# First line targeted therapies in breast cancer: focus on bevacizumab

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**Abstract:** The heterogeneity of metastatic breast cancer mandates the need to select therapies taking into account tumor and patient characteristics. Chemotherapy is indicated in the palliative setting especially when the disease is unresponsive to hormonal therapy or is hormone-receptor negative. The main chemotherapeutic agents are anthracyclines, taxanes, and capecitabine. The knowledge of the effects of currently approved agents and of the biology of breast cancer have paved the way for the evaluation of new treatment options, among which are anti-angiogenic agents. Angiogenesis inhibition has resulted in clinically significant improvements in the outcome of a variety of malignancies, including breast cancer. Bevacizumab, a monoclonal antibody anti-vascular endothelial growth factor (VEGF), is the most extensively studied anti-angiogenic compound. According to the results of a phase III trial in patients with untreated metastatic breast cancer, bevacizumab increases both objective response rate and median progression-free survival when combined with standard chemotherapy vs chemotherapy alone. The combination of anti-angiogenic drugs and other biologic agents is also being explored in an attempt to improve efficacy.

**Keywords:** angiogenesis, bevacizumab, breast cancer, monoclonal antibody

## Introduction to first-line management of breast cancer, advances in targeted therapies

Advanced breast cancer is still an incurable disease, the main objectives of treatment including life prolongation and quality improvement. Patients with metastatic disease that is hormone-receptor negative and HER-2 negative should be offered chemotherapy alone. The most commonly used cytotoxic agents are anthracyclines, taxanes, and capecitabine. These agents can be used as monotherapy or in combination depending on patient and disease characteristics. A 36%–41% response rate for first-line anthracyclines has been reported (Sledge et al 2003). This is comparable with that for other agents, including docetaxel (Sjostrom et al 1999) (response rates 23%–42% in anthracycline-pretreated patients), paclitaxel (Paridaens et al 2000) (response rates 14%–34%), and capecitabine (O'Shaughnessy et al 2001) (response rates 30%–58%). Probably, an aggressive combination regimen may be particularly suited to patients with rapidly progressing disease and/or visceral metastases. Patients with more indolent disease and older patients would be more likely to benefit from a less aggressive approach with a single agent.

The therapeutic armamentarium for advanced breast cancer has recently expanded with the use of new biologic agents, the best studied of which is trastuzumab, a humanized monoclonal antibody directed against the HER-2, which is indicated in a subgroup of breast cancer patients who have human HER-2 gene amplification. A randomized phase II trial reported the statistically significant benefit of adding trastuzumab to either combination adriamycin and cyclophosphamide (in patients who had not received adjuvant anthracyclines) or single agent paclitaxel for treatment in

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the metastatic setting. In particular, patients receiving trastuzumab had improved time to progression (TTP) than those who did not receive it (7.4 vs 4.6 months, p < 0.001) (Slamon et al 2001). Furthermore, indications for trastuzumab in combination with chemotherapy have been recently extended to the adjuvant setting. In particular, trastuzumab combined with paclitaxel after doxorubicin and cyclophosphamide has been shown to improve outcome in patients with surgically operable HER-2 positive breast cancer (Romond et al 2005). However, trastuzumab resistance usually develops and this mandates a non-cross resistant further approach (Konecny et al 2006). Lapatinib, an orally active small molecule, inhibits the tyrosine kinase activity of both epidermal growth factor receptor (EGFR) and HER-2. Some early data seem to support lapatinib anti-tumor activity as a single agent in patients with HER-2 positive breast cancer with central nervous system metastases refractory to trastuzumab (Lin et al 2006). This finding is important because HER-2 positive tumors frequently spread to the central nervous system, where the tumor is sheltered from trastuzumab and most chemotherapeutic agents. In a phase II study of lapatinib in 36 patients with trastuzumab-refractory metastatic breast cancer, 3 partial responses and 8 stable diseases were achieved (Blackwell et al 2005). Recently, in a phase III study, women with metastatic HER-2 positive breast cancer who had been previously treated with anthracycline, taxane, and trastuzumab, were randomly assigned to receive lapatinib plus capecitabine or capecitabine alone. In the interim analysis, the hazard ratio for disease progression was 0.49 (95% confidence interval [CI], 0.34–0.71; p < 0.001), with 49 events in the combination therapy group and 72 events in monotherapy group. The median TTP was 8.4 months and 4.4 months, in the two arms, respectively (Geyer et al 2006). This study has led to the approval of lapatinib in the US for advanced/metastatic breast cancer overexpressing HER-2 in combination with capecitabine.

Pertuzumab is a humanized monoclonal antibody that binds to another extracellular domain of HER-2 (Spicer 2004). Pertuzumab inhibits the dimerization of HER, interrupting intracellular cell signaling and activating inflammatory pathways to elucidate antibody-dependent apoptosis. Synergy has been shown between trastuzumab and pertuzumab in cell culture, which overexpresses HER-2 (Nahta et al 2004).

Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is another targeted therapy, which holds great promise in the treatment of breast cancer. The combination of bevacizumab with standard chemotherapeutic agents has been associated with only modest increases in toxicity, and the results of ongoing trials are, we hope, going to clarify the most appropriate use of these new agents.

# Review of pharmacology, mode of action, and pharmacokinetics of bevacizumab

Angiogenesis is critical to tumor growth, invasion and metastasis (Folkman 1995). Several humoral factors stimulate this process either by inducing the enzymatic breakdown of the perivascular basement membrane or by inducing chemotaxis of endothelial cells. Many malignant cells produce VEGF, which serves as an autocrine factor for induction, proliferation, and migration of vascular endothelial cells. These activities are mediated through the two receptors for VEGF, flt-1, and KDR, which are found predominantly on vascular endothelial cells (Ferrara 1992) (Fig. 1). Hypoxia is a key signal for the induction of angiogenesis; hypoxia-inducible factors (HIF-1 and HIF-2) are heterodimeric transcription factors consisting of $\alpha$ and $\beta$ subunits. The $\beta$ subunit is constitutively expressed while the $\alpha$ subunit is protected from degradation only under hypoxic conditions (Salceda and Caro 1997). VEGF has also been implicated in oncogenesis, through mutual regulation of the VEGF gene by tumor suppressor genes and dominant transforming oncogenes, such as von Hippel-Lindau (VHL) (Siemeister et al 1996; Chiarugi et al 1998).

Several studies have demonstrated a correlation between high levels of VEGF and increased risk of metastatic disease and overall poor prognosis in a variety of cancers, such as non small lung cancer (NSCLC), renal cancer, and breast cancer (Ranieri et al 2006). In particular, clinical-pathologic correlations also confirm the central role of angiogenesis in breast cancer progression (Schneider and Miller 2005). HIF-$\alpha$ expression is associated with increased proliferation and expression of the estrogen receptor and VEGF (Bos et al 2001). VEGF production occurs early in breast cancer and is expressed at high levels in ductal carcinoma in situ (Brown et al 1995). Moreover, microvessel density (MVD) was shown to be higher in invasive breast cancers, associated with a shorter relapse-free and overall survival in both node-positive and node-negative cancers (Gasparini et al 1997, 1999), and, finally, predictive for therapeutic failure with both hormonal therapy and chemotherapy (Foekens et al 2001). VEGF expression has also been quantified via immmunohistochemistry in breast cancer specimens and a correlation with a poorer outcome has been observed.

# VEGF signaling pathway
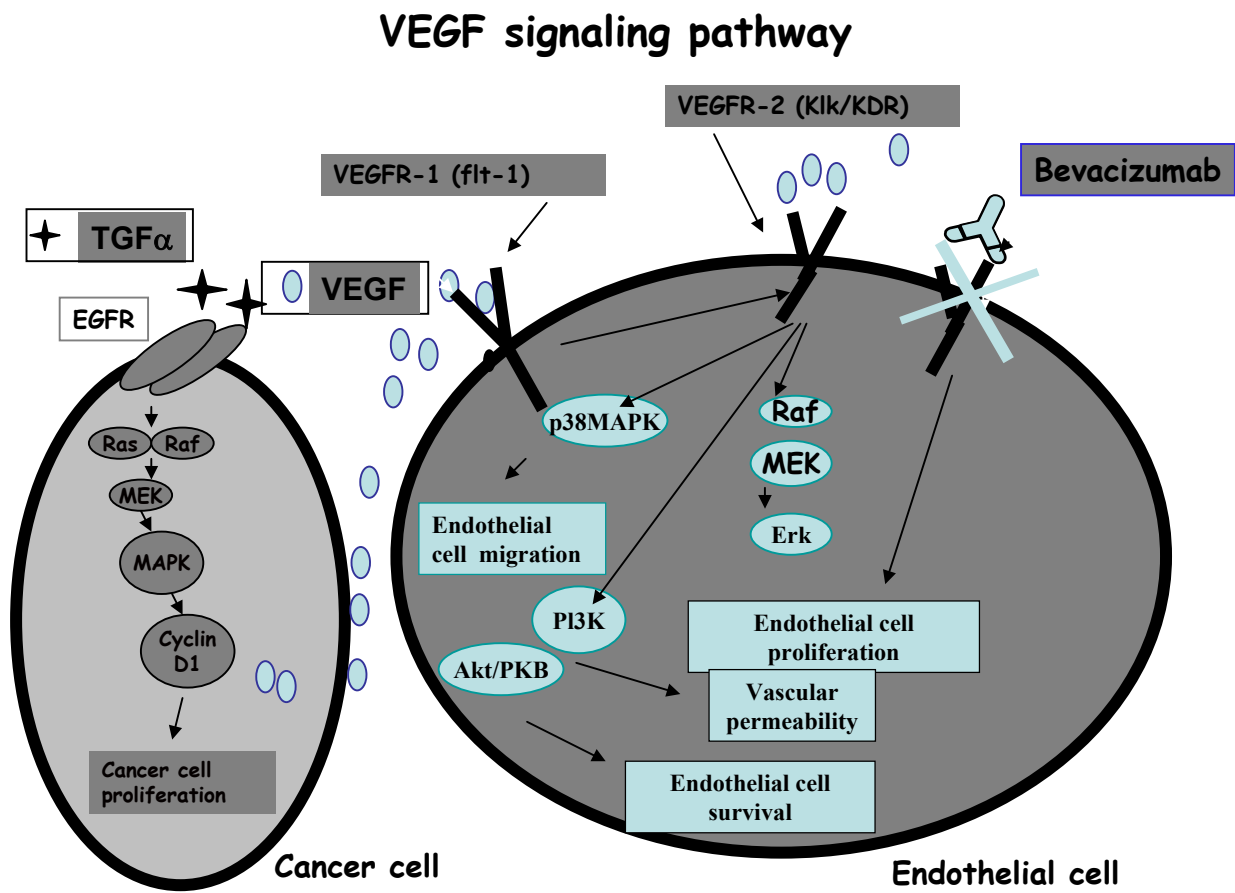


**Figure 1** A simplified scheme of the VEGF/VEGFR pathway. The development of blood vessels is regulated by production of several growth factors, such as TGF-α and VEGF, that are secreted by cancer cells to stimulate normal endothelial cell growth through paracrine mechanisms. VEGF binds to two different receptors: VGFR-1 (flt-1) and VEGFR-2 (flk/KDR). VEFG is a potent and specific mitogen for endothelial cells, activates angiogenesis and enhances vascular permeability.
**Abbreviations:** VEGF, vascular endothelial growth factor; TGF-α, transforming growth factor-α; VEGFR-1, vascular endothelial growth factor receptor-1; VEGFR-2, vascular endothelial growth factor receptor-2.

The use of anti-VEGF antibodies has been extensively studied in preclinical in vivo models and a dose-dependent inhibition of tumor growth has been demonstrated (Kim et al 1993). Furthermore, a synergistic anti-tumor activity can be seen when bevacizumab is administered in conjunction with cisplatin (Kabbinavar et al 1995). Bevacizumab is approved in the US and Europe for the first-line treatment of metastastic colorectal cancer when given in combination with fluorouracil and irinotecan, based on the demonstration of an overall survival benefit over standard chemotherapy alone (Hurwitz et al 2004). A number of phase I/II/III clinical studies in several cancers have then been undertaken. Bevacizumab has activity as a single agent in patients with previously treated metastatic breast cancer, inducing a 10% response rate (Cobleigh et al 2003); this single-agent activity suggests two mechanisms of action: namely a cytotoxic and a cytostatic effect.

The pharmacokinetic profile of bevacizumab was investigated in a phase I study, in which 25 patients with metastatic cancer who had failed prior therapies were treated at doses ranging from 0.1 to 10 mg/kg on days 0, 28, 35, and 42, administered by a 90-minute intravenous infusion. Maximum concentration values ranged from 2.8 to 284 μg/mL. The half-life was 21 days following a single dose of bevacizumab. Overall, the pharmacokinetics profile indicates that when bevacizumab was administered once followed by a 28-day washout period and then weekly for 3 weeks at doses ranging from 0.1 to 10 mg/kg, the disposition was characterized by a low clearance and a volume of distribution consistent with limited extravascular distribution (Gordon et al 2001). Serum VEGF concentrations were also evaluated in this study. Although increases in serum total VEGF concentration were seen, this was likely a result of an increase in VEGF synthesis/distribution, a decrease in VEGF clearance caused by complex formation between VEGF and bevacizumab, or both. Furthermore, free serum VEGF concentrations were found to be reduced and, at doses of ≥0.3 mg/kg, were below

the detectable limit of the assay after the administration of bevacizumab and remained undetectable for the duration of the study. Based on these data, a phase Ib study was conducted to achieve sustained exposure to the antibody when it was given weekly for 8 weeks concurrently with 2 cycles of standard chemotherapy administered every 28 days (doxorubicin or carboplatin plus paclitaxel) or weekly for 6 out of 8 weeks (fluorouracil plus leucovorin). No pharmacokinetic interaction between bevacizumab and any of the concomitant chemotherapy regimens was observed. The concentration-time profiles were consistent with those seen in the former study. The mean terminal half-life of bevacizumab was 13 days (Margolin et al 2001).

## Efficacy studies, combination studies

The initial phase I/II trial of bevacizumab as a single agent in 75 patients who had progressed on at least one standard treatment for metastatic breast cancer has been reported (Cobleigh et al 2003). Objective responses were achieved, including one confirmed complete response and four confirmed partial responses. The overall response rate was 9.3% and median duration of confirmed response was 5.5 months (range, 2.3 to 13.7 months). At the final tumor assessment, 16% of patients achieved stable disease or an ongoing response (Cobleigh et al 2003).

A number of trials using bevacizumab with chemotherapy have been reported. Preclinical models of combination of bevacizumab and docetaxel demonstrate synergistic suppression of capillary vessel formation. Based upon these data, 21 patients with inflammatory and locally advanced breast cancer were treated with bevacizumab for cycle 1 (15 mg/kg on day 1) followed by 6 cycles of bevacizumab

with doxorubicin (50 mg/m$^2$) and docetaxel (75 mg/m$^2$) every 3 weeks. After locoregional therapy, patients received 8 cycles of bevacizumab alone and hormonal therapy when indicated. A median decrease of 66.7% in phosphorylated VEGFR in tumor cells (p = 0.004) and a median increase of 128.9% in tumor apoptosis (p = 0.0008) were seen after bevacizumab alone. These changes persisted with the addition of chemotherapy (Wedam et al 2006). All 21 patients were assessed for response; no complete responses were observed, while 14 patients had a clinical partial response for an overall response rate of 67% (95% CI, 43%–85.4%). Five patients had stable disease and 2 patients had progressive disease. Another randomized phase II trial was conducted in 49 patients to evaluate the vascular effects on tumor regression with combination bevacizumab/docetaxel vs docetaxel alone in the treatment of locally advanced breast cancer. Seven complete clinical responses were achieved while 32 partial responses and 5 disease progressions were reported. Out of the 37 patients who underwent surgery, the median number of pathologically positive lymph nodes was 1 while 43% had negative lymph nodes (Lyons et al 2006).

The combination of weekly docetaxel (35 mg/m$^2$) plus bevacizumab (10 mg/kg on days 1 and 15) was tested in 27 patients with advanced breast cancer as first- or second-line therapy (Ramaswamy et al 2006). The overall response rate was 52 % with 14 partial responses and 9 stable diseases; the median response duration was 6.0 months (95% CI, 4.6–6.5 months), and the median progression-free survival was 7.5 months (95% CI, 6.2–8.3 months). Pretreatment E-selectin, required for the antiangiogenic activity of endostatin, was significantly associated with response after controlling for performance status (odds ratio [OR], 1.6; 95% CI, 1.0-2.5; p = 0.05), age (OR, 1.6; 95% CI, 1.0–2.6;

**Table 1** Phase III combination studies of bevacizumab

| Patient population | Metastatic breast cancer[a] | Metastatic breast cancer[b] |
|---|---|---|
| **N. patients** | **680** | **462** |
| Schedule | Arm 1<br>Paclitaxel: 90 mg/m$^2$ on days 1, 8, 15<br><br>Arm 2<br>Paclitaxel: 90 mg/m$^2$ on days 1, 8, 15<br>Bevacizumab: 10 mg/kg on days 1, 15 | Arm 1<br>Capecitabine: 2500 mg/m$^2$/day for 14 out of 21 days<br><br>Arm 2<br>Capecitabine: 2500 mg/m$^2$ /day for 14 out of 21 days<br>Bevacizumab: 15 mg/kg q 3 weeks |
| Efficacy endpoints | Response rate: 14.2% (arm 1) vs 28.2% (arm 2); p < 0.0001<br><br>Progression-free survival: 6.11 (arm 1) vs 10.97 (arm 2) months | Response rate: 9.1% (arm 1) vs 19.8% (arm 2); p = 0.001<br><br>Progression-free survival: 4.86 (arm 1) vs 4.17 (arm 2) months |

[a]Miller et al (2005b); [b]Miller et al (2005a).

p = 0.05), estrogen receptor negativity (OR, 1.8; 95% CI, 1.0–3.0; p = 0.04), and disease-free interval (OR, 1.6; 95% CI, 1.0–2.5; p = 0.05). Likewise, the decrease in E-selectin after cycle 1 persisted after controlling for performance status (OR, 0.1; 95% CI, 0.0–0.9; p = 0.04), age (OR, 0.1; 95% CI, 0.0–0.9; p = 0.04), estrogen receptor negativity (OR, 0.1; 95% CI, 0.0–0.8; p = 0.04), visceral disease (OR, 1.0; 95% CI, 0.0–1.0; p = 0.04), and disease-free interval (OR, 0.1; 95% CI, 0.1–0.9; p = 0.03). Preclinical data supporting the role of E-selectin in angiogenesis, coupled with preliminary results of current trials, justify larger prospective studies evaluating E-selectin as a marker of response to bevacizumab-containing therapy.

The above activity results were also confirmed by phase III trials in heavily pretreated breast cancer patients, which demonstrated a significant increase in objective responses with the addition of bevacizumab to chemotherapy while improvement in progression-free survival was not always observed (Table 1). In particular, results from the E2100 study (paclitaxel vs paclitaxel plus bevacizumab) as first-line therapy in metastatic breast cancer showed a significant increase in objective response rate (14.2% vs 28.2%; p < 0.0001) and progression-free survival (6.11 vs 10.97 months; p < 0.001) with the addition of bevacizumab (Miller et al 2005b). In another phase III study, 462 patients were treated with capecitabine (2500 mg/m$^2$/day for 14 out of 21 days) with or without bevacizumab (15 mg/kg every 3 weeks). Adding bevacizumab to capecitabine increased the objective response rate (19.8 vs 9.1%, p = 0.001), although it did not affect progression-free (4.86 vs 4.17 months) or overall survival (15.1 vs 14.5 months) (Miller et al 2005a). Based on the promising response rates of these studies, and the increase in progression-free survival seen in E2100 trial, it would seem reasonable to extend the study of these combinations to the adjuvant setting.

In vitro studies have demonstrated that HER-2 signaling increased HIF-1α protein synthesis rather than inhibited its degradation; this represents a novel mechanism for the regulation of HIF-1 and VEGF expression (Laughner et al 2001). Moreover, in another preclinical study, exposure to trastuzumab significantly decreased VEGF in HER-2 overexpressing cells (Epstein et al 2002). In vivo experiments have shown reduction in xenograft volume using a combination of trastuzumab and bevacizuamb compared with single-agent control (Epstein et al 2002). Furthermore, the association between HER-2 and VEGF predict clinical outcome in primary breast cancer (Konecny et al 2004). Taken together, these data support the use of combination therapies directed against both HER-2 and VEGF for treatment of breast cancers with HER-2 overexpression. Recently, a phase I trial of bevacizumab (at doses of 3, 5, or 10 mg/kg every 14 days) with trastuzumab (4 mg/kg loading dose, then 2 mg/kg weekly until progression) was reported. Preliminary response assessment in 9 patients was 1 complete response, 4 partial responses, and 2 stable diseases (Pegram et al 2004).

Preliminary data also suggest that estrogen modulates VEGF-induced angiogenesis in physiologic and pathologic conditions. Estrogen-induced VEGF expression may promote breast cancer growth. Therefore, combination therapy with an aromatase inhibitor and bevacizumab may be more effective than either agent alone. Preliminary data of the combination of letrozole (2.5 mg daily) and bevacizumab (15 mg/kg i.v. every 3 weeks) show satisfactory tolerability (Traina et al 2005).

There is also a rationale to support simultaneous blockade of VEGF and EGFR pathways. EGFR can transactivate VEGF promoter via a PI3K dependent pathway (Maity et al 2000 and Clarke et al 2001). Moreover, several studies have demonstrated that blockade of the EGFR pathway results in an antiangiogenic effect (Bruns et al 2000). An increased production of VEGF could represent one possible mechanism by which tumor cells escape anti-EGFR monoclonal antibody therapy (Viloria-Petit et al 2001). A study has tested the strategy of combining bevacizumab and erlotinib, an EGFR-tyrosine kinase inhibitor, in metastatic breast cancer. This combination demonstrated activity which was related to circulating endothelial and tumor cells (Rugo et al 2004).

## Safety and tolerability

A phase I/II dose escalation trial of bevacizumab (ranging from 3 to 20 mg/kg) (Cobleigh et al 2003) evaluated the safety profile of the compound. Eighteen patients were treated at 3 mg/kg, 41 at 10 mg/kg, and 16 at 20 mg/kg, every other week. The first infusion was given over 90 minutes. If there were no infusion-related adverse events, the second infusion could be given over 60 minutes and subsequent infusions over 30 minutes. Overall, serious adverse events occurred in 15 out of 75 patients. In particular, 5 cases of hypertension were reported as serious adverse events (3 at 3 mg/kg, 1 at 10 mg/kg, 1 at 20 mg/kg), including 1 case of hypertensive encephalopathy in a patients without history of hypertension. Two patients developed suclavian/axillary vein thrombosis which resolved with anticoagulation therapy. Other 2 patients treated at 20 mg/kg developed headache with nausea and vomiting that was reported as serious. The symptoms developed 1–3 days after bevacizumab infusions, responded to

dexamethasone, and were not correlated with hypertension or brain metastases. Congestive heart failure was reported in 2 patients, at doses of 10 and 20 mg/kg, respectively. Both patients had previously received doxorubicin at cumulative doses of 240 and 300 mg/m². Thirty-nine percent of patients had an adverse event on the first 2 days after the first dose of bevacizumab, but all events were grade 1–2 except for 1 case of grade 3 myalgia. No significant bleeding episodes were reported, and this was not in keeping with that seen in patients with NSCLC (Sandler et al 2006). In fact, bleeding occurred in 25.3% of patients and never exceeded grade 1. Another common adverse event was hypertension, which occurred in 15 of 75 patients and required medical treatment in 14. Four of 17 patients who developed hypertension also had ≥ grade 2 proteinuria at some point during the study, including one patient who developed nephrotic syndrome. Furthermore, ≥ grade 1 proteinuria was documented in 17 of 72 evaluated patients. The mechanism of this adverse event has not been fully determined, but it is likely correlated to glomerular damage, given the predominance of albumin in the urine and the presence of membranoproliferative glomerulonephritis in the renal biopsy in 1 patient enrolled in this study. VEGF is constitutively expressed in the glomerulus, and glomerular endothelial repair may be mediated though VEGF (Ostendorf et al 1999). It is possible that low erythropoietin levels in cancer patients may worsen the situation because erythropoietin stimulates VEGF release in the glomerulus (Alvarez et al 1998). Hemoptysis was not reported, despite the fact that 28% of patients had lung metastases at the time of study enrolment. However, the high incidence of headache associated with nausea and vomiting at the dose of 20 mg/kg, suggested that 10 mg/kg every 2 weeks is the recommended dose.

In the phase III E2100 study, the main toxicities were grade 3 hypertension (in 13% of patients) and proteinuria (in 2.5% of patients). These two side-effects were never observed in the single-agent paclitaxel arm (Miller et al 2005b). In the other phase III study (capecitabine vs capecitabine plus bevicizumab), no significant differences were found in the incidence of diarrhea, hand-foot syndrome, thromboembolic events, or serious bleeding episodes between the two treatment groups. Only grade 3–4 treatment-requiring hypertension was more frequent in patients receiving bevacizumab (17.9% vs 0.5%) (Miller et al 2005a).

The previously mentioned association between bevacizumab and trastuzumab was associated with grade 1/2 toxicities which included diarrhea, fatigue, and nausea. A single grade 2 allergic reaction, one grade 2 hypertension, and one grade 2 proteinuria were also observed. No patients had left ventricular ejection failure (Pegram et al 2004).

## Patient-focused perspectives such as quality of life, patient satisfaction/ acceptability

In the previously mentioned E2100 study, the Functional Assessment of Cancer Therapy Breast (FACT-.B) was administered to trial participants at baseline and at weeks 17 and 33 to assess breast cancer-specific symptoms and concerns, and overall health-related quality of life (HRQL). The FACT-B was completed by 610 patients at baseline, 481 at 17 weeks, and 356 at 33 weeks. There was insufficient evidence to conclude that patients receiving bevacizumab in addition to paclitaxel differed on self-reported symptom burden and HRQL with respect to those receiving paclitaxel alone. Bevacizumab significantly improved clinical outcome without compromising HRQL and this reinforces the idea that a survival advantage can be obtained without quality of life impairment (Wagner et al 2006).

In the other phase III study (capecitabine vs capecitabine plus bevacizumab), the FACT-B questionnaire was administered at baseline, every 6 weeks until 24 weeks, and then every 9 weeks. Time to deterioration in quality of life (TDQ), as measured by the Trial Outcome Index (TOI), was the primary end point. TOI is the sum of the physical well-being, functional well-being, and breast cancer-specific questions in the FACT-B. A decline in TOI of more than 5 points from baseline, disease progression, or death were considered a clinically meaningful deterioration in quality of life. A total of 370 subjects (176 in the control arm, 194 in the experimental arm) completed baseline, and at least 1 subsequent quality of life assessment. Time to deterioration in quality of life did not differ between treatment groups (2.86 vs 2.92 months; p = 0.633). Overall survival (15.1 vs 14.5 months) and time to deterioration in quality of life as measured by FACT-B were comparable in both treatment groups (Miller et al 2005a).

## Conclusion, place in therapy

The main challenge in the use of bevacizumab and other biologic therapies in advanced breast cancer is clearly identifying predicting factors, which may drive therapy appropriately. Correlation studies of outcome and tumor VEGF expression or VEGF receptor expression, are currently underway. Hopefully, these studies may provide help in understanding the mechanism of anti-VEGF therapy and will be helpful to optimize the use of anti-angiogenic agents. However, in

colorectal cancer, where bevacizumab has shown a significant benefit in randomized trials, tumor VEGF levels do not appear to be correlated with outcome. Therefore, the activity of bevacizumab may relate to something more complex than simply the presence or absence of VEGF in the tumor. An interesting question is whether the use of more or less selective inhibitors will be the best strategy. A final major challenge is the identification of markers that accurately predict whether patients are good candidates for this treatment approach. Hypertension is known to be the most frequent bevacizumab side-effect; to the best of our knowledge, no studies are evaluating hypertension as a predictive marker of response. This would be a novel approach potentially able to provide us with some new insights.

The combination of bevacizumab with standard chemotherapeutic agent has been associated with only modest increases in toxicity. Minimizing toxicity while improving response rate and time to progression will be an important goal in the effort to convert metastatic breast cancer into a somehow chronic, manageable disease.

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