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Development of bevacizumab in advanced cervical cancer: pharmacodynamic modeling, survival impact and toxicology

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Abstract

Historically, patients with metastatic, persistent or recurrent cervical cancer had limited therapeutic options. Despite several Phase II/III clinical trials, the combination of cisplatin and paclitaxel remained the most effective chemotherapeutic regimen. In 2014, publication of Gynecologic Oncology Group 240 represented the emergence of an alternate and effective therapeutic option. This prospective, randomized, Phase III clinical trial explored the impact of adding the antiangiogenic agent bevacizumab to two separate cytotoxic chemotherapy backbones. Importantly, the study met its primary end point, showing a survival advantage of approximately 4 months without detriment in quality of life. As such, a review of bevacizumab and its application in patients with advanced-stage cervical cancer is warranted.

Keywords

bevacizumab; cervical cancer; pharmacodynamics; pharmacokinetics; prognostic criteria; quality of life; survival

The burden of gynecologic malignancies remains a stimulus toward scientific investigation and the discovery/development of novel therapeutic agents. In 2014, it is estimated that there will be 86,970 new cases of ovarian, uterine and cervical cancer in the USA, with 26,880 deaths [1]. Due to lack of an effective screening strategy, patients with ovarian cancer are diagnosed with an advanced stage disease and require surgical cytoreduction as well as systemic chemotherapy. Conversely, the Pap smear, an effective screening strategy for cervical cancer, has translated into prevention and early detection with improved survival. Globally, however, cervical cancer continues to be the most lethal gynecologic malignancy, with 529,800 new cases and 275,100 deaths in 2011 [2]. This discrepancy between global and regional disease burden is attributable to the disproportionately high number of cervical cancer cases in resource-poor countries that lack adequate infrastructure and screening programs.

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Importantly, despite appropriate screening and early detection, a subset of patients with cervical cancer will present with metastatic disease or develop disease recurrence after primary therapy. In the context of metastatic or recurrent disease, a complete cure is rare, and treatment focuses on palliation of symptoms, disease control and prolongation of life [3]. Chemotherapeutic options for patients with advanced stage or recurrent cervical cancer have been explored and are based on clinical trials completed under the auspices of cooperative groups, most notably the Gynecologic Oncology Group (GOG). Since Thigpen's initial paper in 1981, a number of single drug and combination regimens have been studied in the treatment of advanced and metastatic cervical cancer with limited gains in overall survival (OS) [4–20]. Ultimately, cisplatin + paclitaxel was established as the backbone for future trials, with OS approaching 13 months [4].

The poor oncologic outcome in this patient population catalyzed the exploration of novel treatment paradigms. In an era of personalized and molecular medicine, the development of biologic therapies, to be used alone or in conjunction with cytotoxic chemotherapy, is a clinical priority. The biologic agent with the greatest clinical experience in the gynecologic cancer arena is the antiangiogenic agent bevacizumab. With publication of GOG 240, bevacizumab was shown, for the first time, to improve both OS and progression-free survival without a significant decrement in quality of life (QoL) in a patient population previously lacking effective therapeutic options (i.e., women with advanced cervical cancer). This trial led to regulatory approval on 14 August 2014 by the US FDA for bevacizumab in this population [21].

This review article will discuss the pharmacokinetics/pharmacodynamics of bevacizumab, its clinical efficacy in the treatment of patients with advanced stage, persistent or recurrent cervical cancer, as well as QoL implications, biomarker discovery, and potential predictors of response.

Bevacizumab in solid malignancies

Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to and neutralizes the biologic activity of VEGF (Figure 1) [22]. The drug is produced by using recombinant DNA technology in a Chinese hamster ovarian cell expression system, in a nutrient medium containing the antibiotic gentamicin which is purified by a process that includes viral inactivation and removal [23].

Bevacizumab was first studied in patients with renal cell carcinoma, because of its unique VEGF-driven biology, and five other common solid tumors with high therapeutic need: colorectal, prostate, lung and breast cancers, and glioblastoma [24]. Additional studies were conducted in patients with wet age-related macular degeneration, showing results comparable to the previously used ranibizumab [25]. Phase III bevacizumab trials were then conducted in metastatic colorectal cancer [26,27], metastatic non-small-cell lung cancer [28], metastatic breast cancer (mBC) [29] and recurrent glioblastoma [30,31], all of which met their primary end points, thus supporting FDA approval of bevacizumab for these indications (Table 1) [32]. Importantly, the accelerated approval of bevacizumab in patients with mBC was reversed by the FDA in 2011, after prolonged follow-up failed to show an OS

improvement. Analogously, despite four prospective Phase III clinical trials illustrating an improved progression-free survival (PFS) in patients with ovarian cancer, lack of an OS advantage in the bevacizumab containing arms has been an impediment to FDA approval in this disease (Table 2) [33–39].

Conversely, when studied in patients with advanced stage, recurrent or persistent cervical cancer in GOG 240, bevacizumab was associated with a significant improvement in PFS and OS, without a decrement in measured QoL parameters [21]. The above represents the first time a targeted agent resulted in an OS advantage in patients with gynecologic cancer, with practice changing implications.

The combination of a significant improvement in PFS with a loss of significance at the time of OS analysis has resulted in continued debate regarding appropriate study end points. In diseases where additional effective therapies are available at the time of progression (on study), a meaningful PFS difference is commonly diluted by postprogression treatment and crossover. This is best represented by recent data indicating that over 50% of subjects with advanced ovarian cancer treated on an antiangiogenic trial received seven or more cytotoxic anticancer regimens [36]. The above paradigm likely explains the lack of a significant OS difference with the use of bevacizumab in patients with recurrent or advanced stage breast and ovarian cancers, where cytotoxic chemotherapy regimens are effective at prolonging life after disease progression.

Conversely, in the setting of advanced stage or recurrent cervical cancer, no effective therapies exist, and the survival advantage of bevacizumab is maintained [40]. As explained by Broglio *et al.*, a significant PFS advantage (hazard ration [HR]: 0.73; p = 0.03) translates into a significant OS advantage (HR 0.61; p = 0.008) when median survival postprogression on study is estimated to be 6 months [40]. Conversely, in the setting where alternate treatment options exist, the postprogression survival is extended, and the survival advantage is diluted. With an analogous calculated PFS, in a simulated study, the HR for OS would rise to 1.29 (p = 0.262) if postprogression survival is estimated to be 18 months.

Antiangiogenic therapy in cervical cancer: the biologic rational

Patients with cervical cancer are routinely exposed to radiation and chemotherapy at the time of primary therapy, potentially altering disease biology. Chemosensitizing radiation may select for radio-resistant and chemotherapy-resistant cell populations, particularly if there is crossover with respect to mechanisms of drug resistance. Additionally, cancer foci recurring or persisting in the previously irradiated field may have compromised blood supply and associated relative hypoxia, limiting delivery of cytotoxic drugs. These unique characteristics may explain the limited response to retreatment with traditional chemotherapy in patients with recurrent cervical cancer, highlighting the importance of studying novel biologic strategies.

Biologically, abnormal vascularity identified on colposcopic examination may suggest invasive disease. Mechanistically, this is explained by the effects of E6/E7 on the angiogenic pathway. Upregulation of the E6 oncoprotein is hypothesized to directly stimulate VEGF

production [41,42]. In transgenic mice experiments, investigators were able to reproduce invasive squamous cell carcinoma of the epidermis with *E6* and *E7* oncogene expression [43]. Ultimately, E6-mediated degradation of p53 and E7 inactivation of pRb result in increased VEGF and hypoxia inducible factor 1α, promoting angiogenesis and tumor growth (Figure 2).

Clinical evidence that angiogenesis plays a role in cervical cancer has accumulated over the last decade. VEGF-induced tumor angiogenesis has been associated with adverse oncologic outcomes in patients with cervical cancer [24,45–49]. In an early study, high intratumoral microvessel density was associated with poor prognosis and remained significant in a multivariable model [47]. More recently, intratumoral VEGF was shown to be upregulated in cervical cancer specimens relative to control cervical tissues, with higher VEGF levels being associated with advanced stage, increase risk of nodal metastasis, and worse PFS and OS [50–53]. Additionally, cluster of differentiation 31 expression, found on endothelial cell surfaces and used as an immunohistochemical marker of angiogenesis, has been shown to be significantly associated with tumor size and the presence of lymph vascular space involvement in patients with clinical stage 1B squamous cell cervical cancer [54].

Bevacizumab: pharmacokinetics & pharmacodynamics

Monoclonal antibodies have rapidly evolved into a robust segment of developmental therapeutics in the treatment of solid malignancies. There are several antibody isotypes (IgA, IgD, IgE, IgG and IgM) each with well-described pharmacologic properties. The most prevalent isotype, IgG, constitutes nearly 85% of serum immunoglobulins and is the primary derivative for therapeutic development secondary to its role in humoral protection [55].

IgG monomers are constructed of four polypeptide chains: two heavy chains and two light chains connected by disulfide bonds at the ‘hinge region’ (Figure 3) [55]. The variable region contains short peptide sequences known as the complimentary determining regions, representing the antigen-binding site. The F_C region consists of constant heavy chains involved in essential interactions with components of the immune system.

The pharmacokinetics of bevacizumab was initially described using a two-compartment model. Bevacizumab deposition is characterized by low clearance and a long elimination half-life. These characteristics allow for predictable target tissue levels despite variable dosing schedules (ranging from every 2–3 weeks on clinical trials) [56].

In population-based studies, there was no identifiable difference in bevacizumab pharmacokinetics in relation to age. Conversely, hypoalbuminemia and high tumor burden resulted in more rapid drug clearance (19% faster in patients with low levels of serum albumin [<29 g/l] and 7% faster in subjects with higher tumor burden) [56].

In clinical trials, the typical value for central volume (V_c) was 2.73 l for female patients, with a peripheral volume (V_p) of 1.69 l [23].

Furthermore, the evaluation of bevacizumab metabolism in rabbits mirrored that expected for a native IgG molecule which does not bind to VEGF [23]. This metabolism was

predominantly mediated by proteolytic catabolism and is independent of renal or hepatic elimination. The binding of IgG to the FcRn receptor results in protection from cellular metabolism and a long terminal half-life [57,58]. Importantly, the elimination pharmacokinetics of bevacizumab is linear at doses ranging from 1.5 to 10 mg/kg/week.

According to the two-compartmental model, the elimination half-life of bevacizumab is 18 days for a typical female patient [23,56].

Bevacizumab in cervical cancer

In the first case series describing the use of bevacizumab in patients with recurrent cervical cancer, despite heavy pretreatment (median of three prior regimens), there was a 67% overall response rate [59]. Treatment was well tolerated, with only one grade 4 adverse event (AE) noted (Table 3).

These preliminary results catalyzed the development of GOG protocol 227C, a Phase II trial designed to evaluate the efficacy and tolerability of bevacizumab in the treatment of recurrent cervical cancer (Table 3) [61]. Among the 46 eligible and evaluable patients, 38 (82.6%) received prior pelvic radiation as well as either one (n = 34; 74%) or two (n = 12; 26%) cytotoxic regimens for recurrent disease. Eleven patients (23.9%; two-sided 90% CI: 14–37%) survived progression free for at least 6 months, and five patients (10.9%; two-sided 90% CI: 4–22%) had partial responses, with a median response duration of 6.2 months (range, 2.83–8.28 months). The median PFS and OS times were 3.40 months (95% CI: 2.53–4.53 months) and 7.29 months (95% CI: 6.11–10.41 months), respectively. These results compared favorably with historical Phase II trials in this setting [62].

Given the clinical activity noted in the pretreated population, Radiation Therapy Oncology Group protocol 0417 was developed, exploring the safety and efficacy of the addition of bevacizumab to standard chemoradiation (Table 3) [63]. Between 2006 and 2009, a total of 60 patients were enrolled. The median follow-up was 12.4 months (range: 4.6–31.4 months). Most patients had FIGO stage 2B (63%) disease and with a Zubrod performance status (PS) of 0 (67%). Eighty percent of cases were squamous. There were no treatment-related serious AEs. More recently, oncologic outcomes were published, with 81% 3-year OS and a 23% locoregional failure rate [64].

Another Phase II clinical trial exploring the combination of cisplatin 50 mg/m^2 day 1 + topotecan 0.75 mg/m^2 days 1, 2, 3 + bevacizumab 15 mg/kg day 1 on a 21-day cycle was recently published [65]. A total of 27 patients with persistent or recurrent cervical cancer, with no prior chemotherapy for recurrence, were enrolled. The 6-month PFS was 59% (80% CI: 46–70%), with median PFS and OS of 7.1 months and 13.2 months, respectively. Unfortunately, grade 3–4 hematologic toxicity was common (thrombocytopenia 82%, leukopenia 74%, anemia 63%, neutropenia 56%) on this treatment regimen. The majority of patients (78%) required unanticipated hospital admissions for supportive care and/or management of toxicities.

GOG protocol 240

With publication of these Phase II studies, advancement of bevacizumab into the Phase III arena was a scientific priority. GOG protocol 240, a four-arm, prospective, randomized trial exploring platinum and nonplatinum doublets with and without the antiangiogenic agent bevacizumab, was designed and met its accrual goal in less than 3 years (Figure 4: GOG 240 schema) [21].

From April 2009 to January 2012, the trial accrued 452 patients. Over 220 patients were treated with each of the chemotherapy backbones, and patients were well matched for histology ($p = 0.308$), ethnicity ($p = 0.800$) and disease status: recurrent versus persistent versus advanced ($p = 0.298$). The majority of patients had a GOG PS of 0 (PS 0–1 required for enrollment). A total of 75% of the entire study group had previously received platinum and this was evenly distributed between the two backbones ($p = 0.666$). The topotecan + paclitaxel arm was shown to not be superior or inferior to the cisplatin + paclitaxel arm (HR: 1.20; 95% CI: 0.82–1.76). Median OS in the topotecan containing doublet was 12.5 months versus 15 months in the cisplatin + paclitaxel arm. These results were interpreted as indicating that the nonplatinum chemotherapy doublet was not superior to cisplatin + paclitaxel for efficacy.

The investigators showed a significant improvement in OS in the bevacizumab-containing arms relative to chemotherapy alone (17 months vs 13.3 months, respectively; HR: 0.71; 95% CI: 0.54–0.95; $p = 0.0035$). significant improvement in PFS was also identified (8.2 months bevacizumab-containing arms and 5.9 months in the chemotherapy alone arms; HR: 0.67; 95% CI: 0.54–0.82; $p = 0.0002$). Exploratory subanalysis further indicated the beneficial effects of bevacizumab in patients with prior platinum exposure, recurrent or persistent disease and squamous histology. Importantly, the benefits of bevacizumab persisted in patients with recurrent disease in a previously irradiated field, which was hypothesized to be relatively hypoxic. These findings represent the first time a targeted antiangiogenic agent has shown an improvement in OS in patients with gynecologic cancer.

More recently, the final protocol-specified OS analysis for GOG 240 was presented at the Annual Meeting of the European Society of Medical Oncology in Madrid, Spain (2014) following acceptance as a late breaking abstract [66]. As of 7 March 2014, 348 deaths had occurred and the regimens administering bevacizumab continued to demonstrate a significant improvement in OS over chemotherapy alone: 16.8 months versus 13.3 months; HR: 0.765 (95% CI: 0.62–0.95; $p = 0.0068$). Overall, a total of 20 patients who had been treated on the chemotherapy alone arms went on to receive salvage therapy with bevacizumab.

Bevacizumab & QoL on GOG 240

As with all new drugs, the therapeutic benefits are weighed against possible toxicity and an impact on QoL. In GOG 240, eight subjects (four in each arm) experienced a treatment-related death. Within the bevacizumab-containing arms, there was an increase in grade ≥3 GI

and GU fistula (n = 5), as well as grade ≥2 hypertension, grade ≥4 neutropenia and grade ≥3 thrombocytopenia.

The full QoL data were presented at the European Society of Medical Oncology Annual Meeting (Amsterdam, The Netherlands, 2013) [67]. The primary and coprimary QoL end points were measured by the Trial Outcome Index of the Functional Assessment of Cancer Therapy-Cervix (FACT-Cx TOI) and FACT/GOG-Neurotoxicity subscale, respectively. The secondary QoL end point was worst pain in 24 h by the Brief Pain Inventory. The QoL parameters were assessed precycle 1, 2, and 5 and at 6 and 9 months postcycle 1. Of the 452 patients enrolled on study, 96% completed baseline QoL assessments, and 63% completed assessment at 9 months postcycle 1. The completion rates were not statistically different among the treatment regimens at any of the five assessment points (p = 0.67).

The fitted mixed model estimates indicated that patients receiving chemotherapy + bevacizumab reported 1.2 points (98.75% CI: −4.1–1.7; p = 0.3) lower on average in the FACT-Cx TOI scores than those treated with chemotherapy alone. The fitted MEMD (mixed effects mixed distribution) model estimates indicated patients treated with chemotherapy + bevacizumab were less likely to report neurotoxic symptoms (OR: 0.58; 98.75% CI: 0.29–1.17; p = 0.053). Severity of reported neurotoxic symptoms did not differ between the two groups (p = 0.7). The fitted MEMD model estimates also indicated that both groups had similar odds of complaining of pain (OR: 0.89; 95% CI: 0.36–1.42; p = 0.7) and reported similar severity of pain when they had it (p = 0.16).

The above results indicate that the improvement in OS and PFS attributed to the addition of bevacizumab to the doublet chemotherapy backbone was not accompanied by a significant deterioration in QoL.

Predictors of response: application of the Moore criteria to the GOG 240 population

In 2010, Moore *et al.* developed a model of prognostic factors predictive of (non-) response to chemotherapy in patients with advanced stage or recurrent cervical cancer [68]. GOG protocols 110, 169 and 179 were used for model development (training data set) and patients from GOG 149 were used for model validation (testing data set).

A total of 428 patients with advanced cervical cancer who received a cisplatin-containing combination in GOG protocols 110, 169 and 179 were evaluated for baseline clinical characteristics and multivariate analysis was conducted to identify factors independently prognostic/predictive of response using a logistic regression model. As detailed above, predictive model was developed and externally validated using an independent protocol (GOG 149). Multivariate analysis identified five factors (African–American, PS >0, pelvic disease, prior radiosensitizer and time interval from diagnosis to first recurrence <1 year) independently prognostic of poor response [68]. When patients were classified into three risk groups (low risk: 0–1 factor; mid risk: 2–3 factors; high risk: 4–5 factors), patients with four to five risk factors were estimated to have a response rate of only 13%, and median PFS

and OS of 2.8 months and 5.5 months, respectively. The accuracy of the index was supported by both internal and external data sets.

Given the above findings, these prognosticators where evaluated prospectively as an exploratory end point in GOG 240 and the results were presented at the 2014 Society of Gynecologic Oncology Annual Meeting (FL, USA) [69]. Importantly, for the entire GOG 240 study population, the Moore criteria were prospectively validated. Interestingly, those patients with higher risk stratification (i.e., mid-risk and high-risk) appeared to derive the greatest benefit through the incorporation of antiangiogenesis therapy.

Proposed mechanisms of AEs

Hypertension, thromboembolic events, and fistula were observed more frequently among women receiving chemotherapy plus bevacizumab in the GOG 240 population. While the mechanism of anti-VEGF therapy-induced hypertension has not been fully elucidated, nitric oxide pathway inhibition, rarefaction and oxidative stress may be critical in its pathogenesis [70]. Although nephrotic syndrome was not observed in GOG 240, glomerular injury may develop with diminished effect of VEGF in maintaining the filtration barrier.

Because VEGF has a maintenance role for normal endothelium function, thromboembolic events may result from endothelial cell pertubations induced by anti-VEGF therapy, resulting in nonphysiologic endothelial cell apoptosis [71]. Abnormal apoptosis of endothelial cells can lead to exposure of the highly prothrombotic basement membrane. Alternatively, because VEGF signaling is essential for the production of platelet inhibitors prostaglandin I-2 and nitric oxide, the prothrombotic effect of bevacizumab may also derive from a platelet-dependent mechanism [71]. Sequestration of VEGF depletes prostaglandin I-2 and nitric oxide, resulting in platelet activation.

Inhibition of VEGF signaling has been shown to reduce vascular density in a variety of tissues in animal models, including small intestinal villi, pancreatic islets, thyroid and adrenal cortex [72]. The trigger of vascular regression may manifest by local detachment or death of endothelial cells, with excessive VEGF inhibition on the capillary beds of small intestinal villi contributing directly to gastrointestinal perforation by inducing regression of normal blood vessels. Risk factors for gastrointestinal perforation among patients receiving bevacizumab for colorectal cancer include primary tumor intact, recent history of sigmoidoscopy or colonoscopy and/ or previous adjuvant radiotherapy [73]. Among women with newly diagnosed ovarian cancer, risk factors for gastrointestinal AEs include a history of treatment for inflammatory bowel disease and bowel resection at primary surgery [74]. It is possible that the pathophysiology concerning intestinal vascular regression and some shared risk factors (e.g., prior pelvic radiotherapy) may contribute to the development of fistula among women with advanced cervical cancer treated with anti-VEGF therapy.

Conclusion

As our understanding of tumor biology and the tumor microenvironment progresses, therapeutics have analogously evolved from traditional cytotoxic molecules to novel monoclonal antibodies, peptibody conjugates, targeted biologic therapies and most recently

immunotherapeutics. The importance of GOG 240 centers on the fact that it represents the first time a targeted agent has reached its primary end point, improving OS, in patients with gynecologic cancer. As detailed above, this survival benefit was not associated with a decrement in QoL, and additional studies are ongoing to help identify potential predictors of response, including the exploration of gene signatures [71]. Unlike patients with advanced stage ovarian or mBC, where salvage therapy commonly translates into partial or complete response, patients with metastatic or recurrent cervical have failed to show meaningful response to multimodal therapy in prior studies. With the publication of GOG 240, it is anticipated that patients with what was traditionally viewed as poor prognosis cervical cancer may achieve durable remission, improving QoL, and potentially opening the door to alternate novel therapies.

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EXECUTIVE SUMMARY

Angiogenesis is essential for tumor growth & has been identified as a therapeutic target in solid malignancies

- Biologically, angiogenesis (abnormal vascularity) imparts an aggressive course in colposcopic exam of the cervix.
- US FDA approval of bevacizumab in colorectal, renal, non-small-cell lung cancer and glioblastoma.
- FDA approval anticipated in metastatic cervical cancer following publication of Gynecologic Oncology Group (GOG) 240.

Bevacizumab, a monoclonal antibody directed against VEGF (ligand) was developed & tested in various solid tumors

- It is a recombinant humanized monoclonal IgG1 antibody (93% human, 7% murine sequences – molecular weight 149 kDa).
- Pharmacokinetics are described by a two-compartment model.
- Binding of the IgG to the FcRn receptor results in protection from cellular metabolism and the long terminal half-life.
- Metabolism of bevacizumab is more rapid in patients with low albumin and higher volume of disease.

Phase II clinical trials were conducted, & demonstrated the safety & efcacy of bevacizumab in patients with cervical cancer

- Response rate of 33–35% in a heavily pretreated population.
- Only one grade 4 adverse event in the combined studies.

GOG 240

- Accrued 452 patients with advanced stage, metastatic or recurrent cervical cancer over a 3-year period.
- Showed both progression-free survival and overall survival advantage with the addition of bevacizumab to cytotoxic chemotherapy.
- GOG 240 represents the first time a targeted agent has reached its primary end point, improving overall survival, in patients with gynecologic cancer with practice changing implications.
- No decrement in quality of life.
- Moore prognostic criteria applied to GOG 240, indicating that patients with worst prognostic classifcation may benefit most from treatment with bevacizumab.

Conclusion

- Patients with advanced stage cervical cancer had limited therapeutic options prior to publication of GOG 240.
- Bevacizumab is anticipated to receive FDA approval for the treatment of recurrent, metastatic or advanced stage cervical cancer in the USA (already received in EMA).
- Developing biomarkers predictive of response is critical, and application of a proangiogenic gene signature to the GOG 240 population is implicit.

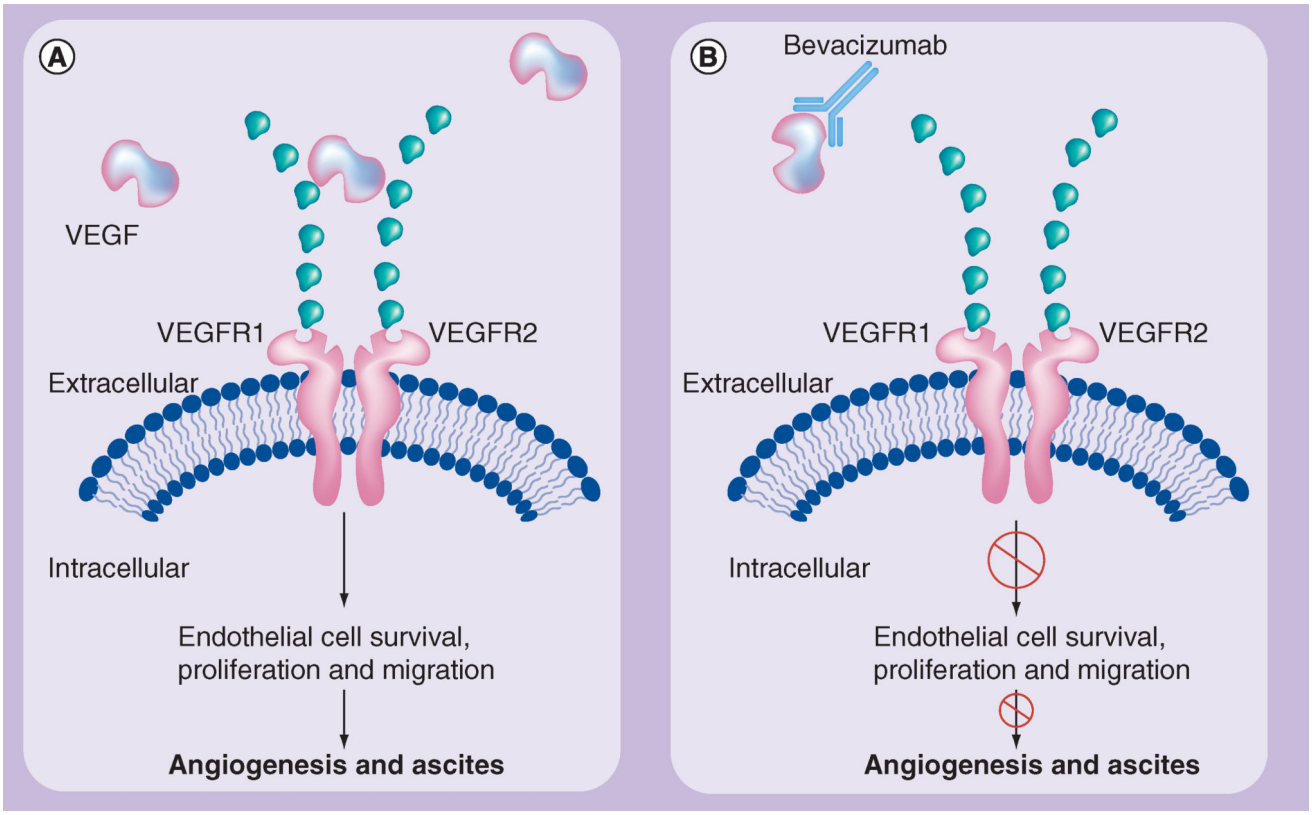

Figure 1.

Bevacizumab mode of action: binding and neutralizing VEGF ligand, preventing interaction with the transmembrane receptor.

Adapted with permission from [22].

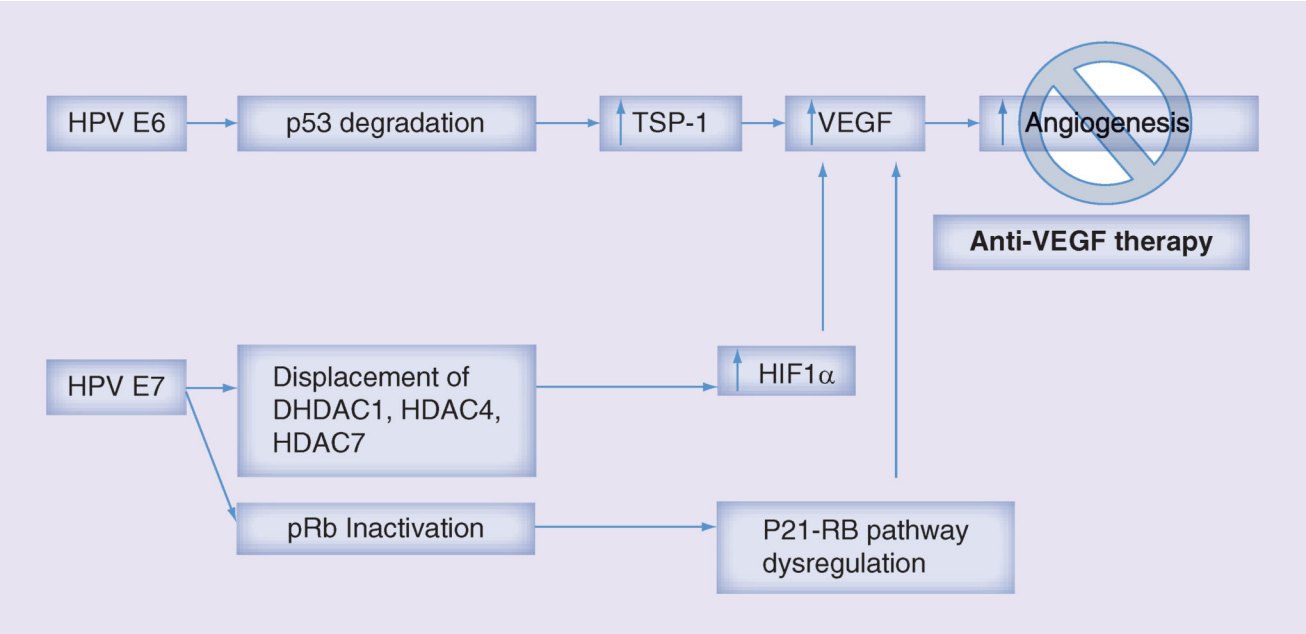

Figure 2.
Biologic rational of bevacizumab use in cervical carcinoma.
Adapted with permission from [44].

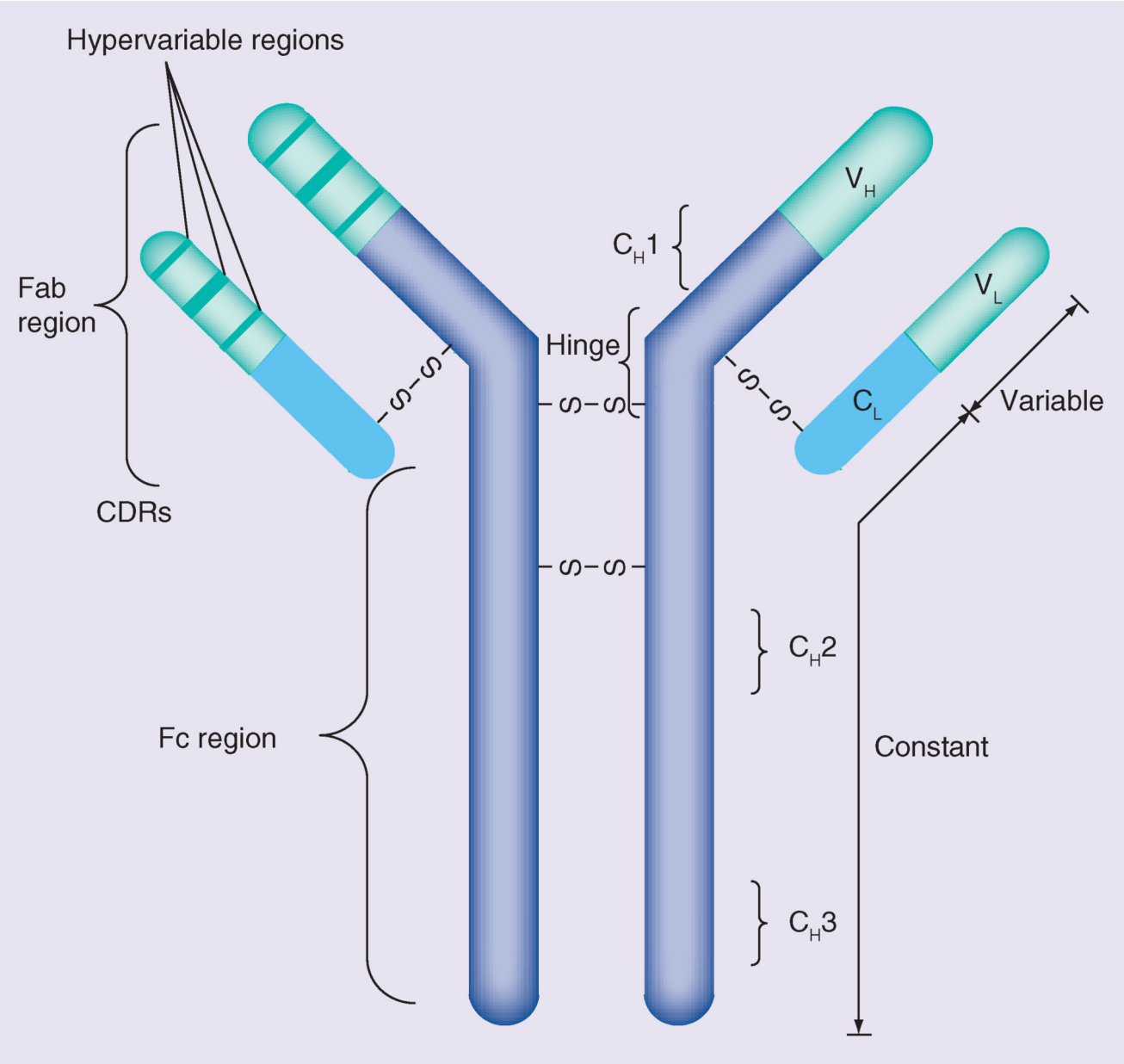

Figure 3.

Generalized structure of a monoclonal antibody monomer.

CDR: Complimentary determining region; C_H: Constant heavy chain; C_L: Constant light chain; S: Sulfde; V_H: Variable heavy chain; V_L: Variable light chain.

Adapted with permission from [55].

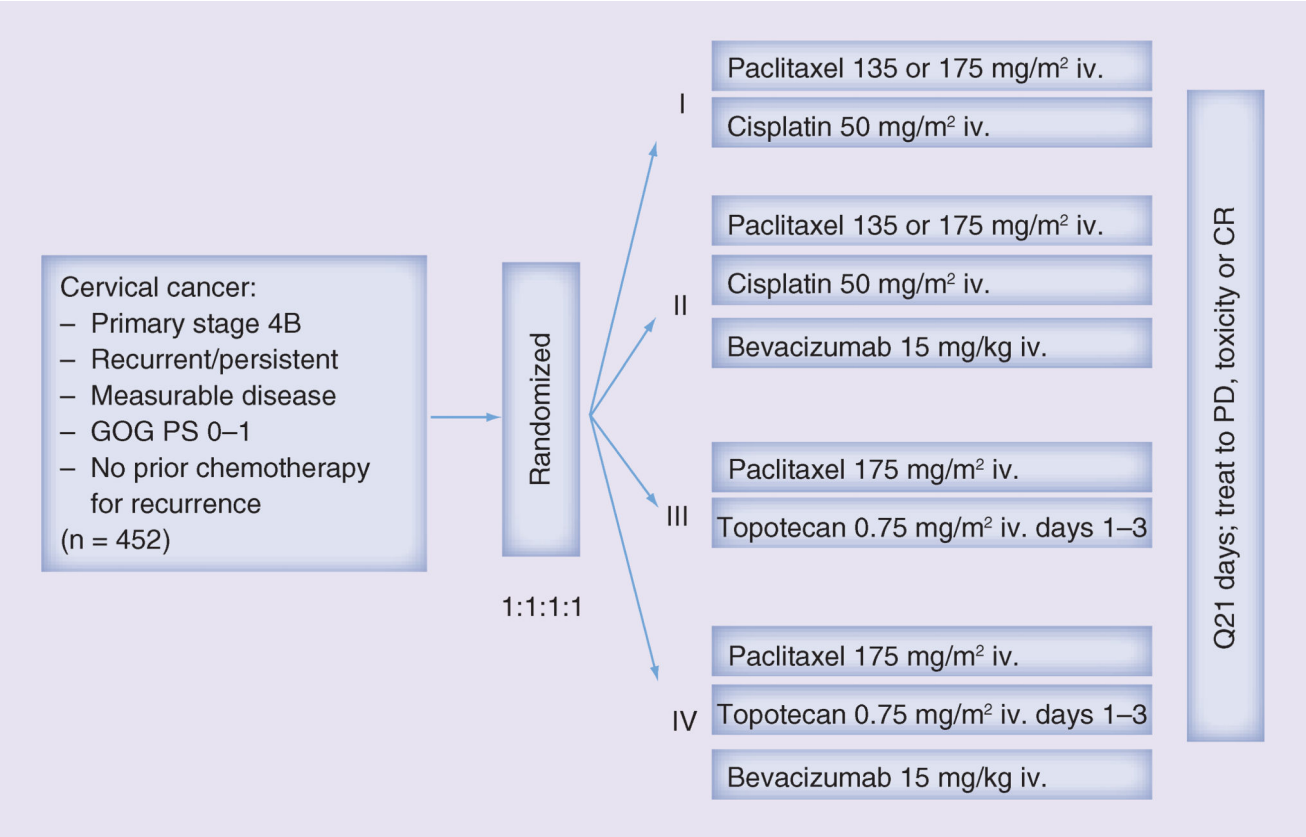

Figure 4.

Gynecologic Oncology Group protocol 240 schema.

CR: Complete response; GOG: Gynecologic Oncology Group; iv.: Intravenous; PD: Progressive disease; PS: Performance status; Q21 days: Every 21 days.

Table 1

Registration trials resulting in US FDA approval of bevacizumab.

Study	Disease site	n	Eligibility criteria	Regimen studied	Outcome measure			AEs	Ref.
					Visual acuity	*Median PFS (months)*	*Median OS (months)*		
Ocular indication									
Martin *et al.*	AMD	1208	Visual acuity between 20/25 and 20/320	Ranibizumab monthly Bevacizumab monthly	8.0 letters gained 8.5 letters gained			Equivalent rates of MI, death and stroke between arms	[25]
Solid tumors									
Hurwitz *et al.*	Colorectal cancer	813	ECOG PS 0–1 First line Metastatic	ILF + placebo ILF + bev 5 mg/kg iv. Q2w		6.2 10.6 (HR: 0.54; 95% CI: 0.45–0.66)	15. 6 20.3 (HR: 0.66; 95% CI: 0.54–0.81)	Leukopenia (37%); diarrhea (32%); HTN (11%); bleeding (3%); GI perforation (1.5%)	[26]
Giantonio *et al.*	Colorectal cancer	829	Adv stage Metastatic	FOLFOX-4 + placebo FOLFOX-4 + bev 10 mg/kg Q2w Bev 10 mg/kg Q2w		4.7 7.3 2.7 (HR: 0.52; 95% CI: 0.42–0.65)†	10.8 13.0 N/R (HR: 0.75; 95% CI: 0.63–0.89)	HTN (6%); emesis (10%); bleeding (3%); neuropathy (16%); thromboembolism (3%)	[27]
Sandler *et al.*	Nonsquamous NSCLC	878	ECOG PS 0–1 First line Locally adv Metastatic Recurrent	Carbo/paclitaxel+ placebo Carbo/paclitaxel + bev 15 mg/kg Q3w		4.8 6.4 (HR: 0.65; 95% CI: 0.56–0.76)	10.3 12.3 (HR: 0.80; 95% CI: 0.69–0.93)	Leukopenia (25%); HTN (7%); proteinuria (3%); bleeding (4%)	[28]
Miller *et al.*	Breast cancer	722	ECOG 0−1 Locally recurrent Metastatic	Paclitaxel + placebo Paclitaxel + bev 10 mg/kg Q2w		5.8 11.4 (HR: 0.42; 95% CI: 0.34–0.52)	24.8 26.5 (HR: 0.87; 95% CI: 0.72–1.05)‡	Infection (9%); Fatigue (9%); HTN (15%); neuropathy (23%)	[29]

Study	Disease site	n	Eligibility criteria	Regimen studied	Outcome measure			AEs	Ref.
					Visual acuity	*Median PFS (months)*	*Median OS (months)*		
Friedman *et al.*	GBM	167	KPS >70%	Bev 10 mg/kg Q2w		42.6% (6 months PFS)	9.3	HTN (8%); thromboembolic disease (6%)	[30]
			First or second recurrence	Bev 10 mg/kg Q2w + irinotecan		50.3% (6 months PFS)	8.8		
Kreisl *et al.*	GBM	48	KPS >60%	Bev 10 mg/kg Q2w		16 weeks	31 weeks	Thromboembolism (12.5%); HTN (4%); hypophosphatemia (4%)	[31]
			Recurrent (no limit on number of prior therapies)	Transition to bev + irinotecan at progression		29% (6 months PFS)	57% (6 months survival)		
						Arm closed early due to futility			
Escudier *et al.*	Renal cell cancer	649	KPS >70%	IFN-α-2a + placebo		5.4[§]	21.3	Fatigue (12%); asthenia (10%); proteinuria (7%); HTN (3%); bleeding (3%)	[32]
			First line	IFN-α-2a + bev 10 mg/kg Q2w		10.2[§]	23.3		
			Metastatic No CNS mets			(HR: 0.63; 95% CI: 0.52–0.75)	(HR: 0.91; 95% CI: 0.76 –1.10)		
AURELIA	Ovarian cancer	361	ECOG PS 0–2	iv. paclitaxel or iv. topotecan or iv. PLD		3.4	13.3	HTN (20.1%); proteinuria (12.8%); fatigue (2.2%); GI perforation (1.7%); thromboembolic disease (3.4%)	[39][¶]
			Platinum-resistant recurrence	Chemo as above + bev 15 mg/kg Q3w		6.7	16.6		
						(HR: 0.48; 95% CI: 0.36–0.60)	(HR: 0.85; 95% CI: 0.66 –1.08)		
Tewari *et al.*	Cervical cancer	452	GOG PS 0–1	Chemotherapy + placebo		5.9	13.3	Fistula (3%); HTN (2%); neutropenia (35%); thromboembolism (8%); bleeding (5%)	[21][¶]
			Recurrent/ persistent or metastatic	Chemotherapy + bev 15 mg/kg Q3w		8.2	17.0		
						(HR: 0.67; 95% CI: 0.54–0.82)	(HR: 0.71; 97% CI: 0.54–0.94)		

[†] Diference between FOLFOX + placebo vs FOLFOX + bev.

[‡] Lack of a signifcant OS advantage resulted in the US FDA revoking initial approval of bevacizumab use in patients with metastatic/recurrent breast cancer.

[§] Signifcantly greater than historical controls for both treatment arms ($p < 0.0001$).

¶Regulatory approval granted by the US FDA on 14 August 2014 (recurrent/persistent and metastatic cervical cancer) and on 14 November 2014 (platinum-resistant ovarian cancer).

Adv: Advanced; AE: Grade 3 or 4 adverse events on bevacizumab; AMD: Age-related macular degeneration; Bev: Bevacizumab; Carbo: Carboplatin; Chemo: Paclitaxel + cisplatin vs paclitaxel + topotecan; ECOG: Eastern Cooperative Oncology Group; FOLFOX-4: Oxaliplatin + leucovorin + fuorouracil; GBM: Glioblastoma; GI: Gastrointestinal; GOG: Gynecologic Oncology Group; HR: Hazard ratio; HTN: Hypertension; ILF: Irinotecan + fuorouracil + leucovorin; iv.: Intravenous; KPS: Karnofsky performance score; Mets: Metastases; MI: Myocardial infarction; NSCLC: Non-small-cell lung cancer; OS: Overall survival; PFS: Progression-free survival; PLD: Pegylated liposomal doxorubicin; PS: Performance status; Q2w: Every 2 weeks; Q3w: Every 3 weeks.

Table 2

Prospective Phase III clinical trials incorporating bevacizumab in the treatment of ovarian cancer indicating a progression-free survival advantage, but no overall survival advantage.

Trial	n	Eligibility	Arms	Grade 3–4 AEs[†]	Primary end point	Secondary end point	Ref.
GOG 218	1873	Incompletely and completely[‡] resected stage 3 or any stage 4; GOG PS 0–2	iv. carboplatin (AUC 5) + iv. paclitaxel (175 mg/m^2) + placebo followed by maintenance placebo Q3w iv. carboplatin (AUC 5) + iv. paclitaxel (175 mg/m^2) + iv. bevacizumab (15 mg/kg) + placebo maintenance Q3w iv. carboplatin (AUC 5) + iv. Paclitaxel (175 mg/m^2) + iv. bevacizumab (15 mg/kg) + iv. bevacizumab (15 mg/kg) maintenance Q3w	HTN; (22.9%); GI events (2.6%); proteinuria (1.6%); VTE (6.7%)	Median PFS; 10.3 vs 11.2 vs 14.1 months; HR: 0.717; (0.625–0.824); p < 0.001	Median OS; 39.3 vs 38.7 vs 39.7 months; HR: 0.915 (0.727–1.15); p = 0.45	[35]
ICON 7	1528	Stage 1–2A (clear cell, grade 3); stage 2B-4; ECOG PS 0–2	iv. carboplatin (AUC 5) + iv. paclitaxel (175 mg/m^2) Q3w iv. carboplatin (AUC 5) + iv. paclitaxel (175 mg/m^2) + iv. bevacizumab (7.5mg/kg) + iv. bevacizumab (7.5 mg/kg) maintenance Q3w	Bleeding (1%); HTN (6%); VTE (4%); GIP (1%); neutropenia (17%)	Median PFS; 17.3 vs 19.0 months; HR: 0.81 (0.70–0.94); p = 0.0041	Median OS; 58.6 vs 58 months; HR: 0.99 (0.85–1.14); p = 0.85	[34]
OCEANS	484	Platinum sensitive recurrent ovarian cancer[§]; ECOG PS 0–1	iv. carboplatin (AUC 4) + iv. gemcitabine (1000 mg/m^2) + placebo Q3w iv. carboplatin (AUC 4) + iv. gemcitabine (1000 mg/m^2) + iv. bevacizumab (15 mg/kg) Q3w	HTN (17.4%); proteinuria (8.5%); bleeding (5.7%); F/A (1.6%); VTE (4%)	Median PFS; 8.4 vs 12.4 months; HR: 0.484 (0.388–0.605); p < 0.0001	OS data immature; ORR; 78.5 vs 57.4%; p < 0.0001, DOR; 10.4 vs 7.4 months; HR: 0.534 (0.408–0.698)	[36]
AURELIA[#]	361	Platinum resistant recurrence[¶]; ≤2 prior chemotherapy regimens; no e/o rectosigmoid involvement; ECOG PS 0–2	iv. paclitaxel (80 mg/m^2) days 1, 8, 15, 22 Q4w or iv. topotecan (4 mg/m^2) days 1, 8, 15 Q4w or iv. PLD (40 mg/m^2) Q4w Chemotherapy as above plus iv. bevacizumab (15 mg/kg) Q3w	HTN (20.1%); proteinuria (12.8%); F/A (2.2%); GIP (1.7%); VTE (3.4%)	Median PFS; 3.4 vs 6.7 months; HR: 0.48; (0.36–0.60); p < 0.001	Median OS; 13.3 vs 16.6 months; HR: 0.85 (0.66–1.08); p = 0.174	[39]

GOG 213 is a randomized Phase III trial designed to determine whether secondary cytoreductive surgery and/or the incorporation of bevacizumab to second-line chemotherapy improves progression-free survival in patients with platinum-sensitive recurrent ovarian cancer. At the time of manuscript production the data from GOG 213 were under embargo by the Society of Gynecologic Oncology.

†Investigational arms; a: Maintenance vs chemotherapy only arm; b: control vs bevacizumab throughout arms.

[†]Investigational arms; a: Maintenance vs chemotherapy only arm; b: control vs bevacizumab throughout arms.

[‡]After protocol modifcation patients with optimally resected stage 3 disease were eligible.

[§]Progression-free interval at least 6 months.

[¶]Based on the data from the AURELIA study, the US FDA approved bevacizumab for platinum-resistant, recurrent epithelial ovarian cancer on 14 November 2014 (see Table 1)

[#]Progression-free interval less than or equal to 6 months.

AE: Adverse events; DOR: Duration of response; e/o: Evidence of; ECOG: Eastern Cooperative Oncology Group; F/A: Fistula/abscess; GIP: Gastrointestinal perforation; HR: Hazard ratio; HTN: Hypertension; iv.: Intravenous; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PLD: Pegylated liposomal doxorubicin; PS: Performance status; VTE: Venous thromboembolism; Q3w: Every 3 weeks; Q4w: Every 4 weeks. Adapted with permission from [37].

Table 3

Phase II clinical trials of bevacizumab in cervical cancer.

Study	Drug	n	Eligibility	Pathology	OS (months)	PFS (months)	RR (%)	Grade 3–4 AEs	Ref.
Monk *et al.*	Bevacizumab 15 mg/kg Q3w	46	Second line (74%); third line (26%); GOG PS 0–2	Squamous, adenosquamous	7.3	3.4	35	HTN (15%); thromboembolism (11%); anemia (4%); vaginal bleeding (2%); neutropenia (2%); pain (13%); GI (8.7%); cardiovascular (4.3%); pulmonary (2%); fistula (2%)	[60]
Schefter *et al.*	Cisplatin 40 mg/m^2+ radiation therapy + brachytherapy + bevacizumab 10 mg/kg Q2w for three cycles	49	Untreated patients with st age 1B-3B cervical cancer	Squamous (80%)	NR	NR	NR	No treatment related SAEs; hematalogic AE 80%	[58]
Zighelboim *et al.*	Cisplatin 50 mg/m^2 day 1 + topotecan 0.75 mg/m^2 days 1, 2, 3 + bevacizumab 15 mg/kg day 1 Q3w	27	First recurrence; GOG PS 0–1	Squamous (67%), adenocarcinoma (33%)	13.2	7.1	35	Leukopenia (74%); neutropenia (56%); thrombocytopenia (81%); anemia (63%); GI (19%); pain (33%); metabolic (48%); infection (19%)	[61]

AE: Adverse event; GI: gastrointestinal; GOG: Gynecologic Oncology Group; HTN: Hypertension; NR: Not reported; OS: Overall survival; PFS: Progression-free survival; PS: Performance status; Q3w: Every 3 weeks; RR: Response rate; SAE: Serious adverse event.