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Future use of bevacizumab and other anti-angiogenic agents in breast cancer

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ABSTRACT

Bevacizumab, the first commercially available angiogenesis inhibitor for the treatment of breast cancer, offers significant clinical benefits in the management of this disease. When combined with paclitaxel as first-line treatment of metastatic breast cancer, it significantly increases both median progression-free survival and 1-year survival when compared with treatment with paclitaxel alone. Furthermore, the addition of bevacizumab to capecitabine in patients with more refractory advanced breast cancer was also found to be clinically active, significantly increasing response rate but not extending progression-free survival. Both the mechanism of action of bevacizumab and its clinical activity in advanced disease suggest that it should be active in adjuvant and neoadjuvant therapy. Inhibition of vascular endothelial growth factor should inhibit the growth of existing micrometastases following surgery (adjuvant therapy), and could enhance patient eligibility for breast conservation by decreasing tumour size (neoadjuvant therapy). A clinical trial programme is underway to evaluate the role of bevacizumab in combination with other anticancer agents in the first-line metastatic, adjuvant and neoadjuvant treatment of breast cancer.

1. Introduction

Angiogenesis is the process of formation of new blood vessels from existing vasculature and is essential for tumour growth and metastasis. Without sufficient blood supply providing oxygen and nutrients, tumours cannot develop beyond about 2 mm in diameter.[1] To grow further, the tumour must develop a blood supply network through angiogenesis. Formation of new blood vessels is a highly regulated process, and one of the key mediators is vascular endothelial growth factor (VEGF).[2] VEGF has a very limited physiological role in adults so provides an ideal target for therapeutic agents designed to inhibit tumour development.[3]

Bevacizumab (Avastin®) acts to prevent angiogenesis by inhibiting VEGF signalling.[4] Additionally, bevacizumab potentially increases the effectiveness of other anti-cancer therapies through the normalisation of tumour vasculature, reduction of intratumoral pressure and improved tumour oxygenation.[5–7] Data from the E2100 phase III study, described in detail elsewhere in this supplement, demonstrate that bevacizumab provides clinical benefits for patients with metastatic breast cancer.[8] When added to paclitaxel treatment in first-line therapy for metastatic breast cancer, bevacizumab doubled median progression-free survival and also significantly increased 1-year survival. Furthermore,

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bevacizumab had an acceptable risk/benefit profile and adverse events were generally manageable with careful monitoring.

While to date bevacizumab has primarily been used in the advanced disease setting, the mechanism of action and clinical activity of bevacizumab suggest that it may have a role in the treatment of all stages of breast cancer. Inhibition of VEGF signalling in the adjuvant setting, where angiogenesis has a major role, could play an important part in preventing relapse. In the neoadjuvant setting, combined with other anti-tumour strategies, inhibition of VEGF by bevacizumab might enhance cytotoxic activity and thus increase patient eligibility for breast conservation. Bevacizumab doublets with chemotherapy agents such as taxanes, doxorubicin and fluoropyrimidines are active in the preclinical setting [9–12] and are currently being studied clinically; these studies will add to the information already available regarding the safety and efficacy profile of the strategy of combining bevacizumab with cytotoxic agents. [13–16]

Cancer therapies with demonstrated efficacy in the metastatic setting are frequently more effective in early disease; these include hormonal treatments, cytotoxic chemotherapies and newer, targeted, agents such as trastuzumab. One reason for this is that tumours at earlier stages of development have fewer acquired genetic defects in cell signalling pathways, so in contrast to advanced disease, there may be fewer dysregulated normal processes. This would provide the more advanced tumour with a greater number of alternative pathways that can evade the actions of therapeutic agents. Indirect support for this concept can be seen if the results of the E2100 trial, which tested the benefit of adding bevacizumab to paclitaxel in previously untreated metastatic disease, are contrasted with those of the sister trial which tested the benefit of adding this agent to capecitabine in patients who had already received at least one line of chemotherapy for advanced breast cancer. [14] This phase III trial randomised 462 patients with anthracycline- and taxane-refractory disease to receive capecitabine with or without bevacizumab. Combination therapy with bevacizumab significantly increased response rates whether designated by an independent review facility or local investigators; however, progression-free survival, the primary endpoint, was similar in both groups. [14] In the adjuvant setting, VEGF inhibition could therefore have even greater benefit, potentially leading to a cure for more patients by preventing metastatic growth through the inhibition of neovascularisation of micrometastases and the regression of the blood supply of existing larger metastases. Normalisation of any remaining tumour vasculature by anti-VEGF therapy has the potential to improve the delivery of concomitant adjuvant therapies.

A comprehensive clinical trial programme is underway to evaluate the safety and efficacy of bevacizumab in combination with chemotherapy and other anticancer agents in the treatment of first-line metastatic (Table 1), adjuvant (Table 2) and neoadjuvant breast cancer.

2. First-line metastatic breast cancer treatments

2.1. Human epidermal growth factor receptor-2-negative disease

As mentioned previously, bevacizumab doubled progression-free survival when combined with paclitaxel in the first line therapy of advanced breast cancer. [8] However, many clinicians use the alternative taxane, docetaxel, in part because the superior efficacy of this agent over paclitaxel was demonstrated in a phase III study in which both were given on a 3-weekly basis. [17] Several phase II trials have indicated the feasibility of the combination of bevacizumab and docetaxel in both early and advanced breast cancer. [15,18] Therefore it is a logical question as to whether bevacizumab would give similar benefits when combined with docetaxel. This has been tested in the AVADO study, a randomised, double-blind, placebo-controlled, multicentre phase III trial investigating the safety and efficacy of bevacizumab in combination with docetaxel for first-line metastatic breast cancer (Figure 1). Recruitment for AVADO completed in March 2007. A total of 736 patients were enrolled to receive up to nine cycles of docetaxel (100 mg/m^2) plus bevacizumab (7.5 mg/kg or 15 mg/kg) or placebo every 3 weeks. The primary endpoint is progression-free survival. The AVADO study is powered to evaluate the difference in progression-free survival between each of the bevacizumab arms and the placebo arm. An exploratory analysis will compare progression-free survival in the two bevacizumab arms. Results from AVADO, expected in early 2008, will add to current data on the use of bevacizumab at a lower dose than that currently used in breast cancer. However, it is likely that optimal dosage will be affected by inter-patient pharmacokinetic variability. It has been recognised that the 'maximum tolerated dose (MTD)' approach traditionally used with cytotoxic therapy may not be suitable for use with many biologic agents, including anti-angiogenic agents, where the most clinically effective dose – the optimal biological dose (OBD) – could be lower than the MTD. However, the OBD of an anti-angiogenic agent may prove difficult to establish without the prior determination of suitable surrogate markers for efficacy. [19]

RIBBON-1 is an ongoing randomised, placebo-controlled, multicentre, phase III trial examining the efficacy and safety of first-line bevacizumab combined with three different classes of chemotherapy agents for the treatment of metastatic breast cancer (Figure 2). This

Table 1 – First-line studies in locally recurrent or metastatic disease involving bevacizumab

Study	Phase	*n*	Eligibility	Study design	Primary endpoint
MO19391	IIIb	~2300	HER2– LR or mBC (HER2+ if prior trastuzumab)	Taxane-based chemotherapy plus bevacizumab (10 mg/kg q2w or 15 mg/kg q3w)	Safety
RIBBON-1	III	1239	HER2– LR or mBC	Docetaxel (75 or 100 mg/m^2), or paclitaxel protein-bound particles (260 mg/m^2) or anthracycline-based combination, or capecitabine (1000 mg/m^2) with or without bevacizumab (15 mg/kg) q3w	PFS
AVADO	III	736	HER2– LR or mBC	Docetaxel (100 mg/m^2) plus placebo or bevacizumab (7.5 or 15 mg/kg) q3w	PFS
E1105	III	490	HER2+ LR or mBC	Weekly paclitaxel with or without carboplatin plus trastuzumab with or without bevacizumab	PFS
C40503	III	360	ER+/PR+ mBC	Aromatase inhibitors or tamoxifen, administered orally each day with or without bevacizumab (15 mg/kg) q3w	PFS
AVEREL	III	410	HER2+ LR or mBC	Docetaxel plus trastuzumab with or without bevacizumab (15 mg/kg) q3w	PFS
CA023	II	225	mBC	Bevacizumab plus either weekly, 2-weekly or 3-weekly nab-paclitaxel	TBC
B9E-US-S377	II	180	mBC	Paclitaxel plus bevacizumab versus gemcitabine, paclitaxel and bevacizumab	TTP
TORI-B-01	II	150	HER2– mBC	Bevacizumab plus docetaxel versus docetaxel	TTP
AVF4057g	II	145	LR or mBC	Bevacizumab plus paclitaxel and sunitinib	PFS
CA163-115	II	120	LR or mBC	Two schedules of ixabepilone plus bevacizumab and paclitaxel plus bevacizumab	ORR
DOCET_L_00712	II	100	mBC	HER2– patients: bevacizumab plus docetaxel. HER2+ patients: bevacizumab, trastuzumab and docetaxel	PFS
AVF3544s	II	80	ER+/PR+ postmenopausal mBC	Bevacizumab plus either anastrozole or fulvestrant	TTP
CA043	II	50	mBC	Bevacizumab plus nab-paclitaxel	Safety, tolerability, PFS
NCI-7703	I/II	45	mBC	Bevacizumab plus paclitaxel and vorinostat	MTD, ORR, OS, recommended phase II dose
OSU-06027	II	39	mBC	Bevacizumab plus trastuzumab and docetaxel	PFS, safety
AVF3678s	II	35	LR or mBC	Bevacizumab plus nab-paclitaxel	PFS

HER2– = human epidermal growth factor receptor 2 negative; LR = locally recurrent; mBC = metastatic breast cancer; HER2+ = human epidermal growth factor receptor 2 positive; q2w = every 2 weeks; q3w = every 3 weeks; PFS = progression-free survival; TBC = to be confirmed; TTP = time to disease progression; ORR = objective response rate; ER+ = oestrogen receptor positive; PR+ = progesterone receptor positive; MTD = maximum tolerated dose; ORR = overall response rate; OS = overall survival.

trial is being carried out to definitively establish the clinical benefits and toxicity of adding bevacizumab to standard chemotherapy in first-line treatment. Patients receive a regimen of anthracycline-based chemotherapy, single-agent taxane (docetaxel or paclitaxel protein-bound particles) or single-agent capecitabine every 3 weeks as deemed appropriate by the investigator. Recruitment was completed in August 2007, by which time a total of 1239 patients had been enrolled. Patients were randomised at a 2:1 ratio to receive either bevacizumab (15 mg/kg) or placebo every 3 weeks (320 to the anthracycline cohort, 306 to the taxane cohort, and 613 to the capecitabine cohort). The primary trial endpoint is progression-free survival of patients receiving bevacizumab plus chemotherapy compared with chemotherapy alone. Upon disease progression,

Table 2 – Adjuvant studies involving bevacizumab

Study	Phase	*n*	Eligibility	Therapy regimen	Primary endpoint
E5103	III	4950	Resected chemotherapy-, hormone therapy- and radiation-naive LN+ stage II or III HER2– BC	Doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2) with or without bevacizumab (15 mg/kg) q3w, followed by paclitaxel (80 mg/m^2) plus bevacizumab (15 mg/kg) q3w. Maintenance therapy none or bevacizumab (15 mg/kg) q3w	Disease-free survival
BEATRICE	III	2530	Resected triple-negative T1a–T3 BC	Choice of a number of anthracycline- and/or taxane-based chemotherapy regimens with or without 12 months of bevacizumab 5 mg/kg weekly equivalent	Invasive disease-free survival
E2104	II	204	Resected chemotherapy-, hormone therapy- and radiation-naive LN+ stage II or III HER2– BC	Doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2) with or without bevacizumab (10 mg/kg) q2w. Followed by paclitaxel (175 mg/m^2) plus bevacizumab (10 mg/kg) q2w. Maintenance therapy with bevacizumab (10 mg/kg) q2w	Safety (incidence of cardiac dysfunction)
CA045	II	200	BC	Dose-dense doxorubicin plus cyclophosphamide followed by either nab-paclitaxel or paclitaxel with bevacizumab	Incidence of treatment-emergent toxicities
DOCET_L_00714	II	150	LN+, high risk LN– BC	Bevacizumab +/- trastuzumab with three docetaxel-based chemotherapy regimens	Cardiac safety
05-055	II	100	BC	Bevacizumab versus bevacizumab plus cyclophosphamide and methotrexate	Determine feasibility of bevacizumab, determine side effects alone versus in metronomic combination
CDR0000529855	II	75	Early stage BC	Bevacizumab plus doxorubicin and cyclophosphamide. Followed by bevacizumab plus paclitaxel albumin-stabilised nanoparticle formulation	Safety
AVF3359s	II	30	LN+ BC	Bevacizumab plus dose dense chemotherapy	Incidence of treatment failure, 2 and 5 year disease free survival

LN+ = lymph node positive; HER2– = human epidermal growth factor receptor 2 negative; BC = breast cancer; q3w = every 3 weeks; q2w = every 2 weeks; LN– = lymph node negative.

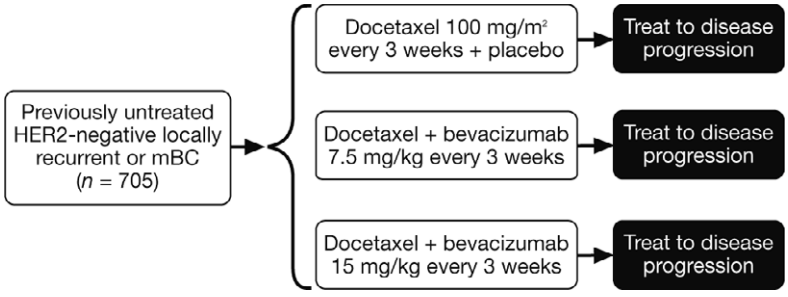

Fig. 1 – Phase III trial of docetaxel with or without bevacizumab in first-line locally recurrent or metastatic breast cancer (AVADO).

patients may either continue on, or cross over to, bevacizumab and receive chemotherapy at the investigator's discretion.

Approximately 400 centres, in up to 50 countries, are participating in study MO19391, which has recruited 1634 patients as of February 2008. MO19391 is an open-label, single-arm, multicentre study to assess the safety of bevacizumab in combination with taxane-based chemotherapy as a first-line treatment for metastatic breast cancer. Patients will receive taxane-based ther-

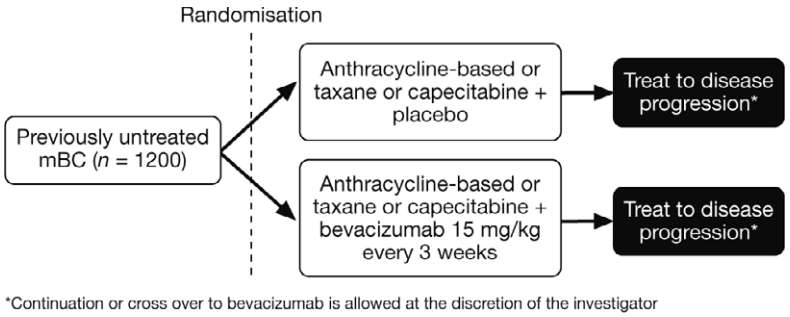

Fig. 2 – Phase III trial of first-line chemotherapy regimens with or without bevacizumab in metastatic breast cancer (RIBBON-1).

apy at the discretion of the treating physician plus bevacizumab every 2 weeks (10 mg/kg) or 3 weeks (15 mg/kg). The primary trial endpoint will be the safety profile of bevacizumab in combination with chemotherapy.

2.2. Human epidermal growth factor receptor-2-positive disease

Trastuzumab is the standard of care in both early and advanced human epidermal growth factor receptor-2 (HER2)-positive disease. Indeed, patients with HER2-positive breast cancer have been excluded from most trials of bevacizumab because of the proven benefits of HER2-based therapy in this disease. There is, however, significant cross-talk between the VEGF and HER2 pathways,[20–23] with preclinical data indicating that combining bevacizumab and trastuzumab leads to greater tumour reduction than is achieved with either agent alone.[24,25] Bevacizumab and trastuzumab have different modes of action to chemotherapy, so may well be able to be combined with standard doses of chemotherapy.

A phase I/II trial has demonstrated the feasibility of administering the two agents together.[26,27] Patients aged $\leqslant$75 years with surgically unresectable, locally or regionally relapsed or metastatic breast cancer, with HER2 amplification and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 were enrolled in phase I.[26] Prior bevacizumab therapy was not permitted, although prior trastuzumab was. Five responses were reported out of nine patients in phase I who had received trastuzumab plus bevacizumab, including one patient who had previously progressed on trastuzumab.[26] Inclusion/exclusion criteria for phase II were similar to those for phase I, except that patients could not have received prior trastuzumab therapy or chemotherapy for metastatic disease.[27] Treatment consisted of a 4 mg/kg loading dose of trastuzumab, followed by 2 mg/kg every week plus bevacizumab 10 mg/kg every 2 weeks (the bevacizumab dose recommended after phase I). Preliminary efficacy data revealed 20 clinical responses, giving an overall response rate of 54%.[27] A further 11 patients had stable disease as their best response. Thirteen drug-related cardiac adverse events have been reported to date: seven grade 1, five grade 2 and one grade 4.[27]

Given this highly encouraging preliminary evidence of activity of the combination in the absence of chemotherapy, the obvious extension of this is to test the doublet with chemotherapy. The randomised, open-label, multicentre, phase III AVEREL study will enrol 410 patients with HER2-positive advanced breast cancer in order to evaluate the efficacy and safety of the combination of bevacizumab, trastuzumab and docetaxel compared with the standard therapy of trastuzumab plus docetaxel. As of February 2008, 152 patients had been randomised to receive an 8 mg/kg loading dose of trastuzumab followed by trastuzumab (6 mg/kg) and docetaxel (100 mg/m^2), plus either bevacizumab (15 mg/kg) or placebo every 3 weeks. The primary endpoint is progression-free survival.

ECOG is also planning further investigation of the addition of bevacizumab to chemotherapy plus trastuzumab in HER2-positive disease. Phase III trial E1105 will recruit 490 patients for randomisation to bevacizumab or placebo in addition to a backbone therapy regimen consisting of six 4-weekly cycles of trastuzumab and paclitaxel, with or without carboplatin. Patients will then receive maintenance therapy with trastuzumab plus bevacizumab or placebo until disease progression or unacceptable toxicity. The primary endpoint is progression-free survival.

2.3. Hormone receptor-positive disease

Cross-talk also occurs between the VEGF pathway and hormone receptor pathways. VEGF expression is significantly correlated with the oestrogen receptor (ER) status of the patient and inversely correlated with the tumour grade.[28] Also, VEGF expression may be hormonally regulated in both the female reproductive cycle and breast cancer.[29–32] A phase II study investigated the feasibility of the combination of bevacizumab (15 mg/kg every 3 weeks) with the aromatase inhibitor letrozole (2.5 mg/day orally) in 43 patients with hormone

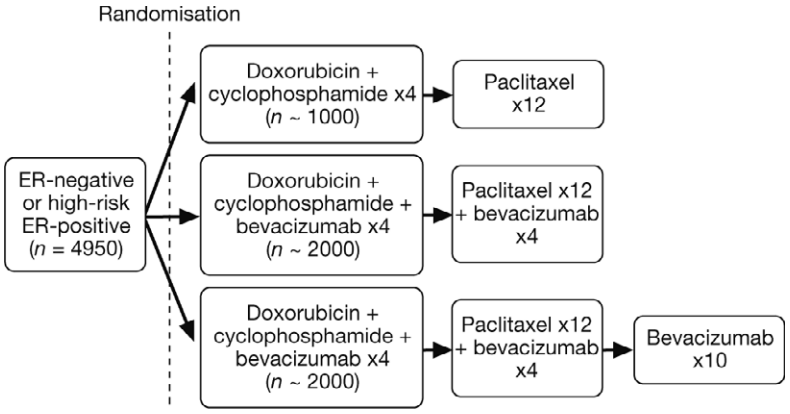

Fig. 3 – Phase III trial of standard chemotherapy regimens with or without bevacizumab as adjuvant therapy for ER-negative or high-risk ER-positive, HER2-negative breast cancer (E5103).

receptor-positive metastatic breast cancer.[33] Thirty-seven patients were evaluable for efficacy; just three (7%) had received prior chemotherapy for advanced disease. Three clinical responses were reported (8%), with a total clinical benefit rate (response plus stable disease) of 78%.[33] Median progression-free survival was 10 months, which compares favourably with historical data for first-line single-agent letrozole (9.4 months).[34] The combination of bevacizumab and letrozole was well tolerated with only one patient (2%) experiencing a grade 4 adverse event (hyponatraemia). The most frequently occurring grade 3 events were hypertension (seven patients, 16%), headache (two patients, 5%) and proteinuria (two patients, 5%).[33]

Study C40503 is a randomised, double-blind, placebo-controlled phase III trial investigating bevacizumab in combination with aromatase inhibitors or tamoxifen, which will begin recruiting during 2008. A planned 360 patients with ER or progesterone receptor-positive metastatic breast cancer will receive aromatase inhibitors or tamoxifen daily, with either placebo or bevacizumab (15 mg/kg) administered every 3 weeks. The primary trial endpoint will be progression-free survival.

3. Adjuvant breast cancer treatment

Adjuvant therapy aims to prevent development of metastatic disease through the elimination of micrometastases. As the VEGF pathway plays a major role in the early stages of tumour development, its inhibition could have an important role in preventing tumour recurrence. In 1994, Judah Folkman's group demonstrated that, in an animal model, primary lung tumours suppress neovascularisation and growth of metastases, and that this effect is mediated in part by angiostatin, an anti-angiogenic factor that inhibits VEGF activity.[35] Clinical trials are underway to evaluate the use of bevacizumab in the adjuvant setting.

ECOG trial E2104 is a two-armed, non-randomised pilot study to evaluate the efficacy of bevacizumab as an adjuvant therapy in patients with HER2-negative, lymph node-positive early breast cancer. Accrual onto each arm of the trial was carried out sequentially in cohorts of 106 patients, beginning with arm A. Patients in arm A of the trial received four cycles of doxorubicin (60 mg/m^2), cyclophosphamide (600 mg/m^2) and bevacizumab (10 mg/kg) every 2 weeks, followed by four cycles of paclitaxel (175 mg/m^2) and bevacizumab (10 mg/kg) every 2 weeks. Patients then received bevacizumab (10 mg/kg) alone for 18 2-week cycles. Patients in arm B of the trial received four cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 weeks, followed by four cycles of paclitaxel (175 mg/m^2) and bevacizumab (10 mg/kg) every 2 weeks. This was followed by bevacizumab (10 mg/kg) alone for 22 2-week cycles. Growth factor support with granulocyte colony-stimulating factor was used during chemotherapy, but not required with single-agent bevacizumab. The primary endpoint is safety concerning the incidence of clinically apparent cardiac dysfunction. Preliminary safety data indicate that this combination is feasible, with cardiac toxicity within acceptable limits in both trial arms.[36]

A planned 4950 patients will participate in the ECOG study E5103, a randomised, phase III trial to evaluate the efficacy and safety of bevacizumab as an adjuvant therapy in combination with chemotherapy (Figure 3). Eligible patients have ER-negative or high-risk ER-positive, HER2-negative early breast cancer. Patients in arm A of the trial will receive four cycles of doxorubicin (60 mg/m^2), cyclophosphamide (600 mg/m^2) and placebo every 2 or 3 weeks (at the discretion of the investigator), followed by 12 cycles of weekly paclitaxel (80 mg/m^2) plus placebo. Patients in arm B of the trial will receive four cycles of doxorubicin (60 mg/m^2), cyclophosphamide (600 mg/m^2) and bevacizumab (15 mg/kg) every 2 or 3 weeks, followed by 12 cycles of weekly paclitaxel (80 mg/m^2) in combination with four cycles of bevacizumab (15 mg/kg) every 3 weeks. Patients in arm C

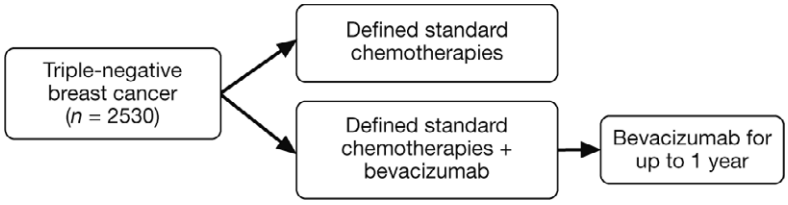

Fig. 4 – Phase III trial of standard chemotherapy regimens with or without bevacizumab as adjuvant therapy for triple-negative breast cancer (BEATRICE).

of the trial will receive doxorubicin, cyclophosphamide and bevacizumab followed by weekly paclitaxel and bevacizumab as in arm B, with an additional 10 3-weekly cycles of bevacizumab (15 mg/kg). The primary trial endpoint is disease-free survival.

BEATRICE, which began recruitment in November 2007, is a phase III trial testing the benefit of bevacizumab in the adjuvant setting in 2530 patients with triple-negative breast cancer (Figure 4). A range of standard chemotherapy regimens are permitted, and the comparison is between standard chemotherapy and the same chemotherapy plus 12 months of bevacizumab commencing concurrently with chemotherapy. The primary endpoint is invasive disease-free survival. In addition, there is a translational research sub-protocol based on prospective collection of tumour samples from consenting patients.

An additional phase III trial, BETH, will investigate the potential benefit of the addition of bevacizumab to standard combinations of chemotherapy and trastuzumab in patients with HER2-positive early breast cancer.

4. Neoadjuvant breast cancer treatment

The aim of neoadjuvant therapy is to improve clinical outcomes and to increase patient eligibility for breast-conserving surgery. The mechanism of action of bevacizumab suggests that inhibition of VEGF signalling has the potential to decrease the size of a tumour by reducing its blood supply and enhancing the activity of cytotoxic therapies. This suggests that bevacizumab could provide important clinical benefits in the neoadjuvant setting.

Preliminary data from AVF2307s, an ongoing phase II trial of neoadjuvant bevacizumab plus docetaxel being performed at Case Comprehensive Cancer Center, demonstrated reduced tumour vascular permeability and microvessel density in patients with locally advanced, unresectable breast cancer compared with docetaxel alone.[37] The addition of bevacizumab to docetaxel did not significantly increase grade 3 toxicity, and grade 4 toxicity was rare.[18] A pilot study in inflammatory breast cancer has shown a larger decrease in vascular tumour permeability parameters using bevacizumab in combination with docetaxel and doxorubicin compared with docetaxel plus doxorubicin alone.[38] Clinical trials are now planned to establish the benefits of combining bevacizumab with neoadjuvant regimens for the treatment of breast cancer.

TORI-B-02 is a randomised, placebo-controlled, double-blind, multicentre, phase II trial to evaluate the potential of bevacizumab to facilitate breast conservation surgery by reducing tumour size. Ninety patients are being randomised to four treatment arms in a 2:1:2:1 ratio (A:B:C:D) to evaluate three different bevacizumab doses compared with placebo. The chemotherapy backbone is six cycles of TAC (docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks), plus bevacizumab (7.5 mg/kg every 3 weeks) in arm A, placebo (7.5 mg/kg every 3 weeks) in arm B, bevacizumab (15 mg/kg every 3 weeks) in arm C and placebo (15 mg/kg every 3 weeks) in arm D. Patients will receive a loading dose of bevacizumab or placebo (7.5 or 15 mg/kg, as appropriate for trial arm) before commencing chemotherapy. After completing chemotherapy, patients eligible for surgery will undergo resection. Patients in arms A and C of the trial will then receive bevacizumab at the previous dose until disease progression. Patients in arms B and D will not receive any further therapy before disease progression. The primary endpoint of the study will be the safety and toxicity of chemotherapy combined with bevacizumab as a preoperative therapy for breast cancer.

One thousand two hundred patients with HER2-negative palpable and operable breast cancer will participate in NSABP B-40, a randomised phase III trial evaluating the addition of bevacizumab to three different neoadjuvant chemotherapy regimens. This study will build upon the findings of TORI-B-02 and assess the potential benefit of neoadjuvant bevacizumab in a larger population. Patients will be randomised to receive four cycles of either docetaxel (100 mg/m^2), docetaxel (75 mg/m^2) plus capecitabine (825 mg/m^2 twice-daily, days 1–14) or docetaxel (75 mg/m^2) plus gemcitabine (1000 mg/m^2 days 1–8), each with or without bevacizumab (15 mg/kg) every 3 weeks. Patients will then receive four 3-weekly cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2). Patients receiving bevacizumab within the first stage of treatment will also receive bevacizumab (15 mg/kg) during the first two cycles of doxorubicin and cyclophosphamide treatment. All patients eligible for surgery will undergo resection

Table 3 – Agents in development that inhibit the VEGF pathway

Agent	Class	Target
Bevacizumab	MAb	VEGF
Sunitinib	TKI	VEGF receptor-1, -2, -3, PDGFR, c-Kit, Flt3
Sorafenib	TKI	Raf-1, VEGF receptor-2, -3
Vandetanib	TKI	VEGF receptor-2, -3, EGFR
Motesanib	TKI	VEGF receptor, PDGFR, c-Kit
Aflibercept/VEGF-Trap	Soluble VEGF receptor	VEGF
Vatalanib	TKI	VEGF receptor
Axitinib	TKI	VEGF, PDGFR, CSF-1
Pazopanib	TKI	VEGF receptor-1, -3, c-Kit
AMG706	TKI	VEGF receptor-1, -2, -3, PDGFR, c-Kit, Ret

VEGF = vascular endothelial growth factor; Mab = monoclonal antibody; TKI = tyrosine kinase inhibitor; PDGFR = platelet-derived growth factor receptor; EGFR = epidermal growth factor receptor; CSF-1 = colony stimulating factor 1.

and those who received bevacizumab prior to surgery will receive 10 cycles of adjuvant bevacizumab (15 mg/kg) administered every 3 weeks. The primary endpoint of the study is to evaluate the rate of pathological complete response of the primary tumour.

5. Ongoing trials for other anti-VEGF agents in breast cancer

In addition to bevacizumab, other drugs inhibiting the VEGF pathway are currently in development for the treatment of breast cancer (Table 3). Apart from bevacizumab, sunitinib and pazopanib are the only anti-VEGF agents that have reached phase III trials for breast cancer (Table 4).

One ongoing phase III sunitinib trial (A6181107) is comparing the efficacy and safety of sunitinib and capecitabine in patients in whom treatment with both anthracyclines and taxanes was unsuccessful (or those who were unsuccessfully treated with a taxane and are unsuitable for anthracycline therapy). A total of 700 patients will be randomised to receive single-agent therapy with either sunitinib or capecitabine. The primary endpoint is progression-free survival. A further ongoing phase III trial (A6181099) compares capecitabine plus sunitinib with capecitabine alone in a similar patient population to that studied in the AVF2119g trial of bevacizumab and capecitabine.[14] Patients must have locally recurrent or metastatic breast cancer that has been previously treated with both anthracycline- and taxane-containing regimens in any setting. Progression must have occurred after a first-line regimen for metastatic breast cancer unless the disease-free interval was less than 12 months after adjuvant therapy. An ongoing phase III trial is comparing the efficacy and safety of pazopanib in combination with lapatinib with that of lapatinib alone in patients with ErbB2-overexpressing inflammatory breast cancer. The primary endpoint is progression-free survival and the estimated enrolment is 320 patients.

6. Conclusions

The improvement in median progression-free survival shown in the E2100 study, in conjunction with the mechanism of action of bevacizumab, makes it a good candidate for use in combination with other chemotherapy agents in advanced breast cancer. Furthermore, its mechanism of action and historical precedent strongly suggest that bevacizumab will also be effective in the treatment of breast cancer at earlier stages. An extensive clinical trial programme for bevacizumab is underway in early and advanced breast cancer settings in combination with the major chemotherapy regimens, and the results of these trials are eagerly awaited.

As no predictive marker for the success of bevacizumab therapy has yet been identified, it is important that a biomarker research programme is performed in conjunction with the trials discussed here. In addition to analysis of the expression of potential markers at the RNA and/or protein level, this will also investigate the relationship between specific single nucleotide polymorphisms and benefit from bevacizumab at the DNA level. Many ongoing trials in both early and advanced disease involve the taking of patient blood samples at various stages of therapy for biomarker analysis. The difficulty of obtaining biopsy material from patients with metastatic disease makes analysis at the tumour level less feasible in this setting, although this is currently ongoing in neoadjuvant, and some adjuvant, trials. It is hypothesised that the importance of VEGF in angiogenesis diminishes in more advanced breast cancers that have received a greater number of lines of therapy, but there is no direct clinical evidence to support this. Although such evidence would represent an important contribution to our understanding of the activity of bevacizumab, the problems associated with

Table 4 – Clinical status of studies involving anti-VEGF agents for the treatment of breast cancer

Agent	Phase	*n*	Trial design
Sunitinib	III	740	Comparison of sunitinib plus paclitaxel versus bevacizumab plus paclitaxel in breast cancer. Primary endpoint: PFS
	III	700	Sunitinib versus capecitabine in advanced breast cancer previously treated with a taxane and an anthracycline. Primary endpoint: PFS
	III	550	Comparison of sunitinib plus docetaxel versus docetaxel in advanced mBC. Primary endpoint: PFS
	III	430	Sunitinib plus capecitabine versus capecitabine in previously treated breast cancer. Primary endpoint: PFS
	II	200	Sunitinib versus standard of care in untreated, advanced, ER–, PR–, HER2– LR or mBC. Primary endpoint: PFS
	II	145	Evaluation of efficacy and safety of sunitinib in combination with bevacizumab and paclitaxel in previously untreated mBC. Primary endpoint: PFS
	II	128	Sunitinib plus trastuzumab in LR or mBC. Primary endpoint: ORR
	II	60	Evaluating consolidation anti-angiogenic therapy with sunitinib after response to taxane chemotherapy induction. Primary endpoint: PFS
	II	20	Sunitinib plus docetaxel and trastuzumab in breast cancer over-expressing HER2. Primary endpoint: safety profile of combination
	II	20	Sunitinib plus docetaxel in LR or mBC. Primary endpoint: safety and activity of combination
	I/II	72	Comparison of sunitinib and exemestane in first-line treatment of hormone receptor positive mBC. Primary endpoint: PFS
	I	20	Sunitinib plus paclitaxel in previously untreated LR or mBC. Primary endpoint: safety of combination
Vatalanib	II	32	Valatanib plus letrozole in mBC
	I/II	7	Valatanib plus trastuzumab in HER2 over-expressing locally recurrent or mBC. Primary endpoints: safety, response rate
	I	24	Valatanib plus docetaxel in mBC (and gynaecological cancers). Primary endpoint: MTD/DLT
Sorafenib	II	54	Sorafenib in mBC. Primary endpoint: response rate
	I/II	50	Sorafenib plus anastrazole in mBC. Primary endpoint: clinical benefit rate
	I	40	Sorafenib plus paclitaxel following doxorubicin/cyclophosphamide in early-stage node-positive breast cancer. Primary endpoint: safety
	I	62	Sorafenib plus bevacizumab in advanced mBC
Aflibercept/VEGF-Trap	II	45	VEGF-Trap in mBC previously treated with anthracycline and/or taxane. Primary endpoints: PFS, ORR
Motesanib	II	273	Motesanib plus paclitaxel versus bevacizumab plus paclitaxel in HER2– LR or mBC. Primary endpoint: ORR
	I/II	TBC	Motesanib plus paclitaxel or docetaxel in LR or mBC.
Axitinib	I/II	168	Axitinib plus docetaxel versus docetaxel in untreated mBC. Primary endpoint: time to progression
Pazopanib	III	320	Pazopanib plus lapatinib in inflammatory breast cancer over-expressing ErbB2. Primary endpoint: PFS
	II	140	Pazopanib plus lapatinib versus lapatinib in untreated HER2+ mBC. Primary endpoint: rate of disease progression at 12 weeks.

VEGF = vascular endothelial growth factor; PFS = progression-free survival; mBC = metastatic breast cancer; ER– = oestrogen receptor negative; PR– = progesterone receptor negative; HER2– = human epidermal growth factor receptor 2 negative; LR = locally recurrent; ORR = overall response rate; MTD = maximum tolerated dose; DLT = dose-limiting toxicity; HER2+ = human epidermal growth factor receptor 2 positive.

obtaining the requisite samples make such a study very difficult to perform.

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Conflict of interest statement

Professor Bell has received honoraria and advisory board fees from F. Hoffmann-La Roche Ltd. Professor Cameron has received honoraria and advisory board fees from F. Hoffmann-La Roche Ltd and Pfizer and research funding from F. Hoffmann-La Roche Ltd.

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