Philip J. DiSaia, M.D.
Group Chair

Administrative Office
Four Penn Center
1600 John F. Kennedy Boulevard, Suite 1020
Philadelphia, Pennsylvania 19103
Phone: 215-854-0770 Fax: 215-854-0716

Laura L. Reese
Executive Director of Operations

Gynecologic Oncology Group

Larry J. Copeland, M.D.
Group Vice Chair

Finance/Development Office
2127 Espey Court
Suite 100
Crofton, Maryland 21114
Phone: 410-721-7126 Fax: 301-261-3972

Mary C. Sharp
Chief Financial Officer

PROTOCOL GOG-0262/ACRIN 6695 (06/20/2011)

GOG-0262: A PHASE III TRIAL OF EVERY-3-WEEKS PACLITAXEL VERSUS DOSE DENSE WEEKLY PACLITAXEL IN COMBINATION WITH CARBOPLATIN WITH OR WITHOUT CONCURRENT AND CONSOLIDATION BEVACIZUMAB (NSC #704865, IND #113912) IN THE TREATMENT OF PRIMARY STAGE II, III OR IV EPITHELIAL OVARIAN, PERITONEAL OR FALLOPIAN TUBE CANCER and ACRIN 6695: PERFUSION CT IMAGING TO EVALUATE TREATMENT RESPONSE IN PATIENTS PARTICIPATING IN GOG-0262 (06/20/2011) (02/06/2012) (04/30/2012)

NCI Version Date: 09/26/2012
Includes Revisions #1-6

POINTS:
PER CAPITA – 20 **(01/18/2011) (04/30/2012)**
MEMBERSHIP – 6

TRANSLATIONAL RESEARCH PER CAPITA – Award based on specimen submission. 3.0 points for FFPE tumor block (2.0 points for 2nd choice: 20 unstained slides +8 cores); 1.0 point for whole blood; 3.0 points for frozen tumor; 1.0 point for frozen plasma; 1.0 point for frozen serum **TR Specimens will not be collected from patients enrolled after 02/08/2012. (04/30/2012)**

STUDY CHAIR	STUDY CO-CHAIR
JOHN K. CHAN, M.D.	RICHARD PENSON, M.D.
UNIV OF CALIFORNIA-SAN FRANCISCO	See GOG Website Directory
UCSF HELEN DILLER FAMILY	
COMPREHENSIVE CARE CENTER	NURSE CONTACT
1600 DIVISADERO STREET	KATHLEEN CAVANAUGH, N.P.
ROOM A747, BOX 1702	UNIV OF CALIFORNIA-SAN FRANCISCO
SAN FRANCISCO, CA 94143-1702	UCSF HELEN DILLER FAMILY
415-885-7561	COMPREHENSIVE CARE CENTER
FAX: 415-885-3586	1600 DIVISADERO STREET
E-MAIL: chanjohn@obgyn.ucsf.edu	ROOM A747, BOX 1702,
	SAN FRANCISCO, CA 94143-1702
TRANSLATIONAL RESEARCH CO-CHAIR	415-885-7206
MICHAEL J. BIRRER, M.D., PH.D.	FAX: 415-885-3586
See GOG Website Directory	E-MAIL: Kathleen.Cavanaugh@ucsfmedctr.org
QUALITY OF LIFE CO-CHAIR	STATISTICIAN
BRADLEY J. MONK, M.D.	MARK BRADY, PH.D
See GOG Website Directory	See GOG Website Directory

PARTIAL PROTOCOL— CONTACT ACRIN PROTOCOL DEVELOPMENT AND REGULATORY COMPLIANCE FOR A COMPLETE PROTOCOL

OPEN TO PATIENT ENTRY SEPTEMBER 27, 2010
REVISED JANUARY 18, 2011
REVISED JUNE 20, 2011
REVISED DECEMBER 19, 2011
REVISED FEBRUARY 6, 2012
TEMPORARILY SUSPENDED TO PATIENT ENTRY FEBRUARY 8, 2012
RE-OPENED TO PATIENT ENTRY AND REVISED APRIL 30, 2012
REVISED OCTOBER 22, 2012

Please note that this study is only open for participation at sites in the U.S., Sunnybrook Health Sciences Center, Toronto, Canada, and KGOG

Philip J. DiSaia, M.D.
Group Chair

Administrative Office
Four Penn Center
1600 John F. Kennedy Boulevard, Suite 1020
Philadelphia, Pennsylvania 19103
Phone: 215-854-0770 Fax: 215-854-0716

Laura L. Reese
Executive Director of Operations

Gynecologic Oncology Group

Larry J. Copeland, M.D.
Group Vice Chair

Finance/Development Office
2127 Espey Court
Suite 100
Crofton, Maryland 21114
Phone: 410-721-7126 Fax: 301-261-3972

Mary C. Sharp
Chief Financial Officer

PROTOCOL GOG-0262/ACRIN 6695 (*06/20/2011*)

GOG-0262: A PHASE III TRIAL OF EVERY-3-WEEKS PACLITAXEL VERSUS DOSE DENSE WEEKLY PACLITAXEL IN COMBINATION WITH CARBOPLATIN WITH OR WITHOUT CONCURRENT AND CONSOLIDATION BEVACIZUMAB (NSC #704865, IND #113912) IN THE TREATMENT OF PRIMARY STAGE II, III OR IV EPITHELIAL OVARIAN, PERITONEAL OR FALLOPIAN TUBE CANCER and ACRIN 6695: PERFUSION CT IMAGING TO EVALUATE TREATMENT RESPONSE IN PATIENTS PARTICIPATING IN GOG-0262 **(06/20/2011) (02/06/2012) (04/30/2012)**

NCI Version Date: 09/26/2012
Includes Revisions #1-6

PATHOLOGIST	TRANSLATIONAL RESEARCH SCIENTIST
HELEN MICHAEL, M.D.	HEATHER A LANKES, PH.D., M.P.H.
See GOG Website Directory	See GOG Website Directory
ACRIN RADIOLOGIST **(06/20/2011)**	ACRIN MEDICAL PHYSICIST **(06/20/2011)**
CHAAN NG, M.D.	TING-YIM LEE, PH.D.
MD ANDERSON CANCER CENTER	IMAGING RESEARCH LABS
DIAGNOSTIC RADIOLOGY – UNIT 1473	ROBARTS RESEARCH INSTITUTE
PO BOX 301402	PO BOX 5015
HOUSTON, TX 77230-1402	LONDON, ONTARIO N6A 5K8, CANADA
713-792-6759	519-663-5777, ext 24131
FAX: 713-745-1302	FAX: 519-931-5224
E-MAIL: cng@mdanderson.org	E-MAIL: tlee@imaging.robarts.ca
ACRIN STATISTICIAN **(06/20/2011)**	ACRIN GYNECOLOGIC ONCOLOGIST **(06/20/2011)**
ZHENG-ZHANG, PH.D.	ROBERT COLEMAN, M.D.
BROWN UNIVERSITY	See GOG Website Directory
121 S. MAIN STREET	
PROVIDENCE, RI 02912	
401-863-2578	
FAX: 401-863-9182	
E-MAIL: zzhang@stat.brown.edu	

OPEN TO PATIENT ENTRY SEPTEMBER 27, 2010
REVISED JANUARY 18, 2011
REVISED JUNE 20, 2011
REVISED DECEMBER 19, 2011
REVISED FEBRUARY 6, 2012
TEMPORARILY SUSPENDED TO PATIENT ENTRY FEBRUARY 8, 2012
RE-OPENED TO PATIENT ENTRY AND REVISED APRIL 30, 2012
REVISED OCTOBER 22, 2012

Please note that this study is only open for participation at sites in the U.S., Sunnybrook Health Sciences Center, Toronto, Canada, and KGOG

Philip J. DiSaia, M.D.
Group Chair

Administrative Office
Four Penn Center
1600 John F. Kennedy Boulevard, Suite 1020
Philadelphia, Pennsylvania 19103
Phone: 215-854-0770 Fax: 215-854-0716

Laura L. Reese
Executive Director of Operations

Gynecologic Oncology Group

Larry J. Copeland, M.D.
Group Vice Chair

Finance/Development Office
2127 Espey Court
Suite 100
Crofton, Maryland 21114
Phone: 410-721-7126 Fax: 301-261-3972

Mary C. Sharp
Chief Financial Officer

PROTOCOL GOG-0262/ACRIN 6695 (06/20/2011)

GOG-0262: A PHASE III TRIAL OF EVERY-3-WEEKS PACLITAXEL VERSUS DOSE DENSE WEEKLY PACLITAXEL IN COMBINATION WITH CARBOPLATIN WITH OR WITHOUT CONCURRENT AND CONSOLIDATION BEVACIZUMAB (NSC #704865, IND #113912) IN THE TREATMENT OF PRIMARY STAGE II, III OR IV EPITHELIAL OVARIAN, PERITONEAL OR FALLOPIAN TUBE CANCER and ACRIN 6695: PERFUSION CT IMAGING TO EVALUATE TREATMENT RESPONSE IN PATIENTS PARTICIPATING IN GOG-0262 **(06/20/2011) (02/06/2012) (04/30/2012)**

NCI Version Date: 09/26/2012
Includes Revisions #1-6

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION **(01/18/2011)**

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206	Please refer to the patient enrollment section for instructions on using the OPEN system.	GOG Statistical and Data Center at Roswell Park Cancer Institute Elm and Carlton Streets Buffalo, NY 14263 ***Call GOG User support 716-845-7767 to obtain user name and password to submit electronic data*** Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.

The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol.

CTSU sites should follow procedures outlined in the protocol for Site Registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.

Note: Non lead group institutions will order the following supplies from the CTSU Operations Office: hard copy GOG-0262 QOL Scantron forms.

For patient eligibility or treatment-related questions contact the Study Chair of the Coordinating Group

For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org. A copy of all IRB correspondence including approved Informed Consent Forms must be sent to ACRIN for review.

The CTSU Web site is located at: https://www.ctsu.org

OPEN TO PATIENT ENTRY SEPTEMBER 20, 2010
REVISED JANUARY 18, 2011
REVISED JUNE 20, 2011
REVISED DECEMBER 19, 2011
REVISED FEBRUARY 6, 2012
TEMPORARILY SUSPENDED TO PATIENT ENTRY FEBRUARY 8, 2012
RE-OPENED TO PATIENT ENTRY AND REVISED APRIL 30, 2012
REVISED OCTOBER 22, 2012

Please note that this study is only open for participation at sites in the U.S., Sunnybrook Health Sciences Center, Toronto, Canada, and KGOG

Philip J. DiSaia, M.D.
Group Chair

Administrative Office
Four Penn Center
1600 John F. Kennedy Boulevard, Suite 1020
Philadelphia, Pennsylvania 19103
Phone: 215-854-0770 Fax: 215-854-0716

Laura L. Reese
Executive Director of Operations

Gynecologic Oncology Group

Larry J. Copeland, M.D.
Group Vice Chair

Finance/Development Office
2127 Espey Court
Suite 100
Crofton, Maryland 21114
Phone: 410-721-7126 Fax: 301-261-3972

Mary C. Sharp
Chief Financial Officer

PROTOCOL GOG-0262/ACRIN 6695 (06/20/2011)

GOG-0262: A PHASE III TRIAL OF EVERY-3-WEEKS PACLITAXEL VERSUS DOSE DENSE WEEKLY PACLITAXEL IN COMBINATION WITH CARBOPLATIN WITH OR WITHOUT CONCURRENT AND CONSOLIDATION BEVACIZUMAB (NSC #704865, IND #113912) IN THE TREATMENT OF PRIMARY STAGE II, III OR IV EPITHELIAL OVARIAN, PERITONEAL OR FALLOPIAN TUBE CANCER and ACRIN 6695: PERFUSION CT IMAGING TO EVALUATE TREATMENT RESPONSE IN PATIENTS PARTICIPATING IN GOG-0262 **(06/20/2011) (02/06/2012) (04/30/2012)**

NCI Version Date: 09/26/2012
Includes Revisions #1-6

For perfusion CT imaging questions for ACRIN 6695, please contact imagearchive@acr.org (06/20/2011)
GOG will forward to ACRIN Data Management the patient enrollment information for patients to enroll in the ACRIN 6695 study. (06/20/2011)
For the ACRIN 6695 imaging study, data management will be performed by ACRIN. ACRIN case report forms, clinical reports, and transmittals must be sent to ACRIN as directed by the protocol post-registration. The forms may be sent to ACRIN electronically or may be mailed directly to ACRIN. (06/20/2011)
For the ACRIN 6695 imaging study, data query and delinquency reports will be sent directly to the enrolling site by ACRIN. Please send query responses and delinquent data to ACRIN Data Management and do not copy the GOG SDC or CTSU Data Operations. (06/20/2011)

OPEN TO PATIENT ENTRY SEPTEMBER 20, 2010
REVISED JANUARY 18, 2011
REVISED JUNE 20, 2011
REVISED DECEMBER 19, 2011
REVISED FEBRUARY 6, 2012
TEMPORARILY SUSPENDED TO PATIENT ENTRY FEBRUARY 8, 2012
RE-OPENED TO PATIENT ENTRY AND REVISED APRIL 30, 2012
REVISED OCTOBER 22, 2012

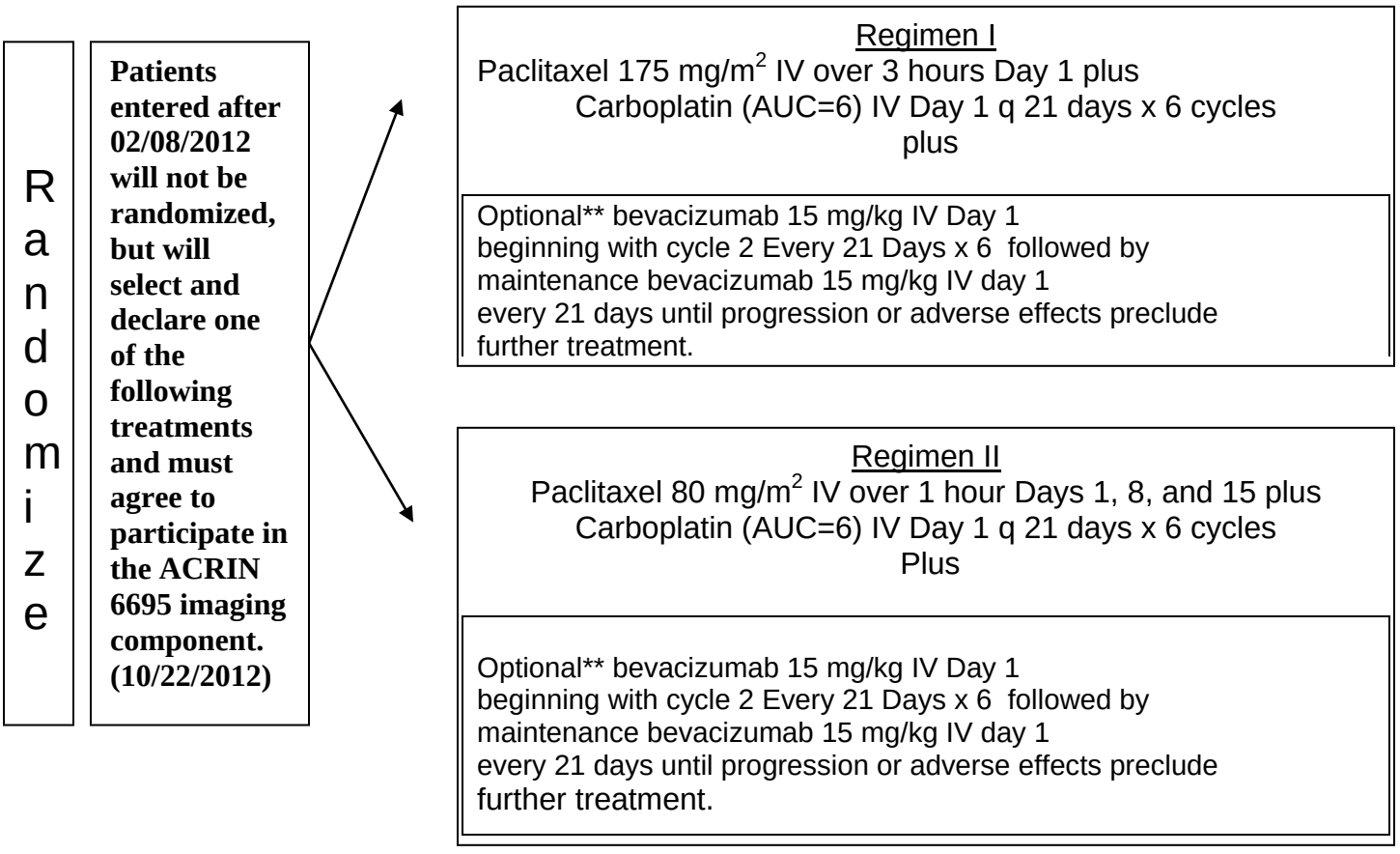
Please note that this study is only open for participation at sites in the U.S., Sunnybrook Health Sciences Center, Toronto, Canada, and KGOG

SCHEMA for GOG 0262 **(06/20/2011) (04/30/2012)**

Target Population:

- •Primary epithelial ovarian, peritoneal or fallopian tube cancer
- •Neoadjuvant*, suboptimally debulked FIGO Stage II, III or IV disease. **(10/22/2012)**
- •Patients must have measurable disease. At least one target lesion must have a minimum length of 1 cm in both the long and short axis (determined at the local site).

Between September 27, 2010 and February 8, 2012, the following treatment options were randomly assigned to patients enrolled into this study. Beginning 04/30/2012, all patients are required to participate in the ACRIN 6695 imaging component, and the chemotherapy regimen (as described below) is selected and declared prior to enrolling in the study.



*Patients undergoing neoadjuvant chemotherapy (NACT) with interval cytoreductive surgery (ICS) must be recorded prior to registration. After core needle biopsy to establish diagnosis, patients will receive 3 cycles of NACT with ICS between cycles 3 and 4, followed by 3 additional cycles of chemotherapy. If chosen, bevacizumab will be administered during cycles 2, 5, and 6, but omitted during cycles 1, 3 and 4

** Prior to enrolling onto this study, each patient will choose whether the study treatment will include concurrent and maintenance bevacizumab. Note: patients enrolled onto this trial will not be eligible for therapy on other clinical trials evaluating consolidation or maintenance therapy.

OUTCOME MEASURES

•Primary Endpoint:

-Progression-free survival (PFS)

•Secondary Endpoints:

-Overall Survival (OS)

-Response Rate (RR)

-Toxicity

-Translational Research – Please see Section 7.3 and Appendix III **(01/18/2011)**

As of 02/08/2012, the translational research portion of this study is complete; patients enrolled after this date will not have TR specimens collected.

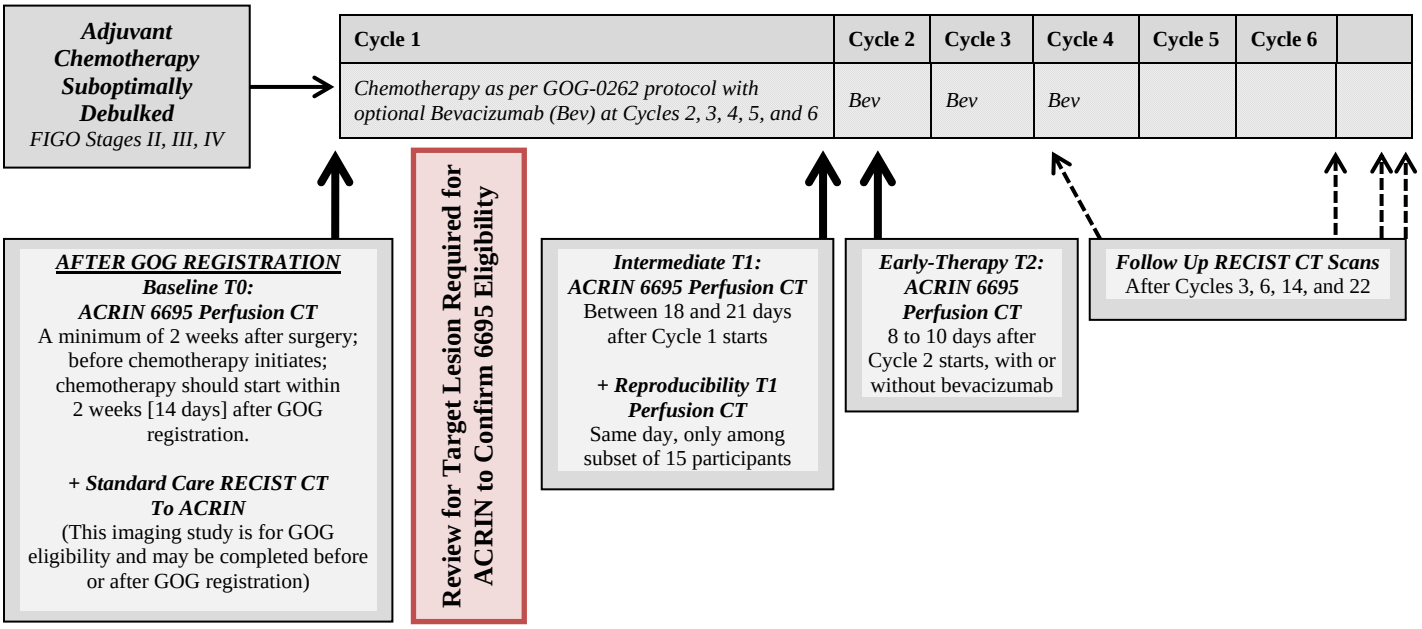
-Quality of Life – Please see Section 7.4 **(06/20/2011)**

As of 02/08/2012, the QOL portion of this study is complete; patients enrolled after this date will not have QOL assessments.

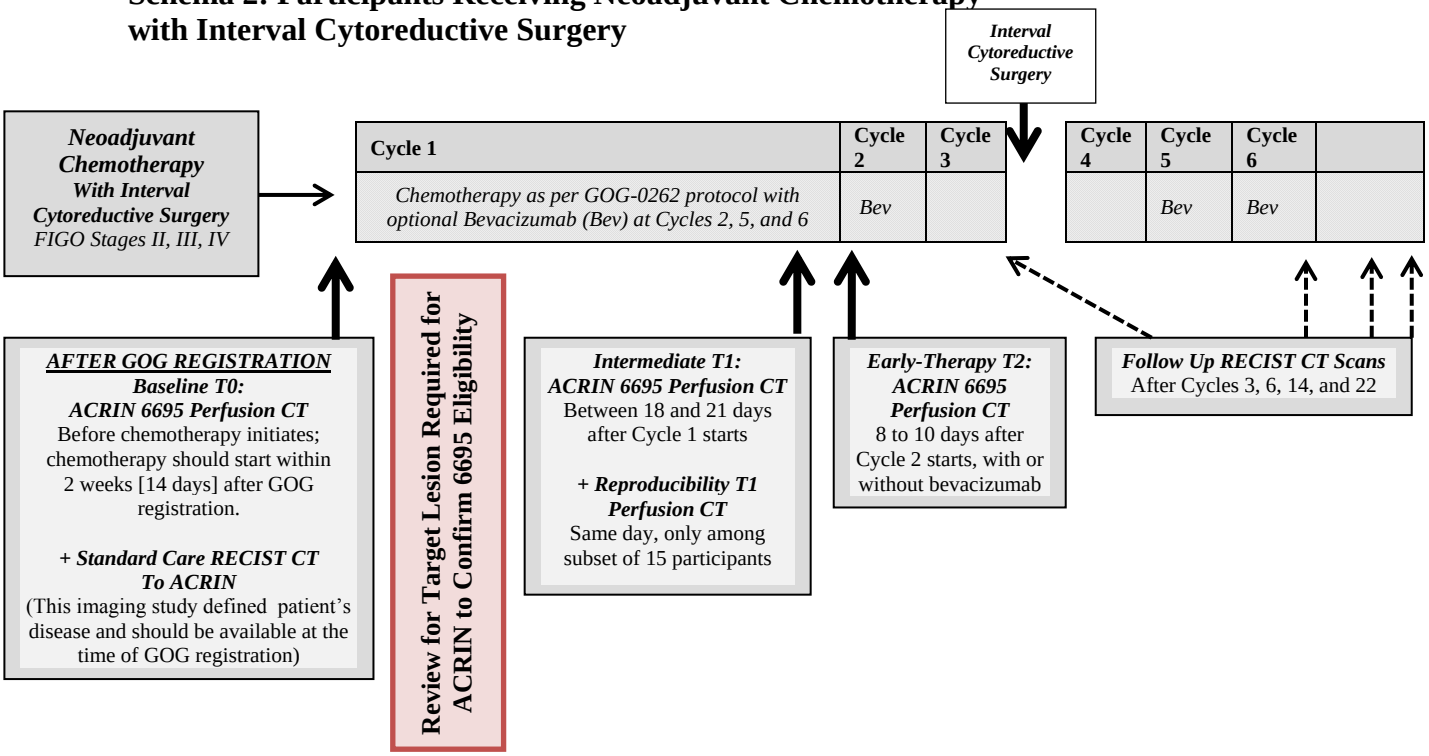
- Prior to cycle 1 (preferably prior to randomization) (t = 0 weeks)
- Prior to cycle 4 (t = 9 weeks after starting treatment)
- 18 weeks after starting treatment (For those patients who are receiving bevacizumab this time point corresponds to just prior to the 7th cycle of treatment.)
- 36 weeks after starting treatment. (For those patients who are receiving bevacizumab this time point corresponds to just prior to the 13th cycle of treatment.)
- 63 weeks after starting treatment

ACRIN 6695 Schema **(06/20/2011) (10/22/2012)**
ALL PATIENTS ENROLLED AFTER 02/08/2012
MUST PARTICIPATE IN THE ACRIN 6695 COMPONENT (04/30/2012)

Schema 1: Participants Undergoing Adjuvant Chemotherapy After Suboptimally Debulked Disease



Schema 2: Participants Receiving Neoadjuvant Chemotherapy with Interval Cytoreductive Surgery



•Imaging Endpoints:

- Changes in tumor perfusion parameters as quantified by vascularity or blood volume (BV); perfusion or blood flow (BF); mean transit time (MTT); and microvascular permeability or permeability surface area product (PS), from T0 to T1, T0 to T2, and T1 to T2.

TABLE OF CONTENTS **(01/18/2011) (06/20/2011) (10/22/2012)**

1.0 OBJECTIVES

1.1 Primary Objectives

1.11 To determine if the weekly paclitaxel regimen increases the time until first progression or death (PFS) compared to the every-3-week paclitaxel regimen in women with primary stage II, III or IV epithelial ovarian, peritoneal or fallopian tube cancer who are receiving carboplatin with or without bevacizumab. **(06/20/2011)**

1.2 Secondary Objectives

1.21 To determine if the weekly paclitaxel increases the duration of overall survival compared to the every-3-week paclitaxel when combined with carboplatin with or without bevacizumab.

1.22 To compare the weekly paclitaxel to the every-3-week paclitaxel with respect to the incidence of severe or serious adverse events when it is combined with carboplatin with or without bevacizumab.

1.23 To compare the weekly paclitaxel to the every-3-week paclitaxel with respect to patients' self-report quality of life as measured by the FACT-O-TOI, when paclitaxel is combined with carboplatin with or without bevacizumab.

1.3 Translational Research Objectives **As of 02/08/2012, the translational research portion of this study is complete. (04/30/2012)**

1.31 To evaluate single nucleotide polymorphisms (SNPs) associated with progression-free survival and toxicity in advanced stage epithelial ovarian, peritoneal and fallopian tube cancer using genome wide association studies (GWAS).

1.32 To evaluate genomic signatures in tumor tissues which are predictive for patient survival in advanced stage epithelial ovarian, peritoneal and fallopian tube cancer.

1.33 To evaluate the association between serum and plasma biomarkers and response to anti-angiogenesis therapy in advanced stage epithelial ovarian, peritoneal and fallopian tube cancer.

1.4 Imaging Primary Objectives **(06/20/2011) (10/22/2012)**

1.41 To determine whether larger changes in the tumor perfusion parameters from baseline T0 to early-therapy T2 are prognostic of higher progression-free survival (PFS) rate at 6 months (PFS-6) from enrollment in patients treated with weekly or every-3-week paclitaxel regimens, who are receiving carboplatin with or without bevacizumab.

1.5 Imaging Secondary Objectives **(06/20/2011) (10/22/2012)**

1.51 To determine whether larger changes in tumor perfusion parameters from baseline T0 to intermediate T1 and from T1 to T2 are prognostic of higher PFS-6 in patients treated with weekly or every-3-week paclitaxel regimens, who are receiving carboplatin with or without bevacizumab.

1.52 To determine whether larger changes in tumor perfusion parameters values from T0 to T1, T0 to T2, and T1 to T2 are prognostic of better overall survival in all treatment arms.

1.53 To assess the association between changes in tumor perfusion parameters before and after chemotherapy initiation (T0 to T1) and subsequent best tumor response according to standard anatomic response evaluation criteria (RECIST).

1.54 To assess the association between tumor perfusion parameters before chemotherapy and subsequent best tumor response according to standard anatomic response evaluation criteria (RECIST), PFS-6, and overall survival.

1.55 To test the assumption that tumor perfusion parameters are reliable, user-independent, and reproducible parameters of tumor microvascular characteristics. A subgroup of 15 patients will have repeat CT Perfusion studies at the intermediate T1 time point.

2.0 BACKGROUND AND RATIONALE

2.1 Preclinical studies on significance of frequent dosing of paclitaxel

Despite good initial responses to chemotherapy, 75% of ovarian cancer patients ultimately die of complications associated with disease progression.[1] Consequently, there is a strong impetus to investigate new therapies to improve the outcome of patients afflicted with this deadly disease. Prior studies have shown that paclitaxel administered in a more continuous manner exhibits proapoptotic and antiangiogenic properties, increasing its antineoplastic effects.[2-4] Symmans et al performed serial fine-needle aspirates after paclitaxel infusions in patients undergoing neoadjuvant therapy, and found that the apoptotic response to paclitaxel was subsided within four days, suggesting that more frequent dosing might be beneficial to maintain apoptotic effect.[5] Preclinical studies also demonstrated that tumor apoptotic response after paclitaxel treatment was associated with decreased interstitial pressure, vasodilatation, and increased endothelial surface area resulting in an improved intratumoral perfusion and drug delivery to cancer cells.[2,6,7]

2.2 Clinical Trials in Breast and Other Cancers

Several phase II studies in metastatic breast cancer have shown that weekly paclitaxel produced significant response rates.[8-12] The largest of these, by Perez et al, reported a 21.5% response rate and a 41.8% overall clinical benefit.[9] Studies in early breast cancer

have also demonstrated the superiority of weekly paclitaxel compared to every 3-week administration. Given the encouraging results from phase II studies, the appropriate scheduling of taxanes has received significant attention in the neoadjuvant, adjuvant, and metastatic setting in breast and other cancers.

In a neoadjuvant study, Green et al. randomly assigned 258 patients with stage I-IIIA breast cancer to either weekly (total of 12 doses) or 3-weekly (four cycles) administration of paclitaxel followed by four cycles of fluorouracil/ doxorubicin/cyclophosphamide (FAC) in standard doses 3-weekly. Patients receiving weekly paclitaxel had a higher pathologic complete response rate at 28.8% compared to those treated with the 3-weekly schedule at 15.7%. (p=.02). [13]

In the adjuvant setting, the Sparano and the ECOG study group investigators performed a phase III study of 4950 patients with node-positive or high-risk node-negative breast cancer after adjuvant therapy with doxorubicin-cyclophosphamide then randomized to either paclitaxel or docetaxel given weekly or every 3 weeks. The Intergroup E-1199 investigators showed a significant improvement in disease-free survival favoring the weekly schedule of paclitaxel (hazard ratio =1.27;95% CI, 1.07 to 1.51; p=0.006).[14]

In patients with metastatic breast cancer, Seidman and the Cancer and Leukemia Group B (CALGB) 9840 investigators showed that weekly paclitaxel was superior to every-3-weeks paclitaxel for the treatment of metastatic breast cancer. In fact, weekly paclitaxel doubled the time to progression and increased the response rate from 29% to 42% compared to every-3-weeks paclitaxel without affecting patients' quality of life.[15] This conglomerate of preclinical and clinical evidence makes weekly paclitaxel the optimal way of administering this drug in breast cancer patients.

2.3 Early Clinical Trial Evidence in Ovarian Cancer

The weekly administration of paclitaxel has been investigated as treatment of platinum-resistant ovarian cancer by several groups with reports suggesting that approximately 10–20% of patients will achieve an objective response to the regimen.[16-19] Of particular interest is that the data demonstrate that weekly delivery of the drug can produce a favorable effect in the setting of tumors not only shown to be platinum-resistant but are also clinically-defined to be resistant to paclitaxel, previously delivered on a ''standard'' every three-week schedule.[17] To directly address this issue, the Gynecologic Oncology Group (GOG) initiated a phase II trial of single agent weekly paclitaxel in women with both platinum and paclitaxel-resistant ovarian cancer. Markman et al found an objective response rate of 20.9%. Serious adverse events were relatively uncommon (neuropathy-grade 2: 21%; grade 3: 4%; and grade 3 fatigue: 8%).[17] These authors concluded that weekly administration of paclitaxel can be a useful management approach in women with both platinum and paclitaxel (given every 3 weeks)-resistant ovarian cancer. Therefore, it would be appropriate to directly compare weekly to every 3-week paclitaxel delivery in the setting of primary chemotherapy of advanced ovarian cancer.

2.4 Japanese Gynecologic Oncology Group Study—Dose Dense Paclitaxel **(06/20/2011)**

The Japanese Gynecologic Oncology Group performed a randomized phase III trial of conventional paclitaxel and carboplatin (c-TC) versus dose dense weekly paclitaxel and carboplatin (dd-TC) in women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. The patients were randomly assigned to receive carboplatin (AUC=6) with either paclitaxel at 180 mg/m^2 on day 1 (c-TC) or paclitaxel at 80 mg/m^2 on days 1, 8, and 15 (dd-TC). The treatments were repeated every 3 weeks for six cycles. Of 637 patients, the median duration of PFS in the c-TC group and dd-TC group was 17.1 and 27.9 months, respectively (p=0.0014), and overall survival at 2 years was 77.7% and 83.6%, respectively (p=0.05). The median follow-up was 29 months. Grade 3 and 4 anemia was reported more frequently in the dd-TC group, and other toxicities were similar in both groups. These authors concluded that dose dense weekly TC improves PFS as compared with c-TC in patients with advanced epithelial ovarian cancer. [20]

2.5 European Organisation for Research and Treatment of Cancer (EORTC) on Neoadjuvant Chemotherapy **(06/20/2011)**

The European Organisation for Research and Treatment of Cancer randomized patients to primary debulking surgery followed by platinum-based chemotherapy versus neoadjuvant platinum-based chemotherapy followed by debulking surgery.[21] Of 670 patients, the hazard ratio for death in the group assigned to neoadjuvant chemotherapy followed by interval debulking, as compared with the group assigned to primary debulking surgery followed by chemotherapy, was 0.98 (90% confidence interval [CI], 0.84 to 1.13; P = 0.01 for noninferiority), and the hazard ratio for progressive disease was 1.01 (90% CI, 0.89 to 1.15). Postoperative rates of adverse effects and mortality tended to be higher after primary debulking than after interval debulking. These investigators concluded that neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to primary debulking surgery followed by chemotherapy as a treatment option for patients with bulky stage IIIC or IV ovarian carcinoma. Although it is not the intent of this current GOG study to compare neoadjuvant chemotherapy followed by interval debulking vs. primary surgery with adjuvant chemotherapy, it is important to include this subset of patients in a randomized clinical trial under the Gynecologic Oncology Group to address this unmet need. In addition, the inclusion of this group will also identify and characterize these patients to assess the feasibilty of designing future trials in this population. Moreover, the translational research opportunities using tumor samples from before and after chemotherapy in the patients undergoing neoadjuvant chemotherapy are important to our understanding of ovarian cancer in response to therapy.

2.6 Angiogenesis and Bevacizumab **(06/20/2011)**

Preclinical studies have suggested that paclitaxel administered in a more continuous manner exhibits antiangiogenic properties and subsequently increasing its antineoplastic effects. Likewise, the rationale for targeting vascular endothelial growth factor (VEGF) in the treatment of ovarian cancer based on both human and preclinical studies has received considerable attention. The former have demonstrated VEGF overexpression

and its association with tumor angiogenesis, ascites formation, malignant progression and early recurrence and death from disease, often independent of known prognostic factors.[22-27] The latter have established that anti-VEGF therapy may impede tumor progression,[10] clear malignant effusions,[28] and enhance the activity of cytotoxic agents.[29-31] Prior results from phase II clinical trials have demonstrated the efficacy of this bevacizumab (humanized anti-VEGF monoclonal antibody) in ovarian cancer.[32-34] Bevacizumab, the first U.S. Food and Drug Administration-approved anti-angiogenesis drug, significantly increases overall survival or progression-free survival of patients with metastatic colorectal cancer, non-small cell lung cancer, and breast cancer when given in combination with conventional chemotherapeutic regimens.[35-37]

The GOG has recently completed a study in which all of the patients received IV paclitaxel 175 mg/m^2 and carboplatin AUC 6 q 3 weeks for 6 cycles. These patients were randomly allocated to add either 21 cycles of placebo, or 5 cycles of bevacizumab followed by 16 cycles of placebo, or 21 cycles of bevacizumab. The placebo or bevacizumab supplement to chemotherapy was to begin with the second cycle of treatment. The preliminary results from this study indicate that the duration of progression-free survival is not appreciable altered when bevacizumab is only given concurrently with chemotherapy. However, when it is given concurrently with chemotherapy and as maintenance therapy, PFS is prolonged significantly ($p<0.001$). Due to the fact that the results of GOG-0218 have not yet been published and evaluated by the FDA, the current study will permit each patient to choose whether she will receive bevacizumab with her randomly assigned study treatment. If a patient enrolls onto this trial and elects to receive bevacizumab then it will begin with the second cycle of therapy and continue until the onset of disease progression or an adverse event precludes further therapy. Also, the randomization procedure will balance the randomized study treatments within the groups of patients who opt to receive bevacizumab and those who do not.

2.7 Rationale of current study

Given that the activity of paclitaxel is directly related to the cell cycle, we hypothesized that more frequent (weekly) administration of this drug might improve efficacy in the treatment of patients with primary advanced ovarian, fallopian tube or primary peritoneal cancer.

2.8 Quality of Life **(06/20/2011)**

This trial will help determine if dose-dense weekly paclitaxel, when combined with standard doses of carboplatin with or without bevacizumab, prolongs PFS after suboptimal cytoreductive surgery of epithelial ovarian, fallopian tube and primary peritoneal cancer. Patient-reported outcomes may differ when dose-dense weekly paclitaxel replaces standard every-3-week paclitaxel. Specifically, the primary objective of measuring QoL in this trial is to determine if dose-dense weekly paclitaxel (Regimen II) reduces disease-related symptoms (improves QoL) more quickly and for more prolonged periods of time than chemotherapy containing every-3-week paclitaxel. In addition, other objectives of measuring QoL include determining if dose-dense weekly paclitaxel alters QoL as a result of treatment-related toxicity such as neuropathy not captured though traditional physician reported measures.

Data from protocol GOG-0170D suggest that bevacizumab may, among responders, not only reduce tumor volume as measured though traditional disease response monitoring, but may also clear ascites and pleural effusions leading to reduced abdominal bloating and pain thus improving QoL.[38] These results await confirmation by the prospective GOG trial GOG-0218 entitled: "A Phase III Trial of Carboplatin and Paclitaxel Plus Placebo Versus Carboplatin and Paclitaxel Plus Concurrent Bevacizumab Followed by Placebo, Versus Carboplatin and Paclitaxel Plus Concurrent and Extended Bevacizumab, in Women With Newly Diagnosed, Previously Untreated, Stage III or IV, Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer." Indeed, VEGF appears to be obligatory for ascites formation by increasing vascular permeability.[39] Thus, neutralization of VEGF activity should dramatically improve QoL after just one or two doses of bevacizumab by reducing malignant ascites formation. Moreover, since taxanes have anti-angiogenesis activity, it is hypothesized that a combination of bevacizumab and dose-dense weekly paclitaxel could be synergistic.[40] Unfortunately, QoL was not monitored in GOG Protocol 0170-D and the results of the QoL component of GOG-0218 are pending.

Since most women with stage III and stage IV epithelial ovarian, primary peritoneal and fallopian tube cancer will succumb to their malignancy and since many regimens have similar efficacy, differences in QoL may help determine the optimal treatment regimen in this setting. In addition, systematic documentation of QoL among those enrolled onto this trial may assist in providing information to future non-trial patients regarding the expected effects of therapy as they make their treatment choices. To date, five completed phase III studies in the upfront treatment of ovarian cancer have implemented QoL outcome measures in their study design, and in every instance QoL was helpful in determining the best regimen. For example, OV.10 established the benefit of paclitaxel in treating ovarian carcinoma,[41] the AGO trial established the benefit of carboplatin,[42] and the SCOTROC trial established the role of docetaxel[43] and in all of these studies QoL was an important endpoint. More recently, Protocol GOG-0152 was the first prospective trial to study QoL in ovarian cancer performed in the GOG. This study included patients similar to the current study and demonstrated the feasibility of obtaining high quality QoL data from this population within this cooperative group.[44] GOG-0152 again illustrated the critical importance of measuring QoL. This study showed that endpoints useful in evaluating optimal therapies in the upfront management of ovarian cancer may be missed if only physician reported endpoints are measured. For example, this study found important difference in neurotoxicity between regimens by measuring QoL and demonstrated that baseline QoL (as measured by the FACT-O) was prognostic of overall survival. Importantly, the recently completed study, GOG-0182 did not contain a QoL component. This trial showed no difference in the anti-tumor activity between the six regimens studied in this clinical trial, the opportunity to pick the best regimen was compromised because QoL was not measured.[45] In the current trial, QoL will be assessed using the Trial Outcome Index of the Functional Assessment of Cancer Therapy-Ovary (FACT-O TOI).[46, 47] This 26-item summary score captures the FACT-G QOL dimensions of Physical Well-Being (7 items), Functional Well-Being (7 items), and the Ovarian Cancer Subscale (12 items). By combining these three subscales, one is assured of capturing the full range of physical aspects of QOL in advanced ovarian cancer, including pain, fatigue, abdominal symptoms and functional status. By combining questions GP4, O1, and O3, which

assess abdominal pain, swelling and cramps respectively, a comprehensive patient reported assessment of disease-related abdominal symptoms including ascites can be evaluated. Also, the abdominal pain module piloted in protocol GOG-0172[48] will be included.[49]

One of the most important dose limiting toxicities of dose-dense weekly paclitaxel is neuropathy.[50] The GOG has validated the FACT/GOG Neurotoxicity (Ntx) subscale for assessing platinum/paclitaxel-induced neurologic symptoms. The 11-item questionnaire includes four sensory items and is an efficient alternative in measuring this toxicity in clinical trials without compromising its performance.[51]

The timing of the QoL assessments is critical to capture data useful in discriminating subtle differences between regimens. This is complicated by the fact that the acute effects of cytotoxic therapy may cause a decrease in QoL. In order to capture early difference in QoL as a result of dose-dense weekly paclitaxel, assessment time points during this trial will be weighted toward the early part of this study. In addition, since some subjects may only complete a few cycles of therapy, it is important to have early assessment points. Finally, in order to avoid the confounding effects of acute chemotherapy related toxicity, questionnaires will be completed just before (21 days after the last dose) the next cycle of chemotherapy and focus on QoL within the last seven days. **(10/22/2012)**

Together, measuring QoL both acutely and long term as well as evaluating the toxicity and impact of QoL of dose dense weekly paclitaxel with or without bevacizumab will provide critical information to patients and caregivers alike as to the relative benefits of the regimens studied in this clinical trial.

2.9 Rationale for Perfusion CT Imaging in Current Study **(06/20/2011) (10/22/2012)**

Historical biomarkers for ovarian carcinoma have assessed tumor size using imaging technology and measured levels of the surface glycoprotein antigen CA125, but these biomarkers are less than optimal for defining patient response to chemotherapy, especially newer antiangiogenic agents. Further, tissue biopsy remains impractical and undesirable in patients with ovarian cancer and, therefore, the identification of non-invasive biomarkers for ovarian carcinoma is of critical importance.[52]

Antiangiogenic agents produce disease stabilization (cytostatic) rather than tumor regression (cytotoxic), so conventional imaging strategies that rely on changes in tumor size are inappropriate.[53] Both World Health Organization (WHO) and/or RECIST morphological criteria do not lend themselves easily to assessing new therapies, which often induce lesion necrosis without reducing tumor volume**.** With the cytostatic effects of newer agents, measures of efficacy such as response rate or time-to-progression might overlook important clinical effects of these agents. Primary endpoints of PFS and overall survival remain the most valid and least ambiguous endpoints for clinical efficacy in antiangiogenic therapies but require significant time and expense to reach. Therefore, the identification of alternative, early-efficacy biomarkers is of paramount importance; such biomarkers have the potential to guide drug choice with appropriate dosing, evaluate pharmacologic response, and assess drug resistance.[54] The challenge in the development of reliable imaging biomarkers in ovarian carcinoma and other

gynecological malignancies is the requirement that the images reflect the clinical relevance of pharmacologic response.

Computed tomography (CT) continues to be the mainstay for all anatomical imaging in oncology. The advent of newer functional CT imaging parameters offers evaluation of changes in tumor vascularity before evidence of tumor volume changes by morphological evaluation using WHO or RECIST criteria. Microvascular functional parameters in tumors can also be derived by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)[55-56] and ultrasound (US).[57] Although MRI offers the advantage of superior contrast resolution without the burden of radiation exposure, the absolute quantification of tumor microvascular functional parameters is difficult because the relationship between signal intensity and contrast (gadolinium) concentration, especially in arteries, is non-linear.[58] Color/power Doppler US with/out (microbubble) contrast provides qualitative rather than quantitative assessments of blood flow (BF), blood volume (BV), in addition, the reproducibility of US is strongly dependent on operator skills.[59] In contrast, DCE-CT, known as perfusion CT, can be easily incorporated into routine RECIST imaging CT protocols without extensive training of personnel and can provide quantitative functional information about the tumor vasculature, albeit at the expense of radiation exposure. However, newer image reconstruction techniques can reduce current perfusion CT radiation exposure by 5 to 10 times without sacrificing image quality.[60-62] If this proof-of-concept study is successful, future studies may be feasible with reduced dose techniques, allowing repeated studies on the same patient without concern for excessive radiation dose.

The advantage of perfusion CT, is that it provides quantitative (versus relative) functional information for diagnosis, staging, and assessment of tumor grade. When assessed at different time points during treatment, perfusion CT follows microvascular changes in angiogenesis, as reflected by the derived functional parameters: BF, BV, mean transit time (MTT), and capillary permeability surface product (PS). These markers may assist in prognosis and therapy monitoring.[62] Microvascular functional parameters will be derived from the kinetic analysis of perfusion CT data using CT Perfusion software (GE Healthcare).

Perfusion CT has seen a wide spectrum of clinical applications in non-gynecologic carcinomas, providing prognostic information based on tumor vascularity and predicting therapeutic effects of various treatment regimens, including chemoradiation and antiangiogenic drugs.[63] In fact, the true value of perfusion CT may be found in the monitoring of response to new antiangiogenic drugs. Preliminary data from metastatic colon cancer studies have suggested an association between progressive disease, poor response to chemotherapy, and perfusion CT parameters.[64-65] In head and neck cancers, perfusion CT has been able to identify tumors more likely to have a favorable outcome following radiotherapy.[66] Further, head and neck studies have shown perfusion CT predicts local and regional failure in patients receiving radiotherapy, linking lower perfusion as an independent indicator to poor response to radiotherapy.[67] Similarly, Gandhi et al found that the presence of high tumor perfusion rates predicted a favorable response to induction chemotherapy.[68-69]

In rodent liver cancer, Kan et al reported that perfusion CT was able to assess changes in liver tumor perfusion in response to antiangiogenic treatment.[70] In a clinical trial of

patients who had rectal cancer treated with bevacizumab, Willett et al found that perfusion CT characteristics of tumor were correlated with microvascular density.[71] More importantly, perfusion CT was able to detect antivascular effects in tumors within 2 weeks after initiation of antiangiogenic treatment. In patients with hepatocellular carcinoma, Zhu et al confirmed a reduction of BF, BV, and PS after bevacizumb treatment, but an increase in MTT values; baseline MTT and changes in MTT after therapy correlated with the clinical outcome.[72]

Because the pharmacokinetics, imaging approaches, and clinical outcomes differ by disease site, evaluation of perfusion CT as a biomarker of the response to chemotherapy in treating recurrent ovarian epithelial carcinoma and other gynecological disorders is of paramount importance. While RECIST criteria offer a simplified extraction of imaging data for wide application in clinical trials, the development and validation of clinical trial-acceptable methods and standards to incorporate perfusion CT imaging for derivation of angiogenesis related functional parameters will improve RECIST methodology. If successful, the use of functional imaging parameters as surrogate endpoints in clinical trials could facilitate earlier "go/no go" decisions on drug compounds, faster regulatory approval for new drugs, and earlier use in clinical care. Additionally, early validation of non-response to costly novel therapeutic agents may allow re-allocation of these limited resources.

By adding perfusion CT imaging to the GOG-0262 adjuvant (or neoadjuvant) chemotherapy treatment study, the quantitative functional parameters of perfusion CT can be further defined, and researchers may show these parameters act as early predictors of response to therapy, PFS, and overall survival in patients ovarian cancer. This proof-of-concept study may demonstrate perfusion CT findings act as surrogate markers of ovarian cancer response to chemotherapy and as predictors of patient outcomes.

2.10 Inclusion of Women and Minorities **(06/20/2011)**

The Gynecologic Oncology Group and GOG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire ovarian, fallopian tube and primary peritoneal cancer population treated by participating institutions.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

Patients enrolled after February 8, 2012 must participate in the ACRIN 6695 component at ACRIN-qualified institutions. (04/30/2012) (10/22/2012)

3.11 Primary Surgery and Neoadjuvant Chemotherapy with Interval Cytoreductive Surgery Patients: **(06/20/2011) (10/22/2012)**

Patients must have measurable disease. At least one target lesion must have a minimum length of 1 cm in both the long and short axis (determined at the local site). For primary surgery patients, if no radiographic evidence of measurable disease is obtained prior to registration this can be based on surgical findings; imaging then would need to be completed in the 14 days between GOG registration and chemotherapy initiation. (04/30/2012)

After GOG registration, the American College of Radiology [ACR] Imaging Core Laboratory will confirm target lesion as required per protocol. The GOG-eligibility (RECIST) scan and baseline T0 perfusion CT scans will be reviewed prior to the intermediate T1 perfusion CT time point.

3.111 Primary Surgery Patients: **(06/20/2011)**

Patients with a histologic diagnosis of epithelial ovarian cancer, peritoneal primary carcinoma or fallopian tube cancer, Stage II -IV suboptimally debulked (any residual disease > 1 cm). FIGO stage (Appendix I) is assessed following the completion of initial abdominal surgery, appropriate imaging studies and with appropriate tissue available for histologic evaluation. The minimum surgery required is an abdominal surgery providing tissue for histologic evaluation and establishing and documenting the primary site and stage, If additional surgery was performed, it should have been in accordance with appropriate surgery for ovarian or peritoneal carcinoma described in the GOG Surgical Procedures Manual (https://gogmember.gog.org/manuals/pdf/surgman.pdf). **(01/18/2011) (04/30/2012)**

3.112 Neoadjuvant Chemotherapy (NAC) with Interval Cytoreductive Surgery (ICS) Patients: **(06/20/2011)**

For patients undergoing NAC-ICS, a core tissue (not fine needle aspiration) biopsy is required. The tissue must be consistent with a müllerian origin. Patients will require documentation of at least stage II or extraovarian sites of disease acquired via imaging or surgery (without attempt at cytoreduction).

3.12 Patients with the following histologic epithelial cell types are eligible: Serous, endometrioid, clear cell, mucinous adenocarcinoma, undifferentiated carcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma not otherwise specified (N.O.S.). However, the histologic features of the tumor must be compatible with a primary Müllerian epithelial adenocarcinoma. Patients may have co-existing fallopian tube carcinoma in-situ so long as the primary origin of invasive tumor is ovarian, peritoneal or fallopian tube. Of note, patients with clear cell and mucinous tumors will be eligible unless there is a higher priority protocol.

3.13 Patients must have adequate:

3.131 Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/mcl. This ANC cannot have been induced or supported by granulocyte colony stimulating factors.

3.132 Platelets greater than or equal to 100,000/mcl.

3.133 Renal function: Creatinine ≤ 1.5 x institutional upper limit normal (ULN).

3.134 Hepatic function:

3.1341 Bilirubin less than or equal to 1.5 x ULN.

3.1342 SGOT less than or equal to 3 x ULN and alkaline phosphatase less than or equal to 2.5 x ULN.

3.135 Neurologic function: Neuropathy (sensory and motor) less than or equal to CTCAE Grade 1.

3.14 Patients must have a GOG Performance Status of 0, 1, or 2.

3.15 Patients must be entered within 12 weeks of diagnostic/staging surgery.

3.16 Patients who have met the pre-entry requirements specified in Section 7.0.

3.17 An approved informed consent and authorization permitting release of personal health information and must be signed by the patient or guardian.

**** Only applies for patients who elect to receive bevacizumab**

3.18** Patients in this trial may receive ovarian estrogen +/- progestin replacement therapy as indicated at the lowest effective dose(s) for control of menopausal symptoms at any time, but not high-dose progestins for management of anorexia while on protocol-directed therapy or prior to disease progression due to thrombophlebitis risk.**

3.19** Patients must have adequate blood coagulation parameters: PT such that international normalized ratio (INR) is ≤ 1.5 (or an in-range INR, usually

between 2 and 3, if a patient is on a stable dose of therapeutic warfarin for management of venous thrombosis including pulmonary thrombo-embolus) and a PTT < 1.2 times the upper limit of normal. (Heparin, lovenox or alternative anticoagulants are acceptable.)**

3.110 All patients enrolled into GOG-0262 at sites where ACRIN 6695 is open will be enrolled in the advanced imaging protocol. Patients receiving adjuvant or neoadjuvant chemotherapy are eligible for ACRIN 6695. **The following sentence does not apply to those patients entered after 02/08/2012:** If a patient declines to participate in the perfusion imaging portion of the protocol, a clinical rationale for declination of imaging form will be completed as part of the data submission for ACRIN 6695. **(06/20/2011)**

3.2 Ineligible Patients

3.21 Patients with a current diagnosis of borderline epithelial ovarian tumor (formerly "tumors of low malignant potential") or recurrent invasive epithelial ovarian, primary peritoneal or fallopian tube cancer treated with surgery only (such as patients with stage I-A or I-B low grade epithelial ovarian or fallopian tube cancers) are not eligible. Patients with a prior diagnosis of a borderline tumor that was surgically resected and who subsequently develop an unrelated, new invasive epithelial ovarian, peritoneal primary or fallopian tube cancer are eligible, provided that they have not received prior chemotherapy for any ovarian tumor.

3.22 Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis. Prior radiation for localized cancer of the breast, head and neck, or skin is permitted, provided that it was completed more than three years prior to registration, and the patient remains free of recurrent or metastatic disease.

3.23 Patients who have received prior chemotherapy for any abdominal or pelvic tumor including neo-adjuvant chemotherapy for their ovarian, primary peritoneal or fallopian tube cancer. Patients may have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than three years prior to registration, and that the patient remains free of recurrent or metastatic disease.

3.24 Patients who have received any targeted therapy (including but not limited to vaccines, antibodies, tyrosine kinase inhibitors) or hormonal therapy for management of their epithelial ovarian, fallopian tube or peritoneal primary cancer.

3.25 Patients with synchronous primary endometrial cancer, or a past history of primary endometrial cancer, unless all of the following conditions are met: Stage not greater than I-A, grade 1 or 2, no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including papillary serous, clear cell or other FIGO grade 3 lesions.

3.26 With the exception of non-melanoma skin cancer, patients with other invasive malignancies who had (or have) any evidence of the other cancer present within the last five years or whose previous cancer treatment contraindicates this protocol therapy.

.

3.27 Patients with acute hepatitis or active infection that requires parenteral antibiotics.

3.28 Patients with clinically significant cardiovascular disease. This includes:

3.281 Myocardial infarction or unstable angina < 6 months prior to registration.

3.282 New York Heart Association (NYHA) Grade II or greater congestive heart failure (Appendix II).

3.283 Serious cardiac arrhythmia requiring medication. This does not include asymptomatic, atrial fibrillation with controlled ventricular rate.

3.29 Patients who are pregnant or nursing. To date, no fetal studies in animals or humans have been performed. (For patients who elect to receive bevacizumab: The possibility of harm to a fetus is likely. Bevacizumab specifically inhibits VEGF, which is responsible for formation of new blood vessels during development, and antibodies can cross the placenta. Therefore, bevacizumab should not be administered to pregnant women. Subjects will be apprised of the large potential risk to a developing fetus. It is not known whether bevacizumab is excreted in human milk. Because many drugs are excreted in human milk, bevacizumab should not be administered to nursing women. Patients of childbearing potential must agree to use contraceptive measures during study therapy and for at least six months after completion of bevacizumab therapy.) **(10/22/2012)**

3.210 Patients under the age of 18.

3.211 Patients who have received prior therapy with any anti-VEGF drug, including bevacizumab.

3.212 Patients with medical history or conditions not otherwise previously specified which in the opinion of the investigator should exclude participation in this study. The investigator should feel free to consult the SDC Randomization Desk for uncertainty in this regard.

3.213 Patients with known allergy to cremophor or polysorbate 80. **(06/20/2011)**

****Only applies to patients who elect to receive bevacizumab**

3.214** Patients with serious non-healing wound, ulcer, or bone fracture. This includes history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 28 days. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly wound examinations (see Section 7.1).******

3.215** Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving major vessels.******

3.216** Patients with history or evidence upon physical examination of CNS disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastases, or history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage within six months of the first date of treatment on this study. ******

3.2161** Patients with CTCAE Grade 2 or greater peripheral vascular disease [at least brief (<24 hours) episodes of ischemia managed non-surgically and without permanent deficit].**

3.2162** Patients with a history of CVA within six months.**

3.217** Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.** **(06/20/2011)**

3.218** Patients with clinically significant proteinuria. Urine protein should be screened by urine protein-creatinine ratio (UPCR). The UPCR has been found to correlate directly with the amount of protein excreted in a 24 hour urine collection.[73-77] Specifically, a UPCR of 1.0 is equivalent to 1.0 gram of protein in a 24-hour urine collection. Obtain at least 4 ml of a random urine sample in a sterile container (does not have to be a 24-hour urine). Send sample to lab with request for urine protein and creatinine levels [separate requests]. The lab will measure protein concentration (mg/dL) and creatinine concentration (mg/dL). The UPCR is derived as follows: protein concentration (mg/dL)/creatinine (mg/dL). Patients must have a UPCR < 1.0 to allow participation in the study.** **(06/20/2011)**

3.219** Patients with or with anticipation of invasive procedures as defined below:

3.2191** Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to the first date of bevacizumab therapy (cycle 2).**

3.2192** Major surgical procedure anticipated during the course of the study. This includes, but is not limited to abdominal surgery (laparotomy or laparoscopy) prior to disease progression as defined in section 8, such as colostomy or enterostomy reversal, secondary cytoreductive surgery, or second look surgery. Please consult with the SDC Randomization Desk prior to patient entry for any questions related to the classification of surgical procedures.** **(02/06/2012)**

3.2193** Any tissue biopsy, such as a core biopsy, within 7 days prior to the first date of bevacizumab therapy (cycle 2).**

3.2110** Patients with clinical symptoms or signs of gastrointestinal obstruction **and** who require parenteral hydration and/or nutrition.******

3.2111** Patients with metastatis tumor in the parenchyma of the liver or lungs with proximity to large vessels which could make the patients at high risk of lethal hemorrhage during treatment with bevacizumab (ie. hemoptysis, liver rupture).**

§§ This section applies to the ACRIN 6695 imaging portion of the trial; eligibility assessment for target lesion (Section 3.2112 below) will be completed after registration to the GOG trial and completion of the baseline T0 CT scan. (06/20/2011) (10/22/2012)

Patients enrolled after February 8, 2012 must participate in the ACRIN 6695 component at ACRIN-qualified sites. Patients whose target lesion meets the protocol criteria for ACRIN 6695 will continue on both the GOG-0262 treatment study and the ACRIN 6695 imaging study. Patients whose target lesion does not meet the protocol criteria for ACRIN 6695 will continue on the GOG-0262 treatment study but will be considered off-study for ACRIN 6695. The ACR Imaging Core Lab or ACRIN Headquarters staff will inform the site whether the participant will continue with additional perfusion CT imaging after baseline T0 per ACRIN 6695 study protocol. **(04/30/2012) (10/22/2012)**

ACRIN 6695 Eligible Patients (10/22/2012)

3.2112**§§** Confirmation of ACRIN 6695 eligibility after the baseline T0 perfusion CT will be assessed by the ACR Imaging Core Lab: At least one target lesion must have a minimum length of 1 cm in both the long and short axis (as determined by the local site), at least half of the target lesion must have attenuation greater than or equal to 10 Hounsfield Units (HU) on the unenhanced CT, and at least half of the lesion must have maximum enhancement greater than or equal to 5 HU in the perfusion CT scan (as determined by the ACR Imaging Core Lab).

ACRIN 6695 Ineligible Patients (10/22/2012)

3.2113**§§** Patients with contraindication to iodinated contrast for perfusion CT imaging. **(06/20/2011)**

3.2114**§§** Patients who receive Metformin within 48 hours before perfusion CT imaging. **(06/20/2011)**

4.0 STUDY MODALITIES

4.1 Paclitaxel (NSC #673089)

4.11 Formulation: Paclitaxel is supplied as a 6mg/mL non-aqueous solution in multi dose vials containing 30mg/5mL, 100mg/16.7mL, or 300mg/50mL of paclitaxel. In addition to 6mg of paclitaxel, each mL of sterile non-pyrogenic solution contains 527mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

4.12 Storage: Unopened vials of paclitaxel are stable to the date indicated on the package when stored between 20 to 25°C (68 to 77°F). Protect from light.

4.13 Preparation: Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride for Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C / 77°F) and room lighting conditions.

NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing, has not resulted in significant leaching of DEHP.

All patients should be premedicated with corticosteroids, diphenhydramine, and H_2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Patients who experience severe hypersensitivity reactions to drug may need to repeat the premedication and to be rechallenged with a dilute solution and slow infusion. Severe hypersensitivity reactions to paclitaxel do not have to proceed with a re challenge. Docetaxel may be substituted.

4.14 Adverse Effects: Consult the package insert for the most current and complete information.

4.15 Supplier: Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

4.2 Carboplatin (Paraplatin® - NSC #241240)

4.21 Formulation: Carboplatin is supplied as a sterile, pyrogen-free, 10mg/mL aqueous solution in multi-dose vials containing 50mg/5mL, 150mg/15mL, 450mg/45mL, or 600mg/60mL of carboplatin.

4.22 Storage: Unopened vials of carboplatin are stable to the date indicated on the package when stored at 25°C (77°F). Excursions from 15 to 30°C (59 to 86°F) are permitted. Protect from light. Carboplatin multi dose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries.

4.23 Preparation: Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride for Injection, USP. When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C / 77°F). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution. Institutional pharmacy policy may allow refrigeration and longer storage.
NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must NOT be used for the preparation or administration of carboplatin. **(01/18/2011)**

4.24 Adverse Effects: Consult the package insert for the most current and complete information.

4.25 Supplier: Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

4.26 Dose Calculations **(01/18/2011)**

See Appendix V.

4.3 Bevacizumab (NSC #704865, IND #113912)

All investigators who receive a copy of the protocol should also obtain a copy of the Investigator's Brochure (IB). IB's are available from the Pharmaceutical Management Branch, CTEP, DCTD, NCI and may be obtained by emailing the IB Coordinator (ibcoordinator@mail.nih.gov) or by calling the IB Coordinator at 301-496-5725.

4.31 Description: Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions. Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

4.32 How Supplied: Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration in a 400 mg (25mg/ml – 16 mL fill) glass vial containing bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

4.33 Preparation: Vials contain no preservatives and are intended for single use only. Place the calculated dose in 100 mL of 0.9% sodium chloride for injection.

4.34 Storage and stability: Upon receipt, refrigerate bevacizumab (2^{o} to 8^{o} C). Do not freeze. Do not shake. Shelf-life studies of rhuMAb VEGF are ongoing. The sterile single use vials contain no antibacterial preservatives. Discard vials 8 hours after initial entry. Once diluted in 0.9% sodium chloride, administer solutions of bevacizumab within 8 hours.

4.35 Route of Administration: Bevacizumab is administered as a continuous intravenous infusion. Administer the initial dose over a minimum of 90 minutes. If no adverse reactions occur, administer the second dose over a minimum of 60 minutes. If no adverse reactions occur after the second dose, administer subsequent doses over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

To insure complete delivery of bevacizumab, flush the IV infusion line with 0.9% sodium chloride. The following are two recommended methods for flushing the bevacizumab IV infusion line:

4.351 When the bevacizumab infusion is complete, add an additional 50mL of 0.9% sodium chloride for injection to the bevacizumab infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.

4.352 Replace the empty bevacizumab infusion bag with a 50mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing.

Please note: the flush is not included in the total recommended infusion times.

4.36 Agent Ordering and Agent Accountability: NCI supplied agents must be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Agent may be requested by completing a Clinical Drug Request (NIH-986) and mailing it to the Drug Management and Authorization Section, PMB, DCTD, NCI, 9000 Rockville Pike, EPN Room 7149, Bethesda, MD 20892-7422 or faxing it to (301) 480-4612. For questions call (301) 496-5725.

4.37 Agent Inventory Records: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record (DAR) Form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

4.38 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Bevacizumab (rhuMAb VEGF, NSC 704865) **(12/19/2011)**

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, 2011[1]

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		***Anemia (Gr. 3)***
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		***Febrile neutropenia (Gr. 3)***
CARDIAC DISORDERS			
		Acute coronary syndrome	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Supraventricular tachycardia		***Supraventricular tachycardia (Gr. 3)***
		Ventricular arrhythmia	
		Ventricular fibrillation	
EAR AND LABYRINTH DISORDERS			
	Vertigo		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr. 3)***
	Colitis		***Colitis (Gr. 3)***
	Constipation		***Constipation (Gr. 3)***
	Diarrhea		***Diarrhea (Gr. 3)***
	Dyspepsia		***Dyspepsia (Gr. 2)***
		Gastrointestinal fistula[2]	
	Gastrointestinal hemorrhage[3]		***Gastrointestinal hemorrhage[3] (Gr. 2)***
	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[f]		***Infection[f] (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]	

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

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

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

[4]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.

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

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

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

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

[9]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.

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

[11]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.

[12]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Disseminated intravascular coagulation
CARDIAC DISORDERS - Pericardial effusion
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Gait disturbance; Sudden death NOS
HEPATOBILIARY 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.

4.381 General Information on Adverse Effects of Bevacizumab

Based on clinical trials with bevacizumab as monotherapy or in combination with chemotherapy, the most common adverse events of any severity include asthenia, pain, headache, hypertension, diarrhea, stomatitis, constipation, epistaxis, dyspnea, dermatitis and proteinuria. The most common grade 3-4 adverse events were asthenia, pain, hypertension, diarrhea and leukopenia. The most serious AEs include life-threatening or fatal hemorrhage, arterial thromboembolic events, gastrointestinal perforation and wound dehiscence; these events were uncommon but occurred at an increased frequency compared to placebo or chemotherapy controls in randomized studies.

The following is a description of major adverse events associated with bevacizumab therapy. A list of Comprehensive Adverse Events and Potential Risks (CAEPR) in NCI-CTCAE v3.0 terms is included above.

Reference may also be made to the Investigators' Brochure and the FDA package insert (www.fda.gov/cder/foi/label/2004/125085lbl.pdf).

Infusion-Related Reactions: Infusion reactions with bevacizumab were uncommon (< 3%) and rarely severe (0.2%). Infusion reactions may include rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Currently, there is no adequate information on the safety of retreatment with bevacizumab in patients who have experienced severe infusion-related reactions.

Hypertension: Hypertension is common in patients treated with bevacizumab, with an incidence of 20-30% across trials. Initiation or increase of anti-hypertensive medications may be required, but in most cases, blood pressure (BP) can be controlled with routine oral drugs. However, incidents of hypertensive crisis with encephalopathy or cardiovascular sequelae have been rarely reported. BP should be closely monitored during bevacizumab therapy and the goal of BP control should be consistent with general medical practice. Bevacizumab therapy should be suspended in the event of uncontrolled hypertension.

Proteinuria: Proteinuria has been seen in all bevacizumab studies to date, ranging in severity from an asymptomatic increase in urine protein (incidence of about 20%) to rare instances of nephrotic syndrome (0.5% incidence). Pathologic findings on renal biopsies in two patients showed proliferative glomerulonephritis. NCI-CTCAE grade 3 proteinuria (> 3.5gm/24 hour urine) is uncommon, but the risk may be higher in patients with advanced RCC. In the Phase II randomized study in RCC, 24-hour urine was collected in a subset of patients enrolled, and grade 3 proteinuria was found in 4 patients in the 10 mg/kg-regimen (n=37), 2 patients in the 3mg/kg regimen (n=35) and none in the placebo regimen (n=38). The safety of continuing bevacizumab in patients with moderate or severe proteinuria has not been adequately tested.

Hemorrhage: The incidence of hemorrhage is increased with bevacizumab therapy. Epistaxis is common, occurring in 20-40% of patients, but it is generally mild and rarely requires medical intervention. Life-threatening and fatal hemorrhagic events have been observed in bevacizumab studies and included pulmonary hemorrhage, CNS bleeding and gastrointestinal (GI) bleeding. In a Phase II study in non-small cell lung cancer, 6 cases of life-threatening hemoptysis or hematemesis were reported among 66 patients treated with bevacizumab and chemotherapy; 4 of these events were fatal.[31] In the pivotal Phase III trial in advanced colorectal cancer, the rate of GI hemorrhage (all grades) was 24% in the IFL/bevacizumab regimen compared to 6% in the IFL regimen; grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL. Serious GI hemorrhage has

also been observed in clinical trials with bevacizumab in patients with pancreatic cancer or varices treated with bevacizumab.

Arterial Thromboembolic Events: The risk of arterial thromboembolic events is increased with bevacizumab therapy, and such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction and other peripheral or visceral arterial thrombosis. In the pivotal trial in CRC (AVF2107), the incidence of arterial thromboembolic events was 1% in the IFL/placebo regimen compared to 3% in the IFL/ bevacizumab regimen. A pooled analysis of five randomized studies showed a two-fold increase in these events (4.4% vs 1.9%). Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk.[32] In patients $\geq$ 65 years treated with bevacizumab and chemotherapy, the rate of arterial thromboembolic events was approximately 8.5%.

Gastrointestinal Perforation/Fistula: GI perforations/fistulas were rare but occurred at an increased rate in bevacizumab -containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal phase 3 trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/ bevacizumab and 4% in patients receiving 5-FU/ bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, ovarian cancer or co-morbid GI conditions such as diverticulitis and gastric ulcer. Fistulae (e.g. tracheo-esophageal, recto-vaginal) have also been observed. A review of published data from phase II trials of bevacizumab and historical cohort studies of open-label use of bevacizumab as a single agent and in combination with cytotoxic drugs specifically for treatment of epithelial ovarian and primary peritoneal cancer revealed an overall incidence rate of 5.2% in 308 patients, about double the rate seen in other solid tumor populations. While not all of these GI perforations and fistulae required open surgical management and most patients recovered, prospective pre-clinical and clinical work is needed to identify mechanisms and risk factors **GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain, fever of unclear source, or rectal/abdominal abscess.**

Wound Healing Complications: Bevacizumab delays wound healing in rabbits, and it may also compromise or delay wound healing in patients. Bowel anastomotic dehiscence and skin wound dehiscence have been reported in clinical trials with bevacizumab. The appropriate interval between surgery and initiation of bevacizumab required to avoid the risk of impaired wound healing has not been determined. However, all clinical trials with bevacizumab have required a minimum of 28 days from prior major surgery; experience in the pivotal trial in advanced CRC suggests that initiation of bevacizumab 29-50 days following

surgery should be associated with a very low incidence of wound dehiscence. The optimal interval between termination of bevacizumab and subsequent elective surgery has not been determined either. In the pivotal study in CRC, 40 patients on the IFL/bevacizumab regimen and 25 patients on the ILF/placebo regimen underwent major surgery while on study; among them, significant post-operative bleeding or wound healing complications occurred in 4 of the 40 patients from the IFL/bevacizumab regimen and none of the 25 patients from the IFL alone regimen. Decisions on the timing of elective surgery should take into consideration the half-life of bevacizumab (average 21 days, with a range of 11-50 days).

Congestive Heart Failure: The risk of left ventricular dysfunction may be increased in patients with prior or concurrent anthracycline treatment. In phase 3 controlled clinical trials in metastatic breast cancer (AVF 2119g) in which all patients had received prior anthracyclines, congestive heart failure (CHF) or cardiomyopathy were reported in 7 patients (3%) in the bevacizumab /capecitabine regimen compared to 2 (1%) in the capecitabine-only regimen. No increase in CHF was observed in CRC trials with bevacizumab in combination with IFL or 5-FU.

Venous Thrombosis: Venous thromboembolic events reported in bevacizumab trials included lower extremity deep vein thrombosis (DVT), pulmonary embolism and rarely, mesenteric or portal vein thrombosis. In the pivotal Phase III trial of IFL ± bevacizumab (given at 5 mg/kg q2w), the overall incidences of G3-4 venous thromboembolic events were comparable in the two regimens (15.1 vs 13.6%).

Fertility and Pregnancy: Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. However, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. In addition, bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. As an IgG1, it may also be secreted in human milk. Therefore, fertile men and women on bevacizumab studies must use adequate contraceptive measures and women should avoid breast feeding. The duration of such precautions after discontinuation of bevacizumab should take into consideration the half-life of the agent (average 21 days, with a range of 11 to 50 days).

Immunogenicity**:** As a therapeutic protein, there is a potential for immunogenicity with bevacizumab. With the currently available assay with limited sensitivity, high titer human anti- bevacizumab antibodies have not been detected in approximately 500 patients treated with bevacizumab.

Neutropenia and Infection: An increased incidence of neutropenia has been reported in patients receiving bevacizumab and chemotherapy compared to chemotherapy alone. In AVF2107g, the incidence of NCI-CTC Grade 3 or 4 neutropenia was increased in patients with mCRC receiving IFL+ bevacizumab (21%) compared to patients receiving IFL alone (14%). In E4599, the incidence of NCI-CTC Grade 4 neutropenia was increased in patients with NSCLC receiving paclitaxel-carboplatin (PC) plus bevacizumab (26.2%) compared with patients receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus bevacizumab vs. 1.8% for PC alone). There were 19 (4.5%) infections with NCI-CTC Grade 3 or 4 neutropenia in the PC plus bevacizumab regimen of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving PC alone, of which none were fatal. During the first 6 cycles of treatment the incidence of serious infections including pneumonia, febrile neutropenia, catheter infections and wound infections was increased in the PC plus bevacizumab regimen [58 patients (13.6%)] compared to the PC alone regimen [29 patients (6.6%)].

4.4 Docetaxel (Taxotere® RP-56976, NSC #628503)

4.41 Formulation: Docetaxel is supplied as a sterile, non-pyrogenic, non-aqueous viscous solution in single dose vials containing 20mg/0.5mL or 80mg/2mL of docetaxel. Each mL contains 40mg docetaxel (anhydrous) and 1040mg polysorbate 80.

4.42 Docetaxel requires dilution prior to use. A sterile, non-pyrogenic, single dose diluent is supplied for this purpose. The diluent for docetaxel contains 13% (w/w) ethanol in water for injection and is supplied in vials.

4.43 Storage: Unopened vials of docetaxel are stable to the date indicated on the package when stored between 2 and 25°C (36 and 77°F). If the vials are stored under refrigeration, allow the vials to stand at room temperature for appoximately 5 minutes. Protect from light. **(06/20/2011)**

4.44 Preparation: Docetaxel must be combined with its supplied diluent (final concentration = 10mg/mL) and then further diluted prior to infusion. Docetaxel should be diluted in 0.9% Sodium Chloride for Injection, USP or 5% Dextrose Injection, USP to produce a final concentration of 0.3 to 0.74mg/mL. The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours. The final dilution of infusion, if stored between 2°C and 25°C (36°F and 77°F) is stable for 4 hours. The fully prepared docetaxel infusion solution should be used within 4 hours (including the infusion duration).NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.**(06/20/2011)**

All patients should be premedicated with oral corticosteroids for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

4.45 Adverse Effects: Consult the package insert for the most current and complete information.

4.46 Supplier: Commercially available from Aventis. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

4.5 Pathology Requirements

Stained pathology slides of the epithelial ovarian carcinoma, primary peritoneal carcinoma or fallopian tube carcinoma that demonstrate the primary tumor and the most advanced stage of the disease are required for central review by the GOG Pathology Committee to confirm eligibility for the protocol. If the disease stage II, III or IV is documented by some method other than pathology, the method of stage documentation needs to be stated (eg, CT, MRI, etc). See sections 7.2 and 10.2 for specific requirements and instructions for the stained pathology slides, pathology reports and forms. **(06/20/2011)**

4.6 **ACRIN 6695 Perfusion CT with Iodinated Contrast (10/22/2012)**

Patients enrolled after February 8, 2012 must participate in the ACRIN 6695 component at ACRIN-qualified sites. (06/20/2011) (04/30/2012)

Perfusion CT will be performed at participating institutions that are ACRIN qualified for the perfusion CT imaging. The participating institutions must have the appropriate CT scanner for the required scanning protocols. For an institution to be eligible, the CT scanner should be capable of imaging a 2.8 to 12 cm section of the abdomen/ pelvis repeatedly every 2.5 to 15 s for a period up to 3 minutes.

Patients who consent and are enrolled in GOG-0262/ACRIN 6695 will be assessed for the presence of a target lesion.

The **local site** radiologist will assess on the standard practice unenhanced CT scan the potential target lesion as follows:

§4.6 (a) ≥ 1 cm in both the long and short axis;
§4.6 (b) At least one half of the tumor has an attenuation of ≥ 10 HU on the unenhanced CT scan;

The ACRIN T0, T1, and T2 Forms, completed at the site, will include these technical data and will be submitted through the ACRIN web data center. Dose-length product (DLP) and $CTDI_{vol}$ of each scan per case (T0, T1, and T2) and the total DLP of all case scans are required.

The ACR Imaging Core Lab will confirm patient eligibility for ACRIN 6695 based on the protocol target lesion requirements. This determination will take place once all pre-treatment imaging, including the baseline T0 perfusion CT images and pre-treatment standard-of-care CT assessed for measureable disease and RECIST criteria, are submitted to the ACR Imaging Core Lab.

Images should be received and acknowledged at the ACR Core Lab via TRIAD or media within 7 days after the baseline T0 perfusion CT acquisition to allow the ACR Core Lab to review the target lesion criteria and determine if the participant will continue on the ACRIN 6695 study. The ACR Imaging Core Lab will evaluate the potential target lesion once all required images are received.

The potential target lesion will be confirmed by the **ACR Imaging Core Lab** if:

§4.6 (a) The size of the tumor is ≥ 1 cm in both the long and short axis;

§4.6 (b) At least one half of the tumor has an attenuation of ≥ 10 HU on the unenhanced CT scan;

§4.6 (c) At least one half of the tumor has a maximum enhancement of ≥ 5 HU on the perfusion CT scan.

Patients whose target lesions meet the protocol criteria for ACRIN 6695 will continue on both the GOG-0262 treatment study and the ACRIN 6695 imaging study.

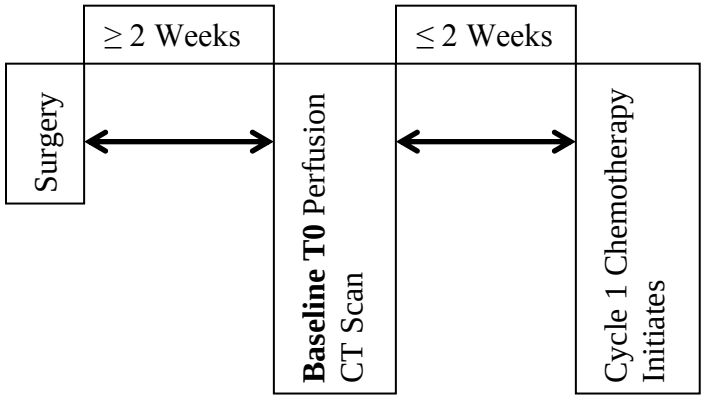
Patients whose target lesions do not meet the protocol criteria for ACRIN 6695 will continue on the GOG-0262 treatment study but will be considered off-study for ACRIN 6695.

The ACR Imaging Core Lab or ACRIN Headquarters staff will inform the site whether the participant will continue with additional perfusion CT imaging per ACRIN 6695 study protocol.

4.61 **Perfusion CT Scan Timeline and Analysis (10/22/2012)**

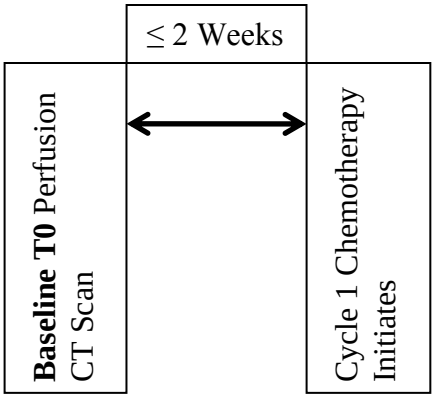
4.611 **Baseline T0** Perfusion CT**: After Primary Surgery With Sub-Optimal Debulking.** For primary surgery patients with sub-optimal debulking, the baseline T0 perfusion CT should be performed a minimum of 2 weeks after surgery to allow for inflammation reduction after surgery. The baseline T0 perfusion CT scan must be performed after GOG registration and before protocol chemotherapy initiates (within the 2 weeks [14 days] from GOG registration to Cycle 1 chemotherapy) The baseline T0 perfusion CT can be completed the day of GOG registration (after consent) or the day of chemotherapy initiation as long as the imaging is completed prior to chemotherapy administration.

Figure 1. Sample Timeline for Baseline T0 Perfusion CT Imaging in Patients in the Primary Surgery Cohort



4.612 **Baseline T0** Perfusion CT**: Before Neoadjuvant Chemotherapy Without Primary Surgery.** For patients receiving neoadjuvant chemotherapy, the baseline T0 perfusion CT scan must be performed after GOG registration and before protocol chemotherapy initiates (within the 2 weeks [14 days] from GOG registration to chemotherapy starting). The baseline T0 perfusion CT can be completed the day of GOG registration (after consent) or the day of chemotherapy initiation as long as the imaging is completed prior to chemotherapy administration.. **(02/06/2012) (04/30/2012)**

Figure 2. Sample Timeline for Baseline T0 Perfusion CT Imaging in Patients in the Neoadjuvant Chemotherapy Cohort



4.613 **Intermediate T1 Perfusion CT:** For all patients, intermediate T1 perfusion CT will be performed between days 18 and 21 after the start of Cycle 1 chemotherapy. If for any reason (e.g., toxicity), the three-week timeline to complete Cycle 1 chemotherapy is delayed, then the intermediate T1 scan may be completed within the three days before Cycle 2 is initiated.

A total of 15 patients will be asked to complete the reproducibility T1 perfusion CT scan. After one (1) participant has been scanned at a participating site at all three time points, and with clearance from the ACR Core Lab, patients will be asked to have a reproducibility T1 perfusion CT scan, if they have consented per local IRB procedures. A total of 15 participants will complete this series. The reproducibility T1 will be completed the same day as the intermediate T1 perfusion CT. The patient may get up from the CT scanner between the scans for approximately 15 minutes. **(04/30/2012) (10/22/2012)**

4.614 **Early-Therapy T2 Perfusion CT:** For all patients, T2 perfusion CT will be performed between days 8 to 10 after the start of Cycle 2 chemotherapy with or without bevacizumab. **(04/30/2012) (10/22/2012)**

4.615 **Analysis of ACRIN 6695 Perfusion CT Images:** Kinetic analysis of the perfusion CT scan will be performed using CT Perfusion software (GE Healthcare) to derive tumor functional perfusion parameters including: vascularity or blood volume (BV); perfusion or blood flow (BF); mean transit time (MTT); and microvascular permeability or permeability surface area product (PS).

4.62 **Perfusion CT Scanning Procedures (10/22/2012)**

At each time point, every patient will have an abdominal strap put on with gentle pressure over the area of the perfusion scan to decrease the breathing motion of the abdomen or pelvis during the perfusion scan. Additional information about the perfusion CT scan parameters is available in Appendix VII of the protocol and in the *ACRIN 6695 / GOG-0262 Imaging Manual* available online at www.acrin.org/6695_protocol.aspx under Imaging Materials.

4.621 **Baseline T0** Perfusion CT Scan Protocol **(10/22/2012)**

4.6211 **Baseline T0 Perfusion CT scan:** Follow timeline procedures as described above in Section 4.61, as parameters differ depending on surgical status.

An unenhanced CT scan of the abdomen and pelvis using the standard scanning protocol at the institution is required for the GOG-0262 trial to confirm residual disease eligibility after primary surgery among those participants. The unenhanced "GOG-eligibility" CT scan must be completed within 28 days before chemotherapy initiation. If the unenhanced CT scan needs to be completed after GOG registration, it is recommended that the perfusion CT scan be completed same-day to eliminate the need for an additional patient visit. The GOG-registration scan will need to be submitted to ACRIN for assessment of target lesion criteria per Section 4.61 above.

4.6212 **Localization scan:** A localization scan is required if the patient has had their conventional CT performed previously. The abdomen and pelvis are scanned as in the GOG eligibility scan but as a limited scan with limited radiation dose technique. A 2.8 to 12 cm section of the abdomen/pelvis covering the maximal cross-section of or the whole potential target lesion is defined from this scan or the GOG eligibility scan.

4.6213 **Perfusion CT scan:** A perfusion scan of the 2.8 to 12 cm section of the abdomen/pelvis localized above is set up as follows:

4.62131 Contrast dose: 0.7 to 0.8 ml per kg of body weight up to maximum of 70 ml of contrast at a concentration of 300 – 370 mgI•ml $^{-1}$ (or mgI/ml) **(02/06/2012)**

4.62132 Injection rate: 2 to 4 ml•sec^{-1} (or ml/sec) **(02/06/2012)**

4.62133 Scanning delay with regard to injection: a delay of less than or equal to five seconds between scanning and injection is allowed **(02/06/2012)**

4.62134 Scanning protocol: See Appendix VII for more detailed guidelines on 64-(with/out table toggling), 128-, 256-, and 320-slice CT scanners

4.62135 Contrast-enhanced, institutional standard care CT scan: If the pre-treatment scan for RECIST-criteria assessment needs to be completed at the time of baseline T0 perfusion CT, a contrast-enhanced CT scan of the abdomen and pelvis using standard techniques for radiographic assessment of disease at your institution (see Section 7.1 Table and Section 8.2) may be acquired the same day, but after, the completion of the perfusion CT. This guidance is provided for timing of scans only in consideration of participant convenience and institutional standard practices. For additional information, see the *ACRIN 6695 / GOG-0262 Imaging Manual* available online at www.acrin.org/6695_protocol.aspx under Imaging Materials.**(02/06/2012)**

4.622 **Intermediate T1** Perfusion CT Scan Protocol **(10/22/2012)**

4.6221 **Assessment of kidney sufficiency:** Participants' kidney function will need to be assessed prior to study-related imaging using contrast. If no creatinine assessment has been completed in the 28 days prior to perfusion CT for the trial, then a measurement will need to be completed to ensure renal function is within study parameters: Creatinine ≤ 1.5 x institutional upper limit normal (ULN). If creatinine is found to be outside of study parameters, the participant will not continue with ACRIN 6695 perfusion CT scans intermediate T1 or early-therapy T2.

4.6222 **Localization scan:** The abdomen and pelvis are scanned as in the localization scan at baseline T0. This scan is used to locate the same 2.8 to 12 cm section of the abdomen/pelvis that is scanned with the perfusion protocol at baseline T0, ensuring coverage of the target lesion identified in the baseline T0 scan.

4.6223 **Perfusion CT scan:** A perfusion scan of the 2.8 to 12 cm section of the abdomen/pelvis localized above is performed as in baseline T0.

4.6224 **Reproducibility T1 Perfusion CT scan:** After one (1) participant has been scanned at each participating site at all time points, and with clearance from the ACR Imaging Core Lab, patients will be asked to have a reproducibility T1 scan, if they have consented per local IRB procedures. A total of 15 participants will complete this series. The same CT parameters will be repeated after a wait of approximately 15 minutes.**(02/06/2012)**

4.623 **Early-Therapy T2** Perfusion CT Scan Protocol **(10/22/2012)**

4.6231 **Assessment of kidney sufficiency:** Participants' kidney function will need to be assessed prior to study-related imaging using contrast. If no creatinine assessment has been completed in the 28 days prior to perfusion CT for the trial, then a measurement will need to be completed to ensure renal function is within study parameters: Creatinine ≤ 1.5 x institutional ULN. If creatinine is found to be outside of study parameters, the participant will not continue with ACRIN 6695 perfusion CT scan early-therapy T2.

4.6232 **Localization scan:** The abdomen and pelvis are scanned as in the localization scan at baseline T0. This scan is used to locate the same 2.8 to 12 cm section of the abdomen /pelvis that is scanned with the perfusion protocol at T0 and T1, ensuring coverage of the target lesion identified in the T0 and T1 scans.

4.6233 **Perfusion CT scan:** A perfusion scan of the 2.8 to 12 cm section of the abdomen/pelvis localized above is performed as in baseline T0 and intermediate T1.

4.63 **<u>Reporting of Imaging AEs and SAEs</u> (10/22/2012)**
Adverse events (AEs) and serious adverse events (SAEs) reported within 24 hours after each perfusion CT scan will need to be submitted to ACRIN per the procedures outlined in section 10.3.

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE **(01/18/2011)**

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for GOG-0262 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Sites must submit, all IRB approvals (initial and continuing) on NCI sponsored adult Cooperative Group phase I, II & III prevention and treatment studies to the CTSU Regulatory Office, at the Coalition of Cancer Cooperative Groups in Philadelphia. A CTSU IRB/Regulatory Approval Transmittal Sheet should be submitted along with the CTSU IRB Certification Form or its equivalent. (CTSU forms can be downloaded at https://www.ctsu.org/public/rss2_page.aspx). IRB submissions can be faxed or e mailed (preferred methods) or mailed to

Email, Mail or Fax to:
Cancer Trials Support Unit (CTSU)
ATTN: Coalition of Cancer Cooperative Groups (CCCG)
Suite1100
1818 Market Street
Philadelphia, PA 19103
FAX: 1-215-569-0206
CTSURegulatory@ctsu.coccg.org

5.1 Patient Entry and Registration **(01/18/2011)**

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms. All baseline laboratory tests and pre-study evaluations must be performed, including tumor and blood samples, within the time period specified in the protocol.

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

  Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records. The confirmation provides the patient identification number, treatment arm and if applicable; any necessary instructional information. To print a copy of the completed Fast Fact Sheet go to the confirmation page and open the "view summary" box.

  Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

When a suitable candidate has been identified for protocol entry, the following steps should be taken:

5.11 An approved informed consent form and authorization permitting the release of personal health information must be signed by the patient or guardian. Current FDA, NCI and institutional regulations concerning informed consent will be followed.

5.12 All eligibility requirements indicated in Section 3.0 must be satisfied.

5.13 The Fast Fact Sheet (FFS) data must be gathered. Particular attention should be given to correctly ascertaining the patient's FIGO stage, performance status, decision to use neodadjuvant chemotherapy and decision to include bevacizumab. The FFS can be downloaded from the CTSU GOG-0262 web page in the Patient Enrollment section of the registered members' web site at https://www.ctsu.org. **(01/18/2011) (06/20/2011)**

Note: Patients entered after 02/08/2012 will not be randomized. (04/30/2012)

5.14 The institution will enter the patient's name, GOG number, and assigned regimen in the appropriate place in their Log Book to verify the patient's entry. **(01/18/2011)**

5.15 GOG will notify ACRIN and have a copy of the Fast Fact Sheet (FFS) transmitted to ACRIN after each registration. The patient will then be enrolled in ACRIN 6695 and evaluated for lesion eligibility as defined in Section 4.6 and Appendix VIII. **The following sentence does not apply to patients enrolled after February 8, 2012:** Participants who decline entry into the ACRIN 6695 study at an ACRIN-qualified institution should have a copy of their Imaging Declination Form faxed to ACRIN. **(06/20/2011) (04/30/2012)**

5.2 Treatment Plan **(06/20/2011)**

Between September 27, 2010 and February 8, 2012, patients were randomized to one of two treatment regimens in equal proportions. Beginning 04/30/2012, all patients are required to participate in the ACRIN 6695 imaging component, and the chemotherapy regimen is selected and declared prior to enrolling in the study. (04/30/2012)

Patients will be randomized to one of two treatment regimens in equal proportions within strata determined by the patient's stage of disease (stage II vs stage III with no gross residual disease vs stage III with gross residual disease vs stage IV), performance status (0 vs 1 or 2), decision to use neoadjuvant chemotherapy and decision to include bevacizumab with their study regimen.

5.21 Primary surgery followed by adjuvant chemotherapy patients **(06/20/2011)**

5.211 Regimen I: Paclitaxel (175 mg/m^2) IV over 3 hours on day 1 followed by Carboplatin (AUC=6) IV on day 1, every 21 days x 6 cycles

5.212 Regimen II: Paclitaxel (80 mg/m^2) IV over 1 hour day 1, 8 and 15 followed by Carboplatin (AUC=6) IV on day 1, every 21 days x 6 cycles.

FOR BOTH REGIMENS: A CYCLE = 21 DAYS

All drugs are dosed to a maximum body surface area (BSA) of 2.0 m^2 as per GOG Chemotherapy Procedure Manual, and BSA is only recalculated if there is a +/- 10% weight change (either up or down). Bevacizumab dosing is also recalculated for a +/- 10% weight change. **(01/18/2011)**

5.213 In addition to the study treatment the patient may opt to include bevacizumab (15 mg/kg) on day 1 beginning with cycle 2 and continuing until disease progression or adverse events preclude further therapy. Note: the patient's intention to include bevacizumab must be declared at the time the patient is registered onto this study. **(04/30/2012)**

5.22 Neoadjuvant Chemotherapy (NAC) followed by interval cytoreductive surgery (ICS) patients: **(06/20/2011)**

5.221 <u>After core needle biopsy to establish diagnosis, patients will receive 3 cycles of</u> Neoadjuvant Chemotherapy <u>with</u> interval cytoreductive surgery <u>between cycles 3 and 4, followed by 3 additional cycles of chemotherapy. If surgery is contraindicated continue treatment with chemotherapy and Bevacizumab if appropriate.</u> **(04/30/2012)**

Surgery must be performed after the third course of chemotherapy, as soon as nadir counts permit, but within six weeks after the completion of the third chemotherapy cycle. Fourth cycle of chemotherapy is to be administered as soon as possible, but no more than six weeks after secondary surgery. **(02/06/2012)**

Patients undergoing neoadjuvant chemotherapy (NACT) with interval cytoreductive surgery (ICS) must be recorded prior to registration and randomization. After core needle biopsy to establish diagnosis, patients will receive 3 cycles of NACT with ICS between cycles 3 and 4, followed by 3 additional cycles of chemotherapy. If chosen, bevacizumab will be administered during cycles 2, 5, and 6, but omitted during cycles 1, 3 and 4. **(02/06/2012)**

<u>Note: Patients undergoing neoadjuvant chemotherapy with interval cytoreductive surgery must be recorded prior to registration and randomization.</u>

FOR BOTH REGIMENS: A CYCLE = 21 DAYS

All drugs are dosed to a maximum body surface area (BSA) of 2.0 m^2 as per GOG Chemotherapy Procedure Manual, and BSA is only recalculated if there is a +/- 10% weight change (either up or down) and drug dosing is recalculated

with the new BSA. Bevacizumab dosing is also recalculated for a +/- 10% weight change.

5.222 In addition to the study treatment the patient may opt to include bevacizumab (15 mg/kg) with NAC-ICS arm. It will be given on day 1 of cycle 2, 5 and 6 and continuing after cycle 6 every 3 weeks until disease progression or adverse events preclude further therapy. Note: The intent to use bevacizumab must be declared at the time the patient is registered onto this study. **(04/30/2012)**

5.23 Chemotherapy administration (See Appendix VI for GOG General Chemotherapy Guidelines) **(06/20/2011)**

5.24 Antiemetic Regimens (for both regimens)

It is anticipated that nausea and vomiting may be a significant side effect of each regimen. The following representative antiemetic regimens are Suggested during cytotoxic chemotherapy portion of treatment:

- Ondansetron 8-32 mg IV or PO 30 minutes prior to administration of chemotherapy and dexamethasone 10-20 mg IV or PO 30 minutes prior to drug administration OR;

- Dolasetron 1.8 mg/kg IV (max 100 mg) prior to chemotherapy and dexamethasone 10-20 mg IV 30 minutes prior to drug administration

OR;

- Granisetron 10 mcg/kg IV (or 2 mg PO) 30 minutes prior to chemotherapy, dexamethasone 10-20 mg IV 30 minutes prior to chemotherapy, with or without lorazepam 0.5-2.0 mg IV 30 minutes prior to chemotherapy.

- Aprepitant 125 mg PO one hour prior to chemotherapy on day 1 and 80 mg daily PO on days 2 & 3 is advised by ASCO and NCCN in addition to the above choices for patients receiving cisplatin or having nausea or vomiting with carboplatin. (the intravenous formulation may be substituted when available)

5.25 Intravenous Paclitaxel

5.251 Preparative regimen recommended for IV paclitaxel:

- Dexamethasone 20 mg PO 12 and 6 hours prior to paclitaxel or 20 mg IV just prior to IV therapy.
- Diphenhydramine 50 mg IV 30 minutes prior to paclitaxel (alternative is acceptable).
- Cimetidine 300 mg IV 30 minutes prior to paclitaxel (or Ranitidine 50 mg or alternative is acceptable).

Because the number of dexamethasone doses for a weekly paclitaxel regimen may be problematic for some patients, investigators can consider tapering the dexamethasone dose down in subsequent weeks for those patients who have no evidence of hypersensitivity reactions.

5.252 Sequence and timing of drug administration:

Intravenous paclitaxel will be infused over 3 hours in Regimen I and over one hour in Regimen II. Due to the risk of immediate hypersensitivity reaction, paclitaxel should always be the first drug to be infused during any combination. Carboplatin will be administered as a 30 minute infusion, following paclitaxel administration in both regimens.

Bevacizumab administration will be as a continuous intravenous infusion following carboplatin infusion. Anaphylaxis precautions should be observed during bevacizumab administration. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS**. The initial dose should be delivered over 90 minutes as an IV infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

5.26 Dosing of Carboplatin **(01/18/2011)**

See Appendix V for current carboplatin dose calculation instructions.

5.27 Dosing of bevacizumab (Optional, see Section 5.23)

Bevacizumab will be administered at 15 mg/kg IV. Patient weight at screening will be used to determine the bevacizumab dose to be used for the duration of the study. If a patient's weight changes by (plus or minus) ≥ 10% during the course of the study, then the bevacizumab dose will be recalculated.

5.271 Supportive Care Guidelines for bevacizumab:

If an infusion-related adverse reaction occurs, the patient should be pre-medicated with the following prophylactic regimen:

- H_1 blocker (diphenhydramine 25-50 mg IVP or orally one hour prior to injection; or an equivalent dose of an alternate H_1 blocker such as loratadine 10 mg or fexofenadine 60 mg).

- H_2 blocker (famotidine 20 mg IVP or orally one hour prior to injection; or an equivalent dose of an alternate H_2 blocker).

- Dexamethasone (10 mg administered PO 12 and 6 hours prior to bevacizumab injection).

However, the infusion time for bevacizumab may not be decreased for the next infusion. If the next infusion is well tolerated with pre-medication, the infusion time for the next dose may then be decreased by 30 ± 10 minutes as long as the patient continues to be pre-medicated. If a patient experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90 ± 15 minutes. Similarly, if a patient experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60 ± 10 minutes.

5.28 Preparative Regimen for docetaxel when there is a contraindication to IV paclitaxel

The following preparative regimen is suggested as premedication for all patients receiving docetaxel.

Dexamethasone 8 mg PO BID starting one day prior to treatment and continuing for a total of three days duration.
Diphenhydramine 50 mg IV 30 minutes prior to docetaxel.

Docetaxel 75 mg/m^2 will be administered as an intravenous infusion over 1 hour every 3 weeks. **(06/20/2011)**

5.29 Prohibited Concomitant Therapeutic Modalities

Prior to documented disease progression, the following therapeutic modalities are prohibited:

5.291 Reassessment or cytoreductive surgery

5.292 Anti-neoplastic therapy not otherwise specified in the current protocol, including cytotoxic, biologic, hormonal, or radiation therapy, regardless of indication (treatment of measurable disease or consolidation therapy).

5.3 Perfusion CT Imaging Plan **(06/20/2011) (10/22/2012)**

5.31 Perfusion CT Imaging: Confirmed Eligibility Requirement of Target Lesion **(10/22/2012)**

Patients enrolled in the trial with confirmed target lesion for continued eligibility on the ACRIN 6695 sub-study (as assessed from the baseline T0 and pre-treatment RECIST images by the ACR Imaging Core Lab) will undergo intermediate T1 (possibly including a reproducibility T1 on a subset of participants) and early-therapy T2 scans as described in Section 4.6. The same target lesion will need to be imaged on all study-related perfusion CT scans. Patients enrolled with ineligible findings after ACR Core Lab review of pre-treatment images will be considered off-study for ACRIN 6695 only, will

continue with the GOG therapeutic trial, and will not continue with the imaging portion of the study (will not complete intermediate T1 or early-therapy T2).

5.32 Reproducibility Perfusion CT Scan **(02/06/2012) (04/30/2012) (10/22/2012)**

The reproducibility T1 perfusion CT scan will be performed at participating ACRIN sites on a total of 15 patients who consent to complete a second perfusion CT scan at the intermediate T1 time point. Sites will be eligible to enroll participants in the reproducibility T1 cohort after completing a minimum of one patient's perfusion CT scans at all three time points at their institution, and with clearance from the ACR Imaging Core Lab. The ACR Imaging Core Lab will communicate with the local sites to coordinate the scheduling of the reproducibility perfusion CT. The repeated perfusion CT scan will allow the assessment of the reproducibility of the perfusion parameters (BF, BV, MTT, and PS) and contribute towards the validation of the Perfusion CT software package (GE Healthcare) used in the study.

5.33 Image Submission Guidelines **(10/22/2012)**
Perfusion CT and standard-of-care CT images for the baseline T0 time point will be received and acknowledged at the ACR Core Lab via TRIAD or media within 7 days after acquisition of the baseline T0 perfusion CT.

5.331 **For TRIAD Submission:** The preferred image transfer method is via TRIAD, a software application that ACRIN provides for installation on a site's PC. One or several computers of choice within the institutional "firewall" and on the institutional network may be equipped with TRIAD software; Internet access is also required. The TRIAD application can then be configured as a DICOM destination on either scanner(s) and/or PACS system for direct network transfer of study related images into the TRIAD directory. When properly configured, the TRIAD software anonymizes, encrypts, and performs a lossless compression of the images before they are transferred to the ACRIN image archive in Philadelphia. Once equipment-readiness has been determined, imaging personnel from ACRIN will coordinate installation and training for the software.

The Imaging Transmittal Worksheet (ITW) can be found on the ACRIN web site (www.acrin.org/6695_protocol.aspx). The ITW must be completed, signed and sent at the times the images are transmitted.

For more information, contact: TRIAD-support@phila.acr.org or call 215-940-8820.

5.332 **For Submission Via Media:** In the event that the transfer of image data is not available via TRIAD, images may also be sent on a CD/DVD-ROM to the ACRIN core lab for transfer to the image archive. All image data submitted to the ACRIN core lab must be in DICOM format.

The ITW must accompany media submissions. PDF versions of the transmission worksheets are available for downloaded at www.acrin.org/6695_protocol.aspx.

5.333 Images may be mailed to:

American College of Radiology Clinical Research Center
ACR Imaging Core Laboratory
Attn: ACRIN 6695 Imaging Specialist
1818 Market Street 16th floor
Philadelphia, PA 19103

6.0 TREATMENT MODIFICATIONS

In order to maintain dose-intensity and cumulative dose-delivery on this study, reasonable efforts will be made to minimize dose reduction and treatment delays as specified. Any patient whose treatment is delayed must be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met. No dose escalation is planned for this study.

6.1 General Guidelines for Hematologic Toxicity

6.11
Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).

6.12
Lower Limits for ANC and Platelet Count

6.121 **With Cytotoxic Chemotherapy** – Day 1 of a subsequent cycle of cytotoxic chemotherapy will not be administered until the ANC is ≥ 1,000 cells/mcl and the platelet count is ≥ 75,000/mcl. All treatment (including bevacizumab) will be delayed for a maximum of three weeks until these values are achieved. Patients who fail to recover adequate counts within a three-week delay will no longer receive protocol-directed cytotoxic therapy. If the patient opted to include bevacizumab with her study treatment, then bevacizumab can be continued, provided there are not contraindications.

Regimen II: The day 8 and 15 paclitaxel dose will not be given unless the ANC is at least 500 cells/mcl and the platelet count is at least 50,000/mcl. If not given, these doses are omitted and not made up.

During Consolidation (if opted for bevacizumab), day 1 bevacizumab treatment will not be given until the ANC is ≥ 1,000 cells/mcl and the platelet count is ≥ 75,000/mcl. Treatment with bevacizumab will be delayed for a maximum of three weeks until these values are achieved. Patients who fail to recover adequate counts within a three-week delay will no longer receive any protocol-directed therapy.

6.122 In cases where protocol directed cytotoxic therapy has been discontinued for reasons other than cancer progression, please see section 6.6 for guidelines, as patients who have opted to receive bevacizumab will generally still receive bevacizumab.

6.13 Use of Hematopoietic Cytokines and Protective Agents **(06/20/2011)**

6.131 It is anticipated that myelosuppression may be a significant side effect of each regimen. Myeloid growth factors (either filgrastim or pegfilgrastim) can be used (it is recommended that NCCN and/or ASCO guidelines be consulted). If myeloid growth factors are used, it is recommended that filgrastim (dose according to institutional standard) will be administered daily subcutaneously starting 24-72 hours after the

last dose of chemotherapy and continuing through hematopoietic recovery or pegfilgrastim will be administered at 6 mg subcutaneously (one dose per treatment cycle) 24-72 hours after the last dose of chemotherapy. Administration of growth factors on the same day as chemotherapy is not recommended. Pegfilgrastim is not recommended for chemotherapy regimens given less than every 2 weeks. **(06/20/2011)**

6.132 Patients will NOT receive prophylactic thrombopoietic agents.

6.133 Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of the prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They are not indicated in patients being treated with curative intent. They do not alleviate fatigue or increase energy. They should NOT be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted. http://www.fda.gov/Medwatch/safety/2007/safety07.htm **(06/20/2011)**

6.134 Patients may NOT receive amifostine or other protective reagents.

6.14 Dose Modifications for Paclitaxel and Docetaxel

Regimen I: There will be no dose modifications for paclitaxel based on hematologic toxicity. Dose modifications for docetaxel are according to Tables A and B below.

Regimen II: The day 8 and 15 paclitaxel dose will not be given unless the ANC is at least 500 cells/mcl and the platelet count is at least 50,000/mcl. If not given, these doses are omitted and not made up

6.2 Modifications for Hematologic Toxicity (Nadirs)

6.21 Initial occurrence of dose-limiting neutropenia (defined in 6.22) or dose limiting thrombocytopenia (defined in 6.23) will be handled according to Tables A or B

6.22 Dose-Limiting Neutropenia (DLT-ANC) is defined by the occurrence of febrile neutropenia, prolonged Grade 4 neutropenia persisting ≥ 7 days, delay of treatment for more than 7 days because of neutropenia, ANC<1000cells/mcl on day 1, or omission of day 8 or day 15 paclitaxel on Regimen II because of neutropenia. Febrile neutropenia is defined within the CTCAE as a disorder characterized by an ANC <1000/mcl and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour. **(02/06/2012)**

6.23 Dose-limiting thrombocytopenia (DLT-PLT) is defined by any occurrence of Grade 4 thrombocytopenia (<25,000/mcl) or bleeding associated with Grade 3 thrombocytopenia (25,000 to <50,000/mcl), delay of treatment on day 1 of a cycle by more than 7 days because of thrombocytopenia, platelet count of <75,000/mcl on day 1, or inability to give day 8 or day 15 paclitaxel on Regimen II due to thrombocytopenia. There will be no modifications for uncomplicated Grade 3 thrombocytopenia except as above. **(06/20/2011) (02/06/2012)**

Table A: Modification Instructions for Dose-Limiting Hematologic Toxicity Regimen I				
DLT ANC	**DLT PLT**	**First Occurrence**	**Second Occurrence (06/20/2011)**	**Third Occurrence**
Yes	**No**	Reduce carboplatin one AUC unit (and docetaxel by 10 mg/m^2 if pt on docetaxel)	Add G-CSF* and maintain all current drug doses. **(02/06/2012)**	Discontinue Protocol-Directed Cytotoxic Therapy**
Yes	**Yes**	Reduce carboplatin one AUC unit (and docetaxel by 10 mg/m^2 if pt on docetaxel)	Add G-CSF* and Reduce carboplatin one AUC unit (and docetaxel by 10 mg/m^2 if pt on docetaxel) **(02/06/2012)**	Discontinue Protocol-Directed Cytotoxic Therapy**
No	**Yes**	Reduce carboplatin one AUC unit (and docetaxel by 10 mg/m^2 if pt on docetaxel)	Reduce carboplatin one AUC unit (and docetaxel by 10 mg/m^2 if pt on docetaxel).	Discontinue Protocol-Directed Cytotoxic Therapy**

Minimum carboplatin dose = AUC 4.
* See section 6.131. **(06/20/2011) (02/06/2012)**

**Applies to platinum/taxane therapy, not to bevacizumab. See section 6.6 for general guidelines on non-protocol-directed cytotoxic therapy.

Table B: Modification Instructions for Dose-Limiting Hematologic Toxicity Regimen II				
DLT ANC	**DLT PLT**	**First Occurrence**	**Second Occurrence (06/20/2011)**	**Third Occurrence**
Yes	**No**	Reduce carboplatin one AUC unit (and docetaxel by 10 mg/m^2 if pt on docetaxel)	Omit day 15 paclitaxel and administer G-CSF starting after day 8 paclitaxel (if patient on	Reduce caboplatin one AUC, and give G-CSF after day 8

		(02/06/2012)	docetaxel, start G-CSF 24 hours after docetaxel with no further dose reduction) **(02/06/2012)**	paclitaxel. Fourth occurrence: Discontinue Part A Protocol Directed Cytotoxic Therapy. **(02/06/2012)**
Yes	**Yes**	Reduce carboplatin one AUC unit (and docetaxel by 10 mg/m^2 if pt on docetaxel) **(02/06/2012)**	Omit day 15 paclitaxel and administer G-CSF starting after day 8 paclitaxel (if patient on docetaxel, start G-CSF 24 hours after docetaxel) and reduce carboplatin one AUC until (and docetaxel by 10 mg/m^2 if pt on docetaxel) **(02/06/2012)**	Discontinue Part A Protocol-Directed Cytotoxic Therapy**
No	**Yes**	Reduce carboplatin one AUC unit.	Decrease carboplatin one AUC unit.	Discontinue Part A Protocol-Directed Cytotoxic Therapy**

Minimum carboplatin dose = AUC 4.
* See section 6.131. **(06/20/2011) (02/06/2012)**

**Applies to platinum/taxane therapy, not to bevacizumab. See section 6.6 for general guidelines on non-protocol-directed cytotoxic therapy.

If treatment is delayed more than 21 days for reasons of toxicity, then protocol-directed cytotoxic therapy is ended; patient may, at discretion of treating physician, continue with non-protocol directed cytotoxic therapy (dose reductions and growth factors) for up to six total cycles of cytotoxic therapy, and if the patient opted for bevacizumab treatment, protocol bevacizumab may be continued with such therapy. If there are no contraindications, consolidation protocol-directed bevacizumab can still be administered.

6.3 Adjustments for Non-Hematologic Toxicity

Table C: Modifications for Non-Hematologic Toxicity			
Drug	**Regimen Starting Dose**	**Regimen -1 Level**	**Regimen -2 level**
Paclitaxel (3 week)	175 mg/m^2	135 mg/m^2	110 mg/m^2
Paclitaxel (weekly)	80 mg/m^2	70 mg/m^2	60 mg/m^2
Carboplatin	6.0	5.0	4.0
Docetaxel (3 week)	75 mg/m^2	65 mg/m^2	55 mg/m^2

Table C should be used for dose level modifications for non-hematologic toxicity only as indicated specifically in the sections below.

6.31 Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level in paclitaxel and delay in all subsequent protocol-directed therapy for a maximum of three weeks until recovered to Grade 1. If peripheral neuropathy fails to recover to Grade 1 by a maximum delay of three weeks from time therapy is due, or recurs, then paclitaxel should be withheld from all subsequent chemotherapy cycles, and docetaxel should be substituted. Patients on regimen II will be effectively switched to regimen I using docetaxel. Weekly docetaxel will NOT be used.

6.32 Hypertension. Patients receiving bevacizumab should be monitored prior to each dose with measurement of blood pressure (see Section 7.0 Study Parameters). For treatment modification for Bevacizumab-related adverse events, please see Table D in Section 6.4 Medication classes used for management of patients with hypertension receiving bevacizumab include angiotensin-converting enzyme inhibitors, beta blockers, diuretics, and calcium channel blockers. The use of anxiolytics in conjunction with specific anti-hypertensive agents is not prohibited. The goal for blood pressure control should be consistent with general medical practice guidelines (i.e. < 140/90 mmHg in general and < 130/80 mmHg for patients with diabetes).

For controlled hypertension, defined as systolic ≤ 160 mm Hg and diastolic ≤ 90 mm Hg, continue bevacizumab therapy.

6.321 For uncontrolled hypertension (systolic > 160 mm Hg or diastolic > 90) or symptomatic hypertension less than CTCAE Grade 4, hold cytotoxic chemotherapy for up to 1 week if indicated (see below), with anti-hypertensive therapy initiated or continued, as in 6.32. For treatment modification for Bevacizumab-related adverse events, please see Table D in Section 6.4.

- During the period of combination chemotherapy, if the patient has opted to receive bevacizumab, if hypertension is controlled and symptomatic hypertension has resolved by one week after holding treatment, continue all therapy. For treatment modification for Bevacizumab-related adverse events, please see Table D in Section 6.4.

- During the period of combination chemotherapy, if the patients has opted to receive bevacizumab, if hypertension remains uncontrolled or symptomatic hypertension, less than CTCAE Grade 4, persists one week after holding treatment, the next treatment cycle should contain paclitaxel and carboplatin only, if applicable, as otherwise indicated in the protocol, with bevacizumab omitted. For treatment modification for Bevacizumab-related adverse events, please see Table D in Section 6.4.

6.33 Proteinuria. Patients receiving bevacizumab should be monitored by urine analysis for urine protein: creatinine (UPC) ratio prior to every other dose of bevacizumab. For treatment modification for Bevacizumab-related adverse events, please see Table D in Section 6.4.

6.34 Hemorrhage. For treatment modification for Bevacizumab-related adverse events, please see Table D in Section 6.4.

6.35 Thrombosis.

6.351 Arterial Thrombosis

For treatment modification for Bevacizumab-related adverse events, please see Table D in Section 6.4.

6.352 Venous Thrombosis

For treatment modification for Bevacizumab-related adverse events, please see Table D in Section 6.4.

6.36 Coagulopathy. For treatment modification for Bevacizumab-related adverse events, please see Table D in Section 6.4.

6.37 Wound Disruption/Bowel Perforation, Fistula, or GI Leak: For treatment modification for Bevacizumab-related adverse events, please see Table D in Section 6.4.

6.38 Renal toxicity (associated with reduction in GFR) is not expected as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule of each regimen. As such, there are no specific dose modifications for renal toxicity. However, the target AUC dose of carboplatin must be recalculated each cycle in any patient who develops renal insufficiency, defined by serum creatinine greater than 1.5 x institutional upper limit normal (ULN).

6.39 Intestinal obstruction. Bevacizumab will be held for occurrence of CTCAE Grade 3 toxicity, until resolution to ≤CTCAE Grade 1 and will be permanently discontinued for occurrence of CTCAE Grade 4 toxicity. Since the development of intestinal obstruction could be a result of cancer progression, the investigator should take steps to evaluate such patients for the possibility of disease progression according to section 8.0, using clinical, laboratory and radiographic information as clinically indicated; in the event of disease progression as per section 8.0, all protocol-directed therapy would be discontinued.

6.310 Hepatic toxicity is not expected as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule for each regimen. However, the development of Grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level in paclitaxel or reduction of docetaxel by 10 mg/m^2 and delay in subsequent therapy for a maximum of three weeks until recovered to Grade 1.

6.311 There will be no dose modifications for alopecia, nausea, or constipation. It is recommended that routine medical measures be employed to manage nausea, constipation. Grade 3 diarrhea on day of planned treatment will require holding of paclitaxel in patients on weekly paclitaxel and holding of docetaxel in patients on docetaxel. Any grade 3 diarrhea in patients on weekly paclitaxel will mandate a one dose level reduction of paclitaxel in future cycles; in pts on docetaxel it will require a 10 mg/m^2 dose reduction of docetaxel for future cycles. If the diarrhea is clearly infectious and has resolved, the above mandated dose reductions do not apply.

6.312 Treatment Guidelines for Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Bevacizumab should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure. Bevacizumab should be discontinued upon diagnosis of RPLS.

Note: Resumption of bevacizumab may be considered in patients who have documented benefit from the agent, provided that RPLS was mild and has completely resolved clinically and radiographically within 2-4 weeks; decision to resume bevacizumab in these patients must be discussed with the study chair and approved by the sponsor.

6.313 In general, the occurrence of a hypersensitivity reaction to paclitaxel, docetaxel, or bevacizumab is not considered a dose-limiting toxicity. Patients may be retreated at full doses after administration of medication to prevent hypersensitivity reactions, and adjustments in infusion rates should be made (see guidelines for re-treatment with bevacizumab in section 5.271). However, if despite these safety measures repeat attempt at infusion of the inciting drug results in a recurrent hypersensitivity reaction, the inciting drug should be discontinued for the remainder of the study. In the event of any CTCAE Grade 3 or 4 allergic or infusion reaction to bevacizumab, bevacizumab will be permanently discontinued.

6.314 Potential modifications for other non-hematologic toxicities with an impact on organ function of Grade 2 (or greater) require discussion with one of the study co-chairs except where noted below in Section 6.63141. **(10/22/2012)**

6.3141 Special Modifications Study Treatment

6.31411 For any CTCAE Grade 3 non-hematologic adverse event (except controllable nausea/emesis) considered to be at least possibly related to study treatment, protocol directed treatment should be held until symptoms resolve to ≤ CTCAE Grade 1. If a CTCAE Grade 3 adverse event persists for > three weeks or recurs after resumption of therapy, the patient may be taken off protocol directed treatment after consulting with the Study Chair.

6.31412 For any CTCAE Grade 4 non-hematologic adverse event (except controllable nausea/emesis), the patient may be taken off protocol directed treatment therapy after consulting with the Study Chair.

6.4 Dose and Treatment Modifications for Bevacizumab

There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described below. If bevacizumab is interrupted for ANY reasons for more than four weeks (unless otherwise specified), the patient should discontinue bevacizumab therapy on protocol.

Treatment Modification for Bevacizumab-Related Adverse Events
Table D

Event	CTCAE. v4.0 Grade	Action to be Taken
Allergic reactions or Infusion-related reactions Or Anaphylaxis	Grade 1-2	Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. For infusion-associated symptoms not specified above, infusion should be slowed to 50% or less or interrupted. Upon complete resolution of the symptoms, infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle. Subjects who experience bronchospasm (regardless of grade) should discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab
Thromboembolic Event (Arterial); arterial ischemia - Cardiac ischemia - Myocardial infraction - CNS ischemia (TIA, CVA) - any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (new or worsening since bevacizumab	Discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab
Thromboembolic Event Venous)	[Note: Patients with lung cancer requiring therapeutic anticoagulation should discontinue bevacizumab]	
	Grade 3 OR asymptomatic Grade 4	▪ Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2weeks, bevacizumab should be held until the full-dose anticoagulation period is over. ▪ If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during full-dose anticoagulation **IF** <u>all</u> of the criteria below are met: • The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other

Event	CTCAE. v4.0 Grade	Action to be Taken
		conditions) • The subject must not have had hemorrhagic events while on study • The subject must be on stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. ▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab
	Grade 4 (symptomatic)	Discontinue bevacizumab
Hypertension*	[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice]	
	Grade 1 (SBP 120-139 mmHg or DBP80-89 mm Hg)	Consider increased BP monitoring; start anti-hypertensive medication if appropriate
	Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg)	Begin anti-hypertensive therapy and continue bevacizumab
	• Grade 2 symptomatic (SBP 140-160 mmHg or DBP 90-100 mm Hg) • Grade 3 (≥ SBP 160 mmHg or ≥ DBP 100 mmHg	• Start or adjust anti-hypertensive medication • Hold bevacizumab until symptoms resolve **AND** BP < 160/90mmHg
	Grade 4	Discontinue bevacizumab.
Heart Failure or LV dysfunction	Grade 3	Discontinue bevacizumab
	Grade 4	Discontinue bevacizumab
Proteinuria	[Proteinuria should be monitored by urine analysis for urine protein creatinine (UPC) ratio, prior to every other dose of bevacizumab.]**(02/06/2012)**	
	UPC ratio < 3.5 or 24-h urine protein < 3.5 gm	Continue bevacizumab. *Once 24-hour urine is <3.5gm, it is not necessary to repeat 24-hour urine for 2+ proteinuria.
	UPC ratio	Hold bevacizumab until it UPC recovers to <

Event	CTCAE. v4.0 Grade	Action to be Taken
	≥ 3.5 or 24-h urine protein ≥ 3.5 gm	3.5, or 24-h urine protein < 3.5 gm. Discontinue bevacizumab if urine protein does not recover to < 3.5 after 8 weeks or bevacizumab interruption
	Nephrotic syndrome	Discontinue bevacizumab.
Hemorrhage (intracranial or pulmonary)	Grade 2-4	• Discontinue bevacizumab
	Grade 1	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and Hb is stable - there is no bleeding diathesis that would increase the risk of therapy • there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence
Hemorrhage (any other organ systems)	Grade 3	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and Hb is stable - there is no bleeding diathesis that would increase the risk of therapy - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence. • Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy.
	Grade 4	Discontinue bevacizumab
RPLS (Reversible Posterior Leukoencephalopathy syndrome **or PRES** (Posterior Reversible Encephalopathy Syndrome)		• **Discontinue bevacizumab upon diagnosis of RPLS.**
Wound dehiscence requiring medical or surgical intervention		• **Discontinue bevacizumab**
Perforation (GI, or any other organ)		Discontinue bevacizumab
Fistula (GI, pulmonary or any other organ)		Discontinue bevacizumab
Obstruction of GI tract	G2 requiring medical intervention	• Hold bevacizumab until complete resolution

Event	CTCAE. v4.0 Grade	Action to be Taken
	G3-4	• Hold bevacizumab until complete resolution • If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion
Other Unspecified bevacizumab-related AEs (except controlled nausea/vomiting).	Grade 3	• Hold bevacizumab until symptoms resolve to ≤ grade 1
	Grade 4	• Discontinue bevacizumab • **Upon consultation with the study chair,** resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the G4 toxicity is transient, has recovered to ≤ grade 1 and unlikely to recur with retreatment.
• Non-clinically significant labs (e.g. Na <130 (CTCAE Grade 3) should NOT trigger holding Bevacizumab		

6.5 Unanticipated Major Surgical Procedures – For any unanticipated (emergent/urgent) major surgical procedure performed for reasons other than disease progression or CTCAE at least possibly related to bevacizumab, treatment should be held > 28 days post-operatively prior to resumption, so long as other criteria in sections 6.2 and 6.3 are met. Treatment delay is **not** required for minor procedures including a) cystoscopy, b) the removal or insertion of a central venous catheter, nephrostomy tube, or ureteral stent or c) thoracentesis or paracentesis for symptom relief in the absence of disease progression according to section 8. NOTE: the performance of non-emergent abdominal surgery (such as ostomy reversal, interval or secondary cytoreductive surgery, or second look surgery) prior to documentation of disease progression according to section 8 is considered a major protocol violation.

6.6 Guidelines for Use of Cytotoxic Therapy, After Discontinuation of Protocol Directed Cytotoxic Therapy and Prior to Disease Progression

So long as a patient has not developed progressive cancer as per section 8.0 and has not yet received 6 cycles of carboplatin/taxane therapy, if a patient's cytotoxic therapy is continued despite discontinuation of protocol directed treatment for adverse events (as directed specifically in section 6.0), it is recommended that such cytotoxic therapy be administered according to best clinical practice standards, which is the use of a platinum, a taxane, or the combination for up to 6 cycles. There are no specific guidelines in this situation for dose modifications, laboratory testing, or use of growth factor support. **In such situations, treatment data should still be submitted using D2R and T forms**. If the patient opted to include bevacizumab with her study treatment, bevacizumab will still be continued, as long as it is not otherwise contraindicated**.**

7.0 STUDY PARAMETERS

7.1 Observations and Tests

The following observations and tests are to be performed and recorded on the appropriate form(s). **See Section 7.2 and 10.2 for a description of the stained pathology slides that are required for central review by the GOG Pathology Committee to confirm eligibility and for instructions for shipping that material to the GOG Statistical and Data Center. See Section 7.3 for a description of the specimen requirements for translational research for this study.**

	Pre-Treatment	During Cytotoxic Chemotherapy and optional Bevacizumab Treatment			During Bevacizumab-only Treatment **(01/18/2011)**		Post-Treatment
Observations and Tests	Prior to Initial Study Treatment	Weekly	Prior to Each Course	Prior to Every Other Course	Prior to Each Course	Prior to Every Other (or Specified) Course **(02/06/2012)**	Every 3 months for 2 years, every 6 months for 3 years, then annually
History & Physical	1		19,20			19, 20	X
Blood pressure**	1	2	19		19		X
Toxicity Assessment	3		X			X	X
CBC/Differential/ Platelets	3	X*	4			4	5
Urinalysis	3						
Urine Protein-Creatinine Ratio (UPCR)**	3, 6			7		7	18
Serum Creatinine	3		4§ **(10/22/2012)**			4	8
Bilirubin, SGOT, Alkaline Phosphatase	3		4			4	8
Ca/PO4/Mg	3		8			8	8
Serum Pregnancy Test (if childbearing potential exists)	3						
PT/INR, PTT**	3		9			9	8
Audiogram	10						
EKG	1						
QOL Assessment	X			16		16	16
Radiographic Disease	1, 11			12,20		12, 20	12

Assessment							
Chest X-Ray	1, 13						
Serum CA-125 Level	1, 14		15,20		15, 20 **(06/20/2011)**		X
Incision Check**	X						
Perfusion CT §§ **(06/20/2011)**	11, 21, 22 **(10/22/2012)**		21, 22				

* Weekly for first 6 cycles

**Required only for patients who elect to receive bevacizumab treatment

§ Kidney sufficiency will need to be assessed prior to ACRIN 6695 intermediate T1 and early-therapy T2 perfusion CT scans to review kidney health prior to administration of contrast. If creatinine has not been measured within 28 days prior to the perfusion CT scans, sites will need to measure creatinine prior to imaging. If creatinine is not ≤ 1.5 x institutional upper limit normal, then the participant will not continue with ACRIN 6695 imaging but will continue with the GOG therapeutic trial. **(10/22/2012)**

§§ For those patients who elect to participate in the ACRIN 6695 portion of the study. **Patients enrolled after February 8, 2012 must participate in the ACRIN 6695 component. (06/20/2011) (04/30/2012)**

1. Must be obtained within 28 days prior to initiating protocol therapy.
2. Blood pressure should be assessed at least weekly during the first cycle (usually cycle 2 of protocol therapy unless contraindicated) of bevacizumab therapy. During the time between treatments, blood pressure assessment may be done at home by the patient at the investigator's discretion, and the investigator or study nurse will be responsible for obtaining these results from the patient.
3. Must be obtained within 14 days prior to initiating protocol therapy.
4. Must be obtained within 4 days of re-treatment with protocol therapy.
5. Weekly until counts recover from nadir
6. Urine protein should be screened by UPCR (see Section 3. 213 for details). Patients must have a UPCR < 1.0 to allow participation in the study.
7. Patients receiving bevacizumab should be monitored by urine analysis for urine protein: creatinine (UPC) ratio prior to every other dose of bevacizumab

UPC ratio < 3.5	Continue bevacizumab.
UPC ratio ≥ 3.5	Hold bevacizumab until UPC ratio recovers to < 3.5. If therapy is held for > 2 months due to proteinuria, discontinue bevacizumab.
Grade 4 or nephrotic syndrome	Discontinue bevacizumab.

8. When clinically indicated
9. For patients on prophylactic or therapeutic anticoagulation with warfarin, PT INR should be monitored before each treatment. Treatment should be held for PT INR of > 1.5 on prophylactic warfarin or > therapeutic range if on full-dose warfarin**.**
10. For patients with a history of hearing loss; repeat as clinically indicated
11. An initial CT scan or MRI of at least the abdomen and pelvis is required to establish post-surgical baseline for the extent of residual disease within 4 weeks before beginning treatment. The baseline GOG scan may be completed after registration and at the same time as the ACRIN 6695 baseline T0 perfusion CT scan per section 4.6211. **(10/22/2012)**
12. Follow-Up Radiographic Assessment of Disease. In the absence of disease progression by criteria in Section 8.3, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be repeated with the following schedule, regardless of whether or not the patient had measurable disease on initial CT or MRI:
    a) After cycle 3 (before cycle 4) of paclitaxel-carboplatin
    b) After cycle 6 of paclitaxel-carboplatin
    c) After completion of carboplatin and paclitaxel, every 3 months for 2 years, then every 6 months for 3 years, then annually

d) During or after completion of all protocol therapy, as clinically indicated at any time for clinical suspicion of progressive disease, including rising serum CA-125 levels not meeting criteria for disease progression in and of themselves according to section 8.3

If based on any of these evaluations a response (CR or PR) is documented, a same modality imaging study should be performed after more than 4 weeks but within 3 months in order to confirm persistence of response by RECIST criteria. Regardless of the level of response confirmed, imaging will be repeated according to the schedule above.

Imaging assessments as part of this protocol should be discontinued if disease progression is confirmed according to guidelines in section 8.3, regardless of means of confirmation, except that when disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be obtained within two weeks that such progression is documented.

13. Not required if CT or MRI of chest already performed at pre-treatment baseline.
14. Baseline pre-chemotherapy value is required. When available, also include pre-surgical value.
15. Progression can be based upon serum CA-125, only during the period following completion of cytotoxic chemotherapy, if one of the three conditions are met: 1. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart or 2. Patients with elevated CA-125 pretreatment, which never normalizes must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart or 3. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart. When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1).If the patient does not meet criteria for disease progression on the basis of CA-125 elevations, then CA-125 monitoring should be continued according to schedule.
16. See Section 7.4. QoL surveys are to be obtained at five time points: (Patients enrolled after February 8, 2012 will not participate in the QOL component.) **(04/30/2012)**
    - baseline, defined as prior to cycle 1 (preferably prior to randomization);
    - prior to cycle 4 of protocol directed chemotherapy (~ 9 weeks from day 1 of cycle 1 if no longer receiving protocol directed treatment);
    - 18 weeks from day 1 of cycle 1;
    - 36 weeks from day 1 of cycle 1;
    - 63 weeks from day 1 of cycle 1;
17. See Section 3.28. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly wound examinations until complete closure. Any occurrence of fascial dehiscence or deterioration related to the incision should be addressed according to guidelines for treatment modification in Section 6.57 and Adverse Events reporting in Section 10.3.
18. Check UPCR at first post-treatment visit Check the UPCR at subsequent post-treatment follow-up intervals only if the value is > 1.
19. Within one week before and as close to the beginning of the next applicable course as possible.
20. Patients who have not experienced disease progression according to section 8.0, including those who discontinue protocol directed therapy per section 6.0, need to be followed in a consistent fashion to monitor tumor status. Therefore, the schedule of tumor assessment by physical examination, CA125 monitoring and imaging should be conducted according to the time line shown per the study calendar regardless.
21. For primary surgery patients, the baseline T0 perfusion CT should be performed at a minimum of 2 weeks after surgery. Protocol chemotherapy will start a maximum of 14 days after GOG registration. The baseline T0 perfusion CT for patients after primary surgery and those receiving neoadjuvant chemotherapy will need to be completed before first Cycle 1 chemotherapy administration. The baseline T0 perfusion CT may be completed the day of GOG registration (after consent) or the day of chemotherapy initiation as long as the CT scan is completed before chemotherapy administration. For all patients, intermediate T1 imaging occurs between days 18 and 21 after the start of Cycle 1 therapy. For all patients, early-therapy T2 imaging occurs between days 8 and 10 after the start of Cycle 2 therapy, with or without bevacizumab. **(06/20/2011) (02/06/2012) (04/30/2012) (10/22/2012)**
22. Tumor functional perfusion parameters will be collected and will include: vascularity or blood volume (BV); perfusion or blood flow (BF); mean transit time (MTT); and microvascular permeability or permeability surface area product (PS). **(06/20/2011)**

7.2 Stained Pathology Slide Requirements for Central Review to Confirm Protocol Eligibility.

Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility for the protocol. At least one representative H&E stained slide (or slides) demonstrating primary site, histologic cell type, and grade, and **one** H&E stained slide showing the most advanced stage of disease will be required. If the most advanced stage of disease is not documented by histology, the method of stage documentation needs to be stated (e.g. CT, MRI, etc.). If this protocol allows patients with recurrent or persistent disease, slides from recurrence and/or persistent disease will be required only if recurrence/persistent disease is confirmed by histology or cytology.

When submitting pathology material to the GOG Statistical and Data Center individual slides must be labeled with GOG Patient ID, patient initials and the surgical / pathology accession number (e.g., S08-2355) and block identifier (e.g., A6). Do not label the slides with disease site (e.g., right ovary) or procedure date.

Pack the labeled slides into plastic slide cassette(s). Tape plastic slide cassettes shut and wrap in bubble wrap or another type of padded material prior to shipping. Please include the GOG Patient ID, patient initials, and protocol number on all pages of the pathology report and black out the patient's name. Ship pathology slides, three copies of both the Pathology Form F (if required for the protocol) and the official pathology report in your own shipping containing using postal mail at your own expense directly to the **Pathology Materials Coordinator at the GOG Statistical and Data Center, Roswell Park Cancer Institute, Research Studies Center, Carlton and Elm Streets, Buffalo, New York, 14263**; phone (716) 845-5702. The GOG Upload Application in SEDES is an alternative method for submitting pathology reports and Form F to the GOG Statistical and Data Center. Please see section 4.5 and 10.2 for additional requirements and instructions.

7.3 Translational Research

7.31 Specimen Requirements

Patients enrolled after February 8, 2012 will not have specimens collected for translational research. (04/30/2012)

If the patient gives permission for her specimens to be collected for this optional translational research study component, then participating GOG and CTSU Institutions within the United States are required to submit the patient's specimens as outlined below (unless otherwise specified).

A detailed description of the specimen requirements and procedures can be found in Appendix III. **(01/18/2011)**

Required Specimens (Specimen Codes)	**Form SP**	**Collection Time Points**	**Deadlines and Recommendations**
Formalin-Fixed, Paraffin-Embedded Primary Tumor (FP01): 1st Choice: Block 2nd Choice: 20 Unstained Slides + 8 Cores	SP-FP01-0262	Collected prior to initiating front-line chemotherapy **Optional** for Institutions outside the United States	Ship to the GOG Tissue Bank within 8 weeks of registration[1] Submit Form SP online within 8 weeks of registration
Formalin-Fixed, Paraffin-Embedded ICS Tumor (FP02): 1st Choice: Block 2nd Choice: 20 Unstained Slides + 8 Cores **(02/06/2012)**	SP-FP02-0262	**For ICS patients only** Collected during interval cytoreductive surgery (ICS) **Optional** for Institutions outside the United States	Ship to the GOG Tissue Bank within 14 weeks of registration[1] Submit Form SP online within 14 weeks of registration
Formalin-Fixed, Paraffin-Embedded Metastatic Tumor (FM01): 1st Choice: Block 2nd Choice: 20 Unstained Slides + 8 Cores	SP-FM01-0262	*Optional if FP01 is submitted* Collected prior to initiating front-line chemotherapy **Optional** for Institutions outside the United States	Ship to the GOG Tissue Bank within 8 weeks of registration[1] Submit Form SP online within 8 weeks of registration
Whole Blood (WB01) 7-10mL drawn into a purple-top (EDTA) tube	SP-WB01-0262	Collect prior to or after initiating front-line chemotherapy	Ship to the GOG Tissue Bank the day the blood is collected[1] Submit Form SP online within 26 weeks of registration
Pre-Treatment Serum (SB01) prepared from 7-10mL of blood drawn into a plain red top tube	SP-SB01-0262	Collect prior to initiating front-line chemotherapy	Ship to the GOG Tissue Bank within 8 weeks of registration[1] Submit Form SP online within 8 weeks of registration
Pre-Treatment Plasma (PB01) prepared from 7-10mL of blood drawn into a purple top (EDTA) tube	SP-PB01-0262	Collect prior to initiating front-line chemotherapy	Ship to the GOG Tissue Bank within 8 weeks of registration[1] Submit Form SP online within 8 weeks of registration
Frozen Primary Tumor (RP01): 1st choice: Snap Frozen 2nd choice: OCT mold	SP-RP01-0262	**Optional** – Collected prior to initiating front-line chemotherapy	Ship to the GOG Tissue Bank within 8 weeks of registration[1] Submit Form SP online within 8 weeks of registration
Frozen ICS Tumor (RP02): 1st choice: Snap Frozen 2nd choice: OCT mold **(02/06/2012)**	SP-RP02-0262	**For ICS patients only** **Optional** – Collected during interval cytoreductive surgery (ICS)	Ship to the GOG Tissue Bank within 14 weeks of registration[1] Submit Form SP online within 14 weeks of

			registration
Frozen Metastatic Tumor (RM01): 1st choice: Snap Frozen 2nd choice: OCT mold	SP-RM01-0262	**Optional** – Collected prior to initiating front-line chemotherapy	Ship to the GOG Tissue Bank within 8 weeks of registration[1] Submit Form SP online within 8 weeks of registration

[1] Ship specimens to: GOG Tissue Bank / Protocol GOG-0262, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, E-mail: gogbank@nationwidechildrens.org.

7.32 Laboratory Testing

7.321 Evaluation of Single Nucleotide Polymorphisms Using Genome Wide Association Studies

The GOG Tissue Bank will isolate DNA from whole blood specimens. DNA will be distributed to Dr. Michael Birrer (Massachusetts General Hospital Cancer Center) for analysis of single nucleotide polymorphisms (SNPs) using genome wide association studies (GWAS).

7.322 Evaluation of Genomic Signatures in Tumor Tissue

The GOG Tissue Bank will create a tissue microarray (TMA) from all archival formalin-fixed, paraffin-embedded (FFPE) tumor tissue blocks submitted for this study. Unstained sections of the TMA, or of tumors not represented in the TMA, and frozen tumor tissue will be distributed to Dr. Michael Birrer (Massachusetts General Hospital Cancer Center) for the evaluation of genetic signatures.

7.323 Evaluation of Serum and Plasma Biomarkers

Aliquots of frozen serum and plasma will be used to evaluate biomarkers associated with response to anti-angiogenesis therapy (laboratory to be determined).

7.33 Future Research

Details regarding the banking and use of specimens for future research can be found in Appendix III. **(01/18/2011)**

7.4 Quality of Life (QoL) **(06/20/2011)**

Patients enrolled after February 8, 2012 will not participate in the QOL component (04/30/2012)

QoL will be assessed using the Trial Outcome Index of the Functional Assessment of Cancer Therapy-Ovary (FACT-O TOI).[78, 79] This 26-item summary score captures the FACT-G QOL dimensions of Physical Well-Being (7 items), Functional Well-Being (7

items), and the Ovarian Cancer Subscale (12 items). Also, the abdominal pain module piloted in GOG Protocol 0172[80] will be included.[81]

The GOG has validated the FACT/GOG Neurotoxicity (Ntx) subscale for assessing platinum/paclitaxel-induced neurologic symptoms. The 11-item questionnaire includes four sensory items and is an efficient alternative in measuring this toxicity in clinical trials without compromising its performance.[82]

Requests for Scantron Forms should be submitted to the GOG Statistical and Data Center (716-845-5702).

Non-lead group institutions will order hard copy GOG-0262 QOL Scantron forms from the CTSU Operations Office. **(01/18/2011)**

7.41 Quality of Life Assessment Intervals

When determining the specific assessment times, the investigator must balance treatment toxicities, the natural history of the disease, and time since initiating therapy along with an acute awareness of the study objectives. The investigators for the proposed study recommend five assessment points to include:

NOTE: The times in parentheses indicated the assessment points for those patients who do not complete the entire study regimen.

7.411 Prior to cycle 1 (preferably prior to randomization) (t = 0 weeks)

7.412 Prior to cycle 4 (t = 9 weeks after starting treatment), to assess immediate changes in QoL.

7.413 18 weeks after starting treatment to assess intermediate changes in QoL. (For those patients who are receiving bevacizumab this time point corresponds to just prior to the 7th cycle of treatment.)

7.414 36 weeks after starting treatment. (For those patients who are receiving bevacizumab this time point corresponds to just prior to the 13th cycle of treatment.) It is important to note that patients should continue to receive QOL assessments even if they stop the clinical trial early or are on other treatment regimens.

7.415 63 weeks after starting treatment. (For those patients who are receiving bevacizumab this time point corresponds to just prior to the 22nd cycle of treatment.) It is important to note that patients should continue to receive QOL assessments even if they stop the clinical trial early or are on other treatment regimens.

7.5 Continuing Quality Assurance of Perfusion CT Scans **(06/20/2011) (10/22/2012)**

Sites performing perfusion CT scans are required to received and acknowledged at the ACR Core Lab via TRIAD or media within 7 days of acquisition of the baseline T0 perfusion CT scan. Submissions to the ACR Imaging Core Lab must include a completed Image Transmittal Worksheet (ITW) and site-completed Technical Assessment forms. These forms will include an ACRIN identification number and technical information for the perfusion CT scans.

7.51 Target Lesion Verification for Confirmed ACRIN 6695 Eligibility After Baseline T0 Perfusion CT Scan **(02/06/2012)**

The site radiologist will outline the target lesion and measure its size in both the long and short axis using the software tool provided by the site PACS system for RECIST measurement. The radiologist will assess that the size of the tumor is ≥ 1 cm in both the long and short axis and qualitatively determine whether at least half of the selected lesion has an attenuation ≥ 10 HU. The DICOM images with the outlined target lesion will be sent together with the perfusion CT study to the ACR Imaging Core Lab for verification of target selection with the ITW and T0 Form.

At the ACR Imaging Core Lab, the target lesion size will be confirmed using the DICOM image sent by the site. As well, quantitative assessment will be performed to determine if at least half of the target lesion shows attenuation in the unenhanced CT scan greater than or equal to 10 HU and shows maximum enhancement greater than or equal to 5 HU in the perfusion CT scan

To demonstrate the feasibility of multiple sites performing perfusion CT scans on enrolled patients within the ACRIN 6695 study, the number of failed scans (not failed target selection) at interim analysis has to be less than 15% of all scans.

7.52 Scanning Protocol

Timing of the scans (baseline T0, intermediate T1, and early-therapy T2), kVp, mA, slice thickness and time interval used for the perfusion CT scans as noted in the DICOM header will be checked against the protocol (see Appendix VII). Discrepancies will be noted and communicated to the site within a week to ensure that such violations will be corrected in the next scan.

7.53 Radiation Dose

From the information recorded in the ITW and technical assessment forms (T0, T1, and T2 forms), the effective dose and skin dose of perfusion CT scans will be calculated and compared with those listed in Appendix VII. If discrepancies larger than 30% are present, investigation as to the cause of the discrepancies will be initiated by the medical physicist immediately.

7.54 Image Noise

If the standard deviation of CT numbers inside a region in the spinal muscle recorded on the ITW and the technical assessment forms (T0, T1, and T2 forms) is outside of the range of 17-48, investigation will be initiated by the medical physicist immediately.

7.55 Technical Feasibility

The initial technical analysis will be performed under the ACRIN Medical Physicist's supervision. During this initial analysis, early technical issues associated with the perfusion CT analysis will be identified and resolved. The Imaging Co-PI will train the ACR Imaging Core Lab staff in the technical evaluation of the perfusion CT data. To evaluate the successful training and resolution of training issues, the fifteen reproducibility studies will be analyzed independently by both the ACRIN Medical Physicist and the ACR Imaging Core Lab staff. Differences in the analyses of blood flow, blood volume, and capillary permeability surface product maps parameters will be evaluated.

7.56 Perfusion CT Reader Study

All perfusion CT analyses will be done centrally by a single group of experienced readers blinded to the scan's study time point (T0, T1, or T2). In the first stage, before the completion of the interim analysis, the analysis will be performed in the lab of the ACRIN Medical Physicist and under his supervision. During this first phase, all problems and difficulties associated with the analysis of perfusion CT will be identified and resolved. The acquired experience and expertise will be shared with a targeted group of readers (not more than 3) in the ACR Imaging Core Lab for the analysis of the rest of the perfusion CT studies in this protocol after the interim analysis. To ensure that the expertise of the ACRIN Medical Physicist's lab has been successfully shared with the ACR Imaging Core Lab, the 15 reproducibility T1 studies will be analyzed independently by both groups; the differences in the blood flow, blood volume, and capillary permeability surface product values for the target lesion are required to be less than 5% to pass this test.

8.0 EVALUATION CRITERIA

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

8.1 Disease Parameters **(02/06/2012)**

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan, as ≥20 mm by chest x-ray, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters.

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal/pelvic masses (identified by physical exam and not CT or MRI), are considered as non-measurable.

Notes:

Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated

measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be reproducibly measured should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

8.2 Methods for Evaluation of Disease **(02/06/2012)**

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the

scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, subsequent image acquisitions should use the same type of scanner and follow the baseline imaging protocol as closely as possible. If possible, body scans should be performed with breath-hold scanning techniques.

Perfusion CT: Each perfusion CT scan must cover the same target lesion. Regions of interest (ROIs) will be outlined around all target and non-target tumors identified and the average perfusion CT parameters: blood flow, blood volume, mean transit time and microvascular permeability surface area product in each ROI recorded in the ACR Imaging Core Lab. The same set of ROIs from T0 will be reproduced (while accounting for possible expansion/shrinkage of the tumor) in the subsequent perfusion CT scans at T1 and T2 and as in the case of T0 average perfusion CT parameters will be recorded. **(06/20/2011) (10/22/2012)**

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. PET-CT scans are not always done with oral and IV contrast. In addition, the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. **For these reasons, the GOG will not allow PET-CT use for RECIST 1.1 response criteria**.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Note: A ‘positive’ FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

CA-125 (Ovarian, fallopian tube and primary peritoneal cancer trials): CA-125 alone cannot be used to assess response. If CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response. Specific guidelines for CA-125 response (in recurrent ovarian cancer) have been published [*JNCI* 96:487-488, 2004]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria that are to be integrated with objective tumor assessment for use only in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases, e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain.

It is mandatory to obtain cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when measurable disease has met criteria for response or stable disease. This confirmation is necessary to differentiate response or stable disease (versus progressive disease, as an effusion may be a side effect of the treatment).

8.3 Response Criteria

Determination of response should take into consideration all target (See 8.31) and non-target lesions (See 8.32) and if appropriate, biomarkers (See 8.33).

8.31 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
Not evaluable (NE):	When at least one target lesion is not evaluated at a particular time point.

8.32 Evaluation of Non-Target Lesions **(02/06/2012)**

Complete Response (CR):	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s)
Progressive Disease (PD):	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Not evaluable (NE):	When at least one non-target lesion is not evaluated at a particular time point.

Although a clear progression of only "non-target" lesions is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

8.33 Evaluation of Biomarkers

Biomarker-based progression or recurrence involves assessing the patient's longitudinal CA-125 values. The definition of CA-125 progression or recurrence is based on the Gynecologic Cancer Intergroup (GCIG 2005) criteria. CA-125 based progression or recurrence is defined as one of the following conditions occurring:

a. CA-125 is within normal limits prior to treatment but subsequently rises to levels greater than or equal to two times the upper-limit of normal on two occasions at least one week apart.

b. CA-125 is elevated prior to treatment, does not normalize but rises to levels greater than or equal to twice its nadir value on two occasions at least one week apart. **(02/06/2012)**

c. CA-125 is elevated prior to treatment and returns to normal levels, but subsequently rises to levels greater than or equal to two times the upper limit of normal on two occasions at least one week apart.

Note: When recurrence or progression is based on CA-125 criteria alone, radiographic imaging should be obtained within 2 weeks after such progression is documented. If imaging criteria are met for progression, then the date of progression will be defined as the date of the imaging study. **(06/20/2011)**

Biomarker-based progression or recurrence involves two CA-125 measurements: detection followed by confirmation at least one week apart. The date for the onset of biomarker progression is the detection date (the first of these two dates). In the absence of radiographic or clinical evidence of progressive disease, a rise in CA-125 alone, during primary chemotherapy, is not sufficient to declare progression. **(06/20/2011)**

8.34 Evaluation of Perfusion CT Parameters (For ACRIN central review only) **(06/20/2011) (02/06/2012) (10/22/2012)**

The percentage changes of perfusion parameters in the target lesion from T0 to T1, T0 to T2, and T1 to T2 will be determined. The area (volume) weighted average percentage change of the target lesion in a patient for each perfusion parameter will be determined. ROC curve will be used to determine the optimal threshold of percentage change for each perfusion parameter to separate responders (CR, PR, SD) from non-responders (PD) to treatment.

8.4 Evaluation of Best Overall (unconfirmed) Response **(02/06/2012)**

The best overall response is the best time point response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest sum recorded since baseline). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria in some circumstances.

Time Point Response for Patients with Measurable Disease at baseline (i.e., Target Disease)

Target Lesions	Non-Target Lesions	Biomarker CA-125	New Lesions*	Time Point Response
CR	CR	Within normal limits	No	CR
CR	Non-CR/Non-PD	Any value	No	PR
CR	Not evaluated	Any value	No	PR
PR	Non-PD or NE	Any value	No	PR
SD	Non-PD or NE	Any value	No	SD
NE	Non-PD	Any value	No	NE
PD	Any	Any value	Yes or No	PD
Any	PD**	Any value	Yes or No	PD
Any	Any	PD	No	PD
Any	Any	Any value	Yes	PD

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Time Point Response for Patients with only Non-Measurable Disease at baseline (i.e., Non-Target Disease)

Non-Target Lesions	Biomarker CA-125	New Lesions*	Time Point Response
CR	Within normal limits	No	CR
CR	Above normal limits	No	Non-CR/non-PD*
Non-CR/non-PD	Any value	No	Non-CR/non-PD*
NE	Any value	No	NE
Unequivocal PD	Any value	Yes or No	PD
Any	PD	No	PD
Any	Any value	Yes	PD

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion

** 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

8.5 Best Overall Confirmed Response **(02/06/2012)**

Confirmation of CR and PR for determination of best overall response is required for studies with a primary endpoint that includes response.

Confirmed CR and PR for best overall confirmed response

Time Point Response First time point	Time Point Response Subsequent time point	BEST overall confirmed response
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

*If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD.

For this study, the minimum criteria for SD duration is 8 weeks.

Patients with a global deterioration of health status requiring discontinuation of treatment or who die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

8.6 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

8.7 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression or death, whichever occurs first.

8.8 Survival

Survival is defined as the duration of time from study entry to time of death or the date of last contact.

9.0 DURATION OF STUDY

9.1 Patients will receive carboplatin and taxane therapy every 21 days for six cycles, unless disease progression, or adverse events require discontinuing protocol treatment. Those patients who opt to receive bevacizumab will continue this agent until disease progression or adverse events preclude further therapy. The patient may voluntarily withdraw from the study at any time. No form of therapy targeted against a patient's cancer other than that specified in this protocol will be administered until disease progression.

9.2 All patients will be followed for disease status and toxicity (with completion of all required case report forms) until death or voluntary withdrawal from study. In addition, following study therapy, patients will be monitored for delayed toxicity every three months for the first two years, every six months for the next three years, and then annually (or at disease progression or death) with Q forms submitted to the GOG Statistical and Data Center, unless consent is withdrawn.

9.3 Adequate Duration of Study to Evaluate Toxicity. All patients who initiate any study therapy will be evaluated for toxicity.

10.0 STUDY MONITORING AND REPORTING PROCEDURES

10.1 ADVERSE EVENT REPORTING FOR AN INVESTIGATIONAL AGENT

10.11 Definition of Adverse Events (AE)

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs in a patient administered a medical treatment, whether the event is considered related or unrelated to the medical treatment.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov). The CTCAE v4.0 Manual is also available on the GOG member web site (http://www.gog.org under MANUALS).

10.12 Reporting Expedited Adverse Events

The use of investigational agents, and role of the pharmaceutical sponsor, an expedited AE report may need to reach multiple destinations. For patients participating on a GOG trial, all expedited AE reports should be submitted by using the CTEP automated system for expedited reporting (AdEERS). All AdEERS submissions are reviewed by GOG before final submission to CTEP. Submitting a report through AdEERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting. All adverse reactions will be immediately directed to the Study Chair for further action.

The requirement for timely reporting of AEs to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In signing the FDA-1572, the investigator assumes the responsibility for reporting AEs to the NCI. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

10.13 Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of the Investigational Agent

Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days
Possible Probable Definite	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days	7 Calendar Days	Not Required	24-Hrs; 3 Calendar Days	7 Calendar Days

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:

AdEERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 7 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled "Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND."

March 2005

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
  - "7 calendar days" - A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND:

- Reference the SPEER (Specific Protocol Exceptions to Expedited Report) for the subset of AEs that are protocol specific exceptions to expedited reporting via AdEERS. Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If the CAEPR for a protocol agent 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. For questions or comments regarding the SPEER or CAEPR, please contact the AdEERS MD Help Desk at adeersmd@tech-res.com. **(12/19/2011)**

    - All grade 3 or 4 myelosuppression (including neutropenia, anemia and thrombocytopenia), that DOES or DOES NOT require hospitalization is exempt from expedited reporting. However, THESE EVENTS SHOULD STILL BE INCLUDED IN THE ROUTINE TOXICITY CASE REPORT FORMS.

10.14 Procedures for Expedited Adverse Event Reporting: **(01/18/2011) (12/19/2011)**

10.141 AdEERS Expedited Reports: Expedited reports are to be submitted using AdEERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.
In the rare occurrence when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-estrablishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.

AML/MDS events must be reported via AdEERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplatic syndrome, or 3) Treatment related secondary malignancy. **(06/20/2011)**

10.15 Automated CDUS reporting

For studies using investigational agents, the GOG Statistical and Data Center (SDC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDC submits this data quarterly. The AEs reported through AdEERS will also be included with the quarterly CDUS data submissions.

10.2 GOG DATA MANAGEMENT FORMS

The following GOG forms must be completed for all patients registered and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. GOG Protocol forms and instructions can be submitted through or printed from the SDC Electronic Data Entry System (SEDES) online application found at the GOG Web Menu page. All amendments to forms submitted through SEDES must also be submitted through SEDES. The original form and required copies for forms NOT submitted online must be mailed to the GOG SDC. Pathology material (Form F, pathology reports and slides) should be submitted together via mail. The GOG Uploader Application in SEDES is an alternate method for submitting Form BDR, operative reports, Form F and pathology reports to the GOG SDC. ACRIN forms may be submitted through the ACRIN Web data center (www.acrin.org). Please refer to Appendix X for more details on ACRIN data submission. **(06/20/2011)**

Form± **(02/06/2012) (10/22/2012)**	**Due within**	**Event**	**Copies***	**Comments**
Specimen Consent Application **ONLY FOR PATIENTS ENTERED ON OR BEFORE 02/08/2012 (04/30/2012)**		Registration	N/A	Complete online
Form R (Registration Form)		Registration	1	Mandatory submission via SEDES
Abdominal surgery for ovarian cancer: **(06/20/2011)**				
Form C (Surgical Reporting Form)	2	Registration****	1	Mandatory submission via SEDES
Operative Report	2	Registration****	1	Submit to SDC via postal mail or via report uploader
Form OSO (Primary Ovarian Cancer On Study Form)	2	Registration****	1	Mandatory submission via SEDES
Interval cytoreductive surgery: (for NACT and ICS patients only) **(06/20/2011) (02/06/2012)**				
Form C (Surgical Reporting Form)	6	Surgery	1	Mandatory submission via SEDES
Operative Report	6	Surgery	1	Submit to SDC via postal mail or via report uploader
Form OSO (Primary Ovarian Cancer On-Study form	6	Surgery	1	Mandatory submission via SEDES (Form OSO should be completed and submitted after

				the interval cytoreductive surgery)
Form BDR (Pre-Treatment Body Diagram Form)		Registration	1	Submit to SDC via postal mail or via report uploader
Form D2M (Solid Tumor Evaluation Form)		Registration	1	Mandatory submission via SEDES
Abdominal surgery done prior to registration **(06/20/2011) (02/06/2012)** Form F Pathology Report Stained Slides	 6 6 6	 Registration Registration Registration	 1 1 **	Submit to SDC via postal mail or via report uploader **(02/06/2012)**
Neo-adjuvant patients undergoing Interval cytoreductive **core biopsy** (at time of enrollment) **(02/06/2012)** Form F Pathology Report Stained slides **Interval cytoreductive surgery (if positive for disease)** Form F Pathology Report Stained slides	 6 6 6 6 6 6	 Registration Registration Registration Surgery Surgery Surgery	 1 1 ** 1 1 **	Submit to SDC via postal mail or via report uploader Submit to SDC via postal mail or via report uploader
Form BMR (Biomarker Reporting Form)***	2	Prior to each cycle and during follow-up	1	Mandatory submission via SEDES
Form D2R (Cycle Dose Drug Form)#	2	Completion of each cycle of therapy	1	Mandatory submission via SEDES
Form D2M (Solid Tumor Evaluation Form)#	4	Clinical response assessment	1	Mandatory submission via SEDES
Form T (Common Toxicity Reporting Form)#	2	Beginning of each subsequent cycle	1	Mandatory submission via SEDES
QOL Scantron Form+ **ONLY FOR PATIENTS ENTERED ON OR BEFORE 02/08/2012 (04/30/2012)**	2	Prior to cycle 1, 4, and 18, 36 and 63 weeks after starting study therapy		Submit the original scantron form to the GOG SDC via postal mail
Form SP-FP01-0262 for FFPE primary tumor **ONLY FOR PATIENTS ENTERED ON OR BEFORE 02/08/2012 (01/18/2011) (04/30/2012)**	8	Registration	1	Submit via SEDES†

Form SP-FP02-0262 for FFPE ICS tumor (for ICS patients only) **ONLY FOR PATIENTS ENTERED ON OR BEFORE 02/08/2012 (02/06/2012) (04/30/2012)**	14	Registration	1	Submit via SEDES†
Form SP-FM01-0262 for FFPE metastatic tumor **ONLY FOR PATIENTS ENTERED ON OR BEFORE 02/08/2012 (01/18/2011) (04/30/2012)**	8	Registration	1	Submit via SEDES†
Form SP-WB01-0262 for whole blood **ONLY FOR PATIENTS ENTERED ON OR BEFORE 02/08/2012 (04/30/2012)**	6	Registration	1	Submit via SEDES†
Form SP-SB01-0262 for pre-treatment serum **ONLY FOR PATIENTS ENTERED ON OR BEFORE 02/08/2012 (04/30/2012)**	8	Registration	1	Submit via SEDES†
Form SP-PB01-0262 for pre-treatment plasma **ONLY FOR PATIENTS ENTERED ON OR BEFORE 02/08/2012 (04/30/2012)**	8	Registration	1	Submit via SEDES†
Form SP-RP01-0262 for frozen primary tumor (optional) **ONLY FOR PATIENTS ENTERED ON OR BEFORE 02/08/2012 (01/18/2011) (04/30/2012)**	8	Registration	1	Submit via SEDES†
Form SP-RP02-0262 for frozen ICS tumor (for ICS patients only) **ONLY FOR PATIENTS ENTERED ON OR BEFORE 02/08/2012 (02/06/2012) (04/30/2012)**	4	Registration	1	Submit via SEDES†
Form SP-RM01-0262 **ONLY FOR PATIENTS ENTERED ON OR BEFORE 02/08/2012 (01/18/2011)(04/30/2012)**	8	Registration	1	Submit via SEDES†
Form SRGSTAT (Surgical Status Form)	8	30 days after any surgical procedure performed on patients while on study	1	Mandatory submission via SEDES
Form Q0	2	Completion of study Rx and change in Rx	1	Mandatory submission via SEDES
Form Q	2	Disease progression; death; normal follow-up	1	Mandatory submission via SEDES, Submit quarterly for 2 years, semi-annually for 3 more years, annually thereafter
ACRIN Protocol Variation Form §§ **(06/20/2011)(02/06/2012)**	4	Completion at each perfusion imaging		Mandatory submission via ACRIN website

ACRIN Image Transmittal Worksheet §§ **(06/20/2011)(02/06/2012)**	4	Completion at each perfusion imaging		Mandatory submission via ACRIN website
ACRIN Technical Assessment Form §§ **(06/20/2011)(02/06/2012)**	4	Completion at each perfusion imaging		Mandatory submission via ACRIN website
ACRIN Tumor Perfusion Parameter Evaluation Form §§ **(06/20/2011)(02/06/2012)**	4	Completion at each perfusion imaging		Completed by the ACRIN Imaging Core Lab
ACRIN Off Imaging Form §§ **(06/20/2011)(02/06/2012)**	4	Completion of study imaging		Mandatory submission via ACRIN website

* The number of required copies including the original form which must be sent to the Statistical and Data Center, if not completed online through SEDES.

** Pathology slides are required for central review by the GOG Pathology Committee. At least one representative stained slide (or slides) demonstrating the primary tumor, histologic cell type, and grade and **one** slide to show the most advanced stage of disease. . See sec. 4.5 and 7.2 for additional instructions and requirements. For patients receiving interval cytoreductive surgery, F form, Pathology Report and Slides are required for this procedure, if still positive for disease at the time of surgery. **(02/06/2012)**

*** Serial CA-125 values should be reported on Form BMR.

**** This only applies to patients having abdominal surgery for ovarian cancer prior to registration. **(06/20/2011)**

\# In the event that it becomes necessary to modify the dose or stop individual study agents for either protocol-directed reasons or other reasons, continue to submit D2R, T and D2M forms until all study agents are stopped or another anti-cancer therapy is initiated. Do not submit Q0 until all study agents are discontinued (Section 6.6).

\+ Scantron Forms can be ordered from the GOG Statistical and Data Center (716-845-5702)

† Form SP must be submitted via SEDES regardless of whether the specimen is submitted for research.

§§ Only applies for patients who elect to participate in the ACRIN portion of the trial. THIS APPLIES TO ALL PATIENTS ENTERED AFTER 02/08/2012 (06/20/2011) (04/30/2012)

This study will be monitored by the **Abbreviated** Clinical Data System (CDUS) Version 3.0. CDUS data will be submitted quarterly to CTEP by electronic means.

ACRIN will monitor and audit all source data, original records of findings, observations, or other activities related to the perfusion CT imaging in the ACRIN 6695 study. Please see Appendix X for more details. **(06/20/2011)**

10.3 **ACRIN 6695: Expected Risks and Imaging AE and SAE Reporting Requirements for Non-Investigational Agents and Devices (10/22/2012)**

For guidance on AE and SAE reporting procedures for ACRIN research associates, see Appendix IX.

10.31 Risks Associated With ACRIN 6695 Perfusion CT Imaging Component

10.311 Expected Adverse Events Associated With CT Scan

- Anxiety/stress;
- Claustrophobia;
- Discomfort.

10.312 Expected Adverse Events Associated With IV Needle Placement

- Hemorrhage (hematoma at the injection site);
- Plebitis;
- Bleeding;
- Infection;
- Bruising;
- Minor discomfort.

10.313 Expected Adverse Events From Iodinated Contrast Agent

Rare

- Nausea;
- Vomiting;
- Hives;
- Rash.

Rare, but potentially life threatening

- Kidney failure;
- Allergic reaction (anaphylaxis or asthma).

A history of contrast allergy excludes potential participants from this study. The injection may cause discomfort and irritation. The iodine-containing contrast used for CT scanning may cause significant contrast reactions in about one in a thousand (1:1,000) participants. Severe reaction is seen in as low as 4:10,000 to as high as 2:1,000 depending on the type of contrast used. Fatal reactions are exceedingly rare and have been reported in 1:170,000 irrespective of the type of contrast used. The most common reactions are nausea, vomiting, hives, or rash. The risk of death is less than 1:10,000.

Rare but potentially life threatening adverse reactions to IV imaging contrast include kidney failure and allergic reaction (anaphylaxis). Transient inducted nephropathy rarely occurs in patients with normal renal function. Patients with pre-existing renal insufficiency are at greater risk for developing neurotoxicity and further deterioration in renal function. An increase in serum creatinine and blood urea nitrogen is usually noted and these transient renal effects usually resolve within a few days. For patients at risk, adequate hydration is suggested.

The rate of occurrence of adverse reactions is less than 3%. In particular, the more severe respiratory type is about 0.5%. If adverse reactions occur, the perfusion CT scan will be stopped and the patient will be treated with standard medication. The patient's participation in the research study will also be stopped.

10.314 Risks Associated With CT Radiation Exposure

By participating in the study, the patient will have 3 to 4 additional CT scans of the abdomen. The risk of developing fatal cancer anywhere in the body in twenty years' time after the radiation dose received in this research study is about 1 in 175-200.

Skin reddening (erythema) has been reported with repeated perfusion CT scans. The threshold for radiation induced (transient) skin erythema is 2 Gy. The skin dose at each of the time points (T0, T1 and T2) is less than 0.22 Gy. Even with the reproducibility scan for a subset (15) of participants, the maximum radiation dose to the skin will be 0.31 Gy. Thus transient skin erythema is extremely unlikely in this study.

10.32 Source Documentation of Adverse Events

After each study-related perfusion CT scan for the ACRIN 6695 sub-study, the investigator or investigator-designee must seek information on AEs through discussion and, as appropriate, by examination. All AEs and SAEs will be documented in the study participant's chart and reported to ACRIN per Appendix IX guidance.

IMPORTANT: Recording of AEs on source document **does not** constitute reporting. Please ensure that AEs are documented in the participant's chart and are reported to ACRIN in order to satisfy routine reporting requirements; AEs and SAEs are reported to ACRIN and NCI per protocol-specific reporting requirements.

All unresolved AEs should be followed by the investigator until the events are resolved, the participant is lost to follow-up, or the AEs are otherwise explained. Any death or AE occurring at any time after a participant has discontinued or terminated study participation that may be reasonably related to the study imaging effect should be reported.

10.33 Reporting of Adverse Events

Prompt reporting of AEs is the responsibility of each investigator, clinical RA, and/or nurse engaged in clinical research. Anyone uncertain about whether a particular AE should be reported should contact the ACRIN headquarters at **(215) 574-3183** for assistance. However, an AE report should be submitted if there is a reasonable suspicion of the imaging procedure.

All unresolved AEs should be followed by the principal site investigator until the AE is resolved, otherwise explained, or the site has documented due diligence in attempting to procure the requisite medical records.

Any death or AE occurring at any time after a participant has discontinued or terminated study participation that may be **reasonably related** to the ACRIN 6695 imaging sub-study-related perfusion CT or contrast administration should be reported.

Assignment of grades (severity level) and attribution for each AE is to be completed at the site by the site Principal Investigator.

10.34 Routine AE Reporting Process

Routine reporting is defined as documentation of AEs on source documents and the AE case report form (CRF), and submission to ACRIN for preparation of a report for DSMC review, quarterly reports to CDUS, and the final study report. All AEs **must** be reported in routine study data submissions. **Routine study data submissions also are required when AEs are reported through the Adverse Event Expedited Reporting System (AdEERS).**

Expedited reporting is defined as immediate notification of NCI and ACRIN per Table A and section 10.35. Routine reporting requirements also apply.

TABLE A. Expedited Reporting Requirements for Adverse Events that Occur within 24 Hours After the Perfusion CT Scan with Administration of a Commercial Imaging Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to imaging study (per 21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 24 hours after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization

Grade 3 adverse events

[2] For studies using PET or SPECT agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

10.35 Expedited Reporting ACRIN 6695 Imaging Adverse Events

10.351 Expedited AE Reporting Timeline Definitions

- "24 hours; 5 calendar days"—The investigator must initially report the AE via AdEERS within 24 hours of learning of the event, followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
- "10 calendar days"—A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

10.352 Investigator or investigator-designee must use expedited AE reporting for deaths with attribution of possible, probable, or definite occurring during study participation and up to 24 hours after the last study procedure. Deaths should be reported by telephone to ACRIN within 24 hours of first knowledge of the event and followed by an expedited written report within ten (10) days. Routine reporting requirements also apply (these reports should be sent to ACRIN and to the local IRB, in addition to documentation in participant chart).

10.353 All life-threatening/disabling unexpected AEs (considered possibly, probably, or definitely related to the perfusion CT or associated contrast administration) occurring during study participation and up to 24 hours after the last study procedure will reported within ten (10) working days of first knowledge of the event. Routine reporting requirements also apply (these reports should be sent to ACRIN and to the local IRB, in addition to documentation in participant chart).

10.354 All hospitalizations (or prolongation of existing hospitalization) for AEs with the severity (intensity) level of CTCAE grade 3, 4, or 5 and attribution of possibly, probably, or definitely related to the perfusion CT or associated contrast administration must be reported within ten (10) working days of first knowledge of the event, in addition to documentation in participant chart and per instructions in Appendix IX.

10.355 All other SAEs with attribution of possibly, probably, or definitely related to the perfusion CT or associated contrast administration, which include AEs that result in persistent or significant disability or incapacity, or congenital anomaly (birth defect) in the offspring of the study participant must be reported within ten (10) working days of first knowledge of the event during study participation and up to 24 hours after the last study procedure, in addition to documentation in participant chart and per instructions in Appendix IX.

10.356 Significant new information and/or follow-up information (e.g., test results, autopsy, discharge summary) on any on-going SAEs should be promptly reported to ACRIN.

10.357 **24-Hour Telephone Reporting Instructions**
Any AE/SAEs that require 24-hour notification are reported as follows:

10.3571 **ACRIN–AE/SAE Reporting Line: (215) 717-2763**

- The ACRIN–AE/SAE reporting line is monitored by the ACRIN AE Coordinator: Monday through Friday from 8:30am – 4:30pm ET.
- AE/SAEs may be reported via voicemail during off hours.
- The ACRIN AE Coordinator will return your call within 24 hours.

10.3572 **Essential Details for Initiating an AE/SAE Report**

- Name of person reporting the AE/SAE and telephone number
- Institution name and institution number
- Protocol title and number
- Participant's case number and initials
- Site principal investigator name and telephone number
- Date and time of the AE/SAE
- Date and time you learned of the AE/SAE
- Brief description of the AE/SAE
- Site principal investigator's assignment of the grade of the AE
- Site principal investigator's assignment of the attribution of the AE (do not delay initial report if not available)

IMPORTANT: After the 24-hour contact to CIP and ACRIN-AE/SAE reporting lines, an electronic AdEERS must be submitted per the protocol-specific requirements or the regulatory reporting timelines, if not specified in the protocol.

10.358 Completion of AdEERS

All SAEs that occur within 24 hours of the perfusion CT or associated contrast administration require the submission of an electronic AdEERS report within five (5) calendar days of first knowledge of the event is required.

AdEERSMD helpline is available for any questions via phone at **(301) 897-7497**, available 24 hours a day (recorder after hours from 4:30pm – 8:00am Eastern Time).

In the event that the electronic system is down, the AdEERS report must be faxed to the following:

ACRIN SAE Fax Number: **(215) 940-8819**;

ACRIN contact to confirm receipt of AdEERS report:
ACRIN AE Coordinator: **(215) 574-3150 (ACR Front Desk; ask for ACRIN AE Coordinator)**

10.359 Local IRB Reporting

10.3591 Adverse Event Reporting and Local IRB

AEs not requiring expedited reporting are reported to the local IRB in an annual report and/or continuing review report. All expedited AE reports should be sent to your local IRB per the local IRB policies and procedures. Please refer to your local IRB's policies regarding AEs and safety reports.

10.3592 Expedited Serious Adverse Event Reporting and Local IRB

All expedited SAE reports may need to be reported to your local IRB, depending on local IRB policies and procedures.

11.0 STATISTICAL CONSIDERATIONS

Between September 27, 2010 and February 8, 2012, two treatment options were randomly assigned to patients enrolled into this study. Beginning 04/30/2012, all patients are required to participate in the ACRIN 6695 imaging component, and the chemotherapy regimen is selected and declared prior to enrolling in the study. (04/30/2012)

11.1 **Study Design and Treatment Randomization:** This study is a two-arm randomized phase III clinical trial. The randomized study treatments will consist of either 6 cycles of paclitaxel 175 mg/m^2 IV every 3 weeks (CT_{3wk}) or 6 cycles of paclitaxel 80 mg/m^2 IV on days 1, 8 and 15 (CT_{1wk}). In addition, some individuals may elect to receive bevacizumab 15 mg/kg on day 1 of each 3 week cycle (beginning with the 2nd cycle of therapy) until disease progression or adverse events preclude further therapy. A minimization procedure will be used that tends to allocate the two study treatments (CT_{3wk} or CT_{1wk}) in the ratio of 1:1 within the following patient-level stratification factors:

11.11 Stage of disease (stage II vs stage III with no gross residual disease vs stage III with gross residual disease vs stage IV) **(06/20/2011)**
11.12 Initial performance status (0 vs 1 or 2).
11.13 Decision to include bevacizumab with study treatment (yes vs no).
11.14 Decision to use neoadjuvant chemotherapy. **(06/20/2011)**

The assigned study regimen will not be revealed until the patient has been successfully registered onto the study. Interim and final reports will include an accounting of all patients registered onto the study, regardless of their eligibility status or compliance to the assigned treatment.

11.2 **Efficacy and toxicity measures:** The principle observations for evaluating the therapeutic efficacy and safety of treatments are (see Section 8 for definitions).

11.21 Primary efficacy endpoint: Progression-free survival (PFS).
11.22 Secondary efficacy endpoint: Overall survival (OS).
11.23 Safety endpoints: frequency and severity of adverse effects (Common Terminology Criteria for Adverse Events -version 4.0).

For this study the term PFS event rate will be used to denote the incidence rate of first disease progression or death due to any cause.

11.3 **Therapeutic efficacy – Study design and analyses**
Planned accrual goal, accrual rate and study duration: The targeted accrual goal is 625 patients (approximately 312 patients in each treatment group). It is anticipated that at least 250 patients per year with stage IV or suboptimal debulked stage III disease can be enrolled from GOG treatment centers. Therefore the anticipated time to accrue the targeted sample size is 2.5 years. An additional 12 months of post-accrual follow-up is anticipated.

Note: In the event that the targeted accrual for the imaging component (70 patients) is not attained, when the targeted accrual for the therapeutic portion of this study (650 patients) is attained, consideration will be given to extending enrollment and treatment randomization for only those patients who are willing to participate in the imaging component of the study. **(02/06/2012)**

Expected median progression-free and overall survival: The expected median time to death is 30 months and the median time to first progression or death (PFS) is 13 months for patients from the target population treated with standard platinum-taxane therapy. It is currently unknown whether the addition of bevacizumab alters the distribution of these event times.

Primary Hypotheses and overall type I error: The first objective is to determine whether the carboplatin, bevacizumab and weekly paclitaxel regimen reduces the PFS event rate relative to a standard carboplatin, bevacizumab and 3-week paclitaxel regimen in patients with newly diagnosed advanced stage ovarian, fallopian or primary peritoneal cancer. This involves estimating the relative PFS event rate ($\hat{\Delta}_{PFS}$) and testing the null hypothesis (H_1: $\Delta_{1,PFS} = \lambda_{CT1wk}/\lambda_{CT3wk} \geq 1.0$), where $\lambda_{(.)}$ indicates the PFS event rate among those patients treated with the indicated treatment. The type I error for this objective will be limited to 5% (one-tail) including the error spent for interim analyses.

Statistical power for evaluating the relative efficacy of weekly paclitaxel: The primary analysis of progression-free survival will include all patients enrolled onto the study regardless of eligibility or compliance to their assigned study regimen. Patients will be grouped by their randomized treatment for an intention-to-treat analysis (ITT). The treatment event rates will be compared with a logrank test in which the patients are stratified by the stage of their disease (stage II vs Stage III with no gross residual disease vs stage III with gross residual disease vs Stage IV), decision to use neoadjuvant chemotherapy, decision to include bevacizumab with chemotherapy and initial performance status (0 vs 1 or 2). **(06/20/2011)**

The final analysis will occur when there are at least 414 PFS events reported among the patients registered onto the trial. If weekly paclitaxel truly reduces the PFS event rate 25% compared to standard 3-week paclitaxel ($\lambda_{CT1wk}/\lambda_{CT3wk} = 0.75$), then this sample size provides approximately a 90% chance of correctly concluding that the weekly paclitaxel regimen is clinically more efficacious than the standard paclitaxel regimen. Assuming a constant hazard ratio, this effect size is comparable to increasing the expected proportion surviving progression-free more than 13 months (the expected median for a standard platinum-taxane treatment) 9.5% (from 50% to 59.5%). Assuming a constant failure rate, this is comparable to increasing the median time to first progression or death by 4.3 months. An analysis of 13 previous GOG randomized trials involving patients with advanced ovarian cancer indicates that a treatment which reduces the PFS event rate 25%, would be expected to reduce the death rate approximately 23%. Assuming a constant death rate, this is comparable to increasing the expected median overall survival from 30 months to 39 months.

If a patient experiences death due to any immediate cause prior to clinical progression then she will be classified as an uncensored PFS and OS event.

Interim Analyses: Interim analyses will be performed when at least 180 and again when at least 275 of the registered patients have experienced either disease progression or death (due to any cause). The interim analysis will include an assessment of efficacy and an assessment of futility for the hypotheses concerning paclitaxel schedule (H_1).

Futility assessment: The logrank procedure described previously will be used to assess futility. If this procedure at the first interim analysis indicates that the observed PFS event rate among those patients randomized to weekly paclitaxel is greater than or equal to the PFS event rate among those randomized to standard 3-week paclitaxel ($\hat{\Delta}_{1,pfs} \geq 1.00$), then consideration will be given to terminating study accrual. In this case, the study would conclude that it is unlikely that weekly paclitaxel increases the duration of progression-free survival compared to the standard 3-week schedule. If the PFS event rates are independent of the paclitaxel schedule, then there is a 50% chance that the first interim analysis will suggest accrual termination.

The second interim analysis will recommend terminating accrual if the observed PFS event rate is not at least 5% lower among those randomized to the weekly paclitaxel regimen ($\hat{\Delta}_{1,pfs} > 0.95$). If the null hypothesis is true, then this second interim analysis is expected to recommend terminating accrual in 40% of those trials that pass through the first interim analysis. On the other hand, if weekly paclitaxel truly reduces the PFS event rate 25%, then there is only a 2.5% chance of recommending that randomization be terminated for futility at either of these interim analyses.

Efficacy assessment: An O'Brien and Fleming-like alpha spending function (as proposed by Lan and DeMets, Stats in Med, 1983) will be used to establish the critical boundaries for rejecting the null hypothesis at the interim and final analyses. The fraction of the total information available at the time of the interim analysis will be estimated as the total number of PFS events reported divided by the number of PFS events targeted for the final analysis. If the null hypothesis concerning the efficacy of weekly paclitaxel (H_1) is rejected, then consideration will be given to terminating study accrual.

The results of interim analyses are scheduled to be reviewed by the GOG Data Monitoring Committee (DMC) at its semi-annual meetings. This committee meets in January and July each year. The precise dates for these meetings are set more than one year in advance by individuals who have no knowledge of efficacy results. Approximately eight weeks prior to each of these meetings, the database is locked in order to prepare a progress report. If the prerequisite number of events has been attained, an interim analysis is also prepared and presented to the DMC at their next scheduled meeting. The decision to terminate accrual to any particular regimen includes consideration of toxicities, treatment compliance, overall survival and results from external studies. Additionally, the GOG Safety Review Committee (SRC) reviews accumulating summaries of toxicities and all serious adverse event (SAE) reports on an ongoing basis (not efficacy results). This committee also reviews those deaths in which the study treatment may have been a contributing cause. The SRC reports to the DMC and may recommend study amendments pertaining to patient safety. **(02/06/2012)**

Final analysis
The final analysis will also include exploratory analyses to assess the consistency of the treatment effect on PFS across subgroups of patients determined by presence of clinically measurable of disease (clinically measurable vs non-measurable), site of primary disease (ovarian vs extra-ovarian), stage of disease (II vs III vs IV), histologic cell type (papillary serous vs mucinous vs clear cell vs other cell types), Grade (1 and 2 vs 3), age (≤ 60 vs > 60 years) and patient's decision to include bevacizumab with the study treatment. The exploratory analysis also will include an estimate of the treatment hazard ratios among only those patients deemed eligible for the study. **(06/20/2011)**

11.4 *Safety analyses*

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) criteria version 4.0 will be used to classify toxicities observed during treatment. The severity of each toxicity will be assessed according to the NCI CTCAE 4.0 grading system. Patients will be tabulated according to their maximum severity for each organ system or preferred term.

Safety endpoints will be summarized with descriptive statistics for the patients in the safety analysis dataset. The safety analysis dataset will include all patients enrolled to the study who receive any of their assigned study treatment and the patients will be grouped by their assigned treatment. Patients who do not receive any of their assigned study treatment will not be included in these analyses.

11.5 **Quality of Life Analyses**

The principal measure used in this study to assess the quality of life (QoL) is the self-administered FACT-O TOI for ovarian cancer patients and the FACT-GOG/NTX. Each patient will be asked to complete the FACT-O TOI and the FACT-GOG/NTX at the following time points during their participation in the study:

11.51 Prior to cycle 1.
11.52 Prior to cycle 4 (9 weeks after starting treatment),
11.53 18 weeks after staring treatment (3 weeks after cycle 6)
11.54 36 weeks after starting treatment
11.55 63 weeks after starting treatment

Construct and content

The Functional Assessment of Cancer Therapy scale developed for ovarian cancer (FACT-O TOI) is a tool that provides a general QoL score. It consists of 3 subscales: physical well being (7 items), functional well being (7 items) and the Ovarian Cancer subscale (12 items). The FACT-GOG/NTX4 is a four item subscale which assesses patient reported platinum/taxane-induced symptoms of neuropathy.

Hypotheses and analyses
The first QoL question is: Are the FACT-O TOI scores reported by patients at the specified time points during treatment independent of the randomized treatment? This hypotheses is: H_{01}: $T_{CT1wk} = T_{CT3wk}$, where $T_{(.)}$ is a vector of mean TOI scores evaluated at the specific time points for the patients treated according to the indicated treatment

regimen. For the primary analysis this hypotheses will be assessed with a mixed model, adjusting for pretreatment TOI score, age and bevacizumab option. Patients will be included in these analyses regardless of the amount of study treatment they received. For the primary analyses patients will be categorized by their randomized treatment assignment rather than the treatment received. Analyses which classify patients by the actual treatment they received will be considered exploratory.

The primary analysis comparing the self-reported TOI scores for patients receiving CT_{1wk} to those receiving CT_{3wk} will focus on the scores assessed prior to cycle 4 and 18 weeks after starting treatment. These time points are considered appropriate since the cumulative impact of the paclitaxel schedule on TOI scores, if there is any, should be apparent during this time interval. Including subsequent assessments points could washout early differences between these treatment regimens, if the impact of treatment wanes after paclitaxel is stopped. It is anticipated that relatively few patients will withdraw from the study treatment prior to the 7^{th} cycle of treatment.

The second QoL questions is: Are the FACT-NTX4 scores reported by patients at the specified assessment times independent of the randomized treatment. This hypothesis is H_{02}: $X_{CT1wk} = X_{CT3wk}$, where $X_{(.)}$ is a vector of mean FACT-NTX4 scores evaluated at the specific time points for the patients treated according to the indicated treatment regimen. For the primary analysis this hypotheses will be assessed with a mixed effect – mixed distribution model, adjusting for pretreatment age. This model estimates the probability that a patient will report a non-zero FACT-NTX4 score and the mean score for those patients reporting non-zero scores. Patients will be included in these analyses regardless of the amount of study treatment they received. For the primary analyses patients will be categorized by their randomized treatment group rather than the treatment received. Analyses which classify patients by the actual treatment they received will be considered exploratory. The primary analysis comparing the self-reported NTX4 scores for patients receiving CT_{1wk} to those receiving CT_{3wk} will focus on the scores assessed prior to cycle 4 and 18 weeks after starting treatment.

Multiplicity of Outcomes

The overall type I error for these two QoL hypotheses (H_{01}, and H_{02}) will be limited to 5% (two-tail). In order to account for multiple hypotheses, the type I error will be allocated equally to each hypothesis. Specifically, the significance level will be set to 0.025 (0.05/2) for each treatment comparison.

Missing information

Patient death, noncompliance, missed appointments, and patient illiteracy, can lead to missing assessment scores. One or more of the QoL scores may be missing for an individual on any occasion. Missing information is troublesome, particularly in studies involving repeated patient assessments. Data management procedures will be used to reduce missing data. For example, a calendar of events which lists the dates for the required QoL assessments for each patient will be made available to the patient's health care provider as soon as the patient has been registered onto this study. Also, the clinic staff will use the GOG web-based forms tracking system to obtain reminders of the upcoming QoL assessments.

During semi-annual group meetings the data managers and nurses will be given presentations, which describe the goals of this study and stress the importance of obtaining complete assessments. A study contact person will be designated to answer questions that arise throughout the study.

Spanish and English versions of the FACT-O TOI are available. Women who are unable to read or have difficulty reading will not be required to participate in the QoL part of this study. Also, any woman, who does not wish to participate in the QoL portion of this study, can refuse and remain eligible for the therapeutic portion of the study.

TOI and NTX4 Scoring

Within an individual assessment one or more items may not be answered. A subscale score will be computed provided more than 50% of subscale items have a valid response. A subscale score S_i with N_i items will be calculated as:

$$S_i = N_i * \frac{\sum_{j=1} (\delta_{ij} * s_{ij})}{\sum_{j=1} \delta_{ij}}$$

Where δ_{ij} is equal to 1 when the jth item has a valid response, otherwise it is equal to 0 and s_{ij} is the response score of the jth item. The total FACT-O TOI score is the sum of the subscale scores.

Statistical Power Considerations

The GOG has completed a trial in which 415 patients with advanced ovarian cancer were treated with platinum and paclitaxel for 6 cycles every 21 days. These women reported their self-assessed FACT-O TOI prior to initiating treatment, prior to the 4th cycle of treatment, following the 6th cycle of treatment and then 6 months later (GOG-172). Prior to initiating the study treatment, the mean and standard deviation of the FACT-O TOI scores were 67.2 and 15.9, respectively. The mean and standard deviation of the TOI scores prior to cycle 4, after cycle 6 and 12 months after cycle 6 were: (66.6, 15.3), (71.7, 15.6) and (82.7, 14.4), respectively. The correlation between pretreatment assessments and the assessments prior to the 4th cycles and the 6th cycle of treatment was about 0.4 and the correlation between the scores reported prior to cycle 4 and 6 was 0.6.

Using these data and assuming there will be a 10% attrition of patients at each of the assessment times: prior to treatment cycle 4 and 18 weeks after starting treatment, this study is expected to have approximately 82% chance of detecting a 3.5 unit true difference in mean TOI scores between treatments when assessing H_{01}. This power calculation is based on 1000 simulated trials. SAS source code for simulations is available upon request.

11.6 **Analysis of Single Nucleotide Polymorphisms (SNPs)**

Overview
The overall objective of the SNP analyses is first to identify SNPs that are associated with longer survival and then secondly to develop a prognostic index. One additional objective is to determine whether there are SNPs that predict which patients respond favorably to bevacizumab.

In general, the primary challenges related to this objective are: a) the need to identify a relatively small number of prognostic SNPs from among thousands of candidate SNPs, b) the practicality of having a relatively small number of biologic samples relative to the number of candidate SNPs. In order to address these challenges this study will utilize a training dataset to develop a prognostic index and a separate and distinct validation dataset.

Training and validation sets
It is desirable to obtain biologic specimens from all of the patients entered into the randomized portion of this trial. However, all enrolled patients may not submit all of the specified specimens or some specimens may be inevaluable. In order to establish a training set, therefore, this study will target a sample of sequentially enrolled eligible and evaluable patients with at least 125 deaths reported. That is, suppose 250 patients are enrolled annually onto the randomized portion of this study and 85% of these patients provide analyzable specimens for the SNP component of this study. Following a cohort of 212 patients (250*0.85) enrolled over the first year of the study for at least 33 months is expected to yield at least 125 deaths to establish the training set. The actual size of the training cohort may be adjusted depending on the proportion of patients providing analyzable specimens, but the minimum number of events will be fixed. **(06/20/2011)**

A validation cohort will be derived in a similar fashion as the training cohort. That is, the training and validation cohorts will consist of sequentially enrolled eligible patients with analyzable specimens and individuals will not be permitted to be members of both the training and validation cohorts.

Preliminary analyses: Preliminary analyses will precede the primary analyses. The goal of the preliminary analyses will be to identify procedures for detecting outliers, normalizing measurements and eliminating systematic errors.

Analysis of the training dataset: The primary purpose of this analysis is to refine this set of SNPs and then propose a prognostic index based on the refined set of SNPs. Toward this end, a proportional hazards model relating expression levels of each SNP to overall survival and will be fitted to the study data. In order to accommodate multiple testing with potentially correlated markers, multivariate permutation methods will be used to identify those SNPs that are most likely to be prognostic, while limiting the false discovery rate. Specifically, each of the observed times at risk and the corresponding censoring indicator for an individual in the training set will be randomly assigned to one and only one of the SNP profiles in the training set in order to define a permuted dataset. Multiple permuted datasets will be defined in a similar fashion.

Then a proportional hazards model stratified on randomized treatment will be fitted to each SNP using these permuted data sets. For a specified critical p-value, say ξ=0.01, the average number of false positives,ν, can be calculated from these permuted datasets. The average false discovery proportion is then ν/η_ξ , where η_ξ is the number of SNPs with p-values less than ξ in the original dataset. The value of ξ can be varied in order to limit the average false discovery proportion to less than a pre specified value, γ.

Conditioning the final analysis on 125 events, setting ξ=0.01 and assuming proportional hazards, this study design provides approximately a 90% chance of detecting a SNP that occurs in half of the patients and truly doubles the failure rate when comparing patients with and without the SNP. This design also has about an 80% chance of detecting a SNP that occurs in one third of the population and increases the event rate 85% when comparing patient with and without the SNP.

Validation of the prognostic index: Prior to initiating the validation phase, the 'final' classifier will be completely documented (eg, using computer program, pseudo-code or a flow chart). This documentation will be reviewed by individuals in the GOG Statistical and Data Center (SDC) who are not participating in the analyses. The purpose of this review will be to determine whether the final classifier has been unambiguously defined.

Using the coefficients from the stratified multivariate proportional hazards model developed using the training dataset, a prognostic index will be computed for each individual in the validation dataset. The independence between the prognostic index and overall survival will be assessed with another proportional hazards model fitted to the validation dataset. Ideally, the proportional hazards coefficient of the prognostic index would be 1.0. However, the degree to which this coefficient is less than 1.0 reflects the degree to which the training data was over-fitted. If the prognostic index is deemed prognostic then the relationship between the index and the time to recurrence or death can be displayed as: martingale residuals plots, Schoenfeld residual plots, ROC curves or Kaplan-Meier plots.

Predictive index

A true prognostic index can be used to distinguish subgroups of patients who are likely to experience different courses in their disease. A predictive index functions similar to a prognostic index except that its function is treatment specific. Biomarkers that identify biologic pathways which are necessary to respond to a particular treatment are potentially good predictive markers. The procedure for identifying predictive markers is similar to the procedure for identifying prognostics markers. However, rather than identifying markers that are associated with a particular outcome, we attempt to identify markers that are associated with the outcome only when a specific treatment (ie paclitaxel dose density) is applied. In other words, in order to identify predictive SNP profiles, the procedure will focus on SNPs that significantly interact with treatment. Specifically, for each SNP the proportional hazards model will include expression level, an indicator for dose density (standard dose vs dose dense paclitaxel) and an interaction term to express an interaction between these variates. Those SNPs with a significant treatment interaction term are potential predictive biomarkers to be considered for defining an overall predictive index. The procedures for training, index development and validation are similar to those procedures outlined above for prognostic factors.

However, since the statistical power for detecting a predictive marker is considerably less than it is for a prognostic marker the minimum required number of events in the training and validation data will be increased.

The publication which describes the results of the primary SNP analysis for this study will include a description of the accuracy of the final classifier. While other classifiers may also be described, the final classifier will be clearly distinguished from the other classifiers. The documentation describing the final classifier will be available to other investigators from the SDC upon request (see prognostic index validation Section above).

After the study objectives have been completed, the GOG may elect to make some or all of the validation data set available to other investigators. Since the specimens in the training set may become exhausted, any classifiers developed subsequently will not be permitted to claim that they were independently validated without additional supporting external evidence.

11.7 **Anticipated distribution of patients' race and ethnicity (all are female): (10/22/2012)**

Asian	38
American Indian or Native Alaskan	4
Hawaiian or Pacific Islander	4
Black (not Hispanic)	32
White (not Hispanic)	528
Hispanic	19

11.8 Statistical Considerations for the Imaging Study **(06/20/2011) (10/22/2012)**

This section has been intentionally left blank.

This section has been intentionally left blank.

This section has been intentionally left blank.

This section has been intentionally left blank.

This section has been intentionally left blank.

This section has been intentionally left blank.

12.0 BIBLIOGRAPHY **(01/18/2011) (06/20/2011) (10/22/2012)**

1. Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2008. CA Cancer J Clin 58:71-96, 2008.

2. Milross CG, Mason KA, Hunter NR, et al: Relationship of mitotic arrest and apoptosis to antitumor effect of paclitaxel. J Natl Cancer Inst 88:1308-14, 1996.

3. Belotti D, Vergani V, Drudis T, et al: The microtubule-affecting drug paclitaxel has antiangiogenic activity. Clin Cancer Res 2:1843-9, 1996.

4. Lau DH, Xue L, Young LJ, et al: Paclitaxel (Taxol): an inhibitor of angiogenesis in a highly vascularized transgenic breast cancer. Cancer Biother Radiopharm 14:31-6, 1999.

5. Symmans WF, Volm MD, Shapiro RL, et al: Paclitaxel-induced apoptosis and mitotic arrest assessed by serial fine-needle aspiration: implications for early prediction of breast cancer response to neoadjuvant treatment. Clin Cancer Res 6:4610-7, 2000.

6. Griffon-Etienne G, Boucher Y, Brekken C, et al: Taxane-induced apoptosis decompresses blood vessels and lowers interstitial fluid pressure in solid tumors: clinical implications. Cancer Res 59:3776-82, 1999.

7. Milas L, Hunter NR, Mason KA, et al: Role of reoxygenation in induction of enhancement of tumor radioresponse by paclitaxel. Cancer Res 55:3564-8, 1995.

8. Seidman AD, Hudis CA, Albanell J, et al: Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. J Clin Oncol 16:3353-61, 1998.

9. Perez EA, Vogel CL, Irwin DH, et al: Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol 19:4216-23, 2001.

10. Gori S, Mosconi AM, Basurtol C, et al: Weekly paclitaxel in metastatic breast cancer patients: a phase II study. Tumori 88:470-3, 2002.

11. Sato K, Inoue K, Saito T, et al: Multicenter phase II trial of weekly paclitaxel for advanced or metastatic breast cancer: the Saitama Breast Cancer Clinical Study Group (SBCCSG-01). Jpn J Clin Oncol 33:371-6, 2003.

12. Lombardi D, Crivellari D, Scuderi C, et al: Long-term, weekly one-hour infusion of paclitaxel in patients with metastatic breast cancer: a phase II monoinstitutional study. Tumori 90:285-8, 2004.

13. Green MC, Buzdar AU, Smith T, et al: Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. J Clin Oncol 23:5983-92, 2005.

14. Sparano JA, Wang M, Martino S, et al: Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 358:1663-71, 2008.

15. Seidman AD, Berry D, Cirrincione C, et al: Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol 26:1642-9, 2008.

16. Fennelly D, Aghajanian C, Shapiro F, et al: Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. J Clin Oncol 15:187-92, 1997.

17. Markman M, Hall J, Spitz D, et al: Phase II trial of weekly single-agent paclitaxel in platinum/paclitaxel-refractory ovarian cancer. J Clin Oncol 20:2365-9, 2002.

18. Abu-Rustum NR, Aghajanian C, Barakat RR, et al: Salvage weekly paclitaxel in recurrent ovarian cancer. Semin Oncol 24:S15-62-S15-67, 1997.

19. Kita T, Kikuchi Y, Takano M, et al: The effect of single weekly paclitaxel in heavily pretreated patients with recurrent or persistent advanced ovarian cancer. Gynecol Oncol 92:813-8, 2004.

20. Katsumata N, Yasuda M, Takahashi F, Isonishi S, Jobo T, Aoli D, Tsuda H, Sugiyama T, Kodama S, Kimura E, Ochiai K, Noda K. Japanese Gynecologic Oncology Group. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3 open-label, randomized controlled trial. Lancet. 2009 Oct 17:374 (9698): 1331-9. Epub 2009 Sep 18.

21. Vergote I, Trope CG, Amant F, et al: Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 363:943-53, 2010.

22. Yoneda J, Kuniyasu H, Crispens MA, et al: Expression of angiogenesis-related genes and progression of human ovarian carcinomas in nude mice. J Natl Cancer Inst 90:447-54, 1998.

23. Dvorak HF: Vascular permeability factor/vascular endothelial growth factor: a critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. J Clin Oncol 20:4368-80, 2002.

24. Ferrara N: Molecular and biological properties of vascular endothelial growth factor. J Mol Med 77:527-43, 1999.

25. Alvarez AA, Krigman HR, Whitaker RS, et al: The prognostic significance of angiogenesis in epithelial ovarian carcinoma. Clin Cancer Res 5:587-91, 1999.

26. Gasparini G, Fox SB, Verderio P, et al: Determination of angiogenesis adds information to estrogen receptor status in predicting the efficacy of adjuvant tamoxifen in node-positive breast cancer patients. Clin Cancer Res 2:1191-8, 1996.

27. Hollingsworth HC, Kohn EC, Steinberg SM, et al: Tumor angiogenesis in advanced stage ovarian carcinoma. Am J Pathol 147:33-41, 1995.

28. Byrne AT, Ross L, Holash J, et al: Vascular endothelial growth factor-trap decreases tumor burden, inhibits ascites, and causes dramatic vascular remodeling in an ovarian cancer model. Clin Cancer Res 9:5721-8, 2003.

29. Gorski DH, Beckett MA, Jaskowiak NT, et al: Blockage of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation. Cancer Res 59:3374-8, 1999.

30. Hu L, Hofmann J, Zaloudek C, et al: Vascular endothelial growth factor immunoneutralization plus Paclitaxel markedly reduces tumor burden and ascites in athymic mouse model of ovarian cancer. Am J Pathol 161:1917-24, 2002.

31. Lee CG, Heijn M, di Tomaso E, et al: Anti-Vascular endothelial growth factor treatment augments tumor radiation response under normoxic or hypoxic conditions. Cancer Res 60:5565-70, 2000.

32. Burger RA, Sill MW, Monk BJ, et al: Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol 25:5165-71, 2007.

33. Cannistra SA, Matulonis UA, Penson RT, et al: Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol 25:5180-6, 2007.

34. Garcia AA, Hirte H, Fleming G, et al: Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. J Clin Oncol 26:76-82, 2008.

35. Hurwitz H, Fehrenbacher L, Novotny W, et al: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350:2335-42, 2004.

36. Sandler A, Gray R, Perry MC, et al: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 355:2542-50, 2006.

37. Miller K, Wang M, Gralow J, et al: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 357:2666-76, 2007.

38. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2007 Nov 20;25(33):5165-71.

39. Han ES, Monk BJ. Bevacizumab in the treatment of ovarian cancer. Expert Rev Anticancer Ther. 2007 Oct;7(10):1339-45.

40. Schwartz EL. Antivascular actions of microtubule-binding drugs. Clin Cancer Res. 2009 Apr 15;15(8):2594-601.

41. Bezjak A, Tu D, Bacon M, Osoba D, Zee B, Stuart G et al. Quality of life in ovarian cancer patients: comparison of paclitaxel plus cisplatin, with cyclophosphamide plus cisplatin in a randomized study. J Clin Oncol 22:4595-603 2004.

42. du Bois A, Luck HJ, Meier W, Adams HP, Mobus V, Costa S et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 95:1320-9, 2003.

43. Vasey PA, Jayson GC, Gordon A, Gabra H, Coleman R, Atkinson R et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. J Natl Cancer Inst 96:1682-91, 2004.

44. Wenzel L, Huang HQ, Monk BJ, Rose PG, Cella D. Quality-of-life comparisons in a randomized trial of interval secondary cytoreduction in advanced ovarian carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2005 Aug 20;23(24):5605-12.

45. Bookman MA, Brady MF, McGuire WP, Harper PG, Alberts DS, Friedlander M, Colombo N, Fowler JM, Argenta PA, De Geest K, Mutch DG, Burger RA, Swart AM, Trimble EL, Accario-Winslow C, Roth LM. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. J Clin Oncol. 2009 Mar 20;27(9):1419-25.

46. Basen-Engquist K, Bodurka-Bevers D, Fitzgerald MA, Webster K, Cella D, Hu S et al. Reliability and validity of the functional assessment of cancer therapy-ovarian. J Clin Oncol 19:1809-17, 2001.

47. Cain JM, Wenzel LB, Monk BJ, Cella D. Palliative care and quality of life considerations in the management of ovarian cancer. In: Gershenson DM, McGuire WP. Ovarian Cancer: Controversies in Management. New York: Churchill Livingstone 281-307, 1998.

48. Wenzel LB, Huang HQ, Armstrong DK, Walker JL, Cella D; Gynecologic Oncology Group. Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2007 Feb 1;25(4):437-43.

49. Wenzel L, Huang HQ, Cella D, Walker JL, Armstrong DK; Gynecologic Oncology Group. Validation of FACT/GOG-AD subscale for ovarian cancer-related abdominal discomfort: a Gynecologic Oncology Group study. Gynecol Oncol. 2008 Jul;110(1):60-4.

50. Pace A, Nisticò C, Cuppone F, Bria E, Galiè E, Graziano G, Natoli G, Sperduti I, Jandolo B, Calabretta F, Tomao S, Terzoli E. Peripheral neurotoxicity of weekly paclitaxel chemotherapy: a schedule or a dose issue? Clin Breast Cancer. 2007 Apr;7(7):550-4.

51. Huang HQ, Brady MF, Cella D, Fleming G. Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a gynecologic oncology group study. Int J Gynecol Cancer. 2007 Mar-Apr;17(2):387-93.

52. Holash J *et al*. (1999) New model of tumor angiogenesis: dynamic balance between vessel regression and growth mediated by angiopoietins and VEGF. *Oncogene* 18:5356–5362.

53. Spannuth WA, Sood AK and Coleman RL, Angiogenesis as a strategic target for ovarian cancer therapy Nature Clinical Practice Oncology April 2008 Vol 5, No 4

54. Jubb AM *et al*. (2006) Predicting benefit from antiangiogenic agents in malignancy. *Nat Rev Cancer* 6: 626–635.

55. Henderson E, Sykes J, Drost D, Weinmann HJ, Rutt BK, Lee TY. Simultaneous MRI measurement of blood flow, blood volume, and capillary permeability in mammary tumors using two different contrast agents. J Magn Reson Imaging. 2000 Dec;12(6):991-1003

56. Hylton N. Dynamic contrast-enhanced magnetic resonance imaging as an imaging biomarker. J Clin Oncol. 2006 Jul 10;24(20):3293-8

57. Delorme S, Krix M. Contrast-enhanced ultrasound for examining tumor biology. Cancer Imaging. 2006;6:148-52

58. de Bazelaire C, Rofsky NM, Duhamel G, Zhang J, Michaelson MD, George D, et al. Combined T2* and T1 measurements for improved perfusion and permeability studies in high field using dynamic contrast enhancement. Eur Radiol. 2006 Sep;16(9):2083-91

59. Pallwein L, Mitterberger M, Pelzer A, Bartsch G, Strasser H, Pinggera GM, et al. Ultrasound of prostate cancer: recent advances. Eur Radiol. 2008 Apr;18(4):707-15.

60. Thibault JB, Sauer KD, Bouman CA, Hsieh J. A three-dimensional statistical approach to improved image quality for multislice helical CT. Med Phys. 2007 Nov;34(11):4526-44;

61. Lee TY, Bauman G, Hsieh J, Thibault JB, Kozak R. Reducing effective dose from CT Perfusion with adaptive statistical iterative reconstruction (ASIR). RSNA Scientific Assembly and Meeting Program, p696. 2009.

62. Lee TY, Purdie TG, Stewart E. CT imaging of angiogenesis. Q J Nucl Med. 200 Sep;47(3):171-87.)

63. Miles KA, Charnsangavej C and Lee FT *et al.*, Application of CT in the investigation of angiogenesis in oncology, *Acad Radiol* 7 (10) (2000), pp. 840–850.

64. Leggett DA, Kelley BB, Bunce IH, Miles KA. Colorectal cancer: diagnostic potential of CT measurements of hepatic perfusion and implications for contrast enhancement protocols. Radiology 1997;205:716–20.

65. Sommerfeld N, Miles K, Dugdale P, Leggett D, Bunce I. Colorectal cancer: progressive disease is associated with altered liver perfusion on functional CT. In 50th Annual Meeting of the Royal Australia & New Zealand College of Radiologists. 1999

66. Hermans R, Lambin P, Van den Bogaert W, Haustermans K, Van der Goten A, Baert AL. Non-invasive tumour perfusion measurement by dynamic CT: preliminary results. Radiother Oncol 1997;44:159–62

67. Hermans R, Meijerink M, and Van den Bogaert W *et al.*, Tumor perfusion rate determined noninvasively by dynamic computed tomography predicts outcome in head-and-neck cancer after radiotherapy, *Int J Radiat Oncol Biol Phys* 57 (5) (2003), pp. 1351–1356.

68. Gandhi, E.G. Hoeffner and R.C. Carlos, Computed tomography perfusion of squamous cell carcinoma of the upper aerodigestive tract. Initial results, *J Comput Assist Tomogr* 27 (5) (2003), pp. 687–693.

69. Gandhi D, Chepeha DB and Miller T *et al.*, Correlation between initial and early follow-up CT perfusion parameters with endoscopic tumor response in patients with advanced squamous cell carcinomas of the oropharynx treated with organ-preservation therapy, *AJNR Am J Neuroradiol* 27 (1) (2006), pp. 101–106.

70. Kan Z, Phongkitkarun S and Kobayashi S *et al.*, Functional CT for quantifying tumor perfusion in antiangiogenic therapy in a rat model, *Radiology* 237 (1) (2005), pp. 151–158.

71. Willett CG, Boucher Y and di Tomaso *et al.*, Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer, *Nat Med* 10 (2) (2004), pp. 145–147

72. Zhu A.X., Holalkere N.S. and Muzikansky A. *et al.*, Early antiangiogenic activity of bevacizumab evaluated by computed tomography perfusion scan in patients with advanced hepatocellular carcinoma, *Oncologist* 13 (2) (2008), pp. 120–125.

73. Schwab SJ, Christensen RL, Dougherty K, et al: Quantitation of proteinuria by the use of protein-to-creatinine ratios in single urine samples. Arch Intern Med 147:943-4, 1987.

74. Steinhauslin F, Wauters JP: Quantitation of proteinuria in kidney transplant patients: accuracy of the urinary protein/creatinine ratio. Clin Nephrol 43:110-5, 1995.

75. Wilson DM, Anderson RL: Protein-osmolality ratio for the quantitative assessment of proteinuria from a random urinalysis sample. Am J Clin Pathol 100:419-24, 1993.

76. Zelmanovitz T, Gross JL, Oliveira J, et al: Proteinuria is still useful for the screening and diagnosis of overt diabetic nephropathy. Diabetes Care 21:1076-9, 1998.

77. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205-16, 2000.

78. Basen-Engquist K, Bodurka-Bevers D, Fitzgerald MA, Webster K, Cella D, Hu S et al. Reliability and validity of the functional assessment of cancer therapy-ovarian. J Clin Oncol 19:1809-17, 2001.

79. Cain JM, Wenzel LB, Monk BJ, Cella D. Palliative care and quality of life considerations in the management of ovarian cancer. In: Gershenson DM, McGuire WP. Ovarian Cancer: Controversies in Management. New York: Churchill Livingstone 281-307, 1998.

80. Wenzel LB, Huang HQ, Armstrong DK, Walker JL, Cella D; Gynecologic Oncology Group. Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2007 Feb 1;25(4):437-43.

81. Wenzel L, Huang HQ, Cella D, Walker JL, Armstrong DK; Gynecologic Oncology Group. Validation of FACT/GOG-AD subscale for ovarian cancer-related abdominal discomfort: a Gynecologic Oncology Group study. Gynecol Oncol. 2008 Jul;110(1):60-4.

82. Huang HQ, Brady MF, Cella D, Fleming G. Validation and reduction of FACT/GOG-Ntx subscale for platinum/paclitaxel-induced neurologic symptoms: a gynecologic oncology group study. Int J Gynecol Cancer. 2007 Mar-Apr;17(2):387-93.

83. Bonett, D.G. Sample size requirements for estimating intraclass correlations with desired precision. 2002 Statistics in Medicine 21: 1331-1335.