

North Central Cancer Treatment Group

N0735: Phase II Trial of Albumin-Bound Paclitaxel in Combination with Gemcitabine and Bevacizumab in Patients with Metastatic Breast Cancer

Addendum 6 – December 23, 2011

**Summary**

- This addendum is in response to an action letter from Dr. Helen Chen of the National Cancer Institute (NCI) dated December 15, 2011 concerning Bevacizumab. The drug information section and the risks section of the consent forms have been updated to reflect current drug safety information.
- Risk changes in this addendum have been determined by NCI to be a minor alteration in the overall risk-benefit for new patients.
- Determination of the level of IRB review for minor risk changes (expedited versus full board review) is at the discretion of the local IRB.
- Administrative/editorial changes.

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

**Title page** Revised NCI version date and addition of Addendum 6.

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

Page 30: Contact information in the fourth bullet under the “Additional Instructions or Exceptions to ADEERS Expedited Reporting Requirements” section in Section 10.21 has been updated as follows:

Abraxis Bioscience LLC/Celgene, email to ~~SAE Reporting @abraxishio.com~~  
[drugsafety@celgene.com](mailto:drugsafety@celgene.com) or fax to 919-433-8402 **908-673-9115** and email to  
[AbraaxisMedAffairs@abraxishio.com](mailto:AbraaxisMedAffairs@abraxishio.com) or fax to 908-393-8304

**Section 15.0** **Drug Information**

Pages 47-51: Due to the receipt of the updated Comprehensive Adverse Events and Potential Risks list (CAEPR) for Bevacizumab, Section 15.34 has been replaced in its entirety.

**Appendix I** **Consent Form**

Pages 7-9: Due to the Action Letter for Bevacizumab from NCI, the risk sections have been revised as follows:

**Likely**

- ~~Diarrhea~~ (moved to *Less likely*)
- ~~Nausea or the urge to vomit~~ (moved to *Less likely*)
- ~~Vomiting~~ (moved to *Less likely*)
- ~~Fatigue or tiredness~~ (moved to *Less likely*)
- ~~Headache or head pain~~ (moved to *Less likely*)
- High blood pressure

- **Loss of the normal functioning of the ovaries in a woman that can result in temporary or permanent menopause; the impact on fertility (temporary or permanent) is unknown** (*newly added*)

#### Less Likely

- Lack of enough red blood cells (anemia)
- **Fever associated with dangerously low levels of a type of white blood cell (neutrophils)** (*newly added*)
- 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
- **Diarrhea** (*moved from Likely*)
- Heartburn
- Bleeding in some organ(s) of the digestive tract
- **Blockage in an organ(s)/part(s) of the digestive tract** (*newly added*)
- 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
- **Nausea or the urge to vomit** (*moved from Likely*)
- **Vomiting** (*moved from Likely*)
- **Fatigue or tiredness** (*moved from Likely*)
- 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
- **Destruction or death of jawbone** (*newly added*)
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- **Headache or head pain** (*moved from Likely*)

- **Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning** (*newly added*)
- Fainting
- ~~Sudden decrease of kidney function~~ (*moved to Rare but serious*)
- 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 or runny nose, sneezing** (*wording expanded*)
- Itching
- **Skin rash with the presence of macules (flat discolored area) and papules (raised bump)** (*wording expanded*)
- 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

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)
- **Sudden decrease of kidney function** (*moved from Less likely*)
- 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~~ (*deleted*)
- 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



## Action Letter

**DATE:** December 15, 2011

**FROM:** Helen Chen, MD, Associate Branch Chief, IDB, CTEP, DCTD, NCI  
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI  
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

**SUBJECT:** **CONFIDENTIAL COMMUNICATION** – Action Letter for Bevacizumab (rhuMAb VEGF, NSC 704865)

**TO:** Investigators for CTEP-supported Studies Involving Bevacizumab (rhuMAb VEGF, NSC 704865)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with bevacizumab, and to request all trials with bevacizumab be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes bevacizumab. See the accompanying list of CTEP trials with bevacizumab.

**CTEP believes that with the exception of the addition of ovarian failure, which would affect a subset of patients eligible for bevacizumab trials, the other new and/or modified risk information for bevacizumab in the Comprehensive Adverse Events and Potential Risks (CAEPR) list is very similar to the risk information that is already included in the previous version of the CAEPR and thus would have been communicated to patients in the informed consent document (ICD).** Below are CTEP's assessments of the new/modified risks:

- New and/or modified adverse events (AE) terms that are similar to what were already included in the previous CAEPR: (1) Febrile neutropenia is a further specification of the previously identified risk of Neutrophil count decreased, (2) Gastrointestinal obstruction is often a consequence of the previously identified risks of Constipation and Ileus, (3) Osteonecrosis of the jaw is a specific manifestation of the previously identified risks of Infection and Wound dehiscence, and (4) Peripheral sensory neuropathy is an increase in the chemotherapy-rated peripheral neuropathy and therefore only applies to regimens for which neuropathy is already a known risk. When changes such as these are made to the ICD (i.e., changes as to how risk information is presented and/or additional clarifying information and/or small increases/decreases in frequency of risks leading to a new frequency category), it is not necessary to suspend enrollment of new subjects until a revised ICD is reviewed and approved by the Institutional Review Board (IRB).
- The risk of ovarian failure is new. However, this risk is only applicable to female, premenopausal patients and does not pose a risk to the majority of patients that will be eligible for the trials. For this reason, it is not necessary to suspend the entire protocol until IRB approval of the new ICD. The investigators are asked to do the following:

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- Accrual will need to be suspended for premenopausal women until a revised ICD is reviewed and approved by the IRB once the final Action Letter is released.
- Accrual of all other patient populations, for which this new event poses no risk, may continue.

In response to the new/modified risk information CTEP is requiring that all trials with bevacizumab be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at [PIO@CTEP.NCI.NIH.GOV](mailto:PIO@CTEP.NCI.NIH.GOV) by 5 PM ET on December 29, 2011** or as required based on protocol status (see the General Actions Required Based on Protocol Status section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Helen Chen ([helen.chen@nih.gov](mailto:helen.chen@nih.gov); 301-496-1196). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since bevacizumab is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the IRB Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: <http://www.hhs.gov/ohrp/policy/Correspondence/nci200870929.html>.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised CAEPR (Attachment 1) and ICD risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

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## SPECIFIC INSTRUCTION

### Background

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, AdEERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with bevacizumab.

### Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

Protocol Cover Page: Page Number(s): \_\_\_\_\_

Version Date: \_\_\_\_\_

2) Revision of the Protocol CAEPR:

Protocol Section(s) for Insertion of Revised CAEPR (Version 2.2, October 21, 2011): \_\_\_\_

Page Number(s): \_\_\_\_

- The Agent Specific Adverse Event List (ASAEL) is now termed the Specific Protocol Exceptions to Expedited Reporting (SPEER) and includes grades for adverse events found on the SPEER that are used to determine if expedited reporting is required.
- Added New Risk:
  - Likely: Reproductive system and breast disorders - Other (ovarian failure)
  - Less Likely: Febrile neutropenia; Gastrointestinal obstruction
  - Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined: Platelet count decreased; Palmar-plantar erythrodysesthesia syndrome
- Increase in Risk Attribution:
  - Changed to Less Likely from Reported But Undetermined: Osteonecrosis of jaw; Peripheral sensory neuropathy
- Decrease in Risk Attribution:
  - Changed to Less Likely from Likely: Diarrhea; Nausea; Vomiting; Fatigue; Headache
  - Changed to Rare But Serious from Less Likely: Acute kidney injury
- Provided Further Clarification:
  - The following footnote was added to Gastrointestinal obstruction: "Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC."
  - The following footnote was added to Osteonecrosis of jaw: "Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates."

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- The following footnote was added to Peripheral sensory neuropathy: “Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.”
- The following footnote was added to Reproductive system and breast disorders - Other (ovarian failure): “Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation ( $\geq 30$  mIU/mL) was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level  $< 30$  mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.”
- Renal and urinary disorders – Other (renal failure) is now reported as part of Acute kidney injury.
- Respiratory, thoracic, and mediastinal disorders – Other (rhinitis) is now reported as Allergic rhinitis.
- Skin and subcutaneous disorders – Other (rash) is now reported as Rash maculo-papular.
- Small intestinal obstruction is now reported as part of Gastrointestinal obstruction.
- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
  - Added: Febrile neutropenia; Colitis; Myalgia
  - Deleted: Myocardial infarction; Intracranial hemorrhage; Ischemia cerebrovascular

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.2, and associated risk information for the Informed Consent Document (ICD), to the most recent CAEPR Version 2.1. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.1), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

### 3) Revision of the ICD as Specified Below:

The terminology for CTEP’s suggested lay terms may change periodically. The risk profile represents CAEPR risks in lay terms in a one-to-one mapping. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the informed consent document. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the risk profile in any way, please state, “The risk profile has been modified” in the cover memo.

- Added New Risk:
  - Likely: Loss of the normal functioning of the ovaries in a woman that can result in temporary or permanent menopause; the impact on fertility (temporary or permanent) is unknown
  - Less Likely: Fever associated with dangerously low levels of a type of white blood cell (neutrophils); Blockage in an organ(s)/part(s) of the digestive tract
- Increase in Risk Attribution:
  - Changed to Less Likely from Reported But Undetermined: Destruction or death of jawbone; Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning
- Decrease in Risk Attribution:
  - Changed to Less Likely from Likely: Diarrhea; Nausea or the urge to vomit; Vomiting; Fatigue or tiredness; Headache or head pain
  - Changed to Rare But Serious from Less Likely: Sudden decrease of kidney function

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PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to bevacizumab is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

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## Attachment 1: Revised Bevacizumab CAEPR – Version 2.2, October 21, 2011

### Comprehensive Adverse Events and Potential Risks list (CAEPR) for Bevacizumab (rhuMab VEGF, NSC 704865)

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.

**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 2.2, October 21, 2011<sup>1</sup>

Adverse Events with Possible Relationship to Bevacizumab (rhuMab VEGF) (CTCAE 4.0 Term)			Specific Protocol Exceptions to Expedited Reporting (SPEER)  (formerly known as ASAEL)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>			
	Anemia		<i>Anemia (Gr. 3)</i>
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		<i>Febrile neutropenia (Gr. 3)</i>
<b>CARDIAC DISORDERS</b>			
		Acute coronary syndrome	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Supraventricular tachycardia		<i>Supraventricular tachycardia (Gr. 3)</i>
		Ventricular arrhythmia	
		Ventricular fibrillation	
<b>EAR AND LABYRINTH DISORDERS</b>			
	Vertigo		
<b>GASTROINTESTINAL DISORDERS</b>			
	Abdominal pain		<i>Abdominal pain (Gr. 3)</i>
	Colitis		<i>Colitis (Gr. 3)</i>
	Constipation		<i>Constipation (Gr. 3)</i>
	Diarrhea		<i>Diarrhea (Gr. 3)</i>
	Dyspepsia		<i>Dyspepsia (Gr. 2)</i>
		Gastrointestinal fistula <sup>2</sup>	
	Gastrointestinal hemorrhage <sup>3</sup>		<i>Gastrointestinal hemorrhage<sup>3</sup> (Gr. 2)</i>
	Gastrointestinal obstruction <sup>4</sup>		

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		Gastrointestinal perforation <sup>5</sup>	
		Gastrointestinal ulcer <sup>6</sup>	
	Ileus		
	Mucositis oral		<i>Mucositis oral (Gr. 3)</i>
	Nausea		<i>Nausea (Gr. 3)</i>
	Vomiting		<i>Vomiting (Gr. 3)</i>
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>			
	Fatigue		<i>Fatigue (Gr. 3)</i>
	Infusion related reaction		<i>Infusion related reaction (Gr. 2)</i>
	Non-cardiac chest pain		<i>Non-cardiac chest pain (Gr. 3)</i>
	Pain		<i>Pain (Gr. 3)</i>
<b>IMMUNE SYSTEM DISORDERS</b>			
	Allergic reaction		<i>Allergic reaction (Gr. 2)</i>
		Anaphylaxis	
<b>INFECTIONS AND INFESTATIONS</b>			
	Infection <sup>7</sup>		<i>Infection<sup>7</sup> (Gr. 3)</i>
	Infections and infestations - Other (peri-rectal abscess)		
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>			
		Gastrointestinal anastomotic leak	
	Wound dehiscence		<i>Wound dehiscence (Gr. 2)</i>
<b>INVESTIGATIONS</b>			
	Alanine aminotransferase increased		<i>Alanine aminotransferase increased (Gr. 3)</i>
	Alkaline phosphatase increased		<i>Alkaline phosphatase increased (Gr. 3)</i>
	Aspartate aminotransferase increased		<i>Aspartate aminotransferase increased (Gr. 3)</i>
	Blood bilirubin increased		<i>Blood bilirubin increased (Gr. 2)</i>
	Cardiac troponin I increased		
	Neutrophil count decreased		<i>Neutrophil count decreased (Gr. 3)</i>
	Weight loss		<i>Weight loss (Gr. 3)</i>
	White blood cell decreased		<i>White blood cell decreased (Gr. 3)</i>
<b>METABOLISM AND NUTRITION DISORDERS</b>			
	Anorexia		<i>Anorexia (Gr. 3)</i>
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>			
	Arthralgia		<i>Arthralgia (Gr. 3)</i>
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia) <sup>8</sup>		
	Myalgia		<i>Myalgia (Gr. 3)</i>
	Osteonecrosis of jaw <sup>9</sup>		
<b>NERVOUS SYSTEM DISORDERS</b>			
	Dizziness		<i>Dizziness (Gr. 2)</i>
	Headache		<i>Headache (Gr. 3)</i>
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
	Peripheral sensory neuropathy <sup>10</sup>		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
<b>RENAL AND URINARY DISORDERS</b>			
		Acute kidney injury	

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	Hematuria		<b><i>Hematuria (Gr. 3)</i></b>
	Proteinuria		<b><i>Proteinuria (Gr. 2)</i></b>
		Renal and urinary disorders - Other (Nephrotic Syndrome)	
		Urinary fistula	
<b>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</b>			
Reproductive system and breast disorders - Other (ovarian failure) <sup>11</sup>			
		Vaginal fistula	
	Vaginal hemorrhage		<b><i>Vaginal hemorrhage (Gr. 3)</i></b>
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>			
	Allergic rhinitis		<b><i>Allergic rhinitis (Gr. 3)</i></b>
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		<b><i>Cough (Gr. 3)</i></b>
	Dyspnea		<b><i>Dyspnea (Gr. 2)</i></b>
	Epistaxis		<b><i>Epistaxis (Gr. 3)</i></b>
	Hoarseness		<b><i>Hoarseness (Gr. 3)</i></b>
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>			
	Pruritus		<b><i>Pruritus (Gr. 2)</i></b>
	Rash maculo-papular		<b><i>Rash maculo-papular (Gr. 2)</i></b>
	Urticaria		<b><i>Urticaria (Gr. 2)</i></b>
<b>VASCULAR DISORDERS</b>			
Hypertension			<b><i>Hypertension (Gr. 3)</i></b>
	Thromboembolic event		<b><i>Thromboembolic event (Gr. 3)</i></b>
		Vascular disorders - Other (arterial thromboembolic event) <sup>12</sup>	

<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 fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

<sup>3</sup>Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

<sup>4</sup>Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

<sup>5</sup>Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

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<sup>6</sup>Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

<sup>7</sup>Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

<sup>8</sup>Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

<sup>9</sup>Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

<sup>10</sup>Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

<sup>11</sup>Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation ( $\geq 30$  mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level  $< 30$  mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

<sup>12</sup>Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

**Also reported on Bevacizumab (rhuMab VEGF) trials but with the relationship to Bevacizumab (rhuMab VEGF) still undetermined:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Disseminated intravascular coagulation

**CARDIAC DISORDERS** - Pericardial effusion

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Gait disturbance; Sudden death NOS

**HEPATOBIILIARY DISORDERS** - Hepatic failure

**INFECTIONS AND INFESTATIONS** - Infections and infestations - Other (aseptic meningitis)

**INVESTIGATIONS** - Platelet count decreased

**METABOLISM AND NUTRITION DISORDERS** - Hyponatremia

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis)

**NERVOUS SYSTEM DISORDERS** - Dysgeusia; Peripheral motor neuropathy; Seizure

**PSYCHIATRIC DISORDERS** - Confusion

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Adult respiratory distress syndrome; Pneumonitis; Pneumothorax; Pulmonary hypertension

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Palmar-plantar erythrodysesthesia syndrome; Skin ulceration

**Note:** Bevacizumab (rhuMab VEGF) 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.

# Action Letter

## **Attachment 2: Revised ICD section(s) for Bevacizumab**

Please note that the terminology for CTEP's suggested lay terms may change periodically. The risk profile represents CAEPR risks in lay terms in a one-to-one mapping. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the informed consent document. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.

### **Risk Profile for Bevacizumab (CAEPR Version 2.2, October 21, 2011)**

#### **Likely:**

- Loss of the normal functioning of the ovaries in a woman that can result in temporary or permanent menopause; the impact on fertility (temporary or permanent) is unknown
- High blood pressure

#### **Less Likely:**

- Lack of enough red blood cells (anemia)
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- 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
- Diarrhea
- Heartburn
- Bleeding in some organ(s) of the digestive tract
- Blockage in an organ(s)/part(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
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- 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

## Action Letter

- 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
- Destruction or death of jawbone
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- 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
- Fainting
- Blood in the urine
- More protein leaking into the urine than usual, often a sign of kidney disease
- Bleeding in the vagina
- Stuffy or runny nose, sneezing
- Cough
- Shortness of breath
- Nose bleed
- Hoarseness
- Itching
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- 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

### **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

## **Action Letter**

- 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)
- Sudden decrease of kidney function
- A condition in which the kidneys leak a large amount of protein into the urine that can cause complications including swelling and 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

# Action Letter

## Attachment 3: Action Letter GENERAL INSTRUCTIONS

1. **Distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For Cooperative Group studies, please follow instructions from Group Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.
2. Accrual of new patients (**premenopausal women only – see instructions on pages 1-2 of this letter**) must be suspended until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter. This amendment can undergo expedited approval at the discretion of the IRB Chair/designee as explained on the first page of the Action Letter.
3. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.
4. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

## **INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does not already accompany the Action Letter)**

### **General Instructions on Amendment Preparation:**

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. You may substitute different lay terms for each concept if appropriate for your patient population. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.

### **Specific Instructions on Amendment Preparation Based on Protocol Status:**

#### **A. Trials with a current CTEP status of "Active"**

- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy (<http://ctep.cancer.gov/protocolDevelopment/docs/requestsubmissionpolicyfinal.pdf>).
- Suspend accrual of new patients (**premenopausal women only – see instructions on pages 1-2 of this letter**) until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter.

# Action Letter

B. Trials with a current status of “Approved”, “Temporarily Closed to Accrual and Treatment”, or “Temporarily Closed to Accrual”

- The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
- You may include additional non-Action Letter related changes (any type) in your amendment response.

C. Trials with a current CTEP status of “In Review”

- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of “Closed to Accrual”

*If your trial is under a CTEP-held IND:*

- Review and follow ALL the instructions outlined in this RRA.
- The information provided in this memo outlines the ONLY changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP’s editorial and administrative update policy (<http://ctep.cancer.gov/protocolDevelopment/docs/requestsubmissionpolicyfinal.pdf>).

*If your trial is NOT under a CTEP-held IND:*

- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow ALL the instructions outlined in this Action Letter. The information provided in this memo outlines the ONLY changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP’s editorial and administrative update policy (<http://ctep.cancer.gov/protocolDevelopment/docs/requestsubmissionpolicyfinal.pdf>).
- If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.

E. Trials with a current CTEP status of “Closed to Accrual and Treatment” or “Complete”

- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

## North Central Cancer Treatment Group

**Phase II Trial of Albumin-Bound Paclitaxel in Combination with Gemcitabine and Bevacizumab in Patients with Metastatic Breast Cancer**

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

Study Chair: Donald W Northfelt MD (Research Base)\*  
Mayo Clinic  
13400 East Shea Boulevard  
Scottsdale, Arizona 85259  
507/284-1159  
507/284-5280 (FAX)  
[northfelt.donald@mayo.edu](mailto:northfelt.donald@mayo.edu)  
Philip J Stella MD (NCCTG)

NCCTG Breast Committee Scientific Chair: Edith A Perez MD

Study CoChairs: Timothy J Hobday MD (Research Base)  
Wilma L Lingle PhD<sup>√</sup> (Laboratory)  
Monica M Reinholz PhD<sup>√</sup> (Laboratory)  
Pinku Mukherjee PhD<sup>√</sup> (Laboratory)  
Beiyun Chen MD PhD (Pathology)  
Kevin C Halling MD PhD (Pathology)

Statistician: Amylou C Dueck, PhD<sup>√</sup>  
480/301-6159

\*Investigator having NCI responsibility for this protocol

<sup>√</sup>Study contributor(s) not responsible for patient care

**Drug Availability**

**DCTD Supplied Investigational Agents:** None

**Commercial Agents:** None

**Drug Company Supplied:** bevacizumab (Avastin®) IND# 102280 (Exempt); albumin-bound paclitaxel (Abraxane®), gemcitabine (Gemzar®)

<b>Document History</b>	<b>(Effective Date)</b>	<b>Document History</b>	<b>(Effective Date)</b>
Activation	November 7, 2008	Addendum 6	December 23, 2011
Addendum 1	October 30, 2009		
Addendum 2	February 19, 2010		
Addendum 3	July 9, 2010		
Addendum 4	October 22, 2010		
Addendum 5	February 11, 2011		

**Study Participants**    **Date Activated**

Entire NCCTG    07 Nov 2008

NCI Version Date: November 30, 2011

**Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements**

Add 6  
Add 1  
Add 5

- The NCCTG SAE Coordinator will forward a copy a copy of all AdEERS reports to:
  - The NCCTG IND Coordinator who will notify the FDA as warranted by the event and stipulated in the U.S. Code of Federal Regulations.
  - Genentech Drug Safety, fax to (650) 225-4682 or (650) 225-5288, if applicable.
  - Abraxis Bioscience LLC/Celgene, email to [drugsafety@celgene.com](mailto:drugsafety@celgene.com) or fax to 908-673-9115
  - Lilly Global Product Safety, fax to **866-644-1697 or 317-453-3402**
- In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.22 Other Required Expedited Reporting

Add 4,5

EVENT TYPE	REPORTING PROCEDURE
Secondary AML/MDS	<p>Reporting for this event required during and after completion of study treatment via AdEERS.</p> <p>Beginning January 1, 2011, AdEERS will only accept CTCAE v4.0 for this study: Report these events using “Neoplasms benign, malignant and unspecified (including cysts and polyps)” <i>and including the appropriate adverse event:</i></p> <ul style="list-style-type: none"> <li>- Leukemia secondary to oncology chemotherapy OR</li> <li>- Myelodysplastic syndrome OR</li> <li>- Treatment related secondary malignancy</li> </ul>
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	<p>Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form within 5 working days, using CTCAE v3.0.</p> <p>If an AdEERS report has been submitted, this form does not need to be submitted.</p> <p>Fax or mail to the NCCTG SAE Coordinator, NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax (507)284-9628.</p> <p>The NCCTG SAE Coordinator will notify the NCCTG IND Coordinator who will submit to the FDA IND as warranted by the event and stipulated in the U.S. Code of Federal Regulations.</p> <p>You must use CTCAE v3.0 for data submission with this form. The events reported on this form must also appear on the Case Report Forms (i.e., routine data) for this study.</p>

Add 4

Add 4

## 15.3 Bevacizumab

## 15.31 Bevacizumab (also known as Recombinant Humanized Monoclonal Anti-VEGF Antibody, bevacizumab, Avastin®)

- IND number: 102280 (Note: The FDA has determined this protocol to be “exempt” under IND regulations.)
- The most current version of the investigator brochure will be maintained on the secure members section of the NCCTG website until all investigations under the IND have been completed.

Each investigator should obtain a copy of the investigator's brochure prior to initiation of the study. Updated investigator's brochures should be obtained from the website, as they become available.

15.32 Preparation and storage: Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid in 4 mL and 16 mL single-use glass vials to deliver 100 and 400 mg of bevacizumab per vial, respectively, ready for parenteral administration. Bevacizumab vials must be refrigerated at 2-8°C (36-46°F). Bevacizumab vials should be protected from light. Store in the original carton until time of use. The calculated dose should be placed in a sterile, empty IV bag and diluted with a sufficient amount of 0.9% Sodium Chloride Injection to obtain a final volume of 100 mL. Once bevacizumab has been added to a bag of sterile saline, the solution must be used within 8 hours. **DO NOT FREEZE. DO NOT SHAKE.**

## 15.33 Administration: The first dose of bevacizumab should be given over 90 minutes. If well tolerated, second dose may be administered over 60 minutes. Again, if well tolerated, subsequent doses may be administered over 30 minutes. If the patient is pre-medicated for infusion reaction, maintain previous infusion rate for first pre-medicated infusion. If well tolerated with pre-medication, the subsequent infusion time may then be decreased by 30 minutes, as long as the patient continues to be pre-medicated. If the patient experiences infusion-associated adverse events with the 60-minute infusion, all subsequent infusions should be given over 90 minutes. Similarly, if a patient experiences infusion-associated adverse events with the 30-minute infusion, all subsequent doses should be given over 60 minutes.

Add 3,6

## 15.34 Known potential adverse events

**Comprehensive Adverse Events and Potential Risks list (CAEPR)**

for

**Bevacizumab (rhuMAb VEGF, NSC 704865)**

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.

**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 2.2, October 21, 2011<sup>1</sup>

<b>Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term)</b>			<b>Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAE)</b>
<b>Likely (&gt;20%)</b>	<b>Less Likely (&lt;=20%)</b>	<b>Rare but Serious (&lt;3%)</b>	
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>			
	Anemia		<b>Anemia (Gr. 3)</b>
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		<b>Febrile neutropenia (Gr. 3)</b>
<b>CARDIAC DISORDERS</b>			
		Acute coronary syndrome	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Supraventricular tachycardia		<b>Supraventricular tachycardia (Gr. 3)</b>
		Ventricular arrhythmia	
		Ventricular fibrillation	
<b>EAR AND LABYRINTH DISORDERS</b>			
	Vertigo		
<b>GASTROINTESTINAL DISORDERS</b>			
	Abdominal pain		<b>Abdominal pain (Gr. 3)</b>
	Colitis		<b>Colitis (Gr. 3)</b>
	Constipation		<b>Constipation (Gr. 3)</b>
	Diarrhea		<b>Diarrhea (Gr. 3)</b>
	Dyspepsia		<b>Dyspepsia (Gr. 2)</b>
		Gastrointestinal fistula <sup>2</sup>	
	Gastrointestinal hemorrhage <sup>3</sup>		<b>Gastrointestinal hemorrhage<sup>3</sup> (Gr. 2)</b>
	Gastrointestinal obstruction <sup>4</sup>		
		Gastrointestinal perforation <sup>5</sup>	
		Gastrointestinal ulcer <sup>6</sup>	
	Ileus		
	Mucositis oral		<b>Mucositis oral (Gr. 3)</b>
	Nausea		<b>Nausea (Gr. 3)</b>
	Vomiting		<b>Vomiting (Gr. 3)</b>
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>			
	Fatigue		<b>Fatigue (Gr. 3)</b>
	Infusion related reaction		<b>Infusion related reaction (Gr. 2)</b>
	Non-cardiac chest pain		<b>Non-cardiac chest pain (Gr. 3)</b>
	Pain		<b>Pain (Gr. 3)</b>
<b>IMMUNE SYSTEM DISORDERS</b>			
	Allergic reaction		<b>Allergic reaction (Gr. 2)</b>
		Anaphylaxis	
<b>INFECTIONS AND INFESTATIONS</b>			
	Infection <sup>7</sup>		<b>Infection<sup>7</sup> (Gr. 3)</b>
	Infections and infestations -		

	Other (peri-rectal abscess)		
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>			
		Gastrointestinal anastomotic leak	
	Wound dehiscence		<b>Wound dehiscence (Gr. 2)</b>
<b>INVESTIGATIONS</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. 2)</b>
	Cardiac troponin I increased		
	Neutrophil count decreased		<b>Neutrophil count decreased (Gr. 3)</b>
	Weight loss		<b>Weight loss (Gr. 3)</b>
	White blood cell decreased		<b>White blood cell decreased (Gr. 3)</b>
<b>METABOLISM AND NUTRITION DISORDERS</b>			
	Anorexia		<b>Anorexia (Gr. 3)</b>
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>			
	Arthralgia		<b>Arthralgia (Gr. 3)</b>
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia) <sup>8</sup>		
	Myalgia		<b>Myalgia (Gr. 3)</b>
	Osteonecrosis of jaw <sup>9</sup>		
<b>NERVOUS SYSTEM DISORDERS</b>			
	Dizziness		<b>Dizziness (Gr. 2)</b>
	Headache		<b>Headache (Gr. 3)</b>
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
	Peripheral sensory neuropathy <sup>10</sup>		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
<b>RENAL AND URINARY DISORDERS</b>			
		Acute kidney injury	
	Hematuria		<b>Hematuria (Gr. 3)</b>
	Proteinuria		<b>Proteinuria (Gr. 2)</b>
		Renal and urinary disorders - Other (Nephrotic Syndrome)	
		Urinary fistula	
<b>REPRODUCTIVE SYSTEM AND BREAST DISORDERS</b>			
Reproductive system and breast disorders - Other (ovarian failure) <sup>11</sup>			
		Vaginal fistula	

	Vaginal hemorrhage		<b>Vaginal hemorrhage (Gr. 3)</b>
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>			
	Allergic rhinitis		<b>Allergic rhinitis (Gr. 3)</b>
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		<b>Cough (Gr. 3)</b>
	Dyspnea		<b>Dyspnea (Gr. 2)</b>
	Epistaxis		<b>Epistaxis (Gr. 3)</b>
	Hoarseness		<b>Hoarseness (Gr. 3)</b>
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>			
	Pruritus		<b>Pruritus (Gr. 2)</b>
	Rash maculo-papular		<b>Rash maculo-papular (Gr. 2)</b>
	Urticaria		<b>Urticaria (Gr. 2)</b>
<b>VASCULAR DISORDERS</b>			
Hypertension			<b>Hypertension (Gr. 3)</b>
	Thromboembolic event		<b>Thromboembolic event (Gr. 3)</b>
		Vascular disorders - Other (arterial thromboembolic event) <sup>12</sup>	

<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 fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

<sup>3</sup>Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

<sup>4</sup>Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

<sup>5</sup>Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

<sup>6</sup>Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

<sup>7</sup>Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

<sup>8</sup>Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

<sup>9</sup>Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

<sup>10</sup>Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

<sup>11</sup>Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation ( $\geq 30$  mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level  $< 30$  mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

<sup>12</sup>Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

**Also reported on Bevacizumab (rhuMAB VEGF) trials but with the relationship to Bevacizumab (rhuMAB VEGF) still undetermined:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Disseminated intravascular coagulation

**CARDIAC DISORDERS** - Pericardial effusion

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Gait disturbance; Sudden death NOS

**HEPATOBIILIARY DISORDERS** - Hepatic failure

**INFECTIONS AND INFESTATIONS** - Infections and infestations - Other (aseptic meningitis)

**INVESTIGATIONS** - Platelet count decreased

**METABOLISM AND NUTRITION DISORDERS** - Hyponatremia

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis)

**NERVOUS SYSTEM DISORDERS** - Dysgeusia; Peripheral motor neuropathy; Seizure

**PSYCHIATRIC DISORDERS** - Confusion

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Adult respiratory distress syndrome; Pneumonitis; Pneumothorax; Pulmonary hypertension

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Palmar-plantar erythrodysesthesia syndrome; Skin ulceration

**Note:** Bevacizumab (rhuMAB VEGF) 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.

- 15.35 Drug procurement: The NCCTG research base pharmacist will obtain the drug from Genentech. Members will order the drug from the NCCTG research base pharmacist. Submit the NCCTG Clinical Drug Order/Return Form request to:
- Medical Oncology Pharmacist
  - Mayo Clinic
  - Gonda 10-178
  - Rochester, MN 55905
  - FAX (507) 284-3464

*Return any outdated or remaining drug to the research base pharmacy*

Drug inventory records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the investigational bevacizumab received from NCCTG and used only by authorized investigators for the purposes of this clinical trial. Drug storage and accountability are subject to verification by audit. Refer to the NCCTG Audit Manual and the NCCTG Investigators Handbook for further information on the requirements for drug accountability and storage.

## NCI Informed Consent Template for Cancer Treatment Trials

### \*NOTES FOR LOCAL INVESTIGATORS:

- *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 <http://cissecure.nci.nih.gov/ncipubs/details.asp?pid=1035> 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 investigators are instructional and should not be included in the informed consent form given to the prospective research participant.*

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### **Revised:**

### **N0735, Phase II Trial of Weekly Albumin-Bound Paclitaxel in Combination with Gemcitabine and Bevacizumab in Patients with Metastatic Breast Cancer**

*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 breast cancer that has spread to other parts of your body (called metastatic breast cancer).**

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

The purpose of this research study is to find out what effects (good and bad) that the combination of albumin-bound paclitaxel [also known as paclitaxel protein-bound particles for injectable suspension (albumin-bound) or Abraxane®] plus gemcitabine [Gemzar®] and bevacizumab [Avastin®] has on you and your metastatic breast cancer (breast cancer that has spread to other parts of your body).

Gemcitabine, albumin-bound paclitaxel and bevacizumab are approved by the FDA to treat some types of cancer, including breast cancer.

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

About 51 people will take part in this study.

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

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

You will need to have 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 decision will be up to your study doctor. You would likely have the same tests and procedures if you were having chemotherapy for your cancer outside of this clinical trial.

- Routine blood tests and medical exams.
- Pregnancy test (if necessary)
- X-rays, scans (MRI or CT), or ECG (heart test) may also be done if your doctor thinks they are needed

Before you begin treatment you will be given a brief physical exam. About 3 tablespoonfuls of blood will be taken from your vein and you will have other tests done to help us learn about your cancer. X-rays, CT or MRI will be used. Your doctor may also do these tests again during your treatment to see how your cancer is doing.

### **During the study ...**

**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 at the start of the study.**

**They are part of regular cancer care.**

- Medical history and exam, weight
- Routine blood and urine tests - some routine tests will be done at least weekly for the first two cycles

**You will also be asked to complete a survey before you start the study which asks about your quality of life and current symptoms. This survey should take less than 15 minutes.**

Add 1

Add 1

Add 1 **After you start the study, you will need these tests and procedures that are part of regular cancer care. They are not being done more often because you are in this study.**

- Physical exams will be done before every cycle (about every 3 weeks) or more often if your doctor thinks they are needed
- Routine blood and/or urine tests will be done before every cycle or more often if your doctor thinks they are necessary
- After every other cycle (about every 6 weeks), x-ray pictures of the cancer (CT scans, MRI scans, or chest x-rays) will be done
- If the site of the cancer being looked at is easily measured by the doctor's exam, this exam will be done every 3 weeks

**You will also be asked to complete a survey at regular intervals throughout the study which asks about your quality of life and current symptoms. This survey should take less than 15 minutes each time you complete it.**

On the first day of a 21-day treatment cycle, albumin-bound paclitaxel will be given as an infusion into a vein over 30 minutes, followed by gemcitabine, which will also be given as an infusion over 30 minutes. Bevacizumab will be given as an infusion over 90 minutes. Both albumin-bound paclitaxel and gemcitabine will be given in the same way one week later (Day 8 of the cycle), unless you have bad side effects. This treatment will be repeated every 21 days as long as your cancer is not getting worse and you are not having bad side effects.

**albumin-bound paclitaxel plus gemcitabine and bevacizumab:**  
**(A cycle is 3 weeks)**

<b>Drug</b>	<b>Week 1</b>	<b>Week 2</b>	<b>Week 3</b>
albumin-bound paclitaxel IV over 30 minutes	Day 1 of cycle	Day 8 of cycle	rest
gemcitabine IV over 30 minutes	Day 1 of cycle	Day 8 of cycle	rest
bevacizumab IV over 90 minutes*	Day 1 of cycle	rest	rest

The first time you are given bevacizumab, it will take 90 minutes. If you do not have any bad effects, it can be given over 60 minutes the second time and over 30 minutes for the third time and for all future infusion. If you have any problems, bevacizumab will have to be given over a longer period of time again.

**When you are done taking the study drugs...**

When you are done taking the study drugs, your doctor will decide what further treatments you will get. You should ask your doctor what treatment you will get. Your doctor will ask you to visit the office for follow-up exams for at least 5 years.

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

You will be asked to take treatment until the drugs are no longer helpful, or if you or your doctor thinks that the side effects of the treatment are too bad. After you are finished taking treatment the study doctor will ask you to visit the office for follow-up exams for at least 5 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 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 drug or treatment. 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.**

**Risks and side effects related to the drugs in this study include:**

**For albumin-bound paclitaxel [paclitaxel protein-bound particles for injectable suspension (albumin-bound); Abraxane®]**

**Likely side effects of albumin-bound paclitaxel (happen  $\geq$ 20% of the time)**

- Add 2 • **Decreased red blood cells (the oxygen carrying cells) which could make you feel tired (anemia)**
- Add 2 • **Decreased white blood cells (the infection fighting cells) which could put you at risk for infection (leukopenia)**
- Add 2 • **Feeling tired (fatigue)**
- **Nausea (feeling sick to your stomach)**
- **Vomiting (throwing up)**
- **Diarrhea (loose stools)**
- **Constipation (hard stools)**
- **Loss of appetite (not feeling hungry, not wanting to eat)**
- **Hair loss**
- **Muscle and joint pains**
- Add 2 • **Numbness, tingling, or inflammation of the nerves (usually in the hands and feet), which may be painful. (peripheral neuropathy)**
- Add 2 • **Changes in taste sensation (dysgeusia)**

Add 2,5

**Less likely side effects of albumin-bound paclitaxel (happen <20% of the time)**

- Fever
- Infection
- Fall in the number of platelets in your blood leading to a greater chance of bleeding
- Increased level of phosphorus in the blood (hyperphosphatemia)
- Decreased albumin in the blood (hypoalbuminemia)
- Abnormally low calcium in the blood, that can result in muscle cramps, abdominal cramps, spasms (hypocalcemia)
- High blood sugar (hyperglycemia)
- Low blood sugar (hypoglycemia)
- Decreased sodium levels in the blood (hyponatremia)
- Elevated levels of potassium in the blood (hyperkalemia)
- Increased magnesium in the blood (hypermagnesemia)
- Trouble breathing or painful breathing caused by narrowing of airways
- Sores in the mouth and/or throat
- Changes in your liver as seen on a blood test, which may lead to skin yellowing, confusion, and swelling and soreness in your belly
- Nose bleed (epistaxis)
- Dry Skin (xerosis)
- Rash
- Abnormal heart rhythm (abnormal electrocardiogram)
- An infection where the nail and skin meet at the side or the base of a finger or toenail, which can be painful (paronychia)
- Mood changes
- Eye problems, blurred vision, watery eyes, dry eyes

Add 2,5

**Rare but serious risks of albumin-bound paclitaxel (events occurring less than 2-3% of the time)**

- Liver Failure
- Lack of oxygen to the heart muscle which can cause damage to the heart (heart attack)
- Imbalance of salts or chemicals in the blood leading to kidney damage
- Rare reports of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving Abraxane. Most of the individuals were previously exposed to cardiotoxic drugs, such as anthracyclines, or had underlying cardiac history.
- Skin changes at the site of injection
- Slowing of the heart rate (Pulse)
- Allergic reaction (symptoms can include difficulty breathing, flushing, low blood pressure, rash and itching)
- Pulmonary edema
- Cough

**Gemcitabine (Gemzar®) risks and side effects****Likely side effects (happen more than 20% of the time)**

- Fall in the number of white blood cells leading to a greater chance of infection

- **Fall in the number of red blood cells leading to anemia (feeling tired and run down)**
- **Fall in the number of platelets in your blood leading to a greater risk of bleeding**
- **Nausea (feeling sick to your stomach)**
- **Vomiting (throwing up)**
- **Flu-like symptoms such as chills, fever, chills, aching, feeling tired, lack of energy, cough, runny nose, sweating**
- **Fever**
- **Headache**
- **Muscle and joint pains**
- **Weakness**
- **Changes in your liver as seen on a blood test**
- **Loose stools (diarrhea)**
- **Skin rash**
- **Tingling prickling or creeping feeling on the arms, hand, feet, and legs**
- **Shortness of breath**
- **Fluid retention (usually seen as swelling of the hands, feet or face)**

**Less likely, risks from gemcitabine (happen less than or equal to 20% of the time)**

- **Mild changes in your kidneys (protein or blood in your urine)**
- **Mild hair loss**
- **Lining of mouth and throat may be red, irritated or sore**
- **Loss of appetite (not feeling hungry, not wanting to eat)**
- **Sleepiness**
- **Agitation (feeling restless)**
- **Trouble sleeping**

**Rare but serious risks from gemcitabine (happen less than 2-3% of the time)**

- **Rapid pulse**
- **Irregular heartbeat**
- **Drop in blood pressure**
- **Severe changes in liver function tests (may see yellowing of the skin or eyes)**
- **Severe difficulty breathing**
- **Severe kidney problems including kidney failure)**
- **Heart failure**
- **Confusion**
- **Convulsions (“fits”)**
- **Coma**
- **Severe allergic reactions - may include rash, changes in blood pressure, swelling and increased fluid in the tissues, increases in heart rate, difficulty breathing and collapse**
- **Blood vessel inflammation and gangrene (death of soft tissue due to lack of blood supply)**
- **Capillary leak syndrome, which can cause low blood pressure or lessen the amount of oxygen getting to tissue**
- **Severe skin reactions including peeling of the skin or blistering red sores that may require hospitalization**

**Risks and side effects for bevacizumab (Avastin®) include:**

Add 3,6

**Likely**

- High blood pressure
- Loss of the normal functioning of the ovaries in a woman that can result in temporary or permanent menopause; the impact on fertility (temporary or permanent) is unknown

Add 3,6

**Less Likely**

- Lack of enough red blood cells (anemia)
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- 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
- Diarrhea
- Heartburn
- Bleeding in some organ(s) of the digestive tract
- Blockage in an organ(s)/part(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
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- 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
- Destruction or death of jawbone
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)

- **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**
- **Fainting**
- **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 or runny nose, sneezing**
- **Itching**
- **Skin rash with the presence of macules (flat discolored area) and papules (raised bump)**
- **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**

**Rare but serious**

Add  
1,3,6

- **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)**
- **Sudden decrease of kidney function**
- **A condition in which the kidneys leak a large amount of protein into the urine that can cause complications including swelling and 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**

\*\*\*\*\*

**As with any medications, allergic reactions are a possibility.**

**In some people, the side effects from these therapies may be severe or life-threatening. You must contact your doctor immediately if you have:**

- **Diarrhea: if you have more than 4 bowel movements in one day or have diarrhea at night**
- **Mouth sores: if you have pain, redness, swelling, or sores in your mouth that prevent you from eating or drinking**
- **Pain or swelling of the hands or feet: if you have pain, swelling, or redness of your hands or feet that prevents normal activity**
- **Fever or infection: if you have a temperature of 100.5°F or higher, or other signs of infection**
- **Pain in your belly or rectum that is new or getting worse**

**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. Women should not breast-feed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor 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.**

**Women who can become pregnant must have a pregnancy test before taking part in this study. It is possible that you may need a second pregnancy test before starting treatment on this study. If you need a second pregnancy test, you will not have to pay for it. You will be told the results of the pregnancy test. If the pregnancy test is positive, you will not be able to take part in the study.**

**The risks of drawing blood include pain, bruising, or rarely, infection at the needle site.**

**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 we feel that the combination of albumin-bound paclitaxel with gemcitabine and bevacizumab is a promising line of research to improve the treatment of patients with metastatic breast cancer, there is no proof of this yet. We do know that the information from this study will help doctors learn more about combining these 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 (including treatment with albumin-bound paclitaxel, gemcitabine, and bevacizumab) or care for your cancer without being in a study
- Taking part in another study
- 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.

You may also choose not to have any further treatment.

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)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), Office for Human Research Protections (OHRP) or other offices within the Department of Health and Human Services (DHHS), and/or the Office of the Inspector General (OIG) involved in keeping research safe for people
- Genentech, Inc, the drug company providing the bevacizumab (Avastin®) for this study
- Abraxis Oncology and Abraxis Bioscience, the drug company providing albumin-bound paclitaxel (Abraxane®) for this study
- Eli Lilly and Company, the drug company providing gemcitabine (Gemzar®) 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.**

**Genentech will provide you with the bevacizumab free of charge for this study. Steps have been taken to make sure there is enough bevacizumab, free of charge, for all who take part in this study. If, however, bevacizumab becomes FDA approved in this combination while you are being treated, there is a possibility that you and/or your health plan would be asked to purchase the rest of your doses.**

**Abraxis will provide you with the albumin-bound paclitaxel (Abraxane®) free of charge for this study. Steps have been taken to make sure there is enough albumin-bound paclitaxel, free of charge, for all who take part in this study. However, if albumin-bound paclitaxel (Abraxane®) becomes FDA approved in this combination while you are being treated, there is a possibility that you and/or your health plan would be asked to purchase the rest of your doses.**

**Eli Lilly will provide you with the gemcitabine (Gemzar®) free of charge for this study. Steps have been taken to make sure there is enough gemcitabine, free of charge, for all who take part in this study. However, if gemcitabine becomes FDA approved in this combination while you are being treated, there is a possibility that you and/or your health plan would be asked to purchase the rest of your doses.**

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

**You will not need to pay for any tests and procedures that are done just for this research study. This specifically applies to the blood tests done for research purposes and the tests that will be done on your breast cancer tissue sample. You and/or your health plan will also need to pay for all other tests and procedures that you would normally have as part of your regular medical care. These tests and procedures include routine physician visits, blood tests and radiographic studies (x-rays, bone scans, or CT scans) used to assess the effects of the treatment on you and the cancer.**

**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. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in any of these additional studies.**

**You can say “yes” or “no” to each of the following studies. Please mark your choice for each study.**

**About Using Biological Samples for Research**

This study also has laboratory tests that will study small samples of blood and biopsy tissue.

Four (4) blood samples (about 2 teaspoons each) will be collected by drawing some blood from a vein before treatment begins, before your third cycle of treatment, before your sixth cycle of treatment and at the time you stop getting treatment or after six months of treatment, if you’re still getting treatment.

The biopsy tissue sample will be from any surgeries or biopsies you have had in the past for your breast cancer. You will not have any more biopsies done to get this tissue.

The blood and tissue will be sent to 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 researchers better understand your type of cancer. The results of

these tests will not be sent to you or your 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.

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

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

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

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

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

If you want your samples destroyed at any time, write to the Secretary of the \_\_\_\_\_ (local) Institutional Review Board \_\_\_\_\_ (name).

NCCTG has the right to end storage of the samples without telling you. The samples will be the property of NCCTG.

Outside researchers may one day ask for a part of your samples for studies now or for future studies.

**Things to Think About**

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

Your blood and tissue may be helpful for research whether you do or do not have cancer. The research that may be done with your blood and tissue may not help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your blood and tissue will not be given to you or your doctor. The research will not have an effect on your care.

The samples may be stored indefinitely. You have a say in how your stored samples are used in future research. You can still take part in the study without giving your samples.

Your samples will be stored safely at NCCTG and will be given a code (rather than your name) when they are used in research. This code will allow your samples to be used without anyone knowing that they are your samples just by looking at the label.

The choice to let us keep the samples for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your samples can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any blood or tissue that remains will no longer be used for research.

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

Sometimes blood and/or tissue are used for genetic research (about diseases that are passed on in families). Even if your blood and/or tissue are used for this kind of research, the results will not be sent to you and will not be put in your health records.

In the future, we may find that the research we have done is important for your health care or your family's healthcare. If that happens, we will work with your doctor to make sure you get the information and tell you and your family how the research may affect your lives.

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

### **Benefits**

The benefits of research using blood and tissue 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 about your health to others. 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, mark "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 permit my blood samples to be stored and used for future research on cancer:  
 Yes    No   Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_
2. I permit my blood samples to be stored and used in future research to learn about, prevent, or treat other health problems:  
 Yes    No   Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_
3. I permit my tissue samples to be stored and used for future research on cancer:  
 Yes    No   Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_
4. I permit my tissue samples to be stored and used in future research to learn about, prevent, or treat other health problems:  
 Yes    No   Please initial here: \_\_\_\_\_ Date: \_\_\_\_\_

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 samples to be given to outside researchers, it will be given to them with a code number. If researchers outside NCCTG use the samples for future research, they will decide if you will be contacted and, if so, they would have to contact you through the researchers at NCCTG.

I permit NCCTG to give my blood samples to outside researchers:

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

I permit NCCTG to give my tissue samples 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/>

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 \_\_\_\_\_ {enter total 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:**

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**Signature of person obtaining informed consent:**

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

*Note to Local Investigators: Local IRB changes to this document are allowed. Sections “What side effects or risks can I expect from being in the research study?” or “What other choices do I have if I do not take part in this research study?” should always be tried to be used in their entirety. 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.*