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## Ⅱ. プロトコル

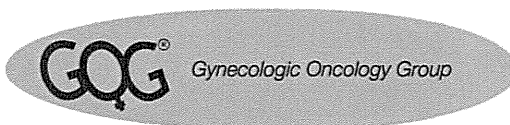
# プロトコル文書

## 英語版

Philip J. DiSaia, M.D.  
Group Chair

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

Laura L. Reese  
Executive Director of Operations



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

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

Mary C. Sharp  
Chief Financial Officer

TO: ALL PRINCIPAL INVESTIGATORS, NURSES AND DATA MANAGERS

FROM: KIA NEFF  
PROTOCOL SECTION

DATE: AUGUST 12, 2013

RE: PROTOCOL GOG-0213 – REVISION # 11

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

NCI Version July 12, 2013

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

**IRB Review Recommendation:**

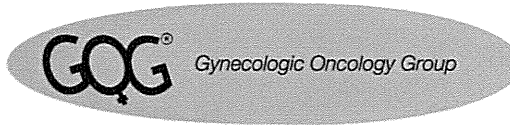
- No review required
- Expedited review; however, site IRB requirements take precedence
- Full board review recommended because there have been changes to the Informed Consent and/or the risk information

Please direct questions about the recommended level of IRB review to your local IRB. The local IRB is responsible for making this determination. If your local IRB does not agree with the GOG’s recommended level of review, please document the IRB’s decision, and the rationale for the decision, in your study files.

Philip J. DiSaia, M.D.  
Group Chair

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

Laura L. Reese  
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Group Vice Chair

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

Mary C. Sharp  
Chief Financial Officer

## SUMMARY OF CHANGES

For Protocol Revision #11 to:

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

NCI Version Date: July 12, 2013  
Protocol Date: August 19, 2013

#	Section	Page(s)	Change
1.	Title Page	1	<u>NCI version date is now July 12, 2013.</u> <u>Includes Revisions #1-11.</u> <u>Paula Rogers has replaced Maria Jung as the nurse contact.</u> <u>Revised footer has been added.</u>
3	TOC	4-6	<u>The table of contents has been renumbered and hyperlinked per NCI requirement.</u> <u>“SUGGESTED PATIENT INFORMATION/INFORMED CONSENT” has been deleted.</u>
4	App. I-V	106-129	<u>Appendices have been added to the end of the document per NCI requirement.</u>
5	IC		The NCI Version Date is now July 12, 2013.

PROTOCOL GOG-0213

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

NCI Version 07/12/13

Includes Revisions #1-11

POINTS:

PER CAPITA –14

MEMBERSHIP –6 and 6 additional if surgical candidate is randomized

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

Distribution:

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

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

STUDY CHAIR

ROBERT L. COLEMAN, MD  
UT MD ANDERSON CANCER CENTER  
DEPT OF GYN ONCOLOGY – Unit 1362  
P.O. BOX 301439  
HOUSTON, TX 77230-1439  
(713) 745-3357  
FAX: (713) 792-7586  
EMAIL: rcoleman@mdanderson.org

STUDY CO-CHAIR

NICOLA M. SPIRTOS, M.D.  
See GOG Website Directory

STUDY CO-CHAIR

DEBORAH ARMSTRONG, M.D.  
See GOG Website Directory

STUDY CO-CHAIR

THOMAS J. HERZOG, M.D.  
See GOG Website Directory

QUALITY OF LIFE CHAIR

KAREN BASEN-ENGQUIST, PhD  
See GOG Website Directory

QUALITY OF LIFE CO-CHAIR

JOHN K. CHAN, MD  
See GOG Website Directory

STUDY CO-CHAIR

PAUL SABBATINI, M.D.  
See GOG Website Directory

STATISTICIAN

MARK BRADY, Ph.D.  
See GOG Website Directory

PATHOLOGIST

RAHEELA ASHFAQ, M.D.  
See GOG Website Directory

TRANSLATIONAL RESEARCH SCIENTIST

KATHLEEN M. DARCY, PhD  
See GOG Website Directory

TRANSLATIONAL RESEARCH

CO-CHAIR

MICHAEL BIRRER, M.D., PhD  
See GOG Website Directory

NURSE CONTACT

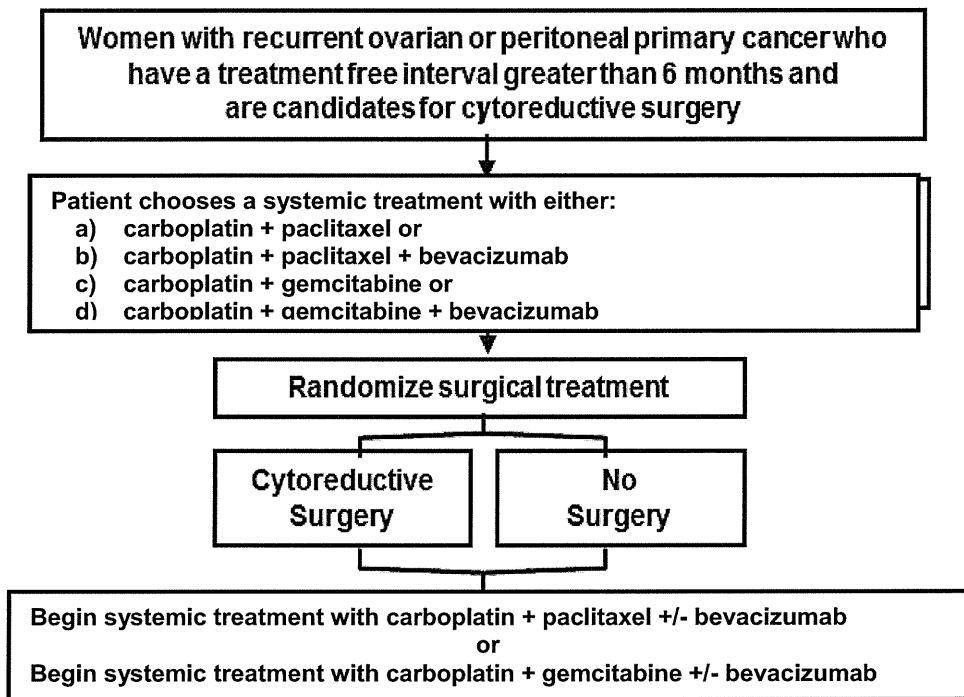
Paula Rogers, R.N.  
(713) 563-4598  
FAX: (713) 563-5592  
EMAIL: pfr Rogers@mdanderson.org

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REVISED SEPTEMBER 26, 2011; REVISED DECEMBER 19, 2011, REVISED OCTOBER 1, 2012; REVISED AUGUST 19, 2013

This protocol was designed and developed by the Gynecologic Oncology Group (GOG). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by GOG nor does GOG assume any responsibility for unauthorized use of this protocol.

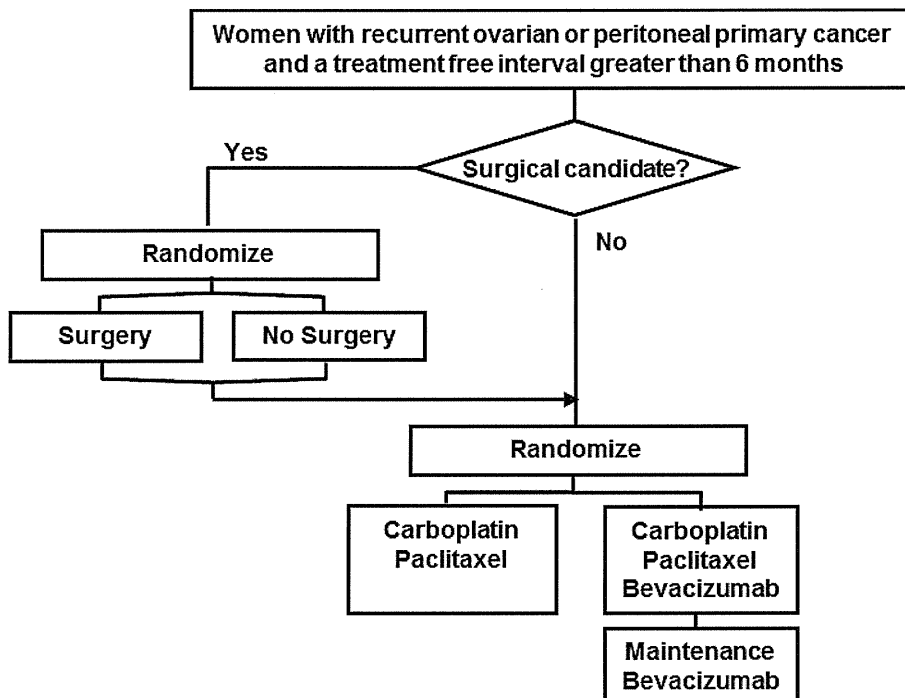


**SCHEMA beginning 8/29/2011(08/29/11)(12/19/11)(10/01/12)**



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

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



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

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

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## 1.0 OBJECTIVES

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

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

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

### 1.2 Primary Objectives:

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

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

- 1.31 To determine if the addition of bevacizumab to the second-line and maintenance phase of treatment increases the duration of progression-free survival relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.
- 1.32 To prospectively determine the incidence of carboplatin and paclitaxel hypersensitivity in these patients undergoing retreatment with both agents as first recurrence therapy.
- 1.33 To determine if surgical secondary cytoreduction in addition to adjuvant chemotherapy increases quality of life (QOL) in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer, as measured by the FACT-O trial outcome index and Rand SF-36 physical functioning scale.

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

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

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

- 1.41 Molecular and biochemical profiles can be identified that are associated with time to first disease recurrence or death.
- 1.42 Molecular determinants can be identified within patients with platinum-sensitive recurrent ovarian, peritoneal primary or Fallopian tube carcinoma which predicts for sensitivity/resistance to combination chemotherapy with or without bevacizumab followed with or without maintenance bevacizumab therapy.

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

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

- 1.51 To define molecular and biochemical profiles associated with the duration of progression-free survival in platinum-sensitive recurrent ovarian, peritoneal primary or Fallopian tube carcinoma treated with combination chemotherapy with or without bevacizumab followed with or without maintenance bevacizumab therapy in the presence or absence of secondary surgical cytoreduction.
- 1.52 To identify molecular determinants that predict sensitivity or resistance to carboplatin and paclitaxel with or without bevacizumab followed with or without maintenance bevacizumab therapy.
- 1.53 To bank DNA from whole blood for research and evaluate the association between single nucleotide polymorphisms (SNPs) and measures of clinical outcome including overall survival, progression-free survival and adverse events.**(06/22/09)**

## 2.0 BACKGROUND AND RATIONALE

### 2.1 Rationale for Selected Approach and Trial Design

Ovarian cancer remains the most lethal primary gynecologic malignancy in the United States. This year over 16,000 women will die from their disease. The principle reason for this outcome is disease recurrence and the emergence of drug resistance. Patients with recurrent disease frequently undergo multiple cycles of multiple drug regimens. Those fortunate to achieve a response to chemotherapy are however, rarely cured and find that their remission cycles are short-lived. Even if a complete response is re-achieved it is usually of a shorter duration than the first disease-free interval. Those not achieving a response to recurrence therapy live less than 2 years. While effective therapy following disease recurrence is a major unmet need, few interventions have successfully altered the natural history of recurrence. We propose to address two important interventions, surgery and combination chemotherapy with biologics, neither previously studied in a prospective randomized design, in order to determine their impact on survival.

### 2.2 Rationale for Surgery

The capacity of cytoreductive surgery to improve survival for patients with advanced, newly diagnosed epithelial ovarian cancer is generally accepted.<sup>1</sup> However, the role of tumor-reductive surgery for patients with recurrent disease continues to evolve.<sup>2</sup> Several series have demonstrated the importance of tumor reductive surgery prior to the initiation of second-line chemotherapy.<sup>1,3,4</sup> Preliminary results indicate a maximal survival benefit for patients rendered visibly disease-free prior to second-line therapy.<sup>1,4,5</sup> The frequency of reported optimal operative outcomes has ranged from 37% to 83% in small series, using various criteria for “optimal cytoreduction”.<sup>6</sup> The relative importance that differences in study cohorts, attitude, technical capability and experience have in accounting for variation of operative outcomes is unknown. In a recent series, the largest yet published, approximately 80% of the patients had complete cytoreduction.<sup>5</sup> Clinical criteria such as the median age, median disease-free interval, amount of prior chemotherapy, performance status, size of intra-abdominal disease, and locations of disease suggests patients in that series to have disease at least as advanced as other reports.<sup>1,3,4,7</sup> That investigation prospectively demonstrated that secondary cytoreductive surgery, followed by salvage chemotherapy, allows survival that is significantly improved. The 34.4 month overall median survival from the time of secondary operation and the 35.9 month overall median survival from the time of recurrence in the most recent series exceed what is typically reported in the salvage chemotherapy literature. Another noteworthy observation from this study was that the median survival after diagnosis of recurrence for patients who did not have salvage chemotherapy before secondary operation (48.4 months) dramatically exceeded the overall median survival for those who were pretreated (24.9 months).



Furthermore, an estimated 40% of the patients operated on before administration of salvage therapy survived more than five years after recurrence compared to only 15% in the pretreated group. Of note, patients whose disease responded to a recent repeat course of platinum containing agents, and patients treated with non-platinum containing agents before secondary operation, both had poor survival, that did not remotely approach the overall group who had secondary cytoreductive operations prior to salvage chemotherapy. Perhaps pretreatment with salvage chemotherapy induces drug resistance. Regardless, limiting the role of surgery to palliation of symptoms for patients who failed multiple salvage regimens and the strategy of treating with salvage chemotherapy before an attempt at secondary cytoreductive surgery may greatly diminish the chances for subsequent survival. Confirmation of this observation within the context of a multi-center randomized trial may dramatically improve the survival potential for women with recurrent epithelial ovarian cancer.

### 2.3 Rationale for Combination Chemotherapy (10/01/12)

Most patients medically suitable to undergo therapy at the time of recurrence will be offered chemotherapy. To date, a limited number of agents (i.e. etoposide, liposomal doxorubicin, topotecan, etc) have been formally approved for administration in this setting. In addition, several other agents have been studied and are documented to have clinical activity. Joining these novel agents are the taxanes and platinates commonly used as standard therapy in the front-line setting. In light of this expansion of potentially active chemotherapeutics, physicians are administering more agents, longer to more patients. Nonetheless, the degree to which this practice is benefiting patients in terms of survival is unclear.

An additional challenge lies in how to determine when to recommend which agents or combinations to patients with recurrent disease. A common determinant for many clinicians lies in reference to the patient's time in remission following front-line therapy. Those disease-free for more than six months are commonly considered to be potentially sensitive to retreatment with platinum. Response characteristics with single agent platinum in this setting produce results similar to patients treated with novel agents. Patients with longer disease-free interval are commonly treated with combination platinum and taxane therapy similar to the regimens received as primary therapy. The degree to which this philosophy of care has affected survival is unknown but data from the limited number of randomized trials would suggest the following:

- Non-platinum novel agents such as topotecan, gemcitabine, liposomal doxorubicin, and paclitaxel have similar response and survival characteristics as compared to platinum in randomized phase III trials.
- No difference in response has been observed in these novel agents among platinum sensitive or resistant patients. However, treatment with liposomal doxorubicin demonstrated a survival benefit in comparison to topotecan in the

absence of a response benefit among patients with platinum-sensitive disease.<sup>8</sup> The reasons for this are not clear but may relate to either intrinsic drug activity or to trial design (limited availability to liposomal doxorubicin in topotecan failures).

- Platinum, and platinum combinations have favorable response characteristics in platinum-sensitive patients.<sup>9,10</sup> Platinum and taxane combination therapy appears to be at least as effective as single agent platinum and data from one large phase III trial would suggest clinical superiority.<sup>11</sup> Although the randomized population in that trial was dissimilar to those commonly treated in the US, a second randomized phase II clinical trial in a more selective population essentially confirmed the observed benefit.<sup>12</sup> Further, a randomized clinical trial of gemcitabine and carboplatin demonstrated superiority in progression-free survival over carboplatin alone in platinum-sensitive patients.<sup>13</sup> Although a survival benefit was not demonstrated, the trial was underpowered to address this endpoint.
- Recently, gemcitabine, carboplatin and bevacizumab was compared to gemcitabine and carboplatin demonstrating further enhancement in progression-free survival (12.4 mos vs 8.4 mos, HR 0.48, 95% CI:0.39-0.61), response rate (79% vs 57%, p<0.0001) and duration of response (10.4 mos vs 7.4 mos, 95% CI: 0.41-0.70). Although immature at the time of reporting, there was no overall survival benefit with nearly 50% of events recorded.<sup>73</sup>

From these observations, it would appear the greatest activity and potential for survival enhancement lies in combination, platinum-based chemotherapy among those deemed potentially platinum (and taxane) sensitive. As demonstrated above, a survival benefit is also suspected in this cohort for surgery. A randomized trial is needed to evaluate the addition of surgery to combination therapy to determine their impact on survival.

### 2.31 Docetaxel

Taxanes are a class of anticancer agents that exert cytotoxic effects by their unique inhibition of microtubular assembly by stabilizing tubulin polymerbundles.<sup>14, 15</sup> Both paclitaxel and docetaxel belong to the taxane family and have demonstrated activity in tumors that are refractory to conventional chemotherapy regimens. Paclitaxel is a diterpene plant product derived from the bark of the Western yew (*Taxus brevifolia*), while docetaxel is a semisynthetic derivative of 10-deacetylbaaccatin III, a compound extracted from the needles of the European yew (*Taxus baccata*). While the relative efficacy of paclitaxel and docetaxel has not been compared clinically, docetaxel has increased activity in vitro, as well as clinical activity in paclitaxel resistant tumors.

#### **In Vitro Activity.**

The cytotoxicity of docetaxel in comparison with paclitaxel was evaluated

in several murine and human long-term cell culture lines. Docetaxel was found to be generally more cytotoxic (1.3-12-fold), a result that could be explained by its higher achievable intracellular concentration, its higher affinity for microtubules, and its slower cellular efflux.<sup>14-21</sup> Furthermore, docetaxel affects centromere organization resulting in abortive mitosis.<sup>22</sup> These cellular events may account for the greater cytotoxicity of docetaxel compared to that seen with paclitaxel. In terms of cross-resistance with other antitumor agents, there was cross-resistance to docetaxel in multidrug-resistant sublines such as P388/DOX<sub>3</sub>, CEM/VLB 1000 and Chinese hamster ovary AUXB1 line.<sup>23</sup> However, no cross-resistance to docetaxel was observed in CHO cells expressing a low level of vincristine-resistance but P-glycoprotein positive.<sup>23</sup> This means that cross-resistance to docetaxel was not definitively observed in sublines expressing the MDR phenotype.<sup>24</sup> These findings were in agreement with cell line studies showing that docetaxel was active in paclitaxel-resistant cells.<sup>16</sup> In addition, there was a lack of cross-resistance to cisplatin in certain cell lines.<sup>17,22</sup>

### **Efficacy in Murine Tumor Models**

In a murine tumor model with B16 melanoma, docetaxel demonstrated clear superiority to paclitaxel, having a 2.7 times greater log cell kill than paclitaxel.<sup>25</sup> Docetaxel at a dose of 100 mg/m<sup>2</sup> has demonstrated significant activity with response rates of 23-40% as second-line therapy in platinum resistant ovarian carcinoma.<sup>26-28</sup> More recently, its activity in paclitaxel-resistant tumors has been studied. The use of docetaxel at a dose of 100 mg/m<sup>2</sup> every 21 days in paclitaxel-resistant breast cancer has demonstrated a 17.5% response rate in 41 evaluable patients.<sup>29</sup> Additionally, the use of docetaxel at this same dose in paclitaxel-resistant ovarian cancer has recently demonstrated a 37.5% response rate in 8 evaluable patients.<sup>30</sup> The in vitro, in vivo and clinical data make docetaxel an excellent agent to evaluate after primary platinum and paclitaxel therapy. Hematologic toxicity is the dose-limiting toxicity, with neutropenic fever occurring in 8- 48% of patients.<sup>26-28</sup> Hematologic toxicity is considerably more severe with poorer hepatic function.<sup>31</sup> A comparative study of patients with or without liver dysfunction treated with docetaxel at a dose of 100 mg/m<sup>2</sup> was recently reported. Patients with impaired liver function defined as an SGOT or SGPT > 1.5 x upper limit of normal or alkaline phosphatase > 2.5 x upper limit of normal, had a higher rate of neutropenic fever 23.8% vs 12.9% (p=0.06) and toxic death 11.9% vs 1.7%, (p=0.001). For that reason strict criteria for hepatic function are required for this study.

### **Efficacy in Humans**

Several phase II and one randomized phase III trial have been conducted evaluating clinical efficacy of docetaxel in primary and recurrent ovarian cancer. Rose et al., reporting on behalf of the GOG, demonstrated a

22.4% overall response rate (5% CR and 17% PR) in 60 patients with platinum and taxane resistant recurrent disease (defined as progression on or within 6 months of completion of primary therapy). Docetaxel for this trial was administered at 100 mg/m<sup>2</sup>. Grade IV hematologic toxicity was observed in 75% of patients at this dose.<sup>32</sup> Similarly, Verschraegen et al., reported a 23% response rate and a median PFS of 3.5 months among 30 assessable patients in a slightly less resistant population. Grade IV granulocytopenia occurred in 72% of protocol patients and like the Rose trial was a reflection of higher docetaxel dosing (100 mg/m<sup>2</sup>).<sup>30</sup> Markman, evaluated docetaxel (75 mg/m<sup>2</sup>) in 30 taxane-resistant ovarian cancer patients. In this study, taxane-resistance was defined as progression on or within 3 months of paclitaxel therapy. Patients with longer intervals from paclitaxel were to be retreated with that agent – and progressed – prior to docetaxel. In this trial, 3 patients (10%) had an objective response. Hematologic toxicity was reduced (30%, Grade IV), likely a reflection of reduced dosing.<sup>33</sup>

Based on objective clinical activity in these resistant patient cohorts, a randomized clinical trial comparing taxane and platinum combination therapy in front line ovarian cancer treatment was conducted and recently reported. Vasey and colleagues reported similar PFS (15.0 vs 14.8 months, HR: 0.97 (0.83-1.13) and OS rate at 24 months (64.2% vs. 68.9%, HR: 1.13 (0.92-1.39) for the docetaxel/carboplatin combination compared with the industry standard paclitaxel/carboplatin. In this 1077 patient trial toxicity was significantly different with more hematological toxicity seen in the docetaxel combination (Grade III/IV granulocytopenia 94% vs. 84%, P < 0.001) but more severe and longer lasting sensory-motor neurotoxicity for paclitaxel/carboplatin (11% vs. 30, P < 0.001).<sup>34</sup> These trials establish clinical efficacy and safety for docetaxel and suggest possible non-cross resistance with paclitaxel. Given the lack of a clear dose response for this agent we propose to utilize 75 mg/m<sup>2</sup> to initiate the trial.

#### 2.4 Rationale for Angiogenesis Targeted Therapy

Angiogenesis is one of the cardinal processes leading to invasion and metastasis of solid tumors. The angiogenic-signaling pathway may be triggered by the release of angiogenic promoters such as vascular endothelial growth factor (VEGF) from tumor cells and normal endothelial cells into the local microenvironment. There is accumulating evidence that angiogenesis plays a central role in ovarian cancer disease progression and prognosis.<sup>35-38</sup> A strong relationship exists between the expression of angiogenesis biomarkers and the behavior of epithelial ovarian cancer, suggesting pharmacological inhibitors of angiogenesis could arrest tumor progression.<sup>39, 40</sup> Neutralizing anti-VEGF monoclonal antibodies have demonstrated therapeutic activity in a variety of pre-clinical solid tumor models.<sup>41</sup> Bevacizumab is a recombinant humanized version