Epithelial Ovarian & Primary Peritoneal Carcinomas

**Title:** A Phase II Evaluation of Intraperitoneal EGEN-001 (IL-12 Plasmid Formulated with PEG-PEI-Cholesterol Lipopolymer) in the Treatment of Persistent or Recurrent Epithelial Ovarian, Fallopian tube or Primary Peritoneal Cancer. (GOG 0170Q)

**Purpose:** To find out if the investigational drug, EGEN-001, works in treating Persistent or Recurrent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer, and to find out what side effects are caused by treatment with this drug.

** Eligibility:** Patients 18 years of age or older who have recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. Histologic documentation of the original primary tumor is required via the pathology report. All patients must have measurable disease as defined by RECIST 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be > 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or > 20 mm when measured by chest x-ray. Lymph nodes must be > 15 mm in short axis when measured by CT or MRI. Patients must have evidence of intra-abdominal/pelvic disease; patients with disease exclusively located outside of the abdominal/pelvic cavity are not eligible.

- Patient must have at least one “target lesion” to be used to assess response on this protocol as defined by RECIST 1.1 (Section 8.1). Tumors within a previously irradiated field will be designated as “non-target” lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy. Patients must not be eligible for a higher priority GOG protocol, if one exists. In general, this would refer to any active GOG Phase III protocol for the same patient population. Patients who have received one prior regimen must have a GOG Performance Status of 0, 1, or 2. Patients who have received two prior regimens must have a GOG Performance Status of 0 or 1. Recovery from effects of recent surgery, radiotherapy, or chemotherapy:

  - Patients should be free of active infection requiring antibiotics (with the exception of uncomplicated UTI). Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to registration. Continuation of hormone replacement therapy is permitted. Any other prior therapy directed at the malignant tumor, including immunologic agents, must be discontinued at least three weeks prior to registration. Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin, or another organ platinum compound. This initial treatment may have included intraperitoneal therapy, consolidation, non-cytotoxic agents or extended therapy administered after surgical or non-surgical assessment.

  - Patients are allowed to receive, but are not required to receive, one additional cytotoxic regimen for management of recurrent or persistent disease according to the following definition: Cytotoxic regimens include any agent that targets the genetic and/or mitotic apparatus of dividing cells, resulting in dose-limiting toxicity to the bone marrow and/or gastrointestinal mucosa. Note: Patients on this non-cytotoxic study are allowed to receive additional cytotoxic chemotherapy for management of recurrent or persistent disease, as defined above. However, due to the novel nature of biologic compounds, patients are encouraged to enroll on second-line non-cytotoxic studies prior to receiving additional cytotoxic therapy. Patients who have received only one prior cytotoxic regimen (platinum based regimen for management of primary disease), must have a platinum-free interval of less than 12 months, or have progressed during platinum-based therapy, or have persistent disease after a platinum-based therapy. Patients must NOT have received any non-cytotoxic therapy for management of recurrent or persistent disease. Patients are allowed to receive, but are not required to receive, biologic (non- cytotoxic) therapy as part of their primary treatment regimen. Patients must have adequate:

  - Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/mcl. Platelets greater than or equal to
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Phase: II

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Approved Enrollment Number: 15

Current Enrollment: 0

Epithelial Ovarian & Primary Peritoneal Carcinomas

Title: GOG-0186J: A Randomized Phase IIB Evaluation of Weekly Paclitaxel (NSC #673089) Plus Pazopanib (NSC #737754) Versus Weekly Paclitaxel Plus Placebo in the Treatment of Persistent or Recurrent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Carcinoma.

Purpose: To compare the effectiveness of the combination of the drugs paclitaxel and pazopanib to the combination of paclitaxel and placebo (sugar pill) in treating cancer and to determine the types and severity of side effects caused by treatment with these drug combinations.

Eligibility: -Patients must have recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal carcinoma. Histologic documentation of the original primary tumor is required via the pathology report.
-Patients must have measurable disease or non-measurable (detectable) disease:
- Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded).
- Each lesion must be greater than or equal to 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or greater than or equal to 20 mm when measured by chest x-ray. Lymph nodes must be greater than or equal to 15 mm in short axis when measured by CT or MRI.
- Non-measurable (detectable) disease in a patient is defined in this protocol as one who does not have measurable disease but has at least one of the following conditions:
Ascites and/or pleural effusion attributed to tumor;
- Solid and/or cystic abnormalities on radiographic imaging that do not meet RECIST 1.1 (see Section 8.1) definitions for target lesions.

-Patients with measurable disease must have at least one “target lesion” to be used to assess response on this protocol as defined by RECIST 1.1 (Section 8.1). Tumors within a previously irradiated field will be designated as “non-target” lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

-Patients must not be eligible for a higher priority GOG protocol, if one exists. In general, this would refer to any active GOG phase III or Rare Tumor protocol for the same patient population. In addition, patients must not be eligible for the currently active phase II cytotoxic protocol in platinum resistant disease.

-Patients who have received one prior regimen must have a GOG Performance Status of 0, 1, or 2. Patients who have received two or three prior regimens must have a GOG Performance Status of 0 or 1.

-Recovery from effects of recent surgery, radiotherapy, or chemotherapy:
Patients should be free of active infection requiring antibiotics (with the exception of uncomplicated UTI).
Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to registration. Any other prior therapy directed at the malignant tumor, including chemotherapy, biological/targeted (non-cytotoxic) agents and immunologic agents, must be discontinued at least three weeks prior to registration. Chimeric or human or humanized monoclonal antibodies (including bevacizumab) or VEGF receptor fusion proteins (including VEGF TRAP/aflibercept) must be discontinued for at least 12 weeks prior to registration.

At least 4 weeks must have elapsed since the patient underwent any major surgery (e.g., major: laparotomy, laparoscopy, thoracotomy, video assisted thoracoscopic surgery (VATS). There is no restriction on minor procedures (e.g., minor: central venous access catheter placement, ureteral stent placement or exchange, paracentesis, thoracentesis).

-Prior therapy
- Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin, or another organ platinum compound. This initial treatment may have included intraperitoneal chemotherapy, consolidation, biologic/targeted (non-cytotoxic) agents (e.g., bevacizumab) or extended therapy administered after surgical or non-surgical assessment. If patients were treated with paclitaxel for their primary disease, this can have been given weekly or every 3 weeks. Patients are allowed to receive, but are not required to receive, two additional cytotoxic regimens for management of recurrent or persistent disease, with no more than 1 non-platinum, non-taxane regimen. Treatment with weekly paclitaxel for recurrent or persistent disease is NOT allowed.
Patients are allowed to receive, but are not required to receive, biologic/targeted (non-cytotoxic) therapy as part of their primary treatment regimen.

Patients must have NOT received any biologic/targeted (non-cytotoxic) therapy targeting the VEGF and/or PDGF pathways for management of recurrent or persistent disease.

For the purposes of this study, Poly (ADP-ribose) polymerase (PARP) inhibitors will be considered “cytotoxic”. Patients are allowed to
receive, but are not required to receive, PARP inhibitors for management of primary or recurrent/persistent disease (either alone or in combination with cytotoxic chemotherapy). PARP inhibitors will NOT count as a prior regimen when given alone.

Patients must have adequate:

-Bone marrow function:
  • Absolute neutrophil count (ANC) greater than or equal to 1,500/mcl.
  • Platelets greater than or equal to 100,000/mcl.
  • Hemoglobin greater than or equal to 9 g/dL.
-Blood coagulation parameters: PT such that international normalized ratio (INR) is less than or equal to 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 less than or equal to 1.5 x ULN.
-Renal function: Creatinine less than or equal to 1.5 x institutional upper limit normal (ULN).
-Urine Protein: Urine protein should be screened by urinalysis. If protein is 2+ or higher, 24-hour urine protein should be obtained and the level must be <1000 mg (<1.0 g/24hrs) for patient enrollment.
-Hepatic function:
  • Bilirubin less than or equal to 1.5 x ULN.
  • AST and ALT less than or equal to 2.5 x ULN and alkaline phosphatase less than or equal to 2.5 x ULN.
  • Subjects who have BOTH bilirubin greater than ULN and AST/ALT greater than ULN are not eligible
-Thyroid function: Patients must have normal baseline thyroid function tests (TSH, T3, T4). A history of hypothyroidism and/or hyperthyroidism is allowed, as long as the patient has stable well controlled thyroid function for a minimum of 2 months.
-Neurologic function: Neuropathy (sensory and motor) less than or equal to grade 1.
-Patients of childbearing potential must have a negative pregnancy test prior to the study entry and be practicing an effective form of contraception. Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects.
-Patients must have signed an approved informed consent and authorization permitting the release of personal health information.
-Patients must meet pre-entry requirements as specified in section 7.0.
-Patients must be greater than or equal to 18 years of age.
-Patients must be capable of taking and absorbing oral medications. A --Patient must be clear of the following: any lesion, whether induced by tumor, radiation or other conditions, which makes it difficult to swallow tablets
  • prior surgical procedures affecting absorption including, but not limited to major resection of stomach or small bowel
  • active peptic ulcer disease
  • malabsorption syndrome
-Any concomitant medications that are associated with a risk of QTc prolongation and/or Torsades de Pointes should be discontinued or replaced with drugs that do not carry these risks, if possible. Patients who must take medication with a risk of possible risk of Torsades de Pointes should be watched carefully for symptoms of QTc prolongation, such as syncope. See Appendix III for a list of concomitant medications associated with QTc.
-Patients with personal or family history of congenital long QTc syndrome are NOT eligible.
-CYP3A4 Inhibitors: Strong inhibitors of CYP3A4 are prohibited. Grapefruit juice is an inhibitor of CYP450 and should not be taken with pazopanib. CYP3A4 Inducers: Strong inducers of CYP3A4 are prohibited. CYP Substrates: Concomitant use of agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. See Section 4.211. Additional information for drug interactions with cytochrome P450 isoenzymes may be found at http://medicine.iupui.edu/flockhart/

Ineligibility Criteria

- Patient who have had previous treatment with pazopanib. Patients who have had previous treatment with weekly paclitaxel for recurrent or persistent disease.
- Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer and other specific malignancies as noted in Section 3.23 and 3.24, are excluded if there is any evidence of other malignancy being present within the last three years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.
- Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis within the last three years 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.
- Patients who have received prior chemotherapy for any abdominal or pelvic tumor OTHER THAN for the treatment of ovarian, fallopian tube, or primary peritoneal cancer within the last three years 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 the patient remains free of recurrent or metastatic disease.
- Patients with clinically significant cardiovascular disease. This includes:
  Uncontrolled hypertension, defined as systolic greater than 140 mm Hg or diastolic greater than 90 mm Hg despite antihypertensive medications.
  Congenital long QT syndrome or baseline QTc greater than 480 milliseconds.
  Myocardial infarction or unstable angina within 6 months prior to registration.
  New York Heart Association (NYHA) Class II or greater congestive heart failure. (see Appendix I)
  History of serious ventricular arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation) or serious cardiac arrhythmia requiring medication. This does not include asymptomatic atrial fibrillation with controlled ventricular rate.
  Patients who have received prior treatment with an anthracycline (including doxorubicin and/or liposomal doxorubicin) must have an echocardiogram assessment and are excluded if they have an ejection fraction less than 50%.
  CTCAE Grade 2 or greater peripheral vascular disease (at least brief less than 24 hrs) episodes of ischemia managed non-surgically and without permanent deficit).
  History of cardiac angioplasty or stenting within 6 months prior to registration. History of coronary artery bypass graft surgery within 6 months prior to registration.
  Arterial thrombosis within 6 months prior to registration.
- 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 prior to the first date of study treatment.
- Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving major vessels.
Patients with history or evidence upon physical examination of CNS disease, including primary brain tumor, seizures which are not controlled with nonenzyme inducing anticonvulsants, any brain metastases, or history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage within six months prior to the first date of study treatment.

- History of allergic reactions attributed to compounds of similar chemical or biologic composition to pazopanib.
- Known HIV-positive subjects on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with pazopanib.
- Patients with any condition that may increase the risk of gastrointestinal bleeding or gastrointestinal perforation, including:
  - active peptic ulcer disease
  - known gastrointestinal intraluminal metastatic lesions (gastrointestinal serosa metastatic lesions are permitted)

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