

North Central Cancer Treatment Group

N0572: A Phase I/II Trial of Sorafenib and CCI-779 in Patients with Recurrent Glioblastoma

Addendum 1 – August 11, 2006

**Summary**

- **Protocol revised due to Action Letter and revised Comprehensive Adverse Events and Potential Risks List (CAEPR) for sorafenib (BAY43-9006) dated June 19, 2006, from Dr John Wright.**
- **All patients enrolled in this study are considered at risk and should be informed of these results according to local IRB requirements. At a minimum, patients should be verbally informed of this information, and the process should be documented in the patient's medical record/study chart. Alternatively, patients should sign the revised informed consent document or an IRB-approved document describing this event.**
- **Any patients with signs or symptoms of gastrointestinal AE should be thoroughly evaluated and closely monitored and supported as clinically dictated.**
- Along with the risk noted in the Action Letter, additional risks have been identified along with the relocation of certain risks. The revised CAEPR listing has been inserted into the Drug Information section of the protocol and the consent form has been updated accordingly.
- A pre-registration component has been added to this study.
- An adverse event stopping rule has been added for Group 2 patients.
- Editorial/administrative changes.

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

**Title page:** Now reflects Addendum 1 and revised NCI version date.

**Protocol Resource Page**

Page 2: **Janis Wobschall** replaces ~~Lori Bratvold~~ as the NCCTG *Research Base* Protocol Development Coordinator.

**Index**

Page 3: Appendix III has been corrected to read ~~PIII~~ **Patient Medication** Diary.

**Schemas**

Pages 4-5: Both the Phase I and Phase II schemas have been revised to include the pre-registration component.

Phase II schema now indicates that the Phase II portion is not open to accrual until the MTD is reached from the Phase I portion of the study.

**Section 3.0 Patient Eligibility**

Pages 18-20:

Due to a pre-registration component being added to this study, an opening statement and a new Section 3.1 have been added as follows and all remaining sections renumbered:

**Phase I only - Prior to checking eligibility and pre-registering a patient, contact the Randomization Center (507/284-4130) for study status and dose level.**

**3.1 Pre-registration – Required Characteristics**

**3.11 Central pathology review submission. This review is mandatory prior to registration to confirm eligibility. It should be initiated as soon after surgery as possible.**

**Section 4.0**

Page 21:

**Test Schedule**

Due to the pre-registration component being added, the following revisions and clarifications have been made:

- The row entitled “**Active Monitoring Phase**” is newly added to the top of the table.
- A new column entitled “**Pre-reg**” has been added.
- The row entitled “**Pathology review (see Section 17.0)**” is newly added and an “**X**” has been added to the “Pre-reg” column.
- The lipid panel also needs to be done prior to registration. Therefore, an “**X**”, along with footnote 1, has been added to the “ $\leq 21$  days prior to reg” column.
- An “**X**” has been added to the column “Prior to each new cycle” for the row “Chemistry: Lipid Panel.”
- (**see Section 14.0**) has been added to the row entitled “Blood sample.”
- The “Pill Diary” row has been revised to read “**Patient Medication Diary.**”
- An “**X**” has been added under the “Weekly (1<sup>st</sup> 4 wk) then q2 wks” column for the Blood Pressure Diary.
- The first sentence of footnote #7 has been revised to read “Blood pressure should be recorded ~~twice daily~~ **weekly**.”
- Footnote #8 is newly added to clarify that for non-surgical patients, the blood sample is to be obtained Day 1 Cycle 1 only and for the surgical patients, the blood sample is to be done  $\leq 72$  hours prior to surgery. Reference to footnote #8 has been added to the X in “Prior to each new cycle ( $\leq 7$  days).”
- Footnote #9 is newly added.

**Section 6.0**

Pages 22-23:

**Registration/Randomization Procedures**

Due to the pre-registration component being added, the following revisions have been made:

- A new heading has been added as Section 6.1 “**Pre-Registration (Step 1)**” and all remaining sections have been renumbered.
- The first sentence of Section 6.11 has been revised to read “To **pre-register** a patient, call (507/284-4130) or fax (507/284-0885) a completed **(Step 1) pre-registration** eligibility checklist...”
- Section 6.13 has the following revisions:
  - The opening statement now reads “Prior to accepting the **pre-registration**, the Random Center...”
  - The second bullet now reads “Patient **pre-registration** eligibility”
- Section 6.15 is newly added.
- A new heading has been added as Section 6.2 “**Registration (Step 2).**”
- Section 6.21 has been newly added.
- Section 6.22 has been newly added.
- Section 6.23 has been newly added.
- Section 6.24 now reads “At the time of registration/~~randomization~~, the following will also be recorded.”

**Section 7.0**

Page 24:

**Protocol Treatment**

The first two sentences of the second paragraph in Section 7.11 have been revised to further clarify the dose escalation as follows:

The first cohort of patients will receive sorafenib 200 mg po bid (dose level 0) with CCI-779 **given at 25 mg at** (dose level 0). If DLT is not reached at this level, the next cohort will be enrolled at a sorafenib dose of 400 mg po bid (~~Sorafenib~~ dose level 1) and CCI-779 **at 25 mg at** (dose level 0).

Page 26-27:

For clarification and better readability purposes, the following revisions have been made to Section 7.2:

- The heading for Section 7.2 now reads “Phase II Patients **(NOT YET OPEN TO ACCRUAL UNTIL THE MTD IS REACHED FROM THE PHASE I PORTION OF THE STUDY) Undergoing Surgery.**”
- Reference to Section 7.21 has been deleted from the paragraph directly under the heading for Section 7.2.
- The Section heading for Section 7.21 has been newly added and reads “**Patients Undergoing Surgery.**”
- Section 7.3 has been revised to read “~~7.3~~ **7.22 Phase II Patients NOT Undergoing Surgery**” and remaining sections have been renumbered.
- The heading of the second table on page 27 has been revised to read “Regimen Description ~~Phase II Patients.~~”

**Section 8.0****Dosage Modification Based on Adverse Events**

Page 29:

Due to the NCI Action Letter, a new CTC Category has been added:

**Gastrointestinal/Perforation, GI/Stop Treatment**

Editorial changes have been made to the Agent column – now only lists sorafenib once.

Section 8.9b title has been clarified to indicate that Section 7.12 should be consulted for dose level reductions.

Page 30:

Section 8.9c title has been clarified to indicate that Section 7.12 should be consulted for dose level reductions.

**Section 10.0****Adverse Event (AE) Reporting and Monitoring**

Page 34:

The last sentence under the first bullet item in Section 10.12 has been revised to correctly direct study personnel to the CAEPR listings as follows:

- Expected AEs for expedited reporting purposes are listed on the CTEP Agent Specific Adverse Event List (ASAEL), a component of the Comprehensive Adverse Events and Potential Risks List (CAEPR). **Refer to Section 15.0 to locate the CAEPR for the CTEP IND agent(s).** ~~To access the CAEPR for an agent under a CTEP IND, contact the AdEERS MD Help Desk at [adeersmd@tech-res.com](mailto:adeersmd@tech-res.com).~~

Page 38:

The first sentence in Section 10.22 under the first bullet item under the “Additional Instructions” section has been revised to read “...(available on the CTEP Home Page at <http://ctep.cancer.gov>) and faxed to 301-230-0159.”

Page 39:

Due to the NCI Action Letter, a new category has been added: **Infection/Infection with unknown ANC/Abdomen NOS.**

**Section 13.0****Treatment/Follow-up Decision at Evaluation of Patient**

Page 44:

Due to the pre-registration component being added to the study, Section 13.5 is newly added as follows:

**A patient is deemed *ineligible* if, at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. Only pre-registration and on-study material must be submitted.**

**Section 14.0****Translational/Pharmacologic Studies**

Page 44:

Section 14.1 is now labeled **Sample Banking-Procurement** – kits are required (see Section 14.41)

Section 14.11 now indicates **Mandatory** samples....

The second bullet in Section 14.11 has been revised to refer to Section 14.2 rather than Section 14.3.

Section 14.111 bullet one now reads: **For non-surgical patients:** Day 1, Cycle 1 (Prior to starting treatment).

Section 14.111 bullet two is newly added: **For Phase II surgical patients: ≤72 hours prior to surgery**

Pages 44-51:

Various clarifications have been made to Section 14.0 and it was also felt that it was too confusing for study personnel to have reference to different sections; therefore, the following sections have been revised:

- Section 14.11211 now reads “Make sure the specimen tubes are correctly labeled with **Biopathology Center (BPC)** patient ID number (see Section ~~14.52~~ **14.42**), specimen type, and date drawn.”
- Section 14.11216 has been now reads “Complete a **BPC specimen** transmittal form and send it with the shipment of specimens (~~see Section 14.519d~~).” Remember to keep a copy of the **BPC specimen** transmittal form for your files.
- The first sentence of Section 14.11217 has been revised to read “Ship the frozen serum to ~~the Biopathology Center~~ **BPC** on dry ice.” The reference now reads (~~see Section 14.4~~).
- ~~(see Section 14.5)~~ has been deleted from Section 14.11221.
- Section 14.11224 now reads “Complete a **BPC specimen** transmittal form and send it with the shipment of specimens (~~see Section 14.5~~). Remember to keep a copy of the **BPC specimen** transmittal form for your records.”
- Section 14.11225 now reads “Ship the blood to ~~the Biopathology Center~~ **BPC** at room temperature. See packaging and shipping instructions below (Section ~~14.4516~~).
- Section 14.11236 now reads “Complete a **BPC specimen** transmittal form and send it with the shipment of specimens (~~see Section 14.519d~~). Remember to keep a copy of the **BPC specimen** transmittal form for your files.”
- Section 14.11237 now reads “Ship the frozen plasma to ~~the Biopathology Center~~ **BPC** on dry ice. See packaging and shipping instructions below (Section ~~14.4515~~).”
- Section 14.212: Reference to Section 14.314 located in the first sentence of has been corrected to read “(see Section **14.216**).” The second sentence now references (**Section 14.215**). The third sentence now references (**Section 14.216**).
- Section 14.213 table now references the sections if OCT is available and if it is not available.

- Section 14.2144 now reads “Complete a **BPC specimen** ~~transmittal form~~ and include it with the shipment of specimens (~~see Section 14.519d~~). Remember to keep a copy of the **BPC specimen** transmittal form for your files.”
- Section 14.2145 now references (Section 14.4513).
- The NOTE item under Section 14.2145 has been renumbered and is now **Section 14.215** and all remaining sections have been renumbered accordingly.
- Sections 14.2157 and 14.2164 now reads: Complete a **BPC specimen** transmittal form...
- Section 14.2158 now references (**Section 14.4**)
- (~~see Section 14.517~~) has been deleted from Section 14.2164.
- Section 14.2165 now references (**Section 14.4**). Sentence 2 now reads: See ~~section on the packaging~~....
- The first sentence of Section 14.417 now reads “Place the **BPC specimen** transmittal form into the plastic bag that contained the kit instructions.”

Page 50: Section 14.3 has the following added to the first sentence: ... (drawn prior to starting protocol treatment **for non-surgical patients and drawn ≤72 hours prior to surgery for surgical patients**) will be collected.

Page 55 Section 14.51 table now indicates Fresh Tumor Tissue (**Phase II Surgical Patients**) rather than (~~only required for Study 2~~) in row 1

Section 14.51 table row 3 now indicates Block of tumor or Unstained Paraffin Slides rather than Unstained Paraffin Slides or Block of tumor and footnote 1 now references **Phase II patients** rather than ~~Group 2~~

### Section 15.0 Drug Information

Pages 59-62: A revised CAEPR listing has been received from NCI. Therefore, Section 15.16 has been replaced in its entirety.

Pages 59-84: Due to the inclusion of the revised CAEPR listing, repagination has occurred.

### Section 16.0 Statistical Considerations and Methodology

Page 74: Due to an adverse event stopping rule being added for the Group 2 patients, Section 16.38 has been revised as follows:

**Adverse Event Stopping Rule:** If 3 out of the first 20 or if at any time after the first 20 patients are enrolled 15% or more patients develop ≥Grade 4 non-hematologic adverse events felt to be at least possibly related to treatment, the study team will review the data to determine the proper course of action. These actions may include further AE monitoring, suspension of accrual, dose modification, and closure of the trial. Accrual to the trial will continue until official notification is received from NCCTG. Due to the limited number of patients in group 2 and the unknown effects of surgery while on study, patients in group 2 will ~~not be included in the toxicity~~ **have a separate adverse event stopping rule. However, group 2 patients will be monitored for adverse events and examination of the adverse event patterns for both groups will be made if undue toxicity is observed in either group. Patients in group 2 must have**

**adequate initial healing of their incision as defined by (1) ability to remove sutures or staples, if applicable, based on adequate appearance of the incision and (2) no evidence of active infection in the incision or evidence of systemic infection. These patients will be closely monitored for evidence of significant delay in wound healing, which will be defined by the treating physician. If 1 out of the first 3 patients or if at any time after the first 3 patients are enrolled 30% or more patients accrued to group 2 develop evidence of significant delays in wound healing, accrual to group 2 will be stopped and the cases will be reviewed by the study team prior to any decisions regarding further accrual to group 2, with amendment to group 2 if indicated at that time. Examination of the adverse event patterns for both groups will be made if undue toxicity is observed in either group.**

### Section 17.0

Page 78:

#### Pathology Considerations

Due to the pre-registration component being added to this study, the follow revisions have been made throughout this section:

- Two opening statements have been added to the beginning of this section to read **“Central pathology review is mandatory prior to registration to confirm eligibility. It should be initiated as soon after surgery as possible”** and **“Note: See Section 6.0 Pre-registration procedures for instructions before submitting pathology materials.”**
- The first two sentences of Section 17.1 have been deleted as follows: ~~Central pathology review is mandatory prior to study entry to confirm eligibility. It should be initiated as soon after surgery as possible.~~
- The opening statement of Section 17.2 now reads **“A call needs to be made to the NCCTG pathology coordinator (507/266-0724) after pre-registration but prior to forwarding the following material:”**
- A new third paragraph has been added to Section 17.2 and reads **“The NCCTG Pathology Coordinator will enter the eligibility status of the patient into the pre-registration database. This will enable the Randomization Center to verify eligibility when the institution proceeds to step 2 of the registration.”**
- Section numbers have been added to the last two paragraphs and are labeled **17.3** and **17.4** respectively.

### Section 18.0

Page 80:

#### Records and Data Collection Procedures

Due to the pre-registration component being added to the study, the following revisions have been made:

- Wording for the heading of column 2 has been changed from “Prior to study entry” to “Pre-reg.”
- The “Pathology Submission Form” has been corrected to read **“Pathology Material.”** Footnote #1 has been added to this entry.
- **Lipid Panel Form** row has been added along with footnote 8.
- Footnote #7 has been added as follows:
  7. **Complete only if patient is NOT registered after he/she is pre-registered.**

Due to multiple Concurrent Treatment Logs being used on this study, two footnotes have been added as follows:

5. **Includes Prefilled Concurrent Treatment Log, Anticonvulsant Concurrent Treatment Log (baseline), and Steroid Concurrent Treatment Log (baseline).**
6. **Includes Prefilled Concurrent Treatment Log, Anticonvulsant Concurrent Treatment Log (active monitoring phase), and Steroids Concurrent Treatment Log (active monitoring phase).**

Under the column “ $\leq 2$  weeks after registration” for the Concurrent Treatment Log reference to footnote #5 has been added beside the X.

Under the column “At each evaluation” for the Concurrent Treatment Log, reference to footnote #6 has been added beside the X.

Under the column “At end of treatment” for the Concurrent Treatment Log, reference to footnote #6 has been added beside the X.

#### **Appendix IA Consent Form (Phase I Patients)**

The title now reflects (Phase I Patients) with “not Undergoing Surgery” deleted.

Page 1: Under the section “Why is this study being done?” the first bullet has been clarified and now reads “To find out the highest safest dose of Sorafenib **and CCI-779.**”

Page 2: For clarification purposes, the last paragraph under “What will happen in the study?” section has been moved and is now included in the previous paragraph as follows:  
 Slides made from your biopsy tissue at the time of primary diagnosis and/or from the time of your recurrence are used for research in this study. This is mandatory to be a part of this study. Your biopsy tissue will be kept by the North Central Cancer Treatment Group (NCCTG). **You and/or your health plan will not have to pay the costs of these tests which are only done for research purposes.**

~~You and/or your health plan will not have to pay the costs of these tests which are only done for research purposes.~~

Page 6: The fifth sentence in the first paragraph under the section “What are the risks of the study?” has been revised as follows for clarification: “Many side effects go away shortly after the sorafenib **and CCI-779** ~~are~~ stopped, but in some cases side effects can be serious, long lasting, or may never go away.”

Page 7: Due to the NCI Action Letter, the following risk has been added: **Hole in the bowel which could happen even long after you have stopped taking sorafenib.**

A revised CAEPR listing has been received from NCI for BAY 43-9006. Therefore the following revisions have been made:

**Likely**

- Skin rash/skin peeling
- Diarrhea
- Tiredness
- **Hand-foot syndrome (redness of the skin on the palm or the bottom of the foot that may affect daily activities)**

**Less Likely**

- ~~• Numbness, tingling, redness, and/or discomfort of hands or feet that may affect daily activities~~
- Nausea and vomiting
- Flu-like symptoms (**feeling achy, feverish**)
- High blood pressure (**may cause headaches or feeling hot, but if serious could cause strokes or other problems**)
- Sores in mouth and/or throat
- Nail changes
- **Allergic reactions**
- Lightning of skin color
- Inflammation of pancreas (**which can cause diabetes or other problems in the future**)
- Hair loss (**scalp or body**)
- Weight loss
- Muscle pain
- Decreased oxygen in blood
- Loss of appetite, not feeling hungry
- Painful swallowing
- Heartburn
- Excess fluid in stomach
- Non-life-threatening skin cancer
- Fluid around lungs
- High blood sugar
- Constipation
- Itching
- Dehydration (**loss of body fluids**)
- Intestinal gas
- Low blood phosphate
- Chills **and/or shaking chills**
- Fever
- Dry skin
- Redness of the face
- Infection
- Decrease in blood counts which may lead to serious infection, tiredness, or bleeding
- Joint pain (**arthritis**)
- Kidney failure
- Inflammation in lungs
- Collapsed lungs
- Bleeding in stomach, intestines, kidney or bladder

- Fever associated with a low white blood cell count
- **Liver injury (as seen on blood tests)**
- **Stomach/abdominal pain (pain in the belly)**

#### Rare but serious

- ~~Abdominal pain (pain in the belly)~~
- **Hole in the bowel which could happen even long after you have stopped taking sorafenib**
- ~~Skin peeling~~
- ~~Allergic reactions~~
- ~~Low protein level in blood~~
- ~~Elevated blood levels of liver enzymes (chemicals made in the liver)~~
- ~~Elevated blood level of amylase (chemical made in the pancreas)~~

Pages 7-8: Per NCI and most IRBs, including side effects that are undetermined to be related to a particular drug is not mandatory; therefore, the “Side effects still undetermined to be related to Sorafenib and CCI-779” have been deleted.

Page 10: The second sentence of the second paragraph under the “What are the costs of tests and procedures?” section has been corrected as follows:  
 These tests and exams are the ~~optional~~ **mandatory** research studies...”

#### **Appendix IB Consent Form (Phase II Patients Undergoing Surgery)**

Page 3: “What will happen in this study” - The row entitled “Day of Surgery (Prior to surgery)” has been deleted from the table as this does not apply.

Page 7: The fifth sentence in the first paragraph under the section “What are the risks of the study?” has been revised as follows for clarification: “Many side effects go away shortly after the sorafenib **and CCI-779 are** ~~is~~ stopped, but in some cases side effects can be serious, long lasting, or may never go away.”

Pages 8-9: Due to the NCI Action Letter, the following risk has been added: **Hole in the bowel which could happen even long after you have stopped taking sorafenib.**

A revised CAEPR listing has been received from NCI for BAY 43-9006. Therefore the following revisions have been made:

#### Likely

- Skin rash/**skin peeling**
- Diarrhea
- Tiredness
- **Hand-foot syndrome (redness of the skin on the palm or the bottom of the foot that may affect daily activities)**

**Less Likely**

- ~~• Numbness, tingling, redness, and/or discomfort of hands or feet that may affect daily activities~~
- Nausea and vomiting
- Flu-like symptoms (**feeling achy, feverish**)
- High blood pressure (**may cause headaches or feeling hot, but if serious could cause strokes or other problems**)
- Sores in mouth and/or throat
- Nail changes
- **Allergic reactions**
- Lightening of skin color
- Inflammation of pancreas (**which can cause diabetes or other problems in the future**)
- Hair loss (**scalp or body**)
- Weight loss
- Muscle pain
- Decreased oxygen in blood
- Loss of appetite, not feeling hungry
- Painful swallowing
- Heartburn
- Excess fluid in stomach
- Non-life-threatening skin cancer
- Fluid around lungs
- High blood sugar
- Constipation
- Itching
- Dehydration (**loss of body fluids**)
- Intestinal gas
- Low blood phosphate
- Chills **and/or shaking chills**
- Fever
- Dry skin
- Redness of the face
- Infection
- Decrease in blood counts which may lead to serious infection, tiredness, or bleeding
- Joint pain (**arthritis**)
- Kidney failure
- Inflammation in lungs
- Collapsed lungs
- Bleeding in stomach, intestines, kidney or bladder
- Fever associated with a low white blood cell count
- **Liver injury (as seen on blood tests)**
- **Stomach/abdominal pain (pain in the belly)**

**Rare but serious**

- ~~• Abdominal pain (**pain in the belly**)~~
- **Hole in the bowel which could happen even long after you have stopped taking sorafenib**
- ~~• Skin peeling~~
- ~~• Allergic reactions~~
- ~~• Low protein level in blood~~
- ~~• Elevated blood levels of liver enzymes (chemicals made in the liver)~~
- ~~• Elevated blood level of amylase (chemical made in the pancreas)~~

Pages 8-9: At the request of our memberships IRB, the side effects that are undetermined to be related to Sorafenib and CCI-779 have been removed. Per a communication received from Patricia R. Schettino, R.Ph. M.S., Associate Chief, Pharmaceutical Management Branch of NCI, this list is not considered mandatory.

Page 10: The second sentence of the second paragraph under the “What are the costs of tests and procedures?” section has been corrected as follows:  
 These tests and exams are the ~~optional~~ **mandatory** research studies...”

#### **Appendix IC Consent Form (Phase I/II Patients not Undergoing Surgery)**

The title now indicates (Phase II Patients not Undergoing Surgery) rather than Phase I/II.

Page 2: For clarification purposes, the last paragraph under “What will happen in the study?” section has been moved and is now included in the previous paragraph as follows:  
 Slides made from your biopsy tissue at the time of primary diagnosis and/or from the time of your recurrence are used for research in this study. This is mandatory to be a part of this study. Your biopsy tissue will be kept by the North Central Cancer Treatment Group (NCCTG). **You and/or your health plan will not have to pay the costs of these tests which are only done for research purposes.**

~~You and/or your health plan will not have to pay the costs of these tests which are only done for research purposes.~~

Page 6: The fifth sentence in the first paragraph under the section “What are the risks of the study?” has been revised as follows for clarification: “Many side effects go away shortly after the sorafenib **and CCI-779 are** stopped, but in some cases side effects can be serious, long lasting, or may never go away.”

Page 7: Due to the NCI Action Letter, the following risk has been added: **Hole in the bowel which could happen even long after you have stopped taking sorafenib.**

A revised CAEPR listing has been received from NCI for BAY 43-9006. Therefore the following revisions have been made:

#### **Likely**

- Skin rash/skin peeling
- Diarrhea
- Tiredness
- **Hand-foot syndrome (redness of the skin on the palm or the bottom of the foot that may affect daily activities)**

**Less Likely**

- ~~• Numbness, tingling, redness, and/or discomfort of hands or feet that may affect daily activities~~
- Nausea and vomiting
- Flu-like symptoms (**feeling achy, feverish**)
- High blood pressure (**may cause headaches or feeling hot, but if serious could cause strokes or other problems**)
- Sores in mouth and/or throat
- Nail changes
- **Allergic reactions**
- Lightening of skin color
- Inflammation of pancreas (**which can cause diabetes or other problems in the future**)
- Hair loss (**scalp or body**)
- Weight loss
- Muscle pain
- Decreased oxygen in blood
- Loss of appetite, not feeling hungry
- Painful swallowing
- Heartburn
- Excess fluid in stomach
- Non-life-threatening skin cancer
- Fluid around lungs
- High blood sugar
- Constipation
- Itching
- Dehydration (**loss of body fluids**)
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- Chills **and/or shaking chills**
- Fever
- Dry skin
- Redness of the face
- Infection
- Decrease in blood counts which may lead to serious infection, tiredness, or bleeding
- Joint pain (**arthritis**)
- Kidney failure
- Inflammation in lungs
- Collapsed lungs
- Bleeding in stomach, intestines, kidney or bladder
- Fever associated with a low white blood cell count
- **Liver injury (as seen on blood tests)**
- **Stomach/abdominal pain (pain in the belly)**

**Rare but serious**

- ~~• Abdominal pain (**pain in the belly**)~~
- **Hole in the bowel which could happen even long after you have stopped taking sorafenib**
- ~~• Skin peeling~~
- ~~• Allergic reactions~~
- ~~• Low protein level in blood~~
- ~~• Elevated blood levels of liver enzymes (chemicals made in the liver)~~
- ~~• Elevated blood level of amylase (chemical made in the pancreas)~~

Pages 8-10: Per NCI and most IRBs, including side effects that are undetermined to be related to a particular drug is not mandatory; therefore, the “Side effects still undetermined to be related to Sorafenib and CCI-779 have been deleted.

Page 10: The second sentence of the second paragraph under the “What are the costs of tests and procedures?” section has been corrected as follows:  
These tests and exams are the ~~optional~~ **mandatory** research studies...”



**ACTION LETTER**

**DATE:** June 19, 2006 *John Wright 6/23/06*

**FROM:** John J. Wright, M.D., Ph.D., Developmental Chemotherapy Section, Investigational Drug Branch, CTEP, DCTD, NCI

**SUBJECT:** Sorafenib (BAY 43-9006) IND Safety Report, AEs# 1094986, 1075523, 1831511

**TO:** Investigators Using Sorafenib, IND 69896

The purpose of this letter is to alert investigators of the following serious adverse events (AEs) that occurred in association with sorafenib in studies sponsored by the National Cancer Institute (NCI), Division of Cancer Treatment and Diagnosis (DCTD). The Agent Specific Expected Adverse Event List is being revised at this time to include gastrointestinal (GI)-perforation (NOS). A revision to the protocol and the informed consent form is **required** by the NCI.

Three cases of GI-perforation (NOS) (two grade 3 and one grade 4) were recently reported in patients receiving sorafenib therapy. All three AEs were assessed by the IDB monitor as possibly attributed to the IND agent sorafenib.

Case 1 (ticket #1094986): 47-year old male with metastatic renal cell cancer enrolled on a phase 2 study received 400 mg sorafenib bid PO on a continuous schedule in combination with  $10 \times 10^6$  IU interferon-alpha 2B (SC) three times per week every 28 days. The patient started sorafenib therapy on March 28, 2005 and received the last dose of sorafenib on May 8, 2006 (Cycle 15, day 13). Symptoms of right lower quadrant pain, as well as fever, nausea, and vomiting started on May 6, 2006. He presented to the ER with these complaints on May 8, 2006 and radiographic findings consistent with acute appendicitis and focal perforation were noted. The appendix was removed under laparoscopic guidance; pathologic assessment indicated that the entire appendix was inflamed involving the full thickness of the wall from the surgical margin to the tip of the appendix. Diagnosis of acute appendicitis (Grade 3).

Case 2 (ticket #1075523): 56-year old male with anaplastic oligodendroglioma enrolled on a phase 1 study received 800 mg sorafenib once on day 1 and then 800 mg PO bid starting on day 2 on a continuous schedule. The patient started sorafenib therapy on April 10, 2006, and received the last dose of sorafenib on April 20, 2006 (Cycle 1, day 11). Mild abdominal pain started on April 18, 2006. The patient presented to the ER on April 20, 2006 with severe abdominal pain associated with distention but no history of vomiting. Radiographic examination revealed free air and subsequently sigmoid colonic perforation was observed during an exploratory laparotomy. He underwent a sigmoid colectomy with descending colostomy and Hartmann pouch formation and pathologic examination of the colon segment revealed diverticular disease with a pericolic abscess consistent with a focal rupture. There was no evidence of cancer. Diagnosis of perforated bowel (grade 3 colon perforation) secondary to an abscessed diverticulum.

**CONFIDENTIAL**

1 of 3

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## ACTION LETTER

Case 3 (ticket #1831511): 65-year old male with epithelial hemangioendothelioma (low grade angiosarcoma) metastatic to the lung enrolled on a phase 2 study received 400 mg sorafenib bid PO on a continuous schedule. The patient started sorafenib therapy on December 22, 2005 and received the last dose of sorafenib on May 15, 2006 (Cycle 6, day 5). The clinical symptom of abdominal pain started on May 13, 2006 and the patient presented to the ER on May 15, 2006 with an acute abdomen and constipation. A CT scan revealed free intraperitoneal air with ascites, with a focal gas collection adjacent to the loop of the jejunum in the mid-abdomen, suspicious for perforation. He underwent an emergency exploratory laparotomy and was found to have diverticulitis with a perforated sigmoid. A hemicolectomy with formation of an end colostomy with Hartmann's pouch was performed. The patient was found to have acute diverticulitis (grade 4 perforation of small bowel) requiring a hemicolectomy.

A total of 1066 patients have been treated on CTEP-sponsored sorafenib studies. CTEP also discussed these reports with Bayer/Onyx Pharmaceuticals, the manufacturers of Sorafenib (BAY43-9006). A review of their database identified 40 cases of small and large bowel perforations, 17 cases clearly associated with diverticulitis and 18 cases with advanced abdominal disease, some with tumor at the site of perforation, some without and most not documented. There were also 2 cases of upper GI ulcers with perforation and 21 upper GI ulcers without perforation.

In view of the potential seriousness of these adverse events, CTEP is requesting that all principal investigators do the following:

- 1) Distribute this letter to all participating investigators and IRBs. The principal investigator or lead organization (e.g., coordinating center or group operations office) also needs to forward a copy of the e-mail or other rapid traceable communication (e.g., fax with return requested) to **Dr. Michael Montello** at [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV) within 7 calendar days of the date of this letter. Failure to comply within the 7-day timeframe may result in the temporary suspension of the principal investigator and enrollment of patients to the study.
- 2) Amend the protocol to describe GI-Perforation (NOS) and include the statement that patients must be taken off therapy after GI-Perforation.
- 3) Amend the informed consent documents to inform patients in lay terms of the potential for GI perforation.
  - For Cooperative Group studies, the revision to the protocol and informed consent form will be made by the Cooperative Group Operations office, forwarded to CTEP for approval, and circulated to the Group's investigators. Please follow any instructions provided by the Cooperative Group.
  - For non-Cooperative Group studies, the principal investigator is required to forward a copy of the revised protocol and informed consent form to CTEP as outlined below.

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## ACTION LETTER

- 4) Patients currently on study should be monitored for gastrointestinal AEs, particularly as they may relate to onset or development of gastrointestinal perforations.
- 5) All patients on and off therapy who develop signs and symptoms suggestive of gastrointestinal AEs should be thoroughly evaluated and closely monitored and supported as clinically dictated.
- 6) Continue to submit to NCI expedited safety reports for all cases of GI-Perforation (NOS).
- 7) Please begin informing new patients or patients currently on treatment of the risk for GI-perforation (NOS) and document the informed consent in the patient chart.
- 8) All patients who enrolled on protocols in this study and are considered at risk should be informed of these results according to local IRB requirements. At a minimum, patients should be verbally informed of this information, and the process should be documented in the patient's medical record/study chart. Alternatively, patients should sign the revised informed consent document or an IRB-approved document describing this event.
- 9) Enrollment may continue while the amendment is prepared and processed by the local IRB, provided the IRB agrees.
- 10) Submit all amendments to the protocol and informed consent form to NCI by **5:00 pm ET on July 19, 2006**. The amendment cover letter must state "these amendments are in response to the memo from Dr. J. Wright ([wrightj@ctep.nci.nih.gov](mailto:wrightj@ctep.nci.nih.gov), phone 301-496-1196) regarding the development of GI-Perforation (NOS). Failure to comply within this timeframe may result in the temporary suspension of the principal investigator and enrollment to the study.

Please submit the amendment, the change memo, and the cover letter to Dr. Michael Montello at [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV).