

**REGIONAL DRUG AND THERAPEUTICS CENTRE
(NEWCASTLE)**

**THE USE OF BEVACIZUMAB IN THE
MANAGEMENT OF METASTATIC BREAST
CANCER**

**Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH**

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ABOUT THIS REPORT

This is one of a series of evaluations prepared by the Regional Drug and Therapeutics Centre (Newcastle). The aim is to give objective information and guidance to commissioners of health services, prescribers and others both on clinical aspects of the subject and on arrangements for prescribing. The reports are prepared by a multidisciplinary team within the Centre and reviewed by health authority personnel and appropriate external specialists. However, responsibility for the content and conclusions rest solely with the Regional Drug and Therapeutics Centre. We welcome comments on reports and suggestions for future topics. The following reports are available:

Subject	Date issued
The use of entecavir in the management of chronic hepatitis B infection	March 2007
The use of natalizumab in the management of multiple sclerosis	March 2007
The use of aromatase inhibitors in the treatment of early stage breast cancer (N)	March 2007
Palonosetron for the prevention of nausea and vomiting associated with cancer chemotherapy	March 2007
Alemtuzumab in the management of chronic lymphocytic leukaemia	March 2007
Omalizumab in the management of severe, persistent, allergic asthma	June 2006
Bortezomib second-line in the management of multiple myeloma	March 2006
Adjuvant docetaxel or paclitaxel in the management of early stage breast cancer (N)	March 2006
Erlotinib in the management of non-small cell lung cancer	March 2006
Ibritumomab in the management of B-cell follicular non-Hodgkin's lymphoma	March 2006
Rituximab in combination with CVP chemotherapy for the management of follicular non-hodgkins lymphoma.	March 2006
Pemetrexed in the management of malignant pleural mesothelioma	February 2006
Pegvisomant in the management of acromegaly	January 2006
Ibandronic acid in the management of hypercalcaemia of malignancy, bone pain and the prevention of skeletal events associated with skeletal metastases	August 2005
Teriparatide in the management of osteoporosis	July 2004
Adefovir dipivoxil for the treatment of chronic hepatitis B infection (N)	May 2004
An update on newer agents for the treatment of pulmonary hypertension	February 2004
Drotrecogin alfa (activated) in the management of severe sepsis (N)	December 2002
Agalsidase alfa and beta in the management of Fabry disease	July 2002
Carbamyl glutamate in the management of N-acetylglutamate synthetase deficiency	July 2002
Erythropoietin in the management of cancer related anaemia	July 2002
Interferon alfa in the management of malignant melanoma	November 2001
Imatinib (Glivec®, STI-571), in the management of chronic myeloid leukaemia (N)	November 2001
Atypical antipsychotics in the management of dementia	June 2001
Iloprost and epoprostenol in the management of pulmonary hypertension	February 2001
Verteporfin for age related macular degeneration	November 2000

Temozolomide for high grade gliomas (N)	May 2000
New drugs for rheumatoid arthritis (N)	May 2000
Ribavirin and interferon alfa for chronic hepatitis C (N)	March 2000
Low molecular weight heparins in venous thrombo-embolic disease	November 1999
Low molecular weight heparins in unstable coronary artery disease	November 1999
Octreotide	July 1999
Drug treatment of obesity (N)	July 1999
Interferon alfa in Hepatitis C (N)	May 1999
Interferon beta in MS (N)	May 1999 (update)
Topotecan for ovarian cancer (N)	December 1998 (update)
Somatotrophin for GHD in adults	December 1998 (update)
Paclitaxel in ovarian cancer (N)	December 1998 (update)
Interferon alfa for haematological malignancy	July 1998
Irinotecan for colorectal cancer (N)	July 1998
Antiretroviral therapy	July 1998
Topotecan for ovarian cancer (N)	July 1998
Dornase alfa for cystic fibrosis	July 1998 (update)
New drugs for Alzheimer's disease (N)	February 1998
Atypical antipsychotics in the management of schizophrenia (N)	February 1998
Somatropin for GHD in adults (N)	January 1998
Taxanes in breast cancer (N)	July 1997
Alglucerase for Gaucher's disease	July 1997 (update)

Agents which have been reviewed by the National Institute for Health and Clinical Excellence (NICE) are indicated by the presence of a **(N)** after the report name. Please refer to the NICE website to access the guidance for these agents/conditions.

Regional Drug and Therapeutics Centre
Wolfson Unit
Claremont Place
Newcastle upon Tyne
NE2 4HH
Telephone 0191 232 1525
Fax 0191 260 6192

e-mail: nyrdtc.di@ncl.ac.uk
Web site : www.nyrdtc.nhs.uk

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SUMMARY

- In England breast cancer is the most common malignancy in females and accounts for about 32% of all cancer cases in women. In 2003 there were 36,509 new cases of female breast cancer registered in England, representing a crude incidence rate of 144 per 100,000 of the female population.
- Approximately 10% of patients present with advanced disease with distant metastases at first diagnosis, and around 50% of women diagnosed with early or localized breast cancer will eventually relapse and develop metastatic or advanced disease.
- Bevacizumab is a recombinant humanised monoclonal antibody which acts as an inhibitor of vascular endothelial growth factor (VEGF). Bevacizumab prevents VEGF from binding to and activating receptors on the surface of vascular endothelial cells thereby inhibiting VEGF-induced angiogenesis and tumour growth.
- Bevacizumab in combination with paclitaxel is licensed as first-line treatment of women with metastatic breast cancer (MBC).
- In a single randomised open-label study, bevacizumab in combination with paclitaxel as first-line therapy for MBC significantly improved progression-free survival (PFS) and objective response rates (ORR) compared to paclitaxel alone. There was a non-significant trend toward prolonged overall survival (OS) with the combination therapy, but follow up was too short to produce definitive survival data.
- The overall safety profile of bevacizumab in patients with locally advanced or MBC was consistent with that observed in the treatment of other tumour types. Although the addition of bevacizumab was associated with higher incidences of hypertension and proteinuria these adverse events were manageable.
- Further data on quality of life (QoL), OS, long-term safety and cost effectiveness are required in order to determine the precise place in therapy of bevacizumab. If clinically significant improvements in OS and QoL can be robustly demonstrated bevacizumab may be considered as an option along with existing recommended therapies for the first-line treatment of MBC in women whose tumours do not overexpress HER-2.
- Bevacizumab must be administered under supervision of a clinician experienced in the use of antineoplastic agents.
- The recommended dose of bevacizumab for the treatment of MBC is 10 mg/kg given once every two weeks or 15 mg/kg given once every three weeks as an intravenous infusion. The total cost of bevacizumab per patient (mean adult female body weight 56kg) per fortnightly dose would be £1,410.
- This equates to a potential cost of approximately £2.0M – £2.1M per 100,000 of the female population, not including the additional cost of paclitaxel or the associated costs of service provision.

- **A number studies are in progress investigating the efficacy and safety of bevacizumab in combination with various other chemotherapy agents and evaluating its potential role in the adjuvant and neoadjuvant settings.**

BACKGROUND

In England breast cancer is the most common malignancy in females and accounts for about 32% (excluding non-melanoma skin cancer) of all cancer cases in women.¹ In 2003 there were 36,509 new cases of female breast cancer registered in England, representing a crude incidence rate of 144 per 100,000 of the female population.¹ Mortality from breast cancer in the UK has fallen dramatically since the introduction of the national breast screening program for women aged between 50 and 70.^{2,3} In the period 1989 to 2004 age-standardised death rates for female breast cancer have fallen by 31%. Around 10,300 women died from breast cancer in England in 2004, a rate of 40.3 deaths per 100,000 women.³ Earlier detection and improved treatment have resulted in higher survival rates. The five year-survival rate among the 132,300 women diagnosed with breast cancer between 1998-2001 was 80%.⁴

Approximately 10% of patients present with advanced disease with distant metastases at the time of first diagnosis (~3,650 women per year).⁵ In addition, around 50% of women diagnosed with early or localized breast cancer will eventually relapse and develop metastatic disease (~16,430 women).⁵ The risk of developing metastatic disease relates to known prognostic factors, including oestrogen-receptor negative status, primary tumour greater than 3cm and axillary node involvement.⁵

Advanced and metastatic breast cancer (MBC) are defined by clinical staging based on the tumour, node and metastasis system (TNM, appendix I).⁶ Locally advanced breast cancer (stage III) includes tumours ≥ 5 cm or those with direct invasion of the skin of the breast or chest wall, and any tumour that has spread to the lymph nodes. MBC (stage IV) is characterised by the presence of disease at distant sites such as the bone, liver, chest wall or lung.

Although systemic treatment of MBC can result in modest improvements in survival time, the disease at this stage is considered incurable. Treatment is largely palliative in intent with the primary aim of improving quality of life through control of disease progression.⁷ The average period of survival after diagnosis with MBC is around 18-24 months.⁸

There is currently no accepted single standard of care for patients with MBC, as treatment plans require an individual patient by patient approach. Endocrine therapy, chemotherapy or biologic therapies are treatment options for many patients with MBC. However, the choice of a specific drug or regimen is dependent on a number of factors, including patient characteristics (age, menopausal status, performance status and co-morbidities) and tumour factors (hormone-receptor status and human epidermal growth factor [HER-2 status]). Previous administration of adjuvant therapy and the resultant response, the extent and site of metastatic disease, and patient preference also influence treatment choice.^{5,9}

First-line systemic treatment of MBC will usually involve hormone therapy for women with oestrogen-receptor-positive disease (usually tamoxifen or an aromatase inhibitor), and chemotherapy for oestrogen-receptor-negative patients (usually an anthracycline-based regimen, or occasionally CMF [cyclophosphamide, methotrexate and 5-fluorouracil]).⁸ Targeted biologic therapies offer an entirely new treatment option for patients with MBC. For patients with overexpression of HER-2 on tumour cells, the monoclonal antibody trastuzumab is an option. Trastuzumab is recommended by the National Institute of Health and Clinical Excellence (NICE) as a monotherapy for patients who have received at least two chemotherapy regimens for

MBC, or in combination with paclitaxel for patients with MBC who have not received previous chemotherapy for metastatic disease and in whom an anthracycline is unsuitable.⁸

BEVACIZUMAB

Bevacizumab (Avastin[®] Roche Products Ltd) is a humanized recombinant monoclonal antibody targeting VEGF.¹⁰ Angiogenesis plays a central role in tumour initiation, growth and distant metastasis in breast cancer.¹¹ VEGF is one of the most potent and specific mediators of angiogenesis, which it elicits by stimulating endothelial cell proliferation, migration, survival and increasing microvascular permeability.^{12,13} Over-expression of VEGF has been observed in a variety of tumours, including breast cancer, and is associated with a poor prognosis.¹²⁻¹⁴ Because of the major role of angiogenesis in tumour development anti-angiogenic drugs have emerged as a key therapeutic strategy in the treatment of breast cancer. Bevacizumab prevents VEGF from binding to and activating its receptors on the surface of vascular endothelial cells thereby inhibiting VEGF-induced angiogenesis and tumour growth.¹⁰

The purpose of this report is to review the efficacy and place in treatment of bevacizumab as first-line therapy in patients with advanced and metastatic breast cancer.

EFFICACY

BEVACIZUMAB AS FIRST-LINE THERAPY

One large, randomised, open-label, phase III trial has evaluated the efficacy and safety of combining bevacizumab with paclitaxel as first-line therapy in patients with previously untreated locally recurrent or MBC (Eastern Cooperative Oncology Group (ECOG) E-2100 trial).¹⁵ Preliminary results of this pivotal study have been presented at several international meetings but have not yet been fully published.¹⁶⁻¹⁹ The final analysis data were however, presented in the European Medicines Agency – European Public Assessment Report (extension of indication).²⁰

A total of 722 patients with locally recurrent (n=13)²¹ or MBC (n=709)²¹ who had not received prior chemotherapy for metastatic disease were enrolled in the study.²⁰ Patients were stratified according to disease-free interval (≤ 24 months vs. > 24 months), number of metastatic sites (< 3 vs. ≥ 3), treatment with prior adjuvant chemotherapy (yes vs. no), and oestrogen receptor status (positive vs. negative vs. unknown). Randomisation was performed on a 1:1 basis with 368 patients randomised to bevacizumab plus paclitaxel, and 354 patients to paclitaxel alone. All patients received intravenous (IV) paclitaxel at a dose of 90 mg/m² on days 1, 8, and 15 of a four-week cycle. Those randomised to bevacizumab received drug at a dose of 10 mg/kg IV on days 1 and 15. All patients received treatment until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Secondary outcome measures included overall response rate (ORR), overall survival (OS), quality of life (QoL) and tolerability. Disease progression and tumour response were assessed by the investigator and confirmed by ECOG according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria. The study was designed to have an 85% power to detect a 33% improvement in PFS

assuming a one-sided type one error of $\cong 2.5\%$, with a recruitment target of 650 eligible patients.¹⁹

Stratified analysis of the primary endpoint of duration of PFS for all randomised patients demonstrated a statistically significant improvement in the median duration of PFS with bevacizumab plus paclitaxel compared with paclitaxel alone (13.3 vs. 6.7 months, HR 0.48 [95% CI 0.39 - 0.59], $p < 0.0001$).²⁰ At the time of analysis 169 patients in the bevacizumab plus paclitaxel arm and 168 patients in the paclitaxel alone arm had died. This represented 70% of the 481 deaths required for the final analysis. Median OS was 22.6 months in the bevacizumab plus paclitaxel arm versus 22.3 months with paclitaxel alone (HR = 0.82 [95% CI 0.66 – 1.03], $p = 0.08$).²⁰ Among patients with measurable disease at baseline (66.8% bevacizumab plus paclitaxel and 75.7% paclitaxel alone), the ORR was statistically higher in the bevacizumab plus paclitaxel arm compared with paclitaxel alone (36.2% vs. 16.4% respectively, $p < 0.0001$).²⁰ In addition a greater percentage of patients in the bevacizumab plus paclitaxel arm achieved a complete response compared to patients in the paclitaxel alone arm (17% vs. 11%, respectively).²⁰ The effect of bevacizumab plus paclitaxel on QoL could not be reliably assessed due to missing data.²⁰

ADVERSE EFFECTS

The overall safety profile of bevacizumab in patients with locally advanced or MBC was consistent with that observed in the treatment of other tumour types.^{10,20,21} The most common serious adverse events (grade 3-5 non-haematological or grade 4 and 5 haematological) observed in this study with a $\geq 2\%$ increased frequency in the bevacizumab plus paclitaxel arm included; hypertension (15.5% vs. 1.4%), proteinuria (3.0% vs. 0%) and fatigue (8.6% vs. 4.9%).^{20,21} Peripheral sensory neuropathy was also increased in the combination arm (23.2% vs. 16.5%), although this difference is likely to have been due to the longer duration treatment and cumulative dose of paclitaxel received by patients in the combination arm (10 vs. 6 treatment cycles, respectively).^{20,21}

DOSAGE, ADMINISTRATION AND COST

The recommended dose of bevacizumab for the treatment of MBC is 10 mg/kg given once every two weeks or 15 mg/kg given once every three weeks as an intravenous (IV) infusion.¹⁰ A phase I/II dose escalation study has shown 10 mg/kg every two weeks to be the optimum dose for the treatment of MBC.²² The equivalent dose of bevacizumab has been subsequently used in all breast cancer trials.²¹ In line with the treatment of metastatic cancer of the colon or rectum, treatment of MBC should be continued until progression of the underlying disease.^{10,15} Because of the possible risk of infusion reactions the first dose of bevacizumab should be administered over 90 minutes as an IV infusion following chemotherapy. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.¹⁰ Bevacizumab should not be administered as an IV push or bolus.

The current costs of bevacizumab are £242.66 for 100 mg/4ml, and £924.40 for 400 mg/16ml.²³ Assuming a mean adult female body weight of 56kg,²⁴ the total cost of bevacizumab per patient per 10mg/kg fortnightly dose would be £1,410. The number of doses which will give maximum benefit has not yet been established. However, the median time to progression in the E-2100 study²⁰ was 13.3 months in the bevacizumab arm, suggesting that a typical patient will require in the region of 13 months treatment with bevacizumab (29 doses) at a total cost of approximately £41,000. If it is assumed that 50% of patients diagnosed with early stage breast cancer will develop metastatic disease at some time during their illness, and that 20 - 25%²⁵ of these would over-express HER-2 and therefore not be suitable candidates for first-line treatment, this would leave 49 - 52 per 100,000 of the female population potentially eligible for treatment with bevacizumab. Based on 13 months treatment this would equate to a potential cost of approximately £2.0M – £2.1M per 100,000 of the female population. These costs do not take into account the additional cost of paclitaxel treatment or the associated costs of service provision.

PLACE IN TREATMENT

Bevacizumab in combination with paclitaxel is licensed as first-line treatment of patients with metastatic breast cancer (MBC).¹⁰ Results from a large randomized clinical trial of patients with previously untreated MBC shows that bevacizumab in combination with paclitaxel as first-line therapy significantly improves PFS.^{20,21} However, there is currently insufficient evidence to determine whether the longer time to progression translates into improved health status and improved OS in those patients randomized to bevacizumab. Tolerability of bevacizumab in patients with locally advanced or MBC was consistent with that observed in the treatment of other tumour types. Although the addition of bevacizumab was associated with higher incidences of hypertension and proteinuria these adverse events were acceptable.¹⁰ Further data on QoL measures during the disease-free interval, OS, long-term safety, and cost effectiveness are required in order to determine the precise place in therapy of bevacizumab in MBC. If clinically significant improvements in OS and QoL can be robustly demonstrated bevacizumab may be considered as an option along with existing recommended therapies for the first-line treatment of women with locally advanced or MBC whose tumours do not overexpress HER-2.

ARRANGEMENTS FOR PRESCRIBING

Bevacizumab must be administered under supervision of a clinician experienced in the use of antineoplastic agents.

FUTURE DEVELOPMENTS

In view of the limited evidence available, there is urgent need for good quality randomised controlled trials to investigate the efficacy and safety of bevacizumab in combination with various other chemotherapy agents and in other settings, including the adjuvant and neoadjuvant settings. Future trials should ensure that data are collected on a range of outcomes, with particular emphasis on QoL during the disease-free interval. These data should be collected in a form that facilitates

accurate cost-effectiveness analysis. In addition, further studies are necessary to develop methods for selecting those patients who would derive the most benefit from VEGF-targeted therapies.

A number of studies are currently underway to evaluate the efficacy and safety of bevacizumab as first-line treatment for MBC in combination with other chemotherapies, including docetaxel (AVADO)²⁶ and capecitabine (RIBBON-1).²⁷

A phase III trial (AVEREL) is also underway to evaluate the combination of bevacizumab, trastuzumab and docetaxel in patients with HER2-positive breast cancer.²⁸

NICE guidance on the diagnosis and treatment of advanced breast cancer is expected to be published in January 2009 (wave 9).²⁹

ACKNOWLEDGEMENTS

We are grateful to the following people for helpful advice and comments in the preparation of this report. The Regional Drug and Therapeutics Centre accepts final responsibility for the content of this document.

Dr. D Dodwell	Consultant Medical Oncologist	Leeds Teaching Hospitals NHS Trust
Dr. A Wardley	Consultant Medical Oncologist	Christie Hospital NHS Trust Manchester

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APPENDICES

Appendix I. Abridged version of the TNM staging system for breast cancer (adapted from the AJCC cancer staging manual, 6th edition).⁶

TNM staging system for breast cancer

Tumour size: (T)

TX	Primary tumour cannot be assessed
TO	No evidence of primary tumour
Tis	carcinoma <i>in situ</i>
T1	Tumour ≤ 2 cm in greatest dimension
T2	> 2 cm but ≤ 5 cm
T3	> 5 cm
T4	Tumour of any size with direct extension to chest wall or skin

Lymph nodes: (N)

NX	Regional lymph nodes cannot be assessed
NO	No regional lymph node metastasis
N1	Metastasis in movable ipsilateral axillary lymph node(s)
N2	Metastasis in ipsilateral axillary lymph nodes fixed or matted
N3	Metastasis in ipsilateral infraclavicular lymph node(s)

Distant metastasis (M)

MX	Distant metastasis cannot be assessed
MO	No distant metastasis
M1	Distant metastasis

Breast cancer clinical stage grouping

Early breast cancer

Stage 0: Ductal carcinoma in situ (DCIS) is cancer that has not spread past the ducts or lobules of the breast (the natural boundaries). It is also called non-invasive cancer.

Stage I: The tumour is small and has not spread to the lymph nodes.

Stage IIa: Any one of these conditions:

- The tumour is smaller than 2 cm, and has spread to 1-3 axillary lymph nodes under the arm.
- The tumour is between 2 cm and 5 cm, but has not spread to the axillary lymph nodes.
- There is no evidence of a tumour in the breast, but there is cancer in the axillary lymph nodes.

Stage IIb: Any one of these conditions:

- The tumour is between 2 cm and 5 cm, and has spread to 1-3 axillary lymph nodes.
- The tumour is larger than 5 cm, but has not spread to the axillary lymph nodes.

Advanced breast cancer

Stage IIIa: Any of these conditions:

- The tumour is smaller than 5 cm, and has spread to 4-9 axillary lymph nodes.
- The tumour is larger than 5 cm, and has spread to 1-9 axillary lymph nodes or internal mammary nodes.

Stage IIIb:

The tumour has spread to the chest wall or caused swelling or ulceration of the breast or is diagnosed as inflammatory breast cancer. It may or may not have spread to the lymph nodes under the arm, but has not spread to other parts of the body.

Stage IIIc:

Tumour of any size that has not spread to distant parts of the body, but has spread to the lymph nodes above the collarbone, under the collarbone, or both the nodes inside the breast and under the arm.

Stage IV:

The tumour can be any size and has spread to distant sites in the body, usually the bones, lungs, liver, or chest wall.

Correlation of clinical and TNM staging system

UICC STAGE	TNM CLASSIFICATION
Stage 0	0 Tis
Stage I	T1, N0, M0
Stage IIa	T0-1, N1, M0 or T2, N0, M0
Stage IIb	T2, N1, M0 or T3, N0, M0
Stage IIIa	T3, N1, M0 or T0-3, N2, M0
Stage IIIb	T4, any N, M0
Stage IIIc	any T, N3, M0
Stage IV	any T, any N, M1

Appendix II. Eastern Cooperative Oncology Group performance status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Adapted from Toxicity and Response Criteria of the Eastern Cooperative Oncology Group.³⁰

Appendix III. Bevacizumab as first-line therapy

Key: CNS – central nervous system; ECOG - Eastern Cooperative Oncology Group; HR – hazard ratio; HER2 - Human epidermal growth factor receptor 2; IV – intravenously; MC = multicentre; NR – not reported; OL – open label; ORR – objective response rate; OS – overall survival; PFS – progression-free survival; R – Randomised; RCT - Randomised controlled trial.

Reference	Design	Intervention	Patient numbers	Inclusion Criteria	Exclusion Criteria	Primary outcome	Results	Adverse effects
ECOG-E2100 15,20,21	Phase III, RCT, OL, MC.	(Arm A) Bevacizumab 10mg/kg IV days 1 and 15, plus paclitaxel 90mg/m ² IV on days 1, 8 and 15 of a 4 week cycle. (Arm B) Paclitaxel 90mg/m ² IV on days 1, 8 and 15 of a 4 week cycle.	R=722 (Arm A) Bevacizumab plus paclitaxel n= 368 (Arm B) Paclitaxel n= 354	Histologically or cytologically confirmed locally recurrent or metastatic breast cancer; HER2-positive only if prior treatment with or contraindication to trastuzumab; no prior chemotherapy for metastatic disease; adjuvant taxane allowed if disease-free interval >12 months; no clinically significant cardiovascular disease; ECOG ³⁰ performance status 0-1, and ≥18 years	Evidence of CNS metastases; uncontrolled hypertension; significant proteinuria (>500mg/day), or use of anticoagulant medication.	PFS Secondary outcomes included; ORR, OS, toxicity and QoL.	Bevacizumab plus paclitaxel significantly improved PFS (13.3 vs. 6.7 months; HR=0.48 [95% CI 0.39 – 0.59], p<0.0001) compared to paclitaxel alone. OS = 22.6 vs. 22.3 months respectively, HR=0.82 [95% CI 0.66 – 1.03], p=0.08) ORR = 36.2% vs. 16.4% respectively, p<0.0001	Grade 3-5 non-haematological or grade 4 and 5 haematological adverse events with a ≥ 2% increased frequency in the bevacizumab plus paclitaxel arm included: hypertension (15.5% vs. 1.4%), proteinuria (3.0% vs. 0%), fatigue (8.6% vs. 4.9%) and peripheral sensory neuropathy (23.2% vs. 16.5%).