Breast Cancer
R E S E A R C H

Antiangiogenic therapy for breast cancer

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Abstract

Angiogenesis is an important component of cancer growth, invasion and metastasis. Therefore, inhibition of angiogenesis is an attractive strategy for treatment of cancer. We describe existing clinical trials of antiangiogenic agents and the challenges facing the clinical development and optimal use of these agents for the treatment of breast cancer. Currently, the most promising approach has been the use of bevacizumab, a humanized monoclonal antibody directed against the most potent pro-angiogenic factor, vascular endothelial growth factor (VEGF). Small molecular inhibitors of VEGF tyrosine kinase activity, such as sorafenib, appear promising. While, the role of sunitinib and inhibitors of mammalian target of rapamycin (mTOR) in breast cancer has to be defined. Several unanswered questions remain, such as choice of drug(s), optimal duration of therapy and patient selection criteria.

Introduction

Angiogenesis is a pivotal component of cancer growth, including invasion and metastasis. Tumours induce blood vessel growth (angiogenesis) by secreting various growth factors (for example, vascular endothelial growth factor (VEGF)). Growth factors, such as basic fibroblast growth factor and VEGF, can induce capillary growth into the tumour, which allows tumour expansion. Thus, angiogenesis is a necessary and required step for transition from a small harmless cluster of cells to a large tumour and is also required for the spread of a tumour, invasion and/or metastasis. The inhibition of angiogenesis is emerging as a new, attractive therapeutic approach to control tumour progression [1]. At present, several antiangiogenic therapies are in clinical trials testing their promise in breast cancer. This review focusses on clinical aspects of treatment of breast cancer with monoclonal antibodies, and tyrosine kinase and mammalian target of rapamycin (mTOR) inhibitors. In addition, new pivotal angiogenic pathways, such as the Notch ligand Delta-like 4 pathway, are briefly reviewed.

Methods

The data were obtained by searching in the PubMed database. The search terms used included 'antiangiogenic therapy', 'targeted therapy' and '(metastatic) breast cancer'. In addition, specific drugs (for example, bevacizumab,

sunitinib, and temsirolimus) were included in the search. Our primary focus was phase II and III trials, as only very few phase III trials were identified. Full articles were obtained and references were checked for additional information when appropriate. Proceedings from conferences of the American Society of Clinical Oncology (ASCO), the American Association of Cancer Research (2005 to 2009), and the San Antonio Breast Cancer Symposium (2005 to 2009) were searched for relevant abstracts. Data were updated through July 2010.

Antiangiogenic therapy

In situ hybridization studies have demonstrated expression of *VEGF* mRNA in many human tumours, including breast cancer. Thus, VEGF appears to be one of the key players, and current antiangiogenic strategies have therefore mainly aimed at blocking the action of VEGF. Such inhibition can be achieved by direct targeting of the ligand (VEGF) at the mRNA or protein level, direct targeting of its receptors (VEGFR1, VEGFR2, and neuro-pilin-1), or by blocking components of the downstream signaling pathway [2,3].

Inhibitors of VEGF: monoclonal antibodies
Bevacizumab in metastatic breast cancer
Bevacizumab (Avastin®; Genentech Inc., San Francisco, CA, USA; Hoffmann-La Roche Ltd, Basel, Switzerland) is a recombinant humanized monoclonal antibody that binds VEGF and prevents it from binding to its receptors [4]. A phase I/II study of bevacizumab monotherapy in patients with previously treated metastatic breast

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cancer (MBC) has shown a response rate (RR) of 7% with a median duration of 5.5 months (range 2.3 to 13.7 months); at tumour assessment on day 154, 16% of the patients had stable disease (SD) or an ongoing response [5]. Clinical studies indicate that the anti-neoplastic activity of bevacizumab as monotherapy is modest. Table 1 summarises the results from phase II trials utilizing bevacizumab in combination with chemotherapy, many of which are still preliminary. In these studies, bevacizumab was given as both first-line and later lines of therapy but the results were not always reported separately [6-18]. A first- and second-line phase II trial of bevacizumab in combination with docetaxel demonstrated a RR of 52% and median progression-free survival (PFS) of 7.5 months [6]. Furthermore, results from a phase II study of bevacizumab plus capecitabine as first-line therapy revealed encouraging results with an 81% clinical benefit rate (CBR; 6% complete response (CR), 33% partial response (PR) and 43% SD (duration not reported)) [15]. In contrast, a phase II trial of pegylated liposomal doxorubicin and bevacizumab had to be stopped prematurely because of toxicity (including one cardiac toxicity grade 4). The efficacy was modest with an RR of 23% and a median PFS of 7.5 months [18].

Results of phase III trials comparing chemotherapy regimens with and without bevacizumab are given in Table 2. A phase III study involving 462 patients with heavily pretreated MBC was rather disappointing. Adding bevacizumab to capecitabine did not improve the primary endpoint PFS (4.8 versus 4.2 months; hazard ratio = 0.98; 95% confidence interval, 0.77 to 1.25) or overall survival (OS; 15.1 versus 14.5 months), despite a doubling in objective RR in the combination arm compared with the capecitabine arm (20 versus 9%) [19]. This lack of benefit raises several questions about the mechanisms of antiangiogenic therapy (see the Discussion section).

A phase III trial (E2100) including 722 patients (90% human epidermal growth factor receptor 2 (HER2)-negative) randomised to first-line treatment with paclitaxel or paclitaxel plus bevacizumab has been completed. Analysis revealed increased RR (21 versus 37%, $P < 0.001$) and a doubling in median PFS (5.9 versus 11.8 months, $P < 0.001$) [20]. The OS, however, was similar in the two groups (25.2 versus 26.7 months, $P = 0.16$). Data on treatment administered after progression were not collected in this trial, precluding an exploratory analysis of the influence of subsequent therapy on OS.

More recently, results from a phase III trial (AVADO) including 736 patients randomised to first-line treatment with docetaxel plus placebo or docetaxel plus bevacizumab (two doses) has been reported. Analysis revealed

Table 1 Phase II trials of bevacizumab in combination with chemotherapy in metastatic breast cancer

Reference	Number of patients	Therapy	ORR (%)	PFS (months)
Ramaswamy *et al.* [6]	27 (78% HER2-negative)	B + docetaxel	52 (1st + 2nd line)	8
Chan *et al.* [7]	43 (21 evaluable)	B + docetaxel	Approximately 40 (1st line)	NR
Hurvitz *et al.* [8]	69 (67 evaluable; HER2-negative)	B + docetaxel	48 (1st line)	8 (TTP)
Perez *et al.* [9]	45 (HER2-negative)	B + docetaxel + capecitabine	49 (1st line) 69 (CBR)	11
Hoelzer *et al.* [10]	61 (57 evaluable)	B + paclitaxel	42 (1st line)	15
	58 (54 evaluable)	B + paclitaxel + gemcitabine	48	20
Guardino *et al.* [11]	21 (17 evaluable)	B + paclitaxel + gemcitabine	88 (CBR)	NR
Rugo *et al.* [12]	46	B + ixabepilone (weekly)	50 (1st line)	NR
	45	B + ixabepione (q3w)	71	NR
	32	B + paclitaxel	56	NR
Danso *et al.* [13]	49 (27 evaluable; HER2-negative)	B + nab-paclitaxel	30 (1st line)	9
Conlin *et al.* [14]	72	B + nab-paclitaxel (three dosing schedules)	42 (1st line)	9 (TTP)
	54		42	6
	76		42	8
Sledge *et al.* [15]	103	B + capecitabine	39 (1st line)	NR
Traina *et al.* [16]	29	B + capecitabine	31 (various; 10 pts with SD >6 months)	NR
Dellapasqua *et al.* [17]	46	B + capecitabine + cyclophosphamide	48 (1st to 3rd line)	10 (TTP)
Rochlitz *et al.* [18]	41	B + pegylated liposomal doxorubicin	23 (1st line)	8

Studies with ≥15 evaluable patients are included. B, bevacizumab; CBR, clinical benefit rate; NR, not reported; ORR, overall response rate; PFS, progression free survival; pts, patients; q3w, every third week; SD, stable disease; TTP, time to progression.

Table 2 Phase III trials of bevacizumab in combination with chemotherapy in metastatic breast cancer

Reference	Number of patients	Therapy	ORR (%)	PFS (months)
Miller *et al.* [19]	232	B (15 mg/kg q3w) + capecitabine	20 (previous anthracycline and taxane)	5 (TTP)
	230	Capecitabine	9 (*P* = 0.001)	4
Miller *et al.* [20] (E2100)	368 (347 intent-to-treat)	B (10 mg/kg q2w) + paclitaxel	37 (1st line)	12 (TTP)
	354 (326 intent-to-treat)	Paclitaxel	21	6 (*P* < 0.001)
Miles *et al.* [21] (AVADO)	248	B (7.5 mg/kg q3w) + docetaxel	55 (1st line)	9 (*P* = 0.045)
	247	B (15 mg/kg q3w) + docetaxel	64	10 (*P* < 0.001)
	241	Placebo + docetaxel	46	8
Robert *et al.* [22] (RIBBON-1)	409	B (15mg/kg q3w) + capecitabine	35 (1st line)	10 (*P* = 0.0011)
	206	Capecitabine	24	6
	415	B (15 mg/kg q3w) + taxane or anthracycline-based therapy	51	11 (*P* = 0.040)
	207	Taxane or anthracycline-based therapy	38	8
Brufsky *et al.* [24,25] (RIBBON-2)	684	B + chemotherapy (capecitabine, gemcitabine, vinorelbine)	40 (2nd line)	7 (*P* = 0.0072)
		Chemotherapy	30	5

B, bevacizumab; ORR, overall response rate; PFS, progression free survival; q2w, every second week; q3w, every third week; TTP, time to progression.

significantly increased RR (46% versus 55% versus 64%, respectively) and PFS (8.2, 9.0 and 10.1 months, respectively), though seemingly to a lesser extent than when combined with weekly paclitaxel [21]. OS was similar in all treatment arms with median values of approximately 31 months.

The phase III trial (RIBBON-1) evaluated first-line chemotherapy (anthracycline-based, taxane or capecitabine) with or without bevacizumab. Among 1,237 patients, the addition of bevacizumab to chemotherapy resulted in an improvement in RR and PFS; however, no significant OS advantage was seen [22]. Thus, although these trials have demonstrated significant improvements in RR and PFS, findings to date have not indicated substantial benefit in terms of survival. Recently, a meta-analysis of PFS and OS data from the three above-mentioned trials (E2100, AVADO, RIBBON-1) including 2,447 patients has been published. Pooled results for PFS showed an improved median PFS (6.7 to 9.2 months; *P* < 0.0001) for the bevacizumab-arm whereas pooled results for OS showed no statistically significant difference between the arms (26.4 versus 26.7 months). However, 1-year survival was greater in the bevacizumab arm (82 versus 77%; *P* = 0.003) [23].

Bevacizumab in combination with second-line standard chemotherapy (taxane, gemcitabine, capecitabine, or vinorelbine) has been evaluated in a phase III trial

including 684 HER2-negative patients (RIBBON-2). The addition of bevacizumab improved the median PFS (5.1 to 7.2 months; hazard ratio = 0.78; *P* = 0.0072). Subgroup analyses showed that PFS was consistently improved in the bevacizumab arms across all chemotherapy cohorts [24,25].

Preclinical studies have suggested that oestrogen modulates VEGF-induced angiogenesis. It has been hypothesised that adding bevacizumab to hormonal therapy could reverse required endocrine resistance. MBC patients who had progressed on hormonal therapy after a previous response were included in a phase II trial in which bevacizumab was added to the anti-hormonal therapy. Results from this study (27 patients) showed no responses but SD in 66% of the patients (duration not reported) [26]. A phase II trial of bevacizumab plus letrozole in 32 postmenopausal women with hormone-receptor-positive advanced breast cancer (ABC) revealed 2 patients with PR and 13 with SD for 6 months or more [27]. Preliminary results from a two arm noncomparative phase II study of bevacizumab combined with anastrozole (25 patients) or fulvestrant (17 patients) as first-line therapy in MBC reported promising results with a PR rate of 24%, a SD rate of 57%, a median PFS of 16.3 months for the anastrozole arm, and median PFS not reached in the fulvestrant arm [28]. A similar phase II study of bevacizumab plus fulvestrant in

33 MBC patients previously treated with an aromatase inhibitor did not meet its statistical endpoint, as only 22% (11% PR + 11% SD ≥6 months) of the patients achieved clinical benefit with a median PFS of 6.2 months [29].

Bevacizumab in early-stage breast cancer: preoperative therapy

Results of phase II trials are given in Table 3 [30-38]. No phase III trials have been reported. A placebo controlled double-blind randomised phase II trial investigated neoadjuvant bevacizumab or placebo followed by docetaxel, doxorubicin, and cyclophosphamide with or without bevacizumab in patients with stage II or III HER2-negative breast cancer. Of 37 patients, 95% obtained objective responses, including 59% with CR. The complete pathological response (pCR) rate has not been reported. Congestive heart failure (CHF) grade 3 was reported in three patients and four patients had a decline in left ventricular ejection fraction >15%; the incidence was similar in the different treatment arms [30]. A phase II study of bevacizumab in combination with docetaxel and cyclophosphamide followed by doxorubicin has shown 38% pCR in the breast and 29% in the breast and axilla among 36 patients. However, one patient died of bilateral pulmonary embolism and one developed CHF [31]. In contrast, no CR was reported in

21 patients with inflammatory or locally advanced breast cancer after preoperative treatment with bevacizumab, doxorubicin and docetaxel [34].

Preliminary results from a study evaluating bevacizumab plus letrozole in the preoperative setting has demonstrated an 18% pCR rate and a 74% overall response rate (ORR) among 22 postmenopausal, hormone-receptor-positive, HER2-negative patients [39].

Bevacizumab in early-stage breast cancer: adjuvant therapy

It has been hypothesised that the most beneficial use of antiangiogenic agents would be in the adjuvant setting. However, concern exists about potential cardiac toxicities, including CHF, particularly in patients receiving bevacizumab in combination with anthracyclines. E2104 is a non-randomised trial designed to evaluate the safety of incorporating bevacizumab in anthracycline-containing adjuvant therapy. Patients with lymph node-positive breast cancer were sequentially assigned to adjuvant chemotherapy consisting of dose dense doxorubicin and cyclophosphamide followed by paclitaxel in combination with bevacizumab (26 doses given every second week; 104 patients) or the same treatment but with sequential treatment with bevacizumab (bevacizumab initiated concurrently with paclitaxel; 122 patients) (Table 4) [40]. After a median follow-up of 15 and 11 months,

Table 3 Trials of bevacizumab in early-stage breast cancer: preoperative therapy

Reference	Phase	Number of patients	Treatment	Response rate (%)
Hurvitz *et al.* [30]	II (randomised)	37 of 90 planned (HER2-negative)	A: TAC + B (7.5 mg/kg)	All regimens: RR 95; CR 59; PR 35
			B: TAC + placebo	A: PR 58; CR 42
			C: TAC + B (15 mg/kg)	B + D: PR 27; CR 64
			D: TAC + placebo (2:1:2:1, randomisation)	D: PR 21; CR 71
Makhoul *et al.* [31]	II	36 (11 HER2-negative)	Bevacizumab + docetaxel + cyclophosphamide (4 cycles) → doxorubicin (4 cycles) → bevacizumab (adjuvant, 9 cycles)	PR 31; CR 39; pCR breast 38; pCR breast + axilla 29
Greil *et al.* [32]	II	18 (HER2-negative)	Bevacizumab × 5* + (docetaxel + capecitabine) × 6*	pCR 22
Balduzzi *et al.* [33]	II	30	Epirubicin + cisplatin + fluorouracil × 4* → bevacizumab + paclitaxel × 3*	pCR 33; CR + PR 87
Wedam *et al.* [34]	II	21 (81% HER2-negative)	Bevacizumab × 1* → bevacizumab + doxorubicin + docetaxel × 6*	PR 67; CR 0
Lyons *et al.* [35]	II	49 (number of patients receiving bevacizumab not reported)	Docetaxel + bevacizumab or docetaxel	CR 14; PR 65
Raefsky *et al.* [36]	II	25	Nab-paclitaxel + carboplatin × 6* + trastuzumab + bevacizumab × 23*	pCR 26; PR 16
Locatelli *et al.* [37]	II (randomised)	23 (19 evaluable; locally advanced)	B → vinorelbine + capecitabine (9 pts)	NR
			B + vinorelbine + capecitabine (14 pts)	NR
Torrisi *et al.* [38]	II	37 (36 evaluable; estrogen and/or progesterone positive)	Bevacizumab + capecitabine + vinorelbine + letrozole	RR 86; pCR 0

Studies with ≥15 evaluable patients are included. B, bevacizumab, in combination with chemotherapy preoperatively plus adjuvant for 52 weeks; CR, complete response; NR, not reported; pCR, pathological complete response; PR, partial response; pts, patients; RR, response rate; TAC, docetaxel, doxorubicin, cyclophosphamide (six cycles preoperatively). *Times of treatment.

Table 4 Trials of bevacizumab in early-stage breast cancer: adjuvant therapy

Reference	Phase	Number of patients	Treatment	Clinical CHF	LVEF <40%	DFS
Miller *et al.* [40]	II (two-arm non-randomised)	104	B[1] + (ddAC → paclitaxel)	2	4	NR
		122 (HER2 status not reported)	ddAC → B + paclitaxel	2	1	NR
Hart *et al.* [41]	IIb (randomised)	59	HER2-negative randomised: B[2] + AC → T	1	NR	NR
		61	B[2] + ACT	2	NR	NR
		39	HER2-positive: B[2] + TCH	0	NR	NR
Mayer *et al.* [42]	II	40	B[2] +/- trastuzumab +/- endocrine therapy	0	0	NR
McArthur *et al.* [112]	II	76	B[2] + ddAC × 4 → nab-paclitaxel × 4	0	0	NR

AC, doxorubicin + cyclophosphamide; ACT, doxorubicin + cyclophosphamide + docetaxel; B[1], bevacizumab 10 mg/kg every second weeks × 26; B[2], bevacizumab15 mg/kg every 3 weeks for a total of 52 weeks; CHF, congestive heart failure; ddAC, dose dense doxorubicin + cyclophosphamide; DFS, diseas-free survival; LVEF, left vntricular ejection fraction; NR, not reported; T, docetaxel; TCH, docetaxel + carboplatin + trastuzumab.

respectively, two patients developed CHF in each arm and declines in left ventricular ejection fraction (LVEF) <40% were recorded in four and one patient, respectively. However, only 8 patients completed therapy in the sequential arm, whereas 52 patients completed therapy in the combination arm. No efficacy data have been reported. Hart and colleagues [41] reported preliminary safety data from a randomised phase II study designed to test the feasibility of bevacizumab in combination with three adjuvant docetaxel-containing regimens (Table 4). Three early CHF cases were reported in patients receiving anthracyclines. No cardiac events were identified using the bevacizumab plus trastuzumab combination. A phase II study of adjuvant bevacizumab concomitant with trastuzumab and/or endocrine therapy after neoadjuvant anthracycline-based therapy among 40 patients showed three recurrences within a median follow-up of 8 months. No patient developed CHF [42].

Several studies are ongoing in the adjuvant setting. E5103 is a phase III trial designed to succeed E2104. The trial compares cyclophosphamide, paclitaxel, pegylated liposomal doxorubicin plus placebo with the same combination of chemotherapy plus bevacizumab with the same combination of chemotherapy plus bevacizumab followed by bevacizumab alone. The study is currently recruiting patients (planned enrolment 4,950 patients; NCT00433511). Another phase III trial (BEATRICE) is designed to assess the benefit of adding bevacizumab to standard adjuvant chemotherapy (anthracycline, taxane or combined anthracycline and taxane based regimens). Approximately 3,000 patients with triple-negative breast cancer will be randomised to receive chemotherapy alone or in combination with bevacizumab for a total duration of 12 months (NCT00528567). Finally, the phase III BETH trial evaluates the addition of bevacizumab to adjuvant

chemotherapy and trastuzumab in patients with HER2-positive breast cancer (estimated enrolment 3,500 patients; NCT00625898).

The tolerability of bevacizumab is generally acceptable, and the drug can readily be administered in combination with chemotherapeutic agents, which, in some circumstances, may be synergistic. Common adverse events include asthenia, headache, hypertension, proteinuria, diarrhoea, nausea, vomiting, and stomatitis. Most adverse events are mild to moderate and clinically manageable. Serious but rare adverse events include gastrointestinal perforation, wound healing complications, episodes of bleeding, and thrombosis [43].

VEGF trap
Novel agents targeting VEGF include the VEGF trap aflibercept (developed by Regeneron, Tarrytown, NY, in collaboration with Sanofi-Aventis, Bridgewater, NJ), which is a fully human, soluble fusion protein. The protein construct consist of parts of the extracellular domains of VEGFR1 and VEGFR2 fused to the Fc segment of human IgG1. Aflibercept binds and neutralises all isoforms of VEGF and placental growth factor (PlGF) and is the most potent VEGF blocker available, binding VEGF with 100- to 1,000-fold higher affinity than other reported VEGF antagonists [44]. A phase II study in 21 patients with MBC previously treated with an anthracycline and/or a taxane reported a 5% PR rate and did not meet efficacy goals [45].

Antibodies targeting integrins
The integrins are a family of at least 24 $\alpha\beta$ heterodimeric glycoproteins involved in cell matrix binding and communication. The α_v integrins are expressed by endothelial cells, particularly during angiogenesis, and are implicated in signal transduction by VEGF, fibroblast

growth factor, and a variety of other cytokines. Several integrin inhibitors are under development - for example, CNTO 95 (Centocor, Horsham, PA, and Janssen-Cilag Pharmaceutical, SRL), a fully human antibody directed against the α_v integrin receptor [46]. We did not identify breast cancer studies.

Anti-placental growth factor antibody

Recently, the effect of a neutralising murine anti-PlGF antibody, TB-403 (Bioinvent International, Lund, Sweden, and ThromboGenics, Leuven, Belgium; Hoffmann-La Roche Ltd, Basel, Switzerland), was reported. Unlike VEGF, PlGF selectively binds VEGFR1 and its co-receptors neuropilin-1 and -2. *In vivo*, the antibody inhibited the growth and metastasis of various tumours, including those resistant to VEGF inhibitors. Distinct from VEGF inhibitors, TB-403 prevented infiltration of angiogenic macrophages and severe tumour hypoxia, and thus did not switch on the angiogenic rescue program responsible for resistance to VEGF. Potentially, the safety profile of the drug is favourable as it did not affect healthy vessels [47]. The drug is currently being investigated in a phase I trial (NCT00702494).

Inhibitors of other receptors related to angiogenesis: tyrosine kinase inhibitors

In parallel with the clinical development of bevacizumab, multiple small molecule inhibitors of the VEGF receptor tyrosine kinases have entered the clinic. A huge number of small molecules are in pre-clinical and clinical development (Table 5). Table 6 summarises the results from trials utilising tyrosine kinase inhibitors, many of which are still preliminary.

Sunitinib (Sutent®, SU11289; Pfizer, New York, NY, USA) is a multitarget inhibitor with activity against VEGF2, platelet-derived growth factor receptor (PDGFR) β, stem cell factor receptor (c-Kit) and FLT3 tyrosine kinase signaling pathways [48]. A phase II trial demonstrated 11% PR and 5% SD among 64 patients with

Table 5 Tyrosine kinase inhibitors targeting the angiogenic pathway currently in clinical development in breast cancer

Drug	Target
Sunitinib	VEGFR2, PDGFR-β, FLT3, c-Kit
Sorafenib	VEGFR1, 2 and 3, PDGFR-β, FLT3, c-Kit, Raf
Pazopanib	VEGFR1, 2 and 3, PDGFR-α/β, c-Kit
Vatalanib	VEGF1, 2 and 3, PDGFR, c-Kit, c-Fos
Cediranib	VEFGR1, 2 and 3, PDGFR, c-Kit
Vandetanib	VEGFR2, EGFR, RETS
AMG 706	VEGFR1, 2 and 3, PDGFR-β, c-kit
Axitinib	VEGFR1, 2 and 3, PDGFR, c-Kit

EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

refractory, late-stage MBC receiving sunitinib as monotherapy; median time to progression and OS were 10 and 38 weeks, respectively [49]. All phase I/II studies of sunitinib in combination with chemotherapy have shown activity and manageable toxicities [49-53]. However, a phase III study of sunitinib plus paclitaxel versus bevacizumab plus paclitaxel as first-line therapy in ABC (NCT00373256) has been terminated prematurely as it would not have met its primary goal (the primary endpoint being PFS). Furthermore, two phase III studies comparing docetaxel plus sunitinib with docetaxel and capecitabine plus sunitinib with capecitabine did not meet their primary endpoint of prolongation of PFS despite a significantly increased ORR (51% versus 39%) in the docetaxel study [54,55]. Finally, a study comparing capecitabine with sunitinib in MBC has been halted because of futility [56].

The most important treatment-related serious adverse events have been pulmonary embolism, thrombocytopenia, tumour haemorrhage, febrile neutropenia, and hypertension. The most common treatment-related adverse events include fatigue, gastrointestinal disorders, such as diarrhoea, nausea, stomatitis, dyspepsia and vomiting, hand-foot syndrome, skin decolouration and anorexia. A retrospective review of 75 patients with gastrointestinal tumours receiving sunitinib in phase I/II trials showed 11% had CHF after repeated doses of sunitinib. The study underscores the importance of cardiac monitoring [57].

Sorafenib (Nexavar®; Bayer AG Health Care, Leverkusen, Germany, and Onyx Pharmaceuticals, Emeryville, CA, USA) is a multikinase inhibitor that targets Raf kinase and the receptor tyrosine kinases VEGFR 1, 2, and 3, PDGFRβ, c-Kit and FLT3 [58]. A phase II study of 54 pretreated MBC patients showed one with PR and 20 with SD (37%) [59]. The findings reflect those obtained in renal cancer, in which SD has been the main finding. A randomised phase IIb study (229 MBC patients) comparing capecitabine plus sorafenib with capecitabine plus placebo has shown significantly increased PFS [60]. In addition, a randomised phase IIb study comparing paclitaxel plus sorafenib with paclitaxel plus placebo as first-line therapy in 237 MBC patients demonstrated significant improvements in time to progression and ORR. However, the primary endpoint, PFS, was not significantly increased [61] (Table 6). Like sunitinib, sorafenib is associated with fatigue, anorexia, diarrhoea, rash, and hand-foot syndrome.

Pazopanib (Armala®, GW786034; GlaxoSmithKline, Middlesex, UK) is a multitarget inhibitor with activity against VEGFR1, 2 and 3 in addition to PDGFRα/β and c-Kit [62]. A phase I study of pazopanib alone in MBC revealed one with PR and 11 with SD among 19 patients [63].

Vatalanib (PTK787/ZK 222584; Novartis Institutes for BioMedical Research Oncology, Basel, Switzerland) and

Table 6 Trials of tyrosine kinase inhibitors targeting the angiogenic pathway in metastatic breast cancer

Reference	Phase	Number of patients	Treatment	Response (%)	PFS (months)
Burstein *et al.* [49]	II	64	Sunitinib	PR 2; SD ≥6 months 8	2.5 (TTP)
Lyandres *et al.* [50]	I	15	Sunitinib + cyclophosphamide + methotrexate	PR 7; SD >6 months 7	NR
Gianni *et al.* [51]	II	13	Sunitinib + docetaxel	PR 61; SD 23	NR
Kozloff *et al.* [52]	I	20	Sunitinib + paclitaxel	CR 10; PR 15	NR
Wildiers *et al.* [53]	II (randomised)	36	Taxane→ sunitinib	NR	3.4
		19	Taxane → no treatment	NR	3.1
NCT00373256	III	NR	Paclitaxel + sunitinib Paclitaxel + bevacizumab	Did not meet primary end point (increased PFS)	
Bergh *et al.* [54]	III	296	Docetaxel + sunitinib	51	8.6; OS 24.8
		297	Docetaxel + placebo	39	8.3; OS 25.5
Crown *et al.* [55]	III	221	Capecitabine + sunitinib	19	5.5; OS 16.4
		221	Capecitabine	16	5.9; OS 16.5
Barrios *et al.* [56]	III	244	Sunitinib	11	2.8; OS 15.3
		238	Capecitabine	16	4.2; OS 24.6
Bianchi *et al.* [59]	II	54	Sorafenib	PR 1; SD ≥6 months 37	NR
Baselga *et al.* [60]	II (randomised)	114	Capecitabine + sorafenib	NR	PFS increased (*P* = 0.0006 versus Capecitabine + placebo)
		115	Capecitabine + placebo		
Gradishar *et al.* [61]	II (randomised)	119	Paclitaxel + sorafenib	67	6.9; TTP 8.1
		118	Paclitaxel + placebo	54	5.6 (*P* = 0.0857); TTP 5.6 (*P* = 0.0171)
Isaacs *et al.* [113]	I/II	35	Anastrozole + sorafenib	CBR 20 (PR + SD ≥6 months)	NR
Taylor *et al.* [63]	I	21	Pazopanib	PR 5; SD ≥6 months 21	3.7 (TTP)
Miller *et al.* [66]	II	46	Vandetanib	SD ≥6 months 2	NR
Boér *et al.* [67]	II (randomised)	35	Docetaxel + vandetanib	NR	9
		29	Docetaxel + placebo	NR	6
de Boer *et al.* [69]	I	13 (9 evaluable)	Motesanib diphosphate + taxane	PR 22; SD ≥6 months 11	NR
Rugo *et al.* [71]	II (randomised)	168	Docetaxel + axitinib	40	8.2 (TTP)
			Docetaxel	23	7.0 (*P* = 0.052)

CBR, clinical benefit rate; CR, complete response; NR, not reported; ORR, overall response; OS, overall survival; PFS, progression free survival; PR, partial response; pts, patients; SD, stable disease; TTP, time to progression.

cediranib (Recentin®, AZD2171; AstraZeneca Pharmaceuticals, London, UK) are pan-VEGF, PDGFR, and c-Kit receptor tyrosine kinase inhibitors [64]. No results have yet been published with regard to breast cancer.

Vandetanib (ZD6474; Zactima®; AstraZeneca, London, UK) is a VEGFR2 inhibitor that also has activity against epidermal growth factor and RETS receptor tyrosine kinases [65]. The compound exhibited little activity in MBC [66]. A randomised phase II study of docetaxel plus vandetanib or placebo as second-line therapy in 64 patients with ABC showed no difference between the two arms [67].

The nicotinamide motesanib diphosphate (AMG 706; Amgen Inc., Thousand Oaks, CA, USA) is a multikinase inhibitor of VEGFR1, 2 and 3, PDGFR and c-Kit [68]. A phase Ib study of motesanib diphosphate in combination with paclitaxel or docetaxel in locally advanced breast cancer is ongoing. Preliminary results have shown that the combinations are tolerable [69].

Axitinib (AG-013736) is a tyrosine kinase inhibitor with activity against VEGFR1, 2 and 3, PDGFR and c-Kit [70]. This agent in combination with docetaxel has been compared to docetaxel in a randomised phase II trial. The addition of axitinib significantly increased

ORR (40% versus 23%) and prolonged time to progression [71].

In general, these above-mentioned trials have shown some activity of tyrosine kinase inhibitors in MBC, although results have been heterogeneous. Thus, phase II randomised trials including sorafenib or axitinib have shown increased PFS [60,71]. On the other hand, other trials have been negative [66,67] and accumulated data from recent trials did not support the use of sunitinib in the treatment of MBC [53-56]. The reason for the lack of effect is probably multifactorial. One explanation could be insufficient dose intensity due to toxicity. Furthermore, the patient populations in many of the studies have been heterogeneous and heavily pretreated. For other reasons see the Discussion section. It is possible, however, that drugs like, for example, sunitinib are active within a small, specific subgroup of patients.

γ-Secretase inhibitors

The Notch-Delta-like signaling pathway plays an important oncogenic role in breast tumour development in animal models and is probably also significant in human breast tumours. Central to Notch activation is γ-secretase, which cleaves Notch, allowing its translocation to the nucleus, where it activates target genes. Thus, inhibition of γ-secretase function would prevent Notch signal transduction [72]. The γ-secretase inhibitor MK-0752 (Merck and Co., Inc., Whitehouse Station, NJ, USA) is currently being evaluated in a phase I/II study.

Inhibition of angiopoietin

AMG 386 (Amgen Inc., Thousand Oaks, CA, USA) is a fusion protein containing a synthetic peptide exhibiting high affinity for angiopoietins fused to the constant region of human IgG1 [73]. By neutralising angiopoietin 1 and 2, the drug inhibits Tie2-dependent stimulation of endothelial cells. Recent data implicate angiopoietin 2 as an important mediator of the angiogenic process. A phase II placebo-controlled trial in HER2-negative ABC comparing the efficacy of paclitaxel plus AMG 386 versus paclitaxel plus bevacizumab versus paclitaxel in combination with both drugs has been initiated (NCT00511459).

mTOR inhibitors

mTOR is a serine-threonine protein kinase downstream of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway. This pathway regulates several cellular functions that are critical to tumourigenesis. Evidence suggests that aberrant activation of this pathway plays a major role in breast cancer cell proliferation and in several anti-cancer drug resistance mechanisms. Additionally, mTOR activation increases translation of hypoxia-inducible factor 1α and thereby VEGF [74].

Currently, the mTOR inhibitors temsirolimus (CCI-779 (cell-cycle inhibitor)-779; Torisel®; Wyeth Pharmaceuticals, Inc., Madison, NJ, USA) [75], everolimus (RAD001, Afinitor®; Novartis Institutes for BioMedical Research Oncology, Basel, Switzerland) [76], and ridaforolimus, formerly known as deforolimus (AP23573; ARIAD Pharmaceuticals Inc., Cambridge, MA, USA; MK-8669; Merck and Co., Inc., Whitehouse Station, NJ, USA) [77] are studied in MBC. A phase II randomised study of two dose levels of temsirolimus in 109 patients with previously treated ABC reported an ORR of 9% (10 with PR) and a CBR of 14% (SD ≥6 months) [78]. Generally, results have been rather disappointing with a lower-than expected RR (Table 6) [74,79]. Thus, monotherapy with mTOR inhibitors has limited activity in breast cancer (and other cancer types). A potential explanation could be related to a collateral effect of mTOR blockade. Thus, mTOR inhibition blocks the natural negative feed-back on the insulin-like growth factor-1 receptor signaling that inhibits PI3K activation. The result is an increase in PI3K and Akt activation, which could potentially counteract the inhibition of mTOR [80]. The adverse side effects of mTOR inhibitor monotherapy are fatigue, skin rash, stomatitis, increased triglycerides, increased glucose and decreased phosphor. However, these side effects are generally mild. Table 7 summarises trials investigating mTOR inhibitors in MBC.

A phase I trial assessing the combination of everolimus and docetaxel has been terminated as the pharmacokinetic analysis showed variable and unpredictable changes in docetaxel clearance, making the combination unfeasible. No objective response was observed in 15 patients [81]. On the other hand, a phase Ib study of everolimus in combination with cisplatin and paclitaxel was well tolerated with significant antitumour activity (RR 23%) [82].

Based on the crosstalk between the oestrogen receptor and the PI3K/Akt/mTOR pathway, several clinical trials have explored the combination of an mTOR inhibitor with endocrine therapy. Early data from a randomised three-arm phase II study of temsirolimus in combination with letrozole in 92 postmenopausal women with ABC has shown clinical activity, with prolonged PFS in the combination arms compared with the letrozole mono-therapy arm [83]. A large phase III study tested temsirolimus combined with letrozole against letrozole alone in 1,112 postmenopausal women with ABC [84]. The study was terminated prematurely because more grade 3 toxicities were reported with the combination arm. In addition, no improvements in RR or PFS were seen with the combination compared to letrozole alone (RR 27% in both treatment arms; PFS 8.8 and 8.9 months, respectively).

Table 7 Trials of mTOR inhibitors in metastatic breast cancer

Reference	Phase	Number of patients	Treatment	Response (%)	PFS (months)
mTOR inhibitor monotherapy					
Chan *et al.* [78]	II (randomised)	109	Temsirolimus (two dose levels)	ORR 9	NR
Ellard *et al.* [79]	II (randomised)	49 (33: daily schedule)	Everolimus (two different schedules)	ORR 12 (daily schedule)	NR
				ORR 0 (weekly schedule)	NR	NR
mTOR inhibitor plus chemotherapy					
Moulder *et al.* [81]*	I	15	Everolimus + docetaxel	RR 0	NR
Mayer *et al.* [82]	Ib	16	Everolimus + cisplatin + paclitaxel	RR 23	NR
mTOR inhibitor plus endocrine therapy					
Carpenter *et al.* [83]	II (randomised)	33: daily	Temsirolimus (two schedules) + letrozole	PR 27	Not reached
		30: intermittent		CR 3, PR 27	Not reached
		29	Letrozole	CR 7 + PR 34	9.2
Chow *et al.* [84]*	III	556	Temsirolimus + letrozole	ORR 27	8.8
		556	Letrozole	ORR 27	8.9

*Study terminated due to toxicity. CR, complete response; mTOR, mammalian target of rapamycin; NR, not reported; ORR, overall response rate; PFS, progression free survival; PR, partial response; RR, response rate.

Table 8 summarises studies investigating preoperative mTOR inhibitors in early-stage breast cancer. A phase II trial of everolimus monotherapy for 14 days prior to surgery in 30 postmenopausal women with early breast cancer has shown significantly reduced tumour cell proliferation [85]. Furthermore, Baselga and colleagues [86] presented the results of the combination of everolimus plus letrozole in a randomised phase II neoadjuvant trial of 270 oestrogen receptor-positive breast cancer patients. The RR with everolimus plus letrozole was superior to that of placebo plus letrozole (68% versus 59%).

Antiangiogenic therapies in combination with other targeting therapies

Angiogenesis is a complex process composed of multiple signaling pathways. Many of these pathways are redundant, with several ligand-receptor combinations resulting in the same eventual downstream events. It is unlikely that tumours are entirely dependent on only one abnormally activated signaling pathway; consequently, treatment with an agent that interferes with a single target may be insufficient. Simultaneous blockade of multiple pathways has become an attractive therapeutic strategy [87]. Table 9 summarises trials using combination targeting therapies.

Bevacizumab plus trastuzumab

The *HER2* gene is overexpressed in 18 to 25% of all primary breast cancers. Trastuzumab (Herceptin®; Genentech Inc., San Francisco, CA, and Hoffmann-La Roche Ltd., Basel, Switzerland) is a recombinant, monoclonal humanised murine antibody directed against the extracellular portion of the HER2 protein. The precise mechanism of its anti-tumour action has not been fully elucidated. Several molecular and cellular effects have been observed, including inhibition of HER2 extracellular proteolysis, disruption of downstream cellular pathways, cell-cycle arrest, inhibition of DNA repair, suppression of angiogenesis, and induction of antibody-dependent cell-mediated cytotoxicity. Measurements of HER2 and VEGF in primary breast tumour tissue have demonstrated a positive association between HER2 and VEGF expression [88]. Therefore, the combination of inhibitors against HER2 and VEGF might be a rational treatment strategy for patients with HER2-positive breast cancer. Preliminary results from a phase II trial (50 patients) of trastuzumab plus bevacizumab as first-line treatment in HER2-positive MBC have demonstrated a 48% RR, including 2 patients with CR [89]. However, 19 cardiac adverse events were reported, one of which was symptomatic (grade 4). Thus, the combination requires stringent cardiac surveillance.

Table 8 Trials of mTOR inhibitors in early-stage breast cancer: preoperative therapy

Reference	Phase	Number of patients	Treatment	Response
Macaskill *et al.* [85]	II	30	Everolimus (14 days prior to surgery)	Reduced cell proliferation
Baselga *et al.* [86]	II (randomised)	270	Everolimus + letrozole	RR 68%
			Letrozole	59%

mTOR, mammalian target of rapamycin; RR, response rate.

Table 9 Antiangiogenic therapy in combination with other targeting therapies

| | | Combination | | | | |
| | | Targeting angiogenesis | | | Targeting HER1 or 2 | |
Reference	Chemotherapy	Monoclonal antibody	Tyrosine kinase inhibitor	mTOR inhibitor	Monoclonal antibody	Tyrosine kinase inhibitor
Hurvitz *et al.* [89]						
Dickler *et al.* [90]		Bevacizumab				Erlotinib
Dickler *et al.* [91]		Bevacizumab				Lapatinib
Blay *et al.* [92]			Sunitinib		Trastuzumab	
Dirix *et al.* [93]	Docetaxel		Sunitinib		Trastuzumab	
Slamon *et al.* [94]			Pazopanib			Lapatinib
O'Regan *et al.* [95]	Paclitaxel			Everolimus	Trastuzumab	
Yardley *et al.* [96]				Ridaforolimus	Trastuzumab	
Mayer *et al.* [97]				Everolimus		Erlotinib

HER, human epidermal growth factor receptor; mTOR, mammalian target of rapamycin.

Bevacizumab plus erlotinib

Erlotinib (Tarceva®; Genentech Inc., San Francisco, CA, USA, and Hoffmann-La Roche Ltd., Basel, Switzerland) is an inhibitor of the HER1 (epidermal growth factor receptor) tyrosine kinase. Results from a phase II trial of the combination of bevacizumab and erlotinib in 38 MBC patients has been disappointing (1 with PR and 4 with SD >6 months) [90].

Bevacizumab plus lapatinib

Lapatinib (Tyverb®, GW572016; GlaxoSmithKline, Middle-sex, UK) is a dual tyrosine kinase inhibitor of HER1 and HER2. Like trastuzumab, the compound may have angiogenic downstream effects. A phase II study of bevacizumab plus lapatinib in 52 (27 evaluable) patients with HER2- positive MBC showed an ORR of 13% and a CBR of 34%. The combination was generally well tolerated [91].

Sunitinib plus trastuzumab

Preliminary results from an ongoing phase II trial in patients with HER2-positive ABC have shown an ORR of 35% and a CBR of 48% among 52 patients receiving sunitinib combined with trastuzumab [92]. Furthermore, the combination of sunitinib, trastuzumab, and docetaxel as first-line therapy in 25 women with HER2-positive MBC showed one with CR and 14 with PR [93].

Pazopanib plus lapatinib

Recently, results from a randomised, phase II study investigating lapatinib alone or in combination with pazopanib as first-line therapy in HER2-positive MBC patients have been presented. A pre-specified interim analysis of 62 patients demonstrated a RR of 44% after treatment with the combination regimen compared with 30% after treatment with lapatinib alone [94]. The study underscores that the combination of VEGF- and HER2-targeted therapies could result in substantial clinical benefit.

Everolimus/ridaforolimus plus trastuzumab

A phase I trial including 22 (17 evaluable) patients with trastuzumab-resistant MBC treated with paclitaxel plus everolimus plus trastuzumab resulted in 5 with PR and 2 with SD >16 weeks [95]. In addition, a phase II trial including 22 (14 evaluable) similar patients treated with a combination of ridaforolimus and trastuzumab has shown 2 with PR [96]. Both combinations were well tolerated.

Everolimus plus erlotinib

A phase Ib study of the combination of everolimus plus erlotinib in 14 patients with MBC showed that the regimen was well tolerated. However, the authors concluded that the combination was clinically ineffective and did not warrant further testing in breast cancer [97].

Combinations of antiangiogenic therapies
Bevacizumab plus sunitinib

A randomised phase II study of paclitaxel plus bevacizumab versus paclitaxel plus bevacizumab plus sunitinib as first-line therapy in HER2-negative MBC reported a high rate of dose modifications and/or discontinuations of sunitinib due to toxicity. The authors concluded that the combination was not feasible and the study was closed [98].

A phase I study of bevacizumab in combination with sunitinib, sorafenib, erlotinib plus cetuximab, or trastuzumab plus lapatinib has shown that all combinations were tolerable and preliminary evidence of antitumour activity was demonstrated (the bevacizumab plus sunitinib combination was discontinued due to toxicity data from other studies) [99].

Discussion

Antiangiogenic drugs work essentially in combination with chemotherapy. One possible mechanism for this phenomenon is normalisation of the tumour vasculature, thereby increasing the concentration of drug in the tumour [100].

Despite the promising activity of antiangiogenic drugs in preclinical tumour models, targeting VEGF signaling appears to be insufficient to permanently inhibit tumour angiogenesis. The reasons for this are likely to be multiple and complex. Some critical issues that may be, at least in part, responsible for the failures have been suggested. Primarily, the choice of the appropriate molecular target is essential to the ultimate success of a given therapeutic intervention. Thus, patient selection strategies are of paramount importance. The challenge remains to identify markers predicting the effects of antiangiogenic treatment (see 'Biomarkers of angiogenesis and evaluation of response' below). In contrast to renal cell cancer, there is no documented constitutive activation of the VEGF pathway in breast cancer. However, it is possible that drugs targeting this pathway are very effective within a small, specific subgroup of patients.

Most current antiangiogenic therapies are based on inhibition of VEGF functions. However, tumours also produce multiple non-VEGF angiogenic factors, making angiogenesis a complex process composed of multiple signaling pathways, many of which are redundant. Thus, a switch on the angiogenic rescue program is possibly responsible for resistance to VEGF. Preclinical studies have identified four potential mechanisms of resistance: upregulation of basic fibroblast growth factor; overexpression of matrix metalloproteinase-9; increased level of stromal-cell-derived factor 1α; and hypoxia-inducible factor 1α-induced recruitment of bone-marrow-derived CD45+ myeloid cells [101,102].

Clonal evolution and tumour adaptation may also result in a tumour that is more tolerant to hypoxia and subsequently less dependent on neovascularization. Finally, substantial inherited variability within VEGF and its receptor (VEGFR2) has been demonstrated, making it plausible that a certain subgroup of patients with a specific genotype may derive sustained benefit from VEGF inhibition [103].

Issues regarding the future of antiangiogenic therapy

The E2100 trial represents the first successful proof-of-concept trial for antiangiogenic therapy in breast cancer [20]. However, in spite of improvements in RR and PFS, all randomised studies of antiangiogenic therapy in breast cancer have so far failed to demonstrate an impact on OS. This may be the reason why there is not yet general agreement on the use of bevacizumab in MBC.

Numerous challenges remain. Several tyrosine kinase inhibitors and other agents targeting the angiogenic pathway are in development. Their role has to be established. Furthermore, we do not know which combinations of antiangiogenic agents and standard agents (chemotherapy, hormonal, or biological) will prove most effective. The timing of angiogenesis therapy is also a challenge. This includes the optimal sequence of such therapies. Furthermore, questions about the duration of therapy and even dosages are unanswered. For example, therapy in patients with response or stable disease might be beneficial but difficult to justify without definite survival advantages.

There is increasing evidence that targeting of tumour epithelium and pericytes by combined VEGF and PDGFR blockade may facilitate the metastatic process. Thus, recent articles report how malignant tumours escape from antiangiogenic therapy by metastatic dissemination [104]. These findings might have important implications for the potential use of antiangiogenic therapy in the adjuvant setting. On the other hand, no clinical evidence for increases in the malignant potential of tumours was demonstrated in patients with MBC treated with bevacizumab and docetaxel in the phase III AVADO study [21,105].

Biomarkers of angiogenesis and evaluation of response

Many biomarkers of angiogenesis have been proposed as predictors for response to antiangiogenetic therapy, but none has yet been identified. Pretreatment plasma levels of VEGF have been evaluated in a range of studies. Generally, elevated levels are indicative of poor prognosis, but do not predict response to antiangiogenic therapy, including bevacizumab. Considerable research has been conducted to test the possibility that single-nucleotide polymorphisms in the germ-line involving angiogenesis-related genes influence the natural history of the disease and its response to treatment. Recently, an association between the VEGF genotype and median OS and severe hypertension has been demonstrated in MBC patients receiving bevacizumab and paclitaxel (E2100) [103]. Other approaches include measuring microvessel density or circulating endothelial cells. Recently, the topic has been reviewed by Jain and colleagues [106] and Murukesh and colleagues [107]. Molecular markers to monitor the effect of mTOR inhibitors have been identified in preclinical studies showing tumour growth inhibition to correlate with a decrease of pS6K1 and p4EBP1 [68]. However, findings from clinical studies are still too limited to base selection of patients and dose selection on these biomarkers.

Another challenge is defining reliable markers for clinical efficacy. Although objective change in tumour size remains an important assessment criterion for the treatment of solid tumours, tumour regression rate or RR might be more relevant as surrogate markers for cytotoxic chemotherapy than for targeted biological agents, which are primarily cytostatic. Thus, assessing only lesion size has demonstrated an inherent limitation when evaluating antiangiogenic drugs. In trials including these agents, disease control or time to progression may be more relevant than conventional response evaluation (PR and CR). Functional imaging - for example, dynamic contrast-enhanced magnetic resonance imaging/computer tomography, positron-emission tomography or contrast-enhanced ultrasound - has been included in several studies. The topics have been comprehensively reviewed by Sessa and colleagues [108] and Marcus and colleagues [109].

Cost
Monoclonal antibodies and tyrosine kinase inhibitors are relatively expensive in comparison with other cancer therapies. Economic evaluations are needed to clarify whether these expensive treatment options are cost effective. In the metastatic setting, where the goal is to improve quality of life and/or delay the time to disease progression, it is not clear whether health care systems can (or should) carry these expenses [110]. Under any circumstances, resource planning will be needed in order to offer these treatments to all suitable patients. Identifying subgroups of patients who will benefit from treatment and avoid administration to patients who are unlikely to respond significantly improve the cost/benefit ratio [111].

Conclusion
Development of drugs targeting angiogenesis is in progress and so far there is support for the use of the antibody bevacizumab in combination with taxanes (paclitaxel) as first-line therapy in HER2-negative MBC. Targeted therapy is an area of research and possibly represents an important step in the treatment of MBC. Results of ongoing trials and maturation of the published trials will hopefully lead to more precise knowledge, and thus more cost-effective use of recent developments. Identification of predictive biomarkers and improvement of our understanding of molecular mechanisms is crucial.

Abbreviations
ABC: advanced breast cancer; CBR: clinical benefit rate; CHF: congestive heart failure; CR: complete response; FDA: Food and Drug Administration; HER: human epidermal growth factor receptor; MBC: metastatic breast cancer; mTOR: mammalian target of rapamycin; ORR: overall response rate; OS: overall survival; pCR: pathological response; PDGFR: platelet-derived growth factor receptor; PFS: progression-free survival; PI3K: phosphatidylinositol 3-kinase; PlGF: placental growth factor; PR: partial response; RR: response rate; SD: stable disease; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor.

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Conception and design of manuscript: DLN, MA. Collection and assembly of data: DLN. Data interpretation: DLN, MA, CK, JLA. Final approval of manuscript: DLN, MA, CK, JLA.

Competing interests
The authors declare that they have no competing interests.

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