Horizon Scanning in Oncology

Bevacizumab (Avastin®) in combination with chemotherapy in previously treated metastatic breast cancer

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1 Drug description

Generic/Brand name/ATC code:

Bevacizumab/(Avastin®) / L01X C07

Developer/Company:

Roche Pharma AG

Description:

bevacizumab inhibits the binding of VEGF to its receptors

Bevacizumab, the active substance of Avastin® is a recombinant humanized monoclonal IgG1 antibody [1]. It binds to the vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, VEGFR-1 and VEGFR-2, on the surface of endothelial cells. Neutralizing the biological activity of VEGF regresses the vascularization of tumours, normalizes remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth [2, 3].

intravenous infusion

recommended dosing regimen for metastatic breast cancer (BC)…

Avastin® is available in 4 ml or 16 ml vials containing 25mg/ml bevacizumab. It is administered by intravenous infusion and must be diluted before use. The recommended dosing regimen for the treatment of metastatic breast cancer (BC) is 10 mg/kg body weight given once every 2 weeks or 15 mg/kg body weight given once every 3 weeks [1, 2].

Adverse events (AEs) associated with bevacizumab treatment may be gastrointestinal perforations, fistulae, wound healing complications, hypertension, proteinuria, arterial and venous thromboembolism, haemorrhage, pulmonary haemorrhage/haemoptysis, congestive heart failure, reversible posterior leucoencephalopathy syndrome and neutropenia [2, 3].

2 Indication

as second-line therapy for metastatic BC

Bevacizumab (Avastin®) in combination with chemotherapy regimens for the treatment of patients with previously treated metastatic BC that is as 2nd or late-line therapy.

3 Current regulatory status

EMA: approved for first-line therapy of BC, but not for second-line

The European Medicines Agency (EMA) [2] approved Avastin® for the use in the European Union,

- in combination with paclitaxel for first-line treatment of patients with metastatic BC [2, 4].

recommended only with paclitaxel as first-line therapy for metastatic BC

- in combination with capecitabine for first-line treatment of patients with metastatic BC in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxanes and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin® in combination with capecitabine.

for metastatic carcinoma of colon or rectum, non-small cell lung cancer, renal cell cancer, advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer

- in combination with fluoropyrimidine-based chemotherapy for treatment of patients with metastatic carcinoma of the colon or rectum.
- in addition to platinum-based chemotherapy for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.
- in combination with interferon alfa-2a for first-line treatment of patients with advanced and/or metastatic renal cell cancer.
- in combination with carboplatin and paclitaxel for the front-line treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer.

FDA:

withdrew the approval for first-line therapy of patients with metastatic HER2-negative BC

In November 2011 the U.S. Food and Drug Administration (FDA) withdrew the approval for Avastin® in combination with paclitaxel for treatment of patients who have not received chemotherapy for metastatic human epidermal growth factor receptor 2 (HER2)-negative BC. This decision was based on the results of 2 trials (AVADO [5] and RIBBON-1 [6]), where bevacizumab has not been shown to provide a benefit, in terms of delay in the growth of tumours, that would justify its serious and potentially life-threatening risks. There is also no evidence that the use of bevacizumab will either help women with BC to live longer or to improve their quality of life (QoL) [7].

for metastatic colorectal cancer, non-squamous non-small cell lung cancer, glioblastoma or metastatic renal cell carcinoma

Avastin® remains on the U.S. market as an approved treatment for [1],

- metastatic colorectal cancer, with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment.
- non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease.
- glioblastoma, as a single agent for adult patients with progressive disease following prior therapy.
- metastatic renal cell carcinoma with interferon alfa.

4 Burden of disease

BC is most common type of cancer in women

In 2009, about 5,000 women were newly diagnosed with BC [8] and 1,500 died from BC in Austria [9]. Thus, with a percentage of 28.5%, BC is the most common type of cancer in females [10]. Between 2005 and 2007 the majority of malignant neoplasm of the breast were diagnosed in women aged 45 to 85 years [11]. The age standardized (per 100,000 population, defined by WHO 2001) incidence rate for BC in women dropped from 75.0 (1998) to 69.4 (2009) in Austria. In the same period, the age standardized death rate declined from 21.6 (1998) to 17.3 (2009) [8, 9, 11]. Several well-established factors have been associated with an increased risk of BC, including age, positive family history, nulliparity, early menarche a personal history of BC and genetic factors [12].

risk factors

TNM staging classification

The American Joint Committee on Cancer has designated a staging by Tumour Node Metastasis (TNM) classification to define BC. The TNM provides a strategy for grouping patients with respect to prognosis. Besides the staging of the primary tumour, the extent to which regional lymph nodes are involved and the absence or presence of distant metastases are taken into account, leading to four main stage groupings (stage T1 to T4) where metastatic disease is coded as stage T4 [13, 14]. Metastases are most common in the bones, liver or the lungs. In 2007, the British Secondary Breast Cancer Taskforce reported that about 5% of women and men diagnosed with BC between 1992 and 1994 had metastases at the time of their primary diagnosis and a further 35% of all those with a primary diagnosis went on to develop metastases within the following 10 years [15]. In Austria, 5.2% of female patients with initially diagnosed BC had disseminated disease [16]. The prognosis for metastatic BC is generally poor and the 15-year cause-specific survival rates range between 7% and 8.3% [17]. The median overall survival (OS) approaches two years, with a range from a few months to many years, with patients with either HER2-overexpression or triple-negative (oestrogen receptor, progesterone receptor, HER2) metastatic BC having an even shorter survival [18].

in Austria 5.2% of women have disseminated disease at diagnoses

prognostic factors for metastatic BC

Prognostic factors for metastatic disease include the length of the relapse-free interval after the initial treatment, the number of metastases, locations involved (worse prognosis with hepatic, lymphangitic pulmonary metastases, bone marrow replacement, carcinomatous meningitis) and biological markers (e.g., good prognosis is associated with hormone receptor positive state). Additionally, weight loss, poor performance status and age less than 35 years in woman with early stage BC have an unfavourable prognosis [18]. Biological markers for prognosis as well as for therapeutic decisions include oestrogen receptor, progesterone receptor and HER2-status [19].

status of oestrogen-, progesterone receptor and HER2 are biomarkers for therapeutic decisions

5 Current treatment

treatment of local disease and treatment of systemic disease

The treatment of BC includes the treatment of local disease with surgery, radiation therapy, or both, and the treatment of systemic disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy or combinations of these. The choice of therapy is based on a number of prognostic and predic-

tive factors like tumour histology, characteristics of the primary tumour, axillary node status, tumour hormone receptor content, HER2- status, presence of detectable metastatic disease, comorbid conditions, age, and menopausal status [20].

for advanced BC: complex management

The management of patients with advanced BC is complex. When making treatment choices there is a trade-off between QoL, the risks of toxicity and the likelihood of benefit in terms of improving symptoms, QoL or survival [15]. Details of the treatment of advanced BC have been described in a recent Horizon Scanning Document on lapatinib [21].

palliative intent

For metastatic BC the therapy is palliative in intent. Goals of treatment include improving QoL and prolongation of life. The treatment of metastatic BC is influenced by many factors and should be tailored individually. Ultimately, the choice of therapy should be based on patient preferences. Clinical advice will take into account the presence or absence of comorbidities, treatment effectiveness, performance status, the site and extent of disease, the presence or absence of symptoms, and the rate at which the disease appears to be progressing [15].

Primary strategy for the treatment of metastatic BC is the administration of systemic therapy that can be divided into three categories– endocrine therapy, chemotherapy and biological therapy [20]. Radiation therapy or surgery may be indicated for patients with limited symptomatic metastases [22].

endocrine therapy:

- endocrine therapy

anastrazole
tamoxifen
letrozole
fulvestrant

Endocrine therapy (e.g. anastrazole, tamoxifen, letrozole or fulvestrant) is appropriate for approximately 70% of patients who have hormone receptor positive advanced BC [15]. Hormone therapy is especially indicated if the patient's disease involves only bone and soft tissue metastases and the patient has either not received adjuvant antioestrogen therapy or has been off such therapy for more than 1 year [22]. It is not used in combination with chemotherapy but is combined in certain circumstances with biological therapy, although high-quality evidence is lacking [15].

chemotherapy:

- chemotherapy

taxanes
capecitabine
vinorelbine
gemcitabine

Chemotherapy is used in the treatment of both hormone receptor positive and negative patients with metastatic BC [15]. Patients whose tumours have progressed on hormone therapy or patients with visceral metastases are also candidates for chemotherapy [22]. A number of different chemotherapy drugs, or classes of drug, are used, including anthracyclines, taxanes, capecitabine, vinorelbine, gemcitabine, alkylating agents and platinum-based drugs [15]. Whether single-agent chemotherapy or combination chemotherapy is preferable for first-line treatment is unclear [22].

biological therapy:

- biological therapy

trastuzumab
lapatinib
bevacizumab

Over the last 10 to 15 years the identification of some of the molecular processes occurring in BC has led to the development of new treatment options using agents which can be directed specifically at these molecular processes. They may be used alone or in combination with chemotherapy or endocrine therapy. There are currently three main biological therapies used in patients with advanced BC – trastuzumab for patients whose tumours have either HER2-overexpression or HER2-gene amplification, lapatinib for patients who have HER2-positive metastatic BC that progressed after treatment with

trastuzumab, and bevacizumab. [15, 22]. According to the National Institute of Clinical Excellence (NICE), trastuzumab is currently the only one of these agents recommended for use in patients with advanced BC, in combination with chemotherapy [15].

- surgery

surgery

Surgery may be indicated for selected patients. Examples include patients who need mastectomies for fungating (marked by ulcerations and necrosis) /painful breast lesions, parenchymal brain or vertebral metastases with spinal cord compression or isolated lung metastases [22].

- radiation therapy

radiation therapy

Radiation therapy has a major role in the palliation of localized symptomatic metastases. Indications include painful bony metastases, unresectable central nervous system metastases, bronchial obstruction, and fungating/painful breast or chest wall lesions. Radiation therapy is also used after surgery for decompression of intracranial or spinal cord metastases and following fixation of pathologic fractures [22].

6 Evidence

A systematic literature search in medical databases (Medline/Pubmed, Embase, Cochrane databases, CRD) in addition to a hand search resulted after removal of duplicates in 216 records overall. Of those, 11 records reporting results of 2 phase III trials and 6 single arm phase II trials, were included [23-33].

2 phase III trials

6 single arm phase II trials

6.1 Efficacy and safety - Phase III studies

Table 1: Summary of efficacy (Ribbon-2)

Study title A Study to Evaluate the Safety and Efficacy of Bevacizumab in Combination With Chemotherapy in Previously Treated Metastatic Breast Cancer (RIBBON 2) [23]		
Study identifier	NCT00281697; EudraCT Number: 2006-006507-36	
Design	Randomised (2:1 ratio), double-blind, placebo-controlled international, multi-centre trial; N = 684 (225 vs. 459); allocation randomly to chemotherapy (capecitabine-,gemcitabine-, vinorelbine-, or taxane-based) + bevacizumab (BV) or chemotherapy + placebo; stratification on the interval from metastatic BC diagnosis to first PD, investigator choice of chemotherapy, and estrogen receptor or progesterone receptor status. ITT-Analysis	
	Duration	Enrolment: February 2006 to June 2008 Median follow-up: 15 months Cut-off date for final analysis: March 31, 2009

Hypothesis	Superiority		
Funding	Genentech, South San Francisco, CA.		
Treatment groups	Intervention	Chemotherapy + BV: Chemotherapy on investigators choice: ▪ capecitabine 1,000 mg/m² orally twice per day on days 1 through 14 every 3 weeks; ▪ docetaxel 75 to 100 mg/m² iv every 3 weeks; nab-paclitaxel 260 mg/m² iv every 3 weeks; ▪ paclitaxel 90 mg/m² iv on days 1, 8, and 15 every 4 weeks or 175 mg/m² iv every 3 weeks; ▪ gemcitabine 1,250 mg/m² iv on days 1 and 8 every 3 weeks; or vinorelbine 30 mg/m² iv every 3 weeks Chemotherapy was continued until PD, unacceptable toxicity, investigator decision, or death. Doses could be modified at investigator discretion. BV: 10 or 15 mg/kg iv every 2 or 3 weeks, respectively, depending on the chemotherapy regimen; BV was continued until PD, unacceptable toxicity, investigator decision, completion of 36 months of BV, or death; BV could continue as monotherapy, if chemotherapy was discontinued before PD.	
	Control	Chemotherapy + placebo: Chemotherapy on investigators choice: ▪ capecitabine 1,000 mg/m² orally twice per day on days 1 through 14 every 3 weeks; ▪ docetaxel 75 to 100 mg/m² iv every 3 weeks; nab-paclitaxel 260 mg/m² iv every 3 weeks; ▪ paclitaxel 90 mg/m² iv on days 1, 8, and 15 every 4 weeks or 175 mg/m² iv every 3 weeks; ▪ gemcitabine 1,250 mg/m² iv on days 1 and 8 every 3 weeks; or vinorelbine 30 mg/m² iv every 3 weeks Chemotherapy was continued until PD, unacceptable toxicity, investigator decision, or death. Doses could be modified at investigator discretion. Placebo: placebo could continue as monotherapy, if chemotherapy was discontinued before PD.	
Endpoints and definitions	Progression-free survival (primary efficacy end point)	PFS	Time from random assignment to first PD or death as a result of any cause.
	Objective response rate (secondary endpoint)	ORR	Percentage of patients with measurable disease who achieved a CR or PR confirmed ≥ 28 days after initial documentation of response (according to RECIST version 1.0).
	overall survival (secondary endpoint)	OS	Time from random assignment until death.
	Progression-free survival within individual chemotherapy regimen (secondary endpoint)	PFS ind	Time from random assignment to first PD or death as a result of any cause.
	1-year survival rate (secondary endpoint)	1ySR	Percentage of patients who were alive 1 year after randomisation

	Safety (secondary endpoint)	S	AEs leading to study drug discontinuation, SAEs, and selected AEs previously associated with BV or chemotherapy
Results and analysis			
Analysis description	Primary analysis: The intent-to-treat (ITT) population was the primary efficacy analysis population. It was pooled over all the chemotherapy cohorts and performed at the two-sided α = .05 level. Time-to-event variables were compared between treatment arms by using a stratified log-rank test, and the duration of time-to-event data was estimated by using the Kaplan-Meier method. The 95% CIs for median time to event were computed by using the Brookmeyer-Crowley method. Hazard Ratios (HRs) for time-to-event variables were estimated by using a stratified Cox regression model.		
Analysis population	Characteristics	684 patients with histologically confirmed, locally recurrent breast cancer or metastatic BC who had received one prior cytotoxic treatment for metastatic BC *Control vs. Intervention:* Median age (years): 55 vs. 55 ECOG performance status 1: 51% vs 50% HER2-negative: 85% vs. 84% HER2-status unknown: 14% vs. 15% ≥ 3 metastatic sites: 47% vs. 44% Visceral disease: 71% vs. 74% Hormone receptor positive disease: 73% vs 72% Triple-negative disease: 21% vs. 24%	
	Inclusion	Age ≥ 18 years; histologically confirmed, locally recurrent or metastatic BC; one prior cytotoxic treatment for metastatic BC; ECOG performance status of 0 or 1.	
	Exclusion	HER2–positive status; prior BV or other VEGF pathway–targeted therapy; untreated brain metastases; unstable angina; congestive heart failure (> Class II); history of myocardial infarction, stroke, or transient ischemic attack within the last 6 months; clinically significant peripheral vascular disease; bleeding diathesis or coagulopathy; history of abdominal fistula, GI perforation, or intraabdominal abscess within the last 6 months; serious non-healing wound; or inadequate organ function.	
Results	Treatment group	Chemotherapy + placebo	Chemotherapy + BV
	Number of subjects	225	459
	PFS (months) median 95% CI	 5.1 4.1 – 6.0	 7.2 6.5 – 7.6
	OS (months) median 95% CI	 16.4 14.6 – 20.2	 18.0 17.1 – 20.2
	1ySR (%) median 95% CI	 66.2 59.7 – 72.8	 69.5 65.0 – 74.0
	Number of subjects	179	362

	ORR (%) CR (%) PR (%)	29.6 1.1 28.5	39.5 2.2 37.3
Effect estimate per comparison	Comparison groups		Intervention vs Control
	PFS	HR	0.78
		95% CI	0.64 – 0.93
		P value	0.0072
	OS	HR	0.90
		95% CI	0.71 – 1.14
		P value	0.3741
	ORR	Point estimate	NR
		Variability	NR
		P value	0.0193

AE ... adverse event; BC ... breast cancer; BV ... bevacizumab; CI ... confidence interval; CR ... complete response; ECOG ... Eastern Cooperative Oncology Group; HER2 ... human epidermal growth factor receptor 2; HR ... hazard ratio; ITT ... intention-to-treat; iv ... intravenous ; NR ... not reported; ORR ... objective response rate; OS ... overall survival; PD ... disease progression; PFS ... progression-free survival; PR ... partial response; RECIST ... Response Evaluation Criteria in Solid Tumours; SAE ... serious adverse event; VEGF ... vascular endothelial growth factor.

Table 2: Most frequent adverse events (RIBBON-2)

Grade (according to NCI CTC AE version 4.0)	**Outcome**	**Chemotherapy + BV** (n= 458)	**Chemotherapy + placebo** (n= 221)
All Grades	SAE	112 (24.5%)	39 (17.6%)
	AE leading to discontinuation	61 (13.3%)	16 (7.2%)
Grade ≥3	AE previously shown to be associated with BV or chemotherapy	161 (35.2%)	50 (22.6%)
	AE leading to death	6 (1.3%)	5 (2.3%)
	Neutropenia	81 (17.7%)	32 (14.5%)
	Hypertension	41 (9.0%)	1 (0.5%)
	Sensory neuropathy	29 (6.3%)	13 (5.9%)
	Proteinuria	14 (3.1%)	1 (0.5%)
	Febrile neutropenia	10 (2.2%)	6 (2.7%)
	Bleeding events	8 (1.7%)	0 (0.0%)
	Left ventricular systolic dysfunction	4 (0.9%)	0 (0.0%)
	ATE	3 (0.7%)	3 (1.4%)
	Wound dehiscence	1	0
	GI perforation	2 (0.4%)	0 (0.0%)
	RPLS	0 (0.0%)	0 (0.0%)

AE ... adverse event; ATE ... arterial thromboembolic event; BV ... bevacizumab; GI ... gastrointestinal; RPLS ... reversible posterior leukoencephalopathy syndrome; SAE ... serious adverse event.

double-blind, placebo-controlled RCT

bevacizumab + chemotherapy for second-line therapy of metastatic HER2-negativ BC

The Ribbon-2 trial [23, 31, 32] was an international, multi-centre, double-blind, placebo-controlled randomised trial (RCT) with study centres in the European Union, USA and various other countries. The aim of the study was to evaluate the efficacy and safety of bevacizumab in combination with chemotherapies for second-line therapy of HER2-negativ metastatic BC. 684 patients aged 18 years or older with metastatic *HER2-negativ* BC, who had received one prior cytotoxic treatment for metastatic BC, were included. 459 of them were allocated to chemotherapy + bevacizumab, while 225 received chemotherapy + placebo. Chemotherapy regimen was given on investigators choice. The median number of doses of the study drug (placebo or bevacizumab) received was 6 for the chemotherapy + placebo arm and 9 for the chemotherapy + bevacizumab arm, with a median duration of treatment of 4 and 6 months, respectively. The median duration of chemotherapy exposure was higher in the chemotherapy + bevacizumab arm by 1 month compared with the chemotherapy + placebo arm for all cohorts except vinorelbine.

significant reduction of risk for PD or death

At the end of the data cut-off, chemotherapy + bevacizumab resulted in a statistically significant reduction in the risk of a disease progression (PD) or death of 22% (HR = 0.78; 95% CI: 0.64 - 0.93; p = 0.0072) and in a 2.1 months improvement in median progression-free survival (PFS) (7.2 vs. 5.1 months).

subgroup analysis: significant only for taxane + bevacizumab

In a predefined subgroup analysis according to different chemotherapy regimens (taxane 304 patients; gemcitabine 160 patients; capecitabine 144 patients; vinorelbine 76 patients), the PFS in favour of the intervention remained significant only for the taxane combination (HR = 0.64; 95% CI: 0.49 - 0.84). For the vinorelbine combination there was even a tendency towards longer PFS in the control group (HR = 1.42; 95% CI: 0.78 - 2.59).

significant for triple negative BC

A subgroup analysis for patients with triple negative metastatic BC (TNBC) (23% of all patients) showed a median improvement in PFS of 3.3 months (HR = 0.494; 95% CI: 0.33-0.74; p=0.0006).

no difference between chemotherapy + bevacizumab and chemotherapy + placebo in ORR, OS and 1-year survival rate

The secondary end point, objective response rate (ORR) was about 10% higher in the bevacizumab group compared to placebo (37.2% vs. 28.5%), which was statistically not significant (p= 0.0193, prespecified α of 0.01). The ORR for the TNBC subgroup was 41% vs. 18% in favour of the bevacizumab group, which was statistically significant (p = 0.0078) [31]. In all analyses the overwhelming majority of confirmed responses in both cohorts were partial responses.

OS in interim results no statistically significant differences

For the overall survival (OS) only interim results are reported so far. There were no statistically significant differences in the interim OS (HR = 0.90; 95% CI: 0.71 – 1.14; p = 0.3741) and in the 1-year survival rate (69.5% vs. 66.2%) for either the whole population or the TNBC subgroup (OS: HR = 0.624; 95% CI: 0.39 – 1.007; p = 0.0534; 1ySR: 63% vs. 50%). The number of deaths were 206 (44.9%) vs. 109 (48.4%) for the whole population and 52 (46%) vs. 29 (62%) for the TNBC subgroup.

most common AEs: neutropenia, sensory neuropathy and hypertension

Selected grade ≥ 3 adverse events (AEs), previously shown to be associated with bevacizumab or chemotherapy (e.g. hypertension, bleeding, proteinuria), as well as serious adverse events (SAEs) were more often observed in the bevacizumab group than in the placebo group (35.4% vs. 22.6%; 24.5% vs. 17.6%). Neutropenia (17.7% vs. 14.5%), sensory neuropathy (6.3% vs. 5.9%) and hypertension (9.0% vs. 0.5%) were the most common grade ≥ 3 AEs. AEs that led to a study discontinuation occurred almost twice as frequently in the bevacizumab group than in the placebo group (13.3% vs.

7.2%). There was no difference in the number of treatment-related deaths as a result of AEs between the two groups (1.3% vs. 2.3%).

Based on these results the authors concluded that bevacizumab in combination with chemotherapy should be considered as second-line therapy for patients with HER2-negative metastatic BC.

Table 3: Summary of efficacy (Miller 2005)

Study title: Randomised phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer [24, 33]			
Study identifier	ClinicalTrial.gov: NCT00109239, NCT00012285 (obsolete); GENENTECH-AVF2119g		
Design	Randomised (1:1 ratio), two-arm open-label multi-centre (96) study; N=462 allocation randomly to 2 treatment groups (230 capecitabine alone, 232 combination treatment); stratification on study site, ECOG performance status (0 or 1) and number of prior chemotherapy regimens for metastatic disease (0 or ≥1) ITT analysis		
	Duration	Enrolment: November 2000 to March 2002 Median follow-up: NR Cut-off date for final analysis: 28 June 2002 (assessment of pharmacokinetics)	
Hypothesis	Superiority of progression-free survival (PFS)		
Funding	Genentech Inc, South San Francisco, CA		
Treatment groups	Intervention	Capecitabine (CAP) + bevacizumab (BV) CAP like in the control arm . BV (15 mg/kg) intravenously during 30-90 minutes on day 1 of each 3-week cycle. Treatment was interrupted in case of proteinuria ≥ 2,000 mg/24h until its resolution, but it was not discontinued for CAP-related toxicities.	
	Control	CAP monotherapy (CAP alone) CAP 2,500 mg/m^2/d, orally twice daily for 14 days followed by a 7-day rest period, administered for a maximum of 35 3-week cycles or until disease progression or unacceptable toxicity. If toxicity occurred and depending on its grade (according to NCI-CTC), CAP was discontinued or interrupted and resumed at a reduced dose.	
Endpoints and definitions	Progression-free survival (primary outcome)	PFS	defined as time from randomisation to the date of disease progression or death as determined by the independent review facility (primary end point) or by the investigators (secondary end point), whichever occurred first. Patients without an event were treated as censored at the time of the last tumour assessment. Tumour assessments more than 42 days after discontinuation of CAP were censored.

	Objective response rate (secondary endpoint)	ORR	Objective response and disease progression were determined using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.0) with minor modifications (i.e. a diameter of at least 2 cm was required to be assessed as a target lesion or an unequivocal progression of a nontarget lesion). To be considered an objective response, all CRs and PRs were to be confirmed at least 4 weeks after the initial response assessment. Tumour response was assessed every 6 weeks until 24 weeks, and then every 9 weeks.
	Duration of response (secondary endpoint)	DoR	Defined as duration of objective response.
	Quality of Life (secondary endpoint)	TDQ	Time to deterioration in Quality of Life (QoL). Measured every 6 weeks until 24 weeks, and then every 9 weeks by the Trial Outcome Index (TOI) which is the sum of the physical well-being, functional well-being, and breast cancer–specific questions in the FACT-B questionnaire Version 4. A decline in TOI of more than five points from baseline, a disease progression, or death were considered a clinically meaningful deterioration in QoL.
	Duration of Survival (secondary endpoint)	DoS	Duration of survival was defined as the time from randomisation to death. All patients were monitored for survival every 4 months.
Results and analysis			
Analysis description	Primary analysis: PFS for the BV + CAP group compared with the CAP-alone group, determined with a two-sided stratified log-rank test performed at the 0.0498 level (type I error of 0.01%). An estimate of the hazard ratio with 95% CIs was determined using a stratified Cox regression model with an indicator variable for treatment group. Median PFS in each treatment group was estimated using the Kaplan-Meier method. All randomly assigned patients were included in the efficacy (ITT) analysis.		
Analysis population	Characteristics	462 women with confirmed metastatic BC *Control(n=230) vs. Intervention(n=232):* Mean age (years): 52 vs. 51 Ethnicity: Black / White (%): 10.9 / 80.4 vs. 12.9 / 80.6 ECOG performance status 0 / 1 / 2 (%): 50 / 50 / 0 vs. 50.4 / 49.1 / 0.4 Hormone Receptor Status: Oestrogen receptor–positive (%): 51.7 vs. 41.8 Progesterone receptor–positive (%): 41.7 vs. 32.3 HER2-positive (%): 20.4 vs. 26.3 Median duration of metastatic disease (years): 1.3 vs. 1.0 Visceral disease (%): 80.0 vs. 77.6 ≥ 3 sites of disease (%): 50.4 vs. 49.1 Prior chemotherapy regimens for metastatic BC 0 / 1 / 2 / 3-5 (%): 16.1 / 42.6 / 37.8 / 3.5 vs. 15.1 / 46.1 / 34.1 / 4.7	

	Inclusion	Women ≥ 18 years of age ; histologically or cytologically confirmed metastatic BC; prior therapy with both an anthracycline and a taxane; at least one, but no more than two, prior chemotherapy regimens for metastatic disease, or no intervening chemotherapy, if relapse occurred within 12 months of completing adjuvant anthracycline and taxane therapy; progression following trastuzumab in case of HER2-positive disease (3+ protein expression by immunohistochemistry or gene amplification by fluorescence in situ hybridization); bidimensionally measurable disease with at least one lesion measuring ≥ 2 cm; ECOG performance status of 0 or 1; adequate renal, hepatic, and hematologic function.	
	Exclusion	History or radiographic evidence of central nervous system disease (screening head computed tomography or brain magnetic resonance image required); other primary malignancy (except basal cell carcinoma of the skin or in situ cervical cancer within 5 years); major surgery within 4 weeks; other antitumour therapy within 21 days; nonhealing wound or fracture, infection requiring parenteral antibiotics, or clinically significant cardiovascular disease; therapeutic anticoagulation (prophylactic anticoagulants to maintain a vascular access device permitted), regular nonsteroidal anti-inflammatory medication or aspirin (> 325 mg/d); administration of bisphosphonates initiated within 21 days before study entry	
Results	Treatment group	*Control (CAP alone)*	*Intervention (CAP + BV)*
	Number of subjects	230	232
	PFS (months) median 95%CI	4.17 NR	4.86 NR
	ORR (%) 95% CI	9.1% 5.4% - 12.9%	19.8% 14.7% - 25.0%
	DoR (months) median 95% CI	7.6 NR	5.0 NR
	DoS* (months) median 95%CI *at data cutoff 38% of all patients had died	14.5 NR	15.1 NR
	Number of subjects	176	194
	TDQ (months) median 95%CI	2.86 NR	2.92 NR
Effect estimate per comparison	*Comparison groups*		*Intervention vs Control*
	PFS	HR	0.98
		95% CI	0.77 - 1.25
		P value	0.857

	ORR	Point estimate	NR
		Variability	NR
		P value	0.001
	DoR	Point estimate	NR
		Variability	NR
		P value	similar
	DoS	Point estimate	NR
		Variability	NR
		P value	similar
	TDQ	Point estimate	NR
		Variability	NR
		P value	0.633

BV … Bevacizumab; CAP … Capecitabine; CI … Confidence interval; DoR … Duration of response; DoS … Duration of survival; ECOG … Eastern Cooperative Oncology Group; FACT-B … Functional Assessment Of Cancer Treatment—Breast; HER2 … Human epidermal growth factor receptor 2; ITT … Intent-to-treat; NCI-CTC … National Cancer Institute Common Toxicity Criteria; NR … Not reported; ORR … Objective response rate; PFS … Progression-free survival; QoL … Quality of Life; RECIST … Response Evaluation Criteria in Solid Tumors; TDQ … Time to deterioration in Quality of Life; TOI … Trial Outcome Index

Table 4: Most frequent adverse events (Miller 2005)

Grade (according to NCI CTC AE version 2.0)	Outcome	Intervention (CAP + BV) (n= 229)	Control (CAP alone) (n= 215)
Grade 1 only AEs>15% in one arm	*Common BV Toxicities*		
	Proteinuria	42 (18.3%)	14 (6.5%)
	Bleeding	60 (26.2%)	19 (8.8%)
Grade 2 only AEs>15% in one arm	*Common CAP Toxicities*		
	Diarrhoea	37 (16.2%)	34 (15.8%)
	Hand-foot syndrome	97 (42.4%)	77 (35.8%)
	Other Common Toxicities		
	Miscellaneous		
	Asthenia	58 (25.3%)	35 (16.3%)
	Headache	26 (11.4%)	9 (4.2%)
	Pain	24 (10.5%)	20 (9.3%)
Grade 3	*Common CAP Toxicities*		
	Diarrhoea	27 (11.8%)	23 (10.7%)
	Stomatitis	4 (1.7%)	0 (0%)
	Hand-foot syndrome	63 (27.5%)	52 (24.2%)
	Common BV Toxicities		
	Hypertension	41 (17.9%)	1 (0.5%)

	Proteinuria	2 (0.9%)	0 (0%)
	Bleeding	1 (0.4%)	1 (0.5%)
	Thrombotic event	9 (3.9%)	5 (2.3%)
	Pulmonary embolism	0 (0%)	0 (0%)
	Other Common Toxicities		
	Hematologic		
	Anaemia	4 (1.7%)	1 (0.5%)
	Leukopenia	6 (2.6%)	3 (1.4%)
	Thrombocytopenia	3 (1.3%)	1 (0.5%)
	Gastrointestinal		
	Nausea	6 (2.6%)	4 (1.9%)
	Anorexia	2 (0.9%)	5 (2.3%)
	Constipation	1 (0.4%)	0 (0%)
	Cardiac		
	Congestive heart failure	5 (2.2%)	0 (0%)
	Cardiomyopathy	1 (0.4%)	0 (0%)
	Infectious		
	Infection	2 (0.9%)	1 (0.5%)
	Fever	1 (0.4%)	2 (0.9%)
	Miscellaneous		
	Asthenia	14 (6.1%)	10 (4.7%)
	Headache	4 (1.7%)	1 (0.5%)
	Pain	7 (3.1%)	4 (1.9%)
Grade 4	*Common CAP Toxicities*		
	Diarrhoea	0 (0%)	0 (0%)
	Stomatitis	0 (0%)	1 (0.5%)
	Hand-foot syndrome	0 (0%)	0 (0%)
	Common BV Toxicities		
	Hypertension, Proteinuria	0 (0%)	0 (0%)
	Bleeding	0 (0%)	0 (0%)
	Thrombotic event	4 (1.7%)	3 (1.4%)
	Pulmonary embolism	3 (1.3%)	3 (1.4%)
	Other Common Toxicities		
	Hematologic		
	Anaemia	0 (0%)	0 (0%)

	Leukopenia	0 (0%)	3 (1.4%)
	Thrombocytopenia	1 (0.4%)	0 (0%)
	Gastrointestinal		
	Nausea, Anorexia, Constipation	0 (0%)	0 (0%)
	Cardiac		
	Congestive heart failure	0 (0%)	1 (0.5%)
	Cardiomyopathy	1 (0.4%)	1 (0.5%)
	Infectious		
	Infection, Fever	0 (0%)	0 (0%)
	Miscellaneous		
	Asthenia	3 (1.3%)	4 (1.9%)
	Headache, Pain	0 (0%)	0 (0%)

BV ... Bevacizumab; CAP ... Capecitabine;

study population and inclusion criteria

treatment group: capecitabine + bevacizumab

control group: capecitabine

In this multi-centre open-label trial [24, 33], 462 women with metastatic breast cancer previously treated with both an anthracycline and a taxane therapy (no more than 2 regimens) received either capecitabine alone or in combination with bevacizumab. HER2 status was not an inclusion criterion, thus 20% and 26% were HER2-positive in the control group and in the intervention group respectively. 230 women were randomly assigned to the control group with capecitabine monotherapy (an orally-administered pro-drug of 5-flourouracil), and 232 women were allocated to the intervention arm to additionally receive bevacizumab (a monoclonal antibody to vascular endothelial growth factor). To be included, patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 and a life expectancy of more than 3 months. Subjects with known HER2-positive status had to have a disease progression following trastuzumab therapy. Among the included patients a minority (about 15%) did not receive their prior anthracycline and taxane therapy for metastatic disease but as an adjuvant chemotherapy and had relapsed within 12 months. However, 93 patients (i.e. 20%) treated did not fulfil the inclusion criteria. Even though the authors mentioned that this fact did not alter outcomes, no information is provided on how these patients were distributed between the two treatment groups and the results are also missing.

20% did not fulfil inclusion criteria

similar PFS

The primary end point PFS did not show favourable results for the intervention group on combined therapy (capecitabine + bevacizumab 4.86 months vs. capecitabine alone 4.17 months; HR 0.98 (95% CI 0.77-1.25; p=0.857)). In contrast, the secondary end point ORR (as assessed by an independent review facility) was significantly improved with the addition of bevacizumab (19.8% vs. 9.1%; p =0.001), but did not translate into an improved PFS, because only a minority of subjects showed tumour responses and responses in the intervention arm were relatively short-lived. Data on complete responses (CR) and partial responses (PR) were not reported.

beneficial ORR, but no data on CRs

similar overall survival

At data cutoff 38% of all patients had died. Median overall survival was similar in the two treatment arms. The median duration of survival (DoS)

was 15.1 months for women in the intervention group and 14.5 months for patients in the control arm.

no difference in quality of life

The secondary endpoint QoL was assessed for a subset of women who have had at least one subsequent QoL assessment after baseline (176 controls, 194 combination therapy subjects). It was measured by the Trial Outcome Index (TOI; the sum of the physical well-being, functional well-being, and breast cancer–specific questions in the Functional Assessment Of Cancer Treatment - Breast questionnaire (FACT-B)). The time to deterioration in QoL (TDQ) did not differ between treatment groups (median capecitabine + bevacizumab 2.92 months vs. capecitabine alone 2.86 months; p=0.633).

SAEs: no difference

The incidence of severe adverse events (SAEs) and AEs leading to study discontinuation were similar between the treatment arms; more detailled data are not reported. These data have to be interpreted with caution due to the before mentioned fact that 20% of patients treated did not fulfil study entry criteria, but it remains unclear to which group these patients were allocated to. For example, 27 patients had received prior therapy within 21 days, 19 have had more than two regimens for metastatic disease and 10 had involvement of the central nervous system, factors that potentially influence the occurrence of AEs.

capecitabine-related toxicity not significantly affected

hand-foot syndrome may be increased

Capecitabine-related AEs occurred slightly more often in the combined intervention arm, although bevacizumab did not significantly increase the capecitabine-related toxicity. There may have been a small increase in *hand-foot syndrome* in the intervention group (grade 2: 42.4% vs. 35.8%; grade 3: 27.5% vs. 24.2%). Other common capecitabine-related AEs were *diarrhoea* (capecitabine + bevacizumab vs. capecitabine alone: grade 2: 16.2% vs. 15.8%; grade 3: 11.8% vs. 10.7%) and *stomatitis* (capecitabine + bevacizumab vs. capecitabine alone: grade 2: 7.0% vs. 5.1%; grade 3: 1.7% vs. 0%; grade 4: 0% vs. 0.5%). 29 patients (12.6%) in the capecitabine group and 28 (12.2%) in the combination group discontinued capecitabine treatment due to toxicity.

bevacizumab-related toxicity

more hypertensive events

more proteinuria and bleedings, mainly grade 1

Among the bevacizumab-related AEs hypertension, proteinuria and bleedings were the most common. Concerning *hypertension* most events in the intervention group were grade 3 AEs (capecitabine + bevacizumab vs. capecitabine alone: grade 1: 3.9% vs. 1.9%; grade 2: 1.7% vs. 0%; grade 3: 17.9% vs. 0.5%). 4 (1.7%) patients discontinued bevacizumab because of hypertension. Most occurrences of proteinuria and bleedings in the combination group were AEs of lower grade: *proteinuria* (capecitabine + bevacizumab vs. capecitabine alone: grade 1: 18.3% vs. 6.5%; grade 2: 3.1% vs. 0.9%; grade 3: 0.9% vs. 0%) and *bleedings* (capecitabine + bevacizumab vs. capecitabine alone: grade 1: 26.2% vs. 8.8%; grade 2: 2.2% vs. 1.9%; grade 3: 0.4% vs. 0.5%). There were no grade 4 haemorrhages reported. 2 (0.9%) women stopped bevacizumab treatment because of grade 3 proteinuria. Over all, more patients in the intervention arm had *congestive heart failure* or *cardiomyopathy* of grade 3 or 4 (capecitabine + bevacizumab vs. capecitabine alone: grade 3: 2.6% vs. 0%; grade 4: 0.4% vs. 0.9%). 5 (2.2%) patients were discontinued from bevacizumab due to grade 3 or 4 cardiac events.

Adverse events of grade 2 which affected more then 10% of patients in at least one treatment arm were nausea, anorexia, infections, asthenia, headache and pain. Besides, the most common events (in more than 2% of the patients) were *asthenia, thrombotic events, pain, nausea, leukopenia* and *anorexia*, all of them grade 3 (for details see Table 4).

The investigators of the study concluded that the safety profile in this heavily pretreated patient population was acceptable. Although the addition of bevacizumab to capecitabine produced a significant improvement in objective response rate, this did not increase progression-free survival.

6.2 Efficacy and safety - further studies

All phase II studies included HER2-negative patients or HER2-positive patients, previously treated with trastuzumab.

bevacizumab + vinorelbine

median TTP was 5.5 months

Results of a single arm phase II study were published in 2008 by *Burstein et al.* [25]. 56 women, who had received one or two prior chemotherapy regimens for metastatic breast cancer, were treated with bevacizumab and vinorelbine. Patients received bevacizumab 10 mg/kg every 2 weeks, and vinorelbine each week, until tumour progression or prohibitive toxicity. The ORR was 34% (95% CI: 22-48%) and median time to progression (TTP) was 5.5 months. The most common AEs were uncomplicated neutropenia (30%), nasal congestion/epistaxis (21%) and hypertension (16%). Three patients had impaired wound healing following surgical procedures.

different doses of bevacizumab

hypertension as most common AE

A phase I/II single arm trial of bevacizumab included 75 previously treated metastatic breast cancer patients [26]. They were treated with escalating doses of bevacizumab ranging from 3 mg/kg to 20 mg/kg administered intravenously every other week. The ORR was 9.3% (confirmed response rate: 6.7%). The median duration of confirmed response was 5.5 months (range, 2.3 to 13.7 months). At the final tumour assessment (day 154), 16% had stable disease or an ongoing response. Four patients discontinued study treatment because of an AE. Hypertension was reported as an AE in 22%.

bevacizumab + erlotinib

median TTP was 11 weeks

84% diarrhoea of any grade

In *Dickler et al.* [27] 38 patients with metastatic BC were enrolled and treated with erlotinib (150 mg daily) and bevacizumab (15 mg/kg every 3 weeks). All patients had one to two prior chemotherapy regimens for metastatic disease. Median TTP was 11 weeks (95% CI: 8-18 weeks). One patient achieved a PR for 52+ months. Fifteen patients had stable disease at first evaluation at 9 weeks and 4 of these patients had stable disease beyond 26 weeks. The most common AEs were diarrhoea of any grade (84%), grade 1 or 2 skin rash (76%) and hypertension (18%).

bevacizumab + metronomic chemotherapy

31.8% PR after median 7.7 months

Another single arm phase II trial [28] investigated bevacizumab in combination with metronomic chemotherapy in 24 patients with anthracycline- and taxane-refractory breast cancer. 50 mg cyclophosphamide were given daily, methotrexate 1 mg/kg every 14 days, and bevacizumab 10 mg/kg every 14 days. Trastuzumab was added in HER2-overexpressing tumours. After a median follow-up of 7.7 months CR was 0% and PR 31.8% (95% CI: 13.9-54.9%). Stable disease ≥ 24 weeks was 31.8% (95% CI: 13.9-54.9%). Median PFS was 7.5 months and OS was 13.6 months. HER2-overexpressing or high proliferative-index tumours had better 6-month PFS (75% vs. 34% in HER2-negative tumours, p = 0.043; 67% vs. 0% in Ki-67 ≥ 20% tumours, p = 0.015). Adverse effects were mild.

bevacizumab + vinorelbine as salvage therapy

ORR was 7.7%

closed early due to lack of efficacy

In 2 further phase II trials bevacizumab in combination with chemotherapy was evaluated as salvage therapy for women with metastatic BC and at least 1 prior chemotherapy regimens. In the first study [29] patients received vinorelbine (50 mg 3 times a week) and bevacizumab (10 mg/kg every 14 days). The therapy was continued until disease progression or the appearance of unacceptable toxicity. The primary endpoint was ORR. The median age of the 13 evaluable patients was 67 (range 41-80) and they were treated for a median of 5 cycles (range 1-9). The ORR was 7.7% with PR in one patient and stable disease in 7 patients. The TTP was 4.5 months. Significant toxicities were uncommon, with grade 3 toxicities occurring in one of the patients (neutropenia). The study was closed early due to lack of efficacy.

bevacizumab + paclitaxel as salvage therapy

median TTP was 4.8 months

1-year survival 55.5%

The second trial [30] investigated paclitaxel (90mg/m2 on days 1, 8 and 15) in combination with bevacizumab (10mg/kg on days 1 and 5) in pre-treated women with metastatic BC. It was second-line chemotherapy for 30% and third-line or more for 70% of patients. A total of 40 patients with median age 61 years (range 32-80) were enrolled. Two patients (5%) achieved CR and 10 patients (25%) PR. The ORR was 30% (95% CI: 15.8 - 44.2). After a median follow-up of 20.6 months, the median TTP was 4.8 months (95% CI: 1.7-7.8), the median survival 13.0 months (95% CI: 10.3 - 15.7), and the probability of 1-year survival 55.5%. Main grade 3-4 AEs were neutropenia (43%), asthenia (10%) and febrile neutropenia (5%). There was one toxic death due to sepsis.

7 Estimated costs

monthly treatment costs € 5,330.-

€ 24,000.- for treatment per person

In Austria, the manufacturer price for one 4ml-vial of Avastin® is € 414.05, and for one 16ml vial € 1,421.90, containing 25mg/ml bevacizumab [34]. The recommended dosing regimen for the treatment of metastatic breast cancer is 10 mg/kg body weight given once every 2 weeks. Assuming a mean body weight of 70 kg a dose of 700 mg bevacizumab (10 mg/kg) should be administered. Therefore, one 16ml vial and three 4ml vials are required, resulting in costs of € 2,664.05 for each injection and, accordingly, in monthly costs of about € 5,330.-. In the RIBBON-2 trial the median number of doses of bevacizumab received was nine, adding up to total costs of about € 24,000.- for a full course therapy.

8 On-going research

2 phase III studies for second-line therapy of metastatic BC

A search in the databases ClinicalTrials.gov and cinicaltrialsregister.eu yielded 2 on-going phase III trials investigating bevacizumab as second-line therapy for patients with metastatic breast cancer:

- NCT00929240 (EudraCT 2008-006872-31): Bevacizumab and capecitabine as maintenance therapy in HER2-negative metastatic BC patients. The completion of the study is planned for September 2013.
- NCT01250379 (EudraCT 2010-020998-16): Bevacizumab in combination with chemotherapy in patients with breast cancer progressing after first-line therapy with Avastin® and chemotherapy. The estimated study completion date is December 2014.

6 phase II studies for second-line therapy of metastatic BC

plenty phase III studies for other indications

In addition, 3 on-going phase II controlled trials and 3 phase II single-arm trials for bevacizumab as second-line therapy for metastatic BC and more than 70 on-going Phase III or IV studies evaluating bevacizumab in a broad variety of indications such as colorectal cancer, non-small cell lung cancer, macular degeneration or breast cancer were found.

9 Commentary

BV currently not approved for second-line treatment of metastatic BC

Bevacizumab in combination with chemotherapy has currently no market approval as a *second-line* therapy for metastatic BC, neither in the US nor in Europe, but it is approved in combination with chemotherapy by the EMA and FDA as first-line therapy for various types of advanced or metastatic cancers like colon carcinoma, non-small cell lung cancer, renal cancer and for *first-line* therapy of metastatic breast cancer. For the latter one, differences existed for the licensed indications since the FDA had limited Avastin® to HER2-*negative* patients only, whereas the EMA did not restrict bevacizumab to HER2-negative patients; its usage, however, was restricted to combination with paclitaxel only [4]. Furthermore, the FDA withdrew approval for Avastin® first-line therapy for BC due to lack of clinical benefit based on the results of the AVADO trial and the RIBBON-1 trial in 2011 [7]. After accelerated approval had been granted in 2008, updated data of these two trials did not confirm an anticipated 5.5 months increase in median PFS, as suggested by initial study results [7]. According to the FDA the toxicity profile was not tolerable for a drug, for which the clinical benefit has not been shown [7].

differences in licensed indications between EMA and FDA

FDA withdrew market application for first-line therapy in HER2-negative patients in 2011

two phase III trials for other lines of therapy

For other lines of therapy, two phase III trials assessing bevacizumab in combination with chemotherapy in previously treated patients with metastatic BC were identified [23, 24, 31-33].

no significant PFS improvement in study with heavily pre-treated women

Miller et al. [24], focused on *heavily pre-treated* women (who already had received both anthracycline and taxane regimens (up to 2)). HER status was not an inclusion criterion and therefore HER2-negative as well as HER2-positive patients were enrolled. When compared to capecitabine monotherapy, the addition of bevacizumab did not improve the primary endpoint PFS or any other reported outcome except ORR. Although various subgroup analyses on the impact of potential prognostic factors had been planned, no results were reported.

better results for ORR in bevacizumab combination arm

+2.1 months in median PFS

no improvements in other outcomes

PFS improved in TNBC and women treated with taxanes

The second phase III trial (RIBBON-2) evaluated second-line bevacizumab in combination with different chemotherapeutic regimens in women with metastatic *HER2-negative* BC. For the primary endpoint, PFS, an absolute gain of 2.1 months was shown for patients treated with bevacizumab in comparison to those with chemotherapy only. The risk of progression or death was reduced by 22% for bevacizumab + chemotherapy, yielding a statistically significant improvement in comparison to placebo + chemotherapy. Yet, for all other endpoints (ORR, OS, 1 year survival) there were no differences between the groups. Among others, subgroup analyses regarding triple-negative BC and type of chemotherapy regimen were performed (n =159), showing improvements in PFS for women with triple-negative BC and for patients who had received taxanes as chemotherapy.

different PFS results possibly depend on study population or cytotoxic agents

The trials showed different results for the primary endpoint PFS. Only in the RIBBON-2 trial, bevacizumab + chemotherapy resulted in a statistically significant prolongation of the PFS. One reason for that may be the different study populations. Overall, women in the trial by Miller et al. were more heavily pre-treated, had more heterogeneous disease (e. g. HER2-status) and poorer prognoses. At study entry, about 40% of the patients had at least 2 prior chemotherapies for metastatic BC, while in the RIBBON-2 trial all participants had received only one prior chemotherapy. The different PFS results may also be caused by the cytotoxic agents used for the combination with bevacizumab. Results from subgroup analyses in the RIBBON-2 trial suggest that the combination with taxanes was primarily responsible for the favourable effects on PFS. More than 40% of the women in the RIBBON-2 trial received a taxane regimen and just 20% capecitabine, which was the only cytotoxic agent used in the Miller trial.

AE comparable in heavily pre-treated patients (Miller et al.), more frequent in RIBBON-2

In terms of adverse events, *Miller et al.* found similar results between the two treatment groups in heavily pre-treated patients, but as already mentioned earlier, about 20% of patients did not fulfil the initial eligibility criteria and it remains unclear how these patients were distributed between the two arms, potentially influencing these results. In the RIBBON-2 study, no difference in treatment-emergent deaths was observed, but selected AEs≥3 (I 35% vs C 23%) and SAEs (I 25% vs C 18%) occurred more often in the combination arm than in the chemotherapy only arm. Consequently, AEs leading to treatment discontinuation were more frequent in the bevacizumab group (I 13% vs C 7%).

inadequate data on QoL

Besides efficacy outcomes, therapy for metastatic BC aims at improving QoL which was not addressed adequately in both trials. Until now, the only result reported by *Miller et al.* [24] was the time to deterioration in QoL with no difference between the groups. A separate report with more detailled information on QoL announced by the authors has not been published yet. QoL has not at all been addressed in the RIBBON-2 trial.

In summary, an increase in PFS by 2.1 months, a higher incidence in AEs and the considerable costs of bevacizumab therapy [35], challenge even off-label use for the second-line therapy of HER2-negative metastatic breast cancer. According to the British "National Institute for Health and Clinical Excellence" (NICE), a planned appraisal of bevacizumab for this indication [36] was suspended in November 2011, because NICE was informed by the manufacturer that application for a centralised marketing authorisation was not planned.

NICE: second-line appraisal suspended, because centralised market application not planned by manufacturer

However, considering the communication between the manufacturer and the FDA [7], it might be possible that the manufacturer will apply for approval of more specific indications, e. g. for a subset of patients like women with triple negative BC, since the RIBBON-2 trial [31] reported a trend towards improved overall survival in these patients. In addition, several trials investigating bevacizumab in triple negative BC patients are registered at ClinicalTrials.gov. Nevertheless, according to the FDA the available evidence does also not demonstrate that Avastin® would confer a meaningful clinical benefit in the light of its risks in this subgroup.

applications for approval in subsets of patients conceivable

Therefore, further research should not only investigate the clinical safety and efficacy of bevacizumab, preferably in terms of OS, but should also clarify if biological markers have to be considered prior to treatment administration. As therapy for metastatic BC usually aims at symptom palliation, especially more information on patient relevant outcomes like QoL is needed.

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