

North Central Cancer Treatment Group

N0821: A Phase II First-Line Study of a Combination of Pemetrexed, Carboplatin and Bevacizumab in Advanced Nonsquamous NSCLC Evaluating Efficacy and Tolerability in Elderly Patients (Age \geq 70 yrs) with Good Performance Status (PS $<$ 2)

Addendum 9 – 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.

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

Title page Updated to reflect Addendum 9 and current NCI version date.

Section 15.0 **Drug Information**
Pages 50-53: Due to the receipt of the updated Comprehensive Adverse Events and Potential Risks List (CAEPR for Bevacizumab, Section 15.35 has been replaced in its entirety.

Pages 50-55: Due to the inclusion of the updated CAEPR for Bevacizumab, repagination has occurred.

Appendix I **Consent Form**
Pages 6-7: Due to the receipt of the Action Letter from NCI, the risks sections for Bevacizumab have been updated 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 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; 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 (≥ 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 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, 2011¹

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%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		<i>Anemia (Gr. 3)</i>
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		<i>Febrile neutropenia (Gr. 3)</i>
CARDIAC DISORDERS			
		Acute coronary syndrome	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Supraventricular tachycardia		<i>Supraventricular tachycardia (Gr. 3)</i>
		Ventricular arrhythmia	
		Ventricular fibrillation	
EAR AND LABYRINTH DISORDERS			
	Vertigo		
GASTROINTESTINAL DISORDERS			
	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 ²	
	Gastrointestinal hemorrhage ³		<i>Gastrointestinal hemorrhage³ (Gr. 2)</i>
	Gastrointestinal obstruction ⁴		

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		Gastrointestinal perforation ⁵	
		Gastrointestinal ulcer ⁶	
	Ileus		
	Mucositis oral		<i>Mucositis oral (Gr. 3)</i>
	Nausea		<i>Nausea (Gr. 3)</i>
	Vomiting		<i>Vomiting (Gr. 3)</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	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>
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		<i>Allergic reaction (Gr. 2)</i>
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection ⁷		<i>Infection⁷ (Gr. 3)</i>
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Gastrointestinal anastomotic leak	
	Wound dehiscence		<i>Wound dehiscence (Gr. 2)</i>
INVESTIGATIONS			
	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>
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		<i>Anorexia (Gr. 3)</i>
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		<i>Arthralgia (Gr. 3)</i>
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia) ⁸		
	Myalgia		<i>Myalgia (Gr. 3)</i>
	Osteonecrosis of jaw ⁹		
NERVOUS SYSTEM DISORDERS			
	Dizziness		<i>Dizziness (Gr. 2)</i>
	Headache		<i>Headache (Gr. 3)</i>
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
	Peripheral sensory neuropathy ¹⁰		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	

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

¹This 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. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

²Gastrointestinal 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.

³Gastrointestinal 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.

⁴Gastrointestinal 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.

⁵Gastrointestinal 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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⁶Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

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

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

⁹Cases 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.

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

¹¹Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥ 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.

¹²Arterial 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.

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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

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- 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

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- 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

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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.

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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

A phase II first-line study of a combination of pemetrexed, carboplatin and bevacizumab in advanced nonsquamous NSCLC evaluating efficacy and tolerability in elderly patients (age \geq 70 yrs) with good performance status (PS $<$ 2)

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

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Statistician: Yingwei Qi \checkmark
507/266-6431

Drug Availability

Commercial Agents: Carboplatin, bevacizumab, pemetrexed

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

\checkmark Study contributor(s) not responsible for patient care.

Document History	(Effective Date)	Document History	(Effective Date)
Activation	December 12, 2008	Update 2	June 18, 2010
Addendum 1	May 1, 2009	Addendum 5	July 16, 2010
Addendum 2	June 26, 2009	Addendum 6	November 5, 2010
Addendum 3	July 17, 2009	Addendum 7	February 4, 2011
Update 1	August 28, 2009	Addendum 8	October 21, 2011
Addendum 4	December 18, 2009	Addendum 9	December 23, 2011

Study Participants Date Activated

Entire NCCTG December 12, 2008

NCI Version Date: November 29, 2011

Add 5,9

15.35 Comprehensive Adverse Events and Potential Risks List (CAEPR)
For Bevacizumab (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 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, 2011¹

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term)			Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAE)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		<i>Anemia (Gr. 3)</i>
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		<i>Febrile neutropenia (Gr. 3)</i>
CARDIAC DISORDERS			
		Acute coronary syndrome	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Supraventricular tachycardia		<i>Supraventricular tachycardia (Gr. 3)</i>
		Ventricular arrhythmia	
		Ventricular fibrillation	
EAR AND LABYRINTH DISORDERS			
	Vertigo		
GASTROINTESTINAL DISORDERS			
	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 ²	
	Gastrointestinal hemorrhage ³		<i>Gastrointestinal hemorrhage³ (Gr. 2)</i>
	Gastrointestinal obstruction ⁴		

		Gastrointestinal perforation ⁵	
		Gastrointestinal ulcer ⁶	
	Ileus		
	Mucositis oral		Mucositis oral (Gr. 3)
	Nausea		Nausea (Gr. 3)
	Vomiting		Vomiting (Gr. 3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		Fatigue (Gr. 3)
	Infusion related reaction		Infusion related reaction (Gr. 2)
	Non-cardiac chest pain		Non-cardiac chest pain (Gr. 3)
	Pain		Pain (Gr. 3)
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		Allergic reaction (Gr. 2)
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection ⁷		Infection⁷ (Gr. 3)
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Gastrointestinal anastomotic leak	
	Wound dehiscence		Wound dehiscence (Gr. 2)
INVESTIGATIONS			
	Alanine aminotransferase increased		Alanine aminotransferase increased (Gr. 3)
	Alkaline phosphatase increased		Alkaline phosphatase increased (Gr. 3)
	Aspartate aminotransferase increased		Aspartate aminotransferase increased (Gr. 3)
	Blood bilirubin increased		Blood bilirubin increased (Gr. 2)
	Cardiac troponin I increased		
	Neutrophil count decreased		Neutrophil count decreased (Gr. 3)
	Weight loss		Weight loss (Gr. 3)
	White blood cell decreased		White blood cell decreased (Gr. 3)
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		Anorexia (Gr. 3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		Arthralgia (Gr. 3)
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia) ⁸		
	Myalgia		Myalgia (Gr. 3)
	Osteonecrosis of jaw ⁹		
NERVOUS SYSTEM DISORDERS			
	Dizziness		Dizziness (Gr. 2)
	Headache		Headache (Gr. 3)
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
	Peripheral sensory neuropathy ¹⁰		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		

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

¹This 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. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

²Gastrointestinal 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.

³Gastrointestinal 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.

⁴Gastrointestinal 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.

⁵Gastrointestinal 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.

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

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

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

⁹Cases 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.

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

¹¹Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥ 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.

¹²Arterial 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.

15.36 Drug procurement: Commercially available.

15.37 Nursing guidelines:

- 15.371 Monitor patients closely for infusion type reactions, including fever, chills, myalgias, rigors, or other allergic reactions. While this is less likely given that bevacizumab is a humanized antibody, there still exists the potential for severe allergic reactions. If these signs or symptoms occur stop the infusion immediately and contact MD. Have emergency equipment nearby and be prepared to administer emergency treatment as ordered by MD.
- 15.372 Monitor urine dipstick at the beginning of each infusion therapy.
- 15.373 Evaluate IV site regularly for signs of infiltration.
- 15.374 Bleeding in the absence of thrombocytopenia is a dose limiting toxicity. Monitor patient closely for hemorrhagic events, including CNS hemorrhage, epistaxis, hematemesis and hemoptysis. Most cases of bleeding have occurred at the tumor site. Advise patient about the potential for bleeding or thrombosis.
- 15.375 In patients receiving treatment for lung cancer, hemoptysis and pulmonary hemorrhage occurred in up to 10% of patients in one study. Monitor these patients especially closely.
- 15.377 Patient may experience grade 1-2 nausea, however vomiting is uncommon. Medicate as ordered and monitor for effectiveness.
- 15.378 Monitor for skin rash, instruct patient to report to MD.
- 15.379a Monitor blood pressure. Administer antihypertensives as ordered by MD.
- 15.379b Monitor for signs and symptoms of DVT or PE, or MI. These have been reported with therapy. Instruct patient to report any calf pain, chest pain or SOB to MD immediately.
- 15.379c Asthenia and headache were reported commonly during therapy (in up to 70% and 50% of patients respectively). Administer acetaminophen as needed. Monitor for its effectiveness. Avoid the use of aspirin, or ibuprofen as this may interfere with the coagulation cascade and further add to the risk of bleeding.
- 15.379d Monitor CBC, including platelets. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the MD.
- 15.379e Patient receiving warfarin therapy for thrombosis should have their PT or INR monitored weekly until two stable therapeutic levels are attained: for patients on warfarin for venous access prophylaxis, routine monitoring is satisfactory.
- 15.379f A rare but serious complication of bevacizumab is wound dehiscence. Patients who have had recent surgery or have other open wounds should be monitored carefully.
- 15.379g Gastrointestinal perforation with or without abdominal abscess is rare but possible. This may present itself as vague abdominal pain associated

with constipation and vomiting. Instruct patient to report abdominal pain to the MD.

15.379h Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a rare (<1%) but serious condition. Presenting symptoms may include changes in mental status, visual disturbance, seizure, or other CNS changes. Patients with this syndrome generally had HTN as well, therefore BP monitoring is important. Instruct patient to report any mental status changes, visual changes, seizures, or other CNS changes to the MD immediately. These may be a sign of RPLS or more serious condition, such as hemorrhagic event in the CNS.

16.0 Statistical Considerations and Methodology

16.1 Study Overview / Rationale: This single arm, one stage, phase II study is designed to primarily assess the 6-month progression-free survival rate (PFS6) of treatment combination pemetrexed, carboplatin and bevacizumab as first-line treatment in elderly patients (≥ 70 years) with advanced nonsquamous NSCLC (Stage IIIB with pleural effusions or IV) and with good PS. Other endpoints of interest that will be evaluated are AE profile, overall survival, confirmed response rate, and quality of life.

Patel et al reported an overall response rate of 55% for advanced nonsquamous NSCLC patients regardless of age in a first-line setting and provides preliminary evidence of efficacy for the treatment combination with an acceptable toxicity profile (34). ECOG 4599 explored treatment combination paclitaxel, carboplatin, and bevacizumab in patients ≥ 70 years with advanced NSCLC in a first-line setting and indicated that increased adverse event rate (regardless of attribution) with this treatment combination may have contributed to the absence of its survival benefit (33). Pemetrexed has been shown to be well tolerated in patients ≥ 70 years with advanced NSCLC. The NCCTG trial (N0426) of pemetrexed and bevacizumab that was recently completed showed mild AE profile (regardless of attribution) in patients ≥ 70 years with advanced NSCLC in the second line setting. Among 13 evaluable patients, only one patient has experienced a grade 4/5 AE (grade 5 disease progression). Four patients have experienced seven grade 3 AEs including 1 fatigue, 1 hyperglycemia, 1 chest pain, 1 anxiety, 1 bilirubin, 1 SGOT and 1 SGPT. Hence, by substituting paclitaxel with pemetrexed, the proposed treatment combination pemetrexed, carboplatin and bevacizumab is expected to have a tolerable AE profile such that efficacy (PFS6) can be better evaluated. Therefore, we propose a single arm, one stage, phase II trial with a Simon design to assess the 6-month progression free survival rate of treatment combination pemetrexed, carboplatin and bevacizumab as first-line treatment in patients ≥ 70 years with advanced NSCLC.

ECOG 4599 trial showed that elderly patients (≥ 70 years) that received treatment combination paclitaxel, carboplatin, and bevacizumab as first-line treatment had a median PFS of 5.9 months (33), which corresponds to a PFS6 rate of approximately 50%. The proportion of progression-free patients at 6 months is our primary endpoint, which will be evaluated using a one-stage phase II Simon design (49). The largest PFS6 rate where the proposed treatment regimen would be considered ineffective in this population is 50%, and the smallest PFS6 rate that would warrant subsequent studies with the proposed regimen in this patient population is 70%.

Appendix I

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

***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 authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

Study Title: N0821, A phase II first-line study of a combination of pemetrexed, carboplatin and bevacizumab in advanced nonsquamous NSCLC evaluating efficacy and tolerability in elderly patients (age \geq 70 yrs) with good performance status (PS $<$ 2)

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 non-small cell lung cancer which has spread beyond the limits that can be cured or safely removed by surgery, such as involvement of another part of your body.

Why is this research study being done?

This study is being done to:

- find out what effects (good and bad) the combination of pemetrexed disodium, carboplatin and bevacizumab has on you and your lung cancer. Pemetrexed disodium, carboplatin and bevacizumab are FDA-approved drugs used in the treatment of cancers such as mesothelioma, lung cancer and colorectal cancer.
- see if the combination of pemetrexed disodium, carboplatin and bevacizumab will help improve survival.
- look at how the body uses this combination of drugs.

How many people will take part in the research study?

About 60 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 the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history
- Complete physical exam
- Blood tests
- X-rays or CT scans or MRIs for tumor measurement
- Random urine collection (at least 4 ml)
- Complete questionnaires

If the exams, tests and procedures above show that you can be in the study, and you choose to take part, the drugs pemetrexed disodium, carboplatin and bevacizumab will be given to you as an outpatient. All drugs will be given as an infusion through a needle into your vein on the first day of each cycle of treatment. Each cycle is 21 days. The doses given to you will be based on your weight. Pemetrexed disodium will be infused over 10 minutes followed by carboplatin to be given over 30 minutes, and then bevacizumab will be infused over about 90 minutes. If you do well with the first dose of bevacizumab, the next dose will be given over 60 minutes and if that infusion goes well, the remaining doses will be given over 30 minutes.

A research blood draw (about 2 teaspoons) will be taken to help see how the treatment will affect your body. You will also fill out a questionnaire before cycles 3 and 5, every 3 months, when you stop treatment, and after you stop treatment to help the investigators find out how treatment is affecting the quality of your life.

Past studies of patients taking pemetrexed disodium have shown that a high level of a certain amino acid in your blood (called homocysteine) may give you a higher risk of getting serious side effects. To try to lower the risk of bad side effects, you will have to take folic acid pills (or an equivalent vitamin supplement) daily, starting at least 3 days before getting the first dose of treatment. You will then need to take it daily until 3 weeks after you have stopped getting pemetrexed disodium. Also, you will be given a shot of vitamin B₁₂ into a muscle in your arm or hip somewhere between 1-28 days before getting treatment with pemetrexed disodium. If you are already taking an equivalent vitamin supplement, you will be given a shot of Vitamin B₁₂ 1 day before getting treatment with Pemetrexed disodium. You will then be given a shot of B₁₂ every 9 weeks until 3 weeks after you have stopped getting pemetrexed disodium..

Add 3

Before you get treatment, you will get a medication (dexamethasone) by mouth the day before, the day of, and the day after all doses of pemetrexed disodium to help stop the development of rash.

You might also get medications before getting treatment that help fight the feeling of being sick to your stomach and throwing up.

During the study

If you choose to take part, then you will need the following tests and procedures each cycle (cycle=3 weeks). They are part of regular cancer care.

- Medical history
- Complete physical exam
- Blood tests

- Random urine collection (at least 4 ml)
- Central review of biopsy tissue slides

After you go on the study, blocks and/or slides made from your biopsy tissue taken at the time of primary diagnosis will be sent to laboratories associated with the North Central Cancer Treatment Group (NCCTG). One part of the tissue will be for central review to confirm the results of your local laboratory review. A different part of the tissue will be for research tests. This is mandatory. These blocks and/or slides will be kept by the North Central Cancer Treatment Group.

Your blood pressure should be checked and recorded weekly on a blood pressure diary during the first cycle of bevacizumab therapy, either at your doctor's office or using any calibrated electronic device (such as those found at a local drug store or pharmacy). The completed blood pressure diary will need to be given to your study doctor each time you see him/her. You should take your blood pressure after you have been sitting at rest for 5 minutes. Contact your study doctor or local doctor if you think you are having any signs (for example, headaches) that might lead you to think your blood pressure is too high.

When you are finished taking the treatment, you will continue

- Folic acid (or an equivalent vitamin supplement) until 3 weeks after you have stopped taking pemetrexed disodium.
- Vitamin B₁₂ until 3 weeks after you have stopped taking pemetrexed disodium.
- Follow-up evaluation 28-42 days after your last dose of the study drugs to see if you have had side effects and to see how you are doing.

Cycle 1

Cycle = 21 days

Day of cycle	What you do
7 days before starting treatment	<ul style="list-style-type: none"> • Vitamin B₁₂ injection into a muscle in your arm or hip will be given before starting the folic acid (or an equivalent vitamin supplement). • Folic acid pills (or an equivalent vitamin supplement) daily starting 7 days before getting the first dose of pemetrexed disodium
After you begin the study, but before you start treatment	<ul style="list-style-type: none"> • Research blood draw (about 2 teaspoons).
1 day before starting treatment	<ul style="list-style-type: none"> • Dexamethasone by mouth twice a day.
1	<ul style="list-style-type: none"> • Dexamethasone by mouth twice a day. • Pemetrexed disodium will be given into a vein in your arm over 10 minutes. • Carboplatin will be given into a vein in your arm over 30 minutes • Bevacizumab will be given into a vein in your arm over 90 minutes.
2	<ul style="list-style-type: none"> • Dexamethasone by mouth twice a day.
Daily	<ul style="list-style-type: none"> • Folic acid (or an equivalent vitamin supplement) pills by mouth.
Weekly	<ul style="list-style-type: none"> • Check blood pressure • Record values on the blood pressure diary
21	<ul style="list-style-type: none"> • Dexamethasone by mouth twice a day.
22 (Day 1 of next cycle)	<ul style="list-style-type: none"> • Return to your study doctor's office for your next exam and to begin the next cycle.

FUTURE CYCLES

Day of cycle	What you do
Prior to each cycle of treatment	<ul style="list-style-type: none"> • Random urine sample. • Routine blood tests (more if your doctor tells you to) to watch for side effects of treatment.
1 day before starting treatment	<ul style="list-style-type: none"> • Dexamethasone by mouth twice a day.
1	<ul style="list-style-type: none"> • Complete questionnaire. • Dexamethasone by mouth twice a day. • Pemetrexed disodium will be given into a vein in your arm over 10 minutes. • Carboplatin will be given into a vein in your arm over 30 minutes (stopped after completing 6 cycles of treatment) • Bevacizumab will be given into a vein in your arm over 60 minutes if the first dose was well-tolerated. If the second dose is well-tolerated all future doses will be given over 30 minutes.
2	<ul style="list-style-type: none"> • Dexamethasone by mouth twice a day.
Daily	<ul style="list-style-type: none"> • Folic acid (or an equivalent vitamin supplement) pills by mouth.
21	<ul style="list-style-type: none"> • Dexamethasone by mouth twice a day.
22 (Day 1 of next cycle)	<ul style="list-style-type: none"> • Return to your doctor's office for your next exam and to begin the next cycle.
Every other cycle	<ul style="list-style-type: none"> • X-rays or CT scans or MRIs for tumor measurement every other cycle (more if your doctor tells you to).
Every 9 weeks	<ul style="list-style-type: none"> • Vitamin B₁₂ injection into a muscle in your arm or hip.

Add 1

How long will I be in the research study?

You will be asked to continue taking treatment as long as your disease does not get worse and you are able to do well with the side effects of the chemotherapy. We would then like to keep track of your medical condition for up to five years. Keeping in touch with you and checking on your condition every year helps us look at the long-term effects of the study.

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.

Add 4

It is important to tell the study doctor if you are thinking about stopping so any risks from the pemetrexed disodium, carboplatin, and bevacizumab can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what followup 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?

Add 4

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 pemetrexed disodium, carboplatin, and bevacizumab. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death. You should talk to your study doctor about any side effects that you have while taking

part in the study.

Risks and side effects related to the **pemetrexed disodium** include the following. Some of the following side effects may cause life-threatening events such as infections, kidney failure, bleeding, and possibly death.

Add 4,8

Likely (events that occur greater than 20% of time)

- Low white blood cells which may lead to infection (Leukopenia)
- Low red blood cells which may lead to fatigue and/or less energy (Anemia)
- Feeling sick to the stomach (nausea)
- Throwing up (vomiting)
- Loss of body fluids (dehydration)
- Loose stools (diarrhea)
- Mouth and throat sores (Stomatitis/Pharyngitis)
- Loss of appetite (Anorexia)
- Mild hair loss (alopecia)
- Abdominal (stomach) pain
- Itchy skin rash
- Shortness of breath (Dyspnea)
- Weakness (Asthenia)
- Less energy
- Cough
- Headache
- Feeling tired (Fatigue)

Add 4,8

Less Likely (events that occur less than or equal to 20% of time)

- Fall in the platelet count that may lead to the risk of bruising and bleeding after an injury (Thrombocytopenia)
- Change in liver function tests (tests that show how the liver is working)
- Decrease in kidney function
- Burning, itchy, red, sore eyes with lots of watering
- Infection in the blood with fever (caused by a fall in the number of white blood cells)
- Inflammation of the skin (swelling, redness, pain)
- Infection such as urinary tract infection
- Blood clots
- Increase in body fluid (edema, swelling)
- Sores on the skin or local redness, pain, and/or swelling at the site of the injection
- Infection of the skin and surrounding tissue (Cellulitis)
- Indigestion or heartburn (Dyspepsia)
- Change in taste sensation (Dysguesia)
- Chest pain that occurs when your heart doesn't get enough oxygen. It can be a warning sign of a heart attack (Angina – unstable)
- Lack of oxygen to the heart muscle which can cause damage to the heart (Heart attack)
- Increased heart rate
- Numbness, tingling, or inflammation of the nerves (usually in the hands and feet) which may be painful (Peripheral neuropathy)
- Inflammation/infection of the lungs (Pneumonitis/pneumonia)
- Difficulty falling or staying asleep (Insomnia)
- Bleeding from the stomach, large intestine and/or small intestine (Gastrointestinal bleeding)
- Blockage in the intestines (Bowel obstruction)
- Infection around the eye, also called pink eye (Conjunctivitis)
- Damage to the kidneys, which may be temporary or permanent (Nephropathy/acute renal failure)
- Abnormal heart beat (Arrhythmia)
- Fever (Pyrexia)
- Irregular or difficulty in passing stool (constipation)

Add 4,8 **Rare but serious**

- Fever, chills, swelling of body, shortness of breath (Allergic reaction)
- Inflammation in the colon (Colitis) has been reported in patients taking Pemetrexed

You may not take aspirin and aspirin-like drugs (i.e., Ibuprofen, Advil®, Motrin®, Aleve®, etc.) for two days before getting treatment, on the day of treatment, and for two days after getting the treatment. Aspirin and aspirin-like drugs can cause trouble with the body's ability to remove pemetrexed disodium, raising the risk of low blood counts that can lead to infections and bleeding. Tylenol, however, may be used.

Risks and side effects related to **carboplatin** include the following:

Likely (events that occur greater than 20% of time)

- Feeling sick to your stomach (nausea)
- Throwing up (vomiting)
- Change in appetite or weight
- Low white blood cell counts leading to an increased risk of infections with or without fever
- Low platelet count leading to an increased risk of bleeding
- Low red blood cell count causing anemia
- Change in blood tests, particularly loss of magnesium

Add 1 **Less likely (events that occur less than or equal to 20% of time)**

- Numbness and/or tingling of the hands and feet, usually this goes away after the drug is stopped, however, for some patients this may not ever go away
- Hearing problems
- Abnormal kidney tests
- Abnormal liver tests
- Low or high blood pressure
- Mouth sores
- Change in taste
- Fever
- Vision problems
- Allergic reactions (rash, hives, redness, itching, swelling, and difficulty in breathing with wheezing)
- Other skin rashes
- Difficult bowel movements (constipation)
- Loose stools (diarrhea)
- Hair loss or thinning

Rare but serious (events that occur less than 2-3% of time)

- Secondary leukemia and/or myelodysplastic syndrome (damage to the bone marrow that affects normal blood cell production)

Risks and side effects related to the bevacizumab include the following:

Add 5,9 **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
5,9

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

Add
5,9

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
- 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 medication, allergic reactions are a possibility. Also, one of the side effects of this treatment is the rare possibility of developing leukemia later in life.

Side effects from the blood draws:

You may have some pain, infection, swelling or bruising around the vein that is used to draw the blood samples. You may be dizzy, but fainting doesn't happen to very many people.

Reproductive risks:

Add 1,3 You should not father a baby while on this study because the drugs in this study can affect an unborn baby. Men must be surgically sterile or use a medically approved contraceptive regimen during and for 3 months after treatment. Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Add 1 If your partner plans to become pregnant, becomes pregnant, misses a period, or thinks she might be pregnant, you must tell the study doctor right away. All reports of pregnancy must be followed to get information about the pregnancy and delivery and the health of the infant. We will talk to you about ways for managing the pregnancy.

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

Are there benefits to taking part in the research study?

Add 4 Taking part in this study may or may not make your health better. While doctors hope the pemetrexed disodium, carboplatin, and bevacizumab will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about pemetrexed disodium, carboplatin, and bevacizumab 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 standard chemotherapy treatment or other care for your cancer without being in the research study
- Taking part in another research study
- Getting no treatment

You should 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:

- The study sponsor, Eli Lilly Pharmaceuticals;
- Representatives of North Central Cancer Treatment Group, the group that is coordinating this study;
- *Local IRB information*; and
- The National Cancer Institute (NCI) and other government agencies, like the Office for Human Research Protection and the Food and Drug Administration (FDA), involved in keeping research safe for people.

[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.

The bevacizumab, pemetrexed and carboplatin can be bought with a prescription. You and/or your health plan will need to pay for all costs associated with this treatment. You and/or your health plan may have to pay for other drugs or treatment that are given to help control side effects as well as the cost of tests or exams to look at possible side effects. The dexamethasone, folic acid, and vitamin B₁₂ injections will need to be paid for by you and/or your health plan.

You will not need to pay for any tests done only for research. This would involve the research studies done on the blood and tissue samples. Other tests such as physical examination, scans, and blood tests that would normally be performed as part of your regular medical care will be the responsibility of you and your health plan.

You will not be paid for being in this study.

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

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

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

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

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

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

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

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

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

Who can answer my questions about the research study?

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

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

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 options. Please mark your choice for each one.

About Using Biological Samples for Research

This study also has mandatory laboratory tests that will be done to study small samples of blood and biopsy tissue. A blood sample (about 2 teaspoons) will be done by drawing some blood from a vein. The blood will be taken after registration, but before treatment starts. The biopsy tissue sample will come from the biopsy that was done to see if you had cancer. No additional biopsies will be done to get this tissue.

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

We would like to keep some of the tissue and blood that is left over for future research. If you agree, this tissue and blood will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research (<http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf>).

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

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

Things to Think About

The choice to let us keep the left over tissue and blood 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 tissue and blood 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 tissue and blood 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 the NCCTG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

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

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

Benefits

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

Risks

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

Making Your Choice

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

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

1. My blood may be kept for use in research to learn about, prevent, or treat cancer.

Yes No Please initial here: _____ Date: _____

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

Yes No Please initial here: _____ Date: _____

3. My tissue may be kept for use in research to learn about, prevent, or treat cancer.

Yes No Please initial here: _____ Date: _____

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

Yes No Please initial here: _____ Date: _____

5. My sample(s) may be sent by NCCTG 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 _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

Signature of person obtaining informed consent:

Date _____

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

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