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REVIEW ARTICLE

Revisiting the Role of Anti-angiogenesis Therapy in Metastatic Breast Cancer

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ABSTRACT

Angiogenesis is essential for tumour growth and metastasis, and constitutes an important process in the control of cancer progression. The use of anti-angiogenic agents, particularly those targeting vascular endothelial growth factor, has become an integral component of anticancer regimens for many tumour types. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, is one of the most extensively studied targeted agents and has demonstrated significant clinical benefits in several solid tumours, including breast cancer. In metastatic breast cancer, randomised phase III trials have consistently demonstrated that bevacizumab, when combined with standard first-line chemotherapy regimens, significantly improved response rate and progression-free survival compared with chemotherapy alone. A recent phase III trial has also demonstrated a statistically significant improvement in progression-free survival with the addition of bevacizumab to second-line chemotherapy regimens in patients with previously treated metastatic breast cancer. Bevacizumab is generally well tolerated, with a limited impact on chemotherapy toxicity. Typical adverse events include hypertension, proteinuria, bleeding, and thromboembolic events, which are usually manageable. The use of bevacizumab in combination with paclitaxel as first-line therapy for human epidermal growth factor receptor-2–negative metastatic breast cancer has been approved in more than 80 countries worldwide, including Hong Kong, Australia, the European Union, Korea, Malaysia, New Zealand, Switzerland, and Taiwan. This article summarises current data pertaining to the efficacy and safety of bevacizumab when combined with chemotherapy for the treatment of metastatic breast cancer from phase III studies and large-scale meta-analyses.

Key Words: *Angiogenesis inhibitors; Bevacizumab; Breast neoplasms; Vascular endothelial growth factor A*

中文摘要

重溫抗血管新生療法在轉移性乳癌中的角色

郭子熹

血管新生是腫瘤生長和轉移的必要條件，因此亦是構成控制腫瘤擴展的一種重要步驟。抗血管新生劑，尤其那些針對血管內皮生長因子的藥物，已成為治療不同腫瘤的重要組成部份。Bevacizumab是一種針對血管內皮生長因子的單克隆抗體，是在不同腫瘤中（包括乳腺癌）有顯著臨床效益的其中一種最廣泛研究的標靶藥物。轉移性乳癌的隨機III期臨床試驗顯示bevacizumab結合標準一線化療方案，與單純化療相比，能顯著提高反應率和無進展生存期。近期的III期臨床試驗也顯示曾接受治療的轉移性乳癌患者的二線化療方案中加入bevacizumab能明顯改善無進展生存期。一般來說，bevacizumab耐受性良好，對化療毒性影響有限。典型的不良反應包括高血壓、蛋白尿、出血和血栓

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栓塞，而這些反應一般可以臨床處理。全球80多個國家，包括香港、澳洲、歐盟、 韓國、馬來西亞、新西蘭、瑞士和台灣，都已經批准使用bevacizumab聯合paclitaxel作一線治療人類表皮生長因子受體-2陰性的轉移性乳癌。本文總結了從轉移性乳癌的III期臨床試驗和大規模的統合分析中所得的數據，討論有關的療效和安全性。

INTRODUCTION

Angiogenesis, the process leading to the formation of new blood vessels from a pre-existing vascular network, is essential for tumour growth and metastasis. This complex process is tightly regulated by pro- and anti-angiogenic growth factors, among which vascular endothelial growth factor (VEGF) is the most potent and specific angiogenic stimulator. VEGF induces proliferation and migration of endothelial cells from pre-existing vessels towards VEGF-expressing cells to form new vascular tubes. Five isoforms of VEGF have been identified so far, namely VEGF-A, -B, -C, -D, and placental growth factor. VEGF-A, generally referred to as VEGF, is the predominant regulator of angiogenesis and binds to VEGF receptor (VEGFR) 1 and VEGFR2 on the surface of vascular endothelial cells to trigger downstream signalling pathways. VEGFR2 has a higher affinity for VEGF and appears to mediate most of the known cellular responses contributing to angiogenesis.[1]

VEGF is continuously expressed throughout the development of many tumour types. In breast cancer, VEGF is the only known pro-angiogenic factor expressed throughout the entire tumour life cycle. During the early stage of breast cancer development, VEGF is the main pro-angiogenic factor secreted by tumours, whereby it acts as a paracrine factor to induce endothelial cell proliferation and blood vessel formation, thereby mediating tumour progression. As the tumour develops further, additional factors are also secreted, including basic fibroblast growth factor and transforming growth factor–beta1, further stimulating angiogenesis.[2] Most women with a first diagnosis of breast cancer have tumours that express only VEGF, but some tumours may express as many as six angiogenic proteins. Elevated VEGF levels are associated with poor prognosis in both lymph node–positive and –negative breast cancer.[3]

Targeting the VEGF pathway has become an important strategy in cancer therapy in view of its pivotal role in angiogenesis, its specificity and association with outcome. Anti-VEGF strategies under investigation include monoclonal antibodies targeting VEGF, VEGF Trap, antibodies to VEGFRs, and small-molecule VEGF receptor tyrosine kinase inhibitors that block ligand-dependent autophosphorylation of VEGFR2.[4] Bevacizumab—a recombinant, humanised, monoclonal anti-VEGF antibody—is one of the most extensively studied targeted agents that has demonstrated significant clinical benefit in several solid tumours.[5] This article focuses on the role of bevacizumab in locally recurrent or metastatic breast cancer and discusses the current data pertaining to the efficacy and safety of bevacizumab used in combination with chemotherapy.

BEVACIZUMAB IN THE TREATMENT OF METASTATIC BREAST CANCER

Early Evidence

The antitumour activity of bevacizumab in breast cancer was first demonstrated in a phase I / II clinical trial in which patients with previously treated metastatic breast cancer were administered an escalating dose of bevacizumab.[6] Bevacizumab was associated with an confirmed overall response rate (ORR) of 6.7% and a median duration of confirmed response of 5.5 months. The study also established the optimal dose of bevacizumab to be 10 mg/kg every other week based on tolerability and activity criteria.

The first randomised phase III trial (AVF2119g) combined bevacizumab with capecitabine as second-line treatment in patients previously treated with anthracycline or taxane-containing chemotherapy.[7] The study randomised 462 patients to receive capecitabine alone or in combination with bevacizumab (15 mg/kg every 3 weeks). Results determined by an independent review facility demonstrated a significant increase in ORR with the addition of bevacizumab to capecitabine (19.8% vs. 9.1%; p = 0.001), but no significant improvement in progression-free survival (PFS; median, 4.86 vs. 4.17 months; hazard ratio [HR] = 0.98) or overall survival (OS; 15.1 vs. 14.5 months). While the study demonstrated the antitumour activity of bevacizumab, the findings suggested that the optimal time to intervene with an anti-VEGF agent might be early in the course of metastatic breast cancer. As cancer progresses, the expression of other

pro-angiogenic factors increases to support tumour growth, making it unlikely for the inhibition of VEGF alone to produce a sustained clinical effect in patients with previously treated highly refractory disease. These observations support targeting VEGF early in the course of disease and as first-line treatment for metastatic breast cancer.[7]

First-line Bevacizumab Studies

The impact of adding bevacizumab to chemotherapy as first-line treatment of metastatic breast cancer was evaluated in three randomised phase III studies.[8-11] In an open-label phase III trial (E2100) of bevacizumab in combination with first-line chemotherapy, 722 patients with predominantly human epidermal growth factor receptor-2 (HER2)–negative breast cancers were randomly assigned to receive weekly paclitaxel as first-line treatment alone or in combination with bevacizumab.[8] The addition of bevacizumab significantly improved PFS (median, 11.8 vs. 5.9 months; $p < 0.001$), the primary endpoint, and nearly doubled the ORR (36.9 vs. 21.2%; $p < 0.001$). However, OS was similar in both treatment arms (26.7 vs. 25.2 months; $p = 0.16$). A subsequent independent review of the E2100 data confirmed improvements in PFS (median, 11.3 vs. 5.8 months; $p < 0.0001$) and ORR (48.9% vs. 22.2%; $p < 0.0001$), validating the benefits of adding bevacizumab to paclitaxel treatment.[9]

The treatment effect of bevacizumab in the E2100 trial was further evaluated in two placebo-controlled randomised phase III trials of first-line chemotherapy (Avastin and Docetaxel [AVADO][10] and Regimens in Bevacizumab for Breast Oncology-1 [RIBBON-1][11]), which explored the use of bevacizumab in combination with different chemotherapy regimens. The AVADO trial compared docetaxel plus placebo with docetaxel plus two doses of bevacizumab, 7.5 and 15 mg/kg, as first-line treatment in 736 patients with HER2-negative, locally recurrent or metastatic breast cancer. Results in the stratified analysis showed that the higher dose of bevacizumab of 15 mg/kg every 3 weeks significantly prolonged PFS, the primary endpoint, when combined with docetaxel compared with docetaxel plus placebo (median, 10.0 vs. 8.1 months; HR = 0.67; $p < 0.001$). The benefit of combining bevacizumab with docetaxel was also seen in the secondary endpoints of ORR, duration of response, and time to treatment failure.[10]

The RIBBON-1 international phase III trial investigated the use of bevacizumab 15 mg/kg every three weeks in combination with several standard chemotherapy regimens compared with those regimens alone for first-line treatment of patients with HER2-negative metastatic breast cancer. The chemotherapy options were capecitabine, taxanes, or anthracyclines administered every three weeks. PFS was the primary endpoint of the study. The addition of bevacizumab to chemotherapy resulted in improvements in median PFS for both the capecitabine (5.7 vs. 8.6 months; HR = 0.69; $p < 0.001$) and taxane-anthracycline (8.0 vs. 9.2 months; HR = 0.64; $p < 0.001$) cohorts. There were no significant differences in OS between the placebo- and bevacizumab-containing arms.[11]

All three randomised phase III trials consistently demonstrated a significant improvement in PFS with bevacizumab treatment, irrespective of the chemotherapy used in the combination. The magnitude of PFS improvement was greater in E2100 than in the AVADO or RIBBON-1 studies (Table 1[8,10,11]). A meta-analysis of pooled data from the three trials confirmed

Table 1. Phase III randomised studies with bevacizumab and chemotherapy as first-line treatment of metastatic breast cancer.

Study	Treatment line	Arms	No.	RR	PFS (months)	OS (months)	Crossover
E2100[8]	First	Paclitaxel q1w ± BV 10 mg/kg q2w	722	36.9% vs. 21.2% ($p < 0.001$)	11.8 vs. 5.9 (HR = 0.6)	26.7 vs. 25.2 (HR = 0.88; $p = 0.16$)	Not allowed
AVADO[10]	First	Docetaxel q3w + BV 15 mg/kg or BV 7.5 mg/kg or placebo q3w	736	64% ($p < 0.001$) vs. 55% ($p = 0.07$) vs. 46%	10.1 (HR = 0.77) vs. 9.0 (HR = 0.86) vs. 8.2	30.2 (HR = 1.03) vs. 30.8 (HR = 1.05) vs. 31.9	Allowed
RIBBON-1[11]	First	Capecitabine q3w +BV 15 mg/kg q3w or placebo q3w; anthracycline/taxane q3w + BV 15 mg/kg q3w or placebo q3w	1237	35.4% vs. 23.6% ($p = 0.009$); 51.3% vs. 37.9% ($p = 0.005$)	8.6 vs. 5.7 (HR = 0.69); 9.2 vs. 8.0 (HR = 0.64)	29.0 vs. 21.2 (HR = 0.85); 25.2 vs. 23.8 (HR = 1.03)	Allowed

Abbreviations: AVADO = Avastin and Docetaxel; BV = bevacizumab; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; q1w = weekly; q2w = every 2 weeks; q3w = every 3 weeks; RIBBON-1 = Regimens in Bevacizumab for Breast Oncology-1; RR = response rate.

a 36% reduction in the risk of a PFS event (HR = 0.64; 95% confidence interval [CI], 0.57-0.71) and no median OS gain (HR = 0.97; 95% CI, 0.86-1.08).[12] Subgroup analyses of the pooled data showed that bevacizumab, when combined with first-line chemotherapy, resulted in clinically meaningful and statistically significant improvements in PFS across all clinically relevant subgroups, regardless of age, presence of triple-negative disease, visceral disease, disease-free interval, or prior (neo)adjuvant chemotherapy.[13] No OS benefit was demonstrated in any clinically relevant subgroups.

The Avastin Therapy for Advanced Breast Cancer (ATHENA) study provided data from a broad patient population more closely reflecting real-world oncology practice.[14] The prospective open-label study included 2251 patients with locally recurrent / metastatic breast cancer who received first-line bevacizumab 10 mg/kg every two weeks or 15 mg/kg every three weeks plus taxane-based chemotherapy (or other non-anthracycline chemotherapy) until disease progression, unacceptable toxicity, or patient withdrawal. Safety was the primary endpoint and time to progression (TTP) was a secondary endpoint. The median follow-up was 12.7 months and 78% of patients received bevacizumab in combination with a taxane-based therapy. Efficacy and safety of the bevacizumab-chemotherapy regimens were found to be consistent with results from the E2100, AVADO, and RIBBON-1 first-line studies. Median TTP was 9.5 months (95% CI, 9.1-9.9) and the ORR (best response) was 52% in the intent-to-treat population, confirming the treatment benefit of bevacizumab.[14] In a subgroup analysis of patients with triple-negative breast cancer (TNBC) in the ATHENA study (n = 585), bevacizumab-containing therapy was associated with a 49% ORR and median TTP of 7.2 months.[15] These data are broadly consistent with results from the randomised phase III trials and the observed efficacy of first-line bevacizumab and chemotherapy for patients with metastatic TNBC.[13,16]

Several other phase II / III or observational studies have investigated the use of bevacizumab in combination with paclitaxel as first-line treatment for HER2-negative locally recurrent or metastatic breast cancer. These include a single-arm clinical trial,[17] an observational study with similar design to the ATHENA study,[18] and phase II / III trials that utilised bevacizumab-paclitaxel combinations as the control arm compared with other chemotherapeutic, targeted, or novel agents.[19-23] The PFS rates of bevacizumab-paclitaxel in these studies were comparable to those reported in the E2100, AVADO, and RIBBON-1 trials, providing further support for the efficacy of bevacizumab-paclitaxel treatment in patients with HER2-negative locally recurrent or metastatic breast cancer (Table 2[17-23]).

Table 2. Additional phase II / III or observational studies that involved the use of bevacizumab and paclitaxel combination therapy in the first-line treatment setting for human epidermal growth factor receptor-2–negative locally recurrent or metastatic breast cancer

Study	Study type / phase	No. of patients	Treatment design/arms	PFS (months)	Remarks
Aogi et al[17]	II	120	P + BV	12.9 TNBC 9.6	OS 35.8 months
Klare et al[18]	Observational	786	According to the European Union label	9.3	OS immature
Martin et al[19]	II	91	P + motesanib	9.5	ORR 49%
		94	P + placebo	9.0	41%
		97	P + BV	11.5	52%
Rugo et al[20]	II	46	Ixabepilone weekly + BV	9.6	ORR 48%
		45	Ixabepilone q3w + BV	11.9	71%
		32	P + BV	13.5	63%
Brufsky et al[21]	II	94	P + BV	8.8	OS 25.0 months
		93	P + BV + gemcitabine	11.3 (HR = 0.82; p = 0.247)	24.3 months
Robert et al[22]	III	242	Sunitinib + P	7.2	Sunitinib + P inferior
		243	BV + P	9.2 (HR = 1.63; p = 0.999)	
Diéras et al[23]	II	56	P + BV + AMG386 10 mg/kg	11.3	No apparent PFS increase with the addition of AMG386 to P and BV at the dose tested
		57	P + BV + AMG386 3 mg/kg	9.2	
		58	P + BV + placebo	12.2	
		57	P + AMG386 10 mg/kg	10.1	

Abbreviations: BV = bevacizumab; HR = hazard ratio; ORR = overall response rate; OS = overall survival; P = paclitaxel (90 mg/m^2 weekly, days 1, 8, and 15); PFS = progression-free survival; q3w = every 3 weeks; TNBC = triple-negative breast cancer.

Safety Profile

The combination of bevacizumab with chemotherapy was associated with a limited increase of toxicities in patients with locally recurrent or metastatic breast cancer, but most adverse events were manageable in clinical practice.[7,8,10,11] The E2100 study reported a significantly higher frequency of grade 3/4 adverse events, including hypertension (14.8% vs. 0%; $p < 0.001$), infection (9.3% vs. 2.9%; $p < 0.001$), proteinuria (3.6% vs. 0%; $p < 0.001$), headache (2.2% vs. 0%; $p = 0.008$), cerebrovascular ischaemia (1.9% vs. 0%; $p = 0.02$), fatigue (9.1% vs. 4.9%; $p = 0.04$), and sensory neuropathy (23.5% vs. 17.7%; $p = 0.05$) in patients who received bevacizumab-paclitaxel therapy than in those who received paclitaxel alone.[8] The AVADO safety data showed an increase of grade 3-5 adverse events, serious adverse events, and study drug discontinuation with the addition of bevacizumab to docetaxel. However, the incidence of grade ≥3 infection, venous or arterial thromboembolic events, congestive heart failure, proteinuria, bleeding, or hypertension were not significantly different in the treatment arms.[10] Adverse events in the RIBBON-1 study were consistent with those observed in previous bevacizumab trials across tumour types, although the overall incidence of grade 3-5 or serious adverse events were higher in the bevacizumab arms compared with the placebo arms.[11]

The role of bevacizumab in the development of severe adverse events has been difficult to assess in individual randomised clinical trials since they are not powered enough to detect significant relationships in low-incidence events. Further safety evaluation of bevacizumab in metastatic breast cancer was provided in a large patient population of the ATHENA study. The most frequently reported grade ≥3 adverse events were neutropenia (5.4%), febrile neutropenia (5.3%), fatigue (4.8%), and hypertension (4.4%). The variations of grade ≥3 adverse events with different bevacizumab-chemotherapy regimens were consistent with the known profiles of each chemotherapy, and no new safety concerns for bevacizumab were observed.[14] Subgroup analysis of the ATHENA study showed that the safety profile of first-line bevacizumab in the TNBC subgroup was consistent with results in the overall population.[15]

Recently, a meta-analysis of randomised phase III bevacizumab trials, including data from almost 4000 patients with locally recurrent or metastatic breast cancer, showed that the use of bevacizumab in advanced breast cancer was associated with a significantly higher risk of grade ≥3 proteinuria (odds ratio [OR] = 27.68), hypertension (OR = 12.76), left ventricular dysfunction (OR = 2.25), and haemorrhagic events (OR = 4.07). No significant relationship was found with fatal events, febrile neutropenia, gastrointestinal perforation, or arterial or venous thromboembolic events.[24]

Progression-free Survival Versus Overall Survival as a Primary Endpoint

The lack of OS benefit corresponding to PFS improvements observed with the addition of bevacizumab to first-line chemotherapy has raised discussion on whether PFS or OS is the more appropriate primary endpoint in metastatic cancer trials. The aims of treatment of metastatic cancer are to improve the quantity and / or quality of patient survival; hence OS remains the fundamental outcome measure of metastatic cancer trials. However, OS can be affected by the duration of post-progression survival and the effect of first-line treatment on OS may be confounded by subsequent lines of therapy.[25] In the E2100, AVADO and RIBBON-1 first-line bevacizumab trials, post-progression survival was relatively long (20 months) and the administration of further lines of therapy were extensive and unbalanced between the arms, which may have confounded analyses. PFS is considered an attractive primary endpoint for clinical trials since the data are available earlier than for OS, are less influenced by competing causes of death than for OS, and are not influenced by second-line treatments.[25]

Second-line Bevacizumab Studies

Early evidence from the AVF2119g study of bevacizumab combined with capecitabine in patients with heavily pretreated metastatic breast cancer demonstrated no difference in PFS, but a significant increase in ORR in the bevacizumab-capecitabine arm compared with the capecitabine only arm (19.8% vs. 9.1%; $p = 0.001$).[7] More recently, the use of bevacizumab combined with standard chemotherapy regimens in the second-line treatment setting for patients with HER2-negative metastatic breast cancer was further investigated in the RIBBON-2 randomised placebo-controlled phase III trial.[26] The combination of bevacizumab with chemotherapy (capecitabine, a taxane, and gemcitabine or vinorelbine) demonstrated a significant increase in median PFS from 5.1 to 7.2 months (HR = 0.78; 95% CI, 0.64-0.93; $p = 0.0072$). The improvement in ORR was 10% in the bevacizumab-chemotherapy arm compared with the placebo-chemotherapy arm (39.5% vs. 29.6%; p =

0.0193), which was consistent with previous trials, although this did not reach statistical significance. There was no statistically significant difference in OS.[26]

The safety profile for bevacizumab in the second-line treatment setting was consistent with that observed in prior phase III trials. The most common grade ≥3 adverse events related to bevacizumab treatment were hypertension (9.0%) and proteinuria (3.1%). There was an increased number of adverse events leading to study discontinuation in the bevacizumab-chemotherapy arm compared with the placebo-chemotherapy arm (13.3% vs. 7.2%).[26]

CURRENT STATUS OF BEVACIZUMAB USE

Bevacizumab in combination with paclitaxel as first-line therapy for HER2-negative metastatic breast cancer has been approved in more than 80 countries worldwide, including Hong Kong, Australia, the European Union, Korea, Malaysia, New Zealand, Switzerland, and Taiwan.

In 2008, the US Food and Drug Administration (FDA) granted accelerated approval for bevacizumab-paclitaxel as first-line treatment of HER2-negative metastatic breast cancer based on the E2100 findings, subject to reassessment of data after completion of the AVADO and RIBBON-1 trials. Although both were considered positive trials, the magnitude of the PFS benefit in the AVADO and RIBBON-1 did not match that of the E2100 study. In addition, there was concern that the HRs for OS favoured the non-bevacizumab arms in the AVADO trial and in the taxane / anthracycline cohort of the RIBBON-1 trial. Consequently in 2011, the FDA revoked the bevacizumab indication in breast cancer based on available phase III data, and concluded that the proof of benefit of bevacizumab in delaying tumour growth in metastatic breast cancer was insufficient to justify the risks of potentially life-threatening side-effects. There was also a lack of evidence demonstrating that bevacizumab would help patients live longer or improve their quality of life. Furthermore, there have been no validated predictive biomarkers identified for bevacizumab efficacy, making selection of patients who may derive a significant benefit from it difficult. Despite withdrawal of the FDA approval, bevacizumab in combination with paclitaxel remains one of the preferred chemotherapy regimens recommended by the latest National Comprehensive Cancer Network guidelines for recurrent or metastatic breast cancer.[27] In other cancer types, bevacizumab has been approved by the FDA and many other regulatory authorities for the treatment of colorectal, lung, and kidney cancers, and glioblastoma multiforme. It has been suggested that results of bevacizumab studies in breast, lung, prostate, ovarian, and pancreatic cancers are not statistically different (test of heterogeneity, $p = 0.42$), yet similar results in different cancers has led to different interpretations of what is considered a clinically meaningful benefit.[28]

In the European Union, bevacizumab in combination with paclitaxel has been approved for first-line treatment of women with metastatic breast cancer since 2009. Following data from the RIBBON-1 study demonstrating a survival benefit of bevacizumab in combination with capecitabine, the European Commission extended the bevacizumab approval to include combination with capecitabine as first-line treatment for metastatic breast cancer. The bevacizumab-capecitabine combination is also approved for first-line use in Japan and Switzerland.

CONCLUSION

Randomised trials of bevacizumab combined with first- or second-line chemotherapy for locally recurrent or metastatic breast cancer have demonstrated significant improvements in PFS relative to chemotherapy alone, although no advantage in OS has been shown. The PFS benefit of first-line bevacizumab-based therapy was observed across all clinically relevant subgroups, regardless of age, presence of triple-negative disease, visceral disease, disease-free interval, or prior (neo) adjuvant chemotherapy. Particularly, the combination of bevacizumab and paclitaxel has demonstrated consistent efficacy across metastatic breast cancer trials, making it an important treatment option in the first- or second-line setting. Based on phase III data, the bevacizumab-paclitaxel combination has been approved and recommended as treatment for HER2-negative metastatic breast cancer in many countries. The addition of bevacizumab to chemotherapy is generally well tolerated and has only limited impact on the known safety profile of chemotherapy alone. Although bevacizumab is associated with an increased risk of severe adverse events, the incidence remains low and most side-effects are manageable. Further clinical trials and research are still warranted to confirm the role of bevacizumab in the adjuvant / neoadjuvant setting, across different breast cancer subgroups, and with different combination regimens. Identifying biomarkers of response will be integral to selecting patients who

will benefit most from bevacizumab therapy and to optimising the use of anti-angiogenic agents in the systemic management of breast cancer.

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