

Update

IN GYNECOLOGIC ONCOLOGY



New Agents for Treating Gynecologic Malignancies

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Targeting Vascular Endothelial Growth Factor (VEGF) for the Treatment of Ovarian Cancer

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Vascular endothelial growth factor (VEGF) is essential for cancer growth, invasion, and metastasis through the promotion of blood vessel development and increased vascular permeability. Overexpression of VEGF and its receptor is common in most cancers and is associated with a poor prognosis. The humanized monoclonal antibody bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA) is the first anti-VEGF agent to prolong survival when added to standard chemotherapy in patients with metastatic colorectal, breast, and non-small cell lung cancer.

Angiogenesis and Ovarian Cancer

Several studies have demonstrated that VEGF is expressed in women with ovarian cancer, particularly in malignant ascites, and its expression has a negative prognostic implication. In a phase 2 trial, single-agent bevacizumab was associated with a 17% objective response rate, a 10-month median duration of response, a 6-month progression-free survival rate of 39%, and a 4.7-month median survival in the second- or third-line treatment of 62 advanced ovarian cancer patients [1]. In a second trial, a combination of bevacizumab plus oral cyclophosphamide showed a 28% objective response rate [2]. The Gynecologic Oncology Group (GOG) trial with bevacizumab was closed early due to an unexpected high rate of bowel perforations (11%). Nonetheless, given its promising activity, bevacizumab is being studied in patients with newly diagnosed stage III ovarian cancer—protocol GOG-218 (carboplatin/ paclitaxel and bevacizumab versus placebo after suboptimal surgery) and an MSKCC trial under the direction of Dr. Jason Konner (intraperitoneal cisplatin/paclitaxel with bevacizumab after optimal surgery).

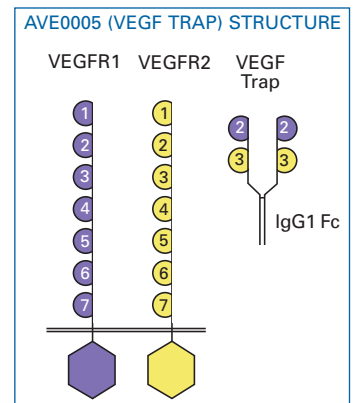


Figure 1. VEGF Trap Compound

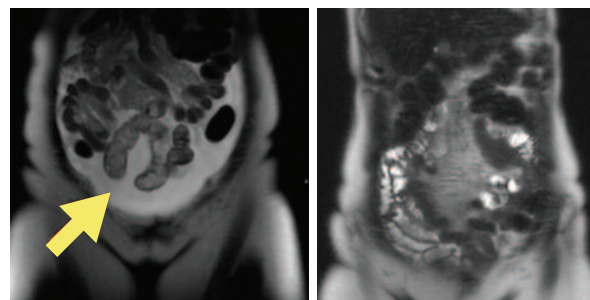


Figure 2. Malignant Ascites Resolved with Intravenous VEGF Trap

Like bevacizumab, VEGF Trap

VEGF Trap

Like bevacizumab, VEGF Trap

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Consolidation Therapy for Ovarian Cancer in First Remission

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The treatment course for advanced ovarian cancer is marked by chemotherapy sensitivity at the outset, with the development of successively shorter responses to subsequent treatment until chemotherapy resistance develops [1]. Aggressive surgical debulking and platinum/taxane therapy have improved median survival from 1 year in 1975 to approximately 5 years in 2005, but the long-term cure rate continues to remain in the 30% range [2]. Approximately 50% of patients will enter a pathologic first complete remission, yet 90% of suboptimally debulked patients and 70% of optimally debulked patients relapse in 18–24 months. Patient outcome can improve by making primary therapy more effective or by applying “consolidation” or “maintenance” approaches to patients in a complete primary remission. We are currently offering patients in a first complete remission enrollment on the following study:

A Randomized, Double-Blind, Placebo-Controlled Multicenter Trial of Abagovomab Maintenance Therapy in Patients with Epithelial Ovarian Cancer after Complete Response to First-Line Therapy

Abagovomab is an anti-idiotypic vaccine targeting CA-125. Anti-idiotypic vaccines attempt to increase the immunogenicity of tumor-associated antigens by presenting the

desired epitope to the tolerant host in a different molecular environment. [3, 4]. This approach assumes that immunization with a given antigen will generate the production of antibodies against the antigen (termed Ab1). Ab1 can generate anti-idiotypic antibodies against Ab1, termed Ab2. Some of the anti-idiotypic antibodies (Ab2 β) express the internal image of the antigen recognized by the Ab1 antibody and can be used as surrogate antigens. Immunization with Ab2 β , can cause the production of anti-anti-idiotypic antibodies (termed Ab3 or Ab1') that recognize the corresponding original antigen identified by Ab1. The anti-idiotypic approach has been used in a variety of clinical studies with colon cancer, melanoma, small cell lung cancer, and neuroblastoma, and some non-randomized studies have suggested a benefit in those patients in whom antibody develops. In a phase 1/2 study of abagovomab (formerly ACA125) [5], 42 patients with advanced/recurrent epithelial ovarian carcinoma received 4 injections of intramuscular alum-precipitated abagovomab at 2-week intervals followed by monthly administration [6]. No systemic toxicity was seen. Immune responses were seen with regards to HAMA (64.2%) and Ab3 (66.7%). The IgG subclass was predominantly IgG1 and IgG2. Cell-mediated cytotoxicity from peripheral blood lymphocytes against CA-125-expressing and non-expressing human ovarian cancer cell lines in 18 patients were evaluated, with measured cell kill increasing in 9 of 18 patients from 19.6% \pm 11.7% to 52.7% \pm 13.6% at the effector:target cell ratio of 100:1 [6]. Cell-mediated lysis was accompanied by the induction of Ab3 in 8 of 9 patients, prompting only a humoral response evaluation in the

remaining patients. The overall survival of all patients vaccinated with ACA125 having an immune response versus none was 19.9 \pm 13.1 months versus 5.3 \pm 4.3 months ($P < 0.0001$).

This international multicenter randomized phase 3 trial of abagovomab versus placebo for stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer patients, with a target accrual of 870 patients, began accruing patients in 2007 under the direction of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) group and the Cooperative Ovarian Cancer Group for Immunotherapy (COGI). Eligible patients have completed standard debulking and platinum with taxane-based chemotherapy (intravenous or intraperitoneal) and are in complete remission. The endpoint of this study is progression-free survival. Eligible patients must enroll by 8 weeks from completion of chemotherapy. ■

For information regarding patient eligibility, please call Paul Sabbatini, MD, or Sandy Pezzulli, NP, at 212-639-6423; or sabbatip@mskcc.org

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A Phase 2 Study of Halichondrin B (E7389) in Recurrent Ovarian Cancer

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There is a great clinical need for new, effective agents for the treatment of recurrent ovarian cancer, particularly for patients who have had prior taxane (paclitaxel or docetaxel) plus platinum (cisplatin or carboplatin)-based chemotherapy. We are conducting an NIH-supported phase 2 study to determine whether the novel agent halichondrin B (E7389) can achieve clinical responses in women with relapsed ovarian cancer.

Halichondrin B is a tubulin inhibitor whose mechanism of action differs from that of other anti-tubulin agents such as paclitaxel and docetaxel, effecting cell cycle block at G2/M, disruption of mitotic spindle formation, and initiation of apoptosis (cell death) [1]. In vivo studies of halichondrin B in mouse xenograft models of ovarian cancer demonstrated “increased survivals, decreased tumor growth rates, and reductions in size and number of metastases”, with activity that was superior to paclitaxel [1, 2]. Halichondrin B may have a wider therapeutic window than other anti-tubulin agents.

For patients with disease that progresses on first-line therapy (primary refractory disease) and patients whose disease progresses within the first 6–12 months of completing first-line platinum-based chemotherapy, the efficacy of treatment with further chemotherapy is

relatively poor. While a number of agents in phase 2 trials have shown some evidence of activity, responses are generally partial at best and observed in only approximately 15–30% of women (depending on the platinum sensitivity of the population). Responses in platinum-resistant patients are seen in only about 15% of patients, and the duration of response is only approximately 4 months.

Halichondrin B holds promise for platinum- and taxane-resistant patients. This study consists of 2 cohorts. The first includes potentially platinum-sensitive patients, and the second includes platinum-resistant patients. Both cohorts have already shown sufficient early activity among the first patients treated to expand the study to the second stage of accrual. Our accrual goal is approximately 40 patients for each cohort.

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A National Phase 2 Study of the Role of Adjuvant Chemotherapy in Completely Resected Uterine Leiomyosarcoma (SARC 005)

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Patients with early-stage uterine leiomyosarcoma (LMS) have a 50–70% chance of relapse/recurrence of disease within approximately the first 2 years after diagnosis. Recurrences are frequently distant (pulmonary or hepatic) and less frequently isolated local recurrences. In one Gynecologic Oncology Group (GOG) study of prognostic factors for recurrence of LMS, only 14% of patients with stage I or II disease had isolated pelvic recurrences as the site of first recurrence [1]. Adjuvant pelvic radiation can decrease local recurrence rates but has not been shown to increase overall survival [2], largely because of distant failure, which sometimes occurs during adjuvant pelvic radiation therapy.

Adjuvant doxorubicin- or epirubicin-based chemotherapy has been beneficial in some trials of soft tissue sarcomas [3, 4], but these studies have included patients with differing histologies and disease sites.

In a phase 2 study of patients with recurrent/persistent LMS who failed to improve

with 0–2 prior chemotherapy regimens, we observed a 53% objective response rate (95% CI, 35–70%) among 34 evaluable patients treated with dose-rate–based gemcitabine plus docetaxel [5]. Approximately 50% of these patients had failed doxorubicin-based therapy. These data were corroborated by a study out of the University at Michigan in which 35 patients with sarcomas of varying histologies were treated with this regimen. Objective responses were observed in 43% of all patients, with complete responses observed in 14%. Responses were seen in patients with LMS as well as in other histologic types of sarcoma. Among the 27 patients who had received prior doxorubicin +/- ifosfamide, responses were seen in 41%. Cell culture studies showed that the sequence of gemcitabine followed by docetaxel resulted in a synergistic effect, which was not observed with the docetaxel followed by gemcitabine [6]. One study assessed the activity of single-agent bolus gemcitabine (1000 mg/m² days 1, 8, and 15) in patients with uterine LMS. Objective responses were seen in 20% of 42 evaluable patients [7].

The encouraging results demonstrating the activity of dose-rate–based gemcitabine plus docetaxel in patients with measurable disease who failed with prior therapy make the investigation of this regimen in the adjuvant setting attractive. The progression-free survival advantage among the LMS patients in the GOG study and the high response rates seen with dose-rate–based gemcitabine plus docetaxel in advanced disease provide the rationale for testing gemcitabine plus docetaxel, followed by doxorubicin, as an adjuvant approach to high-risk resected uterine LMS.

The best estimate of 2-year progression-free survival among patients with stage I and II resected uterine LMS is approximately 30% [1, 8, 9]. Thus, if the 2-year progression-free survival with this treatment regimen were at least 50%, we would consider this adjuvant strategy promising enough for further testing in a phase 3 trial to determine if adjuvant chemotherapy can improve survival.

This phase 2 trial can be used to improve our understanding of how certain easily collected patient and tumor characteristics affect progression-free survival. Uterine sarcomas are staged by the International Federation of Gynecology and Obstetrics (FIGO) staging system for uterine cancers. It is probable that soft tissue sarcoma staging may improve prognostication for outcomes in this disease. We will collect pathology parameters for soft tissue sarcoma staging and explore both FIGO and soft tissue sarcoma staging in terms of their ability to predict progression-free and

overall survival.

Eligible patients are those with completely resected FIGO stage I and II uterine leiomyosarcoma. Patients who have serosal involvement on pathology review are also eligible (even though this could be considered FIGO stage III). Patients need to enroll and start treatment within 12 weeks of surgery. Imaging prior to starting adjuvant chemotherapy is required in order to confirm the absence of metastatic disease.

This large cohort of well-staged and prospectively followed patients will constitute one of the largest cohorts of women with uterine LMS and will provide critical information for ultimately determining interventions that can increase survival.

For information regarding the SARC 005 trial, please call 734-761-1092. ■

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Eligible patients must have received at least 1 taxane-platinum–based regimen, no more than 1 additional cytotoxic regimen, and have measurable disease. Treatment is given on an outpatient basis on days 1 and 8 of a 3-week cycle. Imaging is repeated every other cycle to determine objective radiographic response. ■

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targets the VEGF protein, and MSKCC has been the leading center in the development of this new anti-angiogenic compound (Figure 1). VEGF Trap is anticipated to be more active than other anti-VEGF agents because of its particularly high binding affinity to VEGF and its ability to bind other related pro-angiogenic factors such as VEGF-B and the placental growth factors PIGF1 and PIGF2. Currently, we have 2 trials open for patient enrollment.

VEGF Trap Phase 1

We have enrolled more than 40 patients onto a phase 1 clinical trial to determine the safety, tolerability, pharmacokinetics, and preliminary activity of VEGF Trap in an advanced-cancer patient population (not limited to ovarian cancer). The study is still ongoing. The maximum tolerated dose has not been reached, but peak saturation of the VEGF protein-receptor to the antibody has been seen. VEGF Trap has been well tolerated, with modest adverse events—fatigue, muscle aches, headaches, proteinuria, and hypertension. No patients developed cytopenias, impaired wound healing, bowel perforation, or anti-VEGF Trap antibodies [3]. The study is expected to be completed by

early 2007 after exploring a subcutaneous formulation and a more convenient schedule (once every 3 weeks).

Preliminary reports reveal clinically significant activity with VEGF Trap, particularly in the removal of ascitic fluid. One patient with carboplatin-, taxane-, and gemcitabine-resistant advanced ovarian carcinoma achieved a RECIST-defined partial response after 4 doses of 4.0 mg/kg VEGF Trap, which was associated with a 67% reduction in serum CA-125 levels, radiological resolution of abdominal ascites (Figure 2), and improvement in performance status.

VEGF Trap Phase 2

We began a phase 2 study to evaluate the tumor response rate of VEGF Trap in this population. This is an international, multicenter, randomized, double-blind, two-stage trial with an accrual goal of approximately 200 patients.

The primary objective of the study is to compare the objective response rate of VEGF Trap 4.0 mg/kg and 2.0 mg/kg intravenously every 2 weeks with historical control in patients with advanced ovarian adenocarcinoma resistant to platinum and topotecan and/or liposomal doxorubicin. These doses were based on the available safety, pharmacokinetic, and pharmacodynamic data from the

phase 1 trial. Exploratory studies of biological markers in plasma and of molecular markers in prior tumor samples will be performed to obtain information that might assist in identifying prognostic and predictive patient characteristics. Interim results will be presented at the ASCO meeting in June 2007. ■

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