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（研究分担者：櫻木範明）

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（研究分担者：青木大輔）

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（研究分担者：青谷恵利子）

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Ⅱ. プロトコル

プロトコル文書

英語版

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TO: ALL PRINCIPAL INVESTIGATORS, NURSES AND DATA MANAGERS

FROM: KIA NEFF
PROTOCOL SECTION

DATE: SEPTEMBER 29, 2014

RE: PROTOCOL GOG-0213 – REVISION # 12

Protocol Title: "A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL (OR GEMCITABINE) ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #113912) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #113912)"

NCI Version June 23, 2014

Study Chair: Robert L. Coleman, M.D., (713) 745-3357; email: rcoleman@mdanderson.org

IRB Review Recommendation:

( ) No review required
(X) Expedited review; however, site IRB requirements take precedence
( ) Full board review recommended because there have been changes to the Informed Consent and/or the risk information

*Although there is modified risk information for bevacizumab, CTEP has indicated that **the added risks are very similar to or associated with risks that were already included in the previous version of the CAEPR and would have been communicated to patients in the informed consent document (ICD).** In this case, (1) watering eyes is associated with allergic rhinitis; (2) wound complication is a more general term and includes wound dehiscence; (3) dehydration is associated with other known AEs such as colitis, nausea, and vomiting; (4) infections, other (necrotizing fasciitis) is a specific type of infection, a previously identified risk; (5) an increase in frequency of neutrophil count decreased resulted in this risk being moved from less likely to likely, but this risk was previously identified; (6) an increase in frequency of platelet count decreased resulted in this risk being moved from reported but undetermined to less likely, but this risk is associated with bone marrow suppression which is already reflected in the increase in frequency of neutrophil count decreased.

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), it is not necessary to suspend enrollment of new subjects until a revised informed consent

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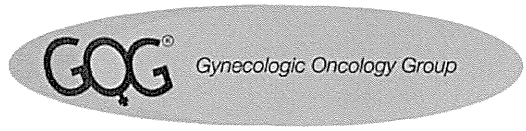

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document is reviewed and approved by the Investigational Review Board (IRB). For this requested amendment, patient enrollment may continue before the IRB reviews and approves such changes to the informed consent; however, changes to the ICDs cannot be implemented until they are approved by the IRB. **Please note that there will be no Action Letter.**

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SUMMARY OF CHANGES

The following changes are being submitted in response to an RA from Dr. Helen Chen (Helen.chen@nih.gov):

For Protocol Revision #12 to:

NCI Protocol #: GOG-0213
Local Protocol #: GOG-0213

NCI Version Date: June 23, 2014
Protocol Date: June 23, 2014

#	Section	Page(s)	Change
1.	Title Page	1	NCT# 00565851 has been added. NCI version date has been updated. Includes Revisions #1-12. Lead Institution and Participation Organizations have been added. Heather Lankes has replaced Kathleen Darcy as Translational Research Scientist. Revised footer has been added.

	4.36	32-37	A Revised CAEPR (Version 2.3, August 1, 2013) has been inserted.
			• Added New Risk:
			  • Less Likely: Dehydration; Wound complication
			  • Rare But Serious: Infections and infestations – Other (necrotizing fasciitis)
			  • Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined: Acidosis; Activated partial thromboplastin time prolonged; Agitation; Alopecia; Anxiety; Arachnoiditis; Arterial injury; Arthritis; Ascites; Ataxia; Atelectasis; Atrioventricular block complete; Atrioventricular block first degree; Back pain; Bladder spasm; Blood antidiuretic hormone abnormal; Blurred vision; Bone marrow hypocellular; Bone pain; Breast pain; Bruising; Burn; Carbon monoxide diffusing capacity decreased; Cardiac arrest; Cataract; CD4 lymphocytes decreased; Central nervous system necrosis; Cerebrospinal fluid leakage; Chelitis; Chest wall pain; Cholecystitis; Chronic kidney disease; Cognitive disturbance; Colonic stenosis; CPK increased; Cystitis noninfective; Death NOS; Depressed level of consciousness; Depression; Dermatitis radiation; Dry eye; Dry mouth; Dry skin; Dysesthesia; Dysphagia; Dysphasia; Ear and labyrinth disorders – Other (tympanic membrane perforation); Edema face; Edema limbs; Edema trunk; Electrocardiogram QT corrected interval prolonged; Encephalopathy; Enterocolitis; Erectile dysfunction; Esophageal pain; Esophageal stenosis; Extraocular muscle paresis; Extrapyramidal disorder; Eye disorders – Other (blindness); Eye disorders – Other (conjunctival hemorrhage); Eye disorders – Other (corneal epithelial defect); Eye disorders – Other (floaters); Eye disorders – Other (ischemic CRVO); Eye disorders – Other (macular pucker); Eye disorders – Other (transient increased IOP > or = 30 mm Hg); Eye disorders – Other (vitreous hemorrhage); Eye pain;

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#	Section	Page(s)	Change

			Facial nerve disorder; Facial pain; Fever; Fibrosis deep connective tissue; Flatulence; Flu like symptoms; Flushing; Forced expiratory volume decreased; Fracture; Gallbladder necrosis; Gallbladder obstruction; Gastrointestinal disorders – Other (peritonitis); Generalized muscle weakness; GGT increased; Head soft tissue necrosis; Hearing impaired; Hemolysis; Hepatic necrosis; Hot flashes; Hydrocephalus; Hypercalcemia; Hyperglycemia; Hyperhidrosis; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperthyroidism; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia; Hypotension; Hypothyroidism; Hypoxia; Injection site reaction; INR increased; Insomnia; Irregular menstruation; Joint effusion; Keratitis; Leukoencephalopathy; Libido decreased; Lipase increased; Localized edema; Lymphocele; Lymphocyte count decreased; Memory impairment; Multi-organ failure; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder – Other (polymyalgia rheumatic); Myocarditis; Nail loss; Nasal congestion; Neck pain; Nervous system disorders – Other (increased intracranial pressure); Optic nerve disorder; Oral pain; Pain in extremity; Pain of skin; Pancreatitis; Paresthesia; Pelvic pain; Pelvic soft tissue necrosis; Phlebitis; Photophobia; Photosensitivity; Proctitis; Psychosis; Pulmonary fibrosis; Purpura; Pyramidal tract syndrome; Rash acneiform; Rectal mucositis; Rectal stenosis; Renal and urinary disorders – Other (dysuria); Renal and urinary disorders – Other (ureterolithiasis); Renal hemorrhage; Respiratory failure; Respiratory, thoracic and mediastinal disorders – Other (dry nares); Respiratory, thoracic and mediastinal disorders – Other (pulmonary infarction); Restrictive cardiomyopathy; Retinal detachment; Retinal tear; Retinopathy; Right ventricular dysfunction; Serum amylase increased; Skin and subcutaneous tissue disorders – Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders – Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Soft tissue necrosis lower limb; Somnolence; Stevens-Johnson syndrome; Tinnitus; Tremor; Tumor pain; Typhlitis; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain; Vaginal discharge; Vasculitis; Vasovagal reaction; Watering eyes; Weight gain
			• Increase in Risk Attribution:
			  • Changed to Likely from Less Likely: Neutrophil count decreased
			  • Changed to Less Likely from Reported But Undetermined: Platelet count decreased
			• Decrease in Risk Attribution:
			  • Changed to Reported But Undetermined from Less Likely: Vertigo
			• Provided Further Clarification:
			  • Supraventricular tachycardia is now reported as Cardiac disorders – Other (supraventricular arrhythmias) and the following footnote (#3) was added, "Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation and atrial flutter."
			  • Gastrointestinal anastomotic leak is now reported as Injury, poisoning and procedural complications – Other (anastomotic leak) and the following footnote (#10) was added, "Anastomotic leak may include Gastrointestinal anastomotic leak;

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#	Section	Page(s)	Change

			Gastric anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak."
			• Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
			  • Added: Dehydration; Platelet count decreased; Wound complication
			• Deleted Risk:
			  • Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined: Pneumonitis; Pneumothorax

2	5.1	44	This section has been updated with OPEN language for patient entry and registration.
3	10.1-10.3	77-85	References to the "Adverse Event Expedited Reporting System (AdEERS)" have been changed to "CTEP Adverse Event Reporting System (CTEP-AERS)" throughout the protocol.
	ICD		Additional changes have been made to the IC document.

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PROTOCOL GOG-0213

A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL (OR GEMCITABINE) ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865, IND #113912) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865, IND #113912)**(12/19/2011) (10/01/12)NCT# 00565851**

NCI Version 06/23/2014

Includes Revisions #1-12

POINTS:

PER CAPITA –14

MEMBERSHIP –6 and 6 additional if surgical candidate is randomized

TRANSLATIONAL RESEARCH PER CAPITA – Award up to 6.5 points based on specimen submissions. Distribution:

- Archival fixed and embedded primary or metastatic tumor (block or 16 unstained slides)-1 point,
- Frozen recurrent tumor-1 point
- Fixed recurrent tumor in a jar of formalin or embedded in a paraffin block-1 point
- Frozen normal tissue-0.5 point
- Fixed normal tissue in a jar of formalin or embedded in a paraffin block-0.5 point
- Frozen pre-op serum-0.5 point
- Frozen pre-op plasma-0.5 point
- Whole blood-0.5 point (for all patients not just patients randomized to surgery)**(06/22/09)**

TRANSLATIONAL RESEARCH MEMBERSHIP - Bonus membership point will be awarded for **submission of satisfactory** fixed primary tumor, frozen recurrent tumor, fixed recurrent tumor, frozen serum and frozen plasma.

Lead Institution: NRG/NRG Oncology

Participating Organizations ()
ALLIANCE / Alliance for Clinical Trials in Oncology
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
SWOG / SWOG

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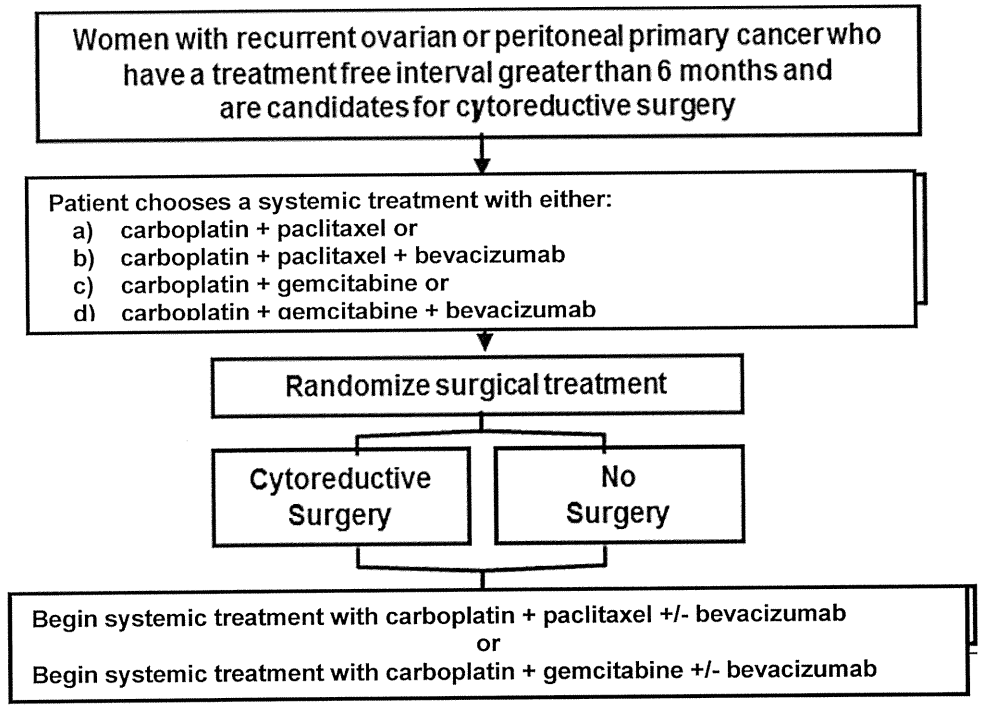
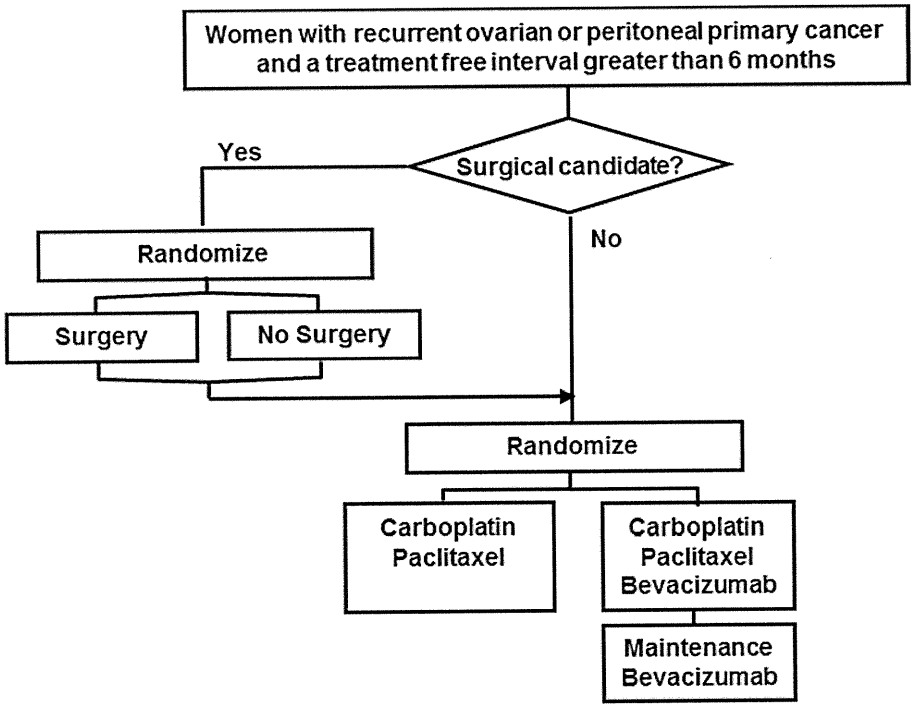
OPEN TO PATIENT ENTRY DECEMBER 06, 2007; REVISED AUGUST 4, 2008; REVISED JUNE 22, 2009; REVISED MARCH 15, 2010; REVISED AUGUST 23, 2010; REVISED JANUARY 3, 2011 REVISED AUGUST 29, 2011; REVISED SEPTEMBER 26, 2011; REVISED DECEMBER 19, 2011, REVISED OCTOBER 1, 2012; REVISED AUGUST 19, 2013; REVISED SEPTEMBER 29, 2014

SCHEMA beginning 8/29/2011(08/29/11) (12/19/11)(10/01/12)



The following schema was in effect between 12/6/2007 to 8/28/2011. Once the accrual goal for evaluating the chemotherapy regimens was attained, that randomization was eliminated and only the surgical randomization remains (see the schema above).**(08/29/11)(12/19/11)**

SCHEMA **(06/22/09)**



Please see Section 7.32 and Appendix III (Specimen Procedures) for details regarding the specimen requirements and laboratory testing for this protocol. Archival tumor, tissue specimens from secondary cytoreductive surgery and two tubes of blood (to make serum and plasma) will only be required from women randomized to surgery and who consent to allow their specimens to submitted and used for this research study. A new specimen requirement was added to this protocol. The collection of whole blood will apply to all of the patients who provide consent regardless of randomization and treatment including those already enrolled on GOG-0213. Women already enrolled on GOG-0213 will need to be re-consented for this collection. If the patient does not give permission, select "No" in the online Specimen Consent Application for the question "Did your patient give permission for her blood to be collected for submission and use for this research study" and enter "patient refusal" as the reason the specimen was not collected/submitted in item 5 on the SP Form for WB01.

Post surgical randomization treatment options now include either paclitaxel or gemcitabine in combination with carboplatin. Either chemotherapy doublet may be administered with bevacizumab at the discretion of the investigator. If chosen, bevacizumab maintenance is given until disease progression or unacceptable toxicity.**(10/01/12)**

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1.0 OBJECTIVES

1.1 Specific Hypotheses: **(08/04/08)**

Two principle hypotheses will be directly addressed in this randomized, phase III clinical trial in recurrent platinum-sensitive ovarian, peritoneal primary or Fallopian tube cancer patients.

1.11 Surgical secondary cytoreduction prior to adjuvant chemotherapy increases the duration of overall survival in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

1.12 The addition of bevacizumab to second-line paclitaxel and carboplatin and maintenance phases of treatment increases the duration of overall survival relative to second-line chemotherapy alone in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary, or Fallopian tube cancer.

1.2 Primary Objectives:

1.21 To determine if surgical secondary cytoreduction in addition to adjuvant chemotherapy increases the duration of overall survival in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

1.22 To determine if the addition of bevacizumab to the second-line and maintenance phases of treatment increases the duration of overall survival relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

1.3 Secondary objectives: **(08/04/08)**

1.31 To determine if the addition of bevacizumab to the second-line and maintenance phase of treatment increases the duration of progression-free survival relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

1.32 To prospectively determine the incidence of carboplatin and paclitaxel hypersensitivity in these patients undergoing retreatment with both agents as first recurrence therapy.

1.33 To determine if surgical secondary cytoreduction in addition to adjuvant chemotherapy increases quality of life (QOL) in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer, as measured by the FACT-O trial outcome index and Rand SF-36 physical functioning scale.

1.34 To determine if the addition of bevacizumab to the second-line and maintenance phases of treatment increases QOL relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian, peritoneal primary or Fallopian tube cancer.

1.4 Translational Research Hypotheses **(08/04/08)**

The following translational research hypotheses will be tested in the tissue and serum specimens submitted from GOG-0213 patients undergoing secondary surgical cytoreduction.

1.41 Molecular and biochemical profiles can be identified that are associated with time to first disease recurrence or death.

1.42 Molecular determinants can be identified within patients with platinum-sensitive recurrent ovarian, peritoneal primary or Fallopian tube carcinoma which predicts for sensitivity/resistance to combination chemotherapy with or without bevacizumab followed with or without maintenance bevacizumab therapy.

1.5 Translational Research Objectives **(08/04/08)**

The following translational research objectives will be evaluated in the tissue and serum specimens submitted from GOG-0213 patients undergoing secondary surgical cytoreduction.

1.51 To define molecular and biochemical profiles associated with the duration of progression-free survival in platinum-sensitive recurrent ovarian, peritoneal primary or Fallopian tube carcinoma treated with combination chemotherapy with or without bevacizumab followed with or without maintenance bevacizumab therapy in the presence or absence of secondary surgical cytoreduction.

1.52 To identify molecular determinants that predict sensitivity or resistance to carboplatin and paclitaxel with or without bevacizumab followed with or without maintenance bevacizumab therapy.

1.53 To bank DNA from whole blood for research and evaluate the association between single nucleotide polymorphisms (SNPs) and measures of clinical outcome including overall survival, progression-free survival and adverse events.**(06/22/09)**