The treatment outcome for patients with relapsed or refractory cervical carcinoma remains dismal. The key is to prevent the disease through the use of the human papillomavirus quadrivalent (types 6, 11, 16, and 18) vaccine, recombinant. This should dramatically decrease the number of patients who develop cervical cancer.

**Title:** Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions.

**Authors:** FUTURE II Study Group.


**Purpose:** Human papillomavirus types 16 (HPV-16) and 18 (HPV-18) cause approximately 70% of cervical cancers worldwide. HPV is the second most common malignancy in women and the leading cause of cancer death in many developing countries. Routine Papanicolaou (Pap) tests have led to an increase in early detection and a decrease in mortality secondary to the disease in the U.S.; however, these studies are costly and have not been effectively implemented in developing countries. The development of a prophylactic HPV vaccine may be a means of improving the statistics regarding the incidence and mortality rate of this disease worldwide.

**Methods:** This was a randomized, double-blind international trial in which 12,167 women between the ages of 15 and 26 years old received three doses of either HPV-6/11/16/18 vaccine (Gardasil) or placebo. The doses were given on day one, month two, and month six. The primary analysis was performed in patients who had no virologic evidence of infection one month following the third dose of vaccine. The primary endpoint of the study was cervical intraepithelial neoplasia grade 2 or 3, adenocarcinoma in situ, or cervical cancer related to HPV-16 or HPV-18.

**Results:** Subjects were followed for an average of three years after their first dose of vaccine or placebo. The primary analysis was performed on 5,305 women in the vaccine group and 5,260 women in the placebo group who had no virologic evidence of infection at the seventh month. The vaccine prevented 98% of the HPV-16/18 related high-grade cervical lesions. One woman in the vaccine group and 42 in the placebo group were diagnosed with cervical intraepithelial neoplasia grade 2 or 3, cervical adenocarcinoma in situ associated with HPV-16, HPV-18, or both. There were relatively few side effects to vaccination. Injection site reactions were higher in the vaccine group than in those receiving placebo (84.4% vs. 77.9%).

**Conclusion:** In young women who had not been previously infected with HPV-16 or HPV-18, those in the vaccination group had a significantly lower occurrence of high-grade cervical intraepithelial neoplasia related to HPV-16 or HPV-18 than those treated with placebo.

**Managed Care Implications:** Vaccination of young women with no virologic evidence of infection with HPV-16 or HPV-18 with Gardasil should be offered and encouraged by all third-party payors.

**Title:** Evaluation of pemetrexed (Alimta, LY231514) as second-line chemotherapy in persistent or recurrent carcinoma of the cervix: a phase 2 study of the gynecologic oncology group.

**Authors:** Miller AS, Blessing JA, Bodurka DC, et al.


**Purpose:** Uterine cancer that has metastasized to or recurred at sites not amendable to treatment with surgery or radiation is associated with a poor prognosis and is
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considered incurable. The focus of treatment remains palliative in this setting. To date, only a handful of drugs, including cisplatin (Platinol), topotecan (Hycamtin), and gemcitabine (Gemzar), have shown activity as a single agent or in combination. Pemetrexed is an antifolate that has demonstrated some activity in patients who are chemotherapy naïve with a diagnosis of cervical cancer. The purpose of this study was to evaluate this drug in patients with recurrent or refractory disease.

**Methods:** This multicenter phase 2 trial was conducted in patients with relapsed or refractory squamous or nonsquamous cell carcinoma of the cervix. Patients had to have measurable disease and to have failed one prior systemic chemotherapy regimen. Pemetrexed was administered at a dose of 900 mg/m² intravenously over 10 minutes every 21 days. Patients with prior radiation therapy were treated at a dose of 700 mg/m². Seven days prior to the initiation of therapy, patients began taking folic acid and vitamin B12 to decrease the toxicity of the pemetrexed as recommended by the manufacturer. Prophylactic growth factor support was not allowed unless patients experienced recurrent episodes of neutropenia following treatment delays. The primary endpoints of the study were response rate and duration of response. Secondary endpoints were progression-free survival (PFS) and overall survival (OS).

**Results:** Twenty-nine patients were entered in the study. Two patients did not receive therapy and were not evaluated. All patients had received prior cisplatin-based therapy and 85% had received previous radiation therapy. Four patients (15%) had a partial remission with a median duration of response of 4.4 months. Response rates were higher in those patients who had not received previous radiation therapy. The median PFS was 3.1 months (range 0.9 to 23.7+ months) and median survival was 7.4 months (range 1.4 to 23.7+ months). The therapy was well tolerated.

**Conclusion:** Pemetrexed at this dosing schedule shows moderate activity against relapsed or refractory cervical cancer. Future studies combining this agent with cisplatin are planned.

**Managed Care Implications:** There are a limited number of drugs that have activity in relapsed or refractory cervical cancer. Approval for pemetrexed should be considered. Additional studies with pemetrexed and cisplatin in the first-line setting may provide additional answers for where this drug belongs in the treatment of these patients.

**Title:** Weekly topotecan as second- or third-line treatment in patients with recurrent or metastatic cervical cancer.

**Authors:** Coronel J, Cetina L, Candlearia M, et al.


**Purpose:** The current standard of care for patients with newly diagnosed cervical cancer is surgery followed by cisplatin-based chemotherapy. Even with these treatments, one-third of these patients will die secondary to local and/or systemic relapse of their disease.

Response rates with salvage chemotherapy are low and short lived. Thus, chemotherapy in this setting is strictly palliative. Due to these dismal statistics, no second- or third-line therapy for relapsed or refractory cervical cancer is considered to be the standard of care. Topotecan has been shown to exert a significant cytotoxic effect on several squamous cancer cell lines of the cervix, uteri, and vulva. Weekly administration in other disease states has been shown to reduce the hematologic toxicity.
of the drug without compromising efficacy.

Methods: Eligible patients were required to have a confirmed diagnosis of persistent or recurrent cervical cancer that was not amenable to curative surgery, radiation, or both modalities. Patients also were required to have measurable disease, adequate end organ (bone marrow, renal, and hepatic) function, and to have failed at least one prior systemic chemotherapy for advance, metastatic, or recurrent disease. Patients were treated with intravenous topotecan at a dose of 3 mg/m² (maximum 5 mg/dose) administered over 30 minutes infused weekly for three weeks in a 28-day cycle. Patients were assessed for response and toxicity.

Results: Eighteen patients were evaluable for efficacy and response to the therapy. No complete or partial responses were noted. However, five (27.7%) of the patients exhibited disease stabilization as a maximum response. The median progression-free interval was 3.5 months (range 3.75 to 4 months) and the median overall survival was seven months (range 6 to 8.7 months). The major toxicity of the regimen was hematologic, with patients experiencing grade 3 neutropenia (22.2%) and leukopenia (27.7%).

Conclusion: Weekly topotecan administration achieved disease stabilization in 27.7% of heavily pretreated patients with relapsed or refractory cervical cancer. This achievement could be of worth in the setting in which disease prolongation is desirable.

Managed Care Implications: Weekly topotecan does not appear to have significant activity in this disease state. Other drugs such as pemetrexed and gemcitabine may be better alternatives in this setting.

Reference: Gynecol Oncol. February 14, 2009 (Epub ahead of print).

Purpose: Patients who undergo routine screening for cervical cancer are usually diagnosed with early-stage disease, which is amenable to cure. However, others do not participate in this screening process and others experience a relapse despite having received adequate initial therapy. The five-year overall survival rate for advanced or relapsed cervical cancer is poor, ranging from 10% to 20%. Cisplatin monotherapy has been the gold standard for treatment of patients with advanced cervical carcinoma until the combination of cisplatin and topotecan demonstrated higher efficacy in terms of response rates, disease-free survival, and overall survival. The epidermal growth factor receptor (EGFR) is expressed in cervical cancer cells, and its expression level has been linked to prognosis and tumor aggressiveness. Based on this data, the purpose of this study was to investigate the efficacy and tolerability of cetuximab (Erbitux), topotecan, and cisplatin in patients with advanced or relapsed cervical cancer.

Methods: This open-label, uncontrolled, multicenter phase 2 trial was conducted in 13 centers. Patients were eligible if they were at least 18 years old, had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2, had measurable disease that was not amenable to cure, and had adequate end-organ function. Treatment consisted of the following: cetuximab 400 mg/m² IV over two hours as a loading dose and 250 mg/m² IV weekly over one hour, followed by topotecan 0.75 mg/m² IV over 30 minutes on days one, two, and three, and cisplatin 50 mg/m² IV
over one hour. Cycles were repeated on a 21-day basis. The endpoints of the study included progression-free survival (PFS), overall survival (OS), and toxicity.

**Results:** Nineteen of 44 planned patients were accrued to the study prior to it being stopped due to excessive toxicity. Grade 3/4 myelosuppression was significant, namely neutropenia documented in 72% of patients, thrombocytopenia in 61% of patients, and anemia in 44.5% of patients. Grade 3/4 nonhematologic toxicity consisted of infection in 39%, febrile neutropenia in 28%, skin reactions in 22%, and five deaths during treatment, three of which were directly related to therapy. Six evaluable patients (32%) achieved a partial response. The median times of PFS and OS were 172 and 220 days, respectively.

**Conclusion:** The combination of cetuximab, topotecan, and cisplatin induced a high rate of adverse events, including death, at this schedule and dosage. Cetuximab plus cisplatin therapy should be explored in this patient group.

**Managed Care Implications:** The high percentage of patients with cervical cancer expressing EGFR makes cetuximab a valuable addition to the treatment armamentarium. The appropriate dosing of other drugs, such as cisplatin, may lead to advances in the treatment of relapsed or advanced disease.

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**Title:** Phase 2 trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group (GOG) study.

**Authors:** Monk BJ, Sill MW, Burger RA, et al.


**Purpose:** Cervical cancer is preventable and usually curable if detected early. Metastatic or recurrent disease not amenable to radical local excision or regional radiation therapy are treated with palliative chemotherapy. Cisplatin, or the combination of cisplatin and topotecan, have become the treatments of choice in this setting. Clearly, more effective agents are needed to treat women with advanced or recurrent cervical carcinoma. There has been reported a strong association with vascular endothelial factor expression in cervical cancer and poor prognosis. Bevacizumab (Avastin) is a humanized antivascular growth factor monoclonal antibody that has shown activity in a number of solid tumors. Its activity in cervical cancer is evaluated here.

**Methods:** Patients with recurrent cervical cancer with measurable disease were eligible. Their performance status had to be GOG level ≤ 2. Bevacizumab was administered at a dose of 15 mg/kg IV every 21 days until disease progression or prohibitive toxicity. The primary endpoint of the study was PFS at six months and toxicity.

**Results:** Fifty patients were initially enrolled, and 46 received therapy and were eligible for response. Thirty-eight patients (83%) received prior radiation therapy as well as one or two previous cytotoxic regimens for recurrent disease. A total of 254 cycles of bevacizumab were administered with a median of four cycles per patient. Eleven patients (24%) survived progression-free for at least six months with five patients (11%) experiencing a partial response to therapy. The median response duration for those patients was 6.2 months (range 2.8 to 8.3 months). The median PFS was 3.4 months (range 2.5 to 4.5 months).
months), and the overall response rate was 7.3 months (range 6.1 and 11.4 months). Grade 3 or 4 adverse events possibly related to bevacizumab included hypertension (n = 7), thromboembolism (n = 5), and GI (n = 4). One grade 5 infection was observed.

**Conclusion:** Bevacizumab seems to be well tolerated and active in the second- and third-line treatment of patients with recurrent cervical cancer and merits phase 3 investigation.

**Managed Care Implications:** Bevacizumab, like cetuximab, has activity in patients with relapsed or refractory cervical cancer. The primary objective of future trials is to evaluate which chemotherapeutic agents may be safely administered in combination with these two agents.

**Title:** A randomized phase 3 trial of four cisplatin (CIS) containing doublet combinations in stage IVB, recurrent or persistent cervical carcinoma: a Gynecologic Oncology Group (GOG) study.

**Authors:** Monk BJ, Sill M, McMeekin DS, et al.


**Purpose:** A prior GOG study of cisplatin vs. cisplatin plus paclitaxel (Taxol) (PC) indicated that PC was superior in terms of response rate (36% vs. 19%; p = 0.002) and progression-free survival (PFS) (4.8 vs. 2.8 months; p < 0.001), but not for overall survival (9.7 vs. 8.8 months) in women with advanced or recurrent cervical cancer. Other trials have shown the superiority of cisplatin and topotecan to single-agent cisplatin. Therefore, these two regimens will be compared to two additional comparative arms in this study: vinorelbine (Navelbine) plus cisplatin and gemcitabine plus cisplatin.

**Methods:** Patients with stage IVB recurrent or persistent cervical cancer not amenable to cure were randomized to one of four treatment arms: regimen 1 – paclitaxel 135 mg/m² IV over 24 hours day one (PC), cisplatin 50 mg/m² IV day one; regimen 2 – vinorelbine 30 mg/m² IV days one and eight (VC), cisplatin 50 mg/m² IV day one; regimen 3 – gemcitabine 1,000 mg/m² IV days one and eight (GC), cisplatin 50 mg/m² IV day one; regimen 4 – topotecan 0.75 mg/m² IV days one, two, and three (TC), cisplatin 50 mg/m² IV day one.

All regimens were repeated every three weeks for six cycles. The primary endpoint was a 33% reduction in death rate of one of the three investigational arms when compared with PC.

**Results:** Five hundred thirteen patients were enrolled. A planned interim analysis recommended early closure since none of the experimental treatment arms demonstrated a significant advantage over PC.

**Conclusion:** VC, GC, and TC are not superior to PC in terms of overall survival. Additional data concerning overall survival, response rate, progression-free survival, and toxicity needs to be assessed.

**Managed Care Implications:** While PC remains the treatment of choice for relapsed or refractory cervical carcinoma, additional benefits may be gained through the addition of agents such as bevacizumab or cetuximab.