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DRUG PROFILE

The safety and efficacy of bevacizumab in the treatment of patients with recurrent or metastatic cervical cancer

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ABSTRACT

Introduction: Bevacizumab is a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF). (Avastin; Genetech, Inc, San Francisco, CA) Angiogenesis is blocked by the binding of bevacizumab to VEGF, inhibiting the binding of this ligand to the VEGF receptor. On 14 August 2014 the Food and Drug Administration (FDA) approved use of bevacizumab in persistent, recurrent, or metastatic cervical cancer.

Areas covered: Herein we review pharmacodynamics and kinetics, clinical data and treatment-related toxicities of bevacizumab in the treatment of metastatic, recurrent or persistent cervical cancer. Additionally, future areas of development are reviewed.

Expert commentary: Anti-angiogenesis therapy with bevacizumab is central to metastatic, persistent, and recurrent cervical cancer treatment. Additional anti-angiogenesis drugs are in development. Future studies will need to establish if the addition of multiple anti-angiogenesis agents or anti-angiogenesis in combination with immunotherapy is more effective than bevacizumab with chemotherapy.

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Bevacizumab; advanced cervical cancer; anti-angiogenesis therapy

1. Introduction

Worldwide cervical cancer is responsible for significant morbidity and mortality in young women. Globally, in 2012 there were 527,600 new cases, making cervical cancer the fourth most common malignancy. There is a disproportional burden of this disease in developing countries where cervical cancer is the third most common etiology of cancer-related death in women [1]. Implementation and execution of screening programs in the United States has dramatically decreased the incidence by targeting the indolent nature of the persistence of human papillomavirus (HPV) infection and treating preinvasive lesions [2]. Despite these advances in screening, cervical cancer continues to be a significant health concern within the United States. Estimates by the American Cancer Society predict 12,820 new cases and 4,120 deaths in 2017 alone [1].

For the last three decades, contemporary investigations have focused on chemotherapeutic agents in recurrent, persistent, and metastatic disease, herein referred to as advanced cervical cancer. The Gynecologic Oncology Group (GOG), an investigational cooperative, incrementally advanced the understanding and management of this disease through studies that established cytotoxic doublets. Despite these strides, advanced cervical cancer remained notable for early treatment failure, deterioration of quality of life (QOL), and median overall survival of 7–12 months [3]. Bevacizumab was approved for the treatment of cervical cancer in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease.

Bevacizumab is a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF)

(Avastin; Genetech, Inc, San Francisco, CA). Bevacizumab is US FDA indicated in the treatment of recurrent metastatic colorectal cancer, recurrent nonsquamous non-small cell lung cancer, progressive glioblastoma, metastatic renal cell carcinoma, and platinum-resistant and platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. Additionally, bevacizumab is FDA approved in the treatment of primary colorectal cancer and primary unresectable non-squamous non-small cell lung cancer. On 14 August 2014, persistent, recurrent, or metastatic cervical cancer was added to the list of FDA-approved indications.

Herein, we review the pharmacology, efficacy, and tolerability of bevacizumab in advanced cervical cancer.

1.1. Pharmacodynamics and kinetics

Bevacizumab is an IgG antibody, composed of the complement-determining regions from a murine monoclonal antibody (7%) and consensus human IgG framework regions (93%), thereby reducing immune antiglobin response [4,5]. Angiogenesis is thwarted by the binding of bevacizumab to VEGF, blocking this ligand to the VEGF receptor (Flt-1 and KDR) found on endothelial cells.

A two-compartment model with first-order elimination replicated the pharmacokinetics of bevacizumab. Data from 491 subjects with solid tumors with 4629 doses indicated the terminal half-life to be 20 days and consistent with other IgG pharmacokinetics. Thus, the long half-life of bevacizumab supported dosing every 2 or 3 weeks [6]. Pharmacokinetic interactions with cisplatin and paclitaxel were evaluated in a cynomolgus monkey (*Macaca*

facicularis) model. The addition of these chemotherapeutics did not alter the safety profiles of these agents [7]. Using several animal models, bevacizumab displayed a multicompartmental pharmacokinetics, similar to other monoclonal antibodies [4,8].

1.2. Phase I studies

In 2001, the first bevacizumab phase I trial was reported. In the 25-subject group, bevacizumab was well tolerated and no Common Toxicity Criteria (CTC) grade 3 or 4 treatment-related toxicities or dose-limiting toxicities (dose range 0.1–10 mg/kg) were observed. Yet, class-specific adverse events (AE) of hypertension and hemorrhage were noted. No subjects developed antibodies to bevacizumab. In single dose administration, the half-life was approximately 21 days at dose greater than 0.3 mg/kg, similar to prior animal models [9]. To address if bevacizumab could be combined safely with chemotherapeutics, a phase Ib investigation was conducted with doxorubicin, carboplatin, and fluorouracil and leucovorin. Adverse events observed were attributed to chemotherapeutic component, and combinations were tolerated without synergistic toxicities [10].

1.3. Bevacizumab phase II investigations in cervical cancer

The year 2006 marked the first published report of bevacizumab use in cervical cancer. In this case series, six subjects with recurrent cervical cancer were treated with bevacizumab (5 mg/kg or 10 mg/kg) every other week, and 5-fluorouracil (250–500 mg weekly) or capecitabine (2000 mg twice daily). The majority of subjects had prior cisplatin radiation ($n = 5$), all had prior platinum-based salvage therapy, and five had topotecan. In this heavily pretreated population, the overall response rate was 33% with one complete and one partial response. (Table 1) [11]

Based on these findings, three phase II investigations were conducted to evaluate (1) single agent bevacizumab, (2) combination topotecan, cisplatin, and bevacizumab, and (3) combination cisplatin, radiation, and bevacizumab in persistent or recurrent squamous cell cervical cancer.

GOG protocol 227 C, 46-subject trial demonstrated a progression-free survival (PFS) and overall survival (OS) of 3.4 and 7.29 months, respectively. At the time of trial design,

investigators anticipated cytostatic, but not cytotoxic effects of bevacizumab; thus, the primary end point was PFS for at least 6 months. Eleven subjects (23.9%) met this end point, and five subjects (10.9%) had a partial response. Bevacizumab was well tolerated in this study. There was one reported grade 5 toxicity, and no grade 4 proteinuria or hypertension requiring discontinuation of therapy. Overall observed response compared favorably to historical phase II GOG trials [12].

Reviewing bevacizumab in combination with topotecan and cisplatin was the next phase II study. In this trial, 27 subjects were administered topotecan 0.75 mg/m² on days 1, 2, 3; cisplatin 50 mg/m² day 1, and bevacizumab 15 mg/kg every 21 days. A median of three cycles per patient (range 1–19) was delivered. Toxicities were noted including one rectovaginal and one vesicovaginal fistula. Hematologic toxicities were common with 78% of patients requiring transfusion. While toxicities were notable, there was a moderate overall response of 35% in the 26 subjects evaluable for response. Median PFS and OS for all subjects were 7.1 months (80% CL: 4.7–10.1 months) and 13.2 months, respectively (80% CL: 8.0–15.4 months) [13].

Finally, to evaluate the efficacy and safety of bevacizumab in combination with radiation and chemotherapy the Radiation Therapy Oncology Group (RTOG) protocol 0417 was initiated in locally advanced cervical cancer patients. A total of 60 subjects were enrolled. There were no serious treatment-related toxicities. The failure rate was 23%, with an 81% 3-year OS [14,15].

1.4. Bevacizumab phase III investigation in advanced cervical cancer

In April 2009, GOG protocol 240 began subject enrollment. From study start to January 2012, 452 subjects were accrued to the study. Using a 2-by-2 factorial design, this trial addressed two questions: the efficacy of a nonplatinum chemotherapy doublet (topotecan–paclitaxel) and the effect of anti-VEGF therapy (bevacizumab). Subjects were randomly assigned to one of two chemotherapy regimens with and without bevacizumab: cisplatin (50 mg/m²) plus paclitaxel (135 mg/m² or 175 mg/m²), topotecan (0.75 mg/m² days 1–3) plus paclitaxel (175 mg/m²). A total of 225 subjects received chemotherapy alone, with the remaining 227 subjects receiving chemotherapy plus bevacizumab. Treatment groups were similar in multiple factors, including

Table 1. Phase II and III trials of bevacizumab in cervical cancer.

	Study (Ref)	Year	<i>n</i>	Agent(s)	Disease state	Response (OS, PFS)
Phase II	Wright [11]	2006	6	Bevacizumab 5–15 mg/kg q 21 days, 5-FU 250–500 mg weekly or 2000 mg BID capecitabine daily	Recurrent	OS 5.1 m
	Monk et al. [12]	2009	46	Bevacizumab 15 mg/kg q 21 days	Recurrent	OS 7.3 m, PFS 3.5 m
	Zigelboim et al. [13]	2013	27	Bevacizumab 15 mg/kg q 21 days, cisplatin 50 mg/m ² day 1, topotecan 0.75 mg/m ² days 1, 2, 3	Recurrent	OS 13.2 m, PFS 7.1 m
	Schefter et al. [15]	2014	49	Bevacizumab 10 mg/kg q 14 days (×3), cisplatin 40 mg/m ² , radiation therapy, brachytherapy	Primary	Not reported
Phase III	Tewari et al. [16]	2014	452	With and without bevacizumab 15 mg/kg q 21 days with 1. cisplatin 50 mg/m ² and paclitaxel 135–175 mg/m ² 2. topotecan 0.75 mg/m ² days 1, 2 and paclitaxel 175 mg/m ² day 1	Recurrent, persistent, metastatic	OS 17 m, PFS 13.3 m

M: months, ref: reference, q: every, BID: twice daily.

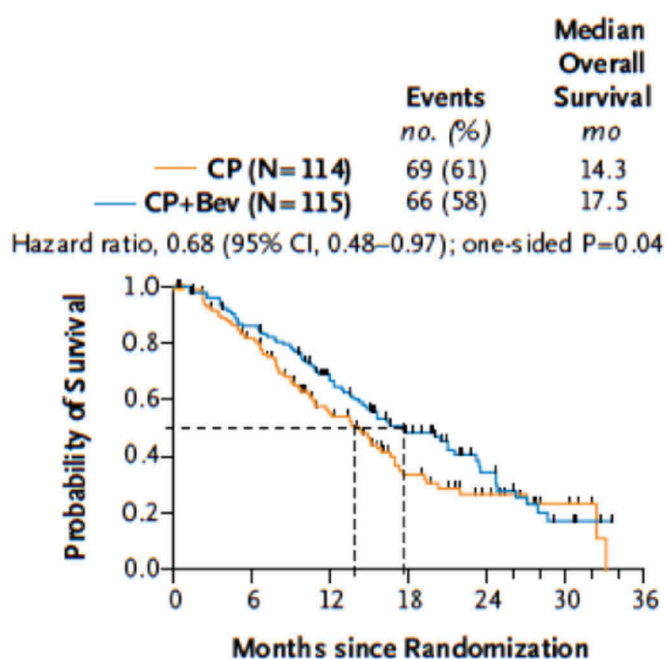


Figure 1. Overall survival in chemotherapy alone (CP) versus chemotherapy plus bevacizumab (CP+Bev) arms in the GOG-240 trial. From [16]. Copyright © (2014) Massachusetts Medical Society. Reprinted with permission.

age, histology, performance status, prior platinum exposure, and disease state. A planned interim analysis was conducted once 174 subjects had died. This first interim analysis demonstrated non-superiority of the non-platinum chemotherapy doublet over cisplatin-paclitaxel but did not answer the question concerning the potential efficacy of bevacizumab in the study population. Thus on 12 March 2012 an early communication was sent to all investigators and patients.

At the second interim analysis, GOG-240 met the primary endpoint of OS improvement among women receiving chemotherapy plus bevacizumab. There was a statistically significant improvement in OS (17 versus 13.3 months; HR of death 0.71 (98% CI, 0.54–0.95); 1-sided $p = 0.004$) and PFS (8.2 versus 5.9 months; HR of progression 0.67 (95% CI, 0.54–0.82) with the addition of bevacizumab to chemotherapy; 2-sided $p = 0.002$). (Figure 1) [16] Of note package insert indicates a 3.9 m improvement in OS as additional data was collected after publication for FDA review (Table 2).

Advancements in this setting are placed in context of QOL, as therapy continues to be palliative. To compare QOL between groups, Functional Assessment of Cancer Therapy-Cancer (FACT-Cx) surveys, single item from the Brief Pain Inventory (BPI), and FACT-Neurotoxicity (FACT-Ntx) were administered at baseline, before cycle 2, before cycle 5, and 6 and 9 months post-cycle 1. Survey results were not statistically different among groups. In comparison among groups the addition of bevacizumab did not result in a significant deterioration in QOL [17]. Unlike other solid tumors, in which patients can oscillate between remissions and recurrent treatment, there are limited options for cervical cancer. Examining the findings of GOG-240 in the context of limited therapeutic options and the improvement in overall survival and without QOL impact demonstrates the clinical significance of this agent.

Table 2. Outcomes of four arms of GOG-240.

Treatment group	Number of events (%)	OS (months)
TP	71 (64)	12.7
TP + bevacizumab	65 (58)	16.2
CP	69 (61)	14.3
CP + bevacizumab	66 (58)	17.5

TP: topotecan and paclitaxel; CP: cisplatin and paclitaxel.

This trial is noteworthy by an improvement in OS not demonstrated by other trials and has become the new standard of care for advanced cervical cancer.

1.5. Bevacizumab investigation primary cervical cancer treatment

The positive results of bevacizumab in the advanced setting bring to question the application of this agent in treating primary local disease. Investigators evaluated the toxicity of combination of bevacizumab and cisplatin with radiation in a single-arm phase II trial, RTOG protocol 0417 ($n = 60$). Subjects had stage IB to IIIB disease and received bevacizumab every 2 weeks for three cycles (10 mg/kg). The primary endpoint was treatment-related AE, and secondary endpoints were OS, disease-free survival, and treatment failure. This combination was feasible and safe with no grade 5 AE and 15 overall AE. Comparing the survival results in RTOG 0417 with that of the chemoradiation group from RTOG 90-01 the addition of bevacizumab is associated with some improvement in OS: 89.8% and 80.2% at 2 and 3 years respectively (RTOG 0417) vs 81.3% and 76.8% at 2 and 3 years, respectively (RTOG 90-01) [18]. Cross study comparisons have several limitations, and this data has yet to be confirmed with phase III investigation. RTOG 0417 does provide positive data on the safety of bevacizumab in this population suggesting a possible application in the treatment of primary diagnosed local disease [14,15].

An additional avenue for bevacizumab utilization in cervical cancer could involve a maintenance dosing follow primary treatment. Maintenance therapy with bevacizumab (15 mg/kg q21 days) following primary surgery and platinum- and taxane-based chemotherapy for newly diagnosed advanced ovarian cancer was associated with a 4-month improvement in PFS relative to the control in a phase III randomized trial. Whether maintenance therapy in cervical cancer will reduce recurrence rates and/or positively impact survival is unknown, and will require further investigation. Investigation is required to determine if with this extended treatment schedule during primary treatment would reduce rates of recurrence and impact survival.

1.6. Treatment-related toxicities

Overall bevacizumab in advanced cervical cancer is well tolerated, with rare yet severe complications. In GOG-240, four treatment-related deaths occurred among those randomized to chemotherapy alone as well as to those randomized to chemotherapy plus bevacizumab. Hypertension is the most common side effect of bevacizumab therapy [16]. Across clinical studies the incidence of grade 3–4 hypertension is 5–18% [19]. More specific to cervical cancer, the observed rate of grade 2 or higher hypertension in GOG-240 was 25%

(compared to 2%, $p < 0.001$). Albeit being a common side effect, hypertension did not limit treatment and no subjects required dose discontinuation during GOG-240.

The pathogenesis of this AE is not fully described; however, there are several proposed mechanisms (Figure 2). Bevacizumab is thought to inhibit nitric-oxide synthase, thus decreasing nitric oxide, a potent mediator of vascular tone. In the setting of reduced vasodilation, vasoconstriction alone can induce hypertension; with the added effect of reducing renal sodium excretion, blood pressure may be further elevated [19]. Furthermore, through endothelial dysfunction, there are avenues for hypertension by promoting vasoconstriction, vascular inflammation, and capillary rarefaction [20].

Hypertension can occur during any point throughout therapy. With initiation of bevacizumab therapy, it is recommended to monitor blood pressure every 2–3 weeks. Once the diagnosis of hypertension is made, it has been suggested that angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers, and calcium-channel blockers be used as first-line agents [23].

In addition to hypertension, proteinuria is another class-specific AE from antiangiogenesis therapy. Patients receiving bevacizumab should have urinalysis every cycle. If 2+ proteinuria is noted, patients should undergo further assessment with 24-hour urine collection. The threshold for discontinuation of therapy is a 24 hour urine collection result of greater than 2 g of protein [19].

In line with preeclampsia signs of hypertension and proteinuria, a rare toxicity includes posterior reversible encephalopathy (PRES). PRES can be associated with significant morbidity. This clinical syndrome is notable for symptoms of headache, emesis, seizures, and visual loss, as well as white-matter

abnormalities on brain magnetic resonance imaging (MRI). In 1 review of the 28 cases reported in the literature, the majority of effected patients were female (73.1%) and had a prior history of hypertension before anti-VEGF therapy (34.6%) [24]. Across clinic trials the incidence is less than 0.5% with onset variable from 16 h to 1 year after initiation of bevacizumab therapy [17]. The management of PRES includes blood pressure control and discontinuation of bevacizumab, and symptoms are typically reversible with these measures [25,26]. Of note, no subjects on GOG protocol 240 experienced PRES.

Although bevacizumab is directed to inhibit vascular expansion, there is also data elucidating endothelial damage and therefore tissue factor activation. Triggering this cascade, VEGF blockage increases expression of proinflammatory genes and ultimately thrombus formation [27]. In GOG-240, there was a higher rate of grade 3 or higher thromboembolism with bevacizumab, eight subjects versus one subject in the chemotherapy alone arm ($p = 0.001$).

Gastrointestinal perforations (GI) and recto-vaginal or vesico-vaginal fistula formation represent some of the most severe bevacizumab complications. Of note, perforations were observed in colorectal and ovarian cancers, while fistulas were observed in cervical cancer more frequently than other diseases. Compared to controls, GI perforations occurred at a higher incidence, with 0.33.2% reported rates across clinical trials (package insert). In a meta-analysis of 17 trials, there was a relative risk of perforation with bevacizumab use of 2.14 (95% CI, 1.19–3.85; $p = 0.011$). Results also noted that incidence was affected in a dose-dependent manner and by tumor type. Mortality of GI perforations across studies was noted to be 21.7% [28]. One subject treated on GOG-240 died as a result of a GI perforation.

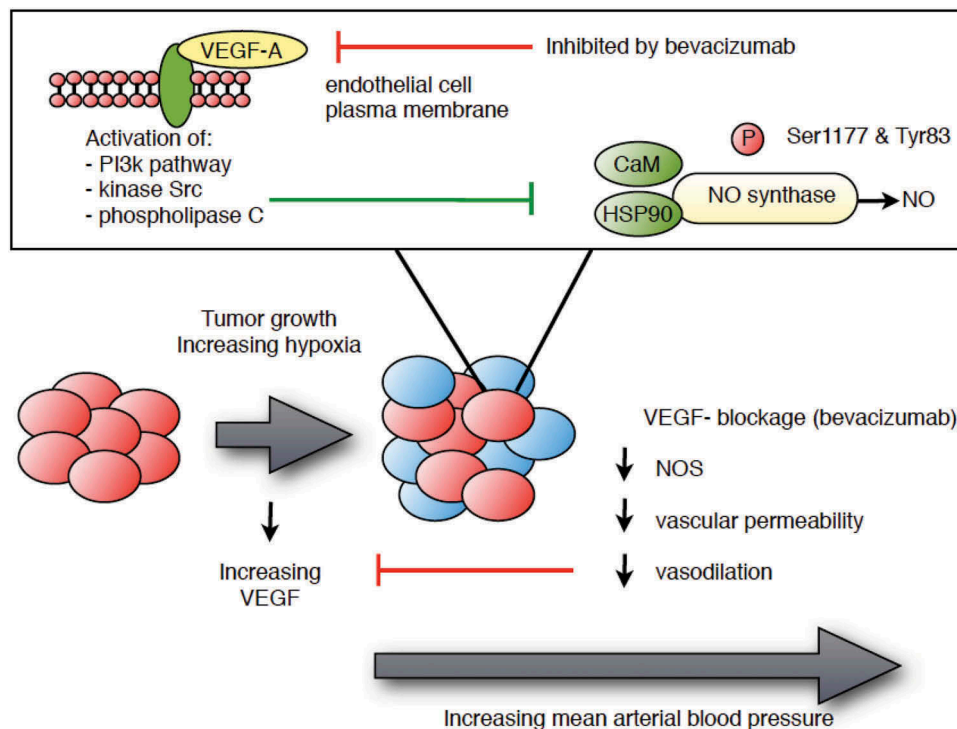


Figure 2. Bevacizumab induced hypertension pathogenesis [21]. Bevacizumab inhibits binding of VEGF-A and intracellular activation of nitric oxide synthase (NOS). NOS is activated by phosphorylation at serine 1177, tyrosine 83, binding of heat shock protein 90 (HSP90), and via calmodulin [22].

Perforations also include non-GI fistula formation. On 24 September 2007, a black box warning was issued by the FDA, advising updated safety labeling to include non-GI fistula formation secondary to clinical studies and post-marketing experience. In GOG-240, there was an increased incidence of grade 3 or higher GI fistula and genitourinary fistula, compared to chemotherapy alone arms, 6% compared to 0%, respectively ($p = 0.002$). None of the fistulas that occurred on the GOG-240 trial required emergency surgical intervention nor resulted in either sepsis or death. Patients with advanced cervical cancer have multiple risk factors for vesico-vaginal and recto-vaginal fistula formation including pelvic disease burden and prior radiation. The clinical benefit of bevacizumab should be weighed in terms of potential impact to QOL.

Bevacizumab is noted to impair surgical and wound healing [29–31]. Recommendations include discontinuing treatment 28 days prior to elective surgery and restarting bevacizumab 28 days after surgery.

Finally, additional FDA warnings have been issued: hemorrhage including hemoptysis, GI bleeding, central nervous system, and vaginal bleeding. In the experience of bevacizumab in advanced cervical cancer, there were no significant clinically relevant central nervous system bleeding, and GI and genitourinary bleeding was uncommon.

2. Expert commentary

Targeting the phenotypic driver of cervical carcinogenesis via tumor-associated angiogenesis with bevacizumab is pivotal. GOG-240 represents the standard of care in advanced cervical cancer, changing practice with the addition of a biologic agent to cytotoxic doublets. Building on the results of GOG-240, additional avenues of angiogenesis inhibition should be explored in the aim of fully exploiting this proven concept.

Several agents, under development, have demonstrated activity in cervical cancer including pazopanib and cediranib. Cediranib is an oral VEGFR1-3 tyrosine kinase and c-KIT inhibitor. Cediranib was evaluated with and without chemotherapy (carboplatin AUC 5 and paclitaxel 175 mg/m²) in a 69-subject randomized, double-blind, placebo-controlled phase II trial. A median PFS extension of 8.1 m versus 6.7 m was noted [80% CL: 0.40–0.85; $p = 0.032$]; study was underpowered for OS data [32]. Future developments will need to elucidate the treatment schedule to maximize the benefit of cediranib in the setting of the current standard of bevacizumab plus chemotherapy. It has been suggested that bevacizumab plus chemotherapy with cediranib maintenance may incorporate both agents [3].

Pazopanib is an oral inhibitor of VEGFR, platelet-derived growth factor receptor, and c-KIT. As a monotherapy, this agent has a modest activity with a 9% response rate and improved PFS (HR, 0.66; CL 90%, 0.48–0.91, $p = 0.013$). Pazopanib was studied in combination with lapatinib, but combination arm was closed early as unacceptable toxicity profile was identified. Anti-VEGF strategies are superior to anti-HER2/neu therapy in this setting [33].

The EGFR target was also explored with nimotuzumab, a humanized IgG1 monoclonal antibody against the EGFR extracellular domain. Nimotuzumab was evaluated in a pilot study comprised of 17 patients with pretreated advanced refractory or progressive cervical cancer, for which the primary outcomes

were defined as efficacy and safety. The study had three phases: first single agent nimotuzumab, concurrent with gemcitabine or cisplatin, and then every two weeks maintenance phase. Nimotuzumab was well tolerated. There were no complete or partial responses observed; stable disease was found in 35% [34]. Study findings are limited as acceptability was addressed; however, study design excluded PFS and OS as endpoints.

In addition to targeted therapies, nano-particle albumin bound (NAB) paclitaxel, a cytotoxic chemotherapy has been evaluated in advanced cervical cancer. NAB-paclitaxel is a 130-nanometer, chrophor-free preparation of paclitaxel [35,36]. NAB-paclitaxel was evaluated in recurrent cervical cancer a phase II trial as a part of the GOG-127 queue. Subjects were treated with 125 mg/m² on days 1, 8, and 15 of a 28-day cycle. The results demonstrated moderate activity with a median PFS and median OS of 5.0 and 9.4 months, respectively. Ten subjects had a partial response, and additional 15 subjects had stable disease [37]. In addition, the study evaluated a heavily pretreated population, with a more frequent dose schedule [38]. So-called metronomic chemotherapy has demonstrated antiangiogenic effects by reducing endothelial repair time, endothelial cell proliferation, migration, and circulating levels of endothelial progenitor cells [21,38,40]. The median PFS and OS for all subjects that met mortality endpoint were 4.8 months and 8.9 months ($n = 7$), respectively. NAB-paclitaxel with or without bevacizumab is tolerable and potentially active in treating recurrent cervical cancer [39].

The angiopoietin/TIE pathway represents an unexplored angiogenic axis in cervical cancer. This pathway consists of three ligands, Ang-1, Ang-2, and Ang-4, that activate the Tie2 receptor expressed on endothelial and lymphatic cells via the Tie2 receptor. Effects exerted included destabilization of mature vasculature, which promoted remodeling of vasculature and the production of new vessels [41]. Trebananib is a peptide-Fc fusion protein that binds Ang-1 and Ang-2, thereby inhibiting angiogenesis. Interrogations of trebananib in recurrent epithelial ovarian cancer demonstrated an extension of PFS by 7.2 m versus 5.4 m (95% CL: 5.8–7.4) compared to single-agent weekly paclitaxel [42].

A major limitation to the use of bevacizumab in advanced cervical cancer is the cost of the drug. In a Markov model of derived cost-effectiveness, the total cost was 13.2 times that of chemotherapy alone, adding \$73,791 per 3.5 months, resulting in an incremental cost-effectiveness ratio (ICER) of 21,083 per month. With a 75% reduction in cost, ICER is 6737 per QOL month, which translates to 23,580 for the 3.5-month gain in OS [43]. Currently, the drug development pipeline may contain agents that will resolve this current financial conflict. With bevacizumab patents set to expire in 2019, bio-similar agents hope to match the efficacy, reconcile the ICER and expand the delivery of this agent to patients in resource-limited settings.

Antiangiogenesis has changed the paradigm of advanced cervical treatment, introducing the first targeted agent. With current drug development in place, it is anticipated that additional agents will be added to this armamentarium.

3. Five-year view

Moving forward from GOG-240 treatment, patients have an incremental OS improvement without durable remission. Now

clinicians are faced with a new population of patients with a high unmet clinical need, those that progress or recur after GOG-240 treatment. With the limitations of cytotoxic agents, immunotherapy is dominating the developmental pipeline and represents the next paradigm of target therapy. Immunotherapy can be broadly divided into vaccination strategies and inhibition of immune tumor tolerance.

Vaccines for the treatment recurrent, persistent cervical cancer modulate T-cell immunity, activating the immune system to destroy cells bearing tumor-associated antigens. The vaccine most widely study, ADXS11-001, was granted Orphan Drug Designation by the FDA in June of 2013. This vaccine exploits the immunogenetic stimulation of *Listeria monocytogenes* stimulating MHC pathways creating T-cell immunity to tumors; in live attenuated bacteria that secrete HPV-16 E7 fusion protein-targeting HPV-transformed cells.

A *L. monocytogenes*-based vaccine, ADXS11-001, underwent phase II investigation of 110 subjects with recurrent or refractory cervical cancer patients that had received prior chemotherapy, radiotherapy, or both. The primary endpoint was 12-month survival, of which 39 of 110 (36%) of subjects met. The response rate was 11% (six complete responses and six partial responses) [44]. Current phase II evaluation with the GOG is underway with the National Research Group (NRG) GOG protocol 265. Primary endpoint is tolerability and safety of ADXS11-001, and secondary objectives include PFS, OS, and objective tumor response. This study is closed for accrual as of 5 May 2014 and results are pending. Based on the current known data, in June of 2013, ADXS11-001 was granted Orphan Drug Designation by the FDA.

The second emerging immunotherapy strategy involves breaking immune tumor tolerance. Tumor existence and persistence is in part of resistance mechanisms implored by malignancies to evade or down regulate the immune system. Programmed death 1 (PD-1) is an immune-checkpoint receptor found on activated T-cells, binding with its ligands, PD-L1 and PD-L2, mediates immunosuppression. PD-L1 is frequently expressed by cervical cancer, and in one report demonstrated in 54% of tumor samples [45].

At the 2016 American Society of Clinical Oncology (ASCO) annual meeting, data was presented on the phase IB pembrolizumab study. This monoclonal antibody is directed against PD-L1, inhibits the binding of the ligand to its receptor. The 24 subjects were treated with 10 mg/kg every 2 weeks for 24 months until to unacceptable toxicity, progress, withdrawal, or death. In this population with confirmed PD-L1 expression in greater than or equal to 1% of tumor or stroma cells by immunohistochemistry testing, the overall response rate was 12.5% [46]. Promising results in this population of advanced cervical cancer patients were heavily pretreated, with 62.5% had received two or more therapies for metastatic disease, and subsequently this agent has entered phase II study (NCI02628067).

There are two additional phase II studies evaluating the tolerability and efficacy of checkpoint inhibition in persistent and recurrent disease – nivolumab, a PD-L1 inhibitor (NCI02257528), and ipilimumab, and monoclonal antibody against CTLA-4 (NCI01693783).

At present, bevacizumab is the only FDA-approved targeted therapy, with chemotherapy, in the treatment of

recurrent, metastatic and persistent cervical cancer. Currently, this combination is the standard of care with the longest phase III demonstrated OS in this population. In the next five years, there are several possible changes to the landscape of this agent in advanced cervical cancer. Immunotherapy clinical study is in the early stages of investigation. Combination therapy would exploit both therapeutic pathways without overlaying toxicities. Additionally, in 2019, bevacizumab will lose its patent exclusivity in the United States, opening the market to biosimilar agents. With cost reduction, we anticipate an expansion of the use of antiangiogenic agents.

Key Issues

- Bevacizumab (Avastin; Genetech, Inc, San Francisco, CA) is a first-in-class anti-angiogenesis, recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF)
- Bevacizumab was approved by the US Food and Drug Administration for the treatment of recurrent, persistent, and metastatic cervical cancer with cisplatin and paclitaxel chemotherapies
- Bevacizumab is the new standard of care for advanced cervical cancer, increasing OS by 3.4 months in a phase III, randomized, multi-center trial.

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Declaration of interest

K Tewari has received grants from Genentech, Amgen, Endocyte, Tesaro, Astra Zeneca, and Aeterna Zentaris, has acted as a consultant for Caris, Clovis, Advaxis and Roche and has received speakers' bureau from Astra Zeneca, Merck and Roche. K Tewari was the Principal Investigator and Study Chair of Gynecologic Oncology Group protocol which met its primary endpoint and led directly to US FDA approval of bevacizumab for advanced cervical cancer. Although I was not paid in this role, after publication of the manuscript in the New England Journal of Medicine I participated in two paid Genentech Advisory Boards so that I could be involved in the regulatory discussions to help get this drug to patients who need it and I am currently on the Genentech/Roche speaker's bureau. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Papers of special note have been highlighted as either of interest (*) or of considerable interest (***) to readers.

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