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Review

The potential of anti-vascular endothelial growth factor therapy in metastatic breast cancer: Clinical experience with anti-angiogenic agents, focusing on bevacizumab

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ABSTRACT

The importance of angiogenesis in tumour growth and development is well known. Overexpression of vascular endothelial growth factor (VEGF), the key mediator of angiogenesis, is associated with poor prognosis in breast cancer. As a result, several therapeutic agents that inhibit the actions of VEGF or its receptors are currently in development for use in metastatic breast cancer (MBC).

This review describes the function of VEGF in normal and tumour angiogenesis, explores the rationale behind the use of anti-VEGF therapy in MBC and details the therapeutic impact of such agents on tumour vasculature. Clinical data from trials of anti-VEGF agents in MBC are discussed, with a particular focus on the efficacy and safety of bevacizumab, the anti-VEGF agent at the most advanced stage of development in this tumour type. Future potential uses of bevacizumab in breast cancer are introduced.

1. Introduction

Treatment for metastatic breast cancer (MBC) has traditionally consisted of hormonal therapies and chemotherapies.[1] An improved understanding of cancer biology and the advent of new technologies have led to the development of agents directed against molecular targets involved in key biological processes in breast cancer development and progression. Angiogenesis, the growth of new blood vessels from existing vasculature, is known to be essential for the development and progression of cancer.[2,3] This has led to the development of many anti-angiogenic agents, which are reviewed here due to their potential and the widespread interest in their use to treat breast cancer.

2. Key role of vascular endothelial growth factor (VEGF) in tumour angiogenesis

Vascular endothelial growth factor (VEGF) is the key pro-angiogenic factor that promotes tumour angiogenesis and

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Table 1 – Members of the VEGF ligand family and their biological functions

Ligand	Receptor	Function
VEGF (VEGF-A)	VEGF receptors-1, -2, neuropilin-1	Angiogenesis, vascular maintenance
VEGF-B	VEGF receptor-1	Unknown
VEGF-C	VEGF receptors-2, -3	Lymphangiogenesis
VEGF-D	VEGF receptors-2, -3	Lymphangiogenesis
VEGF-E (viral factor)	VEGF receptor-2	Angiogenesis
Placental growth factor	VEGF receptor-1, neuropilin-1	Angiogenesis, inflammation

VEGF, vascular endothelial growth factor.

the survival of tumour endothelial cells (reviewed in Ref. [3]). VEGF-A, generally referred to as VEGF, is a member of a family of related molecules, six of which have been identified to date (Table 1).[4,5] Due to alternative splicing of VEGF messenger RNA (mRNA), the VEGF protein occurs as four main isoforms.[6,7] The physiological significance of the different isoforms remains uncertain, but the 165-amino acid molecule, $VEGF_{165}$, is the most abundant.[6] VEGF gene expression is regulated by a number of stimuli, including hypoxia, growth factors, tumour suppressor genes, oncogenes, nitric oxide and human epidermal growth factor receptor-2 (HER-2).[8–13] Physiological effects of VEGF are mainly mediated through binding to an endothelial cell surface receptor, VEGF receptor-2, which also serves as a receptor for other VEGF family members.[14] VEGF binds to VEGF receptor-1 with higher affinity than to VEGF receptor-2,[15,16] but the role of this receptor in angiogenesis remains unclear.

In addition to its role in normal physiological processes (such as embryogenesis and early postnatal growth), VEGF is the key mediator of tumour angiogenesis and thus of tumour development and metastasis. Tumours are unable to grow beyond a diameter of 2 mm in the absence of angiogenesis, due to the inability of oxygen and nutrients to diffuse beyond this distance.[17] Preclinical studies using antibodies against VEGF have demonstrated its importance in tumour angiogenesis. When VEGF is inhibited, both neovascularisation and tumour growth are suppressed in animal models.[18,19] VEGF has other effects on tumours, including inhibition of tumour cell apoptosis,[20] stimulation of metastasis,[21] suppression of the anti-tumour immune response[22] and increasing the permeability of tumour blood vessels, causing a rise in interstitial pressure, which reduces the delivery of chemotherapeutic agents to the tumour.[23]

3. VEGF as a therapeutic target

VEGF has a limited role in normal adult physiology, with functions restricted to wound healing and the female reproductive cycle.[24] Tumour-derived VEGF can therefore be inhibited with minimal effects in adults, and represents a novel approach to anticancer therapy. Vascular regression has been demonstrated to occur rapidly after initiation of anti-VEGF therapy in both preclinical models and cancer patients.[25,26] The morphology and the function of surviving tumour blood vessels are transiently 'normalised' so that they more closely resemble the normal vasculature.[27] These changes reduce intratumoural pressure, facilitating the delivery of other anticancer therapies to the tumour.[23,26–28] Furthermore, neovascularisation and vascular regrowth are both inhibited. Revascularisation occurs rapidly following the withdrawal of anti-VEGF therapy.[29–31]

Interestingly, increased VEGF expression, at both the mRNA and protein levels, has been observed in patients with breast cancer.[32] High VEGF expression is associated with poor clinical outcomes, including reduced survival.[33–38] Studies also suggest a correlation between high VEGF levels and lack of response to chemotherapy or radiotherapy.[39–42] These data support the use of anti-VEGF therapy in breast cancer. Table 2 details the anti-VEGF agents currently in development in this therapeutic area.

4. Bevacizumab in MBC

4.1. *Preclinical data*

Studies of anti-VEGF therapy, initially using A4.6.1, the murine parent antibody of bevacizumab, and later using bevacizumab, have confirmed that inhibiting tumour angiogenesis by targeting VEGF has anti-tumour effects. In breast xenograft models in mice, A4.6.1 significantly inhibited angiogenic activity and tumour growth when given alone, or in combination with doxorubicin, with trastuzumab or with trastuzumab plus capecitabine.[18,43–45]

4.2. *Clinical data*

A phase I/II study of bevacizumab monotherapy (3 mg/kg, 10 mg/kg and 20 mg/kg every 2 weeks) in patients with previously treated MBC reported confirmed responses in 5/75 (6.7%) patients and a median duration of confirmed response of 5.5 months (range 2.3–13.7 months).[46] The highest response rate was observed using 10 mg/kg bevacizumab every 2 weeks. Given the high incidence of headache associated with nausea and vomiting at the 20 mg/kg dose, 10 mg/kg bevacizumab every 2 weeks (or a dose and schedule with similar intensity) was chosen for future trials in breast cancer.

A phase III trial of bevacizumab (15 mg/kg every 3 weeks) plus capecitabine (2500 mg/m^2 daily) in patients with heavily pretreated MBC reported a significantly increased overall response rate compared with capecitabine alone, as determined by an independent review facility (19.8% (95% confidence interval (CI): 14.7–25.0) versus 9.1% (95% CI: 5.4–12.9), respectively; $P = 0.001$).[47] However, there was no difference between the two treatment arms in terms of progression-free survival (PFS) (the primary endpoint of the study; median 4.86 months in the capecitabine plus bevacizumab arm versus 4.17 months in the capecitabine alone arm; hazard ratio (HR) = 0.98 (95% CI: 0.77–1.25)) or overall survival (OS) (median

Table 2 – Anti-VEGF therapeutic agents currently in development for breast cancer

Drug	Mechanism(s) of action	Molecular target(s)	Stage of clinical development
Bevacizumab	Anti-VEGF antibody	VEGF ligand	Approved
Sorafenib (BAY 43-9006)	Tyrosine kinase inhibitor	Raf-1, VEGF receptors-2 and -3, PDGFR-β, Flt-3, c-Kit	Phase II
Sunitinib (SU11248)	Tyrosine kinase inhibitor	VEGF receptors-1, -2 and -3, Flt-3, PDGFR-α, PDGFR-β, c-Kit	Phase II/III
Vatalanib (PTK/ZK)	Tyrosine kinase inhibitor	VEGF receptors-1, -2 and -3, PDGFR-β, c-Kit, c-Fms	Phase II
Vandetanib (ZD6474)	Tyrosine kinase inhibitor	VEGF receptors-2 and -3, EGFR	Phase II
Motesanib (AMG-706)	Tyrosine kinase inhibitor	VEGF receptors-1, -2 and -3, PDGFR, c-Kit	Phase II
Pazopanib	Tyrosine kinase inhibitor	VEGF receptors-1 and -2, PDGFR-β, and c-Kit	Phase II
Axitinib	Tyrosine kinase inhibitor	VEGF receptors-1, -2 and -3, PDGFR, c-kit	Phase II

VEGF, vascular endothelial growth factor; PDGFR, platelet-derived growth factor receptor.

15.1 months versus 14.5 months, respectively). This lack of benefit raises several questions about the mechanisms of anti-angiogenic therapy. One explanation is that as tumours progress, more angiogenic factors are expressed, thus tumours may escape anti-VEGF treatment by utilising alternative pro-angiogenic pathways.[27]

A further phase III trial evaluated weekly paclitaxel with or without bevacizumab (10 mg/kg every 2 weeks) in patients with previously untreated locally recurrent or MBC.[48] The trial was stopped early, at the first scheduled interim analysis, on the recommendation of the independent Data Monitoring Committee, which concluded that the trial had already met its primary efficacy endpoint. Since these interim data were released, a number of data sets have been presented that differ according to data cut-off dates and study population definitions. Data used to support the regulatory submission to the Food and Drug Administration (FDA) were based on the same cut-off date as the interim analysis and these are presented below. Median PFS was approximately doubled, from 5.8 months for patients receiving paclitaxel alone to 11.4 months for patients receiving paclitaxel plus bevacizumab ($P < 0.0001$).[49] In addition, the overall response rate was more than doubled, increasing from 23.4% for paclitaxel alone to 48.0% for paclitaxel plus bevacizumab ($P < 0.0001$; Table 3). At the time of the interim analysis, there was a trend towards increased OS for patients receiving bevacizumab in combination with paclitaxel (26.5 months versus 24.8 months), although the increase was not statistically significant compared with patients receiving paclitaxel alone (HR = 0.87; 95% CI: 0.72–1.05).[49] However, at 1 year, survival in the combination arm was significantly better than in the paclitaxel alone arm (81.4% versus 74.0%; $P = 0.017$).[50] Of note, the censoring rate after 12 months follow-up is >10%, which precludes any valid conclusion on OS. In addition, the impact of subsequent treatment after disease progression on OS remains unclear, particularly for patients in the paclitaxel alone arm. The magnitude of the observed PFS benefit in this trial is one of the largest seen when compared with other randomised trials that have led to the registration of chemotherapy regimens for first-line MBC treatment. Fig. 1 shows improvements in median PFS/TTP (time to disease progression) observed in a number of European registration trials in first-line MBC. Based on these data, the European Medicines Agency (EMEA) and FDA have approved bevacizumab in combination with paclitaxel for the first-line treatment of patients with MBC.

In addition to the phase III data indicating that bevacizumab plus paclitaxel is an effective first-line therapy, safety and efficacy data have been reported from a number of phase II trials of bevacizumab in combination with agents including docetaxel,[51,52] vinorelbine,[53] metronomic chemotherapy[54] and letrozole.[55] A number of large ongoing trials will further evaluate the role and activity of bevacizumab in MBC.

Docetaxel is widely used in the treatment of MBC and has already demonstrated efficacy in combination with bevacizumab in phase II studies.[51,52] A phase III trial (AVADO), which completed recruitment in March 2007, randomised 736 patients to a 3-weekly regimen consisting of docetaxel (100 mg/m^2) in combination with either placebo or bevacizumab at a dose of 7.5 mg/kg every 3 weeks or 15 mg/kg every 3 weeks. This study will evaluate the efficacy of bev-

Table 3 – Summary of efficacy results from the phase III trial of bevacizumab plus paclitaxel in locally recurrent or MBC (E2100)[49,50]

	Paclitaxel	Paclitaxel plus bevacizumab	*P* value
ITT population (*N*)	354	368	
Median PFS (months)	5.8	11.4	<0.0001
Median OS (months)	24.8	26.5	0.14
Patients with measurable disease at baseline (*N*)	273	252	
Overall response rate (%)	23.4	48.0	<0.0001
Complete response (%)	1.8	7.9	
Partial response (%)	21.6	40.1	

MBC, metastatic breast cancer; PFS, progression-free survival and OS, overall survival.

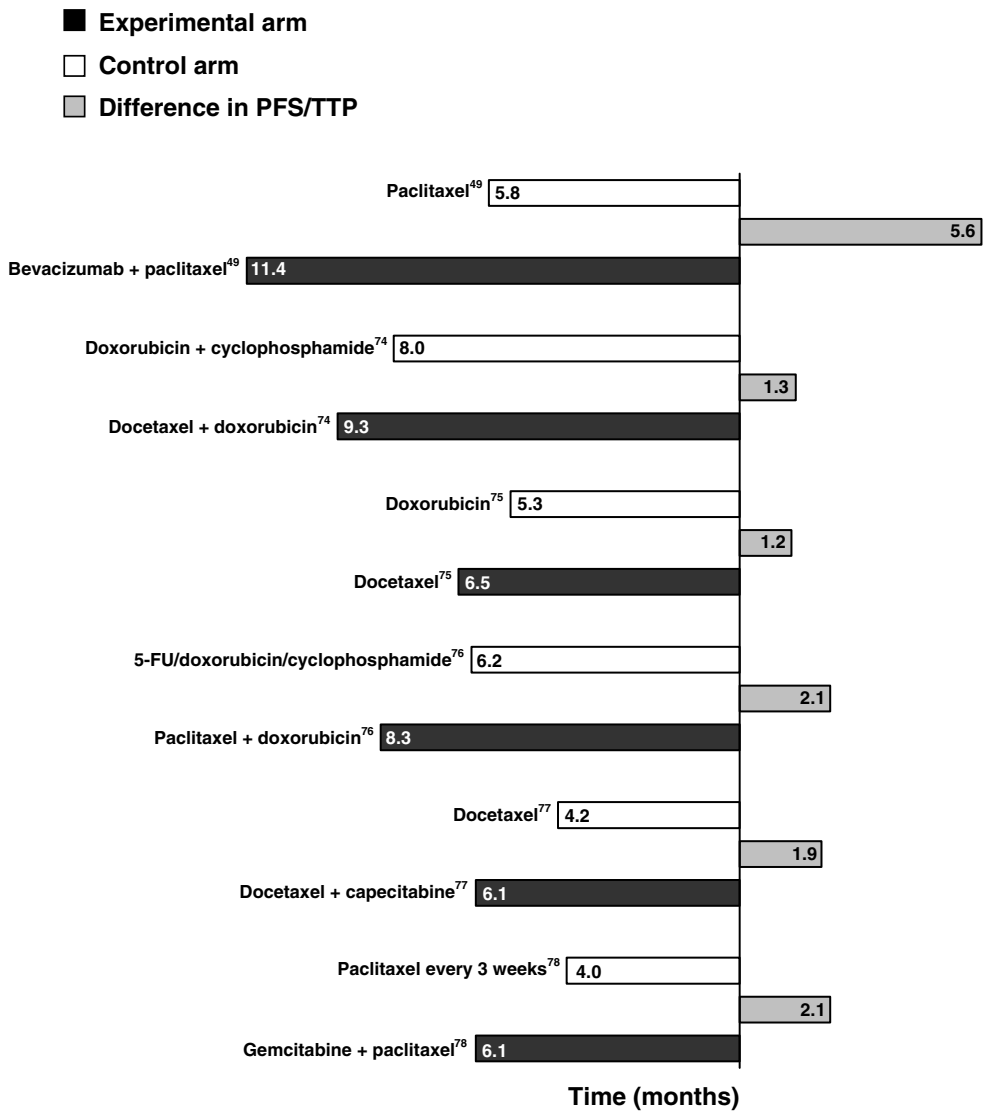

Fig. 1 – Improvements in median PFS/TTP observed in pivotal European registration trials for first-line treatment of MBC.[50,73–77]

acizumab in combination with another taxane and will assess the potential of a lower-dose bevacizumab regimen in MBC.

Another ongoing phase III trial, RIBBON-1, is evaluating the efficacy and safety of first-line chemotherapy (anthracycline-based, taxane or capecitabine) with or without bevacizumab in up to 1200 patients who have not received prior chemotherapy for MBC. The ongoing phase III RIBBON-2 trial is designed to evaluate the efficacy and safety of bevacizumab in combination with standard non-anthracycline-based chemotherapy regimens in patients with previously treated MBC.

A large ongoing phase IV trial, MO19391, is assessing the safety profile of bevacizumab when combined with taxane-based chemotherapy as first-line treatment for patients with locally recurrent or MBC.

Based on preclinical evidence suggesting that the VEGF pathway is interlinked with both the epidermal growth factor receptor (EGFR) and HER-2 pathways,[10,44] a phase I/II trial of bevacizumab in combination with trastuzumab in MBC has produced promising preliminary data.[56,57] Initially, patients were recruited to an open-label, phase I dose–escalation trial; the bevacizumab dose selected for the phase II stage was 10 mg/kg every 2 weeks, which is the regimen recommended for the treatment of breast cancer. Standard-dose trastuzumab was used. Preliminary data have been reported for 37 patients.[57] The regimen appears to be well tolerated and few grade 3/4 events (grade 3 hypertension, N = 7) have been observed. Preliminary efficacy data reveal 19 partial responses, of which 13 are confirmed, and one complete response (overall response rate, 54.1% (95% CI: 44.3–63.9)).[57] A further 11 patients (29.7%) have stable disease. These data suggest that the combination of two antibodies in the treatment of patients with MBC should be further evaluated. Thus, a phase III trial (AVEREL) has been started to investigate the safety and efficacy of adding bevacizumab to first-line trastuzumab and docetaxel in patients (N = 410) with HER-2-positive locally recurrent or MBC.

Attempts to identify markers that predict benefit from bevacizumab, including tumour/serum VEGF levels, expression of k-ras, b-raf and p53, have been unsuccessful so far.[58,59] It has been suggested that measurement of levels of

circulating endothelial cells (CEC) may have utility as a predictive marker; however, the initial relationship between CEC increase and PFS reported in one trial lost its statistical significance upon longer follow-up.[60,61] However, to date there are no data from large randomised trials to clarify this and the clinical utility of CEC measurement is unclear.

5. Safety of bevacizumab in breast cancer

Clinical trials have shown that the basic toxicity profile of bevacizumab is similar in all tumour types investigated. Adverse events related or possibly related to bevacizumab are hypertension, proteinuria, haemorrhage, arterial and venous thromboembolic events, wound-healing complications, gastrointestinal perforations and congestive heart failure (CHF).[62] In breast cancer, most bleeding events have consisted of mild mucocutaneous haemorrhage, usually epistaxis, which was controllable without medical intervention (grade 1/2 bleeding is reported in 15.7–25.3% of patients (Table 4)).[46,47]

In a phase III trial, hypertension was observed in 16.0% of bevacizumab-treated patients with MBC compared with 1.4% in the comparator arm.[50] Data suggest that the incidence of hypertension is likely to be dose-dependent. Hypertension can be managed using oral anti-hypertensive agents such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers.[62] Pre-existing hypertension should be appropriately controlled before starting bevacizumab treatment, and blood pressure should be monitored regularly during treatment. There have been rare reports of reversible posterior leukoencephalopathy syndrome (RPLS) in patients treated with bevacizumab, possibly linked to hypertension.[49] Bevacizumab should be discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

The majority of proteinuria that has occurred with bevacizumab therapy was grade 1 and was not associated with renal dysfunction. Dipstick urinalysis is recommended prior to, and during, therapy. Bevacizumab should be discontinued in patients who develop nephrotic syndrome.

In the E2100 trial, the incidence of grade 3/4 venous thromboembolic events was similar in patients who received bevacizumab and those who did not (3.0% versus 4.3%, respectively (Table 4)).[50] Gastrointestinal perforations have been reported in four patients receiving bevacizumab for breast cancer.[50,63] Wound-healing complications have been observed in trials of neoadjuvant bevacizumab in breast cancer.[62,64]

CHF and/or cardiomyopathy have been reported in trials of bevacizumab in breast cancer.[46–48,65] In the phase III trial of capecitabine with or without bevacizumab, the incidence of such toxicities was increased in the bevacizumab arm compared with control (3.5% versus 1% (Table 4)).[47] A slight increase in the incidence of grade 3/4 left ventricular dysfunction was noted in patients in the bevacizumab arm of the phase III E2100 trial of paclitaxel with or without bevacizumab (2.2% versus 0.3% (Table 4)); all patients who developed grade 3/4 left ventricular dysfunction had received prior anthracyclines.[50] In the phase II study of trastuzumab plus bevacizumab, 13 patients experienced cardiac adverse events, of which only one was grade 3/4 in severity.[57] A phase II trial that investigated the combination of bevacizumab with docetaxel and doxorubicin in inflammatory breast cancer reported two cases of left ventricular ejection fraction decline in 21 patients, both grade 2.[64] In clinical trials, most cases of CHF and/or cardiomyopathy have been successfully managed with medication and some affected patients have been able to continue therapy with bevacizumab.[46,47,64]

6. Optimal dose and schedule

The dose and schedule of bevacizumab recommended for use in MBC was 10 mg/kg every 2 weeks.[46] Subsequent trials have used either this dose regimen or 15 mg/kg every 3 weeks, which has equivalent dose intensity. The approved

Table 4 – Grade ⩾3 adverse events observed in phase III trials of bevacizumab in MBC[47,50]

Adverse event	Incidence (%) in patients with relapsed/refractory MBC		Incidence (%) in patients with previously untreated MBC[a]	
	Capecitabine	Capecitabine plus bevacizumab	Paclitaxel	Paclitaxel plus bevacizumab
Hypertension	0.5[b]	17.9[b]	1.4[b]	16.0
Proteinuria	0	0.9[b]	0	3.0
Thrombosis	3.7	5.6	NR	NR
Arterial thromboembolic event[c]	NR	NR	0	3.6
Venous thromboembolic event	NR	NR	4.3	3.0
Hand-foot syndrome	24.2[b]	27.5[b]	NR	NR
Bleeding	0.5[b]	0.4[b]	0.3	2.2
CHF/cardiomyopathy	1	3	NR	NR
Nausea	1.9[b]	2.6[b]	NR	NR
Neuropathy	NR	NR	18.1	25.3
Fatigue	NR	NR	5.2	10.7
Neutropenia	NR	NR	8.0	17.4
Decreased LVEF[c]	NR	NR	0.3	2.2

MBC, metastatic breast cancer; NR, not reported and LVEF, left ventricular ejection fraction; CHF, congestive heart failure.
a Includes NCI AdEERS mandatory collection in the bevacizumab plus paclitaxel arm only.
b No grade 4.
c Events were double counted where applicable.

dose of bevacizumab for use in metastatic colorectal cancer (5 mg/kg every 2 weeks) is equivalent to half the dose intensity used in breast cancer. The efficacy of the lower-dose regimen in breast cancer is currently being investigated in the AVADO trial. In this trial, if both bevacizumab doses (7.5 mg/kg every 3 weeks and 15 mg/kg every 3 weeks) are found to be superior to the control regimen, the design allows for exploratory comparisons of the two bevacizumab-containing arms with respect to efficacy and safety. Results are expected in 2008.

7. Future directions

Activity in preclinical models and evidence that tumour dependence on VEGF is highest early in disease suggest that anti-VEGF agents may provide their greatest benefit in patients with early disease, when tumours are small and/or there is minimal residual disease post-operatively.[65] Trials to investigate the effectiveness and safety of bevacizumab as adjuvant and neoadjuvant therapy for breast cancer are ongoing or planned.

The pilot study E2104, designed to investigate the addition of bevacizumab to an adjuvant chemotherapy regimen of doxorubicin plus cyclophosphamide, followed by paclitaxel in patients with early breast cancer, has finished recruitment. A large phase III trial (E5103) has been designed to follow on from E2104, and will recruit 4950 patients with early breast cancer. Another large phase III trial (BEATRICE) will assess the benefit of adding bevacizumab to standard adjuvant chemotherapy regimens. Approximately, 2500 patients with triple-negative (HER-2-negative, oestrogen receptor-negative and progesterone receptor-negative) early breast cancer will be randomised to receive chemotherapy (anthracycline- or taxane-based regimens or an anthracycline/taxane combination regimen) or chemotherapy plus bevacizumab for a total duration of 12 months. The addition of bevacizumab to adjuvant chemotherapy and trastuzumab will be studied in a further phase III trial (BETH) in patients with HER-2-positive breast cancer.

In the neoadjuvant setting, a recently published phase II study examined the combination of bevacizumab with doxorubicin and docetaxel in patients with inflammatory or locally advanced breast cancer. Results were encouraging, with effects on tumour vasculature seen after initial treatment with bevacizumab alone.[64] Recent data from a phase II trial of neoadjuvant docetaxel with or without bevacizumab indicate that bevacizumab is well tolerated and potentially effective in this setting.[63]

NSABP B-40 is an ongoing phase III trial evaluating the addition of bevacizumab to either neoadjuvant docetaxel, docetaxel plus capecitabine or neoadjuvant docetaxel plus gemcitabine (for four 3-weekly cycles) followed by doxorubicin plus cyclophosphamide (for four 3-weekly cycles) in patients with operable stage II/IIIa breast cancer. After completing chemotherapy, patients will undergo surgery, and those who previously received bevacizumab will get 10 cycles of post-surgical bevacizumab monotherapy. An additional neoadjuvant phase II trial, TORI B-02, is investigating docetaxel, doxorubicin and cyclophosphamide with or without bevacizumab, with patients in the bevacizumab arm receiving bevacizumab as maintenance therapy following surgery.

8. Clinical data for other anti-VEGF agents in MBC

8.1. *Sunitinib malate (SU11248)*

Sunitinib is a small molecule tyrosine kinase inhibitor (TKI) with activity against VEGF receptors-1, -2 and -3 and other signalling pathway targets including platelet-derived growth factor receptor (PDGFR), c-kit and flt-3. Sunitinib has shown preclinical activity in breast cancer models[66,67] and a phase II trial has reported preliminary data in patients ($N = 64$) with previously treated MBC. Partial responses were seen in 14% of patients and no treatment-related serious adverse events were observed.[68] Further development of sunitinib is ongoing in combination with trastuzumab and in randomised trials versus chemotherapy in patients with triple-negative MBC.

8.2. *Sorafenib (BAY 43-9006)*

Sorafenib is a small molecule TKI with activity against Raf1 and additional activity against VEGF receptors-2 and -3 and other signalling pathway targets. A phase II trial of sorafenib in 54 patients with MBC produced a partial response in one (2%) patient.[69] A second, similar phase II trial also reported only one (5%) partial response.[70] It was concluded that sorafenib has little activity as a single agent in patients with breast cancer; nevertheless, a randomised trial versus chemotherapy as second-line treatment for MBC is planned.

8.3. *Vandetanib (ZD6474)*

Vandetanib is a small molecule TKI of VEGF receptors-2 and -3 and EGFR. No objective responses were reported in a phase II trial of vandetanib, but one patient had stable disease for 24 weeks.[71]

8.4. *Motesanib (AMG-706)*

Motesanib is a small molecule TKI thought to have action against all three VEGF receptors, PDGFR and c-kit. A phase II head-to-head trial comparing motesanib with bevacizumab in the first-line treatment of patients with HER-2-negative breast cancer is ongoing.

8.5. *Pazopanib*

Pazopanib inhibits VEGF receptors-1 and -2, PDGFR-β and c-kit. It is being assessed in a phase II clinical trial in combination with lapatinib in first-line therapy for patients with trastuzumab-naïve HER-2-positive MBC.

8.6. *Axitinib (AG-013736)*

Axitinib is a TKI with activity against VEGF receptors-1, -2 and -3, PDGFR and c-kit. This drug in combination with docetaxel was compared with docetaxel and placebo in a randomised phase II trial. The addition of axitinib significantly increased

the overall response rate (40% versus 23%, $P = 0.038$) and prolonged time to progression (8.2 versus 7 months, $P = 0.052$).[72] Further clinical trials are planned.

9. Conclusions

Due to its key role in tumour angiogenesis, VEGF is an appropriate therapeutic target in breast cancer and appears to be the only pro-angiogenic factor expressed throughout the entire life cycle of a breast tumour. Recently, the anti-VEGF monoclonal antibody, bevacizumab, was approved in the EU for use in combination with paclitaxel for the first-line treatment of patients with MBC, based on the results of the large, randomised phase III E2100 trial. This showed that bevacizumab significantly increased PFS when administered with weekly paclitaxel until disease progression. Although no statistically significant improvement in OS was observed, due in part to the relatively short follow-up period, the clinically relevant PFS difference achieved with paclitaxel plus bevacizumab has already improved patients' therapeutic options. The European registration of bevacizumab for breast cancer brings new hope for patients with MBC. Other phase III clinical trials of bevacizumab are ongoing and will further evaluate bevacizumab in combination with different chemotherapy regimens and targeted therapy such as trastuzumab, in different disease settings in patients with breast cancer.

Conflict of interest statement

None declared.

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