Summary of Changes
Update: June 12, 2008
(Broadcast 6/12/08)

RTOG 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)"

Study Chair: Burton Eisenberg, M.D., (603) 653-3614; Burton.L.Eisenberg@Dartmouth.edu

RTOG 0132 has been updated as follows:

Title page: The contact information for Dr. Blanke was updated.

Section 4.3: In the 2nd paragraph, "RTOG Tissue Bank" was updated to the current name, "RTOG Biospecimen Resource".

Section 8.1: At the end of the section, "RTOG Tissue Bank" was updated to the current name, "RTOG Biospecimen Resource".

Section 10.1: "RTOG Tissue Bank" was updated to the current name, "RTOG Biospecimen Resource", the location of the Biospecimen Resource was added, and the specimen shipping addresses were updated. Corresponding changes also were made in Appendix IV, item "D", "Shipping".

Section 10.1.1 was updated to current RTOG standard.

Section 10.3: "RTOG Tissue Bank" was updated to the current name, "RTOG Biospecimen Resource".

Note: This is an editorial/administrative change to the protocol. NCI now requires that these changes be documented on the protocol title page with the date of the update noted as "Update Date," not as a revision.
RTOG 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]"

Study Chair: Burton Eisenberg, M.D., (603) 653-3614; FAX# (603) 653-9003; Burton.L.Eisenberg@Dartmouth.edu

The Pharmaceutical Management Branch (PMB) of the NCI has notified RTOG that STI-571 (imatinib) will be provided in tablets rather than capsules. The PMB requires that RTOG 0132 be amended accordingly.

The following changes have been made:

- Section 7.1: In the first sentence of the second paragraph, the word, "capsules" was replaced with "tablets".
- Section 7.2.4.1, "How Supplied", was amended with text provided by PMB.
- Section 7.2.4.2: The heading of the section was amended from "Storage" to "Storage/Stability", and the section was amended with text provided by PMB.
SUMMARY OF CHANGES
Amendment 8, Version Date: July 16, 2007

RTOG 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]"

Study Chair: Burton Eisenberg, M.D., (603) 653-3614; FAX# (603) 653-9003; Burton.L.Eisenberg@Dartmouth.edu

RTOG 0132 has been amended as follows:

The "S" prior to the study number (designating Sarcoma) was deleted to update the study number to current RTOG standard. This change was made on the title page, the Schema page, all pages of the Eligibility Checklist, the first page of Appendix I, the sample consent, under “Tissue And Blood Testing” in Appendix I, and throughout Appendix X.

Based on the survival of this population of patients, it is important to collect data concerning long-term adverse events beyond the originally stipulated 5 years. Therefore, the timeframe of long-term follow up of patients was amended from 5 years to follow up for the patient's lifetime. This change was made in the following sections: Section 11.1 (final column on the right of the table and footnote "h"); Section 12.1 (timeframe for the Follow-up Form [F1]); and Appendix I, under "What is involved in the study?" (paragraphs 6, 7, and 9) and in the first paragraph under "How long will I be in the study?".

Other Changes

Section 7.1: In the first paragraph, the dose of Gleevec, 600 mg/day, was added for clarity and for consistency with the Schema.

Section 10.1 and Appendix IV: The contact information for LDS Hospital was updated.
SUMMARY OF CHANGES
Amendment 7, Version Date: August 18, 2006

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]"

Study Chair: Burton Eisenberg, M.D., (603) 653-3614; FAX# (603) 653-9003; Burton.L.Eisenberg@Dartmouth.edu

RTOG S-0132 has been amended as mandated in NCI's August 1, 2006 Action Letter as follows:

Section 7.2.3: A "note" was added as the second paragraph to inform investigators that congestive heart failure is a rare but serious adverse event that they should consider in their evaluation of patients who experience edema while on Gleevec. In addition, NCI's current Comprehensive Adverse Event and Potential Risks list (CAEPR), v. 2.0, was added, and the prior list was deleted.

Appendix I: Under "Risks and Side Effects Associated with Gleevec", the following changes were made as required by NCI and in order to be consistent with the CAEPR list, v. 2.0, in Section 7.2.3:

- In the second paragraph, the phrase, "inflammation of blood vessels", was added after "blood clots".
- At the end of the second paragraph, the following sentence was added: "Decrease in the heart's ability to pump blood is a rare but serious side effect of Gleevec".
- In the third paragraph, the phrase, "liver failure", was added after "liver damage". In the fifth paragraph, the sentence beginning, "A minority have developed signs of congestive heart failure…" was amended to read, "Congestive heart failure is a rare but serious side effect that may develop while patients take Gleevec. Congestive heart failure means that your heart is unable to pump blood to meet your body's needs. Congestive heart failure may result in shortness of breath, tiredness, inability to exercise, fluid build up in the arms and legs, fluid in the lungs, and/or weight gain."

An amended protocol is available on the RTOG Web site, http://www.rtog.org
**SUMMARY OF CHANGES**  
Amendment 6, Version Date: September 30, 2005

**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]”

**Study Chair:** Burton Eisenberg, M.D., (603) 653-3614; FAX# (603) 653-9003;  
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RTOG S-0132 has been amended to change the eligibility requirement from 3 core biopsies to at least one viable tumor core biopsy. Experience at this time indicates that one core of viable tumor specimen has sufficient yield of RNA for purpose of amplification to perform the necessary gene array studies per protocol. Therefore, the protocol has been amended as follows:

**Schema page:** The text of the schema was changed to “Obtain pre-treatment core tissue biopsy specimen(s)”; the cross reference to Appendix V was corrected to Appendix IV; the schema eligibility was changed to “Must agree to have at least one viable core biopsy tumor specimen obtained within 8 weeks prior to registration (see Sections 3.1 and 12.1)”.

**Eligibility Checklist, page 1:** Question # 17 was revised to “Was at least one viable core biopsy tumor specimen obtained within 8 weeks prior to registration?”

**Section 3.1.1:** The third sentence was changed to read: “All patients must have at least one viable core biopsy tumor specimen obtained within 8 weeks prior to registration. (See Appendix IV).” The cross reference to Appendix V was corrected to Appendix IV in the third sentence.

**Section 4.3:** The third sentence was changed to “Obtain core biopsy(ies) (for the biological objectives in Section 2.0) within 8 weeks prior to registration.” The fifth sentence was changed to: “Also snap frozen tumor tissue taken from core biopsy(ies).” In the first sentence, the reference to Appendix IV was corrected to Appendix III, and in the fifth sentence, the reference to Appendix V was corrected to Appendix IV.

**Section 5.2.1:** The zip code for the CTSU was corrected to 19103.

**Section 8.1:**

- The first sentence was rewritten as: “Initially, in all patients an attempt will be made to obtain at least one viable core biopsy tumor specimen as previously described (see Sections 3.1.1, 4.2, 4.3 Appendix IV).” Reference to Appendix V was corrected to Appendix IV here and in Section 10.2.6.1 also.
- In the second, fourth, and fifth sentences, (s) was added to specimen—
  specimen(s).
- In the fifth sentence, “three or more” was deleted.
- In the sixth sentence, “At least two of” was deleted and the first part of the
  sentence reworded as: “The core specimen(s) should provide enough tissue to be
  immediately snap frozen in liquid nitrogen and provide for either tissue fixed....”

**Section 8.2:** The fourth sentence was rewritten as: “However, a core biopsy is
recommended with the objective of obtaining specimen(s) (for paraffin and frozen tissue)
(*See Appendix IV*).” Reference to Appendix V in this sentence and the third paragraph
was corrected to Appendix IV.

**Section 10.1:** The last sentence was revised as: “If the patient progresses at 4 or 8 to 10
weeks and is not a candidate for surgical resection, a core biopsy(ies) is strongly
recommended (*see Appendix IV*) before the patient is removed from protocol treatment.

**Section 10.3:** In the table, Pre-treatment for paraffin embedded and snap frozen
specimens has been combined and “At least” was added to “1 core biopsy” and “2 core
needle biopsies” was deleted. Footnote #1 was revised accordingly as “Core biopsy(ies)
to be collected with an 18 to 14 gauge core needle via CT or ultrasound guidance.”

**Section 11.1:** In footnote e, the reference to Appendix IV was changed to Appendix III
and in footnote f the reference to Appendix V was changed to Appendix IV.

**Section 12.1:** Under Pathology Slides/Blocks, “(from three core biopsies)” was changed
to “(from core biopsy(ies)).” Under Surgical materials, the reference to Appendix V was
corrected to Appendix IV.

**Consent:** Under “What Is Involved In The Study” prior to treatment, fourth bullet, “At
least 3 biopsies” was changed to “At least one biopsy.”

**Appendix IV:** The text of this appendix was changed to reflect the one core biopsy now
required; the instruction regarding labeling with the patient’s last name was deleted and
replaced by labeling with “RTOG protocol number and patient case number.”

**Appendices VI, VII, VIII:** “RTOG S-032/ACRIN 6665 Institution Participation
Guidelines” was added to the titles of these appendices. It was taken out of the header for
all appendices because it did not apply to all.
SUMMARY OF CHANGES
Update Date: July 1, 2005

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)”

Study Chair: Burton Eisenberg, M.D., (603) 653-3614; FAX# (603) 653-9003; Burton.L.Eisenberg@Dartmouth.edu

RTOG S- 0132 has been updated as follows:

The section numbering in Section 7.4 has been corrected as Section 7.4.4 was incorrectly numbered.

NOTE: This is an editorial/administrative change to the protocol. NCI now requires that these changes be documented on the protocol title page with the date of the update noted as “Update Date,” not as a revision.

An updated protocol is available (no password required) on the RTOG website: http://www.rtog.org/
SUMMARY OF CHANGES  
Amendment 5, Version Date: May 26, 2005

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]”

Study Chair: Burton Eisenberg, M.D., (603) 653-3614; FAX# (603) 653-9003; Burton.L.Eisenberg@Dartmouth.edu

RTOG S-0132 has been amended as follows:

Schema page: When the patient treatment path was clarified in Amendment 2, the required PET scan prior to surgery (detailed in Sections 11.1 and 11.6.3) was inadvertently omitted from the Schema page.

The Schema has been corrected as follows: For patients with “Stable or Responding Disease”, after “4-6 additional weeks of Gleevec”, the “Restaging” includes “PET and CT or MRI at 8-10 weeks”.

Section 5.0 was amended to provide instructions for web registration. The last paragraph on page three of the Eligibility Checklist was amended to be consistent with changes in Section 5.0.

Section 7.2.3: As mandated by NCI, the “Comprehensive Adverse Events and Potential Risks List (CAEPR)” for STI-571 (Gleevec) was added, and the prior list of adverse events was deleted.

Section 7.4, “Adverse Events”, was amended to the current RTOG standard.

Section 7.5, “AdEERS Expedited Reporting Requirements”: This section was amended as mandated by NCI, and the prior adverse event reporting section and Appendix III were deleted. The subsequent appendices were appropriately renumbered on the Index page and on each appendix.

The following changes were made in Appendix I:

- The “Risks and Side Effects Associated with Gleevec” were amended to be consistent with the CAEPR list in Section 7.2.3;
- The fourth paragraph of “Risks and Side Effects Associated with Gleevec”, added on 10/28/04, made the seventh paragraph redundant; therefore, the seventh paragraph of this section was deleted;
- Under “What Are My Rights As a Participant”, the first sentence of the third paragraph was amended to correctly indicate the data monitoring of this study.
An amended protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
SUMMARY OF CHANGES
Amendment 4, Version Date: October 28, 2004

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]”

Study Chair: Burton Eisenberg, M.D., (603) 653-3614; FAX# (603) 653-9003; Burton.L.Eisenberg@Dartmouth.edu

RTOG S-0132 has been amended as follows:

Based on information provided by Novartis Pharmaceuticals Corporation, NCI requires that the risks associated with Gleevec in the consent be amended “to inform patients in lay terms of the potential for carcinogenicity in organs of the urogenital region.” Appendix I has been amended accordingly.

Other Changes

Requirements for PET Scanning were updated in Section 11.6 and Appendix VII.

The address for RTOG Headquarters was updated in Sections 7.4.5.1, 12.0 and Appendix XI. The address for ACRIN also was updated in Appendices X and XI.

The email address for LDS Hospital was updated in Section 10.1 and Appendix V.

Appendix VIII: Dr. Badawi has been replaced by Dr. de Vries, and the appropriate contact information was provided. The ACRIN web address was converted to a hyperlink to provide sites with easier access.

An amended protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
SUMMARY OF CHANGES
Revision 3, Version Date: May 10, 2004

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]”

Study Chair: Burton Eisenberg, M.D., (603) 653-3614; FAX# (603) 653-9003; Burton.L.Eisenberg@Dartmouth.edu

RTOG S-0132 has been revised as follows:

NCI updated the adverse events for Gleevec and requires that the protocol and consent be revised accordingly. In Section 7.2.3, “pneumonia” was revised to “pneumonitis/pulmonary infiltrates”, and “Osteonecrosis (avascular necrosis)” was added. Corresponding changes were made to the risks associated with Gleevec in Appendix I, the sample consent.

A revised protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
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]”

Study Chair: Burton Eisenberg, M.D., (603) 653-3614; FAX# (603) 653-9003; Burton.L.Eisenberg@Dartmouth.edu

IRB Review Requirements:
( ) Full board review required
(X) Expedited review allowed; however, site IRB requirements take precedence.
( ) No review required

RTOG S-0132 has been revised as follows:

The patient treatment path was clarified. The following sections were revised for this change: The Schema, Sections 7.1, 8.2, 11.1, footnote “n”, and Appendix I, the section, “What Is Involved In The Study?”.

Eligibility Checklist: The ACRIN study number was added to the top of each page for clarity. In addition, the following changes were made. On page 1:

- Question 9 was added to correspond to Section 3.1.1, and subsequent questions were appropriately renumbered;
- The unit of measurement was added to Questions 11, 12, and 13;
- Question 17 was revised to correspond to Section 4.3;
- The answer for Question 18 was revised from “Y/N” to “Y”, as the pre-treatment PET scan must be done at an ACRIN certified institution;
- Question 19 was revised from “medical/surgical oncologist” to “medical oncologist and surgical oncologist” for clarity.

On page 2, the answers for Questions 2 and 3 were revised from “Y/N” to “Y”.

Section 3.1.1: In the third sentence, the phrase, “All patients must agree to have three core…” was revised to “All patients must have three core…”.

Section 3.2.8, excluding patients with “any known or suspected hypersensitivity to one of the components of the study drug”, was added. This criterion was added to the eligibility list on the Schema page and was added as Question 27 on page 2 of the Eligibility Checklist.

Section 5.1: The last sentence, concerning the ACRIN portion of the registration, was added.
Appendix I: In the third paragraph under “Why Is This Study Being Done?”, the first sentence was revised from “to see if you have” to “to confirm that you have gastrointestinal cancer”; in the first paragraph under “How Long Will I Be In The Study?”, “every 6 months until 5 years after treatment started” was revised for clarity. Appendix VIII was revised to refer sites to ACRIN’s web site for credentialing PET imaging.

Appendix XI: The ACRIN reimbursement amount was updated under “Introduction” and “Additional Information”. The ACRIN reimbursement procedure was updated under numbers 1 and 2. Dr. LaForest’s Fax number was added under “Additional Information”.

At ECOG’s request, the following sections of the ECOG logistics were revised: Sections 5.2.5 and 12.2.

A revised protocol is available (no password required) on the RTOG Web site, http://www.rtog.org
SUMMARY OF CHANGES
Update Date: December 18, 2003

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)”

Study Chair: Burton Eisenberg, M.D., (603) 653-3614; FAX# (603) 653-9003; Burton.L.Eisenberg@Dartmouth.edu

RTOG S-0132 has been updated as follows:

Section 12.0: The Due date for form FO was changed to “At week 4 and at end of pre-surgical Gleevec administration”; for form TF due date was changed to “At week 4, at end of pre-surgical Gleevec administration, and then every e months for 2 years”; and for forms S1 and S2 the due date was changed to “2 weeks after surgery” to be consistent with the protocol text.

Footers at the bottom of pages 44-65 were corrected.

NOTE: This is an editorial/administrative change to the protocol. NCI now requires that these changes be documented on the protocol title page with the date of the update noted as “Update Date,” not as a revision.

An updated protocol is available (no password required) on the RTOG website: http://www.rtog.org/
SUMMARY OF CHANGES
Revision 1, Version Date: October 10, 2003

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)”

Study Chair: Burton Eisenberg, M.D., (603) 653-3614; FAX# (603) 653-9003; Burton.L.Eisenberg@Dartmouth.edu

IRB Review Requirements:
( X ) Full board review required
( ) Expedited review allowed
( ) No review required

RTOG S-0132 has been revised to amend eligibility, PET site qualification, CT and PET data transmission, ACRIN qualification, and ECOG participation as follows:

Title page: Changes: New contact information for study chair Burton Eisenberg, M.D.: Dartmouth-Hitchcock Medical Center, Department of General Surgery, One Medical Center Drive, Lebanon, NH 03756, (603) 653-3614, FAX# (603) 653-9003, Burton.L.Eisenberg@Dartmouth.edu; new contact information for Samuel Singer, M.D. (212) 639-2940, FAX# (646) 422-2300, singers@MSKCC.ORG; Margaret vonMehren, M.D. is listed as the study coordinator for ECOG. The study number, R0132, for ECOG has been added since ECOG is now participating in this study.

Version date: October 10, 2003 has been added. “Includes Revision 1” has been added.

Index: Appendices IX, X, and XI were added here because they were added to the protocol.

Schema page: The following changes were made:

Changed “baseline PET and CT/MRI scan” to “baseline PET and CT or MRI scan” throughout schema; “within 4 weeks” was changed to “within eight (8) weeks before registration prior to Gleevec”; “Obtain four core tissue biopsy specimens” was changed to “Obtain 3 pre-treatment core tissue biopsy specimens for comprehensive biologic assessment” and “(within 8 weeks prior to registration. See Appendix V)” was added. “Drug therapy to start within 4 weeks following registration” was deleted and “Gleevec to start within 2 weeks following registration” was added; “following registration” was deleted from “Take Gleevec 600 mg/day for four weeks.” “If” was added to Progressive Disease and “then” added to PET Scan and “followed by” added before Surgical Resection; “see Appendix V” was added after “candidate”. “Stop Gleevec” was deleted twice. “Four weeks of additional Gleevec” was changed to “Four to 6 weeks of additional Gleevec.” “Progressive Disease” was deleted and the text following was reworded as “Surgical Resection (attempt to debulk all gross tumor with tissue collection for
comprehensive biologic assessment (See Appendix V) or Core Biopsy (if patient is un-resectable or not a surgical candidate); a sentence was added at the end of the schema “Patients in the unresectable or not a surgical candidate category may stay on study Gleevec (600 mg/day) for 24 months at discretion of their physician.” because in some cases there may be one measurable tumor that is progressing and another that is stable or the physician may want to increase the dose of Gleevec in response to progressive disease and keep the patient on drug. The following are the rationales for these changes:

The assumption is that GIST is a low incidence disease and patients at times come from referral sources that may delay their evaluation. An additional 4 weeks for obtaining scans prior to registration assures better compliance to protocol design.

There were some initial problems obtaining the 4 required number of core biopsies as stated in the eligibility criteria prior to Gleevec. Because some patients had less than 4 good cores they were deemed ineligible by present eligibility criteria. We can perform the required correlative studies with 2 frozen and 1 paraffin core and therefore have changed the number of required core biopsies to enhance patient eligibility.

Once the patient is registered, the scans and the biopsies are already completed, it should not be a problem to initiate drug within 2 weeks.

It is difficult to exactly coordinate an 8-week surgical date from the initiation of drug. The additional 2 weeks provides some flexibility in this scheduling and assures that the patients will remain on Gleevec until day prior to surgery.

**Eligibility** (Schema page) the following changes have been made:

The first bullet was changed to read “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.” The corresponding changes were also made in Section 3.1.1. These changes were made because the goal of the study was to evaluate the role of surgical resection either to removal of all gross disease or to debulk as much as possible in patients with extensive or multi-focal disease. The addition of potentially resectable broadens the scope of eligibility and meets the goals of the study.

Added third bullet “Must agree to have three core tissue biopsies performed within 8 weeks prior to registration” for consistency with Section 3.1.1 and Section 12.1.

Under the 4th bullet, “institutional” was added to ULN for clarity. This change was also made on the Eligibility Checklist questions 13, 14,15.

Deleted bullet beginning with “Fasting Glucose” because patients with fasting glucose >200 can have PET scan provided they have controlled diabetes. Therefore the original Section 3.1.8 was deleted accordingly necessitating renumbering Section 3.1.9 to become new 3.1.8.
The 6th bullet, concerning extra abdominal metastatic disease was eliminated. The corresponding change is reflected on Eligibility Checklist in deletion of questions 10 and 11, and in changes to Section 3.1.1 and deletion of Section 3.2.1. These changes were made because there is no reason not to consider patients with limited metastatic disease outside of the abdomen/pelvis, since some of these patients can be resected.

The bullet beginning with “No prior malignancy” was changed to read, “Any prior malignancy is allowed as long as the patient is disease-free from that malignancy”. Corresponding changes were made in Eligibility Checklist adding question 22 and eliminating question 24 and with the addition of Section 3.1.10. These changes were made because this is primarily a study of biological endpoints reflecting the molecular changes of Gleevec on GIST and the presence of a prior malignancy as long as the patient is disease-free from that malignancy should not be an excluding criteria.

Added “Patient must have a medical and surgical oncologist” and “Patient must be able to lie still in PET scanner for 60-120 minutes” to Schema Eligibility for consistency with Section 3.1.3 and Section 3.1.8, respectively.

Added Schema Eligibility of “Age≥18”. The corresponding change is also reflected in Eligibility Checklist, question 24, in Section 3.1.11 where it was added and original Section 3.2.8 where it was deleted. This was done to clarify this eligibility requirement consistently.

Added to Schema Eligibility and Section 3.1.12: “Gleevec to start within 2 weeks following registration.” for further clarification.

Added Schema Eligibility “Institution able to meet PET imaging guidelines” for consistency with Section 3.1.7.

Eligibility Checklist: The following changes were made:

- Question 4, “per day” was added for further clarification.
- Question 5, page 1 was changed to include Gleevec.
- Questions 12 through 21 were renumbered as 10 through 25 because questions 10 and 11 were eliminated, question 22 was added, question 24 was deleted, new questions 24 and 25 added.
- Question 16 was changed from “four” to “three” core biopsies for consistency.
- Question 19, page 1 was changed to “Is the tumor considered to be potentially operable?” for consistency.
- Deleted question 24, page 2, and renumbered question 25 to 24.
- New question 25 added “Does the patient have severe and/or uncontrolled concurrent medical disease?” for consistency with Section 3.2.6.

Section 2.5: “at week 8” was changed to “at week 8 to 10” for consistency. Also, in the fourth line “(See Appendix VIII)” was added to cross reference instructions.
**Section 3.1.1:** In the first sentence, “or intra-abdominal/pelvic” was deleted for consistency. The second sentence was changed to read “visceral, intra-abdominal or pelvic.” Four biopsies was changed to three biopsies, four weeks was changed to 8 weeks and “of” was changed to “prior to” registration and “prior to treatment with study drug” was deleted for consistency; and “See Appendix V “ was added in the third sentence to cross reference tissue procurement instructions.

**Section 3.1.7:** Added after first sentence “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.” This was added for clarification easy reference.

**Section 3.1.9:** This was renumbered—it had been 3.1.10. The text in parentheses at the end of the section was removed for consistency.

**Section 3.1.11:** Added age eligibility of >18 years. **Section 3.2.8** “Age<18” was deleted for clarity and accuracy.

**Section 3.1.13:** All lab tests, and imaging studies done within timeframes specified within Section 4.0. This section was added to provide clarity.

**Sections 3.2.2 through 3.2.6:** have been renumbered **3.2.1 through 3.2.5** to reflect the deletion of the original Section 3.2.1.

**Section 3.2.7:** Deleted this section “Prior malignancy except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer; any other cancer from which the patient has been disease-free for < 5 years”, for consistency with previous changes. Subsequent sections were renumbered as 3.2.6 and 3.2.7 accordingly.

**Section 3.2.9:** This was renumbered as **Section 3.2.7** and was rewritten from “Uncontrollable” to “No uncontrollable” hyperglycemia for clarity.

**Section 4.0:** “All lab tests shall be done within four weeks prior to registration.” was removed to avoid any ambiguity.

**Section 4.3:** In the third sentence the following changes were made: “Obtain” instead of “Strongly encourage” and “3” instead of “4” biopsies; deleted “must be performed,” changed “four” to “8” weeks and changed “of” to “prior to” registration, deleted “prior to treatment with study drug” for clarity and consistency. In the next to last sentence, “one core specimen” was changed to “a core specimen.” In the last sentence, “Also” was added at the beginning and “at least 2” replaced “3” core biopsies. These changes were made for consistency.

**Section 4.4:** For clarity, “within four weeks prior to registration” was added at the end of the sentence.
Sections 4.7 and 11.6.1: “Four” weeks was changed to “8” weeks and “or after” registration was deleted for consistency.

Sections 5.2, 7.4.5, 10.3, and 12.2: These sections were added at the request of ECOG to facilitate their participation.

Section 7.1: In the first and fifth lines, “8” was changed to “8 to 10” weeks; in the third and fifth lines, CT/MRI was changed to CT or MRI for consistency. In the second sentence “four” was changed to “two” weeks for consistency.

Section 7.2.3: On the STI-571 Gleevec: Agent Specific Adverse Event List, “pigmentation changes, e.g., vitiligo, hypopigmentation” was added under the Dermatology/Skin Category per NCI/NIH safety report.

Section 7.2.5: The NCI homepage address was updated here and throughout the protocol including in sections 7.4.1 and 11.2.

Section 7.3.1.1: The fourth sentence was rewritten to clarify dose modification “If any Grade 2 toxicity recurs at this lower dose, Gleevec must be further reduced to 200 mg per day.”

Section 7.3.2.2: Changed all “< Grade” to “≤ Grade” for clarity.

Section 8.1: The first sentence was rewritten as “Initially, in all patients an attempt will be made to obtain at least 3 core needle biopsies...(see...Appendix V).” In the fifth sentence, four was changed to three or more. The last sentence was reworded as “At least 2 of the core specimens should be immediately snap frozen in liquid nitrogen and one should be…” in that three was changed to 2, four was deleted, and the other was deleted. These changes were made for consistency and clarity.

Section 8.2: The third sentence was reworded replacing “four” with “at least 3” and changing “three” frozen core specimens to “2” for consistency. The sentences “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.” were added for clarification since RFA has become an accepted modality for dealing with liver mets. Core biopsy requirement will still be maintained at time of surgical exploration.

Section 10.1: In the first sentence, “four” was deleted and “(both frozen and paraffin)” was added for clarity. In the first sentence of the second paragraph and the last sentence, “to 10” was added to “8 to 10 weeks” for consistency. The last sentence changed “four” to “three or more” core biopsies for consistency. The email address for LDS Hospital was updated to ldhfllinn@ihc.com here and in Appendix V section C.

Section 10.2.7: The first sentence of the third paragraph was changed to read, “GIST cells should exhibit evidence of CD117 staining.” “Desmin (DAKO M0760): No more
than 5% of tumor cells may show staining" was deleted. Also in Section 3.1.1 "A minimum of 25% of the tumor cells should exhibit moderate to strong staining" was deleted. The rationale for this change is that tumor should stain positive for CD117 and its morphology should be consistent with GIST. The 25% criteria may not be reproducible and is not universally accepted as a criterion for diagnosis of GIST.

Section 11.1: Some of the required laboratory studies during weeks 2, 3, 5, 6, and 7 were eliminated; in footnote g, “at 8 weeks” was deleted at the end. The rationale for this change is that there has been enough experience with the use of Gleevec in GIST patients and the routine weekly blood draws are not needed and left to the discretion of the medical oncologist. Footnote f was changed to “See Section 10 and Appendix V.” for clarification. Footnote g superscript was added to week 4 of “PET Scans.”

Section 11.6.1d: This was deleted for consistency. Subsequent sections were re-lettered as d through j as a result.

Section 11.6.3: The first sentence was changed to “The final study will be done just prior to surgery.” because it is necessary to perform the final PET as close to surgical resection as possible.

Section 11.7: At the end of the first sentence, “(see Appendices IX and X)” was added to refer to the new appendices added to the protocol.

Section 12.1: Deleted PET Interpretation Form (IM) because it is not submitted by the site contemporaneously with each PET study. For P2, changed four to three core biopsies for consistency. At week 10, “Surgical materials (P7) (see Section 8.2 and Appendix V, Section B)” was added for clarity; (P6) was corrected to (P4) and (P8) was deleted.

Appendix I: “Under What Is Involved In The Study,” “Prior To Treatment,” the fourth bullet was amended to “At least 3 biopsies of your tumor” instead of “Four biopsies of your tumor” for consistency. Under “Prior to Surgery,” the first bullet was changed to 4 to 10 weeks for consistency. This change was also made in the first sentence under “How Long Will I Be In The Study,”; the second bullet was changed to “Blood tests will be done at weeks 1, 4, and 8-10 prior to surgery” for clarity; the third bullet was revised to “Physical examination at weeks 1 and 8 to 10” and “and 8 to 10” was added to the end of the fourth bullet for consistency. In the second and fourth paragraphs, “and 24-48 hours later” was replaced by “at the discretion of your physician” because in some cases there may be one measurable tumor that is progressing and another that is stable or the physician may want to increase the dose of Gleevec in response to progressive disease and keep the patient on drug. In the third paragraph, blood tests will be done “once a week for 4 weeks” was replaced by “several times prior to surgery” for clarification. In the first sentence in the fourth paragraph, “8 to 10” was added for clarity. Under “What Are The Risks Of The Study,” “and skin pigmentation (color) changes such as less pigment in a tissue or white patches” was added to comply with the NCI/NIH safety report concerning this in layperson’s terms. Under “What About Confidentiality?” the Eastern Cooperative Oncology Group was added to the first paragraph and the statement
“qualified representatives of the drug manufacturer” remains in the third paragraph. Also in the third paragraph, RTOG and ECOG were added to the list of organizations that may inspect patient records.

**Appendix V:** Under “Pre-Treatment,” “ALL PATIENTS” was added to the heading for clarification; the first sentence was changed to “Three or more core biopsies with an 18 to 14 gauge core needle performed by CT or ultrasound guidance are required.” for consistency. Under #2 “Three” was changed to “Two or more” for consistency. A new section B. “POST-TREATMENT—CORE BIOPSY IN THOSE PATIENTS WITH PROGRESSIVE DISEASE OR UNRESECTABLE OR NOT A SURGICAL DANDIDATE” was added for clarification. As a result the subsequent two sections were re-lettered C with “SURGICAL PATIENTS” added to title, and D, where the email address for LDS hospital was updated.

Under “Shipping,” the last paragraph was added for ECOG institutions.

**Appendix VII:** In the first paragraph, “and an image of a standard cylindrical test source of known activity concentration.” was added to the end of the second sentence and “and quantitative accuracy” was added to the third sentence. In **Appendix VIII, Section 2:** A new third sentence was added “In addition, an image of a standard cylindrical test source of known activity concentration is to be sent for assessment of quantitative accuracy.” At the end of the first paragraph, “Instruments likely to qualify include the Siemens/CTI ECAT Exact 47, Exact HR, Exact HR+, Accel, and Biograph, the General Electric 4096 Plus, ADVANCE, Discovery LS, and the ADAC CPET and Allegro. “ was added. The third paragraph beginning with “Instruments” was deleted as the information is covered in other paragraphs of this section. Four additional paragraphs were added. Also in **Appendix VIII, Section 3:** At the end of first sentence, “and one image of a cylindrical test source” was added for consistency. These changes were made because this study includes measurements and comparisons of radiotracer concentration measurements made in vivo by the PET scanners in question. For measurements to be comparable across systems, the systems must be calibrated. Set-up issues, software problems and other local conditions can all affect calibration. To determine the accuracy of each scanner calibration, an image of a cylinder source of known activity concentration will be sent to the core lab. The resulting data may be used to calibrate data arising from the site, or to suggest remedial action on the part of the site.

**Appendix VIII:** The following changes were made:

- **Section 4:** Dr. Badawi’s phone number was corrected to (617) 632-6892.
- **Section 5:** At the end of the first sentence, “and one test source image.” was added for clarification. In the second sentence, “with the PET” was replaced with “with each PET.” for clarity.
- The “Test source study” section was added at the end of PET Instrument Technical Specifications.
Appendix IX was added to provide instructions for PET image submission.

Appendix X was added to provide instructions for CT and MRI Image Collection.

Appendix XI was added to provide the correct instructional guidelines for participation in an ACRIN trial and the General Qualifying Application.