

North Central Cancer Treatment Group

**N0745: Phase I/II Randomized Trial of Sorafenib and Bevacizumab as First-Line Therapy in Patients with Locally Advanced or Metastatic Hepatocellular Carcinoma**

Addendum 9 – February 3, 2012

**Summary**

This addendum is in response to a Request for Amendment (RA) from the National Cancer Institute (NCI) dated December 29, 2011 concerning Sorafenib. The Drug Information section and the Phase II consent form have been updated accordingly.

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

**Title page** Addendum 9 has been added and the NCI version date has been updated.

**Section 15.0 Drug Information**

Page 59-62: Due to the receipt of the RA for Sorafenib, Section 15.11 has been replaced in its entirety.

**Appendices IA & IB Consent Forms**

Page 8: Due to the receipt of the RA for Sorafenib, the “Rare but serious” section of the consent forms have been updated as follows:

**Rare but serious:**

- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Heart attack caused by a blockage of a blood vessel supplying part of the heart
- **Gastrointestinal perforation: A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair** ~~Hole in a part(s) of the digestive tract~~ (*wording expanded*)
- Serious potentially life-threatening type of allergic reaction that may cause breathing difficulty, dizziness, low blood pressure, and loss of consciousness
- Bleeding in the brain
- Collection of symptoms including headache, confusion, seizures, and vision loss associated with imaging findings (MRI, CT Scan)
- Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue
- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer)

## North Central Cancer Treatment Group

**Phase I/II Randomized Trial of Sorafenib and Bevacizumab as First-Line Therapy  
in Patients with Locally Advanced or Metastatic Hepatocellular Carcinoma**

*For any communications regarding this protocol,  
please call the protocol resource person on the following page.*

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**Drug Availability**

**DCTD or DCP Supplied Investigational Agents:** None

**Commercial Agents:** Sorafenib, bevacizumab

**Drug Company Funded:** Bevacizumab (funded by Bayer, Inc.)

**Available through the REACH Program:** Sorafenib

**IND# if investigational:** IND exempt

**\*Investigator having NCI responsibility for this protocol**

✓Study contributor(s) not responsible for patient care.

<b>Document History</b>	<b>(Effective Date)</b>	<b>Document History</b>	<b>(Effective Date)</b>
Activation	April 10, 2009	Addendum 6	April 15, 2011
Addendum 1	July 3, 2009	Update 1	April 15, 2011
Addendum 2	January 15, 2010	Addendum 7	July 8, 2011
Addendum 3	October 8, 2010	Addendum 8	November 4, 2011
Addendum 4	October 8, 2010	Addendum 9	February 3, 2012
Addendum 5	November 19, 2010		

**Study (a) Date Activated****Participants**

Entire NCCTG April 10, 2009

NCI Version Date: January 23, 2012

Potential Drug Interactions: Sorafenib is metabolized by the P450 CYP3A enzyme and has been shown in preclinical studies to inhibit multiple CYP isoforms. Therefore, it is possible that sorafenib may interact with drugs that are metabolized by the P450 CYP isoenzymes or with drugs that inhibit CYP 3A. Close monitoring is recommended for patients taking agents with narrow therapeutic indices and metabolized by the liver, such as warfarin, phenytoin, quinidine, carbamazepine, phenobarbital, cyclosporine, and digoxin. Additionally, sorafenib is 97% to 99% protein bound; however, no drug interactions have been reported in studies, thus far.

Add 3

## 15.11 Reported Adverse Events and Potential Risks

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/aeguidelines.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf) for further clarification. *Frequency is provided based on 2157 patients.* Below is the CAEPR for sorafenib (BAY 43-9006).

**NOTE:** Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, December 21, 2011<sup>1</sup>

Adverse Events with Possible Relationship to Sorafenib (BAY 43-9006) (CTCAE 4.0 Term) [n= 2157]			Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAE)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		<b><i>Anemia (Gr 3)</i></b>
	Febrile neutropenia		
CARDIAC DISORDERS			
		Acute coronary syndrome	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
GASTROINTESTINAL DISORDERS			
Abdominal pain			<b><i>Abdominal pain (Gr 3)</i></b>
	Anal mucositis		
	Ascites		
	Constipation		<b><i>Constipation (Gr 2)</i></b>
Diarrhea			<b><i>Diarrhea (Gr 3)</i></b>
	Gastrointestinal hemorrhage <sup>2</sup>		<b><i>Gastrointestinal hemorrhage<sup>2</sup></i></b>

			<b>(Gr 3)</b>
		Gastrointestinal perforation <sup>3</sup>	
	Mucositis oral		
Nausea			<b>Nausea (Gr 3)</b>
	Rectal mucositis		
	Small intestinal mucositis		
	Vomiting		<b>Vomiting (Gr 3)</b>
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>			
	Edema limbs		
Fatigue			<b>Fatigue (Gr 3)</b>
	Fever		<b>Fever (Gr 2)</b>
	Non-cardiac chest pain		
<b>IMMUNE SYSTEM DISORDERS</b>			
		Anaphylaxis	
<b>INFECTIONS AND INFESTATIONS</b>			
	Infection <sup>4</sup>		
<b>INVESTIGATIONS</b>			
	Activated partial thromboplastin time prolonged		<b>Activated partial thromboplastin time prolonged (Gr 2)</b>
Alanine aminotransferase increased			<b>Alanine aminotransferase increased (Gr 3)</b>
Alkaline phosphatase increased			<b>Alkaline phosphatase increased (Gr 3)</b>
Aspartate aminotransferase increased			<b>Aspartate aminotransferase increased (Gr 3)</b>
Blood bilirubin increased			<b>Blood bilirubin increased (Gr 3)</b>
	Cholesterol high		
Creatinine increased			<b>Creatinine increased (Gr 3)</b>
	GGT increased		
INR increased			<b>INR increased (Gr 2)</b>
	Investigations - Other (bicarbonate, serum-low)		
Lipase increased			<b>Lipase increased (Gr 3)</b>
Lymphocyte count decreased			<b>Lymphocyte count decreased (Gr 3)</b>
	Neutrophil count decreased		<b>Neutrophil count decreased (Gr 4)</b>
Platelet count decreased			<b>Platelet count decreased (Gr 4)</b>
Serum amylase increased			<b>Serum amylase increased (Gr 3)</b>
Weight loss			<b>Weight loss (Gr 2)</b>
White blood cell decreased			<b>White blood cell decreased (Gr 4)</b>
<b>METABOLISM AND NUTRITION DISORDERS</b>			
Anorexia			<b>Anorexia (Gr 3)</b>
	Hypercalcemia		
Hyperglycemia			<b>Hyperglycemia (Gr 3)</b>
	Hyperkalemia		<b>Hyperkalemia (Gr 3)</b>
	Hypertremia		
	Hyperuricemia		
Hypoalbuminemia			<b>Hypoalbuminemia (Gr 3)</b>
Hypocalcemia			<b>Hypocalcemia (Gr 3)</b>
	Hypoglycemia		<b>Hypoglycemia (Gr2)</b>
	Hypokalemia		<b>Hypokalemia (Gr 3)</b>

Hyponatremia			<b>Hyponatremia (Gr 3)</b>
Hypophosphatemia			<b>Hypophosphatemia (Gr 3)</b>
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>			
	Arthralgia		<b>Arthralgia (Gr 3)</b>
	Back pain		<b>Back pain (Gr 3)</b>
	Bone pain		
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		
	Myalgia		
	Pain in extremity		<b>Pain in extremity (Gr 3)</b>
<b>NERVOUS SYSTEM DISORDERS</b>			
	Dizziness		
	Headache		<b>Headache (Gr 3)</b>
		Intracranial hemorrhage	
	Peripheral sensory neuropathy		
		Reversible posterior leukoencephalopathy syndrome	
<b>PSYCHIATRIC DISORDERS</b>			
	Insomnia		
<b>RENAL AND URINARY DISORDERS</b>			
	Acute kidney injury		
	Hematuria		
	Renal hemorrhage		
<b>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</b>			
	Hematosalpinx		
	Ovarian hemorrhage		
	Prostatic hemorrhage		
	Spermatic cord hemorrhage		
	Testicular hemorrhage		
	Uterine hemorrhage		
	Vaginal hemorrhage		
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>			
	Bronchopulmonary hemorrhage		
	Cough		<b>Cough (Gr 2)</b>
	Dyspnea		<b>Dyspnea (Gr 3)</b>
	Epistaxis		
	Laryngeal mucositis		
	Pharyngeal mucositis		
	Tracheal mucositis		
	Voice alteration		
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>			
Alopecia			<b>Alopecia (Gr 2)</b>
	Dry skin		<b>Dry skin (Gr 2)</b>
		Erythema multiforme	
Palmar-plantar erythrodysesthesia syndrome			<b>Palmar-plantar erythrodysesthesia syndrome (Gr 3)</b>

	Pruritus		<b>Pruritus (Gr 3)</b>
Rash maculo-papular			<b>Rash maculo-papular (Gr 3)</b>
		Stevens-Johnson syndrome	
<b>VASCULAR DISORDERS</b>			
	Hypertension		<b>Hypertension (Gr 3)</b>
	Thromboembolic event		

<sup>1</sup>This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV). Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

<sup>2</sup>Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

<sup>3</sup>Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

<sup>4</sup>Includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

**Also reported on sorafenib (BAY 43-9006) trials but with the relationship to sorafenib (BAY 43-9006) still undetermined:**

**CARDIAC DISORDERS** - Atrial fibrillation; Atrial flutter; Chest pain - cardiac; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia

**EAR AND LABYRINTH DISORDERS** - Tinnitus

**ENDOCRINE DISORDERS** - Hyperthyroidism; Hypothyroidism

**EYE DISORDERS** - Blurred vision; Cataract; Extraocular muscle paresis

**GASTROINTESTINAL DISORDERS** - Abdominal distension; Dyspepsia; Dysphagia; Flatulence; Ileus; Pancreatitis; Rectal fistula; Small intestinal obstruction

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Chills; Edema face; Flu like symptoms; Pain

**IMMUNE SYSTEM DISORDERS** - Allergic reaction

**INVESTIGATIONS** - Fibrinogen decreased

**METABOLISM AND NUTRITION DISORDERS** - Dehydration; Hypermagnesemia; Hypertriglyceridemia; Hypomagnesemia

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Arthritis; Generalized muscle weakness

**NERVOUS SYSTEM DISORDERS** - Dysgeusia; Encephalopathy; Ischemia cerebrovascular; Memory impairment; Syncope

**PSYCHIATRIC DISORDERS** - Confusion; Depression

**RENAL AND URINARY DISORDERS** - Proteinuria

**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Erectile dysfunction

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Hypoxia; Pleural effusion; Pneumonitis; Pneumothorax

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Hyperhidrosis; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (non-life threatening squamous cell carcinoma of skin: keratoacanthoma type); Skin hypopigmentation

**VASCULAR DISORDERS** - Flushing; Hypotension; Vasculitis

**Note:** Sorafenib (BAY 43-9006) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

**NCI Informed Consent Template for Cancer Treatment Trials  
(English Language)**

**\*NOTES FOR INFORMED CONSENT AUTHORS: [NOTE: Delete this section when sending to sites]**

- Model text *suggested* for use in the informed consent form is in **bold**. It is *recommended* that the **bold** text be retained when adapting the template to a specific protocol.
- Instructions and examples for informed consent authors are in *[italics]*. *Remember to remove these items before finalizing your consent form.*
- A blank line, \_\_\_\_\_, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term ‘study doctor’ has been used throughout the template because the Principal Investigator of a cancer treatment trial is a physician. If this template is used for a trial where the Principal Investigator is not a physician, another appropriate term should be used instead of ‘study doctor’.
- The template date in the header is for reference to this template only and should not be included in the informed consent form given to the prospective research participant.
- The language should be written in 6<sup>th</sup> grade language. When proofreading the consent form, ask yourself if an average 6<sup>th</sup> grader would understand the study after reading this form.

**\*NOTES FOR LOCAL INVESTIGATORS: [NOTE: Retain this section and asterisk item below for NCCTG model consents]**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is <http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/>
- A blank line, \_\_\_\_\_, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer... What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at <https://cissecure.nci.nih.gov/ncipubs/> or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*\*These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.*

**N0745, Phase I/II Randomized Trial of Sorafenib and Bevacizumab as  
First-Line Therapy in Patients with Locally Advanced or  
Metastatic Hepatocellular Carcinoma**

**Phase I Informed Consent**

*This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.*

**This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.**

**You are being asked to take part in this research study because you have locally advanced or metastatic (spread to other parts of the body) hepatocellular carcinoma.**

**Why is this research study being done?**

The purpose of this research study is to find out if the combination of the two drugs, sorafenib and bevacizumab, is more effective than sorafenib alone. Both of the drugs have been shown to be active in cancers that are otherwise resistant to treatment. Sorafenib is approved by the Food and Drug Administration (FDA) for patients with advanced hepatocellular cancer, although bevacizumab has not yet been shown to have a definitive clinical benefit in this disease. Sorafenib is considered standard of care for this disease. We want to evaluate what effect it will have on your cancer if these two drugs are given together.

The Phase I portion of this study will help determine what doses of bevacizumab and sorafenib will be most effective and still have the most tolerable side effects.

**How many people will take part in the research study?**

Add 1 Up to 21 patients could be enrolled in Phase I (Group A) of the research study, although it is expected that only about 6-12 patients will actually be enrolled in this phase. About 97 patients will take part in the overall study.

## What will happen if I take part in this research study?

### Before you begin the study....

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A physical history and exam, including your weight, height, blood pressure, and tests to rate how well you perform activities of daily living.
- Routine blood tests. About 2 teaspoons of blood will be drawn.
- Chest x-ray.
- Measurement of your tumor by either CT scan or MRI (scans that take pictures of your body's organs).
- Alpha-fetoprotein test (a tumor marker test).
- Use of a scope placed down your throat (esophagoduodenoscopy) to check for enlarged blood vessels, if needed.
- Urine test for protein in your urine.
- Measurement of how long it takes your blood to clot (prothrombin time) if you are taking warfarin. This needs to be done within 21 days before registration.
- An electrocardiogram of your heart (a test that checks for problems with the electrical activity of your heart)
- A MUGA scan or echocardiogram (Echo) to make sure that your heart is healthy enough for you to take the study drugs, if needed. A MUGA scan is a nuclear scan that evaluates the pumping function of the heart. An echocardiogram is a type of ultrasound that helps diagnose heart disease.
- A pregnancy test within 7 days before starting the study, if you are a woman of childbearing age.
- Blood samples for research.

You will be required to give blood (mandatory) for additional research studies. More information about these research studies is given starting on page 12 of this consent form.

## During the study....

### A cycle is 4 weeks long.

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures before you start treatment. They are part of regular cancer care.

- Add 1      Weekly:
- Blood pressure (weekly for first 8 weeks then every 2 weeks after that). You may have your blood pressure taken in your local doctor's office or take it yourself on a blood pressure machine in, for example, a local drug store.
  - Measurement of how long it takes your blood to clot (prothrombin time) if you are taking warfarin (weekly for the first 4 weeks then as instructed by your doctor).

- Add 1      Every 4 weeks (before each new cycle):
- A physical history and exam, including your weight and tests to rate how well you perform activities of daily living.
  - Routine blood tests. About 2 teaspoons of blood will be drawn.
  - Alpha-fetoprotein test (a tumor marker test). This is repeated only if it was high at the time you started this study.
  - Research blood samples will be taken at the same time as the routine blood tests above prior to each cycle (up through cycle 7) and on day 15 of the first cycle. An additional sample, not taken at the same time as routine blood tests, will be taken on day 3 ( $\pm$  24 hours) of cycle 1. Each sample will require 8-10 teaspoonfuls of blood. More information on research bloods and tissue is available starting on page 13.

- Add 1,2      Every 8 weeks:
- EKG
  - A MUGA scan or echocardiogram, if needed.
  - Urine test for protein in your urine while you are being treated with bevacizumab

- Add 1      Other procedures:
- A tissue sample is required at the beginning of the study to confirm your diagnosis. We ask that you also let us use this tissue sample for additional research studies. Allowing us to use this tissue for research studies is not required, but we strongly encourage you to give us permission to use them for this purpose. More information about these research studies is given starting on page 12 of this consent form.
  - CT or MRI for tumor measurement at 8 weeks and then every 8 weeks after that unless your physician feels it is needed more often to confirm a response.
  - Chest x-ray may be done if your physician feels it is needed. A chest x-ray will not be needed if you have a chest CT.
  - You will be given a Blood Pressure Diary to record your blood pressure. Bring the diary with you at each cycle of treatment.
  - You will be given a Patient Medication Diary for Sorafenib. You will complete the diary and record each time you take the sorafenib. Bring the diary with you at each cycle of treatment and you will be given a new one.

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- An assessment of side effects you may be having.

**Treatment in Phase I**

You will be enrolled in Phase I of this study. A total of 6-12 patients will be in the Phase I portion of this study so that we can determine the safest and most effective dose levels for this combination of drugs.

Add 1

Sorafenib is a tablet that can be taken by mouth. How much you take and how often you take it will depend on what dose level you are given. It should be taken with at least 8 ounces of water. It should be taken without food (at least 1 hour before or 2 hours after meals). Do not take sorafenib with grapefruit juice. You will be asked to fill out a Patient Medication Diary and record daily when you take the sorafenib. You should bring the medication diary with you when you come back for a visit or have treatment. You will be given a new pill diary for each cycle of treatment .

Bevacizumab is given through a vein in your arm (intravenously) over 90 minutes. If well-tolerated, the time for administration may be lowered to 60 minutes the next time you get it. If still well-tolerated, the time may be lowered to 30 minutes after that. You will be given bevacizumab on Day 1 and Day 15 of every cycle.

Three (3) patients will be enrolled and started on treatment at the starting dose level. These patients will be observed for side effects for at least 1 cycle (4 weeks) before any other patients are enrolled.

- If side effects experienced by these patients are acceptable, another 3 patients will be enrolled at the same dose level.
- If the first group has side effects that are not tolerable, their dose level will be lowered. Another 3 patients will be enrolled at the lower dose level. All 6 patients will be treated at the new dose level and observed for side effects for another cycle.

Side effects will be evaluated every 4 weeks and a new group of 3 patients enrolled at that time. Up to 12 patients may be enrolled in Phase I. When a safe and effective dose level is reached, Phase I patients will continue on treatment at that dose level.

If your cancer gets worse and/or spreads, you will stop treatment. If at any time while you are on the study you or your doctor feel that the side effects of the drugs are too bad, the dose level of the study drugs you are taking will be changed to lessen the side effects. If the side effects are still too bad, you or your doctor may decide to stop treatment and go off the study.

**When I am finished taking the study drugs....**

Add 3

If your cancer gets worse, if you have unacceptable side effects, or if you decide you no longer want to take part in this study, you will stop taking the study drugs. We will follow you for 3 years from the date of registration, but you will no longer take the study treatment or follow the study treatment schedule. Your doctor will talk to you about other treatment options.

## How long will I be in the research study?

You will be asked to take the study treatment until your cancer gets worse, you have bad side effects, or you and/or your doctor think you should stop. After you are finished taking the study treatment, the study doctor will ask you to visit the office for follow-up exams for at least every 3 months for 1 year after the date you were registered on the study year and then every 6 months for 2 more years.

## Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

## What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the sorafenib or bevacizumab. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

### **Sorafenib**

#### **Likely:**

- Belly pain
- Diarrhea
- Nausea or the urge to vomit
- Fatigue or tiredness
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)
- Increased INR (measure of the ability of the blood to clot properly) which increases the risk of bleeding
- Increased blood level of fat-digesting enzyme (lipase)
- Decreased number of a type of white blood cell (lymphocyte)
- Decreased number of a type of blood cell that help to clot blood (platelet)

- Increased blood level of a digestive enzyme level (amylase)
- Weight loss
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Increased blood sugar level
- Decreased levels of a blood protein called albumin
- Decreased blood level of calcium
- Decreased blood level of sodium
- Decreased blood level of phosphate
- Hair loss
- Swelling and redness of the skin on the palms of the hands and soles of the feet
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)

Add  
1,3**Less likely:**

- Lack of enough red blood cells (anemia)
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Irritation or sores in the lining of the anus
- Fluid collection in the abdomen
- Constipation
- Bleeding in some organ(s) of the digestive tract
- Irritation or sores in the lining of the mouth
- Irritation or sores in the lining of the rectum
- Irritation or sores in the lining of the small bowel
- Vomiting
- Swelling of the extremities (arms and/or legs)
- Fever
- Chest pain not heart-related
- Infection
- Test that shows a problem in blood clotting
- Increased blood level of cholesterol
- Increased blood level of a liver enzyme (GGT)
- Decreased blood level of carbon dioxide
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Increased blood level of calcium
- Increased blood level of potassium
- Increased blood level of sodium
- Increased blood level of uric acid, a waste material from food digestion
- Decreased blood sugar level
- Decreased blood level of potassium
- Joint pain
- Back pain
- Bone pain
- Muscle spasms
- Muscle pain
- Leg and/or arm pain
- Dizziness (or sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking)
- Headache or head pain
- Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning
- Difficulty sleeping or falling asleep
- Sudden or traumatic injury to the kidney
- Blood in the urine
- Bleeding in the kidney

- Presence of blood in a fallopian tube (tube between ovary to uterus [womb])
- Bleeding in the ovary
- Bleeding in the prostate
- Bleeding in the spermatic cord (a structure resembling a cord that suspends the testis within the scrotum and contains the vas deferens [the tube that carries sperm] and other vessels and nerves)
- Bleeding in the testis
- Bleeding in the uterus (womb)
- Bleeding in the vagina
- Bleeding in the respiratory tract
- Cough
- Shortness of breath
- Nose bleed
- Irritation or sores in the lining of the voice box
- Irritation or sores in the lining of the throat
- Irritation or sores in the lining of the windpipe
- Voice change
- Dry skin
- Itching
- High blood pressure
- Formation of a blood clot that breaks loose and is carried by the blood stream to plug another

Add  
1,3,9**Rare but serious:**

- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Heart attack caused by a blockage of a blood vessel supplying part of the heart
- Gastrointestinal perforation: A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
- Serious potentially life-threatening type of allergic reaction that may cause breathing difficulty, dizziness, low blood pressure, and loss of consciousness
- Bleeding in the brain
- Collection of symptoms including headache, confusion, seizures, and vision loss associated with imaging findings (MRI, CT Scan)
- Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue
- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer)

Add 1 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.

Add 1 With the combination of sorafenib and cytotoxic chemotherapy 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

**Bevacizumab**Add  
1,3**Likely:**

- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Headache or head pain
- High blood pressure

Add  
1,3**Less Likely:**

- Lack of enough red blood cells (anemia)
- Fast heartbeat usually originating in an area located above the ventricles
- Feeling of spinning or whirling
- Belly pain
- Inflammation (swelling and redness) of the large bowel (colon)
- Constipation
- Heartburn
- Bleeding in some organ(s) of the digestive tract
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.
- Irritation or sores in the lining of the mouth
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Chest pain not heart-related
- Pain
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Infection
- Infection (collection of pus) around the rectum
- Premature opening of a wound along surgical stitches after surgery
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Weight loss
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Joint pain
- Abnormal changes in the growth plate that may affect the growth of long bones in very young children. This side effect appeared to be reversible after the treatment was stopped but has not been assessed with long-term use of the bevacizumab drug.
- Muscle pain
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Fainting
- Sudden decrease of kidney function
- Blood in the urine
- More protein leaking into the urine than usual, often a sign of kidney disease
- Bleeding in the vagina

- Cough
- Shortness of breath
- Nose bleed
- Hoarseness
- Stuffy nose
- Itching
- Skin rash
- Hives
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

Add  
1,3**Rare but Serious:**

- Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure
- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
- Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Heart attack caused by a blockage or decreased blood supply to the heart
- Irregular heartbeat resulting from an abnormality in the one of the lower chambers of the heart (ventricle)
- Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
- Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue
- Gastrointestinal perforation : A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
- Sore (ulcer) somewhere in the digestive tract
- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Leakage from stomach due to breakdown of an anastomosis (surgical connection of two separate body structures)
- Bleeding in the brain
- Stroke caused by decreased blood flow to the brain
- Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI imaging findings (RPLS)
- A condition in which the kidneys leak a large amount of protein into the urine that can cause complications including swelling and kidney failure
- Kidney failure
- Abnormal hole between part of the urinary system and another organ or tissue
- Abnormal hole between the vagina and another organ or tissue
- Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs
- Bleeding from the lungs
- Hole in the wall that separates the nostrils of the nose

- Abnormal hole between the breathing tube (windpipe) and the tube that goes from mouth to stomach through which food passes (esophagus). This is life-threatening and potentially fatal.
- Blockage or narrowing of a blood vessel (artery) that can cause damage or loss of function including a heart attack or stroke

Add 2

**Reproductive risks:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. It is important you understand that you need to use birth control while on this study and after the end of treatment.

- When getting treated with sorafenib alone, men and women should use adequate birth control for at least 2 weeks after the last administration of sorafenib.
- When getting **both** sorafenib and bevacizumab, men and women should use adequate birth control for at least 6 months after the last administration of bevacizumab.

Women should not breastfeed a baby while on this study or:

- When getting treated with sorafenib alone, women should not breastfeed for at least 2 weeks after the last administration of sorafenib
- When getting **both** sorafenib and bevacizumab, women should not breastfeed for at least 6 months after the last administration of bevacizumab.

Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

**For more information about risks and side effects, ask your study doctor.**

### **Are there benefits to taking part in the research study?**

Taking part in this study may or may not make your health better. While doctors hope the combination of sorafenib and bevacizumab will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about these study drugs as a treatment for cancer. This information could help future cancer patients.

### **What other choices do I have if I do not take part in this research study?**

You do not have to be in this study to receive treatment for your cancer. Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

### **Will my medical information be kept private?**

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be

given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- North Central Cancer Treatment Group (NCCTG), local Institutional Review Board (IRB)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Bayer Pharmaceuticals and Genentech/Roche, the drug companies that are supplying sorafenib and bevacizumab for this study.

*[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]*

## **What are the costs of taking part in this research study?**

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Add 1

Bayer Pharmaceuticals is supplying bevacizumab for this research study at no cost to you while you are taking part in this study. Sorafenib is commercially available and is not supplied, but Bayer has a program called REACH<sup>®</sup> to help you to help you get insurance coverage, Medicare Part D coverage, or financial assistance to pay for the drug. Study staff will provide you with more information on this program. You will need to fill out an enrollment form and talk to REACH counselors who will help you find coverage. You or your health plan may need to pay for costs of the supplies and personnel who give you the bevacizumab and/or sorafenib.

If you should need to take the study agents much longer than usual, the stock of free study agent that has been supplied could run out. If the free supply runs out, your study doctor will discuss with you how to get more drug from the manufacturer. You may be asked to pay for it.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

## **What happens if I am injured because I took part in this research study?**

It is important that you tell your study doctor, \_\_\_\_\_ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at \_\_\_\_\_ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

## What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

## Who can answer my questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor \_\_\_\_\_ [name(s)] at \_\_\_\_\_ [telephone number].

For questions about your rights while taking part in this study, call the \_\_\_\_\_ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at \_\_\_\_\_ (telephone number).

*[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

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**Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study.**

## About Using Biological Samples for Research

### Blood Samples

Add 1 As part of the main study, we will collect blood samples to use in additional research studies.

### It is required that you provide these blood samples for research.

Add 2 All but two of the research blood samples will be taken at the same time as the blood samples for the main study. The extra research blood draws will be taken on Day 3 ( $\pm$  24 hours) of the first cycle and if your cancer gets worse. About 8-10 teaspoons of blood will be drawn each time for these additional studies.

The blood samples will be sent to Mayo Clinic laboratories associated with NCCTG where the tests will be done. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

Add 1

We would like to keep some of the blood that is left over for future research. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases.

### **Tissue Samples**

Add 1 You are required to provide a tissue sample so that we can confirm your diagnosis. We would also like to use leftover tissue samples in additional research. You will not need an additional biopsy done. **The tissue samples for additional research studies are not required, but we strongly encourage you to provide them.**

**You are not required let us use this tissue for additional research in order to take part in the main study.**

Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research.

### **Things to Think About**

Add 1,2 The choice to let us keep the left over blood and/or tissue sample(s) for future research is up to you. No matter what you decide to do, it will not affect your care.

Add 1,2 If you decide now that your blood and/or tissue sample(s) can be kept for future research, you can change your mind at any time. You or your physician will need to write to: Quality Assurance Specialist, N0745, North Central Cancer Treatment Group (NCCTG) Operations Office, 200 First Street SW, Rochester, MN 55905. Then any blood and/or tissue sample(s) that remain will no longer be used for future research.

In the future, people who do research may need to know more about your health. While NCCTG may give researchers reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your blood sample(s) are used for this kind of research, the results will not be put in your health records.

Your blood and/or tissue sample(s) will be used only for research and will not be sold. The research done with your blood and/or tissue sample(s) may help to develop new products in the future.

### **Benefits**

The benefits of research using blood and tissue samples include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

### **Risks**

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

## Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. I agree to provide tissue sample(s) to NCCTG for research testing planned as part of this study.

Yes       No      Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

2. My blood sample(s) may be kept for use in future research to learn about, prevent, or treat cancer.

Yes       No      Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

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

Yes       No      Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

4. My tissue sample(s) may be kept for use in future research to learn about, prevent, or treat cancer.

Yes       No      Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

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

Yes       No      Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

6. NCCTG can contact me in the future to take part in more research.

Yes       No      Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

## How do outside researchers get the sample?

Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call NCCTG and ask for samples for their studies. NCCTG looks at the way that these studies will be done, and decides if any of the samples can be used. NCCTG sends the samples and some information about you to the researcher. NCCTG will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your blood and/or tissue sample(s) to be given to outside researchers, it will be given to them with a code number. If researchers outside NCCTG use the sample(s) for future research, they will decide if you will be contacted and, if so, they would have to contact the researchers at NCCTG. Then NCCTG will contact the clinic where you registered for this study, who will contact you.

**Please read the following statements and mark your choice:**

1. I permit NCCTG to give my blood sample(s) to outside researchers:

Yes                       No                      Please initial here: \_\_\_\_\_                      Date: \_\_\_\_\_

2. I permit NCCTG to give my tissue sample(s) to outside researchers:

Yes                       No                      Please initial here: \_\_\_\_\_                      Date: \_\_\_\_\_

**Where can I get more information?**

You may call the National Cancer Institute's Cancer Information Service at:  
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>
- For NCI's general information about cancer in Spanish, go to <http://www.cancer.gov/espanol>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

**Signature**

**I have been given a copy of all \_\_\_\_\_ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.**

**Printed Participant Name:** \_\_\_\_\_

**Participant Signature:** \_\_\_\_\_

**Date:** \_\_\_\_\_

**Printed name of person obtaining informed consent:**

\_\_\_\_\_

**Signature of person obtaining informed consent:**

\_\_\_\_\_

**Date** \_\_\_\_\_

***Local IRB changes to this document are allowed. Sections “What are the risks of the research study” or “What other choices do I have if I don’t take part in this research study?” should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.***

***Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.***

**NCI Informed Consent Template for Cancer Treatment Trials  
(English Language)**

**\*NOTES FOR INFORMED CONSENT AUTHORS: [NOTE: Delete this section when sending to sites]**

- Model text *suggested* for use in the informed consent form is in **bold**. It is *recommended* that the **bold** text be retained when adapting the template to a specific protocol.
- Instructions and examples for informed consent authors are in *[italics]*. *Remember to remove these items before finalizing your consent form.*
- A blank line, \_\_\_\_\_, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term ‘study doctor’ has been used throughout the template because the Principal Investigator of a cancer treatment trial is a physician. If this template is used for a trial where the Principal Investigator is not a physician, another appropriate term should be used instead of ‘study doctor’.
- The template date in the header is for reference to this template only and should not be included in the informed consent form given to the prospective research participant.
- The language should be written in 6<sup>th</sup> grade language. When proofreading the consent form, ask yourself if an average 6<sup>th</sup> grader would understand the study after reading this form.

**\*NOTES FOR LOCAL INVESTIGATORS: [NOTE: Retain this section and asterisk item below for NCCTG model consents]**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is <http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/>
- A blank line, \_\_\_\_\_, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer... What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at <https://cissecure.nci.nih.gov/ncipubs/> or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*\*These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.*

**N0745, Phase I/II Randomized Trial of Sorafenib and Bevacizumab as First-Line Therapy in Patients with Locally Advanced or Metastatic Hepatocellular Carcinoma**

**Phase II Informed Consent**

*This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.*

**This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.**

**You are being asked to take part in this research study because you have locally advanced or metastatic (spread to other parts of the body) hepatocellular carcinoma.**

**Why is this research study being done?**

The purpose of this research study is to find out if the combination of the two drugs, sorafenib and bevacizumab, is more effective than sorafenib alone. Both of the drugs have been shown to be active in cancers that are otherwise resistant to treatment. Sorafenib is approved by the Food and Drug Administration (FDA) for patients with advanced hepatocellular cancer, although bevacizumab has not yet been shown to have a definitive clinical benefit in this disease. Sorafenib is considered standard of care for this disease. We want to evaluate what effect it will have on your cancer if these two drugs are given together.

**How many people will take part in the research study?**

Add 1 About 97 people will take part in this study. Up to 21 patients could be enrolled in Phase I (Group A) of the research study although it is expected that only 6-12 patients will actually be enrolled in it. The rest of the patients will be enrolled in Phase II (Groups B and C).

## **What will happen if I take part in this research study?**

### **Before you begin the study....**

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- A physical history and exam, including your weight, height, blood pressure, and tests to rate how well you perform activities of daily living.
- Routine blood tests. About 2 teaspoons of blood will be drawn.
- Chest x-ray.
- Measurement of your tumor by either CT scan or MRI (scans that take pictures of your body's organs).
- Alpha-fetoprotein test (a tumor marker test).
- Use of a scope placed down your throat (esophagoduodenoscopy) to check for enlarged blood vessels, if needed.
- Urine test for protein in your urine.
- Measurement of how long it takes your blood to clot (prothrombin time) if you are taking warfarin. This needs to be done within 21 days before registration.
- An electrocardiogram of your heart (a test that checks for problems with the electrical activity of your heart)
- A MUGA scan or echocardiogram (Echo) to make sure that your heart is healthy enough for you to take the study drugs, if needed. A MUGA scan is a nuclear scan that evaluates the pumping function of the heart. An echocardiogram is a type of ultrasound that helps diagnose heart disease.
- A pregnancy test within 7 days before starting the study, if you are a woman of childbearing age.
- Blood samples for research.

Add 1

You will be required to give blood (mandatory) for additional research studies. More information about these research studies is given starting on page 12 of this consent form.

**During the study....****A cycle is 4 weeks long.**

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures before you start treatment. They are part of regular cancer care.

Weekly:

- Blood pressure (weekly for first 8 weeks then every 2 weeks after that). You may have your blood pressure taken in your local doctor's office or take it yourself on a blood pressure machine in, for example, a local drug store.
- Measurement of how long it takes your blood to clot (prothrombin time) if you are taking warfarin (weekly for the first 4 weeks then as instructed by your doctor).

Every 4 weeks (before each new cycle):

- A physical history and exam, including your weight and tests to rate how well you perform activities of daily living.
- Routine blood tests. About 2 teaspoons of blood will be drawn.
- Alpha-fetoprotein test (a tumor marker test). This is repeated only if it was high at the time you started this study.
- Research blood samples will be taken at the same time as the routine blood tests above prior to each cycle (up through cycle 7) and on day 15 of the first cycle. An additional sample, not taken at the same time as routine blood tests, will be taken on day 3 ( $\pm$  24 hours) of cycle 1. Each sample will require 8-10 teaspoonfuls of blood. More information on research bloods and tissue is available starting on page 13.

Add 2

Every 8 weeks:

- EKG
- A MUGA scan or echocardiogram, if needed.
- Urine test for protein in your urine while you are being treated with bevacizumab.

Other procedures:

Add 1

- A tissue sample is required at the beginning of the study to confirm your diagnosis. We ask that you also let us use this tissue sample for additional research studies. Allowing us to use this tissue for research studies is not required, but we strongly encourage you to give us permission to use them for this purpose. More information about these research studies is given starting on page 12 of this consent form.
- CT or MRI for tumor measurement at 8 weeks and then every 8 weeks after that unless your physician feels it is needed more often to confirm a response.
- Chest x-ray may be done if your physician feels it is needed. A chest x-ray will not be needed if you have a chest CT.
- You will be given a Blood Pressure Diary to record your blood pressure. Bring the diary with you at each cycle of treatment.
- You will be given a Patient Medication Diary for Sorafenib. You will complete the diary and record each time you take the sorafenib. Bring the diary with you at each cycle of treatment and you will be given a new one.

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- An assessment of side effects you may be having.

## Treatment on Phase II

Safe and effective dose levels of this drug combination will be determined in the Phase I part of this study.

You will be enrolled in Phase II of the study. You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance (as in the flip of a coin). Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group.

- Add 1,5
- **If you are in Group B:** You will take one sorafenib tablet by mouth twice daily on days 1 through 28 of each cycle. You will have bevacizumab given through a vein in your arm on Days 1 and 15 of each cycle. You will be retreated on this schedule every 4 weeks.
- Add 5
- **If you are in Group C:** You will take two sorafenib tablets by mouth twice daily on days 1 through 28 of each cycle.

Add 5

Sorafenib should be taken with at least 8 ounces of water. It should be taken without food (at least 1 hour before or 2 hours after meals). Do not take sorafenib with grapefruit juice. You will be asked to fill out a Patient Medication Diary and record daily when you take the sorafenib. You should bring the medication diary with you when you come back for a visit or have treatment. You will be given a new pill diary for each cycle of treatment.

Bevacizumab is given through a vein in your arm (intravenously) over 90 minutes. If well-tolerated, the time for administration may be lowered to 60 minutes the next time you get it. If still well-tolerated, the time may be lowered to 30 minutes after that. You will be given bevacizumab on Day 1 and Day 15 of every cycle.

**If your cancer gets worse and/or spreads,** you will stop treatment. If at any time while you are on the study you or your doctor feel that the side effects of the drugs are too bad, you will stop treatment and go off the study.

## When I am finished taking the study drugs....

Add 3

If your cancer gets worse, if you have unacceptable side effects, or if you decide you no longer want to take part in this study, you will stop taking the study drugs. We will follow you for 3 years from the date of registration, but you will no longer take the study treatment or follow the study treatment schedule. Your doctor will talk to you about other treatment options.

## How long will I be in the research study?

You will be asked to take the study treatment until your cancer gets worse, you have bad side effects, or you and/or your doctor think you should stop. After you are finished taking the study treatment, the study doctor will ask you to visit the office for follow-up exams for at least every 3 months for 1 year after the date you were randomized on the study year and then every 6 months for 2 more years.

## Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drugs can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

## What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the sorafenib or bevacizumab. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

## Sorafenib

### Likely:

- Belly pain
- Diarrhea
- Nausea or the urge to vomit
- Fatigue or tiredness
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)
- Increased INR (measure of the ability of the blood to clot properly) which increases the risk of bleeding
- Increased blood level of fat-digesting enzyme (lipase)
- Decreased number of a type of white blood cell (lymphocyte)
- Decreased number of a type of blood cell that help to clot blood (platelet)
- Increased blood level of a digestive enzyme level (amylase)
- Weight loss
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Increased blood sugar level
- Decreased levels of a blood protein called albumin
- Decreased blood level of calcium
- Decreased blood level of sodium
- Decreased blood level of phosphate
- Hair loss

- Swelling and redness of the skin on the palms of the hands and soles of the feet
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)

Add  
1,3**Less likely:**

- Lack of enough red blood cells (anemia)
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Irritation or sores in the lining of the anus
- Fluid collection in the abdomen
- Constipation
- Bleeding in some organ(s) of the digestive tract
- Irritation or sores in the lining of the mouth
- Irritation or sores in the lining of the rectum
- Irritation or sores in the lining of the small bowel
- Vomiting
- Swelling of the extremities (arms and/or legs)
- Fever
- Chest pain not heart-related
- Infection
- Test that shows a problem in blood clotting
- Increased blood level of cholesterol
- Increased blood level of a liver enzyme (GGT)
- Decreased blood level of carbon dioxide
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Increased blood level of calcium
- Increased blood level of potassium
- Increased blood level of sodium
- Increased blood level of uric acid, a waste material from food digestion
- Decreased blood sugar level
- Decreased blood level of potassium
- Joint pain
- Back pain
- Bone pain
- Muscle spasms
- Muscle pain
- Leg and/or arm pain
- Dizziness (or sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking)
- Headache or head pain
- Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning
- Difficulty sleeping or falling asleep
- Sudden or traumatic injury to the kidney
- Blood in the urine
- Bleeding in the kidney
- Presence of blood in a fallopian tube (tube between ovary to uterus [womb])
- Bleeding in the ovary
- Bleeding in the prostate
- Bleeding in the spermatic cord (a structure resembling a cord that suspends the testis within the scrotum and contains the vas deferens [the tube that carries sperm] and other vessels and nerves)
- Bleeding in the testis
- Bleeding in the uterus (womb)
- Bleeding in the vagina
- Bleeding in the respiratory tract

- Cough
- Shortness of breath
- Nose bleed
- Irritation or sores in the lining of the voice box
- Irritation or sores in the lining of the throat
- Irritation or sores in the lining of the windpipe
- Voice change
- Dry skin
- Itching
- High blood pressure
- Formation of a blood clot that breaks loose and is carried by the blood stream to plug another blood vessel

Add  
1,3,9**Rare but serious:**

- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Heart attack caused by a blockage of a blood vessel supplying part of the heart
- Gastrointestinal perforation: A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
- Serious potentially life-threatening type of allergic reaction that may cause breathing difficulty, dizziness, low blood pressure, and loss of consciousness
- Bleeding in the brain
- Collection of symptoms including headache, confusion, seizures, and vision loss associated with imaging findings (MRI, CT Scan)
- Severe reaction of the skin and gut lining that may include rash and shedding or death of tissue
- Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the epidermis (outer layer) to separate from the dermis (middle layer)

Add 1 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.

Add 1 With the combination of sorafenib and cytotoxic chemotherapy 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.

**Bevacizumab****Likely:**Add  
1,3

- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Headache or head pain
- High blood pressure

Add  
1,3**Less Likely:**

- Lack of enough red blood cells (anemia)
- Fast heartbeat usually originating in an area located above the ventricles
- Feeling of spinning or whirling
- Belly pain
- Inflammation (swelling and redness) of the large bowel (colon)
- Constipation
- Heartburn
- Bleeding in some organ(s) of the digestive tract
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.
- Irritation or sores in the lining of the mouth
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Chest pain not heart-related
- Pain
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Infection
- Infection (collection of pus) around the rectum
- Premature opening of a wound along surgical stitches after surgery
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Weight loss
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Joint pain
- Abnormal changes in the growth plate that may affect the growth of long bones in very young children. This side effect appeared to be reversible after the treatment was stopped but has not been assessed with long-term use of the bevacizumab drug.
- Muscle pain
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Fainting
- Sudden decrease of kidney function
- Blood in the urine
- More protein leaking into the urine than usual, often a sign of kidney disease
- Bleeding in the vagina
- Cough
- Shortness of breath
- Nose bleed
- Hoarseness
- Stuffy nose
- Itching
- Skin rash
- Hives

- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

Add  
1,3**Rare but Serious:**

- Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure
- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
- Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Heart attack caused by a blockage or decreased blood supply to the heart
- Irregular heartbeat resulting from an abnormality in the one of the lower chambers of the heart (ventricle)
- Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
- Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue
- Gastrointestinal perforation : A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
- Sore (ulcer) somewhere in the digestive tract
- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Leakage from stomach due to breakdown of an anastomosis (surgical connection of two separate body structures)
- Bleeding in the brain
- Stroke caused by decreased blood flow to the brain
- Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI imaging findings (RPLS)
- A condition in which the kidneys leak a large amount of protein into the urine that can cause complications including swelling and kidney failure
- Kidney failure
- Abnormal hole between part of the urinary system and another organ or tissue
- Abnormal hole between the vagina and another organ or tissue
- Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs
- Bleeding from the lungs
- Hole in the wall that separates the nostrils of the nose
- Abnormal hole between the breathing tube (windpipe) and the tube that goes from mouth to stomach through which food passes (esophagus). This is life-threatening and potentially fatal.
- Blockage or narrowing of a blood vessel (artery) that can cause damage or loss of function including a heart attack or stroke

Add 2

**Reproductive risks:** You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. It is important you understand that you need to use birth control while on this study and after the end of treatment.

- When getting treated with sorafenib alone, men and women should use adequate birth control for at least 2 weeks after the last administration of sorafenib.
- When getting **both** sorafenib and bevacizumab, men and women should use adequate birth control for at least 6 months after the last administration of bevacizumab.

Women should not breastfeed a baby while on this study or:

- When getting treated with sorafenib alone, women should not breastfeed for at least 2 weeks after the last administration of sorafenib.
- When getting **both** sorafenib and bevacizumab, women should not breastfeed for at least 6 months after the last administration of bevacizumab.

Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

**For more information about risks and side effects, ask your study doctor.**

### **Are there benefits to taking part in the research study?**

Taking part in this study may or may not make your health better. While doctors hope the combination of sorafenib and bevacizumab will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about these study drugs as a treatment for cancer. This information could help future cancer patients.

### **What other choices do I have if I do not take part in this research study?**

You do not have to be in this study to receive treatment for your cancer. Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

### **Will my medical information be kept private?**

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- North Central Cancer Treatment Group (NCCTG), Local Institutional Review Board (IRB)

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Bayer Pharmaceuticals and Genentech/Roche, the drug companies that are supplying sorafenib and bevacizumab for this study.

*[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]*

### **What are the costs of taking part in this research study?**

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Add 1

Bayer Pharmaceuticals is supplying bevacizumab for this research study at no cost to you while you are taking part in this study. Sorafenib is commercially available and is not supplied, but Bayer has a program called REACH<sup>®</sup> to help you to help you get insurance coverage, Medicare Part D coverage, or financial assistance to pay for the drug. Study staff will provide you with more information on this program. You will need to fill out an enrollment form and talk to REACH counselors who will help you find coverage. You or your health plan may need to pay for costs of the supplies and personnel who give you the bevacizumab and/or sorafenib.

If you should need to take the study agents much longer than usual, the stock of free study agent that has been supplied could run out. If the free supply runs out, your study doctor will discuss with you how to get more drug from the manufacturer. You may be asked to pay for it.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

### **What happens if I am injured because I took part in this research study?**

It is important that you tell your study doctor, \_\_\_\_\_ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at \_\_\_\_\_ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

### **What are my rights if I take part in this research study?**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your

regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

### **Who can answer my questions about the research study?**

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor \_\_\_\_\_ [name(s)] at \_\_\_\_\_ [telephone number].

For questions about your rights while taking part in this study, call the \_\_\_\_\_ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at \_\_\_\_\_ (telephone number).

*[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

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**Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study.**

### **About Using Biological Samples for Research**

#### **Blood Samples**

Add 1 As part of the main study, we will collect blood samples to use in additional research studies

#### **It is required that you provide these blood samples for research.**

Add 2 All but two of the research blood samples will be taken at the same time as the blood samples for the main study. The extra research blood draws will be taken on Day 3 ( $\pm$  24 hours) of the first cycle and if your cancer gets worse. About 8-10 teaspoons of blood will be drawn each time for these additional studies.

The blood samples will be sent to Mayo Clinic laboratories associated with NCCTG where the tests will be done. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

Add 1 We would like to keep some of the blood that is left over for future research. If you agree, this blood will be kept and may be used in research to learn more about cancer and other diseases.

#### **Tissue Samples**

Add 1 You are required to provide a tissue sample so that we can confirm your diagnosis. We would also like to use leftover tissue samples in additional research. You will not need an additional

biopsy done. **The tissue samples for additional research studies are not required, but we strongly encourage you to provide them.**

**You are not required let us use this tissue for additional research in order to take part in the main study.**

Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research.

## Things to Think About

Add 1,2 The choice to let us keep the left over blood and/or tissue sample(s) for future research is up to you. No matter what you decide to do, it will not affect your care.

Add 1,2 If you decide now that your blood and/or tissue sample(s) can be kept for future research, you can change your mind at any time. You or your physician will need to write to: Quality Assurance Specialist, N0745, North Central Cancer Treatment Group (NCCTG) Operations Office, 200 First Street SW, Rochester, MN 55905. Then any blood and/or tissue sample(s) that remain will no longer be used for future research.

In the future, people who do research may need to know more about your health. While NCCTG may give researchers reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood is used for genetic research (about diseases that are passed on in families). Even if your blood sample(s) are used for this kind of research, the results will not be put in your health records.

Your blood and/or tissue sample(s) will be used only for research and will not be sold. The research done with your blood and/or tissue sample(s) may help to develop new products in the future.

### Benefits

The benefits of research using blood and tissue samples include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

### Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

### Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. I agree to provide tissue sample(s) to NCCTG for research testing planned as part of this study.

Yes  No

Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

2. My blood sample(s) may be kept for use in future research to learn about, prevent, or treat cancer.

Yes  No Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

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

Yes  No Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

4. My tissue sample(s) may be kept for use in future research to learn about, prevent, or treat cancer.

Yes  No Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

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

Yes  No Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

6. NCCTG can contact me in the future to take part in more research.

Yes  No Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

### **How do outside researchers get the sample?**

Researchers from universities, hospitals, and other health organizations do research using blood and tissue. They may call NCCTG and ask for samples for their studies. NCCTG looks at the way that these studies will be done, and decides if any of the samples can be used. NCCTG sends the samples and some information about you to the researcher. NCCTG will not send your name, address, phone number, social security number, or any other identifying information to the researcher. If you allow your blood and/or tissue sample(s) to be given to outside researchers, it will be given to them with a code number. If researchers outside NCCTG use the sample(s) for future research, they will decide if you will be contacted and, if so, they would have to contact the researchers at NCCTG. Then NCCTG will contact the clinic where you registered for this study, who will contact you.

#### ***Please read the following statements and mark your choice:***

1. I permit NCCTG to give my blood sample(s) to outside researchers:

Yes  No Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

2. I permit NCCTG to give my tissue sample(s) to outside researchers:

Yes  No Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

### **Where can I get more information?**

You may call the National Cancer Institute's Cancer Information Service at: 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>
- For NCI's general information about cancer in Spanish, go to <http://www.cancer.gov/espanol>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

### Signature

**I have been given a copy of all \_\_\_\_\_ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.**

**Printed Participant Name:** \_\_\_\_\_

**Participant Signature:** \_\_\_\_\_

**Date:** \_\_\_\_\_

**Printed name of person obtaining informed consent:**

\_\_\_\_\_

**Signature of person obtaining informed consent:**

\_\_\_\_\_

**Date** \_\_\_\_\_

*Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.*

*Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.*