize antibodies which have been validated to recognize specifically the total or phosphorylated forms of these proteins in lysates from frozen GIST specimens. The antibodies are commercially provided and include polyclonal anti PI3-K *(UBI)*, polyclonal anti phospho-PI3-K *(Santa Cruz)*, polyclonal anti MAPK *(Zymed)*, monoclonal anti phosphoMAPK Thr202/Tyr182 *(NEB)*, monoclonal anti STAT1 *(Zymed)*, monoclonal anti phosphoSTAT1 Tyr701 *(Zymed)*, monoclonal anti STAT3 *(Zymed)*, monoclonal anti phosphoSTAT3 Tyr705 *(NEB)*, polyclonal anti AKT *(NEB)*, and polyclonal anti phosphoAKT Ser473 *(NEB)*.[53-63]

10.2.3.3 Total and tyrosine phosphorylated forms of KIT, PI3K, MAPK, STAT1, STAT3, and AKT, will be determined by western blotting of total cell lysates from each of the study patient specimens, pre and post Gleevec. Pre-Gleevec cell lysates will be prepared by grinding a single core needle biopsy specimen that has been snap frozen in liquid nitrogen, whereas post-Gleevec lysates will be prepared in identical manner using flash-frozen tumor *(50 mg)* from the resection specimen in each patient. The pulverized tumor material will be resuspended in ice cold lysis buffer *(1% NP-40, 50 mM Tris pH 8.0, 100 mM sodium fluoride, 30 mM sodium pyrophosphate, 2 mM sodium molybdate, 5 mM EDTA, 2 mM sodium vanadate, 5 µg/ml Aprotinin, 5 µg/ml leupeptin, and 50 µg/ml phenylmethylsulfonyl fluoride)*, incubated on a rocker at 4 C for 30 minutes, then centrifuged to remove insoluble material. The lysates are adjusted to 1 mg/ml total protein concentration *(BioRad protein assay)* by dilution with additional lysis buffer, mixed with SDS-PAGE loading buffer and 30 micrograms per lane resolved by SDS-PAGE under reducing conditions *(4-12% gradient gels),* then electrophoretically transferred to PVDF membranes *(Millipore).* The western blots are blocked in PBS containing 0.1% Tween–20 *(PBS-T)* and either 5% non-fat dry milk or 3% BSA *(depending on antibody)* for 1 hour, then incubated with phospho-specific antibody overnight at 4 C, followed by detection using chemiluminescence methods *(ECL, Amersham).* The blots are then stripped, reblocked, and restained using the corresponding antibody which detects total *(phosphorylated and nonphosphorylated forms)* of the protein. Chemiluminescence signal intensities are quantitated, on non-saturated autoradiograms, by laser scanning densitometry. Standard statistical analysis of sets will be utilized: including paired T-test to analyze and compare data from individual patients pre- and post-Gleevec and clinical response criteria.

10.2.4 Evaluation of proliferation and apoptosis assays pre and post treatment will be performed using paraffin sections. *(Corless)*

10.2.4.1 GIST cell proliferation and apoptosis will be determined in all study patients by immunostaining for Ki-67 and by the TUNEL assay, respectively. These assays will be performed by standard methods, with immunoperoxidase detection of Ki-67 *(Dako)* and TUNEL staining by incorporation of fluorescein-dUTP with peroxidase detection *(Roche Molecular Biochemicals).* Apoptosis and proliferation indices are critical markers against which to judge the biological impact of different categories of KIT mutations, and these markers will also likely shed light on the ramifications of KIT signaling pathway activation. Further, proliferation and apoptosis levels are key benchmarks against which to evaluate GIST gene expression profiles.

10.2.5 *Assessment of Genomic Correlates for GIST Progression*: *(J. Fletcher)*

The aims of these studies are to annotate the study tumors according to common genomic mechanisms which are known to correlate with clinical progression and which may, in some cases, modify signaling mechanisms associated with the KIT oncoproteins. These aims will be accomplished by focused FISH analyses, using BAC clones mapping within consensus GIST chromosomal deletion regions, and by genome-wide low-resolution evaluation by comparative genomic hybridization *(CGH).* The CGH profiles

will be compared for each tumor pre and post-Gleevec to determine whether GIST sublines with particular genomic alterations *(deletions or amplifications)* are particularly sensitive or resistant to Gleevec. Further, these genomic correlates may be crucial in identifying mechanisms underlying Gleevec-related gene expression profiles, as determined by the cDNA array analyses. The FISH analyses will provide complementary data, which will serve both as validation for the CGH analyses, and will enable more sensitive evaluation of key chromosmal deletions of known importance in the biological progression of GISTs.

10.2.6 Analysis of global gene expression pattern pre and post treatment by microarray analysis. *(Eisenberg, vonMehren)*

10.2.6.1 Core biopsies of patients will be performed at baseline. In addition a one gram sample of viable tissue from the resection specimen will be obtained. Samples will be frozen immediately *(see Appendix V)* with a portion saved for pathologic assessment. When received in our lab, RNA will be isolated using FastTrack mRNA isolation kit *(Invitrogen).* Prior to beginning, the tissue homogenizer is cleaned so that it is RNAase–free. Lysis buffer will be added to frozen pellets and homogenized for 3-5 seconds in ddH_2O and ethanol 3 times sequentially, followed by incubation in lysis buffer for 45 minutes at 45^oC. DNA will be sheared and followed by mixing with oligo *(dT)* for 60-90 minutes at room temperature followed by three low salt washes. Then oligo *(dT)* will be pelleted and washed initially using binding buffer. The RNA will be eluted using elution buffer heated to 65° C. Then 2M sodium acetate followed by 95% ethanol will be added and samples frozen overnight. RNA will be re-suspended in elution buffer and quantified by spectophotometry. Poly A^+RNA will be purified utilizing OligoTex mRNA columns *(Qiagen).* If insufficient RNA is available, amplification will be performed.[64] DNA microarray analysis will be performed using the Brown technique.[65] The Fox Chase Microarray Facility uses the Omnigrid with robotic arm from Genemachine *(Santa Clara, CA).* The arrayer has sixteen pins, can print 100 slides per run and utilizes cDNAs in 384-well microtiter plates. The cDNA fragments are amplified from a cDNA human library purchased from Research Genetics containing 10,000 genes. Reference probes will be made from poly A^+ RNA from pre Gleevec treatment biopsies with random primers by reverse transcription and fluorescence-labeling of the nucleotides with Cy3. Sample probes will be made in the same fashion, using poly A^+ RNA from surgical biopsy samples labeled with Cy5. Reference probes and sample probes will be combined and hybridized to an array and then scanned using the Affymetrix/Genetic Microsystems confocal scanner GMS418. In addition, if possible the mRNA will be split prior to labeling. and fluor-flipping will be performed to allow correction for nonlinearities and inconsistencies in dye incorporation. Quantitation of the microarray data is done with Imagene software package from Biodiscovery *(Los Angeles, CA).* Analysis and interpretation of the data sets will be performed by the Bioinformatics Facility in collaboration with the FCCC statistics department using both standard data mining techniques *(e.g. clustering, principal component analysis)* and Bayesian Decomposition, which is being developed for analyzing gene expression array data at Fox Chase under an accelerated grant from the National Medical Testbed. This technique should be especially useful for identification of involved pathways.

10.2.6.2 For identifying specific genes which have undergone a change in response to treatment, standard statistics will be used to assess significance. With 50 samples, we assume 43 responders *(i.e. 7 expected non-responders, mostly with wildtype c-KIT or exon 9 mutation)* yielding 43 independent measurements of the differential expression for each of 10,000 genes. We will treat differential expression as significant when the mean of the measurements is at least 4 standard deviations of the mean away from 1.0. This will still yield ~10 false positives; however, this number is not excessive for followup. Presently the microarray facility at Fox Chase is seeing reproducibility with a standard deviation of approximately 20%. Assuming fluor-flipping to give independent measurements and to eliminate outliers and consistent biological behavior between individuals, we expect to see standard deviations of 14% in the duplicate measurements and 20% in ratios. We expect therefore a standard deviation in the ratios of $\sqrt{43}$ *(20%)* = 3% for a single gene. As such, we expect to be able to see differential expression whenever there is 4*(3%)* = 12% difference in expression between the pre- and post-treated samples for responders. If mRNA amplification is required or fluor-flipping cannot be done, we expect a corresponding increase in the difference required to identify differential expression. Furthermore, we expect that some genes will show larger variation due to interindividual variation. However, the genes of interest in this study should behave similarly between patients and be detectable close to this level.

A second question is the difference between responders and non-responders. With only 7 nonresponders expected, it will be more difficult to pick up significant differences. There are two

approaches. First, the nonresponders can be analyzed like the responders, identifying differences between pre- and post-treatment expression levels; however the expected difference in expression for significance will be ~30%. These genes can then be compared with those obtained in the case of the responders; however, we expect 10 false positives in each case. Second, the post-treatment responders and non-responders can be compared. This is more difficult as it introduces inter-individual variation. However, by pooling normalized gene expression levels prior to forming the ratio, and assuming 20% uncertainty in each measurement, we expect a standard deviation of 3% in measurements of responders and 8% in nonresponders, so that the uncertainty in the ratios of pooled levels would be about 9%. This means that to reduce false positives to only 1 in the 10,000 genes would require a change in expression of roughly 50%. However, this approach is the most promising for identifying the key differences between nonresponders and responders.

10.2.6.3 The amount of mRNA recovered from tissue samples is likely to be small at a number of points in the analysis. As such, it may not be possible to fluor-flip in each experiment. However, the goal of this proposal is the identification of changes within a population of patients rather than within a specific individual. As such, we will average the overall results from multiple patients *(e.g. those responding to Gleevec)* which will improve the reliability of the determined mRNA levels in each group. We will estimate noise levels from these groupings and use standard statistical measures[66] to estimate the significance of the change of the expression level of a given gene. In data mining, the individual genes will be grouped by algorithms into coexpression groups. The noise levels will be used here in two ways. First, for standard data mining algorithms which do not have the ability to use uncertainty estimates, the final results will be viewed in terms of the uncertainties, including comparing different coexpression groups to validate that they are different once the noise is considered. Second, Bayesian Decomposition uses the estimate of the noise during analysis to constrain the model only within the uncertainty. Since we will have multiple measurements of each expression level provided either through fluor-flip and duplicate spotting or through multiple individuals, the analysis by Bayesian Decomposition will automatically include this information when determining coexpression groupings.

10.2.7 *Pathology Review*

A standard pathology review of the pre-treatment and post-treatment biopsy tissue will be performed by a reference pathologist *(Corless).* This will either be performed on the paraffin block or the 10 unheated, unstained slides taken in conjunction with this study or on the original tumor block in the case of recurrent GIST. A diagnosis of gastrointestinal stromal tumor will be confirmed or overturned on the basis of H&E morphology *(recognizing spindled and epithelioid variants of GIST)* and immunohistochemical staining results. It is anticipated that the biopsy tissue will be limited and therefore a formal mitotic index *(50 high power fields)* may not be possible. Nevertheless, the frequency of mitoses in 10 high power fields will be recorded, together with other morphologic parameters *(necrosis, vascular invasion).*

Sections of the biopsy will be stained for the markers listed below using standard immunohistochemical protocols. The diagnosis of gastrointestinal stromal tumor will require the indicated staining results.

CD117 ***(KIT) (DAKO A4502): (10/10/03)*** GIST cells should exhibit evidence of CD117 staining. . Staining may be surface membrane and/or cytoplasmic. Endogenous mast cells present in the tissue will serve as a benchmark for strong staining. The antibody will be titered such that there is no staining of epithelial cells or fibroblasts in control tissues *(e.g. colon, skin).*

S-100, smooth muscle actin, CD34, bcl-2: These stains will be performed but their results will not impact diagnosis. The results will only be used for comparison with stains performed on post-treatment tumor tissue.

Proliferative index: This will be assessed by immunohistochemical staining for Ki-67 *(Novo-Castra MM1 antibody)* and expressed as a percentage of positive nuclei. The result will only be used for comparison with stains performed on post-treatment tissue.

10.2.8 Evaluation of glucose transporter expression in GIST tumors pre- and post-therapy. *(Chris Corless).* Sections of paraffin-embedded pre-treatment and post-treatment tumor samples will be qualitatively evaluated for glucose transporter expression by immunohistochemical staining using a rabbit polyclonal antibody *(East Acres Biological, Southridge, MA).* The binding characteristics of this antibody to GLUT 4 and its use in the immunochemical localization of GLUT 4 have been previously described *(J. Clinical Invest. 89:1767-1774, 1992).* Pilot stains will be performed using various antigen retrieval techniques

(e.g. citrate buffer, enzymatic digestion) to optimize the staining signal. 10% BSA buffer and treatment with methanol/H202 will be performed to keep background to a minimum. The anti-GLUT 4 antibody will be detected by serial incubations with a biotinylated anti-rabbit secondary and avidin/biotin/horse radish peroxidase *(ABC Elite kit, Vector Laboratories)*. The chromagen will be DAB *(Dako Corp., Carpinteria, CA)*. Sections will be examined by an observer blinded to the tumor's response to Gleevec. Images will be recorded with a Polaroid DMC-1 digital microscope camera. Of note, if GLUT 4 is not overexpressed in GIST tumors, the same procedure will be repeated using an antibody to the other glucose transporters including GLUT 1, the second most common glucose transporter overexpressed in tumors.

10.3 ECOG Investigators ***(10/10/03)***

Submission of tissue, described in Section 10.1 and Appendix V, for use in the correlative studies described in Section 10.2 are **required** for patient participation in R0132. The minimum required submissions are:

	Pre-treatment	Surgical
Paraffin-embedded tumor tissue	1 core needle biopsy[1,2]	1 gram non-necrotic[2]
Snap frozen tumor tissue	2 core needle biopsies[1]	3 gram non-necrotic

1 Core biopsies are to be collected with an 18 to 14 gauge core needle via CT or ultrasound guidance.
2 If block is unavailable, submit 10 unheated, unstained slides.

Submit the tissue, the RTOG Pathology submission form AND the ECOG Pathology Material Submission Form (#638) to the RTOG Tissue Bank at the LDS Hospital as indicated in Section 10.1 and Appendix V.

Forward a copy of the ECOG Pathology Material Submission Form (#638) to the ECOG Pathology Coordinating Office, Robert H. Lurie Comprehensive Cancer Center, Northwestern University Medical School, Olson Pavilion - Room 8501, 710 North Fairbanks Court, Chicago, IL 60611.

10.3.1 Reimbursements from RTOG will be distributed to ECOG institutions by the ECOG Coordinating Center, upon receipt of appropriate documentation from RTOG.

10.3.2 Banking of residual material

Upon completion of the defined correlative studies, any residual material from the submitted blocks or slides will be forwarded to and retained at the ECOG Central Repository, ECOG PCO, for possible use in future ECOG approved studies. Any residual blocks will be available for purposes of individual patient management on specific written request. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

11.0 PATIENT ASSESSMENTS *(10/10/03)*

11.1 Study Parameters

Required Studies	**Pre-Tx**	Wk. 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	**Surgical Resection**	Month 3	Month 6	Month 9	Every 3 mos. until month 24[h]	Every 6 mos. from 30 to 60 months
Physical															
History & Physical Exam[a]	X[b]	X			X				X		X	X	X	X	X
Weight & Performance	X	X			X				X		X	X	X	X	X
Toxicity Notation		X			X				X		X	X	X	X	
Laboratory[c]															
CBC/differential Platelets	X[b]	X[b]			X				X		X	X	X	X	
Bilirubin, Creatinine, ALT/AST, Alk Phos, LDH, Glucose	X[b]	X[b]									X	X	X	X	
Serum Pregnancy test[d]	X														
Tumor IHC for KIT *(CD117)*[e]	X														
Tumor Sample submission[f]	X				X[o]				X[o]	X					X[m]
X-Rays & Scans															
X-rays/scans as needed for disease assessment[g]	X				X				X		X[i]	X	X	X	X
PET Scans[g]	X	X			X[g]				X						
Treatment[n] *(See Sec. 7.0)* Daily		X	X	X	X	X	X	X	X[j]	X[k]	X[l]	X	X	X	

a. Total body examination with pulse rate, blood pressure and body temperature.
b. In the event that blood counts or labs were performed within four days of the first dose of the study drug, they do not have to be repeated and may be used as Day 1 values.
c. Assessments may be performed more frequently as clinically indicated.
d. Required for women of reproductive potential. Must be obtained within 7 days prior to study entry and study treatment. Post-menopausal women must be amenorrheic for at least 12 months to be considered of non-childbearing potential.
e. See Appendix IV.
f. See Section 10 and Appendix V.

g. All disease assessment must be performed using the same assessment technique used at pre-treatment *(either CT or MRI).* In order to be considered a "confirmed" response, response evaluation must be confirmed by a repeat disease assessment a minimum of four weeks later. In initial studies, PET scans have been useful in identifying potential tumor response. When combined with conventional imaging, PET scans may allow early prediction of response or progression and thus may prove cost-effective. Thus PET will need to be performed pre-treatment at baseline, within 24 hours to 1 week following initiation of therapy, and just prior to surgery. PET is performed at 4 weeks in patients with progressive disease or preoperatively.
h. Treatment and assessments will be continued on this schedule *(with physical exams, laboratory assessments and tumor assessments every three months for 2 years from treatment start; then every 6 months until year 5.)*
i. First scan to be done within 6 weeks postop if gross residual disease is left at surgical resection.
j. Stop Gleevec on the night before surgery.
k. Within 2-4 weeks postoperative drug re-administration.
l. Continue Gleevec daily for a total of 24 months postoperatively, then discontinue.
m. In the event of tumor recurrence, obtain tissue for paraffin blocks and snap freezing for future designated studies.
n. ***(4/5/04)*** Patients stop protocol treatment if there is evidence by scan criteria of disease progression at any time (4 weeks or 8-10 weeks) and are followed as specified in Sections 11.1 and 12.1. Further treatment off study is at physician's discretion.
o. For progressive disease.

11.2 Criteria for Evaluation and Endpoint Definitions *(RECIST)*

(RECIST criteria can be downloaded from the CTEP website at http://ctep.cancer.gov) (10/10/03)

11.2.1 *Measurability of Lesions*

a. Measurable disease: Lesions that can be accurately measured in at least one dimension by medical photograph *(skin or oral lesion),*palpation, plain x-ray, CT, MRI or other conventional technique with longest diameter 2 cm or greater in the axial plane *(bone lesions not included),* or spiral CT with longest diameter 1 cm or greater. Ultrasound is suitable only for superficial disease *(superficial palpable nodes, subcutaneous lesions, thyroid nodules).* CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis.
b. Non-measurable disease: All other lesions including lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, inflammatory breast disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed and followed by imaging techniques, cystic lesions or disease documented by indirect evidence only *(e.g. by lab values).*

11.2.2 *Objective Status at Each Evaluation*

Objective status is to be recorded at each evaluation. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. All measurable lesions not identified as target are non-target lesions and are included as non-measurable disease. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

- *Complete Response* **(CR):** Complete disappearance of all measurable and non-measurable disease. No new lesions. No disease related symptoms. Normalization of markers and other abnormal lab values. All disease must be assessed using the same technique as baseline.
- *Partial Response* **(PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of longest diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.
- *Stable*: Does not qualify for CR, PR, progression or symptomatic deterioration. All target measurable lesions must be assessed using the same techniques as baseline.
- *Progression:* One or more of the following must occur: 20% increase in the sum of longest diameters of target measurable lesions over smallest sum observed *(over baseline if no decrease during therapy)* using the same techniques as baseline. Unequivocal progression of non-measurable disease in the opinion of the treating physician *(an explanation must be provided).* Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration.

- *Symptomatic deterioration*: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.
- *Assessment inadequate, objective status unknown:* Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

11.2.3 *Objective Status Notes*:

- Non-measurable and non-target measurable disease do not affect objective status except in determination of CR *(must be absent; a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR),* and in determination of progression *(if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).*
- An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.
- Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.
- For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression.
- Appearance or worsening of pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin.
- If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

11.2.4 *Best Response*: This is calculated from the sequence of objective statuses.

CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

Stable/No Response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

Increasing Disease: Objective status of progression or symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

Inadequate Assessment, Response Unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

11.3 Follow-up

Patients will be followed weekly during the first 8 weeks of neoadjuvant Gleevec. After the postoperative time-frame and re-initiation of Gleevec, patients will be followed as noted on study calendar.

11.4 Time to Progression

From date of registration to date of first observation of progressive disease or death due to any cause.

11.5 Time to Death

From date of registration to date of death due to any cause.

11.6 PET Scanning *(10/28/04)*

NOTE: PET images obtained with dedicated NaI-detector scanners were permitted prior to Amendment 4 *(10/28/04)* of the study; however, to optimize the quality of PET images in the remaining patients to be accrued, scans obtained with NaI scanners are no longer permitted.

11.6.1 Initial PET scanning within 8 weeks before registration prior to initiation of drug therapy:

a. The baseline imaging study needs to conform to the PET imaging quality control standards as described in Appendix VII.
b. A whole body PET scan from the base of the skull to the proximal thighs needs to be performed.
c. Patients will be fasted for at least 4 hours prior to imaging.
d. The patient must empty his/her urinary bladder immediately prior to imaging.
e. Transmission scanning matching the areas covered by the emission scan will need to be performed for attenuation correction of the emission scan. This will be done after injection of FDG. If positron emitting transmission sources are used, we recommend at least 3 minutes per bed position for segmented attenuation correction and at least 10 minutes per bed position for measured attenuation correction.

f. Emission scans are to be initiated from the pelvis upward, so that the abdominal or pelvic tumor(s) is/are imaged between 45 and 70 minutes after injection of 10-20 mCi of F-18-FDG. The 20 mCi dose is highly recommended if feasible. Emission data must be collected for at least 7 minutes and will be corrected for scatter, random events and dead-time losses using manufacturer's software. Bed positions should be overlapped to avoid large changes in sensitivity at the joints between the bed positions.
g. The patient must empty his/her urinary bladder immediately after imaging.
h. Image reconstruction generally will depend upon the scanner manufacturer's recommendations. When it is available, we would recommend an iterative reconstruction method, with preference for OSEM reconstruction. For Siemens/CTI HR+ in 2D mode, we recommend the use of OSEM with 8 subsets, 2 iterations, followed by smoothing with a 6-mm 3D Gaussian kernel. For a GE Discovery ST in 2D mode, we recommend the use of OSEM with 21 subsets, 2 iterations, z-axis smoothing, a 4-mm loop filter, and a 7-mm post filter, with a 60 cm FOV.
i. FDG is to be synthesized by standard methods and tested for pyrogenicity and radiochemical purity on each production run, or purchased from nuclear pharmacies licensed to sell F-18-FDG.
j. Both visual and semi-quantitative PET data analyses will be performed *(see Section 11.7).*

11.6.2 *FDG PET Imaging at Week 1*

In addition to the baseline PET scan, an additional PET scan will be obtained shortly after the initiation of therapy, optimally 24 hours following the administration of the first dose of the drug. If not feasible, the scan should be performed during the first week following the start of therapy but no later than day 7. It will be performed using the same technique used for the baseline scan, according to the instructions given in Section 11.6.1.

11.6.3 *FDG PET Imaging Before Surgery* ***(10/10/03)***

The final study will be done just prior to surgery. (It is recommended that whenever possible the study be done in the week prior to surgery). It will be performed using the same technique used for the baseline scan, according to the instructions given in Section 11.6.1. The scan will be read without knowledge of the pathology results obtained after surgery.

11.6.4 *Potential Risks Related to PET Scanning*

The potential risks inherent in this study are as follows: this research study involves exposure to radiation from an intravenous injection of F-18 fluoro-2-deoxy-D-glucose for the PET scans. The amount of radiation exposure *(effective dose)* from three PET scans *(the minimum number to be performed for research purposes),* if each is performed with the maximum injected dose of 20mCi of FDG, is equivalent to a uniform whole-body exposure of approximately 4.5 rem. The exposure from the PET scans is similar to the allowable annual dose for radiation workers *(for example, x-ray technicians).* The risk from radiation exposure of this magnitude is too small to be measured directly and is considered to be low in comparison with other everyday risks.

The placement of intravenous catheters has the associated risk of making the patient temporarily uncomfortable and a small bruise may form. A slight bruise may form where the needle has been in a vessel. There is a slight risk of infection at the site, but sterile technique reduces this risk nearly completely. The patient may also experience claustrophobia from the imaging ring apparatus or discomfort from lying on the scanner table for 60-120 minutes. For the dose of FDG used in this study there are no anticipated toxicities *(other than the radiation exposure mentioned above).*

11.7 PET Data Analysis

The PET and conventional cross-sectional imaging *(CT, MRI)* scans will be submitted electronically to ACRIN and stored in an electronic database *(see Appendices IX and X)* ***(10/10/03)***. The scans will be used for both visual interpretation and semi-quantitative analyses. All scans will be interpreted independently by two readers. Visual comparison of the pretreatment and post-treatment scans will be performed to determine the change in tumor FDG uptake. The change will be rated as follows: marked decrease in activity, slight decrease, no change, slight increase, or marked increase. The visual interpretation of the PET scans will be done without knowledge of the conventional cross-sectional imaging, or other clinical information. These scans will then be re-read with knowledge of the conventional cross-sectional imaging and clinical information.

A subsequent multireader study to assess accuracy and variability across readers will occur if results of statistical analyses for the data from these two readers indicate correlation with glucose transporter expression, size changes on conventional cross-sectional imaging, or ability to predict recurrence. The number of readers will be determined based on those results.

For semi-quantitative analysis, regions of interest *(ROIs)* will be placed about the regions of abnormal FDG uptake *(target lesions)* as determined by visual inspection. If there are three tumor sites or less, ROIs should be placed on all these sites. If there are more than three lesions, ROIs should be placed on the three most intense sites. Given that the typical appearance of GIST tumors on FDG-PET consists of a mass containing a central photopenic center surrounded by a rim of intense FDG uptake, the ROIs will be placed in the axial plane containing the maximum uptake value for that tumor site. ROIs will be drawn on the 70% maximum uptake iso-contour. Four background ROIs will also be drawn by placing copies of the ROI used to measure the tumor in normal-appearing regions of the tissue/organ of origin on the same slice used for tumor analysis. If necessary, the background ROIs may be placed on the contra-lateral side of the body. For each region maximum SUV, average SUV and TBR will be recorded, along with the number of pixels *(SUV and TBR are calculated as indicated below).* This ROI analysis is to be performed by an experienced physician who may use conventional cross-sectional imaging information to help draw the regions of interest. The same reader will do the visual interpretation to be followed by the semiquantitative calculations. This can be done in the same sitting.

For the post-treatment measurements, ROIs will again be drawn in what appears to be the axial plane containing the maximum uptake value for that tumor site. If the tumor has elevated FDG uptake compared to background, the tumor ROI will be drawn on the 70% maximum uptake iso-contour. If the tumor does not have elevated FDG uptake compared to background, the ROI will be drawn around the observer's best estimate of the tumor margin. In this case, information from cross-sectional anatomical images and from the previous FDG image may be used to guide the ROI placement. The post-treatment SUV will then be calculated as specified below.
After correction for radioactive decay, standardized uptake values *(SUV)* are computed according to the following:

$$\text{SUV} = \frac{\text{ROI activity } (mCi/ml)}{\text{injected dose } (mCi)/\text{body wt } (g)}$$

TBRs will be computed for each lesion by calculating the ratios of the mean SUVs for the tumor and background regions.

Conventional cross-sectional images will be interpreted independently by radiologists at participating sites in order to measure the change in size of the lesion. They will have no knowledge of the clinical details *(history, PET results or biopsy results)* of each case. These images will also be independently interpreted by ACRIN investigators.

11.8 PET Criteria for Evaluation of Response and Endpoint Definitions

The imaging done just prior to surgery *(at week 4 in patients with progressive disease, at week 8 in patients with stable or responding disease)* will be used for measurement of the primary endpoint. A number of different measures can be obtained from the PET scans. We have chosen to use the percent decline in the maximum SUV just prior to surgery *(at week 4 in patients with progressive disease, at week 8 in patients with stable or responding disease)* as the primary PET endpoint. Other measures that will be included for subsequent analysis include the following PET measures: use of average SUV, use of SUV-lean, which will be calculated using ideal body weight; percent change in background subtracted SUV; percent change in tumor-to-background ratio; post-therapy SUV alone; and visual analysis results. We will also analyze the scans done during the first week following initiation of therapy to determine if they are predictive of the response just prior to surgery *(at week 4 in patients with progressive disease, at week 8 in patients with stable or responding disease)* and the ultimate pathologic and clinical outcomes.

The PET results will be compared to the pathologic results of glucose transporter expression. The primary endpoint from the pathologic studies will be the correlation of glucose transporter expression at baseline and following treatment to the maximum SUV at baseline and the percent decline in maximum SUV just prior to surgery *(week 4 or 8, depending on the course of the disease).*

12.0 DATA COLLECTION *(10/28/04)*

Data should be submitted to:

RTOG Headquarters
1818 Market Street, Suite 1600
Philadelphia, PA 19103

12.1 Summary of Data Submission

Item *(10/10/03)*	Due *(12/18/03)*
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** Pathology Slides/Blocks **(P2)** (*from three core biopsies)*	Within 2 wks of study entry
PET Technical Assessment Form **(TA)***	***Submitted at baseline, 24 hours to 7 days post treatment initiation, week 8 *(prior to surgery)* or at week 4 if progression seen on CT/MRI scans
Pre-treatment CT/MRI scan **(C1)** Pre-treatment PET scan **(C5)**	
Post-Induction Follow-up Form **(FO)**	At week 4 and at end of pre-surgical Gleevec administration
Treatment Summary Form **(TF)**	At week 4, at end of pre-surgical Gleevec administration, and then every 3 months for 2 years
Surgery Forms **(S1), (S2)** Surgical Pathology Report **(S5)** Headquarters **(P4)** Surgical Materials **(P7)** *(see Section 8.2 and Appendix V, Section B)*	2 weeks after surgery
Follow-up Form **(F1)**	Every 3 months from start of treatment for 2 years; q 6 months x 3 years. Also at progression/relapse and at death.
Follow-up CT/MRI scan **(C2)** Follow-up PET scan **(C4)**	Submitted at 24 hours to 7 days post treatment initiation, week 8 *(prior to surgery)* or at week 4 if progression seen on CT/MRI scans
Autopsy Report **(D3)**	As applicable

12.2 Data Submission Schedule ECOG Institutions *(4/5/04)*

Forms submission: The original data forms as listed in Section 12.0 should be submitted at the required intervals to the ECOG Coordinating Center, Attn: Data, 900 Commonwealth Avenue, Boston, MA 02215. Include the RTOG and ECOG study number and patient ID number. The ECOG Coordinating Center will forward the forms to the RTOG.

The required forms can be accessed on the RTOG web site, http://www.rtog.org/members/forms/0132/main.html *(no password required)*. Do not use ECOG Forms for this study, with the exception of the ECOG Pathology Materials Submission Form *(#638)*.

13.0 STATISTICAL CONSIDERATIONS

13.1 Endpoints

13.1.1 Biological effects of Gleevec

13.1.2 Rate of disease recurrence at two years

13.1.3 Rates of objective response *(complete, partial, stable)*

13.1.4 Major toxicity *(grade ≥ 3)* associated with Gleevec

13.1.5 Correlation of glucose transporter expression and PET interpretations

13.1.6 Tumor changes observed on PET; correlation with size changes observed on conventional cross-sectional imaging

13.1.7 Diagnostic accuracy of PET to predict disease recurrence

13.2 Sample Size

The primary objective of this study is to evaluate the biological effects of Gleevec in malignant GIST by comparing pre- and post-drug tissue samples. This is an exploratory analysis that will serve to generate hypotheses for future study in GIST. Fifty patients with both pre- and post-drug tissue will be evaluated with respect to the biological endpoints described in Section 2.1. Allowing for 10% of patients to be determined ineligible, and an additional 10% of patients without tissue, **the targeted sample size is 63 patients**. This number will be adjusted if necessary to ensure 50 evaluable patients if a higher proportion of patients have no tissue available. For the evaluation of the endpoints 13.1.2, 13.1.3, and 13.1.4, all eligible patients will be included regardless of tissue status. It is expected that 56 eligible patients will be accrued to this study. With 56 patients, the rates of recurrence, response, and major toxicity can be estimated using a binomial distribution with margin of error ≤ 13.1%.

With 50 evaluable patients, the 95% confidence interval for the true correlation, ρ, between glucose transporter expression and SUV on PET will lie entirely above zero if the sample correlation, r, exceeds 0.28. We expect ρ to be notably higher to be clinically useful. The statistical power to exclude zero from the 95% CI for ρ exceeds 90% when $\rho \geq 0.44$. Regarding the clinical endpoints, with 50 evaluable patients the margin of error on percent decrease in SUV is expected to be approximately 12.5%. Pilot data for the correlation of percent decrease in SUV with size changes by conventional cross-sectional imaging provide an estimated $r = 0.50$. Thus the expected power to exclude zero from the 95% confidence interval for ρ for this endpoint also exceeds 90%. The 95% CI for ρ when $r = 0.50$ with 50 patients is *(0.258, 0.683)*. There are no preliminary data regarding the ability of PET to predict recurrence for patients with GISTs.

13.3 Patient Accrual

Patient accrual is projected to be approximately 30 patients per year. At this rate, it will take approximately two years to complete accrual. If the average monthly accrual is less than 1.0 patient per month, the study will be re-evaluated with respect to feasibility.

13.4 Suspension of Accrual Due to Treatment Morbidity

If there is any fatal treatment toxicity, the event will be reported to the study chairs for review. If there are two such fatal toxicities, patient accrual will be suspended, and the study chairs will review all data pertaining to the events and make a recommendation to the RTOG Research Strategy committee about future course of action.

13.5 Analysis Plans

13.5.1 *Statistical Methods*

The rate of disease recurrence at two years will be estimated along with its 95% confidence interval using the Kaplan-Meier[67] method. The response rates and major toxicity rates along with their 95% confidence intervals will be estimated using a binomial distribution.

95% confidence intervals for the correlations between glucose transporter expression and SUV on PET, and between tumor changes on PET and size changes on conventional cross-sectional imaging, will be estimated through Fisher's z-transformation. Relationships between PET interpretations and disease recurrence will be analyzed using Cox proportional hazards regression models.

13.5.2 *Interim Analyses*

Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, these reports contain information about:

- The patient accrual rate with projected completion date;
- Compliance rate of treatment delivery with respect to the protocol prescription;
- Quality of submitted data with respect to timeliness, completeness, and accuracy;
- The frequency and severity of major toxicities.

Through examining the above items, the study chairs and the statistician can identify problems with the execution of the study. These problems will be reported to the RTOG Sarcoma Committee.

13.5.3 *Analyses for Reporting Study Results*

There will be two major analyses of the effects of Gleevec. The first will be an analysis of the biological effects of Gleevec undertaken when each patient has had protocol surgery. Second, there will be an analysis reporting the efficacy results with respect to disease recurrence when each patient has been potentially followed for two years. Initial analyses of PET interpretations will report on their relationship to glucose transporter expression and tumor size changes on conventional imaging. Subsequent analyses, when each patient has been potentially followed for two years, will report on the relationship of PET interpretations to disease recurrence.

The usual components of these analyses are:

- Tabulation of all cases entered, and any cases excluded with reasons for exclusion;
- Institutional accrual;
- Distribution of important baseline variables;
- Observed results with respect to the endpoints described in Section 13.1.

13.6 Inclusion of Women and Minorities

In conformance with the National Institutes of Health *(NIH)* Revitalization Act of 1993 concerning inclusion of women and minorities in clinical research, we have considered differences in prognosis by race and gender. The following table gives the projected accrual for each race and gender category based on institutional study.

Planned Gender and Minority Inclusion

	American Indian or Alaskan Native	Asian	Black or African American	Hispanic or Latino	Native Hawaiian or Pacific Islander	White	Other or Unknown	Total
Female	0	1	3	3	1	24	0	32
Male	0	1	3	3	1	23	0	31
Total	0	2	6	6	2	47	0	63

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APPENDIX I

RTOG S-0132

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A PHASE II TRIAL OF NEOADJUVANT/ADJUVANT STI-571 (GLEEVEC NSC# 716051) FOR PRIMARY AND RECURRENT OPERABLE MALIGNANT GIST EXPRESSING THE KIT RECEPTOR TYROSINE KINASE (CD117) [ACRIN 6665]

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, "Taking Part in Clinical Trials: What Cancer Patients Need To Know," is available from your doctor.

You are being asked to take part in this study because you have gastrointestinal stromal cancer.

WHY IS THIS STUDY BEING DONE? ***(4/5/04)***

The purpose of this study is to find out what effects *(good and bad)* the drug, Gleevec, has on you and your cancer.

This research is being done to see if Gleevec given before and after your surgery will decrease the chances of your tumor recurring and result in improved survival. This study will also gather information to further the understanding on how this type of drug affects you and your tumor.

You are going to have a biopsy (or surgery) to confirm that you have gastrointestinal cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and will be used in research to learn more about biologic factors and inherited traits *(genes)* that may help to predict and treat gastrointestinal stromal cancer in the future.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 63 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY? *(4/5/04)*

If you take part in this study, you will have the following tests and procedures:

Prior to Treatment

- Medical history and physical examination
- Blood tests, including a pregnancy test for women who are able to have children
- X-rays or scans to determine the extent of your disease. These can include ultrasound, MRI, CT, and PET scans.
- At least 3 biopsies of your tumor will be obtained with a needle using ultrasound, CT scan, or by using an endoscope for guidance. An endoscope is an instrument put into your esophagus, which is the tube that goes into your stomach.

Treatment

You will take Gleevec *(6 pills by mouth with 8 ounces of water and with food)* every day for 4 to 10 weeks

- Blood tests will be done at weeks 1, 4, and 8-10
- Physical examination at weeks 1 and 4 and 8
- X-rays or scans to determine the extent of your disease will be done at weeks 4 and 8-10
- Two PET scans will be performed: one during the first week after you start taking Gleevec, and the other right before surgery.

After 4 weeks of Gleevec

Patients whose disease progresses

You will stop taking Gleevec. Your doctor may discuss other available treatments that are not part of this study with you. You may have surgery to remove all or most of your tumor. If your doctor feels that surgery is not in your best medical interest, your doctor will ask you to have a repeat biopsy of your tumor. You will be seen in follow-up visits every 3 months for 2 years, then every 6 months for 3 years.

Patients whose disease responds or remains the same

You will take Gleevec *(6 pills by mouth with 8 ounces of water and with food)* every day for an additional 4-6 weeks *(for a total of 10 weeks).*

After 10 weeks of Gleevec

Patients whose disease progresses

If your disease has progressed by weeks 8-10, you will stop taking Gleevec.

Your doctor may discuss other available treatments that are not part of this study with you. You may have surgery to remove all or most of your tumor. If your doctor feels that surgery is not in your best medical interest, your doctor will ask you to have a repeat biopsy of your tumor. You will be seen in follow-up visits every 3 months for 2 years, then every 6 months for 3 years.

Patients whose disease responds or remains the same but who do not have surgery

If your doctor feels that surgery is not in your best medical interest, your doctor will ask you to have a repeat biopsy of your tumor. You will continue to take Gleevec *(6 pills by mouth with 8 ounces of water and with food)* every day for two years or until your doctor tells you to stop. You will be seen in follow-up visits every 3 months for 2 years, then every 6 months for 3 years.

Patients whose disease responds or remains the same and who have surgery

Blood tests will be done several times prior to surgery, and a physical examination and x-rays or scans to determine the extent of your disease will be done at week 8. You will stop taking Gleevec the night before your surgery. You will then have surgery to remove all or most of your tumor.

Two to four weeks after surgery, you will begin taking Gleevec again *(6 pills by mouth with 8 ounces of water and with food)* every day for two years or until your doctor tells you to stop. A physical examination, blood tests, and x-rays or scans will be done in follow-up visits every 3 months for 2 years, then every 6 months for 3 years.

All Patients

As described above, prior to treatment, some of your tumor will be removed by biopsy and all or some of your tumor will be removed at the time of surgery. If your disease has progressed during the first 4 or 8-10 weeks of treatment, and you do not have surgery, your doctor will ask you to have a repeat biopsy of your tumor.

As is usually done, this tissue will go to the hospital's pathology department for routine testing and diagnosis, and the remaining tumor samples will be stored in a centralized tissue bank. If you consent to participate in this study, you are consenting to the use of the remaining tumor samples for additional tests. The tests will include research into biologic factors and inherited traits *(genes)* that may help to predict and treat gastrointestinal stromal tumors in the future.

Your tissue may be helpful for research, but probably will not help you. It might help people who have cancer and other diseases in the future. Reports/findings about the research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

You may call 801-408-5626 at a later time if you change your mind about allowing the use of your stored tissue for additional tests that are not related to cancer research.

The role of the PET scan is being tested in this study. You will need to eat nothing for at least 4 hours before the PET scan, and a small blood sample will be obtained before the test is begun to confirm that your blood sugar in an acceptable range. For the PET scans, you will have a small tube inserted into one of your veins in your forearm. This tube is needed to inject the radioactive substance (F-18 fluorodeoxyglucose or FDG). Approximately 45 to 60 minutes later, you will be asked to empty your bladder and then you will lie on a comfortable table for 60 to 120 minutes while your body is in the opening of a large doughnut-shaped detection device (PET scanner). The PET device contains crystals which pick up the radiation signals from FDG in your body. The scan is able to target these regions of your body, and with the help of computers, the signals come together to provide a picture of the tumor and your organs. At the completion of the scan, you will be asked to empty your bladder again.

HOW LONG WILL I BE IN THE STUDY? *(4/5/04)*

You will take Gleevec for 4-10 ***(10/10/03)*** weeks prior to surgery. After surgery, you will take Gleevec for 2 years, and you will be seen in follow-up visits every 3 months for 2 years, then every 6 months for 3 years (for a total of 5 years of follow up).

Your doctor may decide to take you off this study if your doctor believes it is in your medical best interest, if funding for this study is stopped, if the drug supply is insufficient, or your condition worsens. You may also be taken off this study if new information becomes available about how to better treat gastrointestinal stromal cancer.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the Gleevec is stopped or after the PET scans are completed, but in some cases side effects can be serious, long-lasting, or permanent.

Risks and Side Effects Associated with Gleevec: ***(10/28/04)***

Common side effects that can occur during treatment with Gleevec are headache, nausea, vomiting, diarrhea, indigestion, dermatitis, eczema, rash, fever, muscle spasms and cramps, pain in the muscles, joints, limbs, and bones, joint swelling and edema of the limbs, face and periorbital (around eyes).

Other possible side effects of Gleevec are anorexia, dizziness, taste disturbance, numbness of the hands or feet, insomnia, irritated eyes (conjunctivitis), increased tear production, inflammation in space around the lungs (pleurisy), nose bleeds, stomach pain or distension, excessive gas, constipation, dry mouth, itching, reddening of the skin, dry skin, cough, shortness of breath, petechia (purplish red spot on the skin), nasopharyngitis (inflammation of the nasal passages), possibility of drug induced pneumonia, unusual hair loss or thinning, night sweats, fatigue, weakness, increased muscle tension, possibility of bone density loss particularly near a joint space, and increased weight and skin pigmentation (color) changes such as less pigment in a tissue or white patches.

Laboratory abnormalities observed in some patients required temporarily interrupting study drug, or reducing the dose. The laboratory abnormalities included elevated liver or renal (kidney) function tests, low platelet or white blood cell counts or red blood cells and disturbances in electrolyte (chemicals found in the blood, e.g. sodium, potassium, magnesium) balance. Lowering of your white blood cell count could lead to an increased risk of infection and slower healing. Lowering of your platelet count could lead to an increased risk of bleeding. Lowering of your red blood cells can lead to fatigue. If you should develop a fever when your white blood count is low, you may need to be hospitalized to receive treatment. Transfusions may be required to counteract the effects of a low platelet count or low red blood cells. Elevated liver tests can lead to liver damage. Your laboratory values will be monitored closely and the dose of your medication will be adjusted if your blood tests are abnormal. It is expected that these effects may be reversed by decreasing the dose of the drug, or by temporarily stopping the study drug.

(**10/28/04**) In a recent report from the maker of Gleevec, rats given Gleevec were found to have a higher occurrence of tumors, both noncancerous and cancerous, of the kidney, bladder, and genital tract than rats not given Gleevec. Growth of these tumors has not been reported in humans taking Gleevec. The significance of this possible side effect of long-term use of Gleevec is unproven at this time.

Gleevec is often associated with edema and occasionally serious fluid retention. Some patients have reported a rapid gain in body weight. Other patients have developed pleural effusions (fluid around lungs) and/or ascites (swollen abdomen), or pulmonary edema (fluid in the lungs), or pericardial effusions (fluid in the sac that surrounds the heart). A minority have developed signs of congestive heart failure. Therefore, you are asked to closely monitor your body weight twice a week and report to your doctor any rapid increase greater than 2 kg (or 5 pounds). (If this happens, a check-up including physical examination, blood tests and X-rays will be performed as required by your condition.)

One patient taking Gleevec who had no known history of liver problems has died on study due to liver failure. The patient was also taking acetaminophen (Tylenol®). It is

recommended to adhere carefully to the instructions and warnings included in the acetaminophen package and if possible restrict your use. Do not take more than 4,000 mg (equal to 12 regular strength tablets or 8 extra strength tablets) within a 24-hour period, unless otherwise instructed by your treating physician.

In a recent report from the manufacturer of Gleevec, rats given Gleevec were found to have tumors, both noncancerous and cancerous, of the kidney, bladder, and genital tract than rats not given Gleevec. Growth of these tumors has not been reported in humans taking Gleevec

Because some over the counter and prescription medication can reduce the effectiveness or enhance the side effects of Gleevec and/or Gleevec can increase the side effects or lessen the effectiveness of some medication, it is recommended that you review all over-the-counter, health food supplements and prescription medications that you are taking with your physician prior to taking them. These may sometimes contain acetaminophen in combination with other drugs. There are many medications (prescription and non-prescription) and dietary supplements (including what are sometimes called "complementary" or "alternative" medications) which may interact with Gleevec. Your doctor will review all of the medications and supplements you are currently taking before your participation on this study. You should not take any new medications or dietary supplements without discussing it with your doctor first. You should also avoid consuming grapefruit products while participating in this study.

Upper Gastrointestinal bleeding and CNS hemorrhages have been reported in a minority of patients. One patient with a history of heart problems experienced chest pain while on study drug.

Some of the symptoms listed above have led in a death in a few patients. You will be closely monitored for any side effects and should report any changes in the way you feel to your doctor. You will be kept fully informed of any events that occur during the course of the trial, which might affect your safety.

Reproductive Risks

In studies on animals, Gleevec caused abortions and also was possibly damaging to unborn babies when given at high doses. You should not become pregnant or father a baby while on this study. Also, you should not nurse your baby while on this study.

You will be asked to practice an effective method of birth control while you are taking Gleevec. In women of childbearing age, birth control should continue for three months after the last dose of Gleevec to ensure that the drug has cleared from the body. Since interactions with oral birth control pills cannot be ruled out, a "barrier" method of contraception (condom, diaphragm) must be used as well. Male patients must use an effective method of birth control when taking Gleevec and should continue use of birth control for three months after receiving the last dose of the drug to ensure that the drug has cleared from the body. Ask about counseling and more information about preventing pregnancy.

Risks and Side Effects Associated with PET scanning:

Not all of the possible side effects of this imaging may be known, but previous studies have shown the more common side effects to be:

* Mild discomfort with placement of the tube in your forearm
* Slight risk of infection
* Possible bruising or bleeding
* Claustrophobia

This research study involves exposure to radiation from an intravenous injection of F-18 fluoro-2-D-deoxyglucose (FDG) for the PET scans. The maximum amount of radiation exposure (effective dose) from three PET scans to be performed for research purposes is equivalent to a uniform whole-body exposure of approximately 4.5 rem. The exposure from the PET scans is similar to the allowable annual dose for radiation workers (for example, x-ray technicians). The risk from radiation exposure of this magnitude is too small to be measured directly and is considered to be low in comparison with other everyday risks.

The placement of intravenous catheters has the associated risk of making you temporarily uncomfortable and a small bruise may form. A slight bruise may form where the needle has been in a blood vessel. There is a slight risk of infection at the site, but sterile technique reduces this risk nearly completely. You may also experience claustrophobia from the imaging ring apparatus or discomfort from lying on the scanner table for 60-120 minutes. For the dose of FDG used in this study there are no anticipated toxicities (other than the radiation exposure mentioned above).

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with gastrointestinal stromal cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: *(1)* surgery alone without Gleevec; (*2*) Gleevec alone without surgical removal of your cancer; (*3*) radiation therapy; *(4)* chemotherapy; *(5)* no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group *(RTOG*) or the Eastern Cooperative Oncology Group (*ECOG*) ***(10/10/03)***. Your personal information may be disclosed if required by law.

Copies of your PET films will be permanently kept on file at the American College of Radiology Imaging Network (ACRIN). This information will be used for research purposes only. All identifying information will be taken off of the films to maintain confidentiality. Additional studies may be done using the data we collect as part of this research project.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration *(FDA),* the National Cancer Institute *(NCI),* qualified representatives of the drug manufacturer, the Radiation Oncology Group (RTOG) and Eastern Cooperative Oncology Group (ECOG)***[10/10/03]*** and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

The Division of Cancer Treatment and Diagnosis, National Cancer Institute, will provide you with Gleevec free of charge for this study. Every effort has been made to ensure that adequate supplies of Gleevec, free of charge, will be available for all participants. There is a remote possibility that you may be asked to purchase subsequent supplies; your physician will discuss this with you should this situation arise.

Taking part in this study may lead to added costs to you or your insurance company. If you have no insurance or if your insurance company refuses to pay for the necessary scans, please discuss this with your doctor. In addition, please ask about any expected added costs or insurance problems that you might have.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For information about your disease and research-related injury, you may contact:

_____	_____
Name	Telephone Number

For information about this study, you may contact:

_____	_____
Name	Telephone Number

For information about your rights as a research subject, you may contact:
(OHRP) suggests that this person not be the investigator or anyone else directly involved with the research)

_____	_____
Name	Telephone Number

WHERE CAN I GET MORE INFORMATION?

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's Web sites for comprehensive clinical trials information **http://cancertrials.nci.nih.gov** or for accurate cancer information including PDQ **http://cancernet.nci.nih.gov.**

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol *(full study plan)*.

_____ _____

Patient Signature *(or legal Representative)* Date

TISSUE AND BLOOD TESTING *(RTOG S-0132)*

1. My tissue may be kept for use in research to learn about, prevent or treat cancer.

   Yes **No**

2. My tissue may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

   Yes **No**

3. Someone may contact me in the future to ask me to take part in more research.

   Yes **No**

Please sign your name here after your circle your answers.

Your Signature: _____ Date:_____

Signature of Doctor/Nurse:_____ Date:_____

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

ZUBROD PERFORMANCE SCALE

0 Fully active, able to carry on all predisease activities without restriction *(Karnofsky 90-100).*

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work *(Karnofsky 70-80).*

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours *(Karnofsky 50-60).*

3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours *(Karnofsky 30-40).*

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair *(Karnofsky 10-20).*

NEW YORK HEART ASSOCIATION CLASS DEFINITIONS

Cardiac	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability to Work
I	None	None	None	Full Time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks.

APPENDIX III

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supersede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff *(215/574-3214)* within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.

a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol *(FAX #215/928-0153).*

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.

5. For those incidents requiring telephone reporting to the National Cancer Institute *(NCI)*, Investigational Drug Branch *(IDB)* or Food and Drug Administration *(FDA)*, the Principal Investigator should first call RTOG *(as outlined above)* unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group *(in the case of RTOG-coordinated intergroup studies)* must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

i. Any fatal *(grade 5)* or life threatening *(grade 4)* adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff

and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.

ii. Unknown adverse reactions *(≥ grade 2)* resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.

iii. All neurotoxicities *(≥ grade 3)* from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch *(IDB)*
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. *Phase I Studies Utilizing Investigational Agents*

- All deaths during therapy with the agent.	Report **by phone** within 24 hours to IDB and RTOG Headquarters. **A written report to follow within 10 working days.
- All deaths within 30 days of termination of the agent.	As above
- All life threatening *(grade 4)* events which may be due to agent.	As above
- First occurrence of any toxicity *(regardless of grade)*.	Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters. **A written report may be required.

ii. *Phase II, III Studies Utilizing Investigational Agents*

- All fatal *(grade 5)* and life threatening *(grade 4)* known adverse reactions due to investigational agent.	Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours **A written report must be sent to RTOG within 10 working days with a copy to IDB. *(Grade 4 myelosuppression not reported to IDB)*
- All fatal *(grade 5)* and life threatening *(grade 4)* unknown adverse reactions resulting from or suspected to be related to investigational agent.	Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**. **A written report to follow within 10 working days.
- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.	**Report **in writing** to RTOG Headquarters and IDB within 10 working days.

**** See attached *(if applicable to this study)* NCI Adverse Drug Reaction Reporting Form

APPENDIX IV

IMMUNOHISTOCHEMICAL DOCUMENTATION OF KIT (CD 117) AND OTHER SUGGESTED ANTIGENS.

To be performed on sections of paraffin-embedded tissue using the following antibodies:*

1. **smooth muscle actin (SMA), clone 1A4, Sigma, no pre-treatment**
2. **desmin, clone D33, Dako, no pre-treatment**
3. **S-100 protein, polyclonal, Dako, no pre-treatment**
4. **CD34, clone Qbend 10, Dako, no pre-treatment**
5. **KIT (CD 117), A4052 polyclonal, Dako, ** heat-induced epitope retrieval**

*** concentrations to be optimized in individual laboratories**
**** steam or microwave for 10 minutes in citrate buffer or 1 M Tris pH10**

APPENDIX V

NEOADJUVANT/ADJUVANT GIST TISSUE PROCUREMENT

A. PRE-TREATMENT—ALL PATIENTS *(10/10/03)*

Three or more core biopsies with a 18 to 14 gauge core needle performed by CT or ultrasound guidance are required. Core needle should be directed towards the outer portion of the tumor in a non-necrotic area. Preparation of the core specimens should be as follows:

1. One core biopsy specimen for the paraffin block: the specimen should be immediately processed into a paraffin embedded tissue block and appropriately labeled as stated in 2. Ten unheated, unstained slides may be substituted for the paraffin block.
   Note: If this is a primary or recurrent GIST and slides are not available from the initial resection, then several slides must be prepared for IHC *(CD 117)* staining and routine histology review by the participating institution and for later review by the reference pathologist. (Corless)
2. Two or more core biopsy specimens for snap frozen tissue: the core specimens should be placed into tissue cassettes and labeled with patient's last name, and wrapped in foil and submerged into liquid nitrogen. This should be done immediately after specimen procurement to prevent degradation. After 10 minutes of liquid nitrogen bath, foil-wrapped cassettes may be placed into a zip lock bag and stored in a -80ºC mechanical freezer until shipping. The zip lock bag should be marked with a black permanent marker. Information should include RTOG case number, tissue anatomic site, RTOG study number, and date. Once frozen, the tissue specimen should not be allowed to thaw.

B. POST-TREATMENT—CORE BIOPSY IN THOSE PATIENTS WITH PROGRESSIVE DISEASE OR UNRESECTABLE OR NOT A SURGICAL CANDIDATE ***(10/10/03)***

Three or more core biopsies with a 18 to 14 gauge core needle performed by CT or ultrasound guidance are required. Core needle should be directed towards the outer portion of the tumor in a non-necrotic area. Preparation of the core specimens should be as follows:

1. One core biopsy specimen for the paraffin block: the specimen should be immediately processed into a paraffin embedded tissue block and appropriately labeled as stated in 2. Ten unheated, unstained slides may be substituted for the paraffin block.
   Note: If this is a primary or recurrent GIST and slides are not available from the initial resection, then several slides must be prepared for IHC *(CD 117)* staining and routine histology review by the participating institution and for later review by the reference pathologist. (Corless)
2. Two or more core biopsy specimens for snap frozen tissue: the core specimens should be placed into tissue cassettes and labeled with patient's last name, and wrapped in foil and submerged into liquid nitrogen. This should be done immediately after specimen procurement to prevent degradation. After 10 minutes of liquid nitrogen bath, foil-wrapped cassettes may be placed into a zip lock bag and stored in a -80ºC mechanical freezer until shipping. The zip lock bag should be marked with a black permanent marker. Information should include RTOG case number, tissue anatomic site, RTOG study number, and date. Once frozen, the tissue specimen should not be allowed to thaw.

C. OPERATIVE SPECIMEN—SURGICAL PATIENTS ***(10/10/03)***

1. A minimum of 1 gram of non-necrotic tumor tissue for paraffin block is needed. Tissue should be appropriately labeled as below in 2. Ten unheated, unstained slides may be substituted for the paraffin block.
2. A minimum of 3 grams of non-necrotic tumor tissue for snap freezing is needed. The sample should be divided into 1 cm^3 (1 gram) pieces and placed into tissue cassettes, wrapped in foil and immersed into liquid nitrogen. This should be done immediately to prevent specimen degradation. After 10 minutes in liquid nitrogen bath, the foil-wrapped cassettes should be placed into a zip lock bag and stored in a -80ºC mechanical freezer until shipping. Each bag should be labeled with a black permanent marker. Information should include RTOG case

number, tissue anatomic site, RTOG study number, and date. Once frozen, the tissue specimens should not be allowed to thaw.

Note: It is advisable to have the RTOG clinical nurse coordinator present at both the pre-treatment tissue procurement and the operative specimen procurement to ensure compliance with proper procedures.

D. SHIPPING ***(10/28/04)***

The frozen specimens need to be shipped overnight in a suitable sealed container (i.e. styrofoam) packed in dry ice. A dry ice label and biohazard label should be fixed to the side of the box. The paraffin blocks or ten slides should be sent in a suitable container by overnight shipping.

The specimens should include the completed RTOG Pathology Submission Form. In addition to maintaining a copy of these forms, also send a copy to RTOG headquarters.
Please notify RTOG Tissue Bank by phone, fax, or e-mail of intent to ship. Do not ship on Friday, Saturday, or Sunday.

Materials should be sent to:

LDS Hospital
Department of Pathology
E. M. Laboratory
8th Avenue & C Street
Salt Lake City, Utah 84143
(801) 408-5626
Fax (801) 408-5020
holly.goold@ ihc.com

NOTE: ECOG institutions are to submit the required samples, the RTOG Pathology submission form AND the ECOG Pathology Material Submission Form (#638) to the RTOG Tissue Bank at the LDS Hospital as described above. A copy of the ECOG Pathology Material Submission Form (#638) is to be submitted to the ECOG PCO. ECOG submission requirements are described Section 10.3.

Appendix VI: Drugs metabolized by CYP450 isoenzymes 2D6 and 3A4

CYP2D6

Substrates

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

Inhibitors

Amiodarone
Celecoxib
Chloroquine
Chlorpromazine
Cimelidine
Citalopram
Clomipramine
Codeine
Deiavirdine
Desipramine
Dextropropoxyphene
Diltiazem
Doxorubicin
Entacapone (high dose)
Fluoxetine
Fluphenazine
Fluvoxamine
Haloperidol
Methadone
Mibefradil
Moclobemide
Nortluoxeline
Paroxetine
Perphenazine
Propafenone
Quinacrine
Quinidine
Ranitidine
Risperidone (weak)
Ritonavir
Sertindole
Sertraline (weak)
Thioridazine
Vaiprolc acid
Venlafaxine (weak)
Vinblastine

Labetalol Lobeline Lomustine	Vincristine Vinorelbine Yohimbine

CYP3A3/4	
Substrates	
Acetaminophen	Chlorpromazine
Aifentanil	Cimetidine
Alosetron	Cisapride
Alprazolam	Citalopram
Amiodarone	Clarithromycin
Amitriptyline (minor)	Clindamycin
Amlodipine	Clomipramine
Anastrozole	Clonazepam
Androsterone	Clozapine
Antipyrine	Cocaine
Astemizole	Codeine (demethylation)
Atorvastatin	Cortisol
Benzphetamine	Cortisone
Bepridil	Cyclobenzaprine
Bexarotene	Cyclophosphamide
Bromazepam	Cyclosporine
Bromocriptine	Dapsone
Budesonide	Dehydroepiandrostendione
Bupropion (minor)	Delavirdine
Buspirone	Desmethyldiazepam
Busutfan	Dexamethasone
Caffeine	Dextromethorphan (minor, N-demethylation)
Cannabinoids	Diazepam (minor; hydroxylation, N-demethylation)
Carbamazepine	
Cevimeline	Nefazodone
Cerivastatin	Nelfinavir
Digitoxin	Nevirapine
Diltiazem	Nicardipine
Disopyramide	Nifedipine
Docetaxel	Niludipine
Dolasetron	Nimodipine
Donepezil	Nisoldipine
Doxorubicin	Nitrendipine
Doxycycline	Omeprazole (sulfonation)
Dronabinol	Ondansetron
Enalapril	Oral contraceptives
Erylhromycin	Orphenadrine
Estadiol	Paclitaxel
Ethinyl estradiol	Pantoprazole
Ethosuximide	Pimozide
Etoposide	Pioglitazone
Exemestene	Pravastatin
Dofetilide (minor)	Prednisone
Felodipine	Progesterone
Fentanyl	Proguanil
Fexotenadine	Propafenone
Finaxteride	Quercetin
Fluoxetine	Quetiapine
Flutamide	Quinidine
Glyburide	Quinine
Granisetron	Repaglinide
Halofantrine	Retinoic acid
Hydrocortixone	Rifampin
Hydroxyarginine	Risperidone
Lfosfamide	Ritonavir
Lmipramine	Salmeterol
Lndinavir	Saquinavir
Lsradipine	Sertindole
Ltraconazole	Sertraline
Ketoconazole	Sibutramine
Lansoprazole (minor)	Sildenfail citrate
Letrozole	Simvastatin
Levobupivicaine	Sirolimus

CYP3A3/4

Lidocaine
Loratadine
Losartan
Lovastatin
Methadone
Mibefradil
Miconazole
Midazolam
Mifepristone
Mirtazapine (N-demethylation)
Montelukast
Navelbine

Toremifene
Trazodone
Tretinoin
Triazolam
Troglitazone
Troleandomycin
Venlafaxine (N-demethylation)
Verapamil
Vinblastine
Sufentanil
Tacrolimus
Tamoxifen
Temazepam
Teniposide
Terfenadine
Testosterone
Tetrahydrocannabinol
Theophylline
Tiagabine
Tolterodine
Vincristine
Warfarin (R-warfarin)
Yohimbine
Zaleplon (minor pathway)
Zatoestron
Zileuton
Ziprasidone
Zolpidem
Zonisamide

Inducers

Carbamazepine
Dexamethasone
Ethosuximide
Glucocorticoids
Griseofulvin
Nafcillin
Nelfinavir
Nevirapine
Oxcarbazepine
Phenobarbital
Phenylbutazone
Phenytoin
Primidone
Progesterone
Rifabutin
Rifampin
Rofecoxib (mild)
St. John's Wort
Sulfadimidine
Sulfinpyrazone
Troglitazone

Inhibitors

Amiodarone
Anastrozole
Azithromycin
Cannabinoids
Cimetidine
Clarithromycin
Clotrimazole
Cyclosporine
Danazol
Delavirdine
Dexamethasone
Diethyldithiocarbamate
Diltiazem
Dirithromycin
Disulfiram
Entacapone (high dose)
Erythromycin
Ethinyl estradiol
Fluconazole (weak)
Fluoxetine
Fluvoxamine
Gestodene
Grapefruit juice
Indinavir
Isoniazid
Itraconazole
Ketoconazole
Metronidazole
Mibefradil
Miconazole (moderate)
Nefazodone
Nelfinavir
Nevirapine
Norfloxacin
Norfluoxetine
Omeprazole (weak)
Oxiconazole
Paroxetine (weak)
Propoxyphene
Quinidine
Quinine
Quinupristin and dalfopristin
Ranitidine
Ritonavir
Saquinavir
Sertindole
Sertraline
Troglitazone
Troleandomycin
Valprioic acid (weak)
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 VII *(10/28/04)*
PET IMAGING QUALITY CONTROL STANDARDS

NOTE: PET images obtained with dedicated NaI-detector scanners were permitted prior to Amendment 4 *(10/28/04)* of the study; however, to optimize the quality of PET images in the remaining patients to be accrued, scans obtained with NaI scanners are no longer permitted.

FDG-PET imaging will be performed using "state-of-the-art" equipment (either a dedicated BGO, LSO or GSO full ring PET system), which will have a field of view appropriate for body imaging (≥ 10 cm), high resolution (FWHM ≤ 6.0 mm), high sensitivity, and post-injection transmission capability. Before an institution will be permitted to enroll patients in this study, the nuclear medicine investigator at that institution will be required to submit the detailed protocol for PET imaging to be used at the institution for this study along with 3 consecutive studies obtained with use of the technique specified in the institutional protocol, and an image of a standard cylindrical test source of known activity concentration. The acceptability of any deviations from the protocol specified below, as well as the acceptability of image quality and quantitative accuracy, will be evaluated by the PET Quality Assurance Committee. The members of the committee are Barry A. Siegel, M.D., (Chair), Farrokh Dehdashti, M.D., and Richard LaForest, Ph.D. ***(10/10/03)***

Daily and monthly steps will be taken to assure quantitative accuracy of PET imaging studies and reliable imaging results at all performance sites. Daily quality assurance includes a simplified chi-square test to assure consistent performance of the PET scanner. The calculation provides a quantitative means of monitoring drift of the scanner electronics with time. A blank scan is also performed daily for later attenuation correction. Either of these measurements may be viewed routinely as an additional measure of performance. A liquid-filled or standardized sealed-source cylinder phantom is used monthly to validate the quantitative accuracy of the images against a dose calibrator. The dose calibrator is itself calibrated daily against standards for constancy and annually for accuracy using NIST-traceable standards. Each month, fine gain calibration of all detectors in the PET system will be performed, followed by recalculation of the sensitivity normalization factors for the scanner.

Transmission scans (each 10 - 15 min in duration for conventional attenuation correction or 3 min in duration for segmented attenuation correction) will be obtained with a rotating Ge-68/Ga-68 rod source or a ring source for each emission scan (alternatively, attenuation measurement may be performed with a Cs-137 source). An algorithm to correct for activity in the field of view should be used for processing of these post-injection transmission images, if provided by the vendor. If imaging is performed with a PET/CT scanner, attenuation correction may be done using CT. Then the corresponding emission images (each 5 - 15 min in duration) will be performed. Alternatively, the individual emission and transmission scans may be acquired in alternating fashion. The PET images will be reconstructed by standard vendor-provided reconstruction algorithms, using either filtered back projection with a Hanning filter (frequency cutoff 0.6 x Nyquist [Nq] = 0.3 cycle/pixel) or the manufacturer's recommended iterative reconstruction algorithm with an appropriate filter. Segmentation of transmission images or a more conventional fully measured transmission image can be used for attenuation correction. Emission data will be corrected for randoms , dead-time and scatter using vendor-provided algorithms. Multiple-bed position studies must be corrected for radioactive decay. The emission images will be reconstructed both with and without attenuation correction, but all regions of interest must be drawn on attenuation-corrected images.

To enable accurate and meaningful SUVs to be calculated, the following information must be recorded for each scan:

- injection time
- tracer dosage
- tracer dosage assay time
- start-of-scan time
- scan duration
- patient height (to be measured on the day of scan)
- patient weight (to be measured on the day of scan)
- blood glucose level prior to scan

APPENDIX VIII *(10/28/04)*

CREDENTIALING PROCEDURES FOR PET IMAGING

ACRIN's standard operating procedure *(SOP)* for credentialing PET imaging can be found on the ACRIN web site at http://www.acrin.org/institutions.html. For this protocol, both patient images and the uniform phantom are required. The ftp password for this protocol is "dmist".

When transmitting the PET form, please copy Dr. de Vries in addition to Dr. Laforest. The contact information for Dr. de Vries is as follows:

Daniel J. de Vries, Ph.D.
Division of Nuclear Medicine
Dana-Farber Cancer Institute
44 Binney Street
Boston, MA 02115
(617) 632- 4596 *(phone)*
(617) 632-3581 *(FAX)*
DDEVRIES@PARTNERS.ORG

APPENDIX IX *(10/10/03)*

INSTRUCTIONS FOR PET IMAGE SUBMISSION

Digitally generated and scanned PET diagnostic images can be transmitted to ACRIN via FTP. The FTP site is located at ftp://xray.acrin.org**.** For each transmission a new folder for each institution and sub-folders for each corresponding exam must be created. Images are then transferred into those folders. An e-mail verifying the transfer and its contents including the name and number of exams as well as image count for each will be sent to rwelsh@phila.acr.org or alevering@phila.acr.org. Transmission will be verified by examining the folders to make certain that all the images were received.

The header recorded on DICOM formatted image data, which often contains information identifying the patient by name, MUST be scrubbed before the image is transferred. This involves replacing the Patient Name tag with the Institution ID or number, replacing Patient ID tag with the ACRIN case number and the study number should be put on the Other Patient ID tag. This can either be done by software present at the institution or software available from ACRIN. Please contact Rex Welsh *(215-574-3215)* for further information.

Images will be stored in the ACRIN image archive once reviewed by Dr. Abbeele. These images will then be routed to other sites involved using either FTP or CDROM where appropriate for purposes of secondary interpretation.

APPENDIX X *(10/28/04)*

INSTRUCTIONS FOR CT AND MRI IMAGE COLLECTION

Image Submission:

All study participants will be imaged using CT or MRI at various timepoints. **For the Pre-Treatment CT or MRI imaging timepoint studies may be accepted on film if digital data is not accessible.** For all other **follow-up timepoints** it is highly recommended by ACRIN that each participating institution submit the image studies in the digital format. (DICOM 3.0). If submitting the scheduled follow-up CT or MRI imaging studies in a digital format is questionable, contact the ACRIN Image Management Center (IMC), either Anthony Levering (215-574-3244; alevering@phila.acr.org) or Rex Welsh (215-574-3214; rwelsh@phila.acr.org), for assistance.

Digitally generated CT or MRI images will be transmitted to the ACRIN Image Management Center *(IMC)* via FTP directly to the image archive. The FTP site is located at **ftp://xray.acrin.org** or **ftp://206.137.103.34.** **(UserID is acr) and (Password is dmist)**

For each transmission a new folder for each institution and sub-folders for each corresponding exam must be created. Images are then transferred into those folders. An email verifying the transfer and its contents including the name and number of exams as well as image count for each will be sent to both **(rwelsh@phila.acr.org), (alevering@phila.acr.org)**

Transmission will be verified by examining the folders to make certain that all the images were received. It is highly recommended that if you encounter any problems, or need assistance getting started with the steps required to transmit the required digital CT or MRI studies to the ACRIN image archive you should contact the Image Management Center *(IMC)* here at ACRIN. *Rex Welsh 215-574-3215 and Anthony Levering 215-574-3244*

The header recorded on DICOM formatted image data, which often contains information identifying the patient by name, will be scrubbed before the image is transferred. This involves replacing the Patient Name tag with the ACRIN Case#^Institution ID, the Patient ID tag with the ACRIN case number again, and the study number should be put on the Other Patient ID tag. If this cannot be done by software present at the institution you will need to contact the ACRIN IMC for further assistance. For this assistance please contact Timothy Welsh at 215-717-2754.

In the event that neither DICOM capability nor transfer of scrubbed image headers is not available, please contact Timothy Welsh at 215-717-2754 at the ACRIN IMC for further assistance.

In the event digital image files are not accessible for the Pre-Treatment CT or MRI exam and it has been specified that plain film is acceptable, original film images ONLY should be sent via common courier (Ex. FedEx, UPS) for digitization and subsequent entry to the image archive. Upon request, film data sent will be digitized here at ACRIN and returned to the participating sites within 72 business hours of receipt.

Mailed plain-film images or images on CD should be addressed and sent as follows

ACRIN CT/MRI FILMS: Study 6665
American College of Radiology
Diagnostic Studies Film Library
1818 Market Street, Suite 1600
Philadelphia, PA. 1910 3
ATTN: Anita Murray

APPENDIX XI ***(10/28/04)***

RTOG S-0132/ACRIN 6665 GIST Gleevec Protocol
Institution Participation Guidelines

Introduction:

This document is intended to be a guideline for interested sites to explain the various steps and qualifications necessary to enable a site to participate in the RTOG S-0132/ACRIN 6665 protocol. Because this is a collaborative study involving the Radiation Therapy Oncology Group (RTOG), the Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN), there are a number of unique logistical requirements that must be met before a patient can be registered to this study.

RTOG is responsible for the parent treatment protocol and ECOG is participating in the trial through the intergroup mechanism. ACRIN is collaborating for the PET imaging aspects of the trial. All participating institutions must be RTOG institutions or ECOG institutions participating via the intergroup process. In addition, participating institutions must submit an ACRIN General Qualifying Application (GQA) Cover Sheet (if the institution is not an ACRIN approved institution). Also, the PET facility to be used for the study (which may be within the institution or at another site) must become "credentialed" by submitting PET images for a quality review by the ACRIN PET Quality Assurance Committee, chaired by Dr. Barry Siegel (see below). Thus, for a site to become fully approved, the timeline will involve submitting an ACRIN GQA Cover Sheet (if needed), having it reviewed, and obtaining PET approval.

The reimbursement for the treatment part of the study will be $2,000 per case. There is an additional $6,513 per case that is intended to cover the imaging expenses associated with the ACRIN component of the study.

Because PET is a relatively new imaging modality, it is recognized that sites will have varying availability of protocol-approved scanners. In addition, it is recognized that some sites may be planning to perform the CT (or MRI) scans required by the protocol, but will have to make arrangements at another facility to obtain the PET studies. This "outside" facility will need to follow the above listed procedures for becoming PET credentialed. Since PET scanners have a fairly wide spectrum of designs and, therefore, image quality, it is imperative to the success of this study that a standard be applied. The requirements for PET site qualification are described fully in Appendix VIII of the protocol.

Please review the information below to determine the steps that will be necessary for your site to participate in this study.

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1. If you are an RTOG or an ECOG institution and also a current ACRIN-approved institution:

- Please review Appendix VIII of the protocol and start the process for PET credentialing. If you have a PET scanner at your institution, please submit the information as noted in the appendix. If your institution does not have a PET scanner and you will be using a scanner at a separate imaging facility, please make note of this on the PET application. The contact named on the PET application will receive the formal approval by e-mail.
- ACRIN is notified when your PET images are approved by the PET Quality Assurance Committee. ACRIN will then inform the ACRIN Institutional Participants Committee (IPC) of this PET credentialing and obtain final approval for your site to participate in the study. (timeline: approximately 2-3 weeks)
- Once final approval has been obtained by the ACRIN IPC, your institution will be notified.
- Reimbursement from ACRIN for the imaging studies will be distributed by ACRIN on a quarterly basis. Please complete a Case Reimbursement Schedule, found on the RTOG and ACRIN web sites for this study in order to specify where the payment should be sent.
- At the same time that you submit your PET images for review, please submit the protocol to your institutional IRB for approval.

This concurrent process of PET and IRB submissions will allow for all requirements to be met once IRB

approval is obtained.

---

2. If you are an RTOG or ECOG institution and <u>your institution IS NOT a current ACRIN-approved institution</u>:

- Please complete the ACRIN GQA Cover Sheet (attached) and submit to the ACRIN Administration address noted below. If your institution does not have a PET scanner and you will be using a scanner from a separate imaging facility, please make note of this on the ACRIN GQA Cover Sheet and the PET application.
- Please review Appendix VIII of the protocol and start the process for PET credentialing. If you have a PET scanner at your institution, please submit the information as noted in the appendix. If your institution does not have a PET scanner and you will be using a scanner at a separate imaging facility, please make note of this on the PET application. The contact named on the PET application will receive the formal approval by e-mail.
- ACRIN will then send the ACRIN Institutional Participants Committee (IPC) the completed ACRIN GQA Cover Sheet and the documentation of this PET credentialing. Through the IPC, ACRIN will then obtain final approval for your site to participate in the study. (timeline: approximately 4 weeks)
- When final approval has been obtained by the ACRIN IPC, your institution will be assigned a four-digit number to identify your site to ACRIN. Your institution will also be notified of the approval to participate in the study.
- Reimbursement from ACRIN for the imaging studies will be distributed by ACRIN on a quarterly basis. Please complete a Case Reimbursement Schedule, found on the RTOG and ACRIN web sites for this study in order to specify where the payment should be sent.
- At the same time that you submit your PET images and one page application for review, please submit the protocol to your institutional IRB for approval.

This concurrent process of application, PET and IRB submissions will allow for all requirements to be met once IRB approval is obtained.

<u>Additional Information:</u>

To find out if your institution is an approved ACRIN site or if you have questions about the ACRIN reimbursement of $6,513.00, please contact Donna Hartfeil at 215-717-2765 or dhartfeil@phila.acr.org

If you have questions regarding the PET Credentialing, please contact Barry Siegel at 314-362-2809 or siegelb@mir.wustl.edu or Richard LaForest at *(314)* 362-8423 / *(314)* 362-8405, FAX *(314)* 362-5428, or laforestr@mir.wustl.edu

If you have questions regarding the RTOG reimbursement of $2000.00, please contact Tom Wudarski at 215-574-3205 or twudarski@phila.acr.org

If you have questions regarding the protocol and forms not related to PET credentialing, please contact the main RTOG number and ask for a Data Manager that works on the S-0132 protocol (215-574-3150).

If you have questions regarding the protocol and forms related to PET and/or imaging, please contact the main ACRIN number and ask for a Data Manager that works on the ACRIN 6665 protocol (215-574-3150).

RTOG Address:
American College of Radiology
RTOG – S-0132
1818 Market Street, Suite 1600
Philadelphia, PA 19103

ACRIN Address:
American College of Radiology
ACRIN 6665
1818 Market Street, Suite 1600
Philadelphia, PA 19103

American College of Radiology Imaging Network
General Qualifying Application Cover Sheet (Intergroup Trials)

PARTICIPANT INSTITUTION

Name of Institution

Street Address

City, State, Zip code

This application is for (check as many as apply):

- ☐ One hospital
- ☐ One hospital with free-standing, non-hospital facilities (clinics, imaging centers, etc.)
- ☐ A multi-hospital system
- ☐ A multi-hospital system with free-standing, non-hospital facilities (clinics, imaging centers, etc.)
- ☐ One free-standing, non-hospital facility (clinic, imaging center, etc.)
- ☐ More than one free-standing, non-hospital facilities (clinics, imaging centers, etc.)
- ☐ Other (specify): _____

Please indicate below the type of interest your institution has in ACRIN Research:

We are interested in full participation as a Core Institution: ☐

We are interested in becoming a Core Institution. At this time, we would like to join the Protocols specified: ☐

_____
_____
_____

We have interest in a specific protocol as a Participating Institution: ☐
Please evaluate this application relative to the following protocol =>

_____

We are participating in a trial through the Intergroup Process: ☐
Name of Intergroup through which you are participating (RTOG, ECOG): _____
ACRIN Study Number: _____

If more than one site is covered by this application, please list other sites:

STAFF

ACRIN Site Investigator (Include CV) _____

(For intergroup trials, please indicate the radiologist responsible for the imaging component of the trial)

Telephone Number _____

Fax Number _____

E-mail Address _____

If Intergroup:
Name of Investigator responsible for treatment component of the trial:

_____

Telephone Number _____

Fax Number _____

E-mail Address _____

I.S. INFRASTRUCTURE

Do you have the I.S. capability to: (Please check)

1. Register and enter data forms over the Internet Yes ☐ No ☐
2. Browser: Internet Explorer 4.0 or Netscape 4.0 higher Yes ☐ No ☐
3. View PDF documents Yes ☐ No ☐

Signature of ACRIN Site Investigator _____ Date_____

Signature of Radiology Department Chair _____ Date_____

Or

If intergroup, signature of Investigator responsible for treatment component of the trial: -
_____ Date: _____

RTOG S-0132/ACRIN 6665 GIST Gleevec Protocol
Institution Participation Guidelines

Please forward entire application to:

American College of Radiology
American College of Radiology Imaging Network
Attn: Diagnostic Administration
1818 Market Street, Suite 1600
Philadelphia, PA 19103
Phone: 215-574-3231
Fax: 215-717-0936
E-mail: capgar@phila.acr.org

For ACRIN HQ Use:

Review #1_____ ☐Approved ☐Additional Info Requested

Review #2_____ ☐Approved ☐Not approved

☐ Core

☐ Participant

☐ Intergroup: Group Name:_____

Comments_____

_____

_____