significant post-operative bleeding or wound healing complications occurred in 4 of the 40 patients from the IFL/bevacizumab arm and none of the 25 patients from the IFL alone arm. Decisions on the timing of elective surgery should take into consideration the half-life of bevacizumab (average 21 days, with a range of 11-50 days).

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

Venous Thrombosis: Venous thromboembolic events reported in bevacizumab trials included lower extremity deep vein thrombosis (DVT), pulmonary embolism and rarely, mesenteric or portal vein thrombosis. In the pivotal phase 3 trial of IFL $\pm$ bevacizumab (given at 5 mg/kg q2w), the overall incidences of G3-4 venous thromboembolic events were comparable in the two arms (15.1 vs 13.6%).

Fertility and Pregnancy: Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. However,

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

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

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), or similar leukoencephalopathy syndrome: RPLS/PRES are clinical syndromes related to vasogenic edema of the white matter and have rarely been reported in association with bevacizumab therapy (<1%). Clinical presentations may include altered mental status, seizure, and cortical blindness. MRI scans are required for diagnosis: typical finding are vasogenic edema in the white matter of the posterior parietal and occipital lobes, and less frequently in the anterior distributions and the gray matter. In RPLS associated with bevacizumab mild or significant BP elevations were seen in some but not all cases. RPLS/ PRES should be in the differential diagnosis in patients presented with unexplained mental status change, visual disturbance, seizure or other CNS finding. MRI is

the key to diagnosis. This syndrome is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent irreversible tissue damage. **(06/22/09)**

Neutropenia: when combined with chemotherapy, bevacizumab increased the risk of neutropenia compared to chemotherapy alone. In a phase 3 trial with IFL +/- bevacizumab in colorectal cancer, grade 3-4 neutropenia was 21% in the bevacizumab arm + IFL vs 14% in the IFL arm (grade 4 neutropenia was 3% vs 2%). In a phase 3 trial with carboplatin and paclitaxel +/- bevacizumab in NSCLC, the bevacizumab-containing arm was associated with an increased rate of grade 4 neutropenia (27% vs 17%), febrile neutropenia (5.4% vs 1.8%), and an increased risk of infection with neutropenia (4.4% vs 2.0%) with three fatal cases in the bevacizumab + chemotherapy arm vs none in the chemotherapy control arm. **(06/22/09)**

4.38 Agent Ordering and Agent Accountability **(08/04/08)**

NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each

participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

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

4.40 Agent Inventory Records - The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record (DAR) Form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.) **(6/22/09)**

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

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

polysorbate 80.

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

4.43 Storage: Unopened vials of docetaxel are stable to the date indicated on the package when stored between 2 and 25°C (36 and 77°F). Protect from light.

4.44 Preparation: Docetaxel must be combined with its supplied diluent (final concentration = 10mg/mL) and then further diluted prior to infusion. Docetaxel should be diluted in 0.9% Sodium Chloride for Injection, USP or 5% Dextrose Injection, USP to produce a final concentration of 0.3 to 0.74mg/mL. The 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.

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

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

4.5 Gemcitabine **(10/01/12)**

4.51 Formulation: Gemcitabine is supplied as a lyophilized powder in sterile vials containing 200 mg or 1 gram of gemcitabine as the hydrochloride salt (expressed as the free base), mannitol and sodium acetate.

4.52 Gemcitabine requires dilution prior to use. The lyophilized product will be reconstituted with normal saline added to the vial in order to make a solution ideally containing 10 mg/ml or </= 40 mg/ml for 200 mg and 1 gram vials.

4.53 Storage: Unopened vials of gemcitabine are stable to the date indicated on the package when stored between 2 and 25°C (36 and 77°F). Once the drug has been reconstituted, it should be stored at controlled room temperature (range, 20 to 25°C) and used within 24 hours.

4.54 Preparation: An appropriate amount of drug will be administered as prepared or diluted with an additional 100 ml of normal saline. Once the drug has been reconstituted, it should be stored at controlled room temperature (range, 20 to 25°C) and used within 24 hours.

4.55 Administration: Gemcitabine will be infused over 1 hour

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

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

4.6 Pathology Requirements **(6/22/09)**

4.61 Eligible Patients: Patients must have histologic diagnosis of epithelial ovarian carcinoma, peritoneal primary or Fallopian tube carcinoma, which is now recurrent. Patients with the following histologic epithelial cell types are eligible: Serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma not otherwise specified (N.O.S.).

4.62 Ineligible Patients: Patients with a gynecologic malignancy other then epithelial ovarian carcinoma, peritoneal primary or Fallopian tube carcinoma.

4.63 Requirements and Instructions: Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility for the protocol. See section 7.2 and 10.2 for specific requirements and instructions for the stained pathology slides, pathology reports and forms.

## 5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

Before patient entries will be accepted, an official signed CTSU IRB Certification Form and a CTSU IRB/Regulatory Approval Transmittal Sheet (forms can be downloaded at **www.ctsu.org**) must be received by the CTSU Regulatory Office. These forms can be faxed or mailed to:

**CTSU Regulatory Office**
**Coalition of National Cancer Cooperative Groups**
**1818 Market Street, Suite 1100**
**Philadelphia, PA 19103**
**1-888-823-5923**
**FAX 215-569-0206**

### 5.1 Patient Entry and Registration

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

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

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

5.13 The Fast Fact Sheet data must be gathered.

5.14 Instructions for web-based registration and randomization can be found by going to the GOG Web Menu page, selecting "Start/finish a patient registration," and then selecting "Directions" found on the left side of the page. Assistance is available from the Statistical and Data center by phone if necessary (800-523-2917).

5.141 In order to obtain investigational drug from the Pharmaceutical Management Branch (PMB), the treating physician must have an active NCI Investigator Number. If the treating physician's investigator number is not active, the drug order will **not** be processed. To obtain or renew an NCI Investigator Number, please visit the CTEP's Investigator Registration page at http://ctep.info.nih.gov/resources/investigator2.html.

5.15 The institution will enter the patient's name, GOG number, and assigned regimen in the appropriate place in their Log Book to verify the patient's entry.

5.2 Treatment Plan **(06/22/09)**

5.21 Patients meeting eligibility requirements will be considered first for the surgical randomization aspect of the trial. Suitability for secondary cytoreduction will be made by the individual patient's Attending Physician. Guidelines for consideration in assessing candidacy for secondary cytoreduction are listed in Section 5.211. If the patient is considered to be a suitable surgical candidate she will undergo randomization as outlined in Section 5.22.

(The following two sentences do not apply to patients enrolled onto the study after August 28, 2011): If the patient is considered not to be a suitable surgical candidate she will be allowed to participate in the chemotherapy randomization aspect of the trial as outlined in Section 5.23. Patients undergoing surgical randomization will also be randomized to a chemotherapy regimen at the same time. **(08/29/11) (12/19/11)**

5.211 Guidelines for Secondary Cytoreduction: The goal of secondary cytoreduction is **COMPLETE REMOVAL OF ALL VISIBLE DISEASE**. While no specific eligibility can be globally provided, patients with recurrent disease which will not be addressed at surgery should not undergo surgical randomization. In general, women with carcinomatosis and/or ascites make poor surgical candidates as the diffusion of disease usually precludes complete cytoreduction. Similarly, women with parenchymal organ disease (e.g. lung, liver, pancreas, kidney, bone, etc) are poor candidates, if the disease is felt unresectable by preoperative evaluation. Assessment of candidacy will be made by physical exam, laboratory and imaging (MRI, PET/CT and/or CT). Although it is recognized that patients with longer treatment-free intervals may be considered better surgical candidates (providing some expansion of the preoperative tumor volume characteristics) than those with shorter treatment-free intervals, the primary tenet of surgery for this study in all women enrolled in this arm is complete surgical resection (no visible residual).

5.22 Randomization I: ***Surgery***: Patients entered onto the surgical arm of the trial will undergo abdominal exploration with cytoreduction as outlined in (Appendix II) within 4 weeks of registration. Chemotherapy will be administered following recovery up to 6 weeks after surgery. A discussion with the study chair is required if study treatment is not initiated within 6 weeks of surgery. **(6/22/09) (03/15/10)**

5.23 Randomization II: ***Chemotherapy.*** **(Between Dec 6, 2007 and August 28, 2011 the following 4 treatment arms were randomly assigned to patients enrolled into this study. Beginning August 29, 2011 all patients are required to be surgical candidates, and only the surgical component of treatment is randomized. For these later patients the systemic treatment, which consists of either paclitaxel+carboplatin (as described for arms I and III) or gemcitabine+carboplatin (as described for arms V and VII) or paclitaxel+carboplatin+bevacizumab (as described for arms II and IV) or**

**gemcitabine+carboplatin+bevacizumab (as described for arms VI and VIII) is selected and declared prior to enrolling onto the study. (08/29/11)(12/19/11) (10/01/12)**

**Patient chooses systemic treatment with either:**
**a) carboplatin + paclitaxel or gemcitabine or**
**b) carboplatin + paclitaxel or gemcitabine + bevacizumab**

5.231 Regimens: **(06/22/09) (03/15/10) (10/01/12)**

| Arm | Surgery | Chemotherapy* | Schedule | Maintenance Regimen |
|---|---|---|---|---|
| **I** | No | Paclitaxel 175 mg/m$^2$ ** Carboplatin AUC 5 | Every 21 days (Section 5.24) | None |
| **II** | No | Paclitaxel 175 mg/m$^2$ ** Bevacizumab 15 mg/kg Carboplatin AUC 5 | Every 21 days (Section 5.25) | Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment. |
| **V** | No | Gemcitabine 1000 mg/m$^2$ d1 & d8 Carboplatin AUC 4 day 1 | Every 21 days (Section 5.24) | None |
| **VI** | No | Gemcitabine 1000 mg/m$^2$ d1 & d8 Bevacizumab 15 mg/kg Carboplatin AUC 4 day 1 | Every 21 days (Section 5.25) | Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment. |
| **III** | Yes | Paclitaxel 175 mg/m$^2$ ** Carboplatin AUC 5 | Every 21 days. (Section 5.24) | None |
| **IV** | Yes | Paclitaxel 175 mg/m$^2$ ** Bevacizumab 15 mg/kg Carboplatin AUC 5 | Every 21 days (Section 5.25) | Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment. |
| **VII** | Yes | Gemcitabine 1000 mg/m$^2$ d1 & d8 Carboplatin AUC 4 day 1 | Every 21 days (Section 5.24) | None |
| **VIII** | Yes | Gemcitabine 1000 mg/m$^2$ d1 & d8 Bevacizumab 15 mg/kg Carboplatin AUC 4 day 1 | Every 21 days (Section 5.25) | Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment. |

*All chemotherapy doses on day one unless otherwise indicated. For those patients randomized to cytoreductive surgery, bevacizumab is to be started at the 2$^{nd}$ cycle of therapy.

** Note: docetaxel 75mg/m$^2$ IV over 1 hour may be substituted for paclitaxel (see Sections 5.233 and 6.161).

5.232 Patients continue to receive maintenance treatment until disease progression or until adverse events prohibit further therapy.

5.233 Sequence and timing of drug administration: **(08/04/08) (03/15/10) (08/29/11) (12/19/11) (10/01/12)**

- **Paclitaxel** will be infused over 3 hours. (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$^2$ see Sections 6.161 and 6.167).
- **Bevacizumab** administration will be as a short intravenous infusion following paclitaxel infusion. Anaphylaxis precautions should be observed during bevacizumab administration. The initial dose would be administered over 90 ± 15 minutes. If no adverse reactions (including fever and or chill) occur, the second dose should be administered over a minimum of 60 ± 10 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes.
- **Bevacizumab has been associated with an increase in wound complications and bowel perforations in post-operative patients. Thus, patients in Randomization I who undergo surgery and are to receive bevacizumab after Randomization II will have the first cycle of therapy without bevacizumab. They will receive it in cycle #2.**
- **Gemcitabine will be administered over 60 minutes on days 1 and 8 of each 21-day cycle. Patients will be monitored prior to each dose with a complete blood count, including differential counts.**
- **Carboplatin** will be administered as a 60-minute infusion. When administered in conjunction with other medications, carboplatin will be infused after the other agents. Carboplatin, either alone or in combination should be premedicated with dexamethasone (either IV or PO), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine).

5.234 Pre-Medication: **(10/01/12)**

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. This regimen should include dexamethasone (either IV or PO), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine).

When carboplatin and paclitaxel are administered with bevacizumab, it is recommended that the preparatory regimen as outlined above should be

given 30 minutes if IV or 60 minutes if PO before infusion to reduce the risk of hypersensitivity associated with these agents.

In the event of a prior bevacizumab hypersensitivity reaction the prophylactic regimen should be repeated prior to subsequent doses of bevacizumab (Section 5.2551). Thus, the patient will be premedicated prior to paclitaxel AND prior to bevacizumab.

For all courses where docetaxel is to be administered, (see Sections 6.161 and 6.167) 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 $H_1$ blocker such as loratadine or fexofenadine) one hour prior to docetaxel.

5.235 Antiemetic Regimens **(10/01/12)**
It is anticipated that nausea and vomiting may be a significant side effect of each regimen. The following representative antiemetic regimens are suggested:

- Ondansetron 8-32 mg IV 30 minutes prior to administration of chemotherapy and dexamethasone 10-20 mg IV 30 minutes prior to drug administration or,
- Granisetron 1 mg IV (or 2 mg PO) 30 minutes prior to chemotherapy plus dexamethasone 10 mg IV, with or without lorazepam 0.5 – 2.0 mg IV 30 minutes prior to chemotherapy.
- Be sure to give prescription(s) for prevention of delayed nausea/vomiting as per institutional guidelines/standards.

5.236 Dosing of Paclitaxel **(06/22/09)**

The initial dose of paclitaxel will be 175 mg/m$^2$. Alterations in this dose are presented in Section 6.1612. As such, patients whose body weight changes by 10% or more should undergo recalculation based on the adjusted body surface area.

5.237 Dosing of bevacizumab **(06/22/09) (08/29/11)**

Bevacizumab will be administered at 15 mg/kg IV. **For patients randomized to the chemotherapy arm, the** weight at screening will be used to determine the bevacizumab dose to be used for the duration of the study. For patients undergoing the second surgical procedure **the** baseline weight for calculating the bevacizumab dose should be post-op. If a patient's weight changes by ≥ 10% during the course of the study, the bevacizumab dose will be recalculated.

5.2371 Supportive Care Guidelines for Bevacizumab

If an infusion-related adverse reaction occurs, the patient should be pre-medicated prior to subsequent doses of bevacizumab (Section 5.234); however, the infusion time for bevacizumab may not be decreased for the next infusion. If a patient experiences an infusion-associated averse event with the 60-minute infusion, all subsequent doses should be given over 90 minutes ± 15 minutes.

5.238 Dosing of Carboplatin **(03/15/10) (08/23/10) (1/3/11)**

**See Appendix V for current Carboplatin dose calculation instructions**

**5.239 Dosing of Gemcitabine (10/01/12)**
**See Section 5.233**

5.24 Duration of treatment – Paclitaxel or Gemcitabine and Carboplatin (Arm I, Arm III, Arm V, and Arm VII): **(06/22/09)**

5.241 Patients with measurable disease achieving clinical complete response (negative physical exam, negative CT scan or MRI and normal CA-125) (CR; Section 8.131) during the chemotherapy phase will be treated with a minimum of 6 cycles of therapy or for 2 additional cycles following the CR designation (maximum of 8 cycles), whichever is greater.

5.242 If stable or partial regression is the maximum documented response, patients will continue their chemotherapy to a maximum of 8 cycles (see Section 8.15) or adverse effects (see Section 6.0). Patients will then be

followed off therapy until documented progression occurs. (See Section 8.14) **(08/04/08)(6/22/09)**

5.243 If progressive disease is observed while on therapy, patients will have study therapy discontinued and will be treated with appropriate alternative chemotherapy.

5.244 Patients without measurable lesions as determined by a CT scan prior to initiating study treatment will continue therapy for 6 cycles or if CA-125 normalizes for 2 cycles beyond CA-125 normalization, whichever is greater as long as: the criteria for progression (See Section 8.14); and the criteria for study termination by drug toxicity (See Section 6.0) have not been met. Patients with normal CA-125 at the start of therapy (without measurable lesions) will have chemotherapy stopped after six cycles. .

5.25 Duration of treatment – Carboplatin, Bevacizumab and Paclitaxel or Gemcitabine (Arm II Arm IV, Arm VI, and Arm VIII) **(06/22/09) (03/15/10)(10/01/12)**

5.251 Patients with measurable disease achieving clinical complete response (CR; Section 8.131) during the chemotherapy phase will be treated for a minimum of 6 cycles of therapy or for 2 additional cycles following the

CR designation (maximum of 8 cycles) and then begin the maintenance regimen. The maintenance phase will be continued until progression or adverse effects preclude additional treatment.

5.252 If stable or partial regression is the maximum documented response, patients will receive up to 8 cycles (minimum of 6 cycles) of therapy and then begin the maintenance regimen. The maintenance phase will be continued until progression or adverse effects preclude additional treatment. **(08/04/08)**

5.253 If progressive disease is observed while on therapy, patients in all arms will have study therapy discontinued and will be treated with appropriate alternative chemotherapy.

5.254 Patients without measurable lesions as determined by a CT scan prior to initiating study treatment will continue chemotherapy and the biologic agent for 6 cycles or if CA-125 normalizes for 2 cycles beyond CA-125 normalization, whichever is greater as long as: the criteria for progression (See Section 8.15); and the criteria for study termination by drug toxicity (See Section 6.0) have not been met. Patients with normal CA-125 at the start of therapy (without measurable disease) will have chemotherapy stopped after six cycles. The maintenance regimen will begin after completing chemotherapy and continue until progression or adverse effects preclude additional treatment.

5.26 Biometric considerations in dose calculation

Maximum body surface area used for dose calculations will be 2.0 $m^2$ as per GOG Chemotherapy Procedures Manual

5.3 Secondary Cytoreduction: **(06/22/09)**

The value of secondary surgical cytoreduction is being evaluated in this trial through a randomization of surgical candidates deemed appropriate by their treating physicians. Participation in the surgical randomization arm of this trial is **NOT** required for entry on this study. Patients with recurrent disease, meeting entry criteria but deemed not appropriate for surgical exploration are eligible to participate in the chemotherapy randomization. Those patients for whom their treating physicians consider appropriate for surgery will be randomized to either secondary cytoreduction or no surgery prior to a second randomization of chemotherapy. Surgical exploration should be undertaken within 28 days of registration onto this study.

5.31 Procedures and goals of secondary cytoreduction are outlined in Appendix II.

5.32 Please see Section 7.3 for a summary of the specimen requirements and laboratory testing for this protocol. In addition, please carefully review Appendix III for a detailed description of the Specimen Procedures for GOG-0213.

## 6.0 TREATMENT MODIFICATIONS

6.1 Dose Modifications:
Since chemotherapy in the recurrent setting is largely palliative, infusion without routine use of growth factor support will be attempted. Certain chemotherapy combinations have additive hematologic toxicity and other combinations are characterized by differing hematologic toxicity. Therefore, dose modification will be based on dose-limiting toxicity (DLT) for either or both neutropenia (ANC) or thrombocytopenia (PLT) and conducted as outlined in the following table below.

If a dose reduction is indicated, recalculate chemotherapy dosages using the baseline weight and serum creatinine. **(03/15/10)**

6.11 Dose-limiting neutropenia (DLT-ANC) is defined as:
- Febrile neutropenia: febrile is defined as fever ≥ 38.5°C, with or without documented infection in the presence of an ANC of 1000 cells/mm$^3$ or less
- Prolonged Grade IV ANC persisting ≥ 7 days.
- Uncomplicated Grade IV ANC, < 7 days, is NOT a DLT.

6.12 Dose-limiting thrombocytopenia (DLT-PLT) is defined as:
- Grade IV thrombocytopenia (< 25,000/mm$^3$)
- Grade III thrombocytopenia (25,000 to 50,000/ mm$^3$) complicated by bleeding, easy bruising, petechiae or requiring platelet transfusion (see Section 6.141)
- Uncomplicated Grade III thrombocytopenia is NOT a DLT

6.13 Guidelines for dose modification based on dose-limiting neutropenia and thrombocytopenia: (nadirs)

**Table A**

| DLT ANC‡ | DLT PLT§ | First Occurrence | Second Occurrence | Third Occurrence |
|---|---|---|---|---|
| Yes | No | Reduce the **REGIMEN** drug doses by one level as in Table B-1 * | Add myeloid growth factor **AND** maintain all drug doses | Off Study Treatment, Follow-up Continued |
| Yes | Yes | Reduce the **REGIMEN** drug doses by one level as in Table B-1 * | Off Study Treatment, Follow-up Continued | |
| No | Yes | Decrease one AUC unit **AND** maintain other drug doses * | Off Study Treatment, Follow-up Continued | |

‡ DLT-ANC: Neutropenic Dose-Limiting Toxicity (Section 6.11)

§ DLT-PLT: Thrombocytopenic Dose-Limiting Toxicity (Section 6.12)

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167, dose modifications can be found in Table B-2.

6.14 Adjustments for Hematologic Toxicity **(03/15/10)**

6.141 **Hemorrhage**: Patients receiving bevacizumab who develop a CTCAE V3.0 Grade 3 hemorrhage and receiving full-dose anticoagulation will be taken off study treatment. For all other patients with CTCAE V3.0

Grade 3 hemorrhage, bevacizumab should be held until ALL of the following criteria are met (continue carboplatin and paclitaxel):

- bleeding has resolved
- blood hemoglobin level is stable (serial measures with less than 10% change)
- there is no bleeding diathesis that would increase the risk of therapy
- there is no anatomical or pathologic condition that can increase the risk of hemorrhage recurrence.

Patients who experience delay of resolution according to the above criteria for greater than 3 weeks, recurrence of Grade 3 hemorrhage, or any CTCAE V3.0 Grade 4 hemorrhage will be taken off study treatment.

6.142 **Thrombosis: (03/15/10)**

Arterial Thrombosis
Patients will be taken off study treatment for ≥ CTCAE Grade 3 arterial thrombotic events (including cerebrovascular ischemia, transient ischemic attack, cardiac ischemia/infarction, peripheral or visceral arterial ischemia) or CTCAE Grade 2 arterial thrombotic events new or worsened since beginning bevacizumab therapy.

Venous Thrombosis
All therapy (carboplatin, paclitaxel, and bevacizumab) will be held for CTCAE Grade 3 or asymptomatic CTCAE Grade 4 venous thrombosis. For patients on therapeutic anticoagulation, PT INR or PTT (whichever appropriate) should be monitored closely during bevacizumab therapy. If the planned duration of full-dose anticoagulation is ≤ 3 weeks, treatment should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 3 weeks, treatment may be resumed during the period of full dose anticoagulation if ALL of the following criteria are met (otherwise the patient will be taken off study treatment):

- The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin (or other anticoagulant) or on stable dose of heparin prior to restarting treatment.
- The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels).
- The subject must not have had hemorrhagic events while on study.

- The patient is benefiting from treatment (no evidence of disease progression).

Patients with symptomatic CTCAE Grade 4, or recurrent/worsening thromboembolic events after resumption of bevacizumab, will be taken off study treatment.

6.143 **Coagulopathy**: For CTCAE V3.0 Grade 3 or 4 coagulopathy: hold all therapy (carboplatin, paclitaxel, and bevacizumab), until PT resolves to Grade 1. For patients with PT/INR > therapeutic range while on therapeutic warfarin, hold treatment until PT/INR within therapeutic range. Patients experiencing treatment delay >3 weeks because of failure to meet the above criteria will be taken off study. **(06/22/09) (03/15/10)**

**Table B-1 Regimen modifications for DLTs (6.11-613), hematologic toxicities (6.141-6.143) and delayed hematologic toxicity (6.153) (03/15/10)**

| Arm | Drug | Level –1 | Starting Dose |
|---|---|---|---|
| I and III | Paclitaxel * | 135 mg/m$^2$ | 175 mg/m$^2$ |
| | Carboplatin | AUC 4 | AUC 5 |
| II and IV | Paclitaxel * | 135 mg/m$^2$ | 175 mg/m$^2$ |
| | Bevacizumab | 15 mg/kg | 15 mg/kg |
| | Carboplatin | AUC 4 | AUC 5 |

* See Table B-2 below, for patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167.

**Table B-2 Dose Levels for Docetaxel***

| Arm | Drug | Level –1 | Starting Dose |
|---|---|---|---|
| I-IV | Docetaxel | 65 mg/m$^2$ | 75 mg/m$^2$ |

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167.

6.15 General Guidelines for **Delayed Hematologic Toxicity**

6.151 No subsequent chemotherapy cycle shall begin until the absolute neutrophil count (ANC) ≥ 1,500/mcl and platelets ≥ 100,000/mcl. No subsequent cycle of maintenance bevacizumab shall begin until the ANC is ≥ 1000/mcl and platelets are ≥ 75,000/mcl. **(03/15/10)**

6.152 Failure of the counts to recover appropriately by day 21 will require delay of the subsequent treatment until adequate count recovery.

6.153 Patients who require a delay of greater than 1 but ≤ 2 weeks for adequate count recovery (with or without growth factors) will have subsequent

treatment with a one level dose reduction. Patients who have a second delay of greater than 7 days will require the use of myeloid growth factors in all subsequent cycles. Patients who have a delay of > 2 weeks will have a one level dose reduction and the addition of myeloid growth factors in all subsequent cycles. **(03/15/10)**

6.154 Patients who require a delay of greater than 3 weeks for adequate count recovery (with or without growth factors) will be removed from study treatment, but follow-up will continue.

6.155 There will be no dose modification on the basis of uncomplicated WBC or ANC nadirs.

6.156 Patients will NOT receive prophylactic thrombopoietic agents on this study.

6.1561 Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia.

6.1562 Patients may not receive amifostine or other protective reagents, unless indicated in the study design.

6.16 Adjustments for Non-hematologic Toxicity

Individual agents may be associated with specific non-hematological toxicity which warrants dose modification. Allowable dosing modifications are presented in the following table:

**Table C Regimen modifications for non-hematologic toxicities (see dose adjustments per toxicity type as outlined below**

| Agent | -2 Level | -1 Level | Starting Dose Level |
|---|---|---|---|
| Carboplatin | Off study treatment | AUC 4 | AUC 5 |
| Paclitaxel | 110 mg/m$^2$ | 135 mg/m$^2$ | 175 mg/m$^2$ |
| Bevacizumab | Off study treatment | 15 mg/kg | 15 mg/kg |
| Docetaxel * | 55 mg/m$^2$ | 65 mg/m$^2$ | 75 mg/m$^2$ |

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167.

6.161 **Neurologic toxicity:** Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level in paclitaxel and delay in subsequent therapy (all agents) for a maximum of 3 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. For patients with persistent Grade 2 neurotoxicity, substitute docetaxel, unless medically contraindicated, according to Section 5.233. **(03/15/10)** Patients with persistent Grade 3-4 neurotoxicity should be removed from study.

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 the patient is removed from study. **(08/23/10)**

6.162 **Gastrointestinal toxicity:** There will be no dose modifications for nausea, diarrhea, or constipation. It is recommended that routine medical measures be employed to manage nausea and constipation.

6.163 **Renal toxicity:** If renal function worsens on therapy, an investigation for underlying causes should be undertaken. Calculated or measured creatinine clearance under 40 ml/min or significant worsening of the renal function (50% reduction in calculated CrCl) requires withholding treatment until a cause is identified or renal function improves. In particular, disease progression should be ruled out. In these patients creatinine clearance should be evaluated weekly. If calculated or measured CrCl is less than 40 ml/min after a two-week delay, the Study Chair must be notified. No treatment is to be given to a patient with a calculated or measured CrCl less than 40 ml/min.

6.164 **Proteinuria: (06/22/09)** Patients receiving bevacizumab should be monitored by urine analysis for urine protein: creatinine (UPC) ratio prior to every other dose of bevacizumab.

UPC ratio ≤ 3.5 (CTCAE, v3.0 Grade 0-2) Continue bevacizumab.
UPC ratio > 3.5 hold bevacizumab until UPC ratio recovers to ≤3.5. If bevacizumab is held for > 3 weeks, the patient is removed from study.
Grade 4 or nephrotic syndrome: Patient is removed from study.
*** Please note chemotherapy may be administered if bevacizumab is held for Grade 3 proteinuria.**

6.165 **Hepatic toxicity:** Hepatic toxicity is not expected as a direct complication of chemotherapy in this population using the prescribed dose and schedule for each regimen. However, the development of grade 3 (or greater) elevations in SGOT (AST), alkaline phosphatase or bilirubin requires reduction of one dose level in all study drugs with the exception of carboplatin and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1. If therapy is held for > 3 weeks the patient is removed from study.

6.166 There will be no dose modifications for alopecia.

6.167 **Hypersensitivity reaction to paclitaxel or bevacizumab:** The occurrence of a hypersensitivity reaction to paclitaxel or bevacizumab is **not** considered a dose-limiting toxicity. Patients may be retreated at full doses after administration of medication (such as decadron 20 mg IV and diphenhydramine 50 mg IV 30 minutes prior to reinfusion) to prevent hypersensitivity reaction and may utilize a slow initial infusion rate of the suspected agent which is gradually increased to the standard infusion rate in the absence of reaction (such as 1 cc of the original IV solution diluted in 100 ml over 10 minutes, then 5 cc in 100 ml over 10 minutes then 10 cc in 100 ml over 10 minutes and finally, the original solution at the original speed). However, if despite these safety measures repeat attempt at infusion of the inciting drug results in a recurrent hypersensitivity reaction, the inciting drug should be discontinued for the remainder of the study. In the event of any CTCAE Grade 3 or 4 allergic or infusional reactions to bevacizumab, the patient is removed from study. In the event of recurrent hypersensitivity reaction to paclitaxel, docetaxel should be substituted for paclitaxel, according to guidelines in Sections 5.233 and 6.161.

**Hypersensitivity reaction to carboplatin**: The occurrence of a hypersensitivity reaction to carboplatin may occur in this previously treated population. Successful retreatment has been reported with a modified dilution and infusion schedule.[45, 46] A suggested desensitization protocol that may be used in patients with a carboplatin hypersensitivity is reduced infusion dose of 1:1000 dilution (0.1cc in 100 ml) over 1 hour, followed by a 1:100 dilution (1.0 cc in 100 ml) over 1 hour, followed by a 1:10 dilution (10 cc in 100 ml) over 1 hour, followed by 1:1 concentration for the remaining infusion. Patients experiencing a significant hypersensitivity reaction to carboplatin may be removed at the discretion of the treating physician if it is felt to be unsafe to offer a desensitization program. **(08/29/11)**

6.168 **Hypertension**: Patients receiving bevacizumab should be monitored prior to each dose with measurement of blood pressure. Medication classes used for management of patients with Grade 3 hypertension receiving bevacizumab included ACE inhibitors, Beta blockers, diuretics, and calcium channel blockers.

- For controlled hypertension, defined as systolic $\leq$ 150 mm Hg and diastolic $\leq$ 90 mmHg, continue therapy;

- For uncontrolled hypertension (systolic > 150 mm Hg or diastolic > 90) or symptomatic hypertension less than CTCAE V3.0 Grade 4, hold all therapy (carboplatin, paclitaxel, and bevacizumab) for one week with anti-hypertensive therapy initiated or continued. **(03/15/10)**

- If hypertension is controlled and symptomatic hypertension has resolved by three weeks after holding treatment, continue all therapy.

- If hypertension remains uncontrolled or symptomatic hypertension, less than CTCAE V3.0 Grade 4, persists after three weeks after holding treatment, the patient is removed from study.

- Any patient developing CTCAE V3.0 Grade 4 hypertension will be removed from study.

6.169 **Wound disruption**: Patients will be removed from study in the event of a wound disruption requiring medical or surgical intervention.

6.1610 **Bowel perforation/obstruction/fistula/GI leak**: For new development of bowel perforation, bowel obstruction (partial or complete), fistula, or GI leak (any grade); the patient will be taken off study treatment.

6.1611 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.

6.1612 **Weight loss:** If a patient's weight changes by ≥ 10% during the course of the study, the doses of paclitaxel (or docetaxel) and bevacizumab will be recalculated. For patients undergoing the second surgical procedure the baseline weight for calculating the carboplatin and bevacizumab should be the patient's postoperative weight. **(08/04/08)**

6.1613 **RPLS (Reversible Posterior Leukoencephalopathy Syndrome) or PRES (Posterior Reversible Encephalopathy Syndrome):** Hold bevacizumab in patients with symptoms/ signs suggestion of RPLS/ PRES; subsequent management should include MRI scans and control of HTN. Discontinue bevacizumab upon diagnosis of RPLS/ PRES unless the patient meets the criteria below. **(03/15/10)**

Note: **(06/22/09)**

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

6.17 No dose-escalations are allowed on this study.

## 6.18 Dose modifications for Gemcitabine/carboplatin (Arms V, VI, VII, VIII) (10/01/12)

### 6.181 Carboplatin and Gemcitabine (Day1)

Carboplatin and gemcitabine dosing on Day 1 of each cycle should be held if ANC is <1500/μL, Hgb is <8.5 g/dL, or platelets are <100,000/μL within 24 hours of the scheduled treatment. The chemotherapy can be delayed for a maximum of 3 weeks until these values are achieved. Patients who fail to recover adequate counts (with or without growth factors) within the 3 weeks will no longer receive protocol- defined chemotherapy but will enter into the maintenance phase to receive the study drug (bevacizumab or observation) alone. Study drug can be held for up to 3 weeks if carboplatin and gemcitabine are held in order to allow for same-day administration of carboplatin and gemcitabine and study drug (if chosen).

Dose adjustment for gemcitabine in combination with carboplatin for subsequent cycles is based on toxicity observed during the preceding cycle. The dose of gemcitabine should be permanently reduced to the 800 mg/m$^2$ on Days 1 and 8, in case of any of the following hematologic toxicities:

- Absolute granulocyte count <500 x 10$^6$/L for more than 5 days
- Absolute granulocyte count <100 x 10$^6$/L for more than 3 days
- Febrile neutropenia
- Platelets <25,000 x 10$^6$/L
- Cycle delay of more than one week due to toxicity If any of the above toxicities recur after the initial dose reduction for the subsequent cycles, gemcitabine should be given only on day 1 at 800 mg/m$^2$ (omit gemcitabine on Day 8).

### 6.182 Gemcitabine Dose Modification within a Treatment Cycle (Day 8)

Gemcitabine dosage adjustments for hematologic toxicity within a cycle of treatment is based on the granulocyte and platelet counts taken on Day 8 of therapy, as shown in the Table.

**TABLE: Day 8, Gemcitabine Dose Modification for Hematological Toxicity**

| Absolute granulocyte count (/mm$^3$) | | Platelet count (/mm$^3$) | Gemcitabine Dose |
|---|---|---|---|

| | | | |
|---|---|---|---|
| ≥ 1500 | and | ≥100,000 | 100% D1 dose |
| 1000–1499 | and/or | 75,000–99,999 | 50% D1 dose |
| <1000 | and/or | <75,000 | Omit D8 dose |

If a patient experiences an HSR, platinum desensitization may be allowed after discussion with the Study Chair. For any other dose modifications for non-hematologic toxicity, please follow institutional practice and prescribing information (also outlined in Section 6.16). In general, for severe (Grade 3 or 4) non-hematological toxicities, except nausea/vomiting, therapy with gemcitabine should be held or decreased by 50% depending on the judgment of the treating physician. Patients who require discontinuation of either carboplatin or gemcitabine due to toxicity should continue receiving study drug with the non-discontinued chemotherapy to complete 6 cycles (7–10 cycles if deemed necessary by the investigator and approved by the Study Chair). Patients requiring discontinuation of both carboplatin and gemcitabine prior to disease progression should continue single-agent study drug until disease progression or unacceptable toxicity, as determined by the investigator.