PROTOCOL AND STATISTICAL ANALYSIS PLAN

Study Title: **Trial of Chemotherapy in Ovarian, Fallopian Tube and Peritoneal Carcinoma**

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Neoadjuvant Platinum-based Chemotherapy in Advanced Ovarian, Fallopian Tube, and Primary Peritoneal Carcinoma Trial Protocol

A non-randomized phase II study of neoadjuvant chemotherapy with interval surgical debulking in patients with advanced ovarian, fallopian tube, primary peritoneal carcinoma

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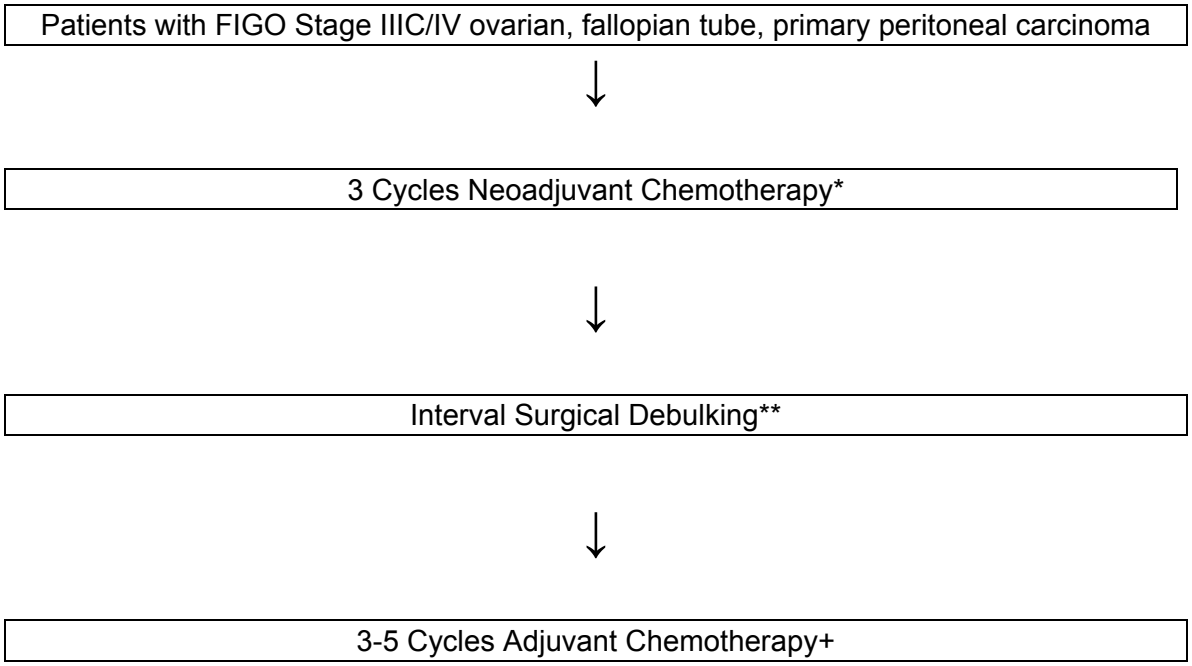
SCHEMA



*Paclitaxel 175mg/m^2 IV over 3 hours followed by Carboplatin AUC 6 IV over 30 minutes every 21 days

**Approximately 3-4 weeks after 3rd cycle of chemotherapy

+Preferably starts within 2 weeks of surgery (exceptions may be made by the Principal Investigator) with same dose parameters as neoadjuvant chemotherapy; adjuvant chemotherapy consists of 3-5 cycles based on discretion of treating physician with the goal that patients are treated with one cycle beyond normalization of CA 125/no radiographic or clinical evidence of disease

OUTCOME MEASURES

PRIMARY ENDPOINT

- Rate of maximal surgical cytoreduction (ie, no gross residual disease)

SECONDARY ENDPOINTS

- Progression-free survival (PFS)
- Overall survival (OS)
- Response rate (RR)
- Toxicity related to treatment
- Surgical outcomes
- Quality of life
- Correlative studies (blood, tumor tissue)

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1.0 OBJECTIVES

This is a prospective study to evaluate the hypothesis that:

a) platinum-based neoadjuvant chemotherapy followed by interval surgical debulking with platinum-based adjuvant chemotherapy is associated with improved maximal surgical cytoreduction rates, comparable survival, decreased morbidity, and increased quality of life in patients with International Federation of Gynecologic Oncology (FIGO, Appendix I) stages IIIC and IV ovarian, primary peritoneal, or fallopian tube cancer when compared to historical controls [20,45], and

b) cancer induced inflammation is a predictor of poor prognosis and response to therapy in this group of ovarian cancer patients.

1.1 Primary Objectives

1.11 To determine maximal surgical cytoreduction debulking rate (see Appendix V), i.e. no gross residual disease, in a group of patients with FIGO stages IIIC and IV ovarian, primary peritoneal, or fallopian tube cancer who received 3 cycles of platinum-based neoadjuvant chemotherapy.

1.2 Secondary Objectives

1.21 To determine progression-free survival in a group of patients with FIGO stages IIIC and IV ovarian, primary peritoneal, or fallopian tube cancer treated by neoadjuvant chemotherapy followed by interval debulking and adjuvant chemotherapy.

1.22 To determine overall survival in a group of patients with FIGO stages IIIC and IV ovarian, primary peritoneal, or fallopian tube cancer treated by neoadjuvant chemotherapy followed by interval debulking and adjuvant chemotherapy.

1.23 To determine response rate to chemotherapy in patients who undergo neoadjuvant chemotherapy followed by interval debulking and adjuvant chemotherapy.

1.24 To evaluate the toxicity from chemotherapy, as measured by the Common Toxicity Criteria for Adverse Events v4.0.

1.25 To evaluate operative outcomes including length of surgery, length of hospital stay, ICU admissions, transfusions, and intraoperative complications (blood loss >1500mL, unintentional damage to organs requiring repair).

1.26 To evaluate Quality of Life (QOL, as measured by the FACT-O TOI) following treatment with this regimen. (Appendix II)

1.27 To assess, in an exploratory manner, the correlation between biologic indicators of inflammation and oxidative stress, including TNF-a, TNF receptor II, protein oxidation, CRP, Il-6 and Il-8 and tumor tissue oxidation before and after neo-adjuvant therapy, and clinical outcomes, including overall survival, tumor response, and quality of life variables.

2.0 BACKGROUND AND RATIONALE

2.1 Standard Management of Advanced Ovarian, Primary Peritoneal, and Fallopian Tube Carcinoma

With over 200,000 new cases of ovarian cancer diagnosed worldwide each year, ovarian cancer is the 2nd most common gynecologic cancer and the most common cause of gynecologic cancer death. It is estimated that there will be an estimated 21,880 new cases of ovarian cancer and 13,850 deaths from the disease in 2010 in the United States[1]. The standard management of advanced epithelial ovarian, primary peritoneal, and fallopian tube cancer is primary debulking surgery followed by systemic chemotherapy with carboplatin and paclitaxel[2-7]. The extent of surgical cytoreduction or debulking at the time of primary surgery improves patient survival[8]. While rates of optimal tumor debulking, defined as less than 1cm residual disease, at centers with experienced gynecologic oncologists have been reported to be as high as 70% in selected institutions, most centers will achieve optimal surgical debulking in only 30-60% of patients with Stage IIIC/IV ovarian, primary peritoneal, or fallopian tube cancer[9,10].

2.2 New Strategies to Improve Outcomes

Five-year overall survival for ovarian cancer is around 50% for all patients. Unfortunately, over 2/3 of patients have stage III or stage IV disease at the time of diagnosis. The 5-year survival for these patients is 30%, as opposed to 90% for patients with disease confined to the ovary. Despite advancements in surgical techniques and chemotherapy, trends in survival have changed little over the past 30 years.

Initial surgical debulking has been the standard of care for patients with ovarian cancer since the 1930's. The landmark study by Griffiths in 1975 showed an inverse relationship between the extent of residual disease after primary surgery and survival[11]. The concept of surgical debulking to improve survival is based on several principles including: 1) elimination of pharmacologic sanctuaries by removal of poorly vascularized masses, 2) increased sensitivity to chemotherapy secondary to higher growth fraction of small residual tumors, and 3) less resistance to chemotherapy as a result of fewer chemotherapy cycles. Bristow published a meta-analysis in 2002 showing that optimal cytoreductive surgery was the most significant determinant of patient survival in those patients with stage III or IV ovarian cancer treated with platinum-based chemotherapy[8]. The definition of "optimal" with respect to surgical debulking for ovarian cancer

has evolved over time. Initially, ≤ 2 cm residual disease was considered optimal, which was subsequently reduced to ≤ 1 cm. More recently, the concept of optimal surgical debulking to less than or equal to 1 cm of residual disease has shifted to maximal surgical debulking, which is defined as no gross residual disease. Frequently patients with advanced ovarian cancer have disease involving the rectosigmoid and the upper abdomen including the liver, porta hepatis, spleen, distal pancreas, and diaphragm. In order to achieve maximal surgical cytoreduction resulting in no gross residual disease, surgeons must perform aggressive surgical procedures including en bloc resection of the uterus, ovaries, and sigmoid colon, liver resection, diaphragm stripping, splenectomy, and distal pancreatectomy. Several reports have indicated acceptable complication rates and feasibility of performing these procedures for the purpose of cytoreductive surgery in ovarian cancer[12-19]. However, maximal and optimal surgical cytoreductive rates vary widely among institutions, ranging from less than 25% to 75% in more experienced centers[8]. Patients with extensive liver disease, pulmonary metastases, or extensive disease throughout the small bowel mesentery generally cannot be maximally debulked to no gross residual disease status prior to initiating adjuvant chemotherapy.

Neoadjuvant chemotherapy, followed by interval surgical cytoreduction and adjuvant chemotherapy, has been proposed as an alternative to initial surgical cytoreduction in patients with advanced ovarian cancer.

2.3 Rationale for Neoadjuvant Chemotherapy and Interval Debulking

There is no evidence to support initial surgical debulking in patients with advanced ovarian cancer that is unlikely to be surgically resectable. There is evidence to suggest that there is survival benefit when surgical debulking to less than 1 cm residual disease is possible. However, the greatest benefit is seen in patients with no gross residual disease after initial cytoreductive surgery. It is also clear that there is no benefit of initial cytoreductive surgery in patients with ovarian cancer when more than 1 cm residual disease remains after attempted debulking.

2.4 Role of Neoadjuvant Platinum-based Chemotherapy and Interval Debulking in Ovarian, Primary Peritoneal, and Fallopian Tube Carcinoma

Vergote et al. conducted a randomized phase III trial comparing upfront debulking surgery with neoadjuvant chemotherapy in patients with Stage IIIC or IV epithelial ovarian carcinoma (EORTC 55971)[20]. Patients were randomized to either primary debulking surgery followed by at least 6 courses of platinum-based chemotherapy (Arm A) or 3 courses of platinum-based neoadjuvant chemotherapy, interval debulking surgery (in patients with a response or stable disease) and at least 3 more courses of platinum-based chemotherapy (Arm B). Seven-hundred eighteen patients were enrolled and 670 were randomized. Less than half of the patients (41.6%) undergoing primary surgery had ≤1cm residual disease at the completion of cytoreductive surgery, as opposed to 80.6% of patients who had ≤1cm residual disease after interval debulking. Only

19.4% of the patients undergoing primary surgery had no residual tumor (maximal surgical debulking) after cytoreductive surgery, compared to 51.2% of patients in the neoadjuvant chemotherapy group. Overall survival and progression-free survival were similar in the two groups. In the primary surgery group, the median overall survival was 29 months, versus 30 months in the neoadjuvant chemotherapy group. The median progression-free survival was 12 months in both groups. In multivariate analyses, absence of residual tumor after surgery was the strongest independent predictor of survival (P<0.001), followed by stage IIIC disease (P=0.001), small tumor size before randomization (P=0.001), endometrioid histologic type (P=0.005), and younger age (P=0.005). They concluded that "neoadjuvant chemotherapy is not inferior to primary cytoreductive surgery for patients with stage IIIC or IV ovarian carcinoma," and that there were "no significant advantages" observed in either arm of the trial "with respect to survival, adverse effects, quality of life, or postoperative morbidity or mortality".

Kumar et al. presented findings from a similar randomized trial at the 2007 Annual ASCO meeting[21]. The trial included 128 patients with epithelial ovarian cancer, who were randomized to either upfront debulking surgery followed by 6 cycles of paclitaxel and carboplatin (Arm A) or neoadjuvant chemotherapy with 3 cycles of paclitaxel and carboplatin followed by interval debulking surgery then 3 more cycles of the same chemotherapy (Arm B). Patients in the neoadjuvant chemotherapy arm had a higher optimal debulking rate ($p < 0.0001$), decreased blood loss during surgery (mean loss 520 ml vs. 373 ml, $p < 0.003$), and reduced postoperative infections (14.8% vs. 2.5%, <0.04). Mean operative time and hospital stay were similar in both arms. The median overall survival and disease free survival were 42 vs. 29 months ($p=0.07$) and 20 vs. 25 months ($p = 0.11$) for arms A and B, respectively, which is not significantly different at a median follow up of 41 months. Quality of life scores were significantly better in the neoadjuvant chemotherapy arm (93 vs. 114, $p < 0.001$). They concluded, "neoadjuvant chemotherapy in advanced epithelial ovarian cancer is associated with a higher optimal debulking rate with reduced postoperative morbidity and improved quality of life".

In 2009, Onda et al. published "Feasibility study of neoadjuvant chemotherapy followed by interval debulking surgery for stage IIIC/IV ovarian, tubal, and peritoneal cancers: Japan Clinical Oncology Group Study JCOG0206" in *Gynecologic Oncology*[22]. The study included 56 patients with clinically diagnosed staged III/IV müllerian carcinomas based on imaging studies, cytology, and tumor markers. All patients underwent diagnostic laparoscopy to confirm the clinical diagnosis. The patient subsequently underwent 4 cycles of paclitaxel and carboplatin followed by interval debulking then 4 more cycles of the same chemotherapy. The primary endpoint was complete clinical remission and the secondary endpoint was the positive predictive value of clinical diagnosis. The authors found that the positive predictive value of clinical diagnosis was 95% for tumor origin, histology, and stage of disease. Complete clinical response was seen in 42% of patients, which was

confirmed with diagnostic laparoscopy at the end of treatment. The median overall survival was 45 months and the median progression-free survival was 14 months.

2.5 Rationale for Clinical Trial Design

2.51 Study Population

A study population limited to patients with probable Stage IIIC or Stage IV ovarian, fallopian tube, or primary peritoneal carcinomas was selected because of the relatively high frequency of these cases and the limited probability that optimal cytoreduction (no visible disease) could be achieved by primary surgery alone. Furthermore, the results of this trial would be better generalized to the population at large with epithelial ovarian and primary peritoneal cancers by including the largest subset of these patients. Patients with early stage epithelial ovarian cancers were not included because > 95 percent of these cases can be optimally debulked by primary surgery, and selective chemotherapy can be given postoperatively.

2.52 Sample Size Considerations

Using previous results from a European study of neoadjuvant chemotherapy, 51.2% of patients in the neoadjuvant arm achieved maximal surgical debulking as compared to 19.4% of patients in the primary debulking control arm.[20] Therefore, based on a hypothesis test of a single proportion with 90% power and a two-sided type I error rate equal to 0.05, the first-stage sample size necessary for this single arm study to detect the same improvement in the percentage of neoadjuvant chemotherapy patients achieving optimal surgical debulking as compared to the European controls is 9 patients. The trial will be terminated if no more than 2 patients achieve maximal surgical debulking, as defined by no gross residual disease. If the 9th patient is enrolled and only two prior patients meet requirements for maximal surgical debulking, then enrollment will be on hold until after surgery for the 9th patient. If maximal surgical debulking is achieved in 3 or more of the 9 patients enrolled, the trial will continue to a second stage, which will involve enrollment of an additional 14 patients for a total of 23. Conservatively allowing 20% drop out or loss to follow up, we plan to enroll 28 total patients.

2.53 Diagnostic Criteria

In the aforementioned publication (see 2.4) by Onda et al. concerning the feasibility of neoadjuvant chemotherapy followed by interval debulking for stage III/IV ovarian, tubal, and peritoneal cancers, the authors reported that the positive predictive value of a combination of imaging studies, cytology, and tumor markers

was 100% for tumor origin and histology, and 95% for stage of disease.[22] Furthermore, they concluded that it would be acceptable to omit diagnostic laparoscopy as a staging test in the future. Based on this data, the diagnostic criteria needed for entry into this trial include evidence of metastatic disease on imaging studies (CT, CT/PET, MRI), cytologic examination of ascites and/or pleural fluid, or fine-needle aspirate of a tumor mass.

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2.54 Choice of Cytotoxic Chemotherapy and Optimum Number Cycles

Since the mid 1980's, platinum-based chemotherapy has been the standard of care in the treatment of ovarian cancer. In GOG 47, 227 patients were randomized to either doxorubicin-cyclophosphamide versus cyclophosphamide-doxorubicin-cisplatin. Patients in the cisplatin arm had statistically significant improved progression-free and overall survival[23]. In a search for better tolerated platinum agents, carboplatin was found to be as effective, and with fewer side effects than cisplatin, including emesis, nephrotoxicity, and neurotoxicity[24-27]. In GOG 111, over 400 patients were randomized to receive cisplatin-cyclophosphamide versus cisplatin-paclitaxel. The paclitaxel arm resulted in significantly prolonged progression-free and overall survival[28]. Because of the convenience of avoiding pre- and post-chemotherapy hydration, and improved side effect profile, carboplatin was evaluated as a possible combination with paclitaxel in two randomized trials. This combination was equivalent in efficacy to cisplatin-paclitaxel, but much better tolerated[29,30]. In 2004, carboplatin-paclitaxel was identified as the standard first-line therapy for ovarian cancer by the Ovarian Cancer Consensus.

There is no prospective data on the recommended number of cytotoxic chemotherapy cycles for advanced epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. However, 6-8 cycles are generally recommended based on historical phase III clinical trials. There is no prospective data indicating that cumulative dose intensity, or number of cycles impacting overall survival.

2.55 Selected Substitution of Docetaxel for Paclitaxel

Publication of results from GOG Protocol 0111[28] and a confirmatory European trial[31] led to adoption of paclitaxel and carboplatin as the standard primary therapy for patients with advanced epithelial and peritoneal primary cancer. However, it is estimated that on the order of 5% of patients in the population eligible for participation in the current trial will develop peripheral neuropathy or refractory acute hypersensitivity infusion reactions which would necessitate discontinuation of paclitaxel. Docetaxel is a novel taxane with reduced potential for neurotoxicity compared with paclitaxel. In addition, docetaxel has been safely substituted for

paclitaxel in patients experiencing severe acute hypersensitivity to paclitaxel refractory where re-challenge is either unsuccessful or deemed unsafe.

With regard to efficacy, there is evidence that docetaxel is an alternative treatment option to paclitaxel for patients with epithelial ovarian and peritoneal primary cancer. Docetaxel has been combined with cisplatin or carboplatin extensively in phase II and III clinical trials. Docetaxel has substantial activity against platinum-refractory ovarian carcinoma[32] and is also active as primary therapy in ovarian cancer.[33,34,34,36] A phase III randomized trial (SCOTROC) of docetaxel and carboplatin versus paclitaxel and carboplatin in patients with advanced epithelial ovarian cancer has recently been published.[37] In this trial, patients received carboplatin at an AUC of 5 with either docetaxel at 75 mg/m^2 1-hour IV infusion or paclitaxel at 175 mg/m^2 3-hour IV infusion. Results of this trial demonstrated no significant difference in median progression-free survival (15.0 months versus 14.8 months), two year overall survival (64.2% versus 68.9%) or objective tumor response (58.7% versus 59.5%) for the combination of docetaxel and carboplatin versus the combination of paclitaxel and carboplatin, respectively. While docetaxel and carboplatin produced more neutropenia (Grade 3-4 neutropenia 94% for docetaxel and carboplatin versus 84% for paclitaxel and carboplatin, $p < .001$) and neutropenic complications than treatment with paclitaxel-carboplatin, the docetaxel and carboplatin regimen was significantly less neurotoxic (Grade 2 neurosensory toxicity in 11% for docetaxel and carboplatin versus 30% for paclitaxel and carboplatin, $p < .001$).

The results of the SCOTROC trial have led many oncologists to select substitution of docetaxel for paclitaxel in first line therapy for patients with advanced epithelial and peritoneal primary cancer. Thus, in order to optimize cytotoxic therapy in all arms of the current trial, reduce the likelihood of protocol violations and avoid imbalances in the type of taxane utilized in each treatment arm, in the current trial docetaxel will be selectively substituted for paclitaxel in circumstances in which peripheral neuropathy or hypersensitivity warrants discontinuation of paclitaxel.

2.56 Post-Remission Therapy

It is expected that all of the chemotherapy regimens employed in this trial will achieve an overall response rate of greater than 75%. However, as many as 90% of patients with stage III and stage IV epithelial ovarian, peritoneal primary and fallopian tube cancer in clinical complete remission will ultimately recur and die of disease. Therefore, a number of strategies are under active consideration to delay or prevent recurrence. Among these strategies include “consolidation” treatment with cytotoxic,

hormonal, or biologic targeted agents. For example, recent data have revealed that continuation of single-agent paclitaxel on a monthly schedule for 12 cycles significantly extended progression-free survival.[38] Certainly consolidation therapy has been implemented variably in clinical practice outside clinical trials with the decision based on physician and patient preference, with no evidence that overall survival is influenced by either treatment of patients in complete clinical remission or for that matter, at the time of clinical disease progression. Due to the lack of evidence that any current consolidation approach is associated with an improvement in overall survival, and our desire to preserve the integrity of the progression-free interval, consolidation therapies will not be used.

2.57 CA-125 as a Biological Marker of Progressive Disease

Serum levels of CA-125, a tumor-associated glycoprotein antigen, are elevated in 80% of patients with epithelial ovarian cancer.[39] CA-125 has been monitored, often on a frequent basis, to verify response to therapy, presence of residual disease, and as early evidence of recurrence. However, CA-125 is not entirely tumor specific, and can be elevated in a variety of benign conditions, such as endometriosis, uterine fibroids, and pelvic inflammation; this is particularly true in pre-menopausal women. In addition, levels of CA-125 can be discordant with tumor response, both as false-positive and false-negative trends. Nonetheless, because imaging modalities such as contrast computed tomography appear to be relatively insensitive in detecting disease progression, it has been standard practice for patients and physicians to interpret a progressive rise in CA-125 post-therapy as evidence of recurrent or progressive disease, and will make therapeutic decisions based solely on the CA-125. This has complicated the assessment of PFS in prior randomized trials, as patients will receive new therapy prior to clinical documentation of progressive disease on the basis of physical examination or radiographic findings. The current trial will employ a conservative formula to define progressive disease based on serial elevation of CA-125 [40] (in addition to other standard definitions in the management of solid tumors), but only following completion of initial chemotherapy. Although imperfect, it is preferable to apply uniform criteria that include CA-125 rather than absorb uncharacterized events that would compromise the secondary endpoint of PFS. Progression during the period of cytotoxic chemotherapy will require radiographic or physical confirmation.

2.6 Quality of Life (QoL)

Most women with stage III and stage IV epithelial ovarian, primary peritoneal, and fallopian tube cancer will succumb to their malignancy therefore, QoL is an important consideration in determining optimal

treatment regimen. The primary objective of measuring QoL in this trial is to determine if the use of neoadjuvant chemotherapy, followed by interval debulking reduces disease related symptoms (improves QoL). In the current trial, QoL will be assessed using the Trial Outcome Index of the Functional Assessment of Cancer Therapy-Ovary (FACT-O TOI).[41,42] 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 item). 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.

The timing of the QoL assessments is critical to capture data useful for this regimen. This is complicated by the fact that the acute affects of cytotoxic therapy may cause a decrease in QoL. In order to avoid the confounding affects 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. Thus assessments will be made:

1. Prior to cycle 1 (t=0 weeks)
2. Prior to surgery (after 3 doses of chemotherapy, t=9 weeks)
3. Prior to cycle 4 (after 3 doses of chemotherapy and at least 1 after surgery, t=10 weeks)
4. 3 weeks after completion of chemotherapy (t=19 weeks)
5. 3 months after completion of chemotherapy (t=28 weeks)

2.7 Biologic Correlates

Human and experimental epithelial cell cancers induce a vigorous innate immune response at both primary and metastatic sites. On cellular level this innate immune response is mediated by tumor associated macrophages (TAMs) and to a lesser extent platelets, mast cells, granulocytes, NK-cells, and fibroblasts. Despite the failure of this innate immune response to induce an adaptive response to the cancer and failure to eliminate the cancer, this innate response intensifies with cancer progression. Macrophages and other immune cells secrete cytokines which induce and maintain this process. At tumor sites these cytokines such as interleukin (IL-) 1,6,8, and 10, tumor necrosis factor (TNF-), α and β, TNF receptor II and tumor growth factor (TGF), and vascular endothelial growth factor (VEGF) play important roles in suppression of the adaptive immune response, induction of a pathologic tumor vasculature and interstitial fluid space, tumor neo-vascularization, progression, metastasis, and resistance to chemo- and radio-therapy. Once in the systemic circulation these cytokines contribute to

development of cachexia, weight loss, protein wasting, decreased performance status and an increase in chemotherapy toxicity. It is now clear that reactive oxygen species (ROS) and reactive nitrogen species (RNS) generated by this process are critical in the regulation and induction of the toxic effects of cytokines. By measuring ROS and RNS of tumor tissue obtained after neoadjuvant chemotherapy, we will be able to determine how measures of tumor protein damage relate to response.

In patients, the intensity of the innate response to cancers may predict for survival and poor response to therapy. Serum levels of certain cytokines such as TNF, IL-6 and the combination of CRP and serum albumin predict negatively for overall survival in some cancers (e.g. lung, colorectal), although this has not been explored in ovarian cancer.

We hypothesize that in patients with ovarian cancer, systemic biologic markers of the innate immune response (i.e cytokines and surrogates for levels of oxidative stress) will correlate with overall survival and allow for the identification of patient subsets that may benefit from anti-inflammatory interventions. Specifically we will capture TNF-a, TNF receptor II, protein oxidation, CRP, Il-6 and Il-8 at three time points and tumor tissue oxidation in operative specimens. This study will provide an exploratory evaluation of this hypothesis and determine the feasibility of assessing the hypothesis in a randomized clinical trial.

2.8 Inclusion of Women and Minorities

This trial 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 epithelial ovarian, fallopian tube, and peritoneal primary cancer population treated by participating institutions.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

3.11 Patients with biopsy proven stage IIIC/IV epithelial ovarian cancer, primary peritoneal, fallopian tube carcinoma. If a core biopsy is not possible, fine-needle aspirate showing adenocarcinoma is acceptable in the setting of a pelvic mass and presence of metastasis outside the pelvis measuring at least 2 cm, regional lymph-node metastasis or proof of stage IV disease, and ratio of CA 125 to CEA greater than 25. If CA 125 to CEA ratio is 25 or lower, barium enema, gastroscopy, and mammography must be negative.[20]

3.12 Patients must have adequate:

Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/µl, equivalent to Common Toxicity Criteria for Adverse Events v4.0(CTCAE) Grade 1. This ANC cannot have been induced or supported by granulocyte colony stimulating factors.

Platelets greater than or equal to 100,000/µl, CTCAE Grade 0-1.

Renal function: Creatinine ≤1.5 x institutional upper limit of normal (ULN), CTCAE Grade 1.

Hepatic function: Bilirubin ≤ 1.5 x ULN, CTCAE Grade 1. SGOT and alkaline phosphatase ≤ 2.5 x ULN, CTCAE Grade 1.

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

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) and a PTT <1.2 x ULN.

3.13 Patients must have a World Health Organization Performance Status ≤2.

3.14 Patients must be a candidate for surgery.

3.15 An approved informed consent must be signed by the patient.

3.2 Ineligible Patients

3.21 Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis are excluded. 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.

3.22 Patients who have received prior chemotherapy for any abdominal or pelvic tumor are excluded. 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.

3.23 Patients with a known synchronous primary endometrial cancer, or a past history of primary endometrial cancer, are excluded, unless all of the following conditions are met: Stage not greater than IA, 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).

3.24 With the exception of non-melanoma skin cancer and other specific malignancies noted above, 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 therapy are excluded.

3.25 Patients with acute hepatitis or active infection that requires parenteral antibiotics are excluded.

3.26 Patients with World Health Organization Performance Status of 3 or 4.

3.27 Patients who are pregnant or nursing.

3.28 Patients under the age of 18.

3.29 Patients with a pelvic mass of any size that is causing pain, or other subjective symptoms that are intolerable to the patient.

3.30 Patients who are not candidates for interval surgical debulking secondary to significant medical comorbidities.

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 IVEX2® 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 H2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions.

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.

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.

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

See Appendix IV

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

4.31 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.

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.

4.32 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). Protect from light.

4.33 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 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.

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.

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

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

4.4 Quality of Life Measures

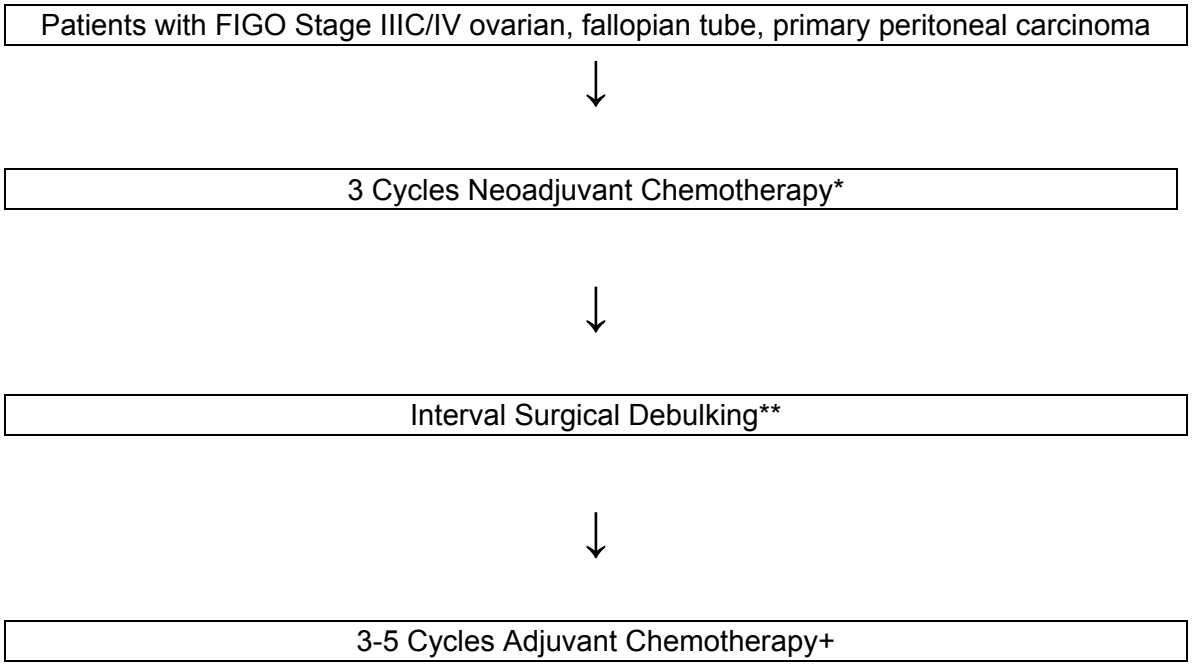
The FACT-O TOI has been selected as the multidimensional, combined generic and disease-specific QOL questionnaire for use with ovarian cancer patients. The questionnaire is a 26-item self-report measure developed specifically for cancer patients and designed to be used in a variety of settings, including clinical trials.

FACT-O TOI displays the QOL measures in the following order, recognizing the need for ease of administration and scoring: (1) FACT-G, (2) Additional Concerns: Ovarian component, (3) Additional items: stomach pain. (See Appendix II)

5.0 TREATMENT PLAN

5.1 Treatment Plan

SCHEMA



*Paclitaxel 175mg/m^2 IV over 3 hours followed by Carboplatin AUC 6 IV over 30 minutes every 21 days

**Approximately 3-4 weeks after 3rd cycle of chemotherapy

+Preferably start within 2 weeks of surgery (exceptions may be made by the Principal Investigator) with the same dosing parameters as neoadjuvant chemotherapy; adjuvant chemotherapy consists of 3-5 cycles based on discretion of treating physician with the goal that patients are treated with one cycle beyond normalization of CA 125/no radiographic or clinical evidence of disease

5.12 Methods of Chemotherapy

5.121 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).

5.122 Sequence and timing of drug administration:

- Paclitaxel will be infused over 3 hours. Due to the risk of immediate hypersensitivity reaction, paclitaxel should always be the first drug to be infused during any combination. (Note, for circumstances in which docetaxel should be substituted for paclitaxel: Docetaxel will be administered as a 1 hour IV infusion at a starting dose of 75 mg/m^2).
- Carboplatin will be administered as a 30 minute infusion, following paclitaxel (or docetaxel) administration.

5.123 Pre-Medication:

5.1231 Paclitaxel

For all courses where paclitaxel is to be administered, it is recommended that a preparative regimen be employed one hour prior to the treatment regimen on that day, to reduce the risk associated with hypersensitivity reactions to these drugs. This regimen should include a standard dose of dexamethasone (12mg IV or PO), an anti-histamine H1 (diphenhydramine 25-50 mg IVP or PO, or an equivalent dose of an alternate H1 blocker such as loratadine 10mg PO), and a standard dose of antihistamine H2 (famotidine 20mg IV or PO).

5.1232 Docetaxel

For all courses in which docetaxel should be substituted for paclitaxel: Docetaxel will be administered as a 1 hour IV infusion at a starting dose of 75 mg/m^2, it is recommended that patients be premedicated with dexamethasone 8 mg orally taken the night before, morning of, and evening after each treatment (total dose, 24 mg/wk), and an anti-histamine H1 (diphenhydramine 25-50 mg IVP or orally, or an equivalent dose of an alternate H1 blocker such as loratadine 10mg PO) one hour prior to docetaxel.

5.124 Antiemetic Regimens

It is anticipated that nausea and vomiting may be a significant side effect of each regimen. The following representative antiemetic regimens are suggested:

• Ondansetron 16 mg IV 30 minutes prior to administration of chemotherapy and dexamethasone 10 mg IV 30 minutes prior to drug administration

OR

• Granisetron 2 mg PO, 30 minutes prior to chemotherapy, with or without lorazepam 0.5 mg IV 30 minutes prior to chemotherapy.

5.125 Dosing of Carboplatin

(See Appendix IV)

5.126 Prohibited Concomitant Therapeutic Modalities

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

- Reassessment or cytoreductive surgery
- 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).

5.2 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 (time references are estimates and are acceptable plus or minus one week):

5.21 Baseline, defined as prior to cycle 1 (t = 0 weeks). This assessment allows a pretreatment baseline against which to compare later results.

5.22 Prior to interval surgical debulking, 3 weeks after 3rd cycle of platinum-based chemotherapy (t = 9 weeks)

5.23 Prior to the 4th cycle of platinum-based chemotherapy (after patient has received 3 doses of chemotherapy and is post surgery, t = 10 weeks)

5.24 3 weeks after completion of platinum-based chemotherapy (t = 19 weeks)

5.25 3 months after completion of platinum-based chemotherapy (t = 28 weeks)

5.3 Biologic correlate sample procurement

5.3.1 One serum sample (10 cc red top) and one plasma sample (5 cc purple top) will be obtained at three time points: 1) Before the first cycle of chemotherapy is administered; 2) Immediately prior to surgery after neoadjuvant therapy is completed; and 3) within 24-72 hours after surgery.

5.3.2 Tumor tissue (approximately 2 grams) will be saved at the time of surgery and snap frozen in liquid nitrogen.

5.3.3 Samples will be collected and stored by the Markey Cancer Center Biospecimen Shared Resource Facility. (See Appendix VII, Biologic Correlates Processing Instructions)

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 Individual Dose Modification Levels

All modifications are relative to the actual starting doses for the specific regimen. For application of individual dose modifications, see specific guidelines below. Allowable drug dose levels and instructions are summarized in Tables A, B, C, and D.

- General Guidelines for Hematologic Toxicity (Section 6.2)
- Hematologic Nadirs, Table A (Section 6.3)
- Dose Levels for Docetaxel, Table B (Section 6.3)
- Delayed Hematologic Recovery, Table C (Section 6.4)
- Non-Hematologic Toxicity Table D (Section 6.5)

6.2 General Guidelines for Hematologic Toxicity

6.21 Initial treatment modifications will consist of cycle delay and/or dose reduction as directed.

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

6.23 Lower Limits for ANC and Platelet Count

6.231 Cytotoxic Chemotherapy -
Courses of treatment with cytotoxic chemotherapy (carboplatin, paclitaxel, docetaxel) will not begin until the ANC is ≥ 1000 cells/mm^3 (CTCAE Grade 1) and the platelet count is ≥ 75,000/mm^3. All treatment 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.

6.24 Use of Hematopoietic Cytokines and Protective Agents

The use of hematopoietic cytokines and protective reagents are restricted as noted:

6.241 In general, patients will NOT receive prophylactic filgrastim (G-CSF), PEG-filgrastim (Neulasta), or sargramostim (GM-CSF) unless they experience treatment delays or recurrent neutropenic complications after treatment modifications as specified. In particular, hematopoietic growth factors should not be used to avoid initial chemotherapy dose modifications as stipulated in the protocol. However, patients may also receive growth factors for management of neutropenic complications in accordance with the NCCN clinical treatment guidelines and facility standard of care treatment practices (note: Neulasta may be administered on the same day as the chemotherapy if prescribed by the attending physician).

6.242 Patients will NOT receive prophylactic thrombopoietic agents unless they experience recurrent Grade 4 thrombocytopenia after treatment modifications as specified below.

6.243 Patients should not receive erythropoietin (EPO). Patients may receive iron supplements, and/or transfusions as clinically indicated for management of anemia.

6.244 Patients may NOT receive amifostine or other protective reagents.

6.25 Dose Modifications for Paclitaxel and Docetaxel

There will be no dose modifications for paclitaxel based on hematologic toxicity. Dose modifications for docetaxel (if substituted for paclitaxel according to protocol guidelines) for hematologic toxicity should be made according to parameters below in Table A, Table B and Table C.

6.3 <u>Modifications for Hematologic Toxicity (Nadirs)</u>

6.31 Initial occurrence of dose-limiting neutropenia (defined in 6.32) or dose limiting thrombocytopenia (defined in 6.33) will be handled according to Table A, using the regimen modifications in Table B.

6.32 Dose-Limiting Neutropenia (DLT-ANC) is defined by the occurrence of febrile neutropenia or prolonged Grade 4 neutropenia persisting ≥ 7 days, delay of treatment for more than 7 days because of neutropenia, ANC of 1000-1499 cells/mcl on day 1. There will be no modifications for uncomplicated Grade 4 neutropenia lasting less than 7

days. Febrile neutropenia is defined within the CTCAE as fever **with or without** clinically or microbiologically documented infection with ANC less than 1,000 /mm^3 and fever greater than or equal to 38.5°C.

6.33 Dose-limiting thrombocytopenia (DLT-PLT) is defined by any occurrence of Grade 4 thrombocytopenia (<25,000/mm^3) or bleeding associated with Grade 3 thrombocytopenia (25,000 to <50,000/mm^3), delay of treatment on day 1 of a cycle by more than 7 days because of thrombocytopenia. There will be no modifications for uncomplicated Grade 3 thrombocytopenia.

Table A: Modification Instructions for Dose-Limiting Hematologic Toxicity (In conjunction with Table B when docetaxel substituted for paclitaxel)

DLT ANC	DLT PLT	First Occurrence	Second Occurrence	Third Occurrence
Yes	**No**	Reduce carboplatin one AUC unit (and docetaxel one dose level*)	Add G-CSF and current drug doses	Discontinue Protocol-Directed Cytotoxic Therapy
Yes	**Yes**	Reduce carboplatin one AUC unit (and docetaxel one dose level*)	Add G-CSF and carboplatin one AUC unit (and docetaxel one dose level*)	Discontinue Protocol-Directed Cytotoxic Therapy
No	**Yes**	Reduce carboplatin one AUC unit (and docetaxel one dose level*)	Decrease carboplatin one AUC unit (and docetaxel one dose level*)	Discontinue Protocol-Directed Cytotoxic Therapy

* See Table B below, for patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Section 6.51.

Table B: Dose Levels for Docetaxel*

Starting Dose Level	Dose Level -1	Dose Level -2
75 mg/m^2	65 mg/m^2	55 mg/m^2

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Section 6.51.

6.4 Modifications for Delayed Hematologic Recovery:

6.41 Delay on the basis of neutropenia (Delay-ANC) is defined if the ANC is less than 1,000 cells/mm^3 (CTCAE Grade 2 or worse) within 24 hours prior to scheduled therapy, or less than 1,000 cells/ mm^3, if the patient received G-CSF during the previous cycle.

6.42 Delay on the basis of thrombocytopenia (Delay-PLT) is defined if the platelet count is less than 75,000/mm^3 within 24 hours prior to scheduled therapy.

6.43 Modifications noted below are only required for management of delays in the absence of dose reductions stipulated by nadir DLT-ANC and/or DLT-PLT (as noted above). In other words, if the patient experiences DLT-ANC and Delay-ANC, make the modifications as indicated for the nadir counts without additional modifications based on delayed recovery.

Table C. Modifications for Delayed Hematologic Recovery		
Category	**Delay (days)**	**Modification**
Delay-ANC	**1-7**	No Change
	8-21	Add G-CSF with Next Cycle
	>21	Discontinue Protocol-Directed
Delay-PLT	**1-7**	No Change
	8-21	Decrease carboplatin one AUC unit (and docetaxel one dose level*)
	>21	Discontinue Protocol-Directed Cytotoxic Therapy**

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Section 6.51.
**Applies to platinum/taxane therapy.

6.5 Adjustments for Non-Hematologic Toxicity

Table D: Modifications for Non-Hematologic Toxicity			
Drug	**Regime n -2**	**Regime n -1**	**Regimen Starting Dose**
Paclitaxel	110 mg/m^2	135 mg/m^2	175 mg/m^2
Carboplatin	4.0	5.0	6.0
Docetaxel	55 mg/m^2	65 mg/m^2	75 mg/m^2

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

6.51 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, then paclitaxel should be withheld from all subsequent chemotherapy cycles and docetaxel at the starting dose level of 75 mg/m^2 substituted for paclitaxel unless medically contraindicated.

In such cases where docetaxel has been substituted for paclitaxel, if CTCAE Grade 3 or 4 peripheral neuropathy occurs during or after the first cycle of docetaxel substitution then subsequent doses of docetaxel will be delayed for a maximum of three weeks until recovered to CTCAE Grade 2. If peripheral neuropathy fails to recover to Grade 2 by a maximum delay of three weeks from time therapy is due, then all docetaxel should be withheld from all subsequent chemotherapy cycles.

There will be no dose modifications in Carboplatin for neurotoxicity.

6.52 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).

6.53 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 and delay in subsequent therapy for a maximum of three weeks until recovered to Grade 1.

6.54 There will be no dose modifications for alopecia, nausea, constipation, or diarrhea. It is recommended that routine medical measures be employed to manage nausea, constipation, and diarrhea.

6.55 In general, the occurrence of a hypersensitivity reaction to paclitaxel, carboplatin, or docetaxel 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. 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 recurrent grade 4 hypersensitivity reaction to paclitaxel, docetaxel should be substituted for paclitaxel.

6.56 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.

7.0 STUDY PARAMETERS

	Pre-treatment Prior to initial chemo-therapy	During platinum-based neoadjuvant chemotherapy			Interval Debulking	During platinum-based Adjuvant chemotherapy					Post-treatment Every 3 months for 2 yrs, every 6 months for 3 yrs, then annually
		Cycle 1	Cycle 2	Cycle 3		Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	
History and physical	X	Prior to each cycle				Prior to each cycle					X
Toxicity Assessment	X	Prior to each cycle				Prior to each cycle					X
Urine or serum pregnancy test (if applicable)	X										
CBC/ Differential/ Platelets	X	Weekly*				Weekly*					As clinically indicated
Complete metabolic panel (including Creatinine and liver function tests), Ca/PO4/Mg	X	Prior to each cycle*				Prior to each cycle*					As clinically indicated
PT/INR, PTT	X										As clinically indicated
EKG	X										
CEA	X										
CT or MRI	X	3 weeks after cycle 3, prior to interval debulking				3 weeks after final cycle of chemotherapy					X
Chest X-Ray	X (unless CT/MRI already performed)										
Serum CA-125 Level	X	Prior to each cycle				Prior to each cycle					X
Blood for biologic study***	X				X**						
Tumor tissue for biologic study					X						
QoL Survey	X	3 weeks after cycle 3, prior to interval debulking surgery				Prior to cycle 4 and 3 weeks after final cycle of chemotherapy					At first 3 month visit

*Laboratory studies may be obtained up to three days prior to each specified time point.
**Prior to surgery and within 24 to 72 hours after surgery
***5 ml Purple top (protein bound HNE, RNS, and protein oxidation) and 10 ml red top (IL-6, IL-8, TNFα, TNF receptor II, CRP)

8.0 EVALUATION CRITERIA

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST v1.0) Committee.[43] Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

8.1 Definitions

8.11 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques (CT, MRI, x-ray) or as ≥ 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

8.12 Non-Measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

8.13 Target Lesions

All measurable lesions, up to a maximum of five lesions per organ, and 10 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

8.14 Non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these

lesions are not required but the presence or absence of each should be noted throughout follow-up.

8.2 Guidelines for Evaluation of Measurable Disease

8.21 Method of Measurement

8.211 General Aspects of Tumor Measurement

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.
Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

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 when both methods have been used to assess the anti-tumor effect of a treatment.

8.212 Specific Methods of Tumor Measurement

8.2121 Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

8.2122 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.

8.2123 Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

PET scanning information will not be evidence of disease progression or measurable disease.

PET CT Fusion studies may not meet technical requirements. Any CT used must use criteria for assessing according to RECIST.

8.2124 Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

8.2125 Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

8.2126 Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

8.2127 Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

8.3 Response Criteria

8.31 Evaluation of Target Lesions

8.311 Complete Response (CR): Disappearance of all target lesions

8.312 Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

8.313 Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

8.32 Evaluation of non-target lesions

8.321 Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level
Note: If serum CA-125 levels are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

8.322 Incomplete Response:

8.3221 Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

8.3222 Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of “non-target” lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail.

8.32221 Progression Based On Serum CA-125
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 pretreatment evaluation should be obtained within 2 weeks that such progression is documented

8.32222 Progression Based on Development or Worsening of Ascites or Pleural Effusions
Suspected progression based solely on developing or worsening ascites or pleural effusions must be verified cytologically

8.33 Evaluation of Best Overall Response

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

X Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." **Every effort should be made to document the objective progression, even after discontinuation of treatment.**

X In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (e.g., fine needle aspirate/biopsy) before confirming the complete response status.

X In rare cases when there is evidence of disease on CT, MRI or physical examination, a discrepancy may exist between trends in CA125 levels and data from either imaging or physical examination. If there is evidence of disease on CT, MRI or physical examination, such disease is shrinking, and there is no evidence of new disease, then rising CA125 levels according to Section 8.32221 would be insufficient to determine disease progression.

X Patients who are not evaluated for response will be classified as either: having no target lesions at the time of enrollment onto the study, not reassessed due to early death, or unknown (not assessable, or insufficient data),

8.4 Confirmatory Measurement/Duration of Response

8.41 Confirmation

In order for a patient to be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met

8.42 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 recurrent disease is objectively documented.

8.5 Definitions Related to Evaluation Unrelated to Objective Response

8.51 Overall Survival is the observed length of life from entry into the study to death, regardless of cause or the date of last contact.

8.52 Progression-Free Survival is the period from study entry until disease progression, death or date of last contact.

The time to progression will be determined by the clinical investigator.

The defined date of disease progression will depend on the method of determination as follows:

8.521 For disease progression defined by imaging or palpation of at least a 20% increase in the sum of the LD of target lesions, the appearance of one or more new lesions, or unequivocal progression of existing non-target lesions, the date of progression will be defined as the date such lesions were first found to be progressed by imaging or palpation.

8.522 For disease progression defined by development or worsening of ascites or pleural effusions, the date of progression will be defined as the date of cytologic verification.

8.523 For disease progression defined by CA125 criteria alone, the date of progression will be defined as the first date of the initial CA125 of greater than or equal to two times the nadir value or upper limit of normal, whichever of these is applicable. Given that imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation is required within 2 weeks of the confirmatory (second) CA125 value, if imaging criteria are met for progression, then the date of progression would be defined as the date of the imaging study.

8.53 Recurrence-Free Survival (patients with no measurable disease) is the period from study entry until disease recurrence, death or date of last contact.

8.54 Subjective Parameters including performance status, specific symptoms, and side effects are graded according to the CTCAE v4.0.

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST), v1.0.

9.0 DURATION OF STUDY

9.1 Patients will receive treatment until disease progression, the development of adverse events requiring discontinuation of protocol treatment, or completion of 8 cycles of carboplatin/paclitaxel chemotherapy, whichever comes first. The patient may voluntarily withdraw from the study at any time.

9.2 All patients will be followed for disease status and toxicity until death or voluntary withdrawal from study to a maximum of five years. 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) to a maximum of five years.

9.3 Adequate Duration of Study to Evaluate Toxicity. The minimal length of trial to evaluate toxicity is defined as receiving one course of therapy and receiving any follow-up information for evaluation of toxicity.

10.0 STUDY MONITORING AND REPORTING PROCEDURES

Informed consent must be obtained and an IRB approved consent form must be signed by the patient prior to initiating any study procedures.

All data will be reported using the University of Kentucky's Markey Cancer Center OnCore data system. Range checks on variables will be in place to reduce the amount of data entry errors.

The Lucille P. Markey Cancer Center Data Safety Monitoring Committee (DSMC) will serve as the data safety monitoring board for this study. The PI is responsible for ensuring that study data is supplied to the DSMC as requested. The PI, in accordance with cancer center policies, is responsible for data management and quality.

11.0 BIOLOGIC STUDIES

11.1 Collection and handling of specimens

One serum sample (10 cc red top SST tube) and one plasma (5 ml EDTA containing tube) sample will be obtained at three time points: 1) Before the first cycle of chemotherapy is administered; 2) Immediately prior to surgery after neoadjuvant therapy is completed; and 3) within 24-72 hours after surgery. Serum levels of cytokine (TNF, TNF receptor II, IL-6 and IL-8) and CRP will be determined and plasma levels of oxidative modified proteins will be measured and the resulting adducted proteins will be identified. Samples will be collected and stored by the Markey Cancer Center Biospecimen Shared Resource Facility.

11.2 Collection and handling of tumor specimens

Tumor tissue (approximately 2 gms) will be saved at the time of surgery and snap frozen in liquid nitrogen.

11.3 Site performing biologic studies

All laboratory testing will be performed in the laboratories of Dr. Daret St. Claire, 306 Health Sciences Research Building, and Dr. Allan Butterfield, 249 Chemistry-Physics Building, University of Kentucky.

11.4 Residual specimen will be stored long-term in the Biospecimen Shared Resource Facility.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design

This study is a single arm feasibility study of neoadjuvant chemotherapy with interval surgical debulking in patients with advanced ovarian, fallopian tube, and primary peritoneal carcinoma to determine the percentage of patients that achieve maximal surgical debulking as defined by no gross residual disease following a Simon's 2-stage design.[44] Other endpoints include overall survival, progression-free survival, surgical and toxicity outcomes, quality of life measures and exploratory biologic correlative studies.

12.2 Sample Size

The primary objective of this study is to determine the percentage of patients that achieve maximal surgical debulking with the use of neoadjuvant chemotherapy in advanced ovarian, fallopian tube, and primary peritoneal carcinomas. The selection of this primary endpoint was due to previous research that suggests complete resection of all macroscopic disease has been shown to be the most important prognostic factor in advanced ovarian carcinoma.[5,20,41,42,43] Using previous results from the larger European study of neoadjuvant chemotherapy, 51.2% of patients in the neoadjuvant arm achieved maximal surgical debulking as compared to 19.4% of patients in the primary debulking control arm.[20] Therefore, based on a hypothesis test of a single proportion with 90% power and a two-sided type I error rate equal to 0.05 the first-stage sample size necessary for this single arm study to detect the same improvement in the percentage of neoadjuvant chemotherapy patients achieving maximal surgical debulking as compared to the European controls is 9 patients. The trial will be terminated if 2 or fewer patients achieve maximal surgical debulking as defined by no gross residual disease. If the trial continues to the second stage, an additional 14 patients will be enrolled for a total of 23. Conservatively allowing 20% drop out or loss to follow up, we plan to enroll 28 total patients.

12.3 Statistical Analysis

Following study completion, the percentage of subjects achieving maximal surgical debulking will be estimated along with exact 95% binomial confidence interval. A chi-square test for one proportion will be employed to test the null hypothesis that the percentage of subjects achieving maximal surgical debulking is equal to 19.4%. Various partial response rates (i.e. proportion of patients with various sizes of residual tumor after debulking) will also be estimated along with exact 95% binomial confidence intervals. We plan to explore options to adjust results for the two-stage design. Analyses of secondary outcomes will include Kaplan-Meier mean estimates of overall and progression-free survival rates. This will be primarily descriptive in nature due to the small patient

numbers; however, these results will be compared against historical US controls as well as the larger European study[45,20].

There will also be information collected on any adverse events, surgical outcomes, biomarkers, and quality of life (QOL) surveys. Toxicities will be graded according to Common Toxicity Criteria (CTCAE) v4.0. Incidence tables will be generated to summarize incidence of patients reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawal, and incidence of serious adverse events. Descriptive statistics (means, standard deviations, medians, and ranges) will be calculated for quality of life survey outcomes collected throughout the study at baseline, 9, 10, 19, and 28 weeks. Percent change in scores from baseline to each of the weeks collected will be calculated for each patient and plots will be constructed to show trends over time for mean scores.

The requested biospecimens from 28 patients will be used for the following purposes and analysis: i) correlation between several inflammation and oxidative stress markers (measured up/down regulated) using the Kappa statistic ; ii) comparisons of biomarker status (measured up/down regulated) using McNemar's test for paired pre vs. post-treatment samples; and iii) estimating association of each marker (up versus down-regulated) with survival time using Kaplan-Meier survival curves, estimating tumor response using proportions and chi-square or Fisher's exact test for comparison of proportions between up vs. down-regulated and two-group comparisons of QOL variables measured quantitatively using either two-sample t-tests or nonparametric analogs between each level (up/down regulated) of each marker. The patient numbers will be adequate for detecting moderate/large correlations for the (i) analysis while analyses (ii) and (iii) will be primarily exploratory.

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APPENDIX I

FIGO STAGE GROUPING FOR PRIMARY CARCINOMA OF THE OVARY

(2009)

These categories are based on findings at clinical examination and/or surgical exploration. The histologic characteristics are to be considered in the staging, as are results of cytologic testing as far as effusions are concerned. It is desirable that a biopsy be performed on suspicious areas outside the pelvis.

Stage I	Growth limited to the ovaries.	
	Stage IA	Growth limited to one ovary; no ascites. No tumor on the external surface; capsule intact.
	Stage IB	Growth limited to both ovaries; no ascites. No tumor on the external surfaces; capsules intact.
	Stage IC*	Tumor either Stage IA or IB but with tumor on the surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage II	Growth involving one or both ovaries with pelvic extension.	
	Stage IIA	Extension and/or metastases to the uterus and/or tubes.
	Stage IIB	Extension to other pelvic tissues.
	Stage IIC*	Tumor either Stage IIA or IIB but with tumor on the surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage III	Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals Stage III. Tumor is limited to the true pelvis but with histologically verified malignant extensions to small bowel or omentum.	
Stage IIIA	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.	
Stage IIIB	Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Nodes negative.	
Stage IIIC	Abdominal implants >2 cm in diameter and/or positive retroperitoneal or inguinal nodes.	

Stage IV	Growth involving one or both ovaries with distant metastasis. If pleural effusion is present there must be positive cytologic test results to allot a case to Stage IV. Parenchymal liver metastasis equals Stage IV.

* In order to evaluate the impact on prognosis of the different criteria for allotting cases to Stage IC or IIC, it would be of value to know if rupture of the capsule was (1) spontaneous or (2) caused by the surgeon and if the source of malignant cells detected was (1) peritoneal washings or (2) ascites.

APPENDIX II

See attached FACT-O TOI

Subject number | Patient name (F, M ,L)

Cycle / Day | Date (DD/MM/YYYY)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the **past 7 days**.

I have a lack of energy	Not at all	A little bit	Somewhat	Quite a bit	Very much
Il have nausea	Not at all	A little bit	Somewhat	Quite a bit	Very much
Because of my physical condition, I have trouble meeting the needs of my family	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have pain	Not at all	A little bit	Somewhat	Quite a bit	Very much
I am bothered by side effects of treatment	Not at all	A little bit	Somewhat	Quite a bit	Very much
I feel ill	Not at all	A little bit	Somewhat	Quite a bit	Very much
I am forced to spend time in bed	Not at all	A little bit	Somewhat	Quite a bit	Very much
I am able to work (include work at home)	Not at all	A little bit	Somewhat	Quite a bit	Very much
My work (include work at home) is fulfilling	Not at all	A little bit	Somewhat	Quite a bit	Very much
I am able to enjoy life	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have accepted my illness	Not at all	A little bit	Somewhat	Quite a bit	Very much
I am sleeping well	Not at all	A little bit	Somewhat	Quite a bit	Very much
I am enjoying the things I usually do for fun	Not at all	A little bit	Somewhat	Quite a bit	Very much
I am content with the quality of my life right now	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have swelling in my stomach area	Not at all	A little bit	Somewhat	Quite a bit	Very much
I am losing weight	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have control of my bowels	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have been vomiting	Not at all	A little bit	Somewhat	Quite a bit	Very much
I am bothered by hair loss	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have a good appetite	Not at all	A little bit	Somewhat	Quite a bit	Very much
I like the appearance of my body	Not at all	A little bit	Somewhat	Quite a bit	Very much

Version date 26 Jan 2012

Subject number | Patient name (F, M ,L)

Cycle / Day | Date (DD/MM/YYYY)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the **past 7 days**.

I am able to get around by myself	Not at all	A little bit	Somewhat	Quite a bit	Very much
I am able to feel like a woman	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have cramps in my stomach area	Not at all	A little bit	Somewhat	Quite a bit	Very much
I am interested in sex	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have concerns about my ability to have children	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have pain in my stomach area	Not at all	A little bit	Somewhat	Quite a bit	Very much
Stomach pain interferes with my daily functioning	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have numbness or tingling in my hands	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have numbness or tingling in my feet	Not at all	A little bit	Somewhat	Quite a bit	Very much
I feel discomfort in my hands	Not at all	A little bit	Somewhat	Quite a bit	Very much
I feel discomfort in my feet	Not at all	A little bit	Somewhat	Quite a bit	Very much

Version date 26 Jan 2012

APPENDIX III

Anaphylaxis Precautions

Equipment Needed
__ Tourniquet
__ Oxygen
__ Oral and endotracheal airways and intubation equipment
__ Epinephrine 1:1000 solution for IV or endotracheal injection
__ Antihistamines
__ Corticosteroids
__ IV infusion solutions, tubing, catheters, and tape

APPENDIX IV

CARBOPLATIN DOSE CALCULATION INSTRUCTION

1) The Cockcroft-Gault formula will be used in GOG trials (not the Jelliffe formula).

2) Conversion of IDMS creatinine levels to “non-IDMS” values will not be permitted.

3) The carboplatin calculation tool on the GOG website has been updated. A legacy carboplatin calculator (using the Jelliffe formula and IDMS to “non-IDMS” conversion) is also available, if needed for dose modifications (see below).

Dosing of Carboplatin:

1) The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.

2) The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin **will not** need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

3) Carboplatin doses will be based on the subject’s weight at baseline and will remain the same throughout the study. However, the doses will be recalculated if the patient has a weight change of greater than or equal to 10% from baseline.

4) In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a **minimum value of 0.7 mg/dl**. If a patient is currently being dosed using a creatinine value less than 0.7 mg/dl, adjust dose with next planned treatment.

5) For trials where patients enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher) baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.

   CALVERT FORMULA:

   Carboplatin dose (mg) = target AUC x (GFR + 25)

   NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.

   Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

   The maximum allowed doses of carboplatin are:

   AUC6=900mg
   AUC5=750mg
   AUC4=600mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\textbf{Creatinine Clearance (mL/min)} = \frac{\textbf{[140-Age (years)] x Weight (kg) x 0.85}}{\textbf{72 x serum creatinine (mg/dl)}}$$

Notes:

1) Weight in kilograms (kg):

   a. Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: http://www.nhlbisupport.com/bmi/
   b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
   c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**.

   d. Adjusted weight calculation:

      Ideal weight (kg) = (((Height (cm)/2.54) – 60) x 2.3) + 45.5

      Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight

   e. If a patient with BMI of greater than or equal to 25 is currently being dosed using actual weight, adjust dose with next planned treatment.

2) The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).

At the time of a dose modification for toxicity:

1) If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

2) If the dose of carboplatin (mg) at the time of dose modification, is higher than the previous dose due to the use of the Cockcroft-Gault formula [when the previous dose was calculated using the Jelliffe formula and IDMS to “non-IDMS” conversion (if applicable)+, use the same method that was used to calculate the previous dose *Jelliffe formula and IDMS to “non-IDMS” conversion (if applicable)], to calculate the dose of carboplatin (mg) at the time of dose reduction. A legacy carboplatin calculator is available on the GOG website for this purpose. This will ensure that the patient is actually receiving a dose reduction.

APPENDIX V

Standards for Operative Note Details

Surgeon is responsible for indicating the extent of surgical cytoreduction in operative findings in dictated operative report. Detail must include one of the following statements regarding the extent of surgical cytoreduction:

"Maximal surgical cytoreduction"	No evidence of gross residual disease
"Optimal surgical cytoreduction"	≤ 1cm gross residual disease*
"Suboptimal surgical cytoreduction"	> 1cm gross residual disease*

*For any evidence of gross residual disease, surgeons must specify the location of residual disease and approximate amount or size of residual disease, preferably with measurements (i.e., "5 cm tumor plaque in left upper quadrant"), but alternatively with anatomical description (ie, "coating entire right hemidiaphragm" or "confluent disease throughout majority of small bowel mesentery").

APPENDIX VI

See attached Standard Chemotherapy Order Sets

UNIVERISTY OF KENTUCKY HOSPITAL
CHANDLER MEDICAL CENTER
LEXINGTON, KENTUCKY

CHEMOTHERAPY ORDERS

NOTE: Use Physician Order Sheet (H310) for all other Medication / lab orders.

Diagnosis:

Allergy:

Is Patient on a Protocol?
YES: 11-GYN-098-MCC
PI Rachel Ware Miller, MD (859 330-4331)

Regimen: Cycle # _____
Docetaxel, Carboplatin every 21 days
These orders are to be used in cases in which docetaxel is substituted for paclitaxel
(3 cycles neoadjuvant, then 3-5 cycles adjuvant)
See Oncore for protocol

Has an informed consent been obtained? ☐ YES

Record in the unit of measure Patient Height		Patient Weight		Patient's BSA	Begin Therapy (Day 1)
in	cm	lb	kg		Date: Time:

Drug (Amt/m² or Amt / kg)	Patient's Dose	Solution & Volume	Route	Infusion Rate	Give on Dates:
Docetaxel **(75mg/m²)**		NS 250 ml (NON-PVC) use non PVC tubing	IV	1 hour	**Day 1**
Carboplatin **AUC 6** SCr * GFR= (140- age) x wt (kg) x 0.85 / 72 x SCr (Cockcroft Gault)	mg Calvert formula: target AUC x (GFR +25)	NS 250 ml	IV	30 minutes	**Day 1**

PRECHEMOTHERAPY MEDICATION ORDERS (e.g., antiemetics, hydration)

1) Maximum BSA for docetaxel calculations is $2m^2$; Dose will not be recalculated unless there is a +/- 10% weight change
2) To calculate the GFR for carboplatin dosing:
   Use **actual weight if BMI<25**. Use **adjusted weight if BMI≥25**. BMI calculator can be found at http://www.nhlbisupport.com/bmi/
   Ideal weight (kg)=[(ht (inches)-60) X 2.3] + 45.5
   Adjusted weight (kg)= 0.4 (actual-ideal) + ideal
3) *In patients with SrCr <0.7mg/dl, the creatinine clearance should be estimated using a minimum value of 0.7mg/dL. In addition, the maximum allowable GFR is 125ml/min therefore the carboplatin dose cannot exceed 900mg (AUC 6), 750mg (AUC 5) or 600mg (AUC 4). Once therapy has been initiated, **DO NOT adjust subsequent doses of carboplatin**, UNLESS SrCr>1.5 ULN, patients weight changes by ≥ 10%, or toxicity as per protocol.
4) For calculation of carboplatin dose there will be no conversion of IDMS creatinine levels to "non-IDMS" values
5) Labs: Hemogram with differential, CMP, magnesium, phosphorus, CA125. Notify MD for **platelets <75,000 or ANC <1000**; SrCr >1.5 ULN; bili >3XULN; AST, alk phos or ALT >5XULN
6) Premedications :
   - 30 minutes prior to docetaxel: dexamethasone 8mg PO
   - Lorazepam 0.5mg IV x 1 prn anticipatory N/V or anxiety
   - 30mins prior to carboplatin – ondansetron 16 mg PO (or other formulary 5HT3)
7) Activate hypersensitivity kit for chemotherapy reaction and notify MD

POSTCHEMOTHERAPY MEDICATION ORDERS (e.g., antiemetics, hydration)

1) Patient should have outpatient Rx for : dexamethasone 8mg PO on PM prior to AND PM of docetaxel; ondansetron 8mg PO BID on Days 2 and 3 OR dexamethasone 8mg PO daily on Days 2 and 3 (NCCN); prochlorperazine (or promethazine) PRN N/V

Signature, Ordering Physician | Printed name, Ordering Physician | Pager #

Printed name, Attending Physician | Date Written | Time Written | Staff initial who penned order

Approved by Dr. Miller 09/10/2014 J443 (10/97)

UNIVERISTY OF KENTUCKY HOSPITAL
CHANDLER MEDICAL CENTER
LEXINGTON, KENTUCKY

CHEMOTHERAPY ORDERS

NOTE: Use Physician Order Sheet (H310) for all other Medication / lab orders.

Diagnosis:

Allergy:

Is Patient on a Protocol?
YES: 11-GYN-098-MCC
PI Rachel Ware Miller, MD(859)330-4331

Regimen: Cycle # _____
Paclitaxel, Carboplatin
every 21 days
(3 cycles neoadjuvant, then 3-5 cycles adjuvant)
See Oncore for protocol

Has an informed consent been obtained? ☐ YES

Record in the unit of measure Patient Height		Patient Weight		Patient's BSA	Begin Therapy (Day 1)
in	cm	lb	kg		Date: Time:

Drug (Amt/m² or Amt / kg)	Patient's Dose	Solution & Volume	Route	Infusion Rate	Give on Dates:
Paclitaxel **(175mg/m²)**		NS 500 ml (NON-PVC) use non PVC tubing	IV	3 hours	**Day 1**
Carboplatin **AUC 6** SCr_____* GFR= (140- age) x wt (kg) x 0.85 / 72 x SCr (Cockcroft Gault)	_____mg Calvert formula: target AUC x (GFR +25)	NS 250 ml	IV	30 minutes	**Day 1**

PRECHEMOTHERAPY MEDICATION ORDERS (e.g., antiemetics, hydration)

1) Maximum BSA for paclitaxel calculations is $2m^2$; Dose will not be recalculated unless there is a +/- 10% weight change
2) To calculate the GFR for carboplatin dosing:
   Use **actual weight if BMI<25**. Use **adjusted weight if BMI≥25**. BMI calculator can be found at http://www.nhlbisupport.com/bmi/
   Ideal weight (kg)=[(ht (inches)-60) X 2.3] + 45.5
   Adjusted weight (kg)= 0.4 (actual-ideal) + ideal
3) *In patients with SrCr <0.7mg/dl, the creatinine clearance should be estimated using a minimum value of 0.7mg/dL. In addition, the maximum allowable GFR is 125ml/min therefore the carboplatin dose cannot exceed 900mg (AUC 6), 750mg (AUC 5) or 600mg (AUC 4). Once therapy has been initiated, **DO NOT adjust subsequent doses of carboplatin**, UNLESS SrCr>1.5 ULN, patients weight changes by ≥ 10%, or toxicity as per protocol.
4) For calculation of carboplatin dose there will be no conversion of IDMS creatinine levels to "non-IDMS" values
5) Labs: Hemogram with differential, CMP, magnesium, phosphorus, CA125. Notify MD for **platelets <75,000 or ANC <1000**; SrCr >1.5 ULN; bili >3XULN; AST, alk phos or ALT >5XULN
6) Premedications :
   - 1 hour prior to paclitaxel: dexamethasone 12mg PO, famotidine 20mg PO, loratadine 10mg PO
   - Lorazepam 0.5mg IV x 1 prn anticipatory N/V or anxiety
   - 30mins prior to carboplatin – ondansetron 16 mg PO (or other formulary 5HT3)
   - Medications listed above may be given IV if patient cannot take PO. In this situation, will need to substitute diphenhydramine 25mg IV for loratadine.
7) Activate hypersensitivity kit for chemotherapy reaction and notify MD

POSTCHEMOTHERAPY MEDICATION ORDERS (e.g., antiemetics, hydration)

1) Patient should have outpatient Rx for :ondansetron 8mg PO BID on Days 2 and 3 OR dexamethasone 8mg PO daily on Days 2 and 3 (NCCN); prochlorperazine (or promethazine) PRN N/V

Signature, Ordering Physician | Printed name, Ordering Physician | Pager #

Printed name, Attending Physician | Date Written | Time Written | Staff initial who penned order

Approved by Dr. Miller 09/10/2014 J443 (10/97)

APPENDIX VII
BIOLOGICAL CORRELATIVE PROCESSING INSTRUCTIONS

A. **Pertinent Study Objective**:

Secondary Objective 1.27: To assess the correlation between biologic indicators of inflammation and oxidative stress, including TNF-α, TNF receptor II, protein oxidation, CRP, IL-6 and IL-8 and tumor tissue oxidation before and after neo-adjuvant therapy, and clinical outcomes, including overall survival, tumor response, and quality of life variables.

B. **Samples required**:

5.3.1 – One serum sample (10 cc SST tube) and one plasma sample (5 cc purple top) will be obtained at three time points:

1. Before the first cycle of chemotherapy.
2. Immediately prior to surgery after Neoadjuvant therapy is completed.
3. 24 TO 72 hours after surgery.

5.3.2 –Tumor tissue (2 gms) will be obtained at the time of surgery and snap frozen in liquid nitrogen.

C. **Sample Processing Instructions**:

Serum Sample

Samples will be collected in a 10 mL red top tube (serum separator tube) at the patient's bedside. This collection will allow for an adequate volume of serum to perform the listed laboratory correlative studies. Samples should be allowed to clot for 30 minutes before centrifugation and processing into aliquots. Samples will be centrifuged at 1000 g for 15 minutes at 4˚ C. Samples will then be aliquoted into 5 cryovials containing a minimum of 0.3 ml (300 µL) and stored in a -80 Celsius freezer to be batched and run at a later date.

Plasma

Samples will be collected in a 5 mL purple top tube at the patient's bedside and placed on ice immediately and until time of processing. This collection will allow for an adequate volume of plasma to perform the listed laboratory correlative studies. After collection at the bedside, the samples should be transported to the lab within 15 minutes for processing and separation into aliquots. Samples will be centrifuged at 3000 rpm for 10 minutes at 4˚ C. Samples will then be aliquoted into 3 cryovials containing a minimum of 0.5 ml (500 µL) and stored in a -80 Celsius freezer to be batched and run at a later date.

Tumor Tissue

A 2 gram sample of tumor tissue will be obtained at the time of surgery and snap frozen in liquid nitrogen.