Ovarian cancer remains the deadliest gynecologic malignancy. In 2007, an estimated 22,430 patients will be diagnosed in the United States while an estimated 15,280 women will die from this disease. While many patients have significant responses to up-front surgery and chemotherapy, up to 85% of advanced stage patients recur and eventually succumb to this disease. There is a need for new and better treatments for women with ovarian cancer.

Recent advances in our understanding of molecular biology have paved the way toward the development of biologic therapies. One such advance is the identification of vascular endothelial growth factor (VEGF), a potent enhancer of angiogenesis, the formation of new blood vessels, which is critical to cancer invasion and metastasis. The discovery of VEGF led to the investigation of agents that could inhibit this factor and halt cancer growth. Through this investigation, bevacizumab (Avastin) and sunitinib (Sutent), an antibody and inhibitor of VEGF respectively, were developed. Bevacizumab is now approved for use in colon cancer and continues to be studied extensively in other cancers, including ovarian cancer (see protocols GOG 218 and CC 07702 highlighted on page 2). Sunitinib is currently undergoing study in a variety of solid tumors, including gynecologic malignancies here at the University of Wisconsin Paul P. Carbone Comprehensive Cancer Center (see protocol GOG 231-C).

One of our translational research laboratories has recently begun to study the role of biologics in cancer prevention and treatment, including Notch 1 in ovarian cancer. Notch 1 is a transmembrane protein that has been found to act as an oncogene in pancreatic cancer, certain subsets of human acute lymphoblastic T cell lymphoma, and Kaposi’s sarcoma. Notch 1 is cleaved by the enzyme y-secretase into its active, intracellular domain. Active Notch 1 is then translocated into the nucleus of a cell where it promotes growth (Figure 1). Studies in pancreatic cancer and Kaposi’s sarcoma have found that inhibiting the enzymatic action of y-secretase cannot only decrease the levels of active Notch 1, but also inhibit tumor cell growth.

Preliminary work in our laboratory has found that Notch 1 is expressed at a high level in ovarian cancer cells. In addition, we have found that treatment with a y-secretase inhibitor can reduce levels of active Notch 1 in these cells. Additional work is underway to determine if Notch 1 inhibition can reduce the growth of ovarian cancer cells. We hope that by further investigating the Notch 1 pathway in ovarian cancer, we may discover new therapeutic targets that may lead to improved outcomes and quality of life for women who suffer from this disease.

**Our Featured Protocols**

**GOG 218: A Phase III Trial of Carboplatin and Paclitaxel Plus Placebo Versus Carboplatin and Paclitaxel Plus Concurrent Bevacizumab In Women with Newly Diagnosed, Previously Untreated, Advanced Stage Epithelial Ovarian and Peritoneal Cancer**

Following initial diagnosis, staging, and surgical cytoreduction, the current standard of care for women with advanced epithelial ovarian and peritoneal cancer is adjuvant chemotherapy with a platinum and taxane combination. While recent advancements have identified a population of women who benefit from intraperitoneal chemotherapy administration, most women with advanced disease suffer recurrence. Although overall five-year survival has increased from 30-45% for all stages of ovarian cancer, five-year survival of women with advanced disease is still only 30%. There is an obvious need for improvement of primary therapies for ovarian cancer.

Bevacizumab (Avastin®) is a monoclonal antibody to VEGF that has been advanced into clinical development for the treatment of solid tumors via inhibition of angiogenesis (see description of VEGF and angiogenesis in previous article). Evidence from phase II and III trials has revealed bevacizumab to not only have anti-tumor activity as a single agent, but to enhance the activity of traditional cytotoxic regimens. The interim analysis of a phase II trial of bevacizumab as a single agent revealed significant improvements in overall survival, progression-free survival and response rate over standard chemotherapy plus placebo.

Currently the University of Wisconsin Paul P. Carbone Comprehensive Cancer Center currently has two clinical trials utilizing bevacizumab in ovarian cancer.

As a full member of the Gynecologic Oncology Group (GOG), we are actively enrolling patients on GOG 218, a phase III, double-blinded trial that randomizes women with newly diagnosed, previously untreated, stage III and IV ovarian or primary peritoneal cancer to one of three arms:

- Carboplatin and paclitaxel plus placebo, followed by 48 weeks of extended placebo
- Six cycles of carboplatin and paclitaxel plus bevacizumab, followed by 48 weeks of extended placebo
- Six cycles of carboplatin and paclitaxel plus bevacizumab, followed by 48 weeks of extended bevacizumab

This trial seeks to answer the question of whether the addition of bevacizumab to standard of care chemotherapy will improve overall survival. In addition, it also asks the question of whether extended maintenance bevacizumab will prolong survival and progression-free interval.

CO 07702 is a phase II protocol for platinum-sensitive recurrent ovarian, primary peritoneal or fallopian tube carcinoma that randomizes women to two arms:

- Carboplatin and gemcitabine plus placebo, followed by placebo until disease progression
- Carboplatin and gemcitabine plus bevacizumab, followed by bevacizumab until disease progression

At disease progression the assigned treatment is unblended to aid providers and patient with further treatment decisions. This study examines the efficacy, safety and toxicity of bevacizumab use in conjunction with carboplatin and gemcitabine.

**GOG 07702: A Phase II Randomized, Blinded, Placebo-controlled Trial of Carboplatin and Gemcitabine plus Bevacizumab in Patients with Platinum-Sensitive Recurrent Ovary, Primary Peritoneal, or Fallopian Tube Carcinoma**

Up to 200 patients will be enrolled on this trial over a period of 18 months at multiple sites across the country. These two protocols underscore our commitment to improving the outcomes of patients with ovarian cancer by investigating new biologic therapies. Within our group we have physicians working both at the laboratory bench as well as the bedside in order to aid in the development of new targeted therapies for women suffering from this disease.

**Protocol Eligibility**

**GOG 218**

- Stage III or IV ovarian or primary peritoneal cancer.
- Patients must be entered between 1 and 12 weeks after initial surgery performed for the combined purpose of diagnosis, staging and cytoreduction.
- Patients with measurable and non-measurable disease are eligible.
- Patients must not have a serious non-healing wound.
- GOG Performance Status 0-2

**CO 07702**

- First recurrence of ovarian, primary peritoneal or fallopian tube carcinoma
- No prior therapy for recurrence
- Must have platinum-sensitive disease, defined as recurrence greater than six months after completion of a platinum-based regimen.
- Must have measurable disease.
- Select eligibility requirements
Our Current Protocols

### Ovarian

**GOG 212** A Randomized Phase III Trial of Maintenance Chemotherapy Comparing Single Agent Paclitaxel or Kyotaxel Versus No Treatment Until Documented Relapse in Women with Advanced Ovarian or Primary Peritoneal Cancer

**GOG 218** A Phase III Trial of Carboplatin and Paclitaxel Plus Placebo Versus Carboplatin and Paclitaxel Plus Concurrent Bevacizumab in Women with Newly Diagnosed, Previously Untreated, Advanced Stage Epithelial Ovarian and Peritoneal Cancer

**CO 07702** A Phase II Randomized, Blinded, Placebo-controlled Trial of Carboplatin and Gemcitabine plus Bevacizumab in Patients with Platinum-Sensitive Recurrent Ovarian, Primary Peritoneal, or Fallopian Tube Carcinoma

### Uterine

**CC 06701** Sentinel Lymph Node Mapping in Early-Stage Endometrial Cancer: Sonohysterographic Injection and Cytologic Analysis of Distention

**GOG 130-E** A Phase II Evaluation of Gemcitabine and Docetaxel in the Treatment of Recurrent or Persistent Carcinosarcoma of the Uterus

**GOG 299** A Randomized Phase III Trial of Doxorubicin/Cisplatin/Paclitaxel and G-CSF versus Carboplatin/Paclitaxel in Patients with Stage III & IV or Recurrent Endometrial Cancer

**GOG 238-B** A Phase II Evaluation of Thalidomide in the Treatment of Recurrent or Persistent Carcinosarcoma of the Uterus

**GOG 231-C** A Phase II Evaluation of Sunitinib Malate in the Treatment of Recurrent of Persistent Leiomyosarcoma of the Uterus

**GOG 232-B** A Phase II Evaluation of Paclitaxel and Carboplatin in the Treatment of Advanced, Persistent or Recurrent Uterine Carcinosarcoma

### Cervical

**CO 02702** Preservation of Ovarian Function via Laproscopic Ovarian Transposition in Patients with Locally Advanced Squamous Cell Carcinoma of the Cervix

**GOG 127-V** A Phase II Evaluation of ABI-007 in the Treatment of Persistent or Recurrent Carcinoma of the Cervix

**GOG 206** Lymphatic Mapping and Sentinel Node Identification in Patients with Stage IB1 Cervical Carcinoma

**GOG 9918** A Phase I Trial of Tailored Radiation Therapy with Concomitant Cetuximab and Cisplatin in the Treatment of Patients with Cervical Cancer

**RTOG 0418** A Phase II Study of Intensity Modulated Radiation Therapy (IMRT) to the Pelvis +/- Chemotherapy for Post-operative Patients with Cervical Carcinoma

### Vulvar

**GOG 173** Intraoperative Lymphatic Mapping and Sentinel Node Identification in Patients with Squamous Cell Carcinoma of the Vulva

### Multiple Sites

**CO 04702** A Phase I Dose-escalation Study of EMO 373066 Administered with Low-Dose Cyclophosphamide to Subjects with Epithelial Cell Adhesion Molecule (EpCAM) Positive Advanced Cancers

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For more information about these clinical trials at the UW Carbone Cancer Center, contact Cancer Connect, (800) 622-8922 or (608) 262-5223 in the Madison area.

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**UW Gynecologic Oncology Research Staff:**
- Sarah L. Stewart, Research Program Manager
- Angela M. Marchant, Clinical Research Associate
- Katy A. Mijal, Clinical Research Associate

A complete listing of all clinical trials at the UW Carbone Cancer Center is also available on our website, www.cancer.wisc.edu.
NEW TEAM MEMBER

Did You Know?

- Our patient Beverly Gehrke, 18 year survivor of Stage III ovarian cancer, recently competed in the Madison Ironman competition.
- The UW Department of OB-GYN was recently approved for a Gynecologic Oncology Fellowship. Currently there are fewer than 40 institutions in the United States training future gynecologic oncologists.
- UWCCC offers integrative medicine consultation and services specifically designed for the unique needs of cancer patients.
- UWCCC offers integrative medicine consultation and services specifically designed for the unique needs of cancer patients.
- Save the date for Discover You!, a community program benefiting the UW Gynecologic Oncology program on February 23, 2008, at the Monona Terrace. Sponsored by the Paul P. Carbone Comprehensive Cancer Center.

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Together We Can Save Lives
Learn More About UW Gynecologic Oncology

Inside This Issue

- Biologic Therapies in Ovarian Cancer by Stephen L. Rose, MD
- Featured Protocols
  - GOG 218: A Phase III Trial of Carboplatin and Paclitaxel Plus Placebo Versus Carboplatin and Paclitaxel Plus Concurrent Bevacizumab In Women with Newly Diagnosed, Previously Untreated, Advanced Stage Epithelial Ovarian and Peritoneal Cancer
  - CO 07702: A Phase II Randomized, Blinded, Placebo-controlled Trial of Carboplatin and Gemcitabine plus Bevacizumab in Patients with Platinum-Sensitive Recurrent Ovary, Primary Peritoneal, or Fallopian Tube Carcinoma

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New Team Member

Introducing

Our patient Beverly Gehrke, 18 year survivor of Stage III ovarian cancer, recently competed in the Madison Ironman competition.

The UW Gynecologic Oncology Program proudly welcomes Laurel W. Rice, MD to our clinical staff and as chair of our OB-Gyn Department.