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Paclitaxel and Bevacizumab in First Line-Treatment Patients with HER-2 Negative Advanced Breast Cancer: Who could Benefit?

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Abstract

Background: Angiogenesis is essential for tumor growth and development of metastases in human breast cancer. Randomized studies have shown that bevacizumab (inhibitor of VEGF) combined with taxane-based regimens increases response rates and prolongs Progression-Free Survival (PFS) of patients with Metastatic Breast Cancer (MBC). However predictive or prognostic markers that identify the appropriate target population, thus improving the cost-effectiveness ratio of this treatment, are still needed. In this retrospective analysis, we investigated the impact of traditional clinical and pathological features in order to identify the subgroups of patients who derive the greatest benefit from antiangiogenic-agents.

Patients and methods: Retrospectively, we included consecutive patients treated with bevacizumab (10 mg/Kg on days 1 and 15) and paclitaxel (90 mg/m^2, on days 1, 8 and 15) as first-line treatment for HER2-negative MBC at our Institution between June 2007 and December 2012.

Results: 33 patients were included. Median age was 50 years (31-68). 78.8%, 12.1% and 9.1% of patients had luminal B, triple negative and luminal A breast cancer, respectively. 66.6% of patients had visceral disease. The overall response rate was 31.2%. Median PFS and overall survival (OS) were 7.7 months (range 1.9-14.0 months) and 95.2 months (range 11.6-205.8 months), respectively. Univariate analysis highlighted a statistically significant relationship between PFS to the first line and the following factors: relapse-free survival (RFS < 12 months vs >12 months; p<0.01), disease control rate (p<0.01), Ca15.3 reduction of more than 50% from baseline (p=0.03), reduction of LDH from baseline (p=0.02). No significant relationship resulted between PFS and the biological characterization of neoplasia, age, having carried out a previous (neo)adjuvant chemotherapy (with or without taxane) or visceral disease at time of relapse. At multivariate analysis, RFS was the only confirmed independent prognostic factor (p=0.01; HR=0.18; 95% CI 0.04-0.73).

Conclusion: Our results confirmed the efficacy and the acceptable toxicity profile of bevacizumab plus paclitaxel as first-line regimen for MBC. RFS may be a useful tool in the clinical practice to select HER-2 negative MBC which may obtain a better prognosis administering this particular regimen.

Keywords: Angiogenesis; Bevacizumab; Breast cancer; Vascular Endotelial Growth Factor (VEGF)

Introduction

Angiogenesis is a key mechanism for tumor growth, survival and development of metastases in human breast cancer. The tumor microvessel density of breast cancer is known to be predictive of bone marrow micrometastases, recurrence and overall survival (OS) [1], establishing angiogenesis as a potential therapeutic target for breast cancer [2]. Within the family of angiogenic stimulators, the Vascular Endothelial Growth Factor (VEGF) and its receptors play a central role in tumor angiogenesis [3]. Expression of VEGF proteins are increased in breast cancer and VEGF overexpression in tissue correlates with a significantly inferior outcome of breast cancer patients [4-6]. Thereafter, VEGF became an attractive target for the development of biological therapy [7].

Bevacizumab is a humanized monoclonal antibody designed to specifically block the binding of VEGF to high-affinity receptors, it has proved to be effective in several solid tumors [8-11]. In the field of breast cancer, bevacizumab has generated many controversies and discussions, in fact randomized studies have shown that bevacizumab combined with taxane-based regimens increases response rates and prolongs progression-free survival (PFS) of patients with HER2-negative metastatic breast cancer (MBC). However, none of the trials showed significant survival (OS) benefit of adding bevacizumab to chemotherapy as first-line treatment of MBC [12-14].

The recent decision by FDA regarding use of bevacizumab in patients with MBC has turned the spotlight on the risk-versus-benefit of adding bevacizumab to chemotherapy [15]. Moreover, the greatest need is to find predictive or prognostic biochemical and clinical markers that permit to identify the appropriate target population, thus improving the cost-effectiveness ratio of this treatment [3].

In our retrospective analyses, we investigated the impact of traditional clinical and pathological features in order to identify the subgroups of Her 2 negative MBC patients who derive the greatest benefit from antiangiogenic-agents.

Patients and Methods

1. Eligibility criteria

Between June 2007 and December 2012, all consecutive Her 2 negative MBC patients treated with first-line chemotherapy plus bevacizumab at our Institution were included. Patients were eligible if they had: Eastern Cooperative Oncology Group performance status 0-2, age between 18 and 80 years, written informed consent, no evidence of central nervous system metastasis, adequate bone marrow and organ functions (WBC >4,000/mm^3 and/or absolute neutrophil count >1,500/mm^3, platelets >100,000/mm^3, AST/ALT <2.5 times the upper normal limit or <5 times the upper normal limit in the presence of liver metastasis, bilirubin <2 mg/dl, creatinine <1.5 mg/dl).

2. Treatment schedule

All patients received 90 mg/m^2 paclitaxel weekly on days 1, 8, and 15 with 10 mg/Kg bevacizumab 10 mg/kg on days 1 and 15. Cycles were repeated every 4 weeks and continued until documented disease progression, unacceptable toxicity, patient refusal or physician's decision. Toxicity was evaluated using the National Cancer Institute-Common Toxicity Criteria (NCI-CTC, version 4.0) [16] before each treatment. Dose modifications and treatment delays were recommended according to the extent of hematological and non hematological toxicity.

3. Response to treatment

Physical examination, complete blood counts and biochemical tests were carried out before each administration of therapy. A computed tomography scan was performed every four cycles and when disease progression was clinically suspected to document the extent of disease and to evaluate the response to treatment. The response was assessed using the Response Evaluation Criteria in Solid Tumors. RECIST 1.1 Response Evaluation Criteria In Solid Tumors) [17].

4. Statistical analysis

Progression-free survival (PFS) was calculated from the first day of paclitaxel plus bevacizumab chemotherapy until the time of the first occurrence of progression, death from any cause or to the date of last follow-up if none of the preceding events had occurred. Overall survival (OS) was calculated from the first day of paclitaxel plus bevacizumab therapy to the date of death or to the date of the last follow-up visit. Patients who were not reported to be deceased at the time of the analysis were censored at the date they were last known to be alive. Survival distribution was estimated by the Kaplan Meier method. The association between categorical variables was estimated by Chi-Square test. The Cox multivariate proportional hazard regression model was used to evaluate the effects of the prognostic factors on survival. Significant differences in probability of surviving between the strata were evaluated by log-rank test. Hazard ratios and 95% confidence intervals (CIs) were estimated from regression coefficients. A significance level of 0.05 was chosen to assess the statistical significance. The clinical variables analysed were: age (<50 years vs > 50 years), Body Mass Index (BMI, <25 vs >25), menopausal status (pre- vs post-menopausal), lymph node status (negative vs positive), grading (G1-G2 vs G3), Ki-67 (<30% vs >30%), lympho-vascular invasion (positive vs negative), necrosis (positive vs negative), hormonal receptors status (<1 % vs > 1%), Herceptest status (0 vs 1+ vs 2+), previous chemotherapy treatment (yes vs not), time to relapse (<12 months vs >12 months), visceral disease (presence vs absence), Ca15.3 and serum lactate dehydrogenase (LDH) serum levels pre- and post-treatment (increased vs decreased). The cut-off value of Ca15.3 was 35 U/ml and the value was considered positive or negative for the marker if the level was above or below the cut-off, respectively. The cut-off point with the highest sensitivity and specificity for estimating pre-treatment LDH serum levels as a function of treatment clinical activity was set after ROC curve analysis at < 437 U/l for PFS. Statistical analysis was performed with MedCalc package (MedCalc® v9.4.2.0).

Results

Thirty-three patients resulted eligible. At time of diagnosis, median age was 50 years. Two patients had metastatic disease at the onset (6%), while major part of them previously underwent quadrantectomy (12 patients, 36%) or radical mastectomy (19 patients, 58%). They were 28 cases of ductal carcinoma, 3 of lobular carcinoma and 2 mixed histotypes. All patients had metastatic disease at study entry, 22 of them had visceral metastases. Previously, 66.7% of patients (n=22) underwent to adjuvant chemotherapy and 24% underwent to neo-adjuvant treatment (n=8); overall taxane based-regimen was performed during (neo-)adjuvant chemotherapy in 12 cases. Most of patients (84.9%) had ER and/or PgR immune-istochemistry positivity while ER and PgR were negative in five cases (triple negative status). In 39.4% of tumors an higher proliferating index (Ki-67>30%) was documented (Table 1).

Based on St. Gallen 2013 definition subtypes [18], most of tumors were luminal B (78.8%). With regard to the other characteristics, ductal tumors (28 cases, 85%) and a grading of 3 were the most commonly observed categories (61%). Lympho-vascular invasion was reported in 14 of cases. Patients characteristics and chi-square analyses are summarized in tables 1 and 2.

Patients received a median of 6 cycles (range 1-9). Of 33 assessable patients, 2 complete remissions (CR) and 8 partial responses (PR) were observed (overall response rate 30.3%). Stable disease (SD) was observed in 13 patients (39.4%) and progressive disease (PD) in 10 patients (30.3%). Overall disease control rate (CR+PR+SD) was obtained in 69.7% of patients. A total of 16 patients achieved tumor control after 8 cycles of chemotherapy plus bevacizumab, so they carried on with only bevacizumab of maintenance and 14 of these obtained a control of disease. Previous taxane-based chemotherapy and a reduction > 50% of Ca 15.3 after 4 cycles resulted significantly related to the prognosis (p respectively 0.01 and 0.01) as shown in Table 2. No other clinical and/or histological variables were statistically correlated to response rate with paclitaxel and bevacizumab regimen (tables 1 and 2).

At time of analysis, 19 patients are still alive; the median Progression Free Survival (PFS) was 7.7 months (range 1.9-14.0 months) and median Overall Survival (OS) 95.2 months (range 11.6-205.8 months) (Figures 1A 1B).

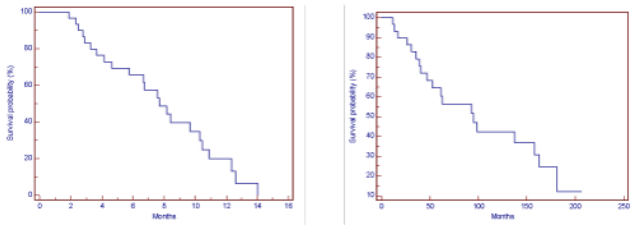

Figure 1A: First line median Progression Free Survival at time of analyses (mPFS 7.7 months, range 1.87-14.03) **Figure 1B:** Median Overall Survival at time of analyses (mOS 95.21 months, range 11.6-205.8)

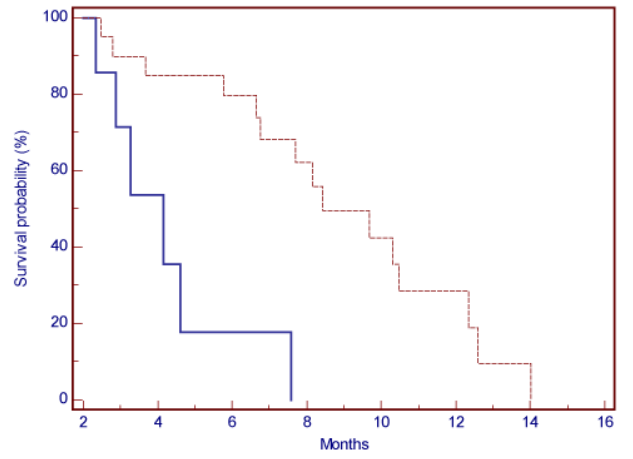

Figure 2: First line PFS based on RFS subgroup (4.16 vs. 8.43 months; p<0.01).

At univariate analysis a better PFS was correlated to a later relapse-free survival (>12 months for patients who did not have a metastatic disease at the onset; p<0.01), achievement of disease control during paclitaxel and bevacizumab regimen (p<0.01) and Ca 15.3 or LDH reduction from baseline (p=0.03 and p=0.02, respectively) (Table 3).

Age, menopausal status, body mass index, biological characteristics of neoplasia (hormonal status, Ki-67, subtype of tumor, lympho-vascular invasion, necrosis, lymph-node status), previously (neo-) adjuvant medical treatment, achievement of response rate during paclitaxel and bevacizumab regimen were not statistically correlated with PFS.

Multivariate analysis revealed that time to relapse was the only significant independent prognostic variable influencing PFS (p=0.04; HR= 0.24, CI 0.06-0.93) (Figure 2) while there was a borderline significance for the achievement of disease control during first line chemotherapy with paclitaxel and bevacizumab (p=0.05; HR=0.29 CI 0.08-1.0); no statistically significant result were reported for Ca15.3 (p=0.11) or LDH reduction (p=0.59).

During bevacizumab and paclitaxel combination therapy, the major experienced toxicities were palmar-plantar erithrodisestesies, epistaxis, gingival and high blood pressure, as reported in Table 4. Overall in our sample, there were no toxicity not already known and no AEs of special interest, except of proteinuria, was more common in later than earlier cycles. There were no treatment related deaths and the regimen was well tolerated.

Discussion

Since endothelial cell migration is a critical event during angiogenesis which is vital to the growth and metastasis of BC, taxanes are inhibitors of cell motility affecting the angiogenic process and contributing to their antineoplastic activity [19, 20] through microtubule-stabilizing cytotoxic activity inhibiting motility and invasiveness of several cell types. But the endothelial stimulating factors, vascular endothelial cell growth factor (VEGF) and basic fibroblast growth factor are able to protect endothelial cells from the angiogenic properties of taxanes. This protective effect can be overcome by the recombinant humanized monoclonal antibody bevacizumab which is directed against VEGF [20]. The synergistic antitumor activity of paclitaxel and bevacizumab may be a result of the increase in paclitaxel concentration in tumor resulting from the downregulation of vascular permeability when coadministered with bevacizumab [21]. A pooled analysis of three randomized phase III trials [12,14,22] showed a 36% lower risk for disease progression or death with the addition of bevacizumab to chemotherapy in previously untreated MBC patients. The efficacy results from the three randomized trials demonstrated an important treatment effect, with a higher ORR (11-28% more responses) and longer PFS interval (31-52% lower risk), without a difference in terms of the OS time. The lack of an OS advantage and the absence of a biomarker to identify patients more likely to benefit from treatment represents limitation to the widespread use of bevacizumab in daily clinical practice [3].Our results, despite the small single-center series, support the clinical benefit seen in larger randomized trials of bevacizumab combined with taxane-based chemotherapy. The overall disease control rate resulted from the present survey (almost 70% of patients) reinforce the growing body of evidence showing the consistently high activity of bevacizumab in combination with weekly paclitaxel. However the PFS resulted from our analysis was lower than the other studies one using bevacizumab in addition to taxane-based chemotherapy (9.2-11.8 months). This salient difference could be explained with the important limit of our study which is the small sample size. Furthermore, our sample population was not homogeneous as the ideal population of clinical trials. Besides, to date, despite extensive research, no biomarkers have been identified to definitively predict patients who might obtain most benefit from bevacizumab therapy or determine which patients might be at risk of progression while receiving bevacizumab [23].Concentrations of before treatment circulating VEGF were not associated with the efficacy of bevacizumab in an analysis of phase III clinical trials [24].However, there is the predictive biomarker VEGF-A, which represents a strong biological rationale supporting the addiction of anti-angiogenics to chemotherapy in Her2 negative MBC, but it is not easily used in clinical practice[3, 25].Besides it was proposed that polymorphisms in component of the VEGF pathway could be used to predict benefit from bevacizumab (VEGF-2578AA and VEGF-1154AA) [26]. Unfortunately these data are not clear and have to be confirmed before entering in clinical practice.

Therefore, our study tried to identify clinical variables to patients selection in daily practice. Despite the small sample size, even our results did not reveal any predictors of response, confirming literature data. Furthermore, patients who achieved a response rate during first

line-chemotherapy with bevacizumab did not show any survival benefit compared with patients who did not have; this finding may confirm the cytostatic role of bevacizumab and it highlights that the goal of therapy with an antiangiogenic drug should be mainly the control of disease rather than its reduction.

From our analysis, the RFS was the only variable which was significantly related with prognosis of patients with MBC. Rossari et al analysed the three main studies with bevacizumab in first-line treatment of MBC in a meta-analysis [3,12-14]; the addition of bevacizumab significantly prolongs PFS in all subgroups of patients, independently from disease free interval (DFI). Definition of DFI differed between the trials: for instance, AVADO and E2100 trials stratified DFI in ≤24 months versus >24 months, while RIBBON-1 considered ≤12 months versus >12 months. On this basis, our results showed that patients who experienced an earlier recurrence of disease after the first diagnosis or after the end of adjuvant chemotherapy (<12 months) had no benefit from the adding of bevacizumab to first-line chemotherapy and consequently had a poor prognosis with a median PFS of only 4 months. On the contrary patients who had a later relapse (>12 months) benefit from the therapy with bevacizumab: they had an improvement of survival which was more than doubled (8,1 months) compared to patients with early disease recurrence. Consequently in the clinical practice the time to relapse may be considered as an easily accessible criteria to select patients who mostly benefit from the addition of anti-angiogenetic drug and to guide therapeutic decisions with a possible cost-saving.

Our results confirmed the potential Ca 15.3 role of predictive response and its already known strong prognostic impact [27-30].

Furthermore, our study showed a consistent PFS benefit regardless of whether adjuvant chemotherapy had been received, including those previously exposed to taxanes in the adjuvant setting. This result is consistent with the literature data that showed similar PFS benefit with the addition of bevacizumab in all subgroups of patients including those previous exposed to taxane. These data suggest that patients previously treated with a taxane can benefit from a retreatment in combination with bevacizumab; the safety profile of bevacizumab in taxane pre-treated patients was consistent with the well-defined safety profile of bevacizumab in combination with taxane therapy [23, 31-34].

We are aware of some limitations in our study. It is a retrospective analysis in a single institution, on a small number of patients. However, to our knowledge, it is the first analysis showing that RFS could predict PFS in HER-2 negative MBC patients who received bevacizumab as first-line treatment. Because of the lack of any other clinical prognostic features, our study suggests that RFS may be easily introduced in clinical practice, as cost-effective and simple index to be performed to select those patients who may obtain a significantly improvement of survival administering this particular regimen.

Characteristics	**Total**	**Yes RR***	**No RR***	**p-value**
	No. of Pt (%)	**No. of Pt**	**No. of Pt**	
Age				
≤50 years	18 (54)	5	13	0.8
>50 years	15 (46)	5	10	
Menopausal status				
Pre-	17 (52)	11	6	0.4
Post-	16 (48)	11	5	
BMI				
<25	15 (46)	10	5	0.3
>25	18 (54)	12	6	
Tumour size**				
pT1-T2	27 (88)	20	7	0.2
pT3-T4	4 (12)	4	0	
Lymph node status (pN)				
pN0	11 (33)	8	3	0.2
pN+	22 (67)	13	9	
Histologic grade				
I-II	13 (39)	6	7	0.2
III	20 (61)	12	8	

Ki-67				
≤ 30%	20 (61)	13	7	0.4
>30%	13 (39)	9	4	
Lympho-vascular invasion				
Yes	14 (42)	5	9	0.7
No	19 (58)	5	14	
ER				
Positive	21 (64)	15	6	0.4
Negative	12 (36)	8	4	
PgR				
Positive	14 (42)	10	4	0.3
Negative	19 (58)	12	7	
Herceptest				
0	24 (73)	7	17	0.6
1+	5 (15)	2	3	
2+ Fish not amplified	4 (12)	2	2	

Table 1: Clinicopahological sample features at time of Breast Cancer diagnosis and prognostic impact

*RR= complete or partial response to paclitaxel and bevacizumab, **2 patients were metastatic at the onset and they did not perform surgery.

Characteristics	**Total**	**Yes RR***	**No RR***	**p-value**
	No. of Pt (%)	**No. of Pt**	**No. of Pt**	
Previous hormonal therapy				
Yes	28 (85)	20	8	0.10
Not	5 (15)	2	3	
Previous taxane-based chemotherapy				
Yes	12 (36)	6	6	0.01
Not	21 (64)	17	4	
Pre-treatment CA15.3				
<35	9 (27)	7	2	0.30
>35	24 (73)	17	7	
Ca15.3 reduction after 4 cycles**				
Yes	16 (48)	15	1	0.01
Not	17 (52)	7	10	
Pre-treatment LDH				
<437	14 (42)	10	4	0.20

>437	19 (58)	11	8	
LDH after 4 cycles				
<437	18 (55)	14	4	0.08
>437	15 (45)	8	7	
Visceral disease				
Yes	22 (67)	4	18	0.05
Not	11 (33)	6	5	
N° of metastatic site				
<3	16 (48)	10	6	0.30
>3	17 (52)	12	5	
Hypertension (all grade)				
Yes	6 (18)	4	2	0.40
No	27 (82)	19	8	

Table 2: Treatment history, laboratory and clinical variables.

*RR= complete or partial response to paclitaxel and bevacizumab. **Only a reduction > 50% was considered.

Parameters	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age, years				-		
≤50 vs >50	1.14	0.49-2.75	0.72			
BMI				-		
≤25 vs >25	1.61	0.69-4.97	0.21			
Menopausal status						
Pre- vs Post-	1.53	0.67-3.75	0.28	-		
Lymph node status (pN)						
pN0 vs pN+	1.03	0.39-2.71	0.93	-		
Histologic grade						
G1-G2 vs G3	0.79	0.25-2.33	0.64	-		
Ki-67						
≤30% vs >30%	0.53	0.16-1.18	0.1	-		
Lympho-vascular invasion						
Negative vs Positive	0.5	0.13-1.08	0.07	-		
Necrosis						
Negative vs Positive	0.73	0.06-7.24	0.75	-		
Estrogen Receptor						
Negative vs Positive	1.38	0.58-3.50	0.43	-		

Progesterone Receptor						
Negative vs Positive	1.39	0.59-3.36	0.42	-		
Previous (neo-) adjuvant chemotherapy						
Yes vs Not	2.29	0.42-3.12	0.23	-		
Previous Taxane-based chemotherapy						
Yes vs Not	0.57	0.19-1.30	0.15	-		
Relapse-free survival						
<12 months vs > 12 months	4.16	3.26-80.7	0.0007	1.41	0.06-0.93	0.04
Overall response rate						
Yes vs Not	1.22	0.50-3.03	0.63	-		
Disease control						
Yes vs Not	3.33	1.9-16.4	0.001	1.23	0.08-1.01	0.05
Visceral disease						
Yes vs Not	0.82	0.33-2.06	0.68	-		
Ca15.3 pre-treatment						
Positive vs Negative	2.17	0.94-7.67	0.06	-		
Ca 15.3 reduction (≥ 50%) after 4 cycles						
Yes vs Not	2.26	1.05-6.16	0.03	0.82	0.15-1.20	0.11
LDH pre-treatment						
<437 vs >437	0.83	0.33-2.04	0.68	-		
LDH reduction after 4 cicles						
Yes vs Not	0.39	0.14-0.83	0.01	0.32	0.42-4.51	0.59
Development of hypertension						
Yes vs Not	1.31	0.49-3.68	0.55	-		

Table 3: Sample features at time of Breast Cancer diagnosis and univariate and multivariate analysis.

AE	**Grade 1-2**	**Grade 3**
	No of pt (%)	**No of pt (%)**
Any AEs	21 (64)	2 (6)
Epistaxis	8 (24)	0
Gengival	2 (6)	0
Hypertension	6 (18)	18
Neutropenia	3 (9)	1(3)
Palmar-plantar Erythrodysesthesia	12 (36)	1(3)

Proteinuria	1(3)	0

Table 4: Experienced adverse events (CTC AE).

* any case of g4 toxicity has been reported

References

1. Fox SB, Leek RD, Bliss J, Mansi JL, Gusterson B, et al. (1997) Association of tumor angiogenesis with bone marrow micrometastases in breast cancer patients. J Natl Cancer Inst 89: 1044-1049.
2. Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, et al. (2005) Randomized phase III trial of capecitabina compared with bevacizumab plus capecitabine in patients previously treated metastatic breast cancer. J Clin Oncol 23: 792-799.
3. Rossari JR, Metzger-Filho O, Paesmans M, Saini KS, Gennari A, et al. (2012) Bevacizumab and Breast Cancer: A Meta-Analysis of First-Line Phase III Studies and a Critical Reappraisal of Available Evidence. J Oncol 2012: 417673.
4. Gasparini G, Fanelli M, Boracchi P, Morabito A, Locopo N, et al. (2000) Behaviour of metastasis in relation to vascular index in patients with node-positive breast cancer treated with adjuvant tamoxifen. Clin Exp Metastasis 18: 15-20.
5. Gasparini G, Toi M, Biganzoli E, Dittadi R, Fanelli M, et al. (2001) Thrombospondin-1 and -2 in node-negative breast cancer: correlation with angiogenic factors, p53, cathepsin D, hormone receptors and prognosis. Oncology 60: 72-80.
6. Bakker JL, Meijers-Heijboer H, Verheul H (2013) Novel strategies towards the use of anti-angiogenic agents in breast cancer. Eur J Pharmacol 717: 36-39.
7. Linderholm BK, Hellborg H, Johansson U, Elmberger G, Skoog L, et al. (2009) Significantly higher levels of vascular endothelial growth factor (VEGF) and shorter survival times for patients with primary operable triple-negative breast cancer. Ann Oncol 20:1639-1646
8. Price TJ, Segelov E, Burge M, Haller DG, Ackland SP, et al. (2013) Current opinion on optimal treatment for colorectal cancer. Expert Rev Anticancer Ther 13: 597-611.
9. Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, et al. (2007) Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer. J Clin Oncol 25: 1539-1544
10. Wang Y, Deng G, Liu X, Cho WC (2013) Monoclonal antibodies in lung cancer. Expert Opin Biol Ther 13: 209-226.
11. Iacovelli R, Alesini D, Palazzo A, Trenta P, Santoni M, et al. (2014) Targeted therapies and complete responses in first line treatment of metastatic renal cell carcinoma. A meta-analysis of published trials. Cancer Treat Rev 40: 271-275.
12. Miles DW, De Haas SL, Dirix LY, Romieu G, Chan A, et al. (2013) Biomarker results from the AVADO phase 3 trial of first-line bevacizumab plus docetaxel for HER2-negative metastatic breast cancer. Br J Cancer 108: 1052-1060
13. Miller KD (2003) E2100: a phase III trial of paclitaxel versus paclitaxel/ bevacizumab for metastatic breast cancer. Clin Breast Cancer 3: 421-422.
14. Robert NJ, Diéras V, Glaspy J, Brufsky AM, Bondarenko I, et al. (2011) RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol 29: 1252-1260.
15. Burstein HJ (2011) Bevacizumab for advanced breast cancer: all tied up with a RIBBON? J Clin Oncol 29: 1232-1235.
16. U. S. Department of health and human service (2010) CTCAE 4. 03 Common Terminology Criteria for Adverse Events (CTCAE) Version 4. 0. May 28
17. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D et al. (2009) New response evaluation criteria in solid tumours. Eur J Cancer 45:228-247
18. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, et al. (2013) Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 24:2206-2223
19. Belotti D, Vergani V, Drudis T, Borsotti P, Pitelli MR, et al. (1996) The microtubule-affecting drug paclitaxel has antiangiogenic activity. Clin Cancer Res 2: 1843-1849.
20. Sweeney CJ, Miller KD, Sissons SE, Nozaki S, Heilman DK, et al. (2001) The antiangiogenic property of docetaxel is synergistic with a recombinant humanized monoclonal antibody against vascular endothelial growth factor or 2-methoxyestradiol but antagonized by endothelial growth factors. Cancer Res 61: 3369-3372.
21. Yanagisawa M, Yorozu K, Kurasawa M, Nakano K, Furugaki K, et al. (2010) Bevacizumab improves the delivery and efficacy of paclitaxel. Anticancer Drugs 21: 687-694.
22. Schneider BP, Gray RJ, Radovich M, Shen F, Vance G,et al. (2013) Prognostic and predictive value of tumor vascular endothelial growth factor gene amplification in metastatic breast cancer treated with paclitaxel with and without bevacizumab; results from ECOG 2100 trial. Clin Cancer Res. 19:1281-1289
23. Chan A, Miles DW, Pivot X (2010) Bevacizumab in combination with taxanes for the first-line treatment of metastatic breast cancer. Ann Oncol 21: 2305-2315.
24. Jubb AM, Buffa FM, Harris AL (2010) Assessment of tumour hypoxia for prediction of response to therapy and cancer prognosis. J Cell Mol Med 14: 18-29.
25. Kruse V, Denys H, Van Den Broecke R, Van Belle S, Cocquyt V (2013) The addition of bevacizumab to standard chemotherapy in breast cancer: which patient benefits the most?. Springerplus 2:202
26. Schneider BP, Wang M, Radovich M, Sledge GW, Badve S, et al. (2008) Association of vascular endothelial growth factor and vascular endothelial growth factor receptor-2 genetic polymorphisms with outcome in a trial of paclitaxel compared with paclitaxel plus bevacizumab in advanced breast cancer: ECOG 2100. JClin Oncol 26: 4672-4678
27. Al-azawi D, Kelly G, Myers E, McDermott EW, Hill AD, et al. (2006) CA 15-3 is predictive of response and disease recurrence following treatment in locally advanced breast cancer. BMC Cancer 6: 220.
28. Horobin JM, Browning MC, McFarlane NP, Smith G, Preece PE, et al. (1991) Potential use of tumour marker CA 15-3 in the staging and prognosis of patients with breast cancer. J R Coll Surg Edinb 36: 219-221.
29. Lee JS, Park S, Park JM, Cho JH, Kim SI, et al. (2013) Elevated levels of preoperative CA 15-3 and CEA serum levels have independently poor prognostic significance in breast cancer. Ann Oncol 24: 1225-1231.
30. Bidard FC, Hajage D, Bachelot T, Delaloge S, Brain E, et al. (2012) Assessment of circulating tumor cells and serum markers for progression-free survival prediction in metastatic breast cancer: a prospective observational study. Breast Cancer Res 14: R29
31. Wagner AD, Thomssen C, Haerting J, Unverzagt S (2012) Vascular-endothelial-growth-factor (VEGF) targeting therapies for endocrine refractory or resistant metastatic breast cancer. Cochrane Database Syst Rev 7: CD008941.
32. Gray R, Bhattacharya S, Bowden C, Miller K, Comis RL (2009) Independent review of E2100: a phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. J Clin Oncol 27: 4966-4972.

33. Miles DW, Chan A, Dirix LY, Cortés J, Pivot X, et al. (2010) Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol 28: 3239-3247.

34. Ince WL, Jubb AM, Holden SN, Holmgren EB, Tobin P, et al. (2005) Association of k-ras, b-raf, and p53 status with the treatment effect of bevacizumab. J Natl Cancer Inst 97: 981-989.