Original Protocol—Section 3, Outlining Inclusion and Exclusion Criteria.

Phase II Study of Bevacizumab and Pemetrexed for Recurrent Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer
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3.0 PATIENT ELIGIBILITY

3.1 Eligibility Criteria

3.1.1 Recurrent epithelial ovarian or primary peritoneal carcinoma. Histologic confirmation of the primary tumor is required. Patients with borderline tumors are not eligible.

3.1.2 Patients must have measurable disease. Measurable disease is defined as at least one lesion that can be accurately measured in one dimension (longest dimension to be recorded). Each lesion must by $\geq$ 20 mm when measured by conventional imaging techniques, including plain radiography, computed tomography and MRI or $\geq$ 10 mm when measured by spiral CT.

3.1.3 Patients must have at least one “target lesion” to assess response by RECIST criteria. Lesions within a previously irradiated field will be considered “non-target” lesions.

3.1.4 Patients must have a GOG performance status of 0 or 1.

3.1.5 Patients must have the ability to interrupt non-steroidal anti-inflammatory (NSAID) treatment 2 days before (5 days for long-acting NSAIDs), the day of, and 2 days following administration of pemetrexed.

3.1.6 Patients must have the ability to take folic acid, vitamin B12 and dexamethasone as described per protocol.

3.1.7 Recovery from effects of recent surgery, radiotherapy or chemotherapy.

3.1.71 Patients should be free of active infection requiring antibiotics.

3.1.72 Any hormonal therapy directed at the tumor must be discontinued at least one week prior to registration. Continuation of hormone replacement therapy (HRT) is permitted.

3.1.73 Any other prior therapy directed at the malignant tumor, including immunologic agents and cytotoxic agents, must be discontinued at least three weeks prior to registration.

3.1.8 Prior therapy.

3.1.81 Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin, or another organoplatinum compound. This initial treatment may have included high-dose therapy, consolidation, or extended therapy administered after surgical or non-surgical assessment.

3.1.82 Patients must have had one prior regimen containing a taxane compound. Patient may have received first-line treatment either intravenously or intraperitoneally.

3.1.83 Patients must NOT have received prior therapy with pemetrexed or bevacizumab.

3.1.84 Patients may have received a total of $\leq$ 2 prior cytotoxic chemotherapy regimens (adjuvant therapy plus one additional regimen). Consolidation or extended therapy as part of first line treatment will be considered as a single regimen.

3.1.85 There is no minimum platinum-free interval required for study.

3.1.9 Patients must have adequate:

3.1.91 Bone marrow function: absolute neutrophil count (ANC) greater than or equal to 1,500/ul, equivalent to Common Toxicity Criteria (CTC) grade 1; Platelets greater than or equal to 100,000/ul.

3.1.92 Creatinine clearance must $\geq$ 45 ml/min.

3.1.93 Hepatic function: bilirubin less than or equal to 1.5 x ULN. AST and alkaline phosphatase less than or equal to 2.5 x ULN.

3.1.94 Neurologic function: neuropathy (sensory and motor) less than or equal to CTC grade 1.

3.1.95 Coagulation: prothrombin time (PT) such that the international normalized ratio (INR) is $\leq$ 1.5 (INR may be between 2 and 3 if a patient is on stable dose of therapeutic warfarin) and a PTT < 1.2 times control.

3.1.10 Patients must have signed informed consent.

3.1.11 Patients must meet pre-entry requirements.

3.1.12 Patients of childbearing potential must have a negative serum pregnancy test prior to study entry, be practicing an effective form of contraception, and cannot be lactating.

3.1.13 Patients may have received prior radiotherapy (to less than 25% of bone marrow), but must start at a Level 1 dose reduction.

3.2 Ineligibility Criteria

3.2.1 Patients with serious, non-healing wound, ulcer or bone fracture.

3.2.2 Patients with clinically significant cardiovascular disease:

3.2.21 Inadequately controlled hypertension (defined as systolic blood pressure > 150 and/or diastolic blood pressure > 100 mmHg on antihypertensive medications)

3.2.22 Any prior history of hypertensive crisis or hypertensive encephalopathy.

3.2.23 Unstable angina within 6 months prior to study enrollment.

3.2.24 New York Heart Association (NYHA) grade II or greater congestive heart failure.

3.2.25 Serious cardiac arrhythmia requiring medication.

3.2.26 Grade II or greater peripheral vascular disease. Patients with claudication within 6 months.

3.2.27 History of myocardial infarction within 6 months.

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

3.2.4 Patients with the presence of ascites or other third space fluid which cannot be controlled by drainage.

3.2.5 Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to day 1 of study or anticipation of need for major surgical procedure during the course of the study.

3.2.6 Patients with history or evidence upon physical examination of central nervous system disease, including primary brain tumor, brain metastases, seizure not controlled with standard medical therapy, history of cerebrovascular accident (CVA, stroke), or transient ischemic attack (TIA) or subarachnoid hemorrhage within 6 months of the first date of treatment on this study.

3.2.7 Minor surgical procedures, other than central venous access placement, such as fine needle aspiration or core biopsy within 7 days prior to day 1 of study.

3.2.8 Patients with proteinuria. At baseline patients will undergo a urine protein-creatinine ratio (UPCR) (Appendix IV). Patients with a UPCR $\geq$ 1.0 at screening should be excluded. Urine dipstick for proteinuria may also be used. Urine dipstick for proteinuria ≥ 2+ (patients discovered to have ≥2+ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible).

3.2.9 Patients whose circumstances do not permit completion of the study or the required follow-up.

3.2.10 Patients who are pregnant or nursing.

3.2.11 Patients under the age of 18.

3.2.12 Patients with other invasive malignancies, with the exception of non-melanoma skin cancer, who had (or have) any evidence of other cancer within the last 5 years or whose previous cancer treatment contraindicates this protocol.

3.2.13 Prior therapy with anti-angiogenic agents or pemetrexed.

3.2.14 Patients with active infection requiring parenteral antibiotics.

3.2.15 History of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months.

3.2.16 Partial or complete small or large bowel obstruction demonstrated radiographically within 3 months prior to study.

3.2.17 Current, recent (within 4 weeks of the first infusion of this study), or planned participation in an experimental drug study other than a Genentech-sponsored bevacizumab cancer study.

3.2.18 Known hypersensitivity to any component of bevacizumab.

3.2.19 Inability to comply with study and/or follow-up procedures.

3.2.20 Life expectancy of less than 12 weeks.