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1 Drug description

Generic/Brand name/ATC code:

Bevacizumab/Avastin®/L01XC07

Developer/Company:

Roche Registration Ltd.

Description:

Bevacizumab (Avastin®) is a recombinant monoclonal antibody that binds to vascular endothelial growth factor (VEGF). By inhibiting VEGF receptor binding, bevacizumab prevents the growth and maintenance of tumour blood vessels [1].

bevacizumab inhibits growth and maintenance of tumour blood vessels

Bevacizumab is used for the treatment of different types of cancer and in various combinations with other drugs. 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 leukoencephalopathy syndrome and neutropenia [2, 3].

In patients with metastatic breast cancer, the recommended dose of bevacizumab is 10 mg/kg given once every two weeks or 15 mg/kg given once every three weeks as an intravenous (IV) infusion; treatment should be continued until progression of the underlying disease or until unacceptable toxicity [3].

intravenous administration

2 Indication

Bevacizumab therapy for patients with human epidermal growth factor 2 (HER2)-negative, locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy.

second-line treatment of locally recurrent or metastatic breast cancer

3 Current regulatory status

To date, neither the EMA nor the FDA have granted marketing authorisation for bevacizumab as second-line therapy for HER2-negative, locally recurrent or metastatic breast cancer that has progressed after first-line treatment with bevacizumab plus chemotherapy.

not approved for second-line treatment of breast cancer by the EMA

The EMA approved Avastin® for the following indications [3]:

- treatment of adult patients with metastatic carcinoma of the colon or rectum (in combination with fluoropyrimidine-based chemotherapy)
- first-line treatment of adult patients with metastatic breast cancer (in combination with paclitaxel)
- first-line treatment of adult patients with metastatic breast cancer in combination with capecitabine (when other chemotherapy options including taxanes or anthracyclines are not considered appropriate)
- first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology (in addition to platinum-based chemotherapy)
- first-line treatment of adult patients with advanced and/or metastatic renal cell cancer (in combination with interferon alfa-2a)
- front-line treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (in combination with carboplatin and paclitaxel)
- treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents (in combination with carboplatin and gemcitabine)
- treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents (in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin)
- in February 2015, the Committee for Medicinal Products for Human Use (CHMP) adopted a new indication: bevacizumab, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix [4].

In December 2014, the EMA granted orphan designation for bevacizumab for the treatment of hereditary haemorrhagic telangiectasia [5].

not approved for breast cancer indication by the FDA

In the US, the FDA approved Avastin® for the treatment of [6]:

- metastatic colorectal cancer, with intravenous 5-fluorouracil-based chemotherapy (first- or second-line treatment)
- metastatic colorectal cancer, with fluoropyrimidine-, irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy (for second-line treatment) in patients who have progressed on a first-line Avastin®-containing regimen

- non-squamous non-small cell lung cancer, with carboplatin and paclitaxel (for first-line treatment) in patients with 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
- cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease
- platinum-resistant, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan.

FDA revoked accelerated approval of breast cancer indication

In February 2008, the FDA granted accelerated approval for Avastin® for the treatment of HER2-negative metastatic breast cancer (in combination with paclitaxel in patients who have not received chemotherapy) [7]. In November 2011, the approval was revoked; the decision was based on a lack of benefit considering delay in the growth of tumours that would justify the potential risks. Furthermore, there was no evidence that Avastin® would lengthen the life of women with breast cancer or would improve their quality of life [8].

4 Burden of disease

invasive ductal carcinoma is the most common form of breast cancer

Breast cancer develops in the tissues of the breast. Non-invasive breast cancer (also termed "carcinoma in situ") does not spread by metastases; the most common type is ductal carcinoma in situ (DCIS). Invasive breast cancer can potentially spread outside the breast; the most common type is ductal carcinoma. Less common types of breast cancer are invasive lobular breast cancer, inflammatory breast cancer and Paget's disease of the breast [9].

most common sites of metastasis: bones, liver, lungs and brain

Locally recurrent breast cancer is defined as cancer that returns to the tissues near the original site or scar (chest, breast or skin). It develops when cancer cells, which remained in the local area despite treatment, start to grow again. Metastatic breast cancer, also termed secondary or advanced breast cancer, develops when cells of the primary tumour spread through the lymphatic or blood system to other sites of the body. Most common sites of metastasis in breast cancer are the bones, liver, lungs and brain [10].

most common malignancy in women in Austria

median age at diagnosis: 61 years

In Austria, breast cancer is the most common malignancy in women. In 2011, 5,423 women in Austria were newly diagnosed with breast cancer and the incidence rate was 76.2 (per 100,000 women per year). The mortality rate in 2011 was 15.9 per 100,000 women [11]. Breast cancer is most common in middle-aged and older women; median age at diagnosis is 61 years. The relative[1] 5-year survival rate for patients with breast cancer is 89.4% [12]. Approximately 5–10% of breast cancer patients have metastasis at the time of diagnosis; approximately one-fifth of these patients will survive 5 years [13].

[1] The relative survival compares the survival of patients diagnosed with cancer with the survival of people in the general population who are the same age, race, and sex and who have not been diagnosed with cancer.

abnormal mammograms often indicate breast cancer diagnosis

In countries where patients have access to breast screening programmes, abnormal mammograms indicate the diagnosis of breast cancer more often than the occurrence of symptoms [14]. The most common symptom is a lump or mass in the breast (which is often painless); less common symptoms are persistent changes to the breast (e.g. thickening, swelling, distortion, tenderness, skin irritation, redness, scaliness) or to the mammilla (ulceration, retraction, or spontaneous discharge) [15].

symptoms of metastatic disease depend on the organs involved

Symptoms of more advanced locoregional disease include axillary adenopathy or skin findings such as erythema, thickening, or dimpling of the overlying skin (peau d'orange). In case of metastasis, symptoms depend on the affected organs (e.g. bone – back or leg pain, liver – abdominal pain, nausea, jaundice, or lungs – shortness of breath or cough) [14].

numerous risk factors

There are numerous risk factors associated with breast cancer. Potentially modifiable factors are weight gain after the age of 18 and/or being overweight or obese (for postmenopausal breast cancer), the use of menopausal hormone therapy (combined estrogen and progestin), physical inactivity, and alcohol consumption. There are indications that long-term, heavy smoking may also increase the risk for breast cancer, particularly among women who start smoking before their first pregnancy. Furthermore, shift work (particularly at night) may be associated with an increased breast cancer risk. Non-modifiable risk factors include high breast tissue density, high bone mineral density, type 2 diabetes mellitus, certain benign breast conditions (e.g. atypical hyperplasia), ductal and lobular carcinoma in situ. Prior high-dose radiation to the chest for cancer treatment at a young age also increases breast cancer risk. Reproductive risk-increasing factors are a long menstrual history, recent use of oral contraceptives or certain contraceptive injections, never having children, and having one's first child after the age of 30 [15].

abnormal mammogram: further examination by imaging procedures

The majority of breast cancer patients are diagnosed by an abnormal mammogram. These patients need to be further examined by means of magnification views, spot compression views and/or targeted ultrasonography to establish the need for tissue sampling or biopsy. In case of clinical suspicion, the lesion should be biopsied regardless of image findings (as 10–15% of such lesions can be mammographically occult) [16].

hormone receptor status needs to be determined

After the diagnosis of breast cancer (defined by the presence of malignant epithelial cells), the hormone receptor status needs to be determined. Patients must be tested for:

- estrogen receptor (ER) and progesterone receptor (PR) expression: ER and PR are prognostic factors for invasive breast cancers; patients who are ER- and/or PR-positive are eligible for neoadjuvant or adjuvant endocrine therapy
- overexpression of HER2 receptors: 20% of patients are HER2-positive and will benefit from HER2-directed therapy [14].

Patients with triple-negative breast cancer (defined by a lack of HER2 overexpression or amplification and low ER and PR expression) typically have a poor prognosis. There is no standard therapy for these patients, and treatment options are limited [17].

TNM staging system

Breast cancer is staged according to the TNM (tumour, nodes and metastases) system of the American Joint Committee on Cancer and the Union for International Cancer Control (AJCC-UICC) [16].

5 Current treatment

ESMO recommendations for locally recurrent breast cancer

In patients with isolated, locally recurrent breast cancer, cure is the main therapeutic target. Therefore, the European Society for Medical Oncology (ESMO) recommends [13]:

- the complete excision of the recurrent tumour (if feasible); in patients with prior breast-conserving surgery, a mastectomy is recommended (III, A)[2]
- full-dose radiotherapy to chest wall and regional lymph node areas in patients not previously irradiated (III, A)
- in patients previously irradiated, re-irradiation to limited areas of the chest wall (considering the duration of the radiation-free period, intensity of existing late radiation effects and the risk of additional locoregional relapse (III, B)
- the value of "secondary" or "pseudo-adjuvant" systemic treatment is not supported by much evidence, the role of chemotherapy in this setting is assessed in ongoing randomised studies (II, B)
- "pseudo-adjuvant" endocrine therapy is a reasonable option regarding the expected benefit and low toxicity (II, B)
- according to expert's opinion, "pseudo-adjuvant" trastuzumab is also acceptable (particularly in patients without prior trastuzumab).

In patients with isolated, locally recurrent breast cancer who are not suitable for local treatment with curative intent, e.g. patients with inoperable or previously irradiated tumours, systemic therapies are the mainstay of treatment. The decision for the appropriate systemic therapy is made considering tumour biology, previous systemic treatments, duration of disease-free interval, patient co-morbidities and preferences [13].

metastatic breast cancer is incurable

Metastatic breast cancer is an incurable disease [18]. Systemic treatment intends to prolong survival and to improve the quality of life of affected patients [19].

ESMO recommendations for advanced breast cancer

For the treatment of patients with ER-positive, HER2-negative advanced breast cancer, the ESMO gives the following recommendations [18]:

- endocrine therapy is the preferred treatment option for hormone receptor-positive disease, even in patients with visceral disease (unless there is endocrine resistance or fast response is needed); LoE: IA[3]
- treatment of premenopausal women: ovarian suppression/ablation combined with additional endocrine therapy; LoE: IA
- tamoxifen should be the additional endocrine agent (unless tamoxifen resistance); LoE: IB
- aromatase inhibitors are an option, invariably require ovarian suppression/ablation

[2] Levels of evidence [I–V] and grades of recommendation [A–E] as used by the ESMO.

[3] Levels of evidence (LoE): IA = strong recommendation, high-quality evidence; IB = strong recommendation, moderate-quality evidence; IC = strong recommendation, low-quality evidence.

- optimal post-aromatase inhibitor treatment is uncertain; tamoxifen, another aromatase inhibitor (with different mechanism of action), high-dose (HD) fulvestrant, megestrol acetate and everolimus plus aromatase inhibitor are available options; LoE: IA
- maintenance endocrine therapy (after chemotherapy) is a reasonable option to maintain the benefit (method not assessed in randomised trials); LoE: IC
- concomitant chemotherapy and endocrine therapy should not be applied outside of a clinical trial (this combination has not shown a survival benefit); LoE: IB
- treatment of postmenopausal women: depending on type and duration of adjuvant endocrine therapy, preferred first-line endocrine therapy is an aromatase inhibitor or tamoxifen; LoE: IA
- fulvestrant HD is also an option; LoE: IB
- for some postmenopausal women with disease progression after a non-steroidal aromatase inhibitor, the addition of everolimus to an aromatase inhibitor is a valid treatment option; however, the toxicities associated with this therapy need to be weighed against the benefits of significant PFS prolongation and survival prolongation (which is not statistically significant).

The American Society for Clinical Oncology (ASCO) [20] also recommends endocrine therapy as the standard first-line treatment in women with hormone receptor-positive, advanced or metastatic breast cancer[4], as it provides less toxicity and better quality of life when compared with chemotherapy.

treatment options for bone metastasis

Patients with recurrent or metastatic breast cancer at diagnosis are stratified according to the presence of bone metastasis [19]. In women with bone metastasis, the administration of intravenous bisphosphonates (in addition to chemotherapy or endocrine therapy) is a palliative care measure without proven impact on overall survival. Patients' benefits from bisphosphonate treatment are fewer skeletal-related events, fewer pathologic fractures and less need for radiation therapy and surgery to treat bone pain. Denosumab may me another treatment option for patients with metastatic breast cancer to bone; the agent was shown to significantly delay time to the first skeletal-related event in a single randomised trial. However, the optimal duration of denosumab treatment and long-term risks are unknown [19].

[4] Except for immediately life-threatening disease or concern regarding endocrine resistance.

6 Evidence

A literature search was conducted on 20 February 2015 in four databases (The Cochrane Library, CRD Database, Embase, Medline). Search terms were "Bevacizumab", "Avastin", "Altuzan", "nsc 704865", "breast cancer", "breast neoplasms", "epidermal growth factor receptor 2", "HER2", "metastasis". Also, when contacted for any further evidence, the manufacturer submitted 4 references.

640 references in total, 2 phase III studies were included

Overall, 640 references were identified. Included in this report are:

- 1 phase III study, comparing bevacizumab plus chemotherapy versus chemotherapy alone as second-line treatment for patients with HER2-negative locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy (TANIA trial) [21]
- 1 randomised, open-label phase III trial assessing maintenance capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-ngeative metastatic breast cancer (IMELDA trial) [22].

6.1 Efficacy and safety – phase III studies

Table 1: Summary of efficacy

Study title Bevacizumab plus chemotherapy versus chemotherapy alone as second-line treatment for patients with HER2-negative locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy (TANIA): an open-label, randomised phase III trial [21].			
Study identifier	NCT01250379, EudraCT Number 2010-020998-16		
Design	Open-label, parallel-group, randomised (1:1 ratio), multicentre (118 centres in 12 countries), ongoing		
	Duration	*Enrolment:* 2011-02-17 to 2013-04-03 *Median follow-up:* 16.1 months (combination group), 15.9 months (chemotherapy-alone group) *Cut-off dates for analyses: 2013-12-20 (primary analysis of PFS), 2015-04 (*final data collection date for primary outcome measure)	
Hypothesis	Superiority For the primary analysis, second-line PFS events were required in 384 of 488 patients for 80% power with a two-sided ∝ of 0.05. Progression-free survival was compared between treatment groups with a two-sided log-rank test, stratified by stratification factors. Median progression-free survival was estimated by the Kaplan-Meier method. A stratified Cox proportional hazards model was used to estimate HRs and 95% CIs.		
Funding	F Hoffmann-La Roche		
Treatment groups	Intervention (n=247)	Second-line single-agent chemotherapy plus bevacizumab (15 mg/kg every 3 weeks or 10 mg/kg every 2 weeks)	
	Control (n=247)	Second-line single-agent chemotherapy at the investigators' discretion ((nanoparticle albumin-bound) paclitaxel, docetaxel, capecitabine, gemcitabine, ((non-)pegylated liposomal) doxorubicin, epirubicin, vinorelbine, cyclophosphamide, ixabepilone)	
Endpoints and definitions	PFS (primary outcome)	PFS	Time from randomisation to disease progression or death on second-line treatment
	PFS in stratification subgroups	-	Assessed in prespecified stratification subgroups (hormone receptor status, first-line PFS, selected second-line chemotherapy, LDH concentration)
	PFS	-	From randomisation until disease progression or death on third-line therapy

Endpoints and definitions *(continuation)*	Objective response rate	ORR	Defined as complete or partial tumour response. Tumour assessment was based on limited Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1; no independent review of tumour assessment was done
	Overall survival	OS	From randomisation to death from any cause
	1-year overall survival	-	Defined as the number of patients alive 1 year after randomisation
	Safety	-	Assessed using Common Terminology Criteria for Adverse Events (version 4.0)
	Patient-reported outcomes	-	Assessed with the Functional Assessment of Cancer Therapy – Breast questionnaire (FACT-B)

Results and analysis

Analysis description	Efficacy analysed in the intention-to-treat population Safety analysed in all patients who received at least one dose of study therapy (bevacizumab or chemotherapy, safety population)			
Analysis population	Inclusion	❖ Age ≥ 18 years ❖ HER2-negative, measurable or non-measurable, locally recurrent or metastatic breast cancer ❖ Disease had to have progressed (according to investigator assessment) after 12 weeks or more of first-line bevacizumab plus chemotherapy for locally recurrent or metastatic breast cancer ❖ Maintenance bevacizumab, maintenance endocrine therapy, or both, before enrolment was allowed ❖ ECOG performance status 0–2 ❖ An estimated life expectancy of 12 weeks or more		
	Exclusion	❖ Previous first-line anti-angiogenic therapy (except bevacizumab) for locally recurrent or metastatic breast cancer ❖ Positive or unknown HER2 status ❖ Inadequately controlled hypertension ❖ A history of nephrotic syndrome, hypertensive crisis, hypertensive encephalopathy, bleeding diathesis, clinically relevant coagulopathy, or grade-3 or -4 venous thromboembolism ❖ A history of myocardial infarction, unstable angina, significant vascular disease, gastrointestinal perforation, abdominal fistula, intraabdominal abscess, or active gastrointestinal bleeding within 6 months preceding study treatment ❖ Known CNS disease (except treated brain metastases)		
	Characteristics		Chemotherapy + bevacizumab	Chemotherapy alone
		Median age (range), years	56 (24–81)	54 (30–77)
		Hormone receptor status, % Triple-negative ER or PgR-positive or both positive	 20 80	 23 76
		Locally recurrent or metastatic disease at first diagnosis, %	15	20
		Disease-free interval, % ≤ 12 months ≤ 24 months	 7 21	 10 23
		Previous (neo)adjuvant chemotherapy, % Taxane Anthracycline Other	 40 63 66	 39 56 58
		Previous (neo)adjuvant bevacizumab, %	2	1
		Previous endocrine therapy for locally recurrent/metastatic breast cancer, %	51	45
		Timing of first-line progression in relation to first-line chemotherapy plus bevacizumab, % During bevacizumab After bevacizumab Unknown/missing/other	 18 79 2	 19 80 <1

Analysis population *(continuation)*	Characteristics *(continuation)*	Invasive ductal, %	81	83
		Invasive lobular, %	15	12
		Metastatic organ sites at baseline, % Visceral Liver Lung ≥ 3 metastatic organ sites Bone only	 75 58 28 32 6	 77 61 30 36 6
		First-line chemotherapy with bevacizumab, % Paclitaxel Docetaxel Capecitabine	 74 13 16	 73 11 19
		First-line PFS Median, months (IQR) < 6 months (%) ≥ 6 months (%)	 14.9 (9.2–24.3) 10 89	 14.1 (8.5–23.3) 13 86
		History of hypertension, %	57	47
		Bevacizumab-free interval before study therapy, % ≤ 6 weeks > 6 weeks Missing	 60 40 0	 67 33 <1
		LDH concentration, % ≤ 1.5 x ULN > 1.5 x ULN	 85 15	 84 16

Descriptive statistics and estimated variability	Treatment group	*Intervention (chemotherapy plus bevacizumab)*	*Control (chemotherapy alone)*
	Number of subjects	N=247	N=247
	PFS Median (95% CI), months	6.3 (5.4–7.2)	4.2 (3.9–4.7)
	Objective response, number (%) CR PR SD PD	38 (21) 1 (<1) 37 (20) 89 (49) 44 (24)	31 (17) 2 (1) 29 (16) 62 (34) 76 (41)
	Duration of response median (95% CI), months	8.3 (6.1–10.3)	10.6 (4.4–16.7)
Effect estimate per comparison	*Comparison groups*		*Chemotherapy + bevacizumab vs. Chemotherapy alone*
	PFS	Stratified HR	0.75
		95% CI	0.61–0.93
		P value	0.0068
		Unstratified HR	0.77
		95% CI	0.63–0.93
	ORR	Absolute difference, %	4.1
		95% CI	-4.2–12.4
		P value	0.35

Abbreviations: CI =confidence interval, CNS = central nervous system, CR = complete response, EGOC = Eastern Cooperative Oncology Group, ER = estrogen receptor, HER2 = human epidermal growth factor 2, HR = hazard ratio, IQR = inter-quartile range, LHD = lactate dehydrogenase, OR = objective response, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PgR = progesterone receptor, PR = partial response, SD = stable disease, ULN = upper limit of normal

Table 2: Most frequent adverse events[5]

Adverse Event (according to CTCAE version 4.0)	**Chemotherapy plus bevacizumab (n=245)**				**Chemotherapy alone (n=238)**			
	Grades 1–2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Grades 1–2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Neutropenia	8 (3)	17 (7)	12 (5)	0	13 (5)	13 (5)	7 (3)	0
Anaemia	11 (4)	5 (2)	0	0	5 (2)	2 (<1)	0	0
Thrombocytopenia	7 (3)	2 (<1)	3 (1)	0	1 (<1)	1 (<1)	0	0
Febrile Neutropenia	0	4 (2)	4 (2)	0	0	0	4 (2)	0
Proteinuria	96 (39)	17 (7)	0	0	51 (21)	1 (<1)	0	0
Hypertension	36 (15)	33 (13)	0	0	25 (11)	17 (7)	0	0
Haemorrhage	19 (8)	0	0	0	6 (3)	0	1 (<1)	0
Hand-foot syndrome	35 (14)	27 (11)	0	0	25 (11)	25 (11)	0	0
Fatigue	24 (10)	8 (3)	0	0	20 (8)	8 (3)	0	0
Mucosal inflammation	13 (5)	4 (2)	0	0	4 (2)	1 (<1)	0	0
Diarrhoea	19 (8)	7 (3)	0	0	20 (8)	8 (3)	0	0
Nausea	22 (9)	4 (2)	0	0	18 (8)	6 (3)	0	0
Vomiting	9 (4)	3 (1)	0	0	18 (8)	3 (1)	0	0
Dyspnoea	4 (2)	0	0	0	2 (<1)	4 (2)	1 (<1)	0
Pulmonary embolism	1 (<1)	3 (1)	2 (<1)	0	0	4 (2)	0	0
Increased GGT	0	8 (3)	2 (<1)	0	0	5 (2)	1 (<1)	0
Increased AST	2 (1)	5 (2)	0	0	1 (<1)	2 (<1)	0	0
Hyponatraemia	1 (<1)	4 (2)	1 (<1)	0	1 (<1)	1 (<1)	0	0

Abbreviations: AE = adverse event, AST = aspartate aminotransferase, CTC = Common Terminology Criteria for Adverse Events, GGT = gamma glutamyltransferase

Table 3: Adverse events of special interest for bevacizumab (second-line safety population)

Adverse events (according to CTCAE version 4.0)	**Chemotherapy plus bevacizumab (n=245)**		**Chemotherapy alone (n=238)**	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Hypertension	69 (28)	33 (13)	42 (18)	17 (7)
Bleeding	32 (13)	1 (<1)	14 (6)	4 (2)
Proteinuria	113 (46)	17 (7)	52 (22)	1 (<1)
Thromboembolic event Venous Arterial	21 (9) 21 (9) 0	8 (3) 8 (3) 0	11 (5) 7 (3) 4 (2)	8 (3) 5 (2) 3 (1)
Febrile neutropenia	8 (3)	8 (3)	4 (2)	4 (2)
Congestive heart failure	5 (2)	5 (2)	1 (<1)	1 (<1)
Wound-healing complication	4 (2)	2 (<1)	1 (<1)	0
Fistula or abscess	1 (<1)	0	2 (<1)	0
Gastrointestinal perforation	2 (<1)	1 (<1)	0	0

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events

[5] AEs occurring at any grade in more than 5% of patients or grade 3 or greater in more than 2% of patients in the second-line therapy safety population.

efficacy and safety of second-line chemotherapy plus bevacizumab was assessed in 494 patients

The TANIA trial [21] assesses the effect of second-line bevacizumab after disease progression on or after first-line bevacizumab plus chemotherapy in locally recurrent or metastatic HER2-negative breast cancer. This open-label, parallel-group, randomised multicentre phase III trial was ongoing until April 2015. A total of 494 patients were randomly assigned (1:1) to receive second-line single-agent chemotherapy at the investigators' discretion either alone (n=247) or with bevacizumab (n=247). Neither patients nor investigators were masked to treatment assignment. The patients were stratified according to hormone receptor status, first-line progression-free survival (PFS), selected second-line chemotherapy and lactate dehydrogenase concentration (LDH). Neither patients nor investigators were masked to treatment assignment.

all patients had disease progression after first-line bevacizumab plus chemotherapy

The patients had a median age of 56 and 54 years in the chemotherapy-plus-bevacizumab group and in the chemotherapy-alone group respectively. 32% in the combination arm and 36% of patients in the chemotherapy-alone arm had ≥ 3 metastatic organ sites and 20% and 23% had triple-negative disease respectively, and in both groups the majority had hormone receptor-positive disease (>76%).

the majority of patients received paclitaxel (plus bevacizumab) as first-line therapy

Previous (neo)adjuvant bevacizumab was administered in 2% of patients in the combination arm and in 1% of patients in the chemotherapy-alone arm. But all patients had experienced disease progression after 12 weeks or more of first-line bevacizumab plus chemotherapy. About 80% of patients progressed after first-line bevacizumab therapy, and 67% in the chemotherapy-alone group in comparison to 60% in the combination arm had a bevacizumab-free interval of ≤ 6 weeks. (Neo)adjuvant chemotherapy consisted of a taxane in 40%/39% of patients, 63%/56% of patients received anthracycline, 66%/58% of patients were treated with other agents in the chemotherapy-plus-bevacizumab group and the chemotherapy-alone group respectively. 51% of patients in the chemotherapy-plus-bevacizumab group and 45% in the chemotherapy-alone group had received previous endocrine therapy for locally recurrent or metastatic breast cancer. In the combination arm, 74% of patients had received first-line chemotherapy with bevacizumab with paclitaxel, 13% with docetaxel and 16% with capecitabine. In the chemotherapy-alone group, first-line chemotherapy with bevacizumab was administered with paclitaxel in 73% of patients, with docetaxel in 11% and with capecitabine in 19% of patients.

second-line chemotherapy with/without bevacizumab

From prespecified standard options, the investigators chose single-agent chemotherapy for each patient: paclitaxel (IV), nanoparticle albumin-bound paclitaxel (IV), docetaxel (IV), capecitabine (orally), gemcitabine (IV), pegylated liposomal doxorubicin (IV), non-pegylated liposomal doxorubicin (IV), doxorubicin (IV), epirubicin (IV), vinorelbine (IV or orally), cyclophosphamide (IV or orally) or ixabepilone (IV). Second-line chemotherapy was continued until disease progression, unacceptable toxicity or patient withdrawal. Depending on the selected chemotherapy regimen, patients received bevacizumab at a dosage of 15 mg/kg every three weeks or 10 mg/kg every two weeks. In case of toxicity, dose reduction or dose modifications were not allowed.

median duration of bevacizumab treatment was 4.5 months

Median follow-up was 16.1 months in the chemotherapy-plus-bevacizumab group and 15.9 months in the chemotherapy-alone group, measured at the data cut-off for the primary analysis of PFS. The median duration of second-line chemotherapy was 4.4 months in the combination group versus 3.9 months in the chemotherapy-alone group. The median duration of bevacizumab treatment was 4.5 months and the median duration of single-agent bevacizumab after termination of chemotherapy was 1.7 months. At the time of data cut-off, second-line therapy was ongoing in 7% of patients of each group; 5% (com-

bination group)/6% (chemotherapy-alone group) of patients changed chemotherapy regimen before disease progression. 12% of combination group patients, compared to 7% of chemotherapy-alone group patients switched to endocrine treatment during second-line therapy before disease progression.

PFS was significantly longer in patients of combination group

The primary endpoint of the TANIA trial was second-line PFS. Median PFS was 6.3 months (95% CI 5.4–7.2)[6] in the chemotherapy-plus-bevacizumab group versus 4.2 months (3.9–4.7) in the chemotherapy-alone group. Stratified hazard ratio (HR) was 0.75 (95% CI 0.61–0.93), two-sided, stratified log-rank p=0.0068; unstratified HR was 0.77 (95% CI 0.63–0.93). According to the authors (data was not provided), analyses of HRs in predefined exploratory subgroups were very similar to the HR in the intention-to-treat population, except for some of the smallest subgroups including less than 50 patients with wide 95% CIs.

Rates of objective responses to second-line therapy (a secondary endpoint) were 17% in the chemotherapy-alone group and 21% in the chemotherapy-plus-bevacizumab group (4.1% absolute difference, 95% CI -4.2–12.4, p=0.35).

4.1% absolute difference in objective response between the groups

In the combination arm, < 1% of patients achieved complete response and 20% achieved partial response. Among the chemotherapy-alone group patients, 1% of patients achieved complete, and 16% partial response. 40% of patients receiving chemotherapy plus bevacizumab and 41% of patients receiving chemotherapy alone had died at the time of data cut-off; overall survival (OS) results are immature. The most common cause of death in both groups was disease progression or breast cancer.

AEs of grade 3 or worse in 59% (combination group) and 46% (chemotherapy-alone group)

Adverse events (AEs) of grade 3 or worse occurred in 59% of combination-group patients and in 46% of patients who received chemotherapy alone. Hypertension of grade ≥ 3 was reported from 13% (combination group) vs. 7% (chemotherapy-alone group) of patients; proteinuria of grade ≥ 3 occurred in 7% (combination group) vs. ≤ 1% (chemotherapy-alone group) of patients. The death of 2% of patients in each group (during second-line therapy and beyond) in the safety population (n=438) was attributed to AEs; causes of death were pancreatitis, cerebrovascular disorder, cardiac failure, cardiotoxicity and sudden death. Serious AEs occurred in 25% of chemotherapy-plus-bevacizumab group patients compared to 18% of chemotherapy-alone patients.

Due to the occurrence of AEs (most commonly proteinuria, venous and pulmonary embolism), 18% of patients discontinued second-line bevacizumab treatment. 16% of combination group patients versus 8% of chemotherapy-alone group patients discontinued chemotherapy because of AEs. Chemotherapy doses were reduced in 47% (combination group) and 37% (chemotherapy-alone group) of patients respectively.

[6] CI = confidence interval

6.2 Efficacy and safety – further studies

phase III trial comparing maintenance capecitabine with or without bevacizumab

The IMELDA trial [22], a randomised, open-label, **phase III trial**, compared the administration of *maintenance* capecitabine and bevacizumab versus bevacizumab alone after initial first-line bevacizumab and docetaxel. 284 patients were eligible, having HER2-negative metastatic breast cancer with at least one measurable lesion (according to Response Evaluation Criteria in Solid Tumours, RECIST, version 1.0). Included patients had a median age of 54 (bevacizumab only) and 49 (bevacizumab and capecitabine) years respectively. Hormone receptor status was triple negative in 22% of patients in the bevacizumab-only group and 27% in bevacizumab-and-capecitabine group patients. 78% of bevacizumab-only patients and 73% of bevacizumab-and-capecitabine patients were ER- or PR-positive or both. 57% of patients in the bevacizumab-only group and 47% of patients in the bevacizumab-plus-capecitabine group had ≥ 3 metastatic organs at baseline.

initial phase: bevacizumab plus docetaxel

maintenance phase: bevacizumab alone or bevacizumab plus capecitabine

Initially, patients received up to six cycles of bevacizumab (15 mg/kg) and docetaxel (75–100 mg/m^2) on day 1 every three weeks. Patients who achieved stable disease or a complete or partial response were randomly assigned to receive bevacizumab alone (15 mg/kg, once every three weeks) or bevacizumab at the same dosage combined with capecitabine (1000 mg/m^2 twice daily on days 1–14, every three weeks). The median treatment duration in the maintenance phase was 3.5 months in the bevacizumab only-group and 8.3 months in patients who received bevacizumab plus capecitabine. Patients received a median of 6 cycles of bevacizumab (bevacizumab-only group) compared to a median of 12 cycles (bevacizumab-plus-capecitabine group).

PFS significantly improved in patients receiving bevacizumab plus capecitabine

median OS prolonged in combination group, but no significance

In patients of the bevacizumab-plus-capecitabine group, PFS was significantly improved compared to PFS in patients of the bevacizumab-only group: median 11.9 months (95% CI 9.8–15.4) versus 4.3 months (95% CI 3.9–6.8), stratified HR 0.38, 95% CI 0.27–0.55, two-sided log-rank $p < 0.0001$; results were consistent with those for time to progression. Median OS was 23.7 months (bevacizumab-only group) versus 39.0 months (bevacizumab-plus-capecitabine group), resulting in a stratified HR of 0.43, 95% CI 0.26–0.69, two-sided log-rank $p = 0.0003$. 1-year OS was 72% for patients receiving bevacizumab only compared to 90% of patients receiving bevacizumab plus capecitabine. Objective response was achieved by 77% (bevacizumab only) and 86% (bevacizumab plus capecitabine) of patients respectively (difference: 9.2 percentage points, 95% CI -2.1–20.3, p=0.11). Clinical benefit was reported in 98% of patients in the bevacizumab-only group and 99% in the bevacizumab-plus-capecitabine group.

higher incidence of grade 3 or worse AEs in combination group

During the initial phase, AEs occurred in 50% (grade 3), 15% (grade 4) and 2% (grade 5) of patients, the most common grade being 3 or worse AEs were haematological. During the maintenance phase, grade 3 or worse AEs occurred in 27% (bevacizumab only) and 49% (bevacizumab plus capecitabine) of patients respectively. Due to an AE, one patient in each group died during the maintenance phase, caused by acute coronary syndrome (bevacizumab-only group) and renal failure (bevacizumab-plus-capecitabine group). Serious AEs occurred in 8% of patients in the bevacizumab-only group and in 11% of patients in the bevacizumab-plus-capecitabine group.

It should be noted that recruitment for this study was terminated prematurely. Some centres stopped accrual or withdrew patients from study treatment as a result of the withdrawn approval of bevacizumab-plus-docetaxel combination therapy.

7 Estimated costs

one dose of Avastin® costs approx. € 2,664

In patients with metastatic breast cancer, the recommended dose of bevacizumab is 10 mg/kg IV given once every two weeks or 15 mg/kg IV given once every three weeks [3]. Bevacizumab (Avastin®) is available in vials of 4 ml (25 mg/ml) at € 414.05 and vials of 16 ml (25 mg/ml) at € 1,421.90 [23]. Assuming a dosage schedule of 10 mg/kg and an average body weight of 70 kg, costs for one dose of bevacizumab are approximately € 2,664.05 (using 1 vial of 16 ml and 3 vials of 4 ml).

costs for ten treatment cycles: approx. € 26,665

The median duration of patients in the TANIA trial [21] who received chemotherapy plus bevacizumab was 4.5 months. In patients participating in the IMELDA trial [22], bevacizumab was administered at a median of 6 cycles (maintenance phase, bevacizumab-only group). Assuming a treatment duration of 20 weeks with a total of 10 intravenous infusions of bevacizumab, costs for bevacizumab treatment are approximately € 26,665. Additionally, costs for chemotherapy and the management of potentially occurring AEs incur.

8 Ongoing research

2 phase III trials and 2 phase II trials were identified

In April 2015, a search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted. The following phase III trials, evaluating the use of bevacizumab in combination regimens in advanced lines of therapy, were identified:

- NCT01935492 (EudraCT Number: 2010-021519-18): An open, randomised phase III study, comparing 8 continuous cycles of chemotherapy with 8 cycles of intermittent (2 times 4 cycles) chemotherapy in first-line treatment, in combination with bevacizumab, and second-line treatment of patients with HER2/neu-negative, incurable, metastatic or unresectable, locally advanced breast cancer. The estimated study completion date is October 2019.
- NCT00601900: Assessing endocrine therapy with or without anti-VEGF therapy for women with hormone receptor-positive advanced breast cancer in a randomised phase III trial. The study is ongoing, primary completion date was June 2014.

Bevacizumab, combined with chemotherapeutic agents for the treatment of advanced breast cancer, is currently also under investigation in phase II trials:

- NCT02175446 (EudraCT Number: 2013-003194-10): A phase II single-arm study evaluating the efficacy and safety of eribulin in combination with bevacizumab for the second-line treatment of HER2-negative metastatic breast cancer progressing after first-line therapy with bevacizumab and paclitaxel. Estimated study completion date is December 2016.
- NCT01989780: Bevacizumab plus paclitaxel optimisation study with interventional maintenance endocrine therapy in advanced or metastatic ER-positive HER2-negative breast cancer (BOOSTER trial, multicentre, randomised phase II). Estimated study completion date is March 2017.

There are numerous studies ongoing, evaluating bevacizumab alone or in combination therapy for different types of cancer, such as renal cell carcinoma, glioma, sarcoma, melanoma, oesophageal or gastric cancer.

numerous phase II studies assessing bevacizumab in various cancer types

9 Commentary

Bevacizumab (Avastin®) is indicated in different types of cancer and in various combinations with other drugs. To date, bevacizumab has not been approved either by the EMA or the FDA for the second-line treatment of patients with HER2-negative, locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy, which corresponds to the indication investigated by the TANIA trial [21] comparing second-line single-agent chemotherapy either alone or with bevacizumab in a total of 494 patients.

neither approved by the EMA nor the FDA for second-line treatment of breast cancer

As regards breast cancer, bevacizumab is approved by the EMA for the first-line treatment of patients with metastatic breast cancer in combination with paclitaxel or capecitabine [3]. In 2010, the CHMP concluded that the combination therapy of Avastin® and docetaxel for metastatic breast cancer (which was approved in 2009) should no longer be used. The decision was based on a negative benefit/risk balance [24]. In 2008, the FDA granted accelerated approval for bevacizumab for the treatment of metastatic HER2-negative breast cancer in combination with paclitaxel in patients who have not received chemotherapy [7]. The approval has been revoked in November 2012, based on a lack of benefit regarding delay in tumour growth and evidence for bevacizumab to improve life expectancy and quality of life of patients [8].

TANIA trial: PFS significantly improved

In the TANIA trial, analyses of PFS showed a median gain of 2.1 months for patients receiving further bevacizumab, resulting in a risk reduction for progression or death by any cause of 25%. Findings of PFS improvement induced by bevacizumab are similar to the results of the RIBBON-2 trial [25]. The phase III trial evaluated the addition of bevacizumab to second-line chemotherapy in patients with locally recurrent or HER2-negative metastatic breast cancer; however, patients in the RIBBON-2 trial did not receive bevacizumab for first-line treatment. Median PFS increased from 5.1 to 7.2 months, stratified HR was 0.78 (95% CI 0.64–0.93, p = 0.0072). In the IMELDA study [22], PFS and OS were significantly longer in patients receiving *maintenance* bevacizumab and capecitabine than in those who received maintenance bevacizumab alone.

Since maintenance therapy following first-line bevacizumab was allowed in the TANIA trial, the majority of patients had a bevacizumab-free interval before study treatment of ≤ 6 weeks. The proportion of patients receiving bevacizumab as maintenance treatment rather than as second-line therapy, however, remains unknown. Thus, it is unclear whether bevacizumab first-line ± maintenance therapy following disease progression or bevacizumab second-line therapy either with or without previous bevacizumab therapy yields better results. In addition, even though endocrine therapy is the preferred treatment option for ER-positive, HER2-negative advanced breast cancer patients [18], only about 50% of the patients had received previous endocrine therapy in the TANIA trial. This raises the question whether patients included were initially undertreated.

immature OS results

The objective response rate in the TANIA study was, with an absolute difference of 4.1%, slightly higher in the combination group than in the chemotherapy-alone group. Since 41% of patients in the chemotherapy-alone group and 40% in the combination group had died at the time of data cut-off, OS results were immature [21].

Results from a systematic review [26] evaluating the efficacy in bevacizumab in breast cancer (first-/second-line setting), including 14 phase III trials with a total of 4,400 patients with metastatic breast cancer, also showed increased response rates in PFS but "no trial demonstrated an OS benefit". In contrast, results of the IMELDA trial showed longer median OS in patients receiving bevacizumab plus capecitabine [22].

higher incidence of AEs in combination group

In the TANIA trial, the incidence of AEs of grade 3 or worse was more frequent in patients of the combination group (59%) than in patients of the chemotherapy-alone group (46%). Serious AEs also occurred more frequently in the combination group (25%) than in the chemotherapy-alone group (18%). These findings concerning AEs are supported by the results of a meta-analysis of randomised controlled trials [27], including a total of 6,436 patients showing that, in patients with advanced cancer, bevacizumab treatment was associated with a slightly higher risk for any severe AE (grade 3 or 4). The death of 2% of patients in each group of the TANIA trial was attributed to AEs. These results are similar to those of a meta-analysis [28] assessing treatment-related mortality with bevacizumab in cancer patients (overall incidence of fatal AEs with bevacizumab was 2.9%, 95% CI, 2.0–4.2%).

the ESMO considers bevacizumab as an option only in selected cases

According to the ESMO guidelines [18], bevacizumab combined with chemotherapy as first- or second-line therapy for metastatic breast cancer provides "only a moderate benefit in PFS and no benefit in OS". Due to the absence of known predictive factors for bevacizumab, recommendations on its use are problematic. Therefore, bevacizumab is only considered as an option in selected cases and it is "not recommended after a first/second line". Similarly, according to the National Comprehensive Cancer Network (NCCN) breast cancer guidelines [19], a series of trials in patients with metastatic breast cancer showed a modest increase of PFS with bevacizumab (mainly in combination with paclitaxel), but none of these studies demonstrated an increase in OS or quality of life.

The ASCO [20] recommends to consider bevacizumab with single-agent chemotherapy only in case of immediately life-threatening disease or severe symptoms (moderate strength of recommendation). The potential moderate benefit of the treatment (improved disease control) faces the high potential harms (unique toxicity, increased costs and barriers to access).

In light of these facts, the additional value of bevacizumab in second-line treatment is uncertain. Furthermore, there are indications that the addition of bevacizumab to chemotherapy (paclitaxel) in patients with HER2-negative metastatic breast cancer is not cost-effective [29]. Thus, the increased costs of adding bevacizumab to chemotherapy have to be considered and weighed against patients' benefits.

further research is required

Since the TANIA trial is the only phase III trial evaluating this particular indication and it is debatable whether the results (PFS and/or AEs) may have been influenced by the open-label design of the study (patients and investigators were not masked to treatment assignment), further evidence is required. Additionally, information regarding patients' quality of life is of utmost importance since the aim of therapy is palliation of symptoms and improvement

of quality of life. Although patient-reported outcomes were assessed in the TANIA trial, using the Functional Assessment of Cancer Therapy – Breast questionnaire, the results were not available yet.

future role of biomarkers

Future trials should include identification of robust predictive biomarkers in order to improve our understanding of molecular biomarkers and mechanisms [26]. Recently, two potential predictive biomarkers (circulating VEGF and tumour neuropilin-1 expression) were identified; however, a prospective trial, randomising or stratifying patients based on VEGF levels to standard therapy is required to validate the results [30]. Since the investigations were made among patients with advanced or metastatic gastric cancer, the applicability of these results to other tumour types is unclear.

unclear mechanisms of resistance to anti-angiogenic therapy

Moreover, it will be important to investigate mechanisms of resistance to anti-angiogenic therapy [31]. A possible explanation for bevacizumab's lack of impact on OS may be that anti-VEGF therapy (despite initial tumour growth suppression) could lead to rapid changes in the biology of metastatic breast cancer that limits the ability of the therapy to improve survival. The existence of alternative VEGF-independent mechanisms of tumour vascularisation, such as vessel co-option (tumours grow along existing blood vessels), may be another reason. Further trials are needed to investigate how VEGF pathway suppression affects the biology of breast cancer [32].

modest benefits need to be weighed against high potential harms and cost-effectiveness

In conclusion, the addition of bevacizumab to standard second-line chemotherapy provides only modest benefits for patients with locally recurrent or metastatic breast cancer. No improvement in relevant outcomes such as OS was ascertained; hence, there is no evidence that bevacizumab extends the life of patients.

Benefits, harms and treatment costs of this therapy must be weighed against each other accurately, especially since bevacizumab is not (yet) approved for the indication in question.

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