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# Bevacizumab

## In First-Line Treatment of Metastatic Breast Cancer

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## Contents



## Abstract

▲ Bevacizumab, a recombinant humanised monoclonal antibody against vascular endothelial growth factor, is approved in Europe as first-line therapy for metastatic breast cancer (mBC) and metastatic carcinoma of the colon or rectum (mCRC); the European Medicines Agency gave a positive opinion recommending its use in non-small-cell lung cancer (NSCLC) and is also considering other indications. In the US, it is licensed for use for mCRC and NSCLC, with its use as first-line treatment in mBC under review by the US FDA.

▲ In the pivotal E2100 trial in >700 previously untreated patients with locally recurrent or mBC, recipients of bevacizumab plus paclitaxel had a statistically and clinically significant increase in progression-free survival versus paclitaxel recipients (13.3 vs 6.7 months; hazard ratio 0.48; $p < 0.001$) [primary endpoint].

▲ There was also a >2-fold higher objective response rate in the bevacizumab plus paclitaxel arm than in the paclitaxel arm; the between-group difference in median overall survival did not reach statistical significance (25.7 vs 23.8 months).

▲ Bevacizumab had an acceptable tolerability profile in these patients, with the majority of adverse events being generally mild to moderate in severity. There are targeted adverse events, including gastrointestinal perforations, wound healing complications and haemorrhage, which although they occur infrequently (incidence ≤2%), are potentially life-threatening and may cause morbidity.

| Features and properties of bevacizumab (Avastin™) | |
|---|---|
| **Indication** | |
| First-line treatment of metastatic breast cancer (focus of this profile) | |
| **Mechanism of action** | |
| Anti-vascular endothelial growth factor (VEGF) recombinant humanised monoclonal $IgG_1$ antibody | Binds to and prevents interaction of VEGF with its receptor; thereby, inhibiting angiogenesis and tumour growth |
| **Dosage and administration (in combination with paclitaxel)** | |
| Dose | 10 or 15 mg/kg |
| Route of administration | Intravenous infusion |
| Frequency of administration | Once every 2 or 3 wks, respectively |
| **Pharmacokinetic profile (after a single 10 mg/kg dose)** | |
| Peak serum level | 251.4 μg/mL |
| Area under the serum concentration-time curve from zero to infinity | 4062 μg • day/mL |
| Elimination half-life | ≈20 days |
| **Tolerability profile (definitely drug-related adverse events; incidence ≥2% higher with bevacizumab plus paclitaxel than with paclitaxel monotherapy)** | |
| Hypertension, proteinuria | |

Breast cancer is the most common malignancy in women, accounting for ≈15% of all female neoplasms worldwide[1] and ≈33% of those in the US.[2] Surgical resection is the preferred treatment for localised breast cancer, with systemic therapy (including chemotherapy, biological and hormonal therapies) used in those with advanced breast cancer.[2,3] Advanced disease is generally associated with a poor prognosis, with a 5-year relative survival rate of 26% in these patients.[2]

A recent focus of pharmacotherapy for advanced or metastatic cancers has been the development of therapeutic agents that target specific tumour-related biological processes and pathways in order to cause regression or destruction of malignant tumours.[4] Angiogenesis is a critical step in the growth and metastatic spread of solid malignant tumours, with vascular endothelial growth factor (VEGF) a potent stimulator and key mediator of tumour angiogenesis.[5,6] Thus, VEGF has recently been recognised as a potential target for therapy of solid tumours.[4] Its overexpression in breast cancer is an indicator of poor prognosis and survival.[7]

Bevacizumab (Avastin™)[1] is a recombinant humanised monoclonal $IgG_1$ antibody against VEGF that prevents VEGF from binding to its receptor and thereby inhibits angiogenesis and tumour growth.[8,9] A review of its use in the first-line therapy of metastatic colorectal carcinoma (approved in the US and the EU), non-small-cell lung cancer (approved in the US) and metastatic breast cancer (now approved in the EU) was published previously in the *American Journal of Cancer*.[10] The focus of the current review is on its use in combination with paclitaxel as first-line therapy in patients with locally recurrent or metastatic breast cancer and provides a brief overview of its pharmacological profile.

## 1. Pharmacodynamic Profile

Bevacizumab is derived from a murine monoclonal anti-VEGF antibody, which is humanised (93% human) by incorporating murine VEGF-binding residues into a human IgG framework (figure 1).[11,12] The *in vitro* binding of bevacizumab to soluble VEGF inhibits the biological activity of VEGF (figure 1), resulting in inhibition of angiogenesis and tumour growth.[13]

### Mechanism of Action

- In several *in vitro* assays, bevacizumab caused dose-dependent inhibition of VEGF-induced proliferation, migration and survival of vascular endothelial cells and increased the permeability of these cells by preventing the binding of soluble VEGF to its receptors on the surface of endothelial cells.[11,13] For example, at bevacizumab concentrations of approximately 0.3 and 3 nmol/L, growth of cultured bovine capillary endothelial cells was inhibited by 50% and 90%.[11]
- Bevacizumab did not exhibit complement-mediated or antibody-dependent cell-mediated cytotoxicity in VEGF-producing or malignant target cells.[13]
- Preclinical evidence also indicates that bevacizumab may improve inefficiencies in blood flow associated with a dilated and disorganised vascular architecture in tumours, thereby improving perfusion of other anticancer drugs.[14] In a human colorectal xenograft model in nude mice, after 7 days' treatment with bevacizumab, there was a significant reduction in intratumoural microvascular density (MVD). Notably, despite this decrease in MVD, the acute administration of a single dose of irinotecan resulted in a trend to an increase in intratumoural concentration of the drug and a significant ($p < 0.05$) increase in tumour perfusion of the drug.[14]
- A 90-minute intravenous infusion of bevacizumab 1–10 mg/kg given on days 0, 28, 35 and 42 consistently increased serum total (free plus bound) VEGF levels 2- to 3-fold in patients with solid malignancies ($n = 5$/group).[15] This increase was thought to reflect an increase in the synthesis and/or distribution of VEGF and/or a decrease in VEGF clearance caused by complex formation between bevacizumab and VEGF,[15] with the latter supported by data from a rat model.[16] Notably, at doses

**1** The use of trade names is for product identification purposes only and does not imply endorsement.

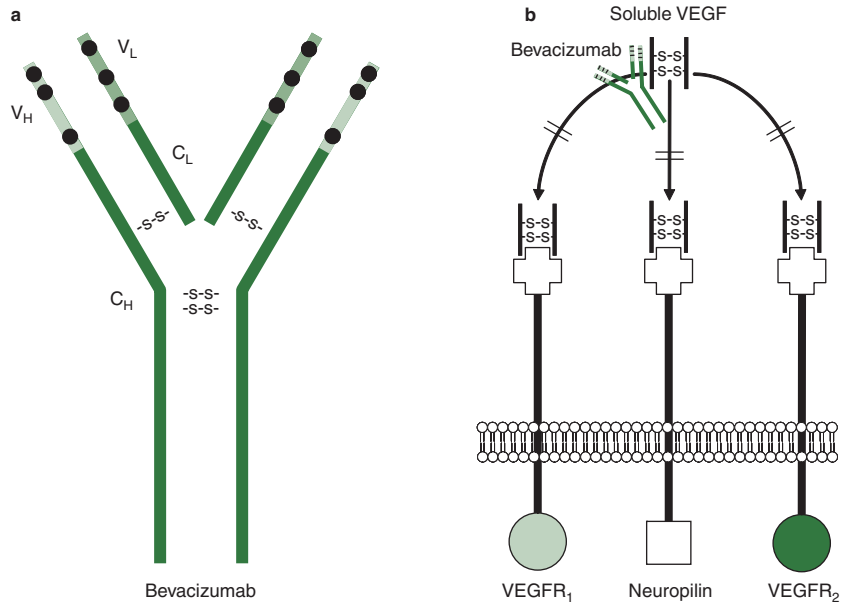


**Fig. 1.** Schematic representation of the structure and mechanism of action of bevacizumab. **(a)** The humanised bevacizumab antibody consists of six murine specificity sequences (black dots) grafted onto a backbone of disulfide-linked heavy and light chains containing variable ($V_H$ and $V_L$) and constant ($C_H$ and $C_L$) regions. [12] **(b)** Binding of bevacizumab to the soluble vascular endothelial growth factor (VEGF) dimer inhibits binding to the receptors VEGFR$_1$ and VEGFR$_2$ and neuropilin (reproduced from Lyseng-Williamson and Robinson[10]).

≥0.3 mg/kg, bevacizumab treatment reduced free serum VEGF levels to below the limit of detection (20 pg/mL) for the duration of the study.[15]

- When coadministered with doxorubicin, carboplatin plus paclitaxel or fluorouracil plus folinic acid (n = 4/group), intravenous bevacizumab 3 mg/kg weekly for 8 weeks resulted in a 4-fold increase in mean serum total VEGF levels in patients with various advanced solid tumours (51 pg/mL at day 0 vs 211 pg/mL at day 49).[17]

### Effects on Angiogenesis and Tumour Growth

- In murine xenograft models of rhabdomyosarcoma, glioblastoma multiforme, leiomyosarcoma and breast cancer, bevacizumab potently and effectively inhibited tumour growth, resulting in an ≈70–96% reduction in tumour weight relative to that in control animals.[11,18]
- In previously untreated patients (n = 21) with inflammatory or locally advanced breast cancer, intravenous bevacizumab exhibited significant antiangiogenic and antitumour effects.[19] Relative to the baseline, there was a significant reduction in parameters reflecting tumour vascular permeability and blood flow (all $p \leq 0.002$), a median 66.7% decrease in VEGF receptor R2 activation in tumour cells ($p = 0.004$) and a median 128.9% increase in tumour apoptosis ($p = 0.0008$) after one cycle of bevacizumab 15 mg/kg. These effects persisted in subsequent 3-week cycles, in which doxorubicin and docetaxel were added to the treatment regimen.[19]

## 2. Pharmacokinetic Profile

The pharmacokinetics of intravenous bevacizumab as mono- or combination therapy are available from studies in patients with various types of cancer,[15,17] a US FDA report[20] and the manufacturer's prescribing information.[8,9] Although no formal studies of drug interactions have been conducted,[8,9] there appear to be no clinically significant

pharmacokinetic interactions between intravenous bevacizumab and a variety of chemotherapy agents, including carboplatin, doxorubicin, fluorouracil (or capecitabine), irinotecan, folinic acid and paclitaxel.[9,20] The lack of interaction reflects the differing metabolic pathways between cytotoxic agents and a protein such as bevacizumab.

### Absorption and Distribution

- In patients with various types of solid tumours (n = 25), bevacizumab exhibited linear pharmacokinetics after single intravenous doses of 0.1–10 mg/kg.[15] Across this dose range, values for mean peak serum levels and the area under the concentration-time curve from zero to infinity were 2.5–251.4 μg/mL and 19.4–4062 μg • day/mL; respective values after a single dose of bevacizumab 10 mg/kg were 251.4 μg/mL and 4062 μg • day/mL. No significant accumulation of bevacizumab occurred after subsequent infusions on days 28, 35, and 42.[15]
- Consistent with mean terminal elimination half-life ($t_{1/2}\beta$) of ≈20 days, drug accumulation has been noted with longer-term treatment. Pooled data from several studies in 208 patients with various solid tumours receiving bevacizumab 3–20 mg/kg every 2 or 3 weeks for up to 1 year showed an accumulation index of 1.4–2.9; in patients receiving bevacizumab 10 mg/kg every other week (n = 86) the index was 2.7–2.9.[8,20] Steady-state levels of bevacizumab were estimated to occur after 100 days in these studies.[8,20]
- The mean central compartment volume of distribution ($V_C$) of bevacizumab was dose-independent across the dose range of 0.1 to 20 mg/kg in patients with advanced solid tumours.[20] Across this dose range, the mean $V_C$ was 37.8–47.1 mL/kg after single bevacizumab doses and 37.9–48.6 mL/kg after multiple doses administered at 1- to 3-week intervals.
- In a population pharmacokinetic analysis of 491 patients receiving bevacizumab 1–20 mg/kg at 1- to 3-week intervals, the mean $V_C$ was 2.92L[9] and was 22% greater in men than in women after correction for bodyweight.[8,9] This corresponds to an initial half-life of bevacizumab of 1.4–1.5 days.[9,20]

### Metabolism and Elimination

- The metabolic profile of bevacizumab is similar to that expected for naturally occurring non-VEGF-binding IgG molecules, as indicated by a study in rabbits using a single intravenous dose of $^{125}$I-bevacizumab.[9]
- The clearance (CL) of bevacizumab is low.[8] CL of bevacizumab varies dependent upon gender, bodyweight and tumour burden,[8] but is not affected by the patient's age.[9,20] In the population-based analysis in 491 patients receiving bevacizumab 1–20 mg/kg every 1–3 weeks, mean CL was 26% greater in men than in women (262 vs 207 mL/day, after correcting for bodyweight),[20] and greater in patients with a higher tumour burden (greater than or equal to the median value of tumour surface area for the study population) than in those with a lower tumour burden (249 vs 199 mL/day).[8]
- The mean $t_{1/2}\beta$ of bevacizumab was ≈20 days in a population pharmacokinetic analysis, and ranged from ≈13–20 days with 1–20 mg/kg doses in clinical studies.[15,17,20] The long $t_{1/2}\beta$ of bevacizumab permits infrequent administration of the drug (i.e. once every 2 or 3 weeks),[8,9] which also allows for convenient coadministration with chemotherapy regimens.

## 3. Therapeutic Efficacy

The efficacy of intravenous bevacizumab as first-line therapy for the treatment of locally recurrent or metastatic breast cancer has been investigated in a large (n = 722), randomised, open-label, multicentre, international, phase III (E2100) trial.[21-23] Discussion focuses on the final analysis data that are available in a scientific discussion document from the European Medicines Agency.[23] Interim data based on 484 events have been reported in an abstract, which is not discussed further.[22]

To be eligible for inclusion, patients had to have no overexpression of human epidermal growth factor receptor type 2 (HER2) or had to have received prior therapy with trastuzumab.[21,23] Those with unknown HER2 status were only considered for inclusion if trastuzumab-based treatment was inappropri-

ate or not indicated. Virtually all patients had disease recurrence after initial local treatment plus some form of adjuvant treatment (radiotherapy, antihormonal therapy or chemotherapy). Stratification factors considered at randomisation (intent-to-treat [ITT] population) were the disease-free interval (≤24 or >24 months), number of metastatic sites (<3 or ≥3), adjuvant chemotherapy (yes or no) and estrogen receptor (ER) status (ER positive, ER negative or ER unknown). Based on a 4-week cycle, patients received intravenous bevacizumab 10 mg/kg on days 1 and 15 and/or a 1-hour intravenous infusion of paclitaxel 90 mg/m$^2$ on days 1, 8 and 15.

The primary efficacy endpoint was amended to be the duration of progression-free survival (PFS) for the ITT population, as requested by the FDA (initially it was time to treatment failure).[23] Secondary endpoints included the objective response rate (ORR) and the duration of response and overall survival (OS), which were assessed by the investigator and confirmed by the Eastern Cooperative Oncology Group according to the Response Evaluation Criteria in Solid Tumors. In addition, relative changes in health-related quality of life (HR-QOL) were assessed using the validated Functional Assessment of Cancer Therapy - Breast (FACT-B) questionnaire.

- Based on Kaplan-Meier estimates, the median duration of PFS in the ITT population was significantly longer in the bevacizumab plus paclitaxel group (n = 368) than in the paclitaxel monotherapy group (n = 354) [13.3 vs 6.7 months], which translates into a clinically relevant 52% reduction in the risk of disease progression in the combination group (hazard ratio [HR] 0.48; 95% CI 0.39, 0.59; p < 0.0001).[23]

- Furthermore, in predefined subgroup analyses, the beneficial increase in PFS with bevacizumab plus paclitaxel therapy was generally seen irrespective of whether patients were stratified based on disease-free interval, ER status, prior adjuvant chemotherapy or the number of metastatic sites, and irrespective of baseline characteristics such as age (<40, 40–65, >65 years of age), the sum of the longest diameters of all target lesions, whether or not patients had received prior taxane therapy and HER2 expression status.[23]

- In these predefined subgroup analyses, the median duration of PFS in the various subgroups ranged from 10.4 to 14.1 months in the bevacizumab plus paclitaxel groups versus 4.6–8.5 months in corresponding paclitaxel monotherapy groups.[23] For example, in those who had received prior taxane therapy, respective median PFS durations were 14.1 versus 4.6 months (n = 71 and 69), corresponding to a 67% reduction in the risk of disease progression for bevacizumab plus paclitaxel recipients. In those who had not been previously treated with taxanes, there was a 36% reduction in the risk of disease progression (median PFS 12.0 vs 8.1 months in the paclitaxel monotherapy group; n = 295 and 285).[23]

- The between-group difference in median OS did not reach statistical significance at a median follow-up of 22.3 and 22.6 months.[23] Median OS was 25.7 months in the bevacizumab plus paclitaxel arm versus 23.8 months in the paclitaxel monotherapy group, based on Kaplan-Meier estimates. The stratified HR for OS for the bevacizumab plus paclitaxel group versus the paclitaxel monotherapy group was 0.82 (95% CI 0.66, 1.03; p = 0.082).

- Notably, the survival rate at 1 year significantly favoured those in the bevacizumab plus paclitaxel group (82.3% vs 73.8% of paclitaxel monotherapy recipients alive; p = 0.007), based on Kaplan-Meier estimates.[23] Ninety-three percent of patients in each arm were followed for at least 1 year. Analyses of OS are ongoing.

- The ORR was >2-fold higher in the bevacizumab plus paclitaxel group (n = 246) than in the paclitaxel monotherapy group (n = 268) for evaluable patients (36.2% vs 16.4%; p < 0.0001).[23] Most of these responses were partial responses. Of those achieving an objective response, complete responses were achieved by 15 of 89 patients (17%) in the bevacizumab plus paclitaxel group and by 5 of 44 (11%) patients in the paclitaxel monotherapy group.

- For evaluable patients with measurable disease who achieved an objective response, the median duration of the objective response was 11.3 months in the bevacizumab plus paclitaxel group (n = 86)

versus 9 months for the 43 patients in the paclitaxel monotherapy group (descriptive analyses only).[23]

- Preliminary data suggest that after 33 weeks' treatment there was less deterioration in HR-QOL in bevacizumab plus paclitaxel recipients than in paclitaxel monotherapy recipients, as assessed by FACT-B scores.[23,24] At this timepoint, the mean decrease from baseline in FACT-B total scores was 24.5 for bevacizumab plus paclitaxel recipients compared with 40 for those in the paclitaxel monotherapy group ($p = 0.0001$; a greater decrease in score means a greater deterioration in HR-QOL) [data on file].[24] Values were estimated from a graph.

## 4. Tolerability

- Although adverse events were common, the tolerability profile of bevacizumab was generally acceptable in patients with advanced breast cancer participating in the phase III trial discussed in section 3, with the majority of adverse events being of mild to moderate severity.[23] The most common adverse events were nausea, vomiting and fatigue/asthenia, all of which occurred with a similar frequency in the bevacizumab plus paclitaxel group to that in the paclitaxel monotherapy group.
- In this trial, adverse events that were considered to be related to bevacizumab treatment (i.e. those that occurred with a ≥2% difference between the treatment arms) were hypertension (15.5% in the bevacizumab plus paclitaxel group vs 1.4% in the paclitaxel group) and proteinuria (3% vs 0%) [descriptive analyses only].[23] Peripheral sensory neuropathy also appeared to occur more frequently in combination therapy than monotherapy recipients (23.2% vs 16.5%), although this was thought to reflect longer duration of treatment and the greater cumulative dose of paclitaxel in the combination group than in the monotherapy group.
- Targeted adverse events are known to occur more frequently in patients receiving bevacizumab-based combination therapy, including hypertension, proteinuria, arterial thromboembolism, haemorrhage, congestive heart failure, gastrointestinal perforation and wound healing.[23] Although infrequent (incidence ≤2%), these events are potentially life-threatening and may cause morbidity.[23] All of these adverse events are associated with special warnings and precautions for the use of bevacizumab in approved indications in Europe[9] and, in the US,[8] there is a black box warning regarding gastrointestinal perforations, wound healing complications and haemorrhage.

## 5. Dosage and Administration

In Europe,[9] in patients with metastatic breast cancer (focus of this review), the recommended dosage of intravenous bevacizumab is 10 mg/kg given once every 2 weeks or 15 mg/kg given once every 3 weeks; the first dose should be given as a 90-minute infusion, with the duration of subsequent infusions reduced to 60 minutes and then 30 minutes dependent upon tolerability. Bevacizumab is given in combination with paclitaxel in this patient population. Recently, the European Medicines Agency has issued a positive opinion recommending approval of bevacizumab as first-line treatment of advanced non-small-cell lung cancer, in combination with chemotherapy;[25] other indications in cancer are also under consideration.

Local prescribing information should be consulted for details of dosage recommendations in other indications and special patient populations, contraindications and precautions.

## 6. Bevacizumab: Current Status as First-Line Treatment in Metastatic Breast Cancer

The European Medicines Agency[9] has recently approved the use of bevacizumab as first-line treatment for metastatic breast cancer. An extended approval application for this indication is currently being considered by the FDA.[26] In a large, well designed, phase III trial in previously untreated patients with locally recurrent or metastatic breast cancer, relative to paclitaxel monotherapy recipients, those receiving intravenous bevacizumab plus paclitaxel had a statistically significant and clinically relevant increase in PFS (median PFS 13.3 vs 6.7 months), with a >2-fold increase in ORR. Beva-

cizumab has an acceptable tolerability profile in this patient population, although targeted adverse events (including gastrointestinal perforations, wound healing complications and haemorrhage) that are potentially life-threatening and may cause morbidity are known to occur infrequently.

## Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

## References


1. World Health Organization. The World Health Report 2002: reducing risks, promoting healthy life [online]. Available from URL: http://www.who.int/whr/2002/en/index.html [Accessed 2006 Aug 22]
2. American Cancer Society. Breast cancer facts and figures 2005-2006 [online]. Available from URL: http://www.cancer.org/downloads/STT/CAFF2005BrF.pdf [Accessed 2006 Aug 22]
3. Puglisi F, Cardoso F, Lebrun F, et al. First-line treatment of metastatic breast cancer: available evidence and current recommendations. Am J Cancer 2006; 5 (2): 99-110
4. Ross JS, Schenkein DP, Pietrusko R, et al. Targeted therapies for cancer 2004. Am J Clin Pathol 2004 Oct; 122 (4): 598-609
5. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. Endocr Rev 2004 Aug; 25 (4): 581-611
6. Yarden Y, Baselga J, Miles D. Molecular approach to breast cancer treatment. Semin Oncol 2004; 31 Suppl. 10: 6-13
7. Lee JS, Kim HS, Jung JJ, et al. Expression of vascular endothelial growth factor in invasive ductal carcinoma of the breast and the relation to angiogenesis and p53 and HER-2/neu protein expression. Appl Immunohistochem Mol Morphol 2002 Dec; 10 (4): 289-95
8. Genentech Inc. Avastin™ (bevacizumab): prescribing information [online]. Available from URL: http://www.gene.com [Accessed 2007 Jul 4]
9. European Medicines Evaluation Agency. Avastin: annex I summary of product characteristics [online]. Available from URL: http://www.emea.europa.eu [Accessed 2007 Jul 7]
10. Lyseng-Williamson KA, Robinson DM. Bevacizumab: a review of its use in advanced colorectal cancer, breast cancer, and NSCLC. Am J Cancer 2006; 5 (1): 43-60
11. Presta LG, Chen H, O'Connor SJ, et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 1997 Oct 15; 57 (20): 4593-9
12. Harris M. Monoclonal antibodies as therapeutic agents for cancer. Lancet Oncol 2004 May; 5 (5): 292-302
13. Wang Y, Fei D, Vanderlaan M, et al. Biological activity of bevacizumab, a humanized anti-VEGF antibody in vitro. Angiogenesis 2004; 7 (4): 335-45
14. 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 2003; 88: 1979-86
15. Gordon MS, Margolin K, Talpaz M, et al. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. J Clin Oncol 2001 Feb 1; 19 (3): 843-50
16. Hsei V, Deguzman GG, Nixon A, et al. Complexation of VEGF with bevacizumab decreases VEGF clearance in rats. Pharm Res 2002; 19 (11): 1753-6
17. 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 2001 Feb 1; 19 (3): 851-6
18. Kim KJ, Li B, Winer J, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumor growth in vivo. Nature 1993 Apr 29; 362: 841-4
19. Wedam SB, Low JA, Yang SX, et al. Antiangiogenic and antitumor effects of bevacizumab in inflammatory and locally advanced breast cancer patients. J Clin Oncol 2006; 24 (5): 769-77
20. Mahmood I. Center for Drug Evaluation and Research. Approval package for: application number STN-125085/0 - clinical pharmacology/TOX review [online]. Available from URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ [Accessed 2005 Nov 28]
21. Miller KD. E2100: a phase III trial of paclitaxel versus paclitaxel/bevacizumab for metastatic breast cancer. Clin Breast Cancer 2003; 3 (6): 421-2
22. Zon R, Miller K, Wang M, et al. A randomized phase III trial of paclitaxel with or without bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: Eastern Cooperative Oncology Group trial E2100 [abstract no. 7]. Eur J Cancer Suppl 2006 Mar; 4 (2): 47
23. European Medicines Agency. Extension of the indication to include Avastin in combination with paclitaxel for first-line treatment of patients with metastatic breast cancer: scientific discussion [online]. Available from URL: http://www.emea.eu [Accessed 2007 May 1]
24. Hoffmann La-Roche Ltd., Avastin plus paclitaxel: higher quality of life score vs paclitaxel alone. Basel: Hoffmann La-Roche Ltd., 2007. (Data on file)
25. Beaulieu D. EU panel issue positive opinion for Avastin in NSCLC [online]. Available from URL: http://www.firstwordplus.com [Accessed 2007 Jul 23]
26. Hoffmann-La Roche Ltd. Avastin filed with FDA in US for treatment of women with advanced breast cancer [online]. Available from URL: http://www.roche.com [Accessed 2006 Aug 29]


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