

**GOG 0252: A Phase III Clinical Trial of Bevacizumab With IV Versus IP Chemotherapy in Ovarian, Fallopian Tube, and Primary Peritoneal Carcinoma: NCI-Supplied Agent: Bevacizumab (NSC #704865, IND #7921)**

*Fast Facts*

**Provided Drug: Bevacizumab**

**Eligible Patients**

1. Patients with a histologic diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, Stage II, III, or IV with either optimal ( $\leq 1$  cm residual disease) or suboptimal residual disease. In the event of a higher priority Phase III GOG protocol becoming available for suboptimal and/or Stage IV patients, the eligibility of this study will narrow and exclude those patients at those participating institutions. All patients must have a procedure for determining diagnosis of epithelial ovarian, fallopian tube, primary peritoneal, with appropriate tissue for histologic evaluation. The minimum surgery required is an abdominal surgery providing tissue for histologic evaluation and establishing and documenting the primary site and stage, as well as a maximal effort at tumor debulking. If additional surgery was performed, it should have been in accordance with appropriate surgery for ovarian or peritoneal carcinoma described in the GOG Surgical Procedures Manual (<https://www.gog.fccc.edu/manuals/pdf/surgman.pdf>). However, the surgeon is not required to have performed all of the items contained in this section of the GOG Surgical Procedures Manual
2. 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.). However, the histologic features of the tumor must be compatible with a primary Müllerian epithelial adenocarcinoma. If doubt exists, it is recommended that the investigator should have the slides reviewed by an independent pathologist or, if necessary, the Pathology Co-Chair, prior to entry. Patients may have co-existing endometrial cancer so long as the primary origin of invasive tumor is ovarian or peritoneal (See Section 3.26 for clarification of synchronous primary endometrial cancer). **Of note: patients with mucinous, low grade and clear cell disease are eligible unless there is a higher priority GOG trial open.**
3. Patients must have adequate:
  - a. Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/mcl, equivalent to Common Terminology Criteria for Adverse Events v3.0 (CTCAE) Grade 1. This ANC cannot have been induced or supported by granulocyte colony stimulating factors.
  - b. Platelets greater than or equal to 100,000/mcl.
  - c. Creatinine no greater than institutional upper normal limits of normal.
  - d. Hepatic function:
    - i. Bilirubin less than or equal to 1.5 x ULN (CTCAE Grade 1).
    - ii. ALT, AST and alkaline phosphatase less than or equal to 2.5 x ULN (CTCAE Grade 1).
  - e. Neurologic function: Neuropathy (sensory and motor) less than or equal to CTCAE Grade 1.
  - f. Blood coagulation parameters: PT such that international normalized ratio (INR) is  $\leq 1.5$  x ULN (or an in-range INR, usually between 2 and 3, if a patient is on a stable dose of therapeutic warfarin) and a PTT  $< 1.5$  times the upper limit of normal (heparin, lovenox or alternative anticoagulants are acceptable). This corresponds to CTCAE version 3.0 grade 1 one or less.
4. Patients with a GOG Performance Status of 0, 1, or 2.
5. Patients must be entered and treated within 12 weeks of their most recent surgery performed for the combined purpose of diagnosis, staging and/or cytoreduction. The first cycle of chemotherapy should not be given until at least seven days after the most recent major surgery, which allows 4 weeks to have elapsed prior to the first bevacizumab dose. (Placement of venous or peritoneal access devices will be considered minor surgery.)
6. Patients who have met the pre-entry requirements specified in Section 7.0.

7. An approved informed consent and authorization permitting release of personal health information must be signed by the patient or guardian.
8. Patients in this trial may receive ovarian estrogen +/- progestin replacement therapy as indicated at the lowest effective dose(s) for control of menopausal symptoms at any time, **but high dose progestin as an appetite stimulant should be avoided due to excess thrombophlebitis risk.**

### **Ineligible Patients**

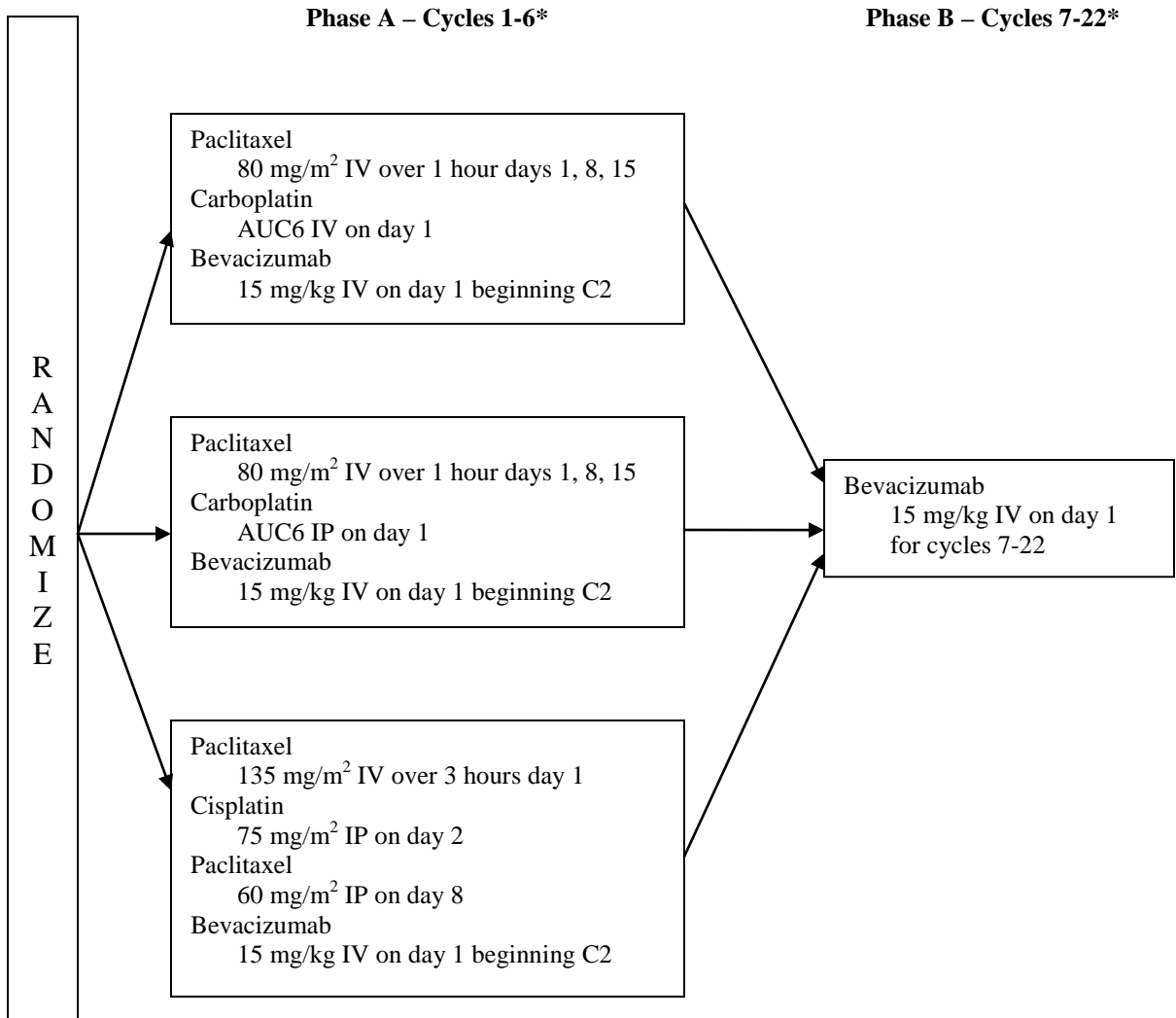
1. Patients with a current diagnosis of borderline epithelial ovarian tumor (formerly “tumors of low malignant potential”) or recurrent invasive epithelial ovarian cancer treated with surgery only (such as those with stage Ia or Ib low Grade lesions) are not eligible. Patients with a prior diagnosis of a borderline tumor that was surgically resected and who subsequently develop an unrelated, new invasive epithelial ovarian or peritoneal primary cancer are eligible, provided that they have not received prior chemotherapy for any ovarian tumor.
2. Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer and other specific malignancies as noted below, are excluded if there is any evidence of the other malignancy being present within the last five years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.
3. 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.
4. Patients who have received prior chemotherapy for any abdominal or pelvic tumor including neo-adjuvant chemotherapy for their ovarian or primary peritoneal cancer 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.
5. Patients who have received any **targeted therapy (including but not limited to vaccines, antibodies, tyrosine kinase inhibitors) or hormonal therapy** for management of their epithelial ovarian or peritoneal primary cancer.
6. Patients with 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 I-B; 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.
7. Patients with acute hepatitis or active infection that requires parenteral antibiotics.
8. Patients with serious non-healing wound, ulcer, or bone fracture. This includes history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 28 days. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly wound examinations (see Section 7.1).
9. Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving major vessels.
10. Patients with history or evidence upon physical examination of major CNS disease (for example: primary brain tumor, metastatic cancer to the brain, seizures not controlled with standard medical therapy, any brain metastases, or history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage within six months of the first date of treatment on this study.)
11. Patients with clinically significant cardiovascular disease. This includes:
  - a. Uncontrolled hypertension, defined as systolic > 150 mm Hg or diastolic > 90 mm Hg.
  - b. Myocardial infarction or unstable angina < 6 months prior to registration.
  - c. New York Heart Association (NYHA) Grade II or greater congestive heart failure (Appendix II).
  - d. Serious cardiac arrhythmia requiring medication. This does not include asymptomatic atrial fibrillation with controlled ventricular rate, or past history of supraventricular tachycardia controlled with medications and that is asymptomatic.
  - e. CTCAE Grade 2 or greater peripheral vascular disease (at least brief (< 24 hrs) episodes of ischemia managed non-surgically and without permanent deficit).

12. Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies. Patients with known allergy to cremophor or polysorbate 80.
13. Patients with clinically significant proteinuria. Urine protein should be screened by urine protein-creatinine ratio (UPCR). The UPCR has been found to correlate directly with the amount of protein excreted in a 24 hour urine collection. Specifically, a UPCR of 1.0 is equivalent to 1.0 gram of protein in a 24 hour urine collection. Obtain at least 4 ml of a random urine sample in a sterile container does not have to be a 24-hour urine). Send sample to lab with request for urine protein and creatinine levels [separate requests]. The lab will measure protein concentration (mg/dL) and creatinine concentration (mg/dL). The UPCR is derived as follows: protein concentration (mg/dL)/creatinine (mg/dL). Patients must have a UPCR < 1.0 to allow participation in the study.
14. Patients with or with anticipation of invasive procedures as defined below:
  - a. Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to the first date of bevacizumab therapy (cycle 2).
  - b. Major surgical procedure anticipated during the course of the study. This includes, but is not limited to abdominal surgery (laparotomy or laparoscopy) prior to disease progression as defined in section 8.3, such as colostomy or enterostomy reversal, interval or secondary cytoreductive surgery, or second look surgery. Please consult with the Study Chair prior to patient entry for any questions related to the classification of surgical procedures.
  - c. Core biopsy, within 7 days prior to the first date of bevacizumab therapy (cycle 2).
15. Patients with GOG Performance Grade of 3 or 4.
16. Patients who are pregnant or nursing. To date, no fetal studies in animals or humans have been performed. The possibility of harm to a fetus is likely. Bevacizumab specifically inhibits VEGF, which is responsible for formation of new blood vessels during development, and antibodies can cross the placenta. Therefore, bevacizumab should not be administered to pregnant women. Subjects will be apprised of the large potential risk to a developing fetus. It is not known whether bevacizumab is excreted in human milk. Because many drugs are excreted in human milk, bevacizumab should not be administered to nursing women. Patients of childbearing potential must agree to use contraceptive measures during study therapy and for at least six months after completion of bevacizumab therapy.
17. Patients under the age of 18.
18. Patients who have received prior therapy with any anti-VEGF drug, including bevacizumab.
19. Patients with clinical symptoms or signs of gastrointestinal obstruction **and** who require parenteral hydration and/or nutrition
20. Patients with medical history or conditions not otherwise previously specified which in the opinion of the investigator should exclude participation in this study. Examples of this would be hearing loss or neuropathy which would prevent cisplatin, paclitaxel administration. The investigator should feel free to consult the Study Chair or Study Co-Chairs for uncertainty in this regard.
21. Patients with metastatic tumor in the parenchyma of the liver or lungs with proximity to large vessels which could make the patient as high risk of lethal hemorrhage during treatment with bevacizumab (i.e. hemoptysis, liver rupture).

#### **Pre-Study Parameters**

1. History and physical including pelvic exam, blood pressure, toxicity assessment,
2. CBC with differential and platelets, serum creatine, bilirubin, ALT, AST, Alk Phos, calcium, PO<sub>4</sub>, magnesium, serum CA-125, PT/INR, PTT, UPC ratio, serum pregnancy test for women of child-bearing potential.
3. Radiographic disease assessment - CT or MRI of at least abdomen and pelvis, Chest x-ray (if CT chest not done)
4. EKG
5. Audiogram – for patients with history of hearing loss

**Treatment**



\*Continue regimen every 3 weeks for six cycles of chemotherapy and a total of 22 cycles including bevacizumab unless toxicity or progression intervenes.