

North Central Cancer Treatment Group

N054C: Phase II Study of Sorafenib/Bevacizumab as Salvage Therapy in Patients with Metastatic Colorectal Cancer

Addendum 1 – May 13, 2009

Summary

- In Section 8.3 the dose modification table has been replaced for clarification
- At the request of NCI, the CAEPR for bevacizumab, dated June 19, 2007 has been added to Section 15.0 and the consent form has been revised accordingly
- The consent form has been revised for sorafenib due to review of the sorafenib version 2.2 CAEPR, dated December 17, 2008
- Administrative/Editorial Changes

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

Title page The NCI version date on the title page has been updated.

Protocol Resource Page

Page 2: The last row of the table has been updated to enter a new Data Management Specialist.

~~Linda L. Berge~~ **Vicki A. Bryhn**
NCCTG *Research Base* Data Management Specialist
Phone: (507) ~~284-5928~~ **266-5350**
Fax: (507) 538-0906
E-mail: ~~berge.linda@mayo.edu~~ bryhn@mayo.edu

Schema

Page 4: The NCCTG abbreviation for sorafenib has been revised to capitalize all letters and remove the ® symbol. The abbreviation is used only internally at Mayo and the symbol is not compatible with the IT system used.

Section 3.0 Patient Eligibility

Pages 10-11: Several editorial corrections have been made, including bullets 1, 5, 8, and 9 in Section 3.15, Section 3.17, 3.21, and 3.25. In Section 3.15, ALT has been removed and only AST will be used to determine eligibility. Numbering in Section 3.2 has been corrected.

3.15:

- Hemoglobin ≥ 9.0 g/~~dL~~ **dL**
- AST/~~ALT~~ ≤ 2.5 x (ULN)
(≤ 5 x ULN for patients with liver involvement)
- Alkaline phosphatase ≤ 3 x ~~ULN~~ **ULN**
- INR < 1.5 unless patients are receiving anti-coagulation therapy. Patients receiving anti-coagulation ~~treatment~~ **therapy** with an agent such as warfarin or heparin are allowed to participate (see Section 4.0) if
INR ≤ 3.0 .

3.17:

Ability to understand and the willingness to sign a written informed consent. **Note:** A signed informed consent must be obtained prior to any study specific procedures.

3.21:

Any of the following....

Note: This study involves investigational agents whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

3.25:

Known brain metastasis. **Note:** Patients with neurological symptoms must undergo a CT scan/MRI of the brain to exclude brain metastasis.

Repagination has occurred from this point forward due to reformatting.

Section 4.0 Test Schedule

Page 13: Row 7 of the table (Chemistry group) has been revised. ALT has been removed as it is no longer required for eligibility.

Page 14: In Footnote 5, the time points for urinalysis have been corrected to remove conflicting information and a minor editorial revision has been made for clarification.

Urinalysis for proteinuria will be monitored ~~at baseline and prior to each treatment~~ by either urine protein (UPC) ratio (see Appendix III) or dipstick **at baseline and** every other cycle (4 weeks) and 24-hour collection **should be** done if indicated....

Footnote 12 has been revised to reduce the number of CT or MRI scans required for tumor measurement.

Should be conducted within 4 days before planned treatment ~~prior to each new cycle, then prior to 4th, and 7th cycles, and then every 4th cycle (every 8 weeks)~~ **every 6 weeks**.

Section 6.0 Registration/Randomization Procedures

Page 16: Section 6.6 has been revised for clarification as follows:
Treatment...supervision of an NCCTG member...

Section 8.0 Dosage Modifications Based on Adverse Events

Pages 19-25: A new table for adverse events “**At Time of Retreatment**” has been added to Section 8.3 as this was inadvertently omitted.

Note: The footnote associated with the “*” next to “Hold” throughout the table has been revised A new asterisk footnote has been added at the end of the new table and placed next to “Hold” throughout this new table as follows:

If any daily doses are missed, they will not be made up. The cycle length remains 14 days despite missed doses.

Wording in the last column of several rows has been modified to clarify when treatment continues and when the patient goes to Event Monitoring. If bevacizumab is discontinued, patient may continue treatment on sorafenib. If either sorafenib OR both agents are discontinued, patient goes to Event Monitoring

Old table

~~→→ Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified ←←~~

CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
<i>BASED ON INTERVAL ADVERSE EVENT</i>			
Blood/Bone Marrow	Neutrophils/granulocytes (ANC/AGC) Grade 2 <1,500 OR Platelets Grade 3 <50,000	Sorafenib	Omit treatment until ANC ≥1500 and platelets ≥50,000 and ↓ by one dose level. If no recovery after a 3-week delay, despite institution of all clinically appropriate symptomatic treatment, discontinue and go to Event Monitoring and then off study.
Cardiac-General	Hypertension	Sorafenib Bevacizumab	See Section 8.5 for management.

→→ Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified ←←

CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
	Left ventricular systolic dysfunction Grade 3 Grade 4	Bevacizumab	Omit bevacizumab until ≤Grade 1 Discontinue bevacizumab

CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
Dermatology/ skin (continued)	Rash: acne/acneiform Grade 2 and 3	Sorafenib	Omit dose. <ul style="list-style-type: none"> • Re-evaluate at least weekly until adverse event resolved to ≤1 or tolerable grade 2. • Re-treat at a one dose level reduction • If adverse event persists >14 days, discontinue. Patient goes to Event Monitoring and then off study. If adverse events related to agent, patient may be taken off treatment at investigator discretion. Patient goes to Event Monitoring and then off study.
	Grade 4 ----- Wound complication, non-infectious (dehiscence) ----- ≥Grade 2	Bevacizumab	Discontinue.
Gastrointestinal	Fistula, GI—abdominal Any grade	Bevacizumab	• Discontinue. Patient goes to Event Monitoring and then off study.
	Leak (including anastomotic); Esophagus, stomach, small bowel, large bowel, biliary ----- Any grade		• Discontinue. Patient goes to Event Monitoring and then off study.
	Obstruction, Esophagus, stomach, small bowel, large bowel Grade 2 ----- Grade 3-4		Omit until resolution. Omit until resolution. If surgery is necessary, patient may restart ≥28 days following surgery and at investigator's discretion
	Perforation, Esophagus, stomach, small bowel, large bowel Any grade	Sorafenib Bevacizumab	• Discontinue. Patient goes to Event Monitoring and then off study.
Hemorrhage/ Bleeding	Non-CNS—Nasal, esophagus, stomach, small bowel, large bowel, biliary, retroperitoneum, peritoneal cavity Grade 3	Sorafenib Bevacizumab	Omit until all of the following criteria are met then resume at same dose: <ul style="list-style-type: none"> • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. • Subjects who experience a repeat Grade 3 hemorrhagic event will discontinue treatment. Patient goes to Event Monitoring and then off study.

	Grade 4		Discontinue. Patient goes to Event Monitoring and then off study.
	Hemorrhage, CNS—Any grade		Discontinue. Patient goes to Event Monitoring and then off study.
	Bronchopulmonary—Grade >2		Discontinue bevacizumab. Patient goes to Event Monitoring and then off study.
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
<i>BASED ON INTERVAL ADVERSE EVENT</i>			
Metabolic/ Laboratory	Proteinuria — Grade 3 (≥ 3.5 g/24 hr) — Grade 4 (nephritic — syndrome)	Bevacizumab	Omit until proteinuria improves to \leq Grade 2. Discontinue. Patient goes to Event Monitoring and then off study.
Neurology	CNS cerebrovascular ischemia — Any grade Neurology—Other (leukoencephalopathy syndrome)	Bevacizumab	Discontinue. Patient goes to Event Monitoring and then off study. Omit pending workup and management, including control of blood pressure. Discontinue if Reversible Posterior Leukoencephalopathy Syndrome (RPLS) diagnosed. Resumption of bevacizumab may be considered in patients who have documented benefit from the agent, provided that RPLS was mild and has completely resolved clinically and radiographically within 2-4 weeks; decision to resume bevacizumab in these patients <u>must</u> be discussed with the study chair and approved by the sponsor
Vascular	Thrombosis/thrombus/ embolism — Grade 1 or 2 — (asymptomatic — thrombosis) — Grade 3/asymptomatic Grade 4 Grade 4 symptomatic	Bevacizumab	No dose modifications Omit. If the planned duration of full dose anticoagulation is <2 weeks, bevacizumab should be omitted until the full dose anticoagulation period is over. If the planned duration of full dose anticoagulation is ≥ 2 weeks, bevacizumab should be discontinued. <ul style="list-style-type: none"> ● The subject must have an in-range INR (usually 2-3 on a stable dose of warfarin (or other anticoagulant) prior to restarting bevacizumab treatment. ● The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation. ● The patient must not have had evidence of tumor involving major blood vessels on any prior CT scan. Discontinue bevacizumab.

	Peripheral arterial ischemia — Any grade		Discontinue all therapy. Patient goes to Event Monitoring and then off study.
	Visceral arterial ischemia (non-myocardial) — Any grade		Discontinue all therapy. Patient goes to Event Monitoring and then off study.
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
All other non-hematologic adverse events (excluding alopecia)	Grade 1-2	Sorafenib	Continue at the same dose level.
	Grade 3-4 (excludes nausea/vomiting that has not been pre-medicated)		Omit treatment until resolved to ≤Grade 1, then resume treatment at the same dose level. If patient experiences a second Grade 3 adverse event, omit dose until adverse event is ≤Grade 1, then reduce dose by one level.
	Grade 3	Bevacizumab	Omit bevacizumab until recovery to ≤Grade 1
	Grade 4		Discontinue bevacizumab

→ → Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified ← ←

CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
AT TIME OF RETREATMENT			
Gastrointestinal	Perforation, GI— colon	Sorafenib Bevacizumab	Discontinue sorafenib and bevacizumab
	Perforation, GI— small bowel NOS, large bowel NOS, stomach, esophagus		Discontinue sorafenib and bevacizumab
	Bowel obstruction— small bowel, large bowel Grade 1 Grade 2		Continue patient on study for partial obstruction NOT requiring medical intervention.

New Table

→ → Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified ← ←

CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
Blood/Bone Marrow	Neutrophils/granulocytes (ANC/AGC) Grade 2 <1,500 OR Platelets Grade 3 <50,000	Sorafenib	Omit treatment until ANC ≥1500 and platelets ≥50,000 and ↓ by one dose level. If no recovery after a 3-week delay, despite institution of all clinically appropriate symptomatic treatment, discontinue sorafenib and go to Event Monitoring.
Cardiac General	Hypertension	Sorafenib Bevacizumab	See Section 8.5 for management.

→ → Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified ← ←

CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
	Left ventricular systolic dysfunction Grade 3 Grade 4	Bevacizumab	Omit bevacizumab until ≤Grade 1 Discontinue bevacizumab. Continue on protocol with sorafenib.

→ → Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified ← ←

CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
Dermatology/skin	Rash: Hand/foot skin reaction (See Section 8.5)	Sorafenib	<p>Omit dose.</p> <ul style="list-style-type: none"> • Re-evaluate at least weekly until adverse event resolved to ≤1 or tolerable grade 2. • Re-treat at a one dose level reduction • If adverse event persists >14 days, discontinue sorafenib. Patient goes to Event Monitoring. <p>If adverse events related to agent, patient may be taken off treatment at investigator discretion. Patient goes to Event Monitoring.</p>
	Rash: acne/acneiform Grade 2 and 3 Grade 4		
	Wound complication, non-infectious (dehiscence) ≥Grade 2	Bevacizumab	Discontinue bevacizumab. Continue on treatment with sorafenib.
Gastrointestinal	Fistula, GI – abdominal Any grade	Bevacizumab	• Discontinue bevacizumab. Continue on treatment with sorafenib.
	Leak (including anastomotic), Esophagus, stomach, small bowel, large bowel, biliary Any grade		• Discontinue bevacizumab. Patient goes to Event Monitoring. Continue treatment with sorafenib.
	Obstruction, Esophagus, stomach, small bowel, large bowel Grade 2 Grade 3-4		Omit until resolution. Omit until resolution. If surgery is necessary, patient may restart ≥28 days following surgery and at investigator’s discretion
	Perforation, Esophagus, stomach, small bowel, large bowel Any grade	Sorafenib Bevacizumab	• Discontinue treatment. Patient goes to Event Monitoring.

→ → Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified ← ←			
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
Hemorrhage/ Bleeding	Non-CNS – Nasal, esophagus, stomach, small bowel, large bowel, biliary, retroperitoneum, peritoneal cavity Grade 3	Sorafenib Bevacizumab	Omit until all of the following criteria are met then resume at same dose: <ul style="list-style-type: none"> • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. • Subjects who experience a repeat Grade 3 hemorrhagic event will discontinue treatment. Patient goes to Event Monitoring.
	Grade 4		Discontinue treatment. Patient goes to Event Monitoring.
	Hemorrhage, CNS - Any grade		Discontinue treatment. Patient goes to Event Monitoring
	Bronchopulmonary - Grade >2		Discontinue bevacizumab. Patient goes to Event Monitoring. Continue treatment with sorafenib.
Metabolic/ Laboratory	Proteinuria Grade 3 (≥3.5 g/24 hr) Grade 4 (nephritic syndrome)	Bevacizumab	Omit until proteinuria improves to ≤Grade 2. Discontinue bevacizumab. Continue treatment with sorafenib.
Neurology	CNS cerebrovascular ischemia Any grade	Bevacizumab	Discontinue bevacizumab. Continue treatment with sorafenib.
	Neurology – Other (leukoencephalopathy syndrome)		Omit pending workup and management, including control of blood pressure. Discontinue bevacizumab and continue treatment with sorafenib if Reversible Posterior Leukoencephalopathy Syndrome (RPLS) diagnosed. Resumption of bevacizumab may be considered in patients who have documented benefit from the agent, provided that RPLS was <u>mild</u> and has <u>completely</u> resolved clinically and radiographically within 2-4 weeks; decision to resume bevacizumab in these patients <u>must</u> be discussed with the study chair and approved by the sponsor.

→ → Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified ← ←

CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
Vascular	Thrombosis/thrombus/ Embolism Grade 1 or 2 (asymptomatic) Grade 3/asymptomatic Grade 4	Bevacizumab	No dose modifications Omit. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be omitted until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is ≥2 weeks, bevacizumab should be discontinued. Continue treatment with sorafenib. <ul style="list-style-type: none"> • The subject must have an in-range INR (usually 2-3 on a stable dose of warfarin (or other anticoagulant) prior to restarting bevacizumab treatment. • The patient must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation. • The patient must not have had evidence of tumor involving major blood vessels on any prior CT scan. Discontinue bevacizumab. Continue treatment with sorafenib.
	Grade 4 symptomatic Peripheral arterial ischemia Any grade		Discontinue all therapy. Patient goes to Event Monitoring.
	Visceral arterial ischemia (non-myocardial) Any grade		Discontinue all therapy. Patient goes to Event Monitoring.
All other non-hematologic adverse events (excluding alopecia)	Grade 1-2 Grade 3-4 (excludes nausea/vomiting that has not been pre-medicated)	Sorafenib	Continue at the same dose level. Omit treatment until resolved to ≤Grade 1, then resume treatment at the same dose level. If patient experiences a second Grade 3 adverse event, omit dose until adverse event is ≤Grade 1, then reduce dose by one level.
	Grade 3	Bevacizumab	Omit bevacizumab until recovery to ≤Grade 1
	Grade 4		Discontinue bevacizumab. Continue treatment with sorafenib.

→ → Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified ← ←				
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE	
AT TIME OF RETREATMENT				
Blood/Bone Marrow	Neutrophils/granulocytes (ANC/AGC) <1500/mm ³ OR Platelets Grade 3 <50,000/mm ³	Sorafenib	Hold dose*. Resume treatment when ANC ≥1500 and platelets ≥50,000 and decrease by one dose level. If no recovery after a 3-week delay, despite institution of all clinically appropriate symptomatic treatment, discontinue sorafenib. Patient goes to Event Monitoring. Dose may not be re-escalated after reduction for adverse event.	
Cardiac General	Hypertension	Sorafenib Bevacizumab	See Section 8.5 for management.	
	Other: Left ventricular systolic dysfunction Grade 3 Grade 4	Bevacizumab	Hold* until resolution to grade ≤1. Then resume treatment. If second recurrence, discontinue bevacizumab. Continue treatment with sorafenib. Discontinue bevacizumab. Continue treatment with sorafenib.	
Dermatology/ Skin	Rash: Hand/foot skin reaction (See Section 8.5) Rash: acne/acneiform Grade 2 and 3 Grade 4	Sorafenib	Hold dose*. <ul style="list-style-type: none"> • Re-evaluate at least weekly until adverse event resolved to ≤1 or tolerable grade 2. • Re-treat at a one dose level reduction • If toxicity returns to grade 3, or intolerable grade 2, despite dose reduction, hold dose. • Re-evaluate at least weekly until adverse event resolved to ≤1 or tolerable grade 2. • Re-treat at a one dose level reduction from the previous dose level • If adverse event persists >3 weeks, discontinue sorafenib. Patient goes to Event Monitoring. • Patients with grade 4 adverse events related to agent may be taken off sorafenib at investigator discretion. If adverse events related to agent, patient may be taken off treatment at investigator discretion. Patient goes to Event Monitoring.	
	Wound complication, non-infectious (dehiscence) ≥grade 2			Discontinue bevacizumab. Continue treatment with sorafenib.
	Gastrointestinal			Fistula, GI – abdominal Any grade
Gastrointestinal	Leak (including anastomotic), Esophagus, stomach, small bowel, large bowel, biliary Any grade	Bevacizumab	Discontinue bevacizumab. Continue treatment with sorafenib.	
	Obstruction, GI Grade 2		Hold* until resolution of obstruction. Then resume treatment.	
	Grade 3-4		Hold* until resolution. If surgery is necessary, patient may restart ≥28 days but ≤56 days following surgery and at investigator's discretion	
	Perforation, GI Any grade		Discontinue bevacizumab. Continue treatment with sorafenib.	

→ → Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified ← ←			
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
AT TIME OF RETREATMENT			
Hemorrhage/ Bleeding	Hemorrhage, non-CNS - Nasal, esophagus, stomach, small bowel, large bowel, biliary, retroperitoneum, peritoneal cavity Grade 3	Sorafenib Bevacizumab	Subjects who are also receiving full-dose anticoagulation will discontinue and go to Event Monitoring. Hold until all of the following criteria are met, then resume at same dose: <ul style="list-style-type: none"> • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Subjects who experience a repeat Grade 3 hemorrhagic event will discontinue treatment and go to Event Monitoring.
	Grade 4 Hemorrhage, CNS Grade 1		Discontinue treatment and go to Event Monitoring Subjects who are also receiving full-dose anticoagulation will discontinue treatment and go to Event Monitoring All other subjects hold until all of the following criteria are met: <ul style="list-style-type: none"> • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
	Grade ≥2		Discontinue treatment and go to Event Monitoring
	Bronchopulmonary Grade 2		Discontinue bevacizumab. Continue treatment with sorafenib.
Metabolic/ Laboratory	Proteinuria Grade 3 (≥3.5 g/24 hr)	Bevacizumab	Hold* until proteinuria improves to ≤grade 2. Then resume treatment. Discontinue bevacizumab. Continue treatment with sorafenib.
	Grade 4 (nephritic syndrome)		Discontinue bevacizumab. Continue treatment with sorafenib.
Neurology	CNS cerebrovascular ischemia Any grade	Bevacizumab	Discontinue bevacizumab. Continue treatment with sorafenib.
	Neurology, Other - Leukoencephalopathy syndrome (radiographic findings)		Hold* pending workup and management, including control of blood pressure. Discontinue bevacizumab if RPLS diagnosed and go to Event Monitoring continue treatment with sorafenib. Resumption of bevacizumab may be considered in patients who have documented benefit from the agent, provided that RPLS was <u>mild</u> and has <u>completely</u> resolved clinically and radiographically within 3 weeks;

→ → Use Common Terminology Criteria for Adverse Events (CTCAE) v3.0 unless otherwise specified ← ←

CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE	
AT TIME OF RETREATMENT				
Vascular	Thrombosis/ thrombus/embolism Grade 3 or 4 (asymptomatic thrombosis)	Bevacizumab	<p>Hold*. If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is ≥3 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met:</p> <ul style="list-style-type: none"> • The subject must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting bevacizumab treatment • The subject must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation <p>Discontinue bevacizumab- Continue treatment with sorafenib.</p>	
	Grade 3-4 (symptomatic thrombosis)			Discontinue bevacizumab. Continue treatment with sorafenib.
	Peripheral arterial ischemia Any grade			Discontinue bevacizumab. Continue treatment with sorafenib.
	Visceral arterial ischemia Any grade		Discontinue bevacizumab. Continue treatment with sorafenib.	
All other non-hematologic adverse events (excluding alopecia)	Grade 2-4 (excludes nausea/vomiting that has not been pre-medicated)	Sorafenib Bevacizumab	<p>Hold* responsible agent/agents until resolved to grade 0-1 adverse event, then decrease by one dose level. If no recovery after a 3-week delay, despite institution of all clinically appropriate symptomatic treatment, discontinue one or both agents according to attribution. If sorafenib OR both agents are discontinued, patient goes to Event Monitoring. If bevacizumab is discontinued, continue treatment with sorafenib.</p>	

* If any daily doses are missed, they will not be made up. The cycle length remains 14 days despite missed doses.

Pages 26-28: Sections 8.4 and 8.6 have been combined into one section and renumbered Section 8.5 “Suggested Dose Modifications for Sorafenib for Hand-Foot Skin Reaction.” The table for “Management of Hypertension” has been moved from Section 8.5 to new Section 8.4.

In Section 8.4 (Management of Hypertension) and Section 8.5 (Suggested Dose Modifications for Sorafenib for Hand-Foot Skin Reaction) the * footnote statement has been revised to provide clearer instructions, as follows:

* **If any doses are missed, they will not be made up.** Patients requiring a delay of >28 days should go off protocol therapy then go to Event Monitoring ~~and then off study.~~

Pages 26-27: In Section 8.4 (Management of Hypertension) the “Based on Interval Events” section has been revised. The last column in the last two rows has been corrected as follows:

Resume bevacizumab at same dose....go to Event Monitoring ~~and then off study.~~

~~Off protocol therapy~~ **Discontinue treatment and go** ~~and then~~ to Event Monitoring ~~and then off study.~~

* **If any doses are missed, they will not be made up.** Patients requiring a delay of >28 days should go off protocol therapy then go to Event Monitoring ~~and then off study.~~

Section 12.0 Descriptive Factors

Page 40: A new descriptive factor numbered 12.4 has been added to capture data on KRAS status.

KRAS status: Wild-type vs. mutated

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

Page 40: Section 13.4 has been corrected and reworded for clarification. More specific information has been added regarding the length of Event Monitoring.

Patients who experience intolerable adverse events **or who refuse further treatment** will go to Event Monitoring and will be followed **for up to a total of 2 years from registration** per Section 18.0. ~~Patients who refuse further treatment at any time will go off study.~~

Section 13.5 has been modified for clarification as follows:

Patients...registration **per Section 18.0.**

Section 15.0 Drug Information

Pages 48-52: The CAEPR for Bevacizumab, dated June 19, 2007, has been inserted in Section 15.14 at the request of NCI.

Section 16.0 Statistical Considerations

Page 80: Section 16.2 has been revised for an editorial correction, as follows:
Sample Size: The 2-stage study design to be utilized is fully described in Section 16. ~~721.~~ ...

Section 17.0 Pathology Considerations/Tissue Biospecimens

Page 86: Section 17.35 has been corrected.
Tissue specimens must be shipped ~~before or~~ ≤30 days following registration.

Section 18.0 Records and Data Collection Procedures

Pages 88-89: Section 18.1 has been revised as follows.

- Four columns for Event monitoring have been added.
- The IHC form is not required and has been deleted.
- In row 8, the Blood Pressure ~~and Pulse~~ form has been renamed as pulse is not collected.
- In row 12, the “~~Nadir~~/Adverse Event Form” has been renamed as nadirs are not being collected.
- Footnote 3 has been deleted since there is no Observation phase in this study. The superscripts within the table have been removed (Adverse Event Form). The subsequent footnote has been renumbered and the table corrected.
- A new footnote 4 has been added to provide information about Event Monitoring.

If patient is still alive 2 years after registration, no further follow-up is required.

Appendix I Consent Form

Page 2 of 18: The third paragraph has been revised for an editorial correction as follows:
You are being asked...your cancer has ~~not~~ gotten worse.

Page 4 of 18: The first two bullets in “During the study” have been revised as follows for clarification:

- You will take 1 sorafenib pill by mouth twice a day on days 1-5 and 8-12 of each cycle. ~~After the first cycle (2 weeks), if you have not had bad side effects from the sorafenib, you may start taking it daily.~~ You should swallow the tablets whole with about 8 ounces of water, taking one pill in the morning and one pill in the afternoon (12 hours apart). Sorafenib should be taken without food (1 hour before or 2 hours after eating). ~~Your doctor may increase your dose of sorafenib by having you take it days 1-4 if he or she feels it is safe to do so.~~
- You will be given bevacizumab through a vein in your arm over about 90 minutes on Day 1 of any every 2 week cycle. **If you tolerate the first treatment of bevacizumab well, the second may be given over only 60 minutes. If you tolerate the second treatment well, the rest of the treatments may be given over only 30 minutes.**

Page 6 of 18: Text has been removed for clarification in the paragraph located in the section “When I am finished taking the study treatment,” as follows:
When you are finished taking the study treatment, we will keep track of your medical condition for up to 2 years after the date you registered on the study. ~~You will not need to return for regularly scheduled visits once you stop taking treatment.~~

Pages 7-8:

The consent form risks for bevacizumab have been updated to conform with the CTEP CAEPR for bevacizumab version 1.2, dated June 19, 2007.

Likely risks of bevacizumab (*events that occur more than 20% of the time*)

- Nose bleeds
- High ~~or low~~ blood pressure (*'low' removed per CAEPR review*)
- **Rash** (*moved from 'Less Likely'*)
- **Headache** (*moved from 'Less Likely'*)
- **Soreness in mouth and throat** (*moved from 'Less Likely' and reworded*)
- ~~Loss of protein in the urine~~ (*moved to 'Less Likely' and reworded*)
- ~~Delay in wound healing or breakdown of a wound that had healed~~ (*moved to 'Rare' and revised*)
- ~~Chills, shivering~~ (*removed per CAEPR*)
- **Fatigue**

Less likely risks of bevacizumab (*events that occur less than or equal 5% to 20% of the time*)

- Blood clots in the ~~arteries or veins~~: **blood clots can occur in the veins** of the legs; **and the lungs** (pulmonary embolism) ~~or abdomen (mesenteric vein thrombosis or bowel ischemia) (could be life-threatening or fatal)~~ **or other organs. These events can be life-threatening.** (*revised and 'arteries' moved to separate risk per CAEPR review*)
- **Clots in the arteries, including stroke or heart attack. These conditions can be life-threatening or fatal.** (*separated from previous risk and expanded per CAEPR review*)
- Mild to moderate bleeding ~~from the lungs~~, in the tumor, stomach, or ~~colon intestines~~, **or other parts of the body.** (*revised per CAEPR review*)
- **Leakage of protein in the urine, which can rarely lead to damage to the kidney** (*moved from 'Likely' and reworded*)
- ~~Bowel perforation (an opening or hole in bowel that may lead to serious infection and/or death and may require surgery to repair)~~ (*moved to 'Rare' and revised*)
- ~~Fistula (an opening in the bowel that connects dying tumor to nearby intestines and may require surgery to repair)~~ (*removed per CAEPR review*)
- **Reactions associated with infusion of the bevacizumab: rash, chills, fever, stiffness** (*moved from 'Rare' and revised per CAEPR review*)
- **Infection in various organs and tissues including skin, abdomen, and the soft tissues around the rectum. In rare incidents, the infections can be serious and life-threatening** (*new per CAEPR review*)
- **Blockage or inflammation of the bowels** (*new per CAEPR review*)
- ~~Feeling sick to the stomach~~ • **Nonspecific stomach or intestinal symptoms: low appetite, heart burn, constipation, diarrhea, nausea, vomiting** (*expanded per CAEPR review*)

- ~~Sores or inflammation (swelling, redness) of the lining of the mouth and/or throat (moved to 'Likely' and reworded per CAEPR review)~~
- **Aches in various body parts, including abdomen, chest, joints, and tumor sites** (new per CAEPR review)
- **Shortness of breath** (moved from 'rare' per CAEPR review)
- ~~Coughing up blood (revised per CAEPR review)~~
- **Other: Hoarseness, watery eyes, stuffy nose, weight loss, dizziness, decrease in red blood cells that may be associated with fatigue** (new per CAEPR review)
- ~~Rash (moved to 'Likely' per CAEPR review)~~
- ~~Muscle pain or weakness (removed per CAEPR)~~
- ~~Voice change (removed per CAEPR)~~
- ~~Headaches (moved to 'Likely' per CAEPR review)~~
- ~~Fever (removed per CAEPR)~~
- ~~Lowered white blood cells (may make you more likely to get infections) (moved to 'rare' and reworded per CAEPR)~~

Rare but serious risks of bevacizumab (events that occur less than 2–35% of time)

- **Serious or fatal bleeding from the tumor, brain, gut, or the lungs, stomach or colon** (which may be life threatening or fatal) (revised per CAEPR review)
- ~~Blockage in the intestines (causes pain and may require surgery) (removed per CAEPR)~~
- ~~Inflammation of the colon (causes pain) (removed per CAEPR)~~
- ~~Very high blood pressure (including dangerously high blood pressure called hypertensive crisis) (removed per CAEPR)~~
- ~~Increase in heart rate (removed per CAEPR)~~
- ~~Congestive heart failure (CHF) which means weakening of the heart muscle leading to difficult breathing and tiredness (revised and combined with new 'heart problems' risk)~~
- ~~Heart attack (revised and combined with new 'heart problems' risk)~~
- ~~Build up of fluid in the sac around the heart, which may affect the heart's ability to pump (revised and combined with new 'heart problems' risk)~~
- **Heart problems (including irregular heartbeats, fluid collections surrounding the heart, heart attack or heart failure)** (combined from three previous risks and reworded per CAEPR review)
- ~~Nephrotic syndrome: kidney problems with loss of protein in urine, swelling of tissues, loss of albumin in blood (removed per CAEPR review)~~
- Stroke (cerebral vascular accident)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome (**less than 1%**): RPLS is a medical condition related to leakiness of blood vessels in the brain. RPLS can cause confusion, blindness, or vision changes, seizures and other symptoms, as well as changes in brain scans. ~~RPLS may~~

go away after bevacizumab is stopped. **This condition usually goes away but** in rare cases, it ~~may be~~ **is** potentially life-threatening and may have long-term effects on brain function.

- ~~Shortness of breath (moved to 'Less Likely; per CAEPR review)~~
- ~~Fluid leaking into the lungs (may be difficult to breathe) (removed per CAEPR)~~
- ~~Allergy that happens at the time the drug is given (fever, chills, rash, itching) (revised and moved to 'Less Likely' per CAEPR)~~
- ~~Chest pain (removed per CAEPR)~~
- ~~Inability to bear children — it is not known for how long, but this may last forever (removed per CAEPR)~~
- ~~Infection (removed per CAEPR)~~
- ~~Respiratory distress (removed per CAEPR)~~
- ~~Kidney failure (removed per CAEPR)~~
- ~~Abcess (removed per CAEPR)~~
- **Bowel perforation (an opening or hole in bowel) and bowel anastomotic dehiscence (a tear or hole in the gastrointestinal tract) that can lead to life-threatening complications and require surgery to repair (moved from 'Less Likely' and revised)**
- ~~Abnormal connection between different parts of the body such as the trachea and the esophagus (tracheoesophageal fistula) Fistula formation defect in the walls of luminal organs such as the nose, upper airways, lungs, esophagus, rectum, or vagina. Fistula formation may lead to life-threatening complications including serious infections, bleeding or dysfunction of the organs. (reworded and expanded per CAEPR review)~~
- **Delayed or poor wound healing after surgery (new per CAEPR review)**
- **Reversible changes in the liver functions (reworded and moved from '...side effects...reported...not known if these side effects were related' per CAEPR review)**
- **Severe allergic reactions that result in difficulty breathing or drop in blood pressure (new per CAEPR review)**
- **Increased rate of low white cell counts when combined with chemotherapies, which may lead to increased incidence of serious and fatal infections. (moved from 'Less Likely' and revised per CAEPR review)**
- **Abnormal changes in the lungs that may cause difficulty breathing or respiratory failure (new per CAEPR review)**
- **Sudden death (new per CAEPR review)**

The following side effects have been reported for patients taking part in other bevacizumab research studies. It is not known if these side effects were related to the bevacizumab: *(removed per CAEPR review)*

- ~~Decrease in blood salts such as potassium or phosphorous~~ *(removed per CAEPR review)*
- Increase in blood sugar *(removed per CAEPR review)*
- ~~Abnormalities in liver function tests~~ *(reworded and moved to 'rare' per CAEPR review)*
- Liver damage *(removed per CAEPR review)*
- Runny or stuffy nose *(moved to 'less likely' and revised per CAEPR review)*
- Abnormal heart rhythm that may be life threatening *(reworded and moved to 'rare' per CAEPR review)*
- ~~Weakness and floppiness of the walls of the windpipe (trachea), which could cause difficulty breathing~~ *(removed per CAEPR review)*
- ~~Nasal septum perforation (a tear in the tissue in your nose between the nostrils)~~ *(removed per CAEPR review)*
- Hypertensive encephalopathy (a condition related to a severe rise in your blood pressure, which can lead to confusion, swelling in the brain, and seizures). *(removed per CAEPR review)*

Pages 8-10: The risks for sorafenib have been updated to conform with the CTEP CAEPR version 2.2 dated December 17, 2008.

Likely risks of sorafenib (events occurring greater than 20% of the time)

- Skin rash *(duplicate of the fourth bullet)*
- Fatigue or tiredness
- Inflammation of the skin on the palms of the hands or soles of the feet
- Rash/flaking or shedding of outer layer of skin, skin peeling
- Anorexia (loss of appetite, not feeling hungry)
- ~~Pruritus (itching)~~ *(Removed per CAEPR review)*
- ~~Drop in the white blood cell count which could be connected with an increased risk of infections~~ *(Removed per CAEPR review)*
- Low blood phosphate level
- Low levels of a blood protein called albumin
- Hair loss
- Loose stools (diarrhea)
- Upset stomach/ache/feeling sick to your stomach (nausea)
- ~~Possible increase in pancreas associated enzymes of amylase and lipase~~ *(Removed per CAEPR review)*

Less likely risks of sorafenib (events occurring less than or equal to 20% of the time)

- Allergic reactions, also known as hypersensitivity reactions (**fever, chills, rash, itching**) (*expanded per CAEPR review*)
- Decrease in a red blood cell protein that carries oxygen in the body
- ~~Drop in the red blood cells in the blood (anemia), which may cause tiredness and shortness of breath~~ (*Removed per CAEPR review*)
- Decreased total number of white blood cells (**leukopenia**) (*expanded per CAEPR review*)
- Decreased number of a type of white blood cell (**neutropenia**) (*expanded per CAEPR review*)
- Infection with or without a low white blood cell count
- Decreased number of blood cells that help to clot blood
- ~~Reduced neutrophils in blood (neutropenia) which may be life-threatening or fatal~~ (*Combined with bullet number 4*)
- Formation or presence of a blood clot inside a blood vessel
- High blood pressure
- Difficulty sleeping or falling asleep
- ~~Depression~~ (*Removed per CAEPR review*)
- ~~Numbness or tingling in the nerves of the hands or feet~~ (*Removed per CAEPR review*)
- Nerve damage causing numbness, tingling, or burning
- ~~ringing in the ears~~ (*Removed per CAEPR review*)
- Hoarseness, laryngitis, loss or change in voice
- Constipation (can't pass or trouble passing stool)
- ~~Mouth sores~~ (*Removed per CAEPR review*)
- ~~Trouble or difficulty swallowing~~ (*Removed per CAEPR review*)
- Dry skin
- ~~Peeling rash~~ (*Removed per CAEPR review*)
- Itching
- ~~Aene~~ (*Removed per CAEPR review*)
- **Pain such as joint, muscles, headache, legs, chest, back pain, inflammation of the joints** (*Revised and combined with next five risks per CAEPR review*)
- ~~Muscle pain~~ (*combined with previous risk*)
- ~~Back pain~~ (*combined with previous risk*)
- ~~Chest pain~~ (*combined with previous risk*)
- ~~Leg pain~~ (*combined with previous risk*)
- ~~Headache~~ (*combined with previous risk*)
- Pain (**non-specific site**) (*expanded per CAEPR review*)
- Swelling of arms and legs

- Cough
- Shortness of breath
- Painful inflammation and ulceration of the lining of the digestive tract
- Bleeding in the digestive tract
- Bleeding in the respiratory tract.
- Bleeding in the reproductive organs or urinary system (such as the bladder or kidney)
- ~~Trouble (difficulty) in initiating or maintaining an erection~~ (*Removed per CAEPR review*)
- ~~Weakness~~ (*Removed per CAEPR review*)
- Dizziness
- Fever (pyrexia)
- Fever with a dangerously low white blood cell count
- ~~Flu like symptoms (fever, aching joints, etc.)~~ (*Removed per CAEPR review*)
- Vomiting
- Weight loss
- Low blood calcium level
- High blood potassium level
- Low blood potassium level
- Low blood sodium level
- High blood sugar
- Low blood sugar
- Increased liver enzymes
- Abnormal liver or bone enzyme level
- Abnormal digestive enzyme level
- Abnormal level of fat-digesting enzyme
- High blood levels of a liver pigment indicative or abnormal liver function
- ~~Decrease in kidney function as measured by blood tests~~ (*Removed per CAEPR review*)
- Kidney failure
- ~~Excessive amounts of air and gases in the stomach~~ (*Removed per CAEPR review*)
- ~~Flushing of the skin~~ (*Removed per CAEPR review*)
- ~~Persistent runny nose~~ (*Removed per CAEPR review*)
- ~~Heartburn~~ (*Removed per CAEPR review*)
- ~~Enlargement of breast tissue in males~~ (*Removed per CAEPR review*)

Rare but serious risks of sorafenib (events occurring less than 3% of the time)

- ~~Decrease in thyroid function, with symptoms of tiredness, sensitivity to cold, and slow metabolic rate (Removed per CAEPR review)~~
- ~~Yellow skin (jaundice) and increases in certain blood tests indicating temporary damage to the liver (Removed per CAEPR review)~~
- Syndrome caused by high blood pressure characterized by headache, confusion, seizures, and vision loss associated with imaging findings
- Decreased blood supply to the heart
- Decreased ability of the heart to pump blood
- Decrease in heart function or heart failure which may be life-threatening or cause death (fatal), heart attack
- ~~Severe increases in blood pressure which may be life-threatening or cause death (fatal) (Removed per CAEPR review)~~
- A hole somewhere in the intestinal tract from the esophagus to the anus (e.g., bowel perforation) which could be life threatening or cause death (fatal)
- ~~Severe life threatening rash (Removed per CAEPR review)~~
- ~~Loss of body fluids (dehydration) (Removed per CAEPR review)~~
- Bleeding into the brain or spinal cord
- ~~Prolonged blood clotting times (Removed per CAEPR review)~~
- ~~If you are taking a blood thinner such as Coumadin or Warfarin, sorafenib may change the amount of blood thinner in your blood. If this happens, you may have unexpected bleeding. Your doctor may need to do some blood tests to check the level of blood thinner in your blood. (Removed per CAEPR review)~~

~~With the combination of sorafenib and cytotoxic agents, myelosuppression (or decreased bone marrow function) has been observed with reported decrease of all blood cells (including red, white cells, and platelets leading respectively to tiredness/pale skin, infection and reduced blood clotting), febrile Neutropenia and neutropenic sepsis (reduction in the number of white blood cells leading to fever and infection). Such events may have a life-threatening or fatal outcome. (Removed per CAEPR review)~~