EXPERT REVIEWS

Bevacizumab: overview of the literature

Expert Rev. Anticancer Ther. 12(5), 567–580 (2012)

Maria Ignez Braghiroli[1], Jorge Sabbaga[1,2] and Paulo M Hoff*[1,2]

[1]*Department of Radiology and Medical Oncology, Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil*
[2]*Centro de Oncologia, Hospital Sírio-Libanês, São Paulo, Brazil*
**Author for correspondence:*
Tel.: +55 11 3893 2735
paulo.hoff@icesp.org.br

Inhibiting the angiogenic process is a clever method of cancer care. Over the last decade, some antiangiogenic compounds have been developed and approved for cancer treatment. Bevacizumab is a humanized monoclonal antibody that inhibits VEGF activity. When used in combination with chemotherapy, it has an important role for treating many types of advanced cancer, including colorectal cancer, renal cell carcinoma, non-small-cell lung cancer, breast cancer, ovarian cancer and glioblastoma multiforme. In this paper we review the basic science behind this molecule's development, as well the major clinical trials in which bevacizumab was involved in oncology.

Keywords: angiogenesis • angiogenesis inhibitor • antiangiogenesis • bevacizumab

Angiogenesis is defined as the formation of new blood vessels by remodeling and expansion of primary vessels; it is important in normal physiologic processes, including tissue growth, wound healing, fetal development and reproductive function, and occurs in a series of complex, interrelated steps [1]. Preclinical and clinical models also suggest that angiogenesis is a necessary step for tumor growth beyond 1–2 mm and for the development of metastasis [2,3]; this is probably related to oxygen deprivation [4,5]. Tumors require oxygen and meet this demand by inducing transcription of hypoxia-inducible genes such as VEGF, FGF and PDGF [6].

VEGF

The original concept of antiangiogenesis is the inhibition of outgrowth of new blood vessels [7]. Without new blood vessels and a functional vasculature, tumors are limited in their ability to grow, and tumor-cell proliferation would give way to apoptosis. Considering that the angiogenesis is a highly regulated process, one can block it by inhibiting one of the proangiogenic pathways, or by activating one of the natural antiangiogenic pathways [8].

In 1983, Dorovak *et al.* published a paper describing a protein that was first called vascular permeability factor (VPF), secreted by a variety of rodent tumor cells [9,10], and detectable in rodent tumor ascites and culture media of tumor cells. Antibody directed against VPF seemed to block the increased peritoneal influx associated with the presence of tumor cells. Further investigating this finding, in 1986 they showed that a variety of human tumor cell lines also secreted a VPF that was closely related to the VPF secreted by rodent tumor cells [11]. The culture media from five of the seven human tumor lines examined contained VPF activity that was neutralized (>90%) by an antibody raised to guinea pig VPF. Comparisons made among matched pairs of tumorigenic and nontumorigenic human cell lines demonstrated that, in both cases, the tumorigenic derivatives secreted some 14-fold or more VPF than the nontumorigenic counterparts. Collectively, these data raised the possibility that expression of VPF was elevated as a consequence of malignant transformation and that this VPF was responsible for some of the increased vessel permeability and fluid accumulation that is commonly associated with neoplastic disease [11]. Confirming its importance, VPF was purified from several other animal and human sources, including a human histiocytic lymphoma cell line [12,13].

In addition to its potent vascular permeability-enhancing activity (on a molar basis, some 50,000-times that of histamine), the molecule known as VPF was also shown to be a selective mitogen for vascular endothelial cells, and it was therefore called VEGF by Ferrara *et al.* after purification from media conditioned by bovine pituitary folliculo stellate cells [14].

Once the possible target had been established, further experiments led to the description of a monoclonal antibody specific for VEGF that was tested in human tumor cell lines injected

 10.1586/ERA.12.13 ISSN 1473-7140

into nude mice [15]. Ferrara *et al.* reported that this experiment inhibited the growth of the tumors, but had no effect on the growth rate of the tumor cells *in vitro* [14]. The density of vessels was decreased in the antibody-treated tumors [15]. Since then, VEGF has been recognized as one of the most important factors involved in tumor angiogenesis.

VEGF is a member of a large family of dimeric glycoproteins that act as growth factors that includes VEGF-A (which is predominant), VEGF-B, VEGF-C, VEGF-D, VEGF-E, PDGF and placenta growth factor [16]. In $VEGF^{-/-}$ and $VEGF^{+/-}$ mice, the lack of vasculogenesis is lethal as a result of abnormal blood vessel development [17–19].

VEGF is released as a result of hypoxia, oxidative and mechanical stress, glucose deprivation and oncogene mutations [20,21]. Other proangiogenic growth factors released include bFGFs, PDGF, TNF and KGF [2]. These factors stimulate cell proliferation and migration, and activate other cells involved in angiogenesis.

VEGF binds with high affinity to the transmembrane tyrosine kinase VEGF receptor (VEGFR)-1, -2 and -3 [22]. Binding of VEGF to VEGFR-2 in endothelial cells results in dimerization of the receptor followed by tyrosine phosphorylation and induction of several proteins including urokinase, tissue-type plasminogen activator, plasminogen activator inhibitor-1, matrix metalloproteinases, and antiapoptotic factors facilitating tumor growth and tumor metastases [22].

Bevacizumab

Bevacizumab (Avastin®; Genentech, Inc., CA, USA) is a recombinant monoclonal antibody that binds and inactivates the biologic activity of VEGF-A, inhibiting angiogenesis and thus, tumor growth and proliferation (Figure 1) [23,24]. It is a humanized monoclonal IgG antibody with molecular weight of 149 kDa that contains human framework regions and the complementarity-determining regions of a murine antibody that inhibits all active isoforms of VEGF. Bevacizumab is produced through recombinant biotechnology from a Chinese hamster ovary mammalian cell line expression system [25]. It maintains the high specificity and affinity of the parental antibody (murine VEGF monoclonal antibody named A4.6.1) for VEGF-A, with reduced immunogenicity and a longer biologic half-life that can reach 21 days [26,27].

VEGFRs are membrane receptors with tyrosine kinase activity [28]. Bevacizumab inhibits the binding of VEGF to its receptor, affecting the vasculature through various mechanisms, including regression of the tumor vasculature, normalization of the tumor vasculature, inhibition of new blood vessel formation and prevention of progenitor cell recruitment from the bone marrow [7,29–31].

Pharmacodynamics

The results of therapy with antiangiogenesis agents are sometimes difficult to estimate. These agents are classically thought to arrest tumor growth rather than to produce tumor regression. Some of the methods currently described to monitor antiangiogenic therapy include observation of phenotypic changes in microvessel density (MVD), vessel diameter and tortuosity, vascular permeability, partial pressure of oxygen and interstitial pressure [32]. Levels of VEGF have been associated with a poor prognosis and an increased risk for metastasis when elevated in different cancer types, and it is a rational candidate when looking to a surrogate marker for bevacizumab activity. However, even though a Phase I trial did find that bevacizumab-treated patients with stable disease had slightly higher baseline VEGF levels than bevacizumab recipients with progressive disease [33], until now no clear association has been found between VEGF level and disease stability or response. An immunohistochemistry analysis of 126 primary tumor samples from a study of bevacizumab in metastatic breast cancer (mBC) could not find a correlation between VEGF RNA expression by *in situ* hybridization and response or failure to respond. Nevertheless, other biomarkers of the angiogenic cascade, including circulating endothelial progenitor cells, bFGF, E-selectin and vascular cell adhesion molecules, are being evaluated [34,35].

Rats implanted with intracranial glioblastoma cells showed a prolonged survival as well as decreased tumor vasculature after administration of A4.6.1. These data support the hypothesis that VEGF production is essential for glioblastoma angiogenesis [36]. Also, Kim *et al.* showed that administration of bevacizumab or A4.6.1 to tumor cell lines had no effect on their proliferation rates [15,37]. In preclinical studies, bevacizumab changed the growth characteristics of tumor spheroids of a human rhabdomyosarcoma cell line from being a rapidly growing malignancy to a dormant microcolony. Neovascularization of the microtumors was completely inhibited and their growth significantly suppressed [38]. These observations suggest that bevacizumab does not act on tumors cells but on endothelial cells, inhibiting blood supply and consequently cell proliferation [15].

Another study supported the findings that A4.6.1 reduces MVD in nude mice with colon adenocarcinoma and also suggested that A4.6.1 improves intratumoral uptake of chemotherapy [39]. These data support a theory that although there is reduced MVD the vessels display normalized vascular functions compared with untreated tumors, allowing improved delivery of blood-borne agents [39].

Most laboratory assays measure total and free serum VEGF concentrations. There is an increase in the concentration of total serum VEGF during treatment with bevacizumab [33,40], possibly related to decreased clearance of VEGF-bound inactive recombinant humanized monoclonal antibody VEGF. Usual laboratory assessments do not distinguish between free and bound VEGF [41].

Pharmacokinetics & metabolism

A detailed description of the pharmacokinetic parameters of bevacizumab is found in the US FDA submission document. The pharmacokinetic profile of bevacizumab was assessed using an assay that measured total serum bevacizumab concentrations. This analysis was based on eight clinical studies (two Phase I, four Phase II and two Phase III) involving a total of 491 patients with various solid tumors who received either bevacizumab monotherapy (1–20 mg/kg intravenously [iv.] once a week or

every 2 or 3 weeks) or combination chemotherapy. Using these dosage parameters, the estimated half-life was approximately 20 days (range: 13–45 days) [201]. In a Phase I study of bevacizumab in 25 patients with advanced solid tumors a linear pharmacokinetic relationship at doses ranging from 0.3 to 10 mg/kg on days 0, 28, 35 and 42 was reported [33]. At doses of 0.1 and 10 mg/kg, the C_{max} was 2.80 and 284 µg/ml, respectively.

The covariates reported to be significantly correlated with bevacizumab disposition were weight, sex, albumin, alkaline phosphatase, aspartate transaminase and chemotherapy administration. The clinical significance of the data is not known but some markers of disease severity (albumin <29 g/dl, alkaline phosphatase >484 U/l) are associated with 20% increase in clearance [42].

Bevacizumab is not known to be excreted in urine or feces. The clearance of bevacizumab varies by bodyweight, gender and tumor burden. Males have a higher bevacizumab clearance (0.262 vs 0.207 l/day) than females. Patients with higher tumor burden have a higher bevacizumab clearance (0.249 vs 0.199 l/day) than patients with tumor burdens below the median. The mean clearance of bevacizumab may vary up to 44% and in the dose range from 0.3 to 10 mg/kg it varies from 2.75 to 5.07 ml/kg per day, after the first dose. Serum VEGF levels were reduced to undetectable levels after the first dose of bevacizumab at >0.3 mg/kg. The exact route of bevacizumab metabolism and elimination has not been described, although it has been proposed that the drug is cleared via the reticuloendothelial system [43].

No formal drug–drug interaction studies of bevacizumab have been completed. In the study presented in the application for FDA approval it was administered concurrently with cytotoxic chemotherapy. The authors measured plasma chemotherapy concentrations on the first dose and after 28 days. Despite the small number of patients and samples collected, they concluded that chemotherapy did not alter the pharmacokinetic parameters of bevacizumab [32]. Some of the agents that have been commonly administered concurrently with bevacizumab are fluorouracil (FU), paclitaxel, irinotecan, doxorubicin, carboplatin, capecitabine and erlotinib [201]. Of note, when given together with anthracyclines, bevacizumab may increase cardiac toxicity and thus, cardiac function should be monitored. Also, irinotecan active metabolite SN-38 could have its plasma level increased by concomitant bevacizumab use in 33%, leading to severe diarrhea or neutropenia [42], so combination with irinotecan should follow a protocol [44].

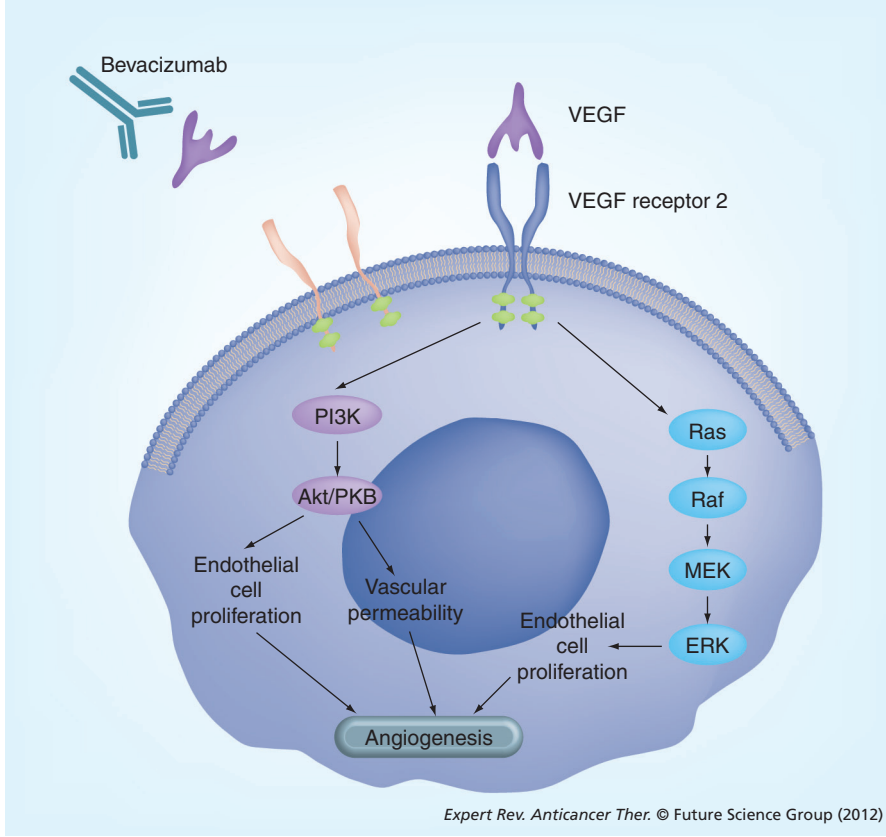

Figure 1. Bevacizumab inactivates the biologic activity of VEGF-A by preventing interaction with the transmembrane tyrosine kinase VEGF receptor, therefore inhibiting angiogenesis and, thus, tumor growth and proliferation.

Side effects

Bevacizumab is generally well tolerated. Across all studies, it was discontinued in 8.4–21% of patients because of adverse reactions. In a Phase I study where 25 patients with metastatic solid tumors received antibody doses of 0.1–10 mg/kg by 90-min iv. infusion, no patient developed antibodies to bevacizumab and no drug-related grade 3–4 infusion-related toxicities were described [33]. The most frequently related adverse events are hypertension and hypertensive crises with neurologic signs, wheezing, desaturation, chest pain, headaches, rigors and diaphoresis. In these circumstances, infusion should be interrupted followed by appropriate medical therapy. Some of the most frequent grade 1–2 adverse events during continuous treatment were asthenia, nausea, vomiting, arthralgia, cough, rash and fever [33].

The most common side effect related to bevacizumab is hypertension. The incidence of any grade pressure elevation is 23.6% and of severe hypertension (grade 3 or 4) ranges from 5–18% in clinical studies [45]. Patients on bevacizumab should have their pressure monitored regularly, and treated with antihypertensive therapy if above the normal limit according to high blood pressure guidelines. Those with previous history may be at increased risk and should be well controlled before starting treatment. Blood pressure should still be monitored even after discontinuation of medication until baseline levels are reached.

Patients who have been through any major surgery should wait at least 28 days or until the surgical wound is fully healed to be treated with bevacizumab. Its use can lead to dehiscence, bruising or bleeding. There are two distinct patterns of bleeding: minor hemorrhage, most commonly grade 1 epistaxis, hemorroidal or gum bleeding; and serious, and in some cases fatal, hemorrhagic events. When minor surgical procedures are performed, the recommendation is to not administer bevacizumab within 7 days. These events occur up to five-times more frequently in patients treated with bevacizumab compared with chemotherapy only. Serious events include CNS hemorrhage, hematemesis, gastrointestinal bleed and hemoptysis. When used as a treatment for lung cancers, serious or fatal pulmonary hemorrhage occurred in four out of 13 (31%) patients with squamous cell histology and two out of 53 (4%) patients with nonsquamous non-small-cell lung cancer (NSCLC) receiving bevacizumab and chemotherapy compared with none of the 32 (0%) patients receiving chemotherapy alone. These results led to a contraindication of its use in patients with squamous cell lung cancers [46].

Arterial thromboembolic events (ATE) appear to occur more commonly in patients receiving bevacizumab (twofold increased risk) and can be fatal in some cases [47]. These ATEs include cerebral infarction, transient ischemic attacks, myocardial infarction and angina. The proposed mechanism involves endothelial dysfunction due to compromised blood vessel integrity and exposure of subendothelial collagen [48]. Across indications, the incidence of grade ≥3 ATEs in the bevacizumab-containing arms was 2.4% compared with 0.7% in the control arms. Attention should be paid to patients with a history of ATE or age greater than 65 years [49]. In patients who suffered any ATE the recommendation is to permanently discontinue bevacizumab [48].

Gastrointestinal perforations can occur, particularly in patients with colorectal and ovarian cancers, and have been fatal in some cases. It may occur at any time during treatment, and patients generally present with abdominal pain, constipation and vomiting [50].

Proteinuria, defined as urinary protein excretion of >300 mg/day, is a less common side effect but its incidence may be as high as 20% [51]. Risk factors include underlying renal disease, previous nephrectomy, uncontrolled hypertension, diabetes mellitus and immunosuppression. In a meta-analysis, grade 3–4 proteinuria was found in 2.2% of the patients [52]. The patients with kidney cancer had the greatest risk (10.2%). Patients receiving bevacizumab should undergo a urinalysis every 3–4 weeks and those with 2+ or greater results should be further investigated with a 24-h urine collection. The medication should be discontinued permanently when ≥3 g/24 h proteinuria with hypoalbuminemia and peripheral edema are present. Kidney biopsy might show findings consistent with thrombotic microangiopathy and at present there is no prophylactic treatment.

Clinical trials

Bevacizumab has been tested in a variety of tumors and diseases. In this article we will review the data used for its approval for oncologic treatment (Table 1).

Phase II/Phase III

Colon

In 2003 Kabbinavar *et al.* published a report on the results of 104 previously untreated patients with metastatic colorectal cancer (mCRC) who were randomized to receive one of the following: 35 patients to 5-FU/leucovorin (LV) plus bevacizumab 5 mg/kg iv., 33 patients to 5-FU/LV plus bevacizumab 10 mg/kg iv. every 2 weeks and 36 patients to 5-FU/LV alone (control arm) [53,54]. Bevacizumab was administered for up to 48 weeks or until disease progression. Patients in the control arm with disease progression were given the option of crossing over to bevacizumab. The primary end points were the time to disease progression (TTP) and response rate (RR) – complete response or partial response (PR). Compared with the FU/LV, treatment with bevacizumab at both dose levels plus FU/LV resulted in RRs of 17 versus 32%, respectively (p = 0.086). TTP was longer in the bevacizumab-treated group (5.2 × 7.4 months, respectively; p = 0.013). Median survival was 21.5 months for the 5-mg/kg arm and 16.1 months for the 10-mg/kg arm, compared with 13.8 months for the control arm (p = 0.137 for the 5 mg/kg vs control and p = 0.582 for the 10 mg/kg vs control). The results of this study supported the use of the 5-mg/kg dose of bevacizumab in later mCRC trials.

Around this time, two randomized Phase III clinical trials established irinotecan-containing regimens as a new standard of care for mCRC [55–59].

However, the positive results of the Phase II trial were repeated in another Phase II study with patients with mCRC that were not considered candidates for irinotecan treatment (over 65 years, ECOG 1 or 2, serum albumin less than 3.5 g/dl, or prior abdominal/pelvic radiotherapy) [60]. They were randomly assigned to 5-FU/LV/placebo (n = 105) or 5-FU/LV/bevacizumab (n = 104). The results showed a median survival of 16.6 months for the 5-FU/LV/bevacizumab group and 12.9 months for the 5-FU/LV/placebo group (p = 0.16). Median progression-free survival (PFS) was 9.2 × 5.5 months (p = 0.0002) and RR were 26.0 × 15.2% (p = 0.055), respectively. This result was included in a combined analysis of three independent studies to conclude that bevacizumab added to 5-FU/LV provides a statistically significant and clinically relevant benefit to patients with previously untreated mCRC [61].

The pivotal multicenter, double-blind, Phase III trial by Hurwitz *et al.* [62] was designed to determine whether the addition of bevacizumab to a combination of irinotecan, fluorouracil and leucovorin (IFL) improves survival among patients with mCRC compared with IFL plus placebo [55]. In this trial, 813 patients with untreated mCRC were randomized to receive either IFL (irinotecan 125 mg/m^2 iv., FU 500 mg/m^2 iv. bolus, and LV 20 mg/m^2 iv.) plus bevacizumab 5 mg/kg iv. twice a week or IFL plus placebo. IFL was administered once weekly for 4 weeks, and the cycle was repeated every 6 weeks. The primary outcome was overall survival (OS) and secondary outcomes included PFS, RR, duration of response and quality of life (QoL). The IFL plus bevacizumab regimen was associated with improvements in all primary and secondary efficacy end points compared with the control regimen. The results showed an overall RR (ORR; 44.8

Table 1. Historical overview of bevacizumab's development and approval.

Month/year	Drug development history
November 2011	US FDA revokes the approval of the breast cancer indication for Avastin® (Genentech, CA, USA)
July 2009	FDA approves its use in breast cancer in combination with paclitaxel in patients who have not received chemotherapy for metastatic her-2 negative tumors. Also, FDA included Avastin as an indication for treatment of metastatic renal cell carcinoma in combination with IFN-α
May 2009	FDA approves Avastin for the treatment of glioblastoma with progressive disease following prior therapy
October 2006	Expanded indication to include its use in first-line therapy for unresectable, locally advanced, recurrent or metastatic nonsquamous, non-small-cell lung cancer in combination with carboplatin and paclitaxel
June 2006	Expand indication to include its use for second-line treatment of metastatic colorectal cancer
February 2004	FDA approval for first-line treatment of metastatic carcinoma of the colon and rectum in combination with 5-fluorouracil-based chemotherapy
November 2001	Recruitment into Phase II renal cancer trial stopped by National Cancer Institute because trial had reached its prespecified efficacy end point
2001	Anti-VEGF monoclonal antibody is called bevacizumab
2001	Phase III trials for breast cancer treatment in USA (iv. infusion)
1998–2000	Phase II trials for renal, lung, colorectal and breast cancer in USA
February 1997	Preclinical for cancer in USA (unknown route)

iv.: Intravenous.
Data taken from [204].

vs 34.8%; p = 0.004), median duration of response (10.4 vs 7.1 months; p = 0.001), PFS (10.6 vs 6.2 months; p < 0.001) and median OS (20.3 vs 15.6 months; p < 0.001). These data established the addition of bevacizumab to bolus IFL as a new and preferred first-line treatment of mCRC for patients with good perfomance status and those who are able to tolerate the toxicities of irinotecan. It is worth noting that the median OS with bevacizumab plus IFL (20.3 months) was comparable to that reported for sequential 5-FU/LV plus irinotecan followed by oxaliplatin (21.5 months) and 5-FU/LV plus oxaliplatin followed by irinotecan (20.6 months) [63,64]. This last pivotal Phase III trial originally included a 5-FU/LV plus bevacizumab arm, which was closed to enrollment after an interim analysis confirmed acceptable safety for IFL/BV. The subgroup analysis comparing 5-FU/LV plus bevacizumab (n = 110) with IFL plus placebo (n = 100) found that bevacizumab was associated with numerically greater results compared with placebo for the primary outcomes of RR (40 vs 37%, respectively), median PFS (8.8 vs 6.8 months) and duration of response (8.5 vs 7.2 months), although the differences were not statistically significant.

The use of bevacizumab in second line was initially evaluated in the Phase III ECOG E3200 trial. It was an open-label, multicenter, randomized, three-arm, controlled trial enrolling 829 adult patients. Patients had to have received a first-line or adjuvant treatment containing a fluoropyrimidine and irinotecan. Treatments included bevacizumab, 10 mg/kg on day 1, every 2 weeks, either alone or in combination with fluorouracil/folinic acid plus oxaliplatin (FOLFOX4), or FOLFOX4 alone. The bevacizumab monotherapy arm was closed to accrual after an interim efficacy analysis suggested a possibly shorter survival in that arm. The results showed a median survival for the FOLFOX4 and bevacizumab group of 12.9 months compared with 10.8 months for FOLFOX4 alone (p = 0.0011), and 10.2 months for bevacizumab alone. The median PFS was 7.3 × 4.7 months for the groups treated with FOLFOX4 plus bevacizumab and FOLFOX 4 alone, respectively (p < 0.0001), and 2.7 months for those treated with bevacizumab alone. ORR was 22.7, 8.6 and 3.3%, respectively (p < 0.0001 for FOLFOX4 with bevacizumab vs FOLFOX4 comparison) [65].

However, these results were not replicated when bevacizumab was given with oxaliplatin-based chemotherapy to untreated patients [66]. In this trial, bevacizumab was added to first-line oxaliplatin-based chemotherapy (capecitabine plus oxaliplatin [XELOX] or FOLFOX-4) in 1401 patients with mCRC. The primary end point was PFS. The median PFS was 9.4 months in the bevacizumab group and 8.0 months in the placebo group (p = 0.0023), median OS was 21.3 × 19.9 months (p = 0.077), respectively, and RR were similar in both arms. This trial failed to confirm OS and RR improvement by the addition of bevacizumab to a first-line oxaliplatin-based regimen [66]. Why this trial failed to confirm the impressive results seen elsewhere remains unanswered, and an observational series still suggested prolongation in survival with this strategy [67].

On 26 February 2004, the FDA approved bevacizumab as a first-line treatment for mCRC patients as a combination treatment along with IFL. On 20 June 2006, they approved bevacizumab to be administered in combination with FOLFOX4 for the second-line treatment of metastatic carcinoma of the colon or rectum.

Finally, combination of targeted drugs did not seem to benefit patients. The addition of bevacizumab to cetuximab, capecitabine and oxaliplatin was tested in the CAIRO trial [68], and to panitumumab in combination with irinotecan or oxaliplatin-based

chemotherapy in the PACCE trial [69]. In the first-line setting for metastatic disease, these regimens worsened PFS and increased toxicity, despite encouraging results in a previous Phase II trial [70]. Also, in the adjuvant scenario, the addition of bevacizumab to chemotherapy did not improve disease-free survival in any of the available trials to date [71,72].

Renal

Clear-cell renal cell carcinoma (RCC), the most common type of RCC (80% of all renal cancers) is a highly vascular tumor and has an interesting relationship with Von Hippel–Lindau (VHL) syndrome, an autosomal dominant disorder with inherited susceptibility to vascular tumors [73]. The lifetime risk of RCC in patients with VHL syndrome approaches 50%, often occurring as bilateral and multifocal tumors [74]. Mutations in the tumor suppressor gene VHL cause overexpression of VEGF and other proangiogenic factors through a mechanism involving hypoxia-inducible factor-α [75]. The fact that VHL somatic mutations occur in >75% of cases of RCC provided a rationale for therapy with an angiogenesis inhibitor. Standard cytotoxic chemotherapy or immunotherapy are associated with a response and clinical benefits in <10% of patients with advanced disease, along with considerable toxicity [76].

Two Phase II trials of bevacizumab in metastatic RCC (mRCC), one of monotherapy and the other of bevacizumab in combination with erlotinib, were published [75,76]. In the bevacizumab monotherapy trial, 116 patients with metastatic clear-cell RCC were randomly assigned to receive placebo, low-dose (3 mg/kg) bevacizumab, or high-dose (10 mg/kg) bevacizumab given iv. every 2 weeks. Most patients (93%) had received prior IL-2. The trial was stopped after the interim analysis met the criteria for early termination. There were four (10%) PRs in the high-dose bevacizumab arm. An intent-to-treat analysis demonstrated a significant prolongation of TTP in the high-dose bevacizumab arm compared with placebo (4.8 × 2.5 months; p = 0.001 by log-rank test). These results highlight the possibility that VEGF blockade may result in a low objective RR but could still lead to a delay in disease progression for the entire cohort [77]. There was no OS difference demonstrated, perhaps because of the crossover design of the study.

The study where bevacizumab was added to erlotinib showed a median PFS of 8.6 months for the 104 patients entered. Objective RRs were similar in the arms: 13% with bevacizumab alone versus 14% for the combination (p = 1.0). At 12 months from randomization, 83% of patients treated with bevacizumab were alive, versus 70% for patients receiving the combination. This study suggested that erlotinib does not add to the efficacy of bevacizumab, and that, at least in RCC, single-agent activity of bevacizumab has been underestimated [78].

Based on the promising Phase II data, Phase III trials were designed to evaluate bevacizumab as first-line treatment for metastatic disease, combined with IFN-α. In the USA, an Intergroup Phase III trial (CALGB 90206) investigated the addition of bevacizumab to IFN-α. In Europe, a similar trial which, however, was blinded and placebo controlled (AVOREN) was conducted, and the data from this latter study supported the approval of bevacizumab plus IFN-α as a treatment for mRCC on 31 July 2009.

The AVOREN trial was a multicenter, randomized, double-blind, Phase III trial with 649 patients with previously untreated mRCC. They received IFN-α-2a (9 million international units [MIU] subcutaneously three times weekly) and bevacizumab (10 mg/kg every 2 weeks; n = 327) or placebo and IFN-α-2a (n = 322) [51]. The primary end point was OS. The final median OS was 23.3 months for patients treated with bevacizumab and IFN-α, versus 21.3 months in the IFN-α and placebo arm (p = 0.1291), and median PFS was 10.2 versus 5.4 months, respectively.

The Intergroup Phase III study investigated the addition of bevacizumab to initial systemic therapy in RCC [79]. A total of 732 patients with metastatic clear-cell RCC without prior systemic therapy were randomly assigned to either IFN-α-2b (IFN-2b) 9 MIU, three times weekly, or the same dose and schedule of IFN-2b in combination with bevacizumab 10 mg/kg, intravenously every 2 weeks. Results showed a median duration of PFS of 8.5 months in the bevacizumab group versus 5.2 months in the control group (p = 0.0001). Increases in PFS were seen with bevacizumab plus IFN-α irrespective of risk group or whether reduced-dose IFN-α was received. Updated results for OS reported in 2010 showed a median OS of 18.3 months for bevacizumab plus IFN-2b and 17.4 months for the monotherapy group (p = 0.097) [80]. In both arms patients received at least one postprotocol antineoplastic therapy, possibly confounding the OS analysis, since these individuals receiving postprotocol therapy had a longer median OS.

The possible effects of secondary therapy have made results from these analyses problematic [78]. In other Phase III studies utilizing either sorafenib or sunitinib, an increased PFS was not accompanied by significant improvements in OS, but when patients receiving secondary therapy were censored, significant differences were noted [81,82].

In a systematic review evaluating the evidence from available randomized clinical trials of sunitinib and bevacizumab in the treatment of advanced mRCC, the effects of sunitinib and bevacizumab on PFS were compared indirectly, with interferon as a common comparator. They included three studies and found a significantly prolonged PFS with both interventions (from 5 months to 8–11 months) compared with interferon. OS was also prolonged, although the follow-up data was insufficient (median OS had not been reached in the bevacizumab group). Their indirect comparison revealed sunitinib to be superior to bevacizumab plus interferon in terms of PFS [83].

Other bevacizumab combinations have been tested. IL-2 (125,000 units/kg/day subcutaneously from Monday to Friday for 6 consecutive weeks followed by a 2-week rest period) was tested in patients with untreated mRCC in association with bevacizumab (10 mg/kg iv. every 2 weeks) [84]. A total of 26 patients were enrolled. The median PFS was 9.6 months and objective RR was 15%. Grade 3 constitutional adverse events (fatigue or fever/chills) and neutropenia were observed in 42 and 12% of patients, respectively. They concluded that bevacizumab plus low-dose IL-2 has only modest clinical activity in mRCC.

Sunitinib was also tested in association with bevacizumab in a Phase I trial in patients with advanced RCC [85]. Three cohorts of three to six patients were treated with escalated doses of daily oral

sunitinib (i.e., 25, 37.5 and 50 mg) for 4 weeks followed by a 2-week break and with fixed doses of bevacizumab (10 mg/kg) iv. once every 2 weeks. A total of 26 patients were enrolled at one of three dose levels. Grade 4 hemorrhage occurred in one patient in each of cohorts 2 and 3. The maximum tolerated dose was determined to be sunitinib 50 mg/bevacizumab 10 mg/kg, and this dose level frequently resulted in grades 3–4 hypertension and hematologic and vascular toxicities. A total of 48% of patients discontinued treatment because of severe adverse events. There was one complete response and 12 PRs, resulting in an objective RR of 52%. In this study the combination caused a high degree of hypertension, and vascular and hematologic toxicities at the highest dose level.

Bevacizumab was combined with sorafenib in a Phase I trial [86]. Patients with mRCC received sorafenib 200 mg twice daily on 28-day cycles and bevacizumab 5 mg/kg every 2 weeks. A total of 47 out of 48 patients completed the first response evaluation. Only four out of 48 individuals stopped therapy owing to toxicities. Maximum tolerated dose was sorafenib 200 mg orally once a day and bevacizumab 5 mg/kg iv. every 2 weeks. A total of 21 out of 46 patients (46%) had PR by RECIST. Median TTP was 11.2 months with ten patients (21%) progression-free at 18 months. This combination is now part of the multiarm Phase II trial – E2804 (BeST) – of combination regimens.

The combination of the mTOR inhibitor everolimus (RAD001) and bevacizumab has also been investigated [87]. Two groups of patients were enrolled: 'A', with no previous treatment with sorafenib or sunitinib; and 'B', with previous treatment with sorafenib and/or sunitinib. Patients received bevacizumab 10 mg/kg iv. every 2 weeks and RAD001 10 mg orally daily. A total of 59 patients (30 Group A and 29 Group B) were enrolled. The final PFS reported are 9.1 and 7.1 months in the untreated and tyrosine kinase inhibitor-pretreated groups, respectively, instead of 9 and 6 months previously presented. Based on the preliminary results, two studies were designed. One is a first-line, large, randomized Phase II study comparing this everolimus and bevacizumab regimen with bevacizumab plus interferon (RECORD 2 trial), and the other a second-line Phase III post-sunitinib study comparing the same regimen with everolimus plus placebo. However, the final PFS data make the rationale for the two large studies described above much weaker [88].

Bevacizumab was also tested in the neoadjuvant setting in patients with advanced RCC. A study assessed the safety and efficacy of presurgical treatment with bevacizumab in mRCC patients, and whether this would predict patient selection for nephrectomy [89]. They evaluated 50 patients who received either bevacizumab plus erlotinib (n = 23) or bevacizumab alone (n = 27) for 8 weeks. A total of 42 out of 50 patients underwent nephrectomy. Median PFS was 11.0 months and median OS was 25.4 months. Three patients discontinued treatment because of wound dehiscence. They concluded that neoadjuvant treatment with bevacizumab yields clinical outcomes comparable to postsurgical treatment, but it may result in wound-healing delays.

Breast

The first Phase III trial using bevacizumab in breast cancer included women with mBC who had received prior therapy with both an anthracycline and a taxane, and at least one, but no more than two, prior chemotherapy regimens [90]. Patients were randomized to capecitabine monotherapy (2500 mg/m^2/day twice daily for 14 days, followed by a 7-day rest period) or the combination of capecitabine plus bevacizumab (15 mg/kg every 21 days). The primary end point was PFS. The results showed that the addition of bevacizumab to capecitabine increased the RRs, but the median OS was 15.1 × 14.5 months and PFS was 4.86 versus 4.17 months, without a benefit for bevacizumab [90].

The following Phase III trial evaluated first-line therapy for mBC and compared 90 mg/m^2 of paclitaxel on days 1, 8 and 15 every 4 weeks, alone or with 10 mg/kg of bevacizumab on days 1 and 15 [91]. The primary end point was PFS. The results showed a PFS of 11.8 × 5.9 months ($p < 0.001$) in favor of combination therapy. ORR, 1-year survival and median OS were 36.9 × 21.2% ($p < 0.001$), 81.2 × 73.4% ($p = 0.01$) and 26.7 × 25.2 months ($p = 0.16$) for paclitaxel and paclitaxel plus bevacizumab, respectively. This trial reached its primary end point, although there was no difference in OS.

Bevacizumab was also combined with docetaxel in the AVADO trial [92,93]. This trial was a Phase III randomized study in women with HER2-negative mBC who had not received chemotherapy for metastatic disease. Individuals were randomly assigned to either docetaxel with bevacizumab 7.5 mg/kg (bevacizumab7.5) or 15 mg/kg (bevacizumab15) or docetaxel with placebo. The primary end point was PFS, which was 8.2 months in the placebo arm, and 9.0 and 10.1 months in the bevacizumab7.5 and bevacizumab15 arms, respectively. Statistical analysis demonstrated that the combination of bevacizumab15 with docetaxel appeared to be superior in terms of PFS compared with placebo plus docetaxel (HR: 0.77; $p = 0.006$). OS was similar in all three treatment arms, with median values of approximately 31 months.

More recently, another trial was published showing results of the combination of bevacizumab with capecitabine, taxane- or anthracycline-based regimens according to previous investigator's choice [94]. The primary end point was PFS and the results were beneficial for each bevacizumab combination (capecitabine cohort: increased from 5.7 to 8.6 months; $p = 0.001$; and taxane/anthracycline cohorts: increased from 8.0 to 9.2 months; $p = 0.001$). No statistically significant differences in OS between the placebo and bevacizumab-containing arms were found.

Since then, no trial has demonstrated significant improvement in OS or in QoL for the addition of bevacizumab. In addition, none of the subsequent studies have confirmed the magnitude of benefit seen in the original trial. A few months ago, the FDA revoked the mBC indication for bevacizumab after the recommendation of its advisory committee, which voted against it. Until the final decision, the drug remains FDA approved for the breast cancer indication (i.e., in combination with paclitaxel) [95]. This combination remains approved in Europe, as does the combination with capecitabine for the first-line treatment of mBC.

Lung

A Phase II randomized trial in patients with advanced NSCLC compared bevacizumab combined with carboplatin plus

paclitaxel [96] versus carboplatin and paclitaxel only [46]. In this study, 99 patients were randomly assigned to bevacizumab7.5 (n = 32) or 15 mg/kg (n = 35) plus carboplatin (area under the curve: 6) and paclitaxel (200 mg/m^2) every 3 weeks, or carboplatin and paclitaxel alone (n = 32). Primary end points were TTP and best confirmed RR. Upon disease progression, patients in the control arm had the option to receive single-agent bevacizumab 15 mg/kg every 3 weeks. The results showed a RR of 31.5 × 18.8%; TTP of 7.4 × 4.2 months and OS of 17.7 × 14.9 months in patients treated with carboplatin and paclitaxel plus bevacizumab (15 mg/kg), and the control arm, respectively. Bleeding was the most prominent adverse event and was manifested in two distinct clinical patterns; minor mucocutaneous hemorrhage and major hemoptysis, which was associated with squamous cell histology, tumor necrosis and cavitation, and disease location close to major blood vessels. These data suggested that the addition of bevacizumab to carboplatin and paclitaxel results in higher RRs, longer TTP and improved OS relative to the chemotherapy regimen.

Considering the results of this Phase II trial, an ECOG (E4599) Phase III study further investigated the role of bevacizumab on recurrent or advanced lung cancer [97]. A total of 878 patients were assigned to chemotherapy with paclitaxel (200 mg/m^2) and carboplatin (area under the curve: 6) with (n = 434) or without (n = 444) bevacizumab (15 mg/kg) every 3 weeks for six cycles. Bevacizumab was administered until disease progression or intolerable toxic effect. Patients with squamous-cell tumors, brain metastases, clinically significant hemoptysis or performance status (ECOG >1) were excluded. There was a significant improvement in OS, PFS and RR for patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone, 12.3 × 10.3 months (p = 0.003), 6.2 × 4.5 months (p = 0.001) and 35 × 15% (p = 0.001), respectively. A preplanned subset analysis showed a benefit for bevacizumab plus chemotherapy on OS among men (11.1 vs 8.7 months) but not women (13.3 vs 13.1 months). Fifteen patients in the bevacizumab group died with a treatment-related cause; five due to pulmonary hemorrhages (2.3 vs 0.5%), and the others gastrointestinal hemorrhage, CNS infarction, gastrointestinal perforation, myocardial infarction and neutropenic sepsis.

Based on this trial, on 11 October 2006, the FDA granted approval for a labeling extension for bevacizumab, administered in combination with carboplatin and paclitaxel, for the initial systemic treatment of patients with unresectable, locally advanced, recurrent or metastatic, nonsquamous NSCLC.

A second Phase III randomized trial, conducted in Europe and Canada (AVAiL), compared cisplatin and gemcitabine with or without bevacizumab (7.5 or 15 mg/kg) in 1043 patients with recurrent or advanced nonsquamous NSCLC [98]. Patients were randomly assigned to receive cisplatin (80 mg/m^2) and gemcitabine (1250 mg/m^2) for up to six cycles plus bevacizumab (7.5 or 15 mg/kg) or placebo every 3 weeks until disease progression. The primary end point was PFS; OS was a secondary end point. The results showed a median PFS of 6.1, 6.7 and 6.5 months, respectively, for chemotherapy alone, chemotherapy plus bevacizumab 7.5 mg/kg, and chemotherapy plus bevacizumab 15 mg/kg (p = 0.002 for bevacizumab low dose and p = 0.03 for bevacizumab high dose). Median OS was >13 months in all treatment groups; although not significantly increased with bevacizumab (HR: 0.93; 95% CI: 0.78–1.11; p = 0.420 and HR: 1.03; 95% CI: 0.86–1.23; p = 0.761) for the 7.5 and 15 mg/kg groups, respectively, versus placebo [99].

The use of bevacizumab in the general population was evaluated in the SAiL trial, which reported on the safety of bevacizumab administration in nonselected patients with advanced NSCLC [100]. Among the 2212 patients included, the incidence of clinically significant (grade ≥3) adverse events was: thromboembolism in 172 (8%) patients, hypertension in 125 (6%), bleeding in 80 (4%), proteinuria in 67 (3%) and pulmonary hemorrhage in 15 (1%). Fifty-seven (3%) patients died because of these adverse events, with thromboembolism (26 patients; 1%) and bleeding (17 patients, 1%) as the most common causes.

Among the trials using bevacizumab in combination with other drugs, there is a Phase II study in which second-line therapy with pemetrexed and bevacizumab every 3 weeks was evaluated in 48 patients [101]. Median OS and PFS were 8.6 and 4.0 months, respectively. The study did not meet its primary end point.

Davila *et al.* evaluated the combination of gemcitabine and oxaliplatin plus bevacizumab as first-line treatment for nonsquamous, stage IIIB or IV NSCLC in a Phase II trial [102]. They evaluated 44 patients and found a median TTP of 5.5 months and a median OS of 13.7 months. Similar results were found in another Phase II trial that evaluated the combination of oxaliplatin, pemetrexed and bevacizumab in patients with previously treated advanced NSCLC [103]. Of the 34 patients evaluable for tumor response, nine (27%) had a PR and 10 (29%) had progressive disease. Median PFS was 5.8 months and median OS was 12.5 months.

Erlotinib plus bevacizumab was compared with cisplatin/gemcitabine and bevacizumab in 224 stage IIIB/IV individuals randomized to one of these regimens [104]. EGFR mutation analysis was available in 161 patients for the experimental and control groups (71.9 vs 71.2%): wild-type (53.2 vs 62.0%), deletion 19 (3.6 vs 1.8%), L858R (4.5 vs 2.7%) and further mutations (9.0 vs 7.1%), respectively. Results for median PFS were 3.7 × 12.6 months (p = 0.0006) and median OS 7.2 × 15.7 months (p = 0.1) for erlotinib plus bevacizumab and chemotherapy plus bevacizumab, respectively. They concluded that the later regimen showed significant superiority compared with the investigational combination.

A great number of different Phase II trials evaluating bevacizumab combinations regimens, followed or not by maintenance therapy until progression, have been published. None of them have shown superiority in terms of PFS or OS [105–107].

A US Intergroup trial, ECOG 1505, is ongoing and will compare cisplatin-based chemotherapy with cisplatin-based chemotherapy plus bevacizumab for 1 year in patients with resected stage IB (with tumors ≥4 cm), stage II and stage III disease. The target accrual for this trial is 1500 patients and the estimated primary completion date is in 2013. An interim report of on-study demographics

and toxicity was reported at the 2011 American Society of Clinical Oncology meeting and the data for the 557 patients showed a significant increase in the risk for grades 3/4 hypertension (0.7 vs 19.7%; p < 0.001), proteinuria (0.7 vs 3.4%; p = 0.03), abdominal pain (0.4 vs 4.6%; p = 0.001) and overall grade 3/4 toxicity (68.5 vs 83.4%; p < 0.001) for the intervention arm [108].

Also in the adjuvant setting, there is an ongoing Memorial Sloan–Kettering Cancer Center pilot study evaluating docetaxel, vinorelbine and bevacizumab as adjuvant chemotherapy for patients with resected stage I–III NSCLC who are unfit for cisplatin-based regimens.

Glioblastoma

The prognosis for patients with glioblastoma is poor, with an estimated 5-year survival rate of 4.75% [202]. Standard treatments for glioblastoma includes surgery, with as much tumor removal as possible, postoperative radiotherapy and chemotherapy with temozolomide [203]. With this approach, the median OS for those who experience recurrence of disease was approximately 25 weeks [109].

Two trials evaluated the efficacy of bevacizumab in patients with previously treated glioblastoma. These are prospective Phase II clinical trials called the AVF3708g trial [110] and the NCI 06-C-0064E trial [111]. They included patients with histologically confirmed glioblastoma that had recurred after prior standard radiotherapy and temozolomide chemotherapy.

The AVF3708g trial was a randomized, noncomparative, multicenter study in which patients with glioblastoma in first or second relapse were assigned to receive bevacizumab 10 mg/kg every 2 weeks on a 6-week cycle (n = 85) or bevacizumab (at the same dosage) in combination with irinotecan (n = 82) every 2 weeks at a dosage of 340 mg/m^2 for patients taking enzyme-inducing antiepileptic drugs or 125 mg/m^2 for patients not taking enzyme-inducing antiepileptic drugs [110]. Efficacy analyses were based on comparisons with historical data. In the bevacizumab-alone and the bevacizumab-plus-irinotecan groups, estimated 6-month PFS rates were 42.6 and 50.3%; objective RRs were 28.2 and 37.8%; and median OS times were 9.2 and 8.7 months, respectively. The estimated 6-month PFS rates were 42.6% (97.5% CI: 29.6–55.5%) in the bevacizumab group and 50.3% (97.5% CI: 36.8–63.9%) in the bevacizumab plus irinotecan group, and these exceeded the 15% rate assumed for salvage chemotherapy and CPT-11 alone (p = 0.0001). Updated results were presented at the 2010 American Society of Clinical Oncology annual meeting, showing a median OS rate at 30 months of 11 and 16% for bevacizumab alone or with irinotecan, respectively [112].

The other Phase II trial was the NCI 06-C-0064E. It was a single-arm, single-center, Phase II trial of bevacizumab in patients with glioblastoma that had recurred after radiotherapy and temozolomide chemotherapy (n = 48) [111]. Bevacizumab 10 mg/kg was given by iv. infusion every 2 weeks on a 4-week cycle. The primary end point of the study was PFS at 6 months. A total of 48 heavily pretreated patients were accrued to this study. Six patients (12.5%) were removed from the study for drug-associated toxicity (five thromboembolic events and one bowel perforation). A total of 34 patients (71%) and 17 patients (35%) achieved radiographic response based on Levin and Macdonald criteria, respectively. Median PFS was 16 weeks, the 6-month PFS was 29%, the 6-month OS was 57% and the median OS was 31 weeks.

On 5 May 2009, the FDA granted accelerated approval to bevacizumab as a single agent for patients with glioblastoma, with progressive disease following prior therapy. At present, bevacizumab alone or in combination with chemotherapy has not been demonstrated to prolong OS and the studies to determine the impact of this agent on OS are ongoing.

In the adjuvant setting bevacizumab has been tested in an open-label, prospective, multicenter single-arm Phase II study that combined bevacizumab biweekly with radiation therapy and temozolomide for the treatment of newly diagnosed glioblastoma [113]. A total of 70 patients with newly diagnosed glioblastoma multiforme were included. After completion of radiotherapy, patients resumed temozolomide for 5 days every 4 weeks and continued biweekly bevacizumab. MGMT promoter methylation was assessed in patient tumor tissue. The OS and PFS were 19.6 and 13.6 months, respectively, compared with 21.1 and 7.6 months in the control cohort, and 14.6 and 6.9 months in the EORTC-NCI Canada cohort. The conclusion was that patients in this study had improved PFS without improved OS compared with the cohorts used as the control group.

The addition of a chemotherapy agent or the substitution of a second cytotoxic agent, such as carboplatin instead of irinotecan, did not impact in patients with progressive disease [114]. As presented by Zuniga *et al.*, tumor progression while on bevacizumab is associated with a poor prognosis and reduced likelihood of response to other agents, although there are no controlled trials in this setting [115].

Ovary

Carboplatin plus paclitaxel and concurrent bevacizumab as well as maintenance treatment could be considered as a viable first-line regimen for women with epithelial ovarian or primary peritoneal cancer according to preliminary results of two trials presented over the past year. The trials are the GOG l 218 and ICON7 [116,117]. Both of them included untreated women with high-risk early-stage or advanced-stage epithelial ovarian cancer, primary peritoneal cancer or Fallopian tube cancer. They demonstrated an approximate 3-month increase in PFS, which was the primary end point of the trials. However, one needs to consider that there was no difference in OS. Therefore, the use of bevacizumab as part of the first-line therapy represents an option but is not yet the standard of care for initial therapy of surgically cytoreduced stage III and IV disease, nor is approved by the FDA. The final results are still necessary in order to further clarify the role of bevacizumab in this scenario. As with breast cancer, questions remain as to whether the improvement in PFS seen with the use of this agent is clinically meaningful and will translate into better QoL or prolonged survival for the treated patients.

Expert commentary & five-year view

Bevacizumab is the result of years of painstaking studies by brilliant scientists, and is certainly one of the most important new drugs in the armamentarium against cancers available today. Its

importance is independent and goes beyond its actual activity against any of the tumor types listed in this review. It will always be the first antiangiogenic drug to be used in clinical practice, and its advent changed forever the way we think about and treat solid tumors. Other monoclonal antibodies and tyrosine kinase inhibitors had already demonstrated that specific targeting is feasible against cancer but bevacizumab showed that a therapy could be directed to molecules outside of the cancer cells, acting on the tumor environment as well.

Despite its recognized importance, bevacizumab is not a miracle drug. Patients are still progressing and dying, and bevacizumab has not increased the cure rates even for those tumors where it is most active. We do not know for sure what makes a tumor resistant to the drug and several questions remain on how we should actually use it. The main questions that remain unanswered are:

- Can we identify a positive or negative predictive factor that would allow us to use it only when it is more likely to work?
- What is the magnitude of benefit that justifies the use of bevacizumab and makes it cost effective?
- Should we use it continuously, even after tumor progression?
- When tumors are exposed to bevacizumab, do they have a 'rebound' when the drug is discontinued?
- Why is the improvement in PFS so seldom associated with a similar impact on OS?
- Why have the adjuvant trials failed so miserably so far?

It will take a lot of effort for those questions to be answered. More importantly, these answers may actually lead to the development of a new generation of better and more potent antiangiogenic drugs that will eventually replace bevacizumab.

Financial & competing interests disclosure

The authors have no 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. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Bevacizumab was the first antiangiogenic drug to be used in clinical practice and its advent changed forever the way we think about and treat solid tumors.
- It has been approved for use in combination with chemotherapy for treating many types of advanced cancer including colorectal cancer, renal cell carcinoma, non-small-cell lung cancer, breast cancer, ovarian cancer and glioblastoma multiforme.
- In metastatic colorectal cancer bevacizumab is approved as first- and second-line treatment in combination with chemotherapy based on fluorouracil and irinotecan, or oxaliplatin.
- Bevacizumab plus IFN-α is approved for the treatment of metastatic renal cell carcinoma.
- Bevacizumab is used for metastatic breast cancer treatment in Europe but this issue is still under discussion in the USA.
- In lung cancer, bevaciumab is approved for treatment of metastatic disease to be used in combination with chemotherapy.

References

1 Herbst RS, Onn A, Sandler A. Angiogenesis and lung cancer: prognostic and therapeutic implications. *J. Clin. Oncol.* 23(14), 3243–3256 (2005).

2 Motl S. Bevacizumab in combination chemotherapy for colorectal and other cancers. *Am. J. Health Syst. Pharm.* 62(10), 1021–1032 (2005).

3 Folkman J. Seminars in medicine of the Beth Israel Hospital, Boston. Clinical applications of research on angiogenesis. *N. Engl. J. Med.* 333(26), 1757–1763 (1995).

4 Akagi Y, Liu W, Zebrowski B, Xie K, Ellis LM. Regulation of vascular endothelial growth factor expression in human colon cancer by insulin-like growth factor-I. *Cancer Res.* 58(17), 4008–4014 (1998).

5 Nasu R, Kimura H, Akagi K, Murata T, Tanaka Y. Blood flow influences vascular growth during tumour angiogenesis. *Br. J. Cancer* 79(5–6), 780–786 (1999).

6 Rosen LS. Clinical experience with angiogenesis signaling inhibitors: focus on vascular endothelial growth factor (VEGF) blockers. *Cancer Control* 9(Suppl. 2), 36–44 (2002).

7 Folkman J, Klagsbrun M. Angiogenic factors. *Science* 235(4787), 442–447 (1987).

8 Potente M, Gerhardt H, Carmeliet P. Basic and therapeutic aspects of angiogenesis. *Cell* 146(6), 873–887 (2011).

9 Senger DR, Galli SJ, Dvorak AM, Perruzzi CA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science* 219(4587), 983–985 (1983).

10 Folkman J. Antiangiogenesis: new concept for therapy of solid tumors. *Ann. Surg.* 175(3), 409–416 (1972).

11 Senger DR, Perruzzi CA, Feder J, Dvorak HF. A highly conserved vascular permeability factor secreted by a variety of human and rodent tumor cell lines. *Cancer Res.* 46(11), 5629–5632 (1986).

12 Connolly DT, Olander JV, Heuvelman D *et al.* Human vascular permeability factor. Isolation from U937 cells. *J. Biol. Chem.* 264(33), 20017–20024 (1989).

13 Senger DR, Connolly DT, Van de Water L, Feder J, Dvorak HF. Purification and NH2-terminal amino acid sequence of guinea pig tumor-secreted vascular permeability factor. *Cancer Res.* 50(6), 1774–1778 (1990).

14 Ferrara N, Henzel WJ. Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells. *Biochem. Biophys. Res. Commun.* 161(2), 851–858 (1989).

15 Kim KJ, Li B, Winer J *et al.* Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth *in vivo*. *Nature* 362(6423), 841–844 (1993).

16 Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science* 246(4935), 1306–1309 (1989).

17 Carmeliet P, Ferreira V, Breier G *et al.* Abnormal blood vessel development and lethality in embryos lacking a single *VEGF* allele. *Nature* 380(6573), 435–439 (1996).

18 Ferrara N, Carver-Moore K, Chen H *et al.* Heterozygous embryonic lethality induced by targeted inactivation of the *VEGF* gene. *Nature* 380(6573), 439–442 (1996).

19 Shalaby F, Rossant J, Yamaguchi TP *et al.* Failure of blood-island formation and vasculogenesis in *Flk-1*-deficient mice. *Nature* 376(6535), 62–66 (1995).

20 Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J. Clin. Oncol.* 23(5), 1011–1027 (2005).

21 Gasparini G, Longo R, Fanelli M, Teicher BA. Combination of antiangiogenic therapy with other anticancer therapies: results, challenges, and open questions. *J. Clin. Oncol.* 23(6), 1295–1311 (2005).

22 Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat. Med.* 9(6), 669–676 (2003).

23 Gerber HP, Ferrara N. Pharmacology and pharmacodynamics of bevacizumab as monotherapy or in combination with cytotoxic therapy in preclinical studies. *Cancer Res.* 65(3), 671–680 (2005).

24 Zondor SD, Medina PJ. Bevacizumab: an angiogenesis inhibitor with efficacy in colorectal and other malignancies. *Ann. Pharmacother.* 38(7–8), 1258–1264 (2004).

25 AVASTIN® package insert. Genentech, CA, USA (2004).

26 Rosen LS. VEGF-targeted therapy: therapeutic potential and recent advances. *Oncologist* 10(6), 382–391 (2005).

27 Wang Y, Fei D, Vanderlaan M, Song A. Biological activity of bevacizumab, a humanized anti-VEGF antibody *in vitro*. *Angiogenesis* 7(4), 335–345 (2004).

28 Ferrara N. Molecular and biological properties of vascular endothelial growth factor. *J. Mol. Med.* 77(7), 527–543 (1999).

29 Presta LG, Chen H, O'Connor SJ *et al.* Humanization of an antivascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. *Cancer Res.* 57(20), 4593–4599 (1997).

30 Wood JM, Bold G, Buchdunger E *et al.* PTK787/ZK 222584, a novel and potent inhibitor of vascular endothelial growth factor receptor tyrosine kinases, impairs vascular endothelial growth factor-induced responses and tumor growth after oral administration. *Cancer Res.* 60(8), 2178–2189 (2000).

31 Kerbel RS. Antiangiogenic therapy: a universal chemosensitization strategy for cancer? *Science* 312(5777), 1171–1175 (2006).

32 Augustin HG. Translating angiogenesis research into the clinic: the challenges ahead. *Br. J. Radiol.* 76(Spec. No. 1), S3–S10 (2003).

33 Gordon MS, Margolin K, Talpaz M *et al.* Phase I safety and pharmacokinetic study of recombinant human antivascular endothelial growth factor in patients with advanced cancer. *J. Clin. Oncol.* 19(3), 843–850 (2001).

34 Jain RK. Normalizing tumor vasculature with antiangiogenic therapy: a new paradigm for combination therapy. *Nat. Med.* 7(9), 987–989 (2001).

35 Brower V. Evidence of efficacy: researchers investigating markers for angiogenesis inhibitors. *J. Natl Cancer Inst.* 95(19), 1425–1427 (2003).

36 Rubenstein JL, Kim J, Ozawa T *et al.* Anti-VEGF antibody treatment of glioblastoma prolongs survival but results in increased vascular cooption. *Neoplasia.* 2(4), 306–314 (2000).

37 Holmgren L, O'Reilly MS, Folkman J. Dormancy of micrometastases: balanced proliferation and apoptosis in the presence of angiogenesis suppression. *Nat. Med.* 1(2), 149–153 (1995).

38 Borgstrom P, Hillan KJ, Sriramarao P, Ferrara N. Complete inhibition of angiogenesis and growth of microtumors by antivascular endothelial growth factor neutralizing antibody: novel concepts of angiostatic therapy from intravital videomicroscopy. *Cancer Res.* 56(17), 4032–4039 (1996).

39 Wildiers H, Guetens G, De Boeck G *et al.* Effect of antivascular endothelial growth factor treatment on the intratumoral uptake of CPT-11. *Br. J. Cancer* 88(12), 1979–1986 (2003).

40 Margolin K, Gordon MS, Holmgren E *et al.* Phase Ib trial of intravenous recombinant humanized monoclonal antibody to vascular endothelial growth factor in combination with chemotherapy in patients with advanced cancer: pharmacologic and long-term safety data. *J. Clin. Oncol.* 19(3), 851–856 (2001).

41 Adams J, Carder PJ, Downey S *et al.* Vascular endothelial growth factor (VEGF) in breast cancer: comparison of plasma, serum, and tissue VEGF and microvessel density and effects of tamoxifen. *Cancer Res.* 60(11), 2898–2905 (2000).

42 AVASTIN® product monograph. Hoffmann-La Roche Limited, ON, Canada (2005).

43 Lin YS, Nguyen C, Mendoza JL *et al.* Preclinical pharmacokinetics, interspecies scaling, and tissue distribution of a humanized monoclonal antibody against vascular endothelial growth factor. *J. Pharmacol. Exp. Ther.* 288(1), 371–378 (1999).

44 BC Cancer Agency Gastrointestinal Tumour Group (UGICIRB). BCCA Protocol Summary for Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Bevacizumab and Capecitabine. Cancer Agency, Vancouver, BC, Canada (2006).

45 Ranpura V, Pulipati B, Chu D, Zhu X, Wu S. Increased risk of high-grade hypertension with bevacizumab in cancer patients: a meta-analysis. *Am. J. Hypertens.* 23(5), 460–468 (2010).

46 Johnson DH, Fehrenbacher L, Novotny WF *et al.* Randomized Phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J. Clin. Oncol.* 22(11), 2184–2191 (2004).

47 Ranpura V, Hapani S, Chuang J, Wu S. Risk of cardiac ischemia and arterial thromboembolic events with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis of randomized controlled trials. *Acta. Oncol.* 49(3), 287–297 (2010).

48 Shord SS, Bressler LR, Tierney LA, Cuellar S, George A. Understanding and managing the possible adverse effects associated with bevacizumab. *Am. J. Health Syst. Pharm.* 66(11), 999–1013 (2009).

49 AVASTIN® prescribing information. Genentech Inc., CA, USA (2011).

50 George Sledge KM, Novotny W, Gaudreault J, Ash M, Cobleigh M. A Phase II trial of single-agent rhumab VEGF (recombinant humanized monoclonal antibody to vascular endothelial cell growth factor) in patients with relapsed metastatic breast cancer. *Proc. Am. Soc. Clin. Oncol.* 19 (2000) (Abstract 5C).

51 Escudier B, Pluzanska A, Koralewski P *et al.* Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind Phase III trial. *Lancet* 370(9605), 2103–2111 (2007).

52 Wu S, Kim C, Baer L, Zhu X. Bevacizumab increases risk for severe proteinuria in cancer patients. *J. Am. Soc. Nephrol.* 21(8), 1381–1389 (2010).

53 Kabbinavar F, Hurwitz HI, Fehrenbacher L *et al.* Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J. Clin. Oncol.* 21(1), 60–65 (2003).

54 Petrelli N, Douglass HO Jr, Herrera L *et al.* The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: a prospective randomized Phase III trial. Gastrointestinal Tumor Study Group. *J. Clin. Oncol.* 7(10), 1419–1426 (1989).

55 Saltz LB, Cox JV, Blanke C *et al.* Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N. Engl. J. Med.* 343(13), 905–914 (2000).

56 Douillard JY, Cunningham D, Roth AD *et al.* Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 355(9209), 1041–1047 (2000).

57 Knight RLM, Pirotta N, Elfring G, Locker P, Saltz L. First-line irinotecan (C), fluorouracil (F), leucovorin (L) especially improves survival (OS) in metastatic colorectal cancer (MCRC) Patients (PT) with favorable prognostic indicators. *Proc. Am. Soc. Clin. Oncol.* 19 (2000) (Abstract 991).

58 Bleiberg H, Cvitkovic E. Characterisation and clinical management of CPT-11 (irinotecan)-induced adverse events: the European perspective. *Eur. J. Cancer* 32A(Suppl. 3), S18–S23 (1996).

59 Rothenberg ML, Cox JV, DeVore RF *et al.* A multicenter, Phase II trial of weekly irinotecan (CPT-11) in patients with previously treated colorectal carcinoma. *Cancer* 85(4), 786–795 (1999).

60 Kabbinavar FF, Schulz J, McCleod M *et al.* Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized Phase II trial. *J. Clin. Oncol.* 23(16), 3697–3705 (2005).

61 Kabbinavar FF, Hambleton J, Mass RD, Hurwitz HI, Bergsland E, Sarkar S. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J. Clin. Oncol.* 23(16), 3706–3712 (2005).

62 Hurwitz H, Fehrenbacher L, Novotny W *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N. Engl. J. Med.* 350(23), 2335–2342 (2004).

63 Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. *N. Engl. J. Med.* 352(5), 476–487 (2005).

64 Tournigand C, Andre T, Achille E *et al.* FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J. Clin. Oncol.* 22(2), 229–237 (2004).

65 Giantonio BJ, Catalano PJ, Meropol NJ *et al.* Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J. Clin. Oncol.* 25(12), 1539–1544 (2007).

66 Saltz LB, Clarke S, Diaz-Rubio E *et al.* Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized Phase III study. *J. Clin. Oncol.* 26(12), 2013–2019 (2008).

67 Grothey A, Sugrue MM, Purdie DM *et al.* Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRITE). *J. Clin. Oncol.* 26(33), 5326–5334 (2008).

68 Tol J, Koopman M, Rodenburg CJ *et al.* A randomised Phase III study on capecitabine, oxaliplatin and bevacizumab with or without cetuximab in first-line advanced colorectal cancer, the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). An interim analysis of toxicity. *Ann. Oncol.* 19(4), 734–738 (2008).

69 Hecht JR, Mitchell E, Chidiac T *et al.* A randomized Phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J. Clin. Oncol.* 27(5), 672–680 (2009).

70 Saltz LB, Lenz HJ, Kindler HL *et al.* Randomized Phase II trial of cetuximab, bevacizumab, and irinotecan compared with cetuximab and bevacizumab alone in irinotecan-refractory colorectal cancer: the BOND-2 study. *J. Clin. Oncol.* 25(29), 4557–4561 (2007).

71 Allegra CJ, Yothers G, O'Connell MJ *et al.* Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: results of NSABP protocol C-08. *J. Clin. Oncol.* 29(1), 11–16 (2011).

72 De Gramont A, Van Cutsem E, Tabernero J *et al.* AVANT: results from a randomized, three-arm multinational Phase III study to investigate bevacizumab with either XELOX or FOLFOX4 versus FOLFOX4 alone as adjuvant treatment for colon cancer. *J. Clin. Oncol.* 29(Suppl. 4) (2011) (Abstract 362).

73 Lonser RR, Glenn GM, Walther M *et al.* von Hippel–Lindau disease. *Lancet* 361(9374), 2059–2067 (2003).

74 Couch V, Lindor NM, Karnes PS, Michels VV. von Hippel–Lindau disease. *Mayo Clin. Proc.* 75(3), 265–272 (2000).

75 Yang JC, Haworth L, Sherry RM *et al.* A randomized trial of bevacizumab, an antivascular endothelial growth factor antibody, for metastatic renal cancer. *N. Engl. J. Med.* 349(5), 427–434 (2003).

76 Hainsworth JD, Sosman JA, Spigel DR, Edwards DL, Baughman C, Greco A. Treatment of metastatic renal cell carcinoma with a combination of bevacizumab and erlotinib. *J. Clin. Oncol.* 23(31), 7889–7896 (2005).

77 Rini BI, Small EJ. Biology and clinical development of vascular endothelial growth factor-targeted therapy in renal cell carcinoma. *J. Clin. Oncol.* 23(5), 1028–1043 (2005).

78 Bukowski RM. Metastatic clear-cell carcinoma of the kidney: therapeutic role of bevacizumab. *Cancer Manag. Res.* 2, 83–96 (2010).

79 Rini BI, Halabi S, Rosenberg JE *et al.* Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. *J. Clin. Oncol.* 28(13), 2137–2143 (2010).

80 Escudier B, Bellmunt J, Negrier S *et al.* Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. *J. Clin. Oncol.* 28(13), 2144–2150 (2010).

81 Escudier B, Eisen T, Stadler WM *et al.* Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety

results of the Phase III treatment approaches in renal cancer global evaluation trial. *J. Clin. Oncol.* 27(20), 3312–3318 (2009).

82 Motzer RJ, Hutson TE, Tomczak P *et al.* Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J. Clin. Oncol.* 27(22), 3584–3590 (2009).

83 Thompson Coon JS, Liu Z, Hoyle M *et al.* Sunitinib and bevacizumab for first-line treatment of metastatic renal cell carcinoma: a systematic review and indirect comparison of clinical effectiveness. *Br. J. Cancer* 101(2), 238–243 (2009).

84 Garcia JA, Mekhail T, Elson P *et al.* Clinical and immunomodulatory effects of bevacizumab and low-dose interleukin-2 in patients with metastatic renal cell carcinoma: results from a Phase II trial. *BJU Int.* 107(4), 562–570 (2011).

85 Feldman DR, Baum MS, Ginsberg MS *et al.* Phase I trial of bevacizumab plus escalated doses of sunitinib in patients with metastatic renal cell carcinoma. *J. Clin. Oncol.* 27(9), 1432–1439 (2009).

86 Sosman JA, Flaherty KT, Atkins MB *et al.* Updated results of Phase I trial of sorafenib (S) and bevacizumab (B) in patients with metastatic renal cell cancer (mRCC). *J. Clin. Oncol.* 26(Suppl.) (2008) (Abstract 5011).

87 Whorf RC, Hainsworth JD, Spigel DR *et al.* Phase II study of bevacizumab and everolimus (RAD001) in the treatment of advanced renal cell carcinoma (RCC). *J. Clin. Oncol.* 26(Suppl.) (2008) (Abstract 5010).

88 Escudier B. How to interpret Phase II data for everolimus plus bevacizumab in renal cell carcinoma. *J. Clin. Oncol.* 28(13), 2125–2126 (2010).

89 Jonasch E, Wood CG, Matin SF *et al.* Phase II presurgical feasibility study of bevacizumab in untreated patients with metastatic renal cell carcinoma. *J. Clin. Oncol.* 27(25), 4076–4081 (2009).

90 Miller KD, Chap LI, Holmes FA *et al.* Randomized Phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J. Clin. Oncol.* 23(4), 792–799 (2005).

91 Miller K, Wang M, Gralow J *et al.* Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N. Engl. J. Med.* 357(26), 2666–2676 (2007).

92 Miles DW, Chan A, Dirix LY *et al.* Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J. Clin. Oncol.* 28(20), 3239–3247 (2010).

93 Sweeney CJ, Miller KD, Sissons SE *et al.* The antiangiogenic property of docetaxel is synergistic with a recombinant humanized monoclonal antibody against vascular endothelial growth factor or 2-methoxyestradiol but antagonized by endothelial growth factors. *Cancer Res.* 61(8), 3369–3372 (2001).

94 Robert NJ, Dieras V, Glaspy J *et al.* RIBBON-1: randomized, double-blind, placebo-controlled, Phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J. Clin. Oncol.* 29(10), 1252–1260 (2011).

95 D'Agostino RB Sr. Changing end points in breast-cancer drug approval – the Avastin story. *N. Engl. J. Med.* 365(2), e2 (2011).

96 Herbst RS, Takeuchi H, Teicher BA. Paclitaxel/carboplatin administration along with antiangiogenic therapy in non-small-cell lung and breast carcinoma models. *Cancer Chemother. Pharmacol.* 41(6), 497–504 (1998).

97 Sandler A, Gray R, Perry MC *et al.* Paclitaxel–carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N. Engl. J. Med.* 355(24), 2542–2550 (2006).

98 Reck M, von Pawel J, Zatloukal P *et al.* Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAIL. *J. Clin. Oncol.* 27(8), 1227–1234 (2009).

99 Reck M, von Pawel J, Zatloukal P *et al.* Overall survival with cisplatin–gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised Phase III trial (AVAIL). *Ann. Oncol.* 21(9), 1804–1809 (2010).

100 Crino L, Dansin E, Garrido P *et al.* Safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous non-small-cell lung cancer (SAiL, MO19390): a Phase 4 study. *Lancet* 11(8), 733–740 (2010).

101 Adjei AA, Mandrekar SJ, Dy GK *et al.* Phase II trial of pemetrexed plus bevacizumab for second-line therapy of patients with advanced non-small-cell lung cancer: NCCTG and SWOG study N0426. *J. Clin. Oncol.* 28(4), 614–619 (2010).

102 Lilenbaum R, Raez L, Tseng J, Seigel L, Davila E. Efficacy and safety of oxaliplatin and gemcitabine with bevacizumab in advanced non-small-cell lung cancer. *J. Thorac. Oncol.* 3(5), 511–515 (2008).

103 Heist RS, Fidias P, Huberman M *et al.* A Phase II study of oxaliplatin, pemetrexed, and bevacizumab in previously treated advanced non-small cell lung cancer. *J. Thorac. Oncol.* 3(10), 1153–1158 (2008).

104 Thomas M, Reuss A, Fischer JR *et al.* Randomized Phase II trial of erlotinib (E)/bevacizumab (B) compared with cisplatin (P)/gemcitabine (G) plus B in first-line treatment of advanced nonsquamous (NS) non-small-cell lung cancer (NSCLC). *J. Clin. Oncol.* 29(Suppl.) (2011) (Abstract 7504).

105 Malhotra B, Evans T, Weiss J *et al.* Carboplatin/pemetrexed/bevacizumab in the treatment of patients with advanced non-small-cell lung cancer: a single-institution experience. *Clin. Lung Cancer* 11(3), 192–197 (2010).

106 Patel JD, Hensing TA, Rademaker A *et al.* Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer. *J. Clin. Oncol.* 27(20), 3284–3289 (2009).

107 Reynolds C, Barrera D, Jotte R *et al.* Phase II trial of nanoparticle albumin-bound paclitaxel, carboplatin, and bevacizumab in first-line patients with advanced nonsquamous non-small-cell lung cancer. *J. Thorac. Oncol.* 4(12), 1537–1543 (2009).

108 Wakelee HA, Dahlberg SE, Keller SM, Gandara DR *et al.* Interim report of on-study demographics and toxicity from E1505, a Phase III randomized trial of adjuvant (adj) chemotherapy (chemo) with or without bevacizumab (B) for completely resected early-stage non-small-cell lung cancer (NSCLC). *J. Clin. Oncol.* 29(Suppl.) (2011) (Abstract 7013).

109 Wong ET, Hess KR, Gleason MJ *et al.* Outcomes and prognostic factors in recurrent glioma patients enrolled onto Phase II clinical trials. *J. Clin. Oncol.* 17(8), 2572–2578 (1999).

110 Friedman HS, Prados MD, Wen PY *et al.* Bevacizumab alone and in combination

with irinotecan in recurrent glioblastoma. *J. Clin. Oncol.* 27(28), 4733–4740 (2009).

111 Kreisl TN, Kim L, Moore K *et al.* Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J. Clin. Oncol.* 27(5), 740–745 (2009).

112 Cloughesy T, Vredenburgh JJ, Day B, Das A, Friedman HS; the BRAIN Investigators. Updated safety and survival of patients with relapsed glioblastoma treated with bevacizumab in the BRAIN study. *J. Clin. Oncol.* 28(Suppl.), 15s (2010) (Abstract 2008).

113 Lai A, Tran A, Nghiemphu PL *et al.* Phase II study of bevacizumab plus temozolomide during and after radiation therapy for patients with newly diagnosed glioblastoma multiforme. *J. Clin. Oncol.* 29(2), 142–148 (2011).

114 Quant E, Norden AD, Drappatz J, Ciampa A. Role of a second chemotherapy in recurrent malignant glioma patients who progress on a bevacizumab-containing regimen. *J. Clin. Oncol.* 26(Suppl.) (2008) (Abstract 2008).

115 Zuniga RM, Torcuator R, Jain R *et al.* Rebound tumour progression after the cessation of bevacizumab therapy in patients with recurrent high-grade glioma. *J. Neurooncol.* 99(2), 237–242 (2010).

116 Burger RA, Brady MF, Bookman MA *et al.* Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): a Gynecologic Oncology Group study. *J. Clin. Oncol.* 28(Suppl.), 18s (2010) (Abstract LBA1).

117 Perren T, Swart AM, Pfisterer J *et al.*; GCIG ICON7 Collaborators. ICON7: a Phase III randomised gynaecologic cancer intergroup trial of concurrent bevacizumab and chemotherapy followed by maintenance bevacizumab, versus chemotherapy alone in women with newly diagnosed epithelial ovarian (EOC), primary peritoneal (PPC) or Fallopian tube cancer (FTC). Presented at: *The 35th ESMO Congress.* Milan, Italy, 8–12 October 2010.

Websites

201 US FDA, 2004. Highlights of prescribing information for AVASTIN® (bevacizumab). www.accessdata.fda.gov/drugsatfda_docs/label/2011/125085s225lbl.pdf

202 Central Brain Tumor Registry of the Unites States (CBTRUS). Five-year relative survival rates for malignant brain and central nervous system tumors by site and gender, SEER 17 Registries, 1995–2007. www.cbtrus.org/2007-2008/2007-20081.html

203 National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: central nervous system cancers (V.2.2011) (2011). www.nccn.org/professionals/physician_gls/pdf/cns.pdf

204 National Cancer Institute. FDA Approval for Bevacizumab. www.cancer.gov/cancertopics/druginfo/fda-bevacizumab