Bevacizumab plus Docetaxel and Cisplatin for Metastatic Breast Cancer: A Pilot Phase II Study

CHENG-JENG TAI[1,2], CHING-SHYANG CHEN[3,4], CHIN-SHENG HUNG[3,4], LI-JEN KUO[3,4], PO-LI WEI[3,4], JENG-FENG CHIOU[5], CHUNG-HUEI HSU[6], HUNG-YI CHIOU[7*] and CHIH-HSIUNG WU[8*]

[1]Division of Hematology and Oncology, Department of Internal Medicine, [3]Division of General Surgery, Department of Surgery, and Departments of [5]Radiation Oncology and [6]Nuclear Medicine, Taipei Medical University Hospital, Taiwan, R.O.C.;
Departments of [2]Internal Medicine, and [4]Surgery, School of Medicine, College of Medicine, Taipei Medical University, Taiwan, R.O.C.;
[7]School of Public Health, College of Public Health and Nutrition, Taipei Medical University, Taiwan, R.O.C.;
[8]Superintendent Office, Taipei Medical University Shuang-Ho Hospital, Taiwan, R.O.C.

Abstract. *Background: Bevacizumab is a monoclonal antibody that prevents angiogenesis by inhibiting vascular endothelial growth factor (VEGF) activity. Clinically, it has been used to treat a diverse range of cancer types. In this pilot phase II study, we investigated the efficacy and safety profiles of bevacizumab in combination with docetaxel plus cisplatin for patients with advanced HER2-negative metastatic breast cancer. Patients and Methods: Between 2005 and 2008, 20 patients with advanced breast cancer were recruited from the Taipei Medical University Hospital. Bevacizumab was administered every two weeks in a 12-cycle treatment with docetaxel plus cisplatin. The primary end-point for this study was the overall response rate. The secondary end-points were progression-free survival and the safety profiles of the combined therapy. Results: The average number of treatment cycles was 10.5 with a response rate of 80%. Neutropenia and neuropathy were the most commonly observed adverse events. Seven patients achieved complete remission and nine patients achieved partial remission. For the overall patient group in this study, the median time-to-progression and overall survival were 28.0 weeks and 52 weeks, respectively. The median time-to-progression and overall survival for the 10 patients that completed all 12 cycles of treatment were 64.0 weeks and 80 weeks, respectively. In one patient, a very rapid reduction in the level of breast cancer lung metastases was observed one week post-treatment. Conclusion: Based on this pilot study, bevacizumab in combination with docetaxel and cisplatin is likely to be an effective treatment option for metastatic breast cancer that warrants further study.*

With an improved understanding over the underlying genomic and proteomic profile of cancer, targeted-chemotherapy, including antibody-based therapies, has become an invaluable tool in the treatment of malignant diseases (1-8). Bevacizumab is a monoclonal antibody that has been effectively used for the treatment of colon, lung, kidney and brain cancer (9-11). By blocking the vascular endothelial growth factor (VEGF) pathway, bevacizumab inhibits angiogenesis and prevents tumor blood vessel formation, which can lead to decreased tumor growth and increased tumor cell death (12, 13). In a phase I/II dose-escalation safety and -efficacy study, bevacizumab-alone showed a modest effect against advanced breast cancer with a well-tolerated toxicity profile; however, a greater, albeit still modest effect was observed when bevacizumab is combined with conventional chemotherapy (14). When combined with chemotherapy, bevacizumab can increase the objective response rate and progression-free survival, however usually not overall survival, while only modestly effecting toxicity (15-17). Here we present a phase II pilot study that focuses on bevacizumab in combination with docetaxel plus cisplatin for the treatment of advanced HER-2-negative metastatic breast cancer. The objective response rate, progression-free survival, rate of remission and safety profiles of the combined treatment of bevacizumab and docetaxel plus cisplatin were assessed herein.

*These Authors contributed to this article equally.

Correspondence to: Chih-Hsiung Wu, MD, Ph.D., Superintendent, Superintendent Office, Taipei Medical University Shuang-Ho Hospital, No.291, Jhongjheng Rd, Jhonghe City, Taipei County 235, Taiwan, R.O.C. Tel: +886 227372181 ext. 3903, Fax: +886 227363051, e-mail: cjtai@tmu.edu.tw

Key Words: Breast cancer, bevacizumab, HER2-negative, docetaxel, cisplatin, metastatic.

Patients and Methods

Patients. During the period of October 2005 to October 2008, 20 patients with advanced breast cancer metastases were recruited by the Taipei Medical University Hospital for a pilot phase II study to measure the safety and efficacy of bevacizumab and docetaxel plus cisplatin treatment. This study was approved by the local Ethics Committee at the Taipei Medical University Hospital. Informed consent was obtained from all participants.

Inclusion criteria: ≤8 years of age; histological and/or cytological signs of invasive ductal breast carcinoma; HER2-negative tumor (grade <3+ immunohistochemical analysis or negative gene amplification by fluorescence *in situ* hybridization); Eastern Cooperation Oncology Group (ECOG) performance status of 0-2; at least one measurable metastatic tumor lesion; adequate renal, hepatic, and hematological function; a left ventricular ejection fraction (LVEF) within normal limits; an absolute neutrophil count of ≥1,000/μl; platelet count of ≥75,000/μl; bilirubin count ≤1.5× the upper limit of normal (ULN); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5× the ULN; creatinine clearance of at least 25 ml/min. Patients with previous hormonal, radiation or chemotherapy treatment for metastatic breast cancer were allowed in this study, as long as all treatments were completed at least two weeks prior to the start of the study protocol. Patients that had not previously received radiation therapy, provided that they were asymptomatic, could also be enrolled in the study. Patients with central nervous system (CNS) progression after whole-brain radiotherapy (WBRT) and/or stereotactic radiosurgery (SRS), as long as the leptomeningeal carcinomatosis was not the only site of CNS involvement, were also eligible. Additionally, patients on low-dose prophylactic anti-coagulant medications, as well as concurrent administration of bisphosphonates for bone metastases, were also eligible for the study.

Exclusion criteria: Patients were excluded from the study if in the last five years they had exhibited any other type of cancer, not including basal-cell, skin carcinoma, or *in situ* cervical cancer; were concurrently on a dosing regimen of any other anti-neoplastic agents; were concurrently using therapeutic anti-coagulant agents, or more than 325 mg of aspirin per day; concurrently exhibiting non-healing wounds and fractures; exhibiting clinical significant cardiovascular disease.

Treatment plan. All eligible patients received 12 treatment cycles. During the first treatment cycle, a 60-min infusion of 8 mg/kg loading dose of bevacizumab was administered to patients, concurrently with docetaxel (45 mg/m^2) plus cisplatin (50 mg/m^2). With the subsequent treatment cycles, every two weeks, a 30-min infusion of 5 mg/kg of bevacizumab was administered concurrently with docetaxel (45 mg/m^2) plus cisplatin (50 mg/m^2). The overall 12-treatment cycle was chosen due to risk assessment and future cost-effectiveness. Based on the ECOG criteria, if patients encountered grade 3 or higher toxicities of proteinuria, persistent hematuria, bilirubinemia, clinical hemorrhage such as gastrointestinal tract bleeding, the treatment would be interrupted. Anti-hypertensive therapy would be administered for the patients' clinical situation at the discretion of the principle investigator.

Patients' evaluation. Pre-treatment evaluation included detailed medical history, physical examination, complete blood count (CBC) and biochemical surveys, electrocardiography (ECG), chest X-ray, bone scan, liver ultrasound and/or abdominal computed tomography (CT) scan. CBC and blood biochemistry were tested prior to each course of chemotherapy. Carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) tumor markers were assayed every 3-4 weeks. Cancer staging procedures were completed every eight weeks and included brain magnetic resonance imaging (MRI) and CT scans of the chest, abdomen, and pelvis. Abdominal sonography and positron emission tomography (PET) scan would be arranged as needed for further evaluation of a patient's clinical status. Patients with fever or severe mucositis also underwent CBC. All material pertaining to treatment response was evaluated by one of the authors and one independent radiologist. All patients were followed-up, as mentioned above, until death or until the end of the study.

Table I. *Patients' characteristics*.

	N=20
Age (years)	
Median	49.5
Range	34-64
ECOG performance status	
0	12
1	5
2	3
Site of disease	
CNS	1
Lung or pleura	12
Liver	19
Bone	18
Breast/chest wall	2
Lymph nodes and other	6
Estrogen-receptor status	
Positive	17
Negative	3
HER2 status	All negative
No. of prior chemotherapy regimens (adjuvant plus metastatic)	
1	4
2	3
≥3	13

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2.

Outcome measures. Adverse events: Adverse events were evaluated according to the ECOG criteria and the National Cancer Institute Common Terminoloty Criteria for Adverse Events, version 3.0 (18). Patients remained in the study until they withdrew consent, experienced unacceptable toxicity, or had progressive disease (PD). PD was defined as a ~20% increase in the longest dimension (LD) sum of the target lesions and an absolute increase in size of at least 5 mm in one or more target lesions, or the appearance of one or more new lesions of ~6 mm in size. Disease in patients was considered to have progressed if they were taken off study for clinical deterioration or died as a result of any cause, regardless of radiographic evidence of progression.

Experimental End-points: The primary endpoint was the objective response rate [complete response (CR) plus partial response (PR)], while the secondary end-point consisted of analysis of the

Table II. *Worst toxicity grade*.

		Patients who did not complete 12 cycles (n=10)				Patients who completed 12 cycles (n=10)			
Median age (range)		49.5 (41-64)				48.5 (34-56)			
Median number of completed cycles (range)		6 (2-9)				12 (12-12)			
		Grade				Grade			
Toxicity	Total	1	2	3	4	1	2	3	4
Neutropenia	20 (100.0%)	0	3	5	2	0	3	6	1
Nausea/vomiting	20 (100.0%)	0	7	3	0	2	4	4	0
Fatigue	20 (100.0%)	0	7	3	0	2	6	2	0
Neuropathy	18 (90.0%)	0	4	4	0	0	4	6	0
Anorexia	17 (85.0%)	3	5	1	0	3	5	0	0
Hypertension	12 (60.0%)	3	2	2	0	2	3	0	0
Diarrhea	4 (20.0%)	0	2	1	0	1	0	0	0
Headache	4 (20.0%)	0	0	0	0	4	0	0	0
Allergy	2 (10.0%)	2	0	0	0	0	0	0	0
Hemorrhage/gastrointestinal tract	2 (10.0%)	2	0	0	0	0	0	0	0
Hemorrhage/genitourinary tract	2 (10.0%)	1	0	0	1	0	0	0	0

Frequency of treatment-related toxicities according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, was based on the worst grade per patient.

progression-free survival and safety profile of the treatment regimen. All measurable lesions were assessed (≤5 target lesions). Treatment response was evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (11). CR was defined as the disappearance of all target and non-target lesions. PR was defined as at least a 30% decrease in the LD sum of target lesions and an absolute decrease of at least 5 mm in one or more target lesions.

Statistical analyses. The response rate (P1) of this study was considered as 70%, and the threshold response rate (P0) as 50%. Under the settings of type I error rate (α) at 0.05 and power (1-β) at 0.8, the required sample size was calculated by Simon's two–stage method. In the first stage, the required sample size was 15 with at least eight responses to enter the second stage.

All analyses were performed by the SPSS 15.0 statistics software (SPSS Inc, Chicago, IL, USA). Age is presented by median and full range; other categorical variables are presented by count and percentage. The time-to-progression was calculated based on the time between the first day of treatment and the date of disease progression; the overall survival time was calculated based on the time between the first day of treatment and the date of death. The progression-free rate and overall survival rates are summarized by the Kaplan–Meier survival curves.

Results

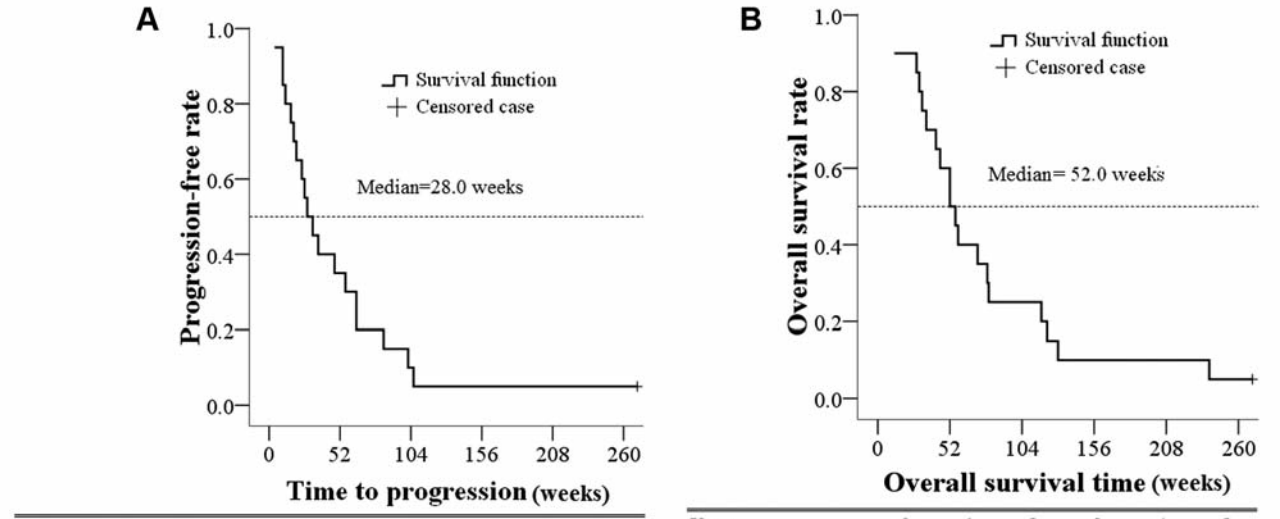
Patients' characteristics. During the period of October 2005 to October 2008, 20 patients were enrolled in this study. The clinical characteristics of these patients are presented in Table I. Ten patients completed all 12 cycles, while the remaining 10 patients only completed 2-9 cycles before withdrawing due to personal reasons, disease progression or treatment toxicity (Table II). At the time of study analysis, 179 cycles (2-week) of treatment had been administered.

Table III. *Overall treatment response*.

Clinical category	N=20
Overall response rate	16 (80%)
Complete response	7 (35.0%)
Partial response	9 (45.0%)
Progressive disease	4 (20%)

Outcome measures. Adverse events: Treatment-related toxicity observed in this study is presented in Table III. Neutropenia, nausea/vomiting, and fatigue (20/20) were the most common observed adverse events, followed by neuropathy (18/20), anorexia (17/20), and hypertension (12/20). It was noted that one patient died due to fulminant hepatitis B with acute hepatic failure, even though lamivudine had been provided to the patient before entering the study. One patient experienced fatal hematuria and, upon entering the study, was found to have invasion into the bladder and gynecological adnexa metastasis. Table II also presents the distribution of toxicities for patients who did and did not complete 12 cycles.

Treatment efficacy: The primary endpoint of the study was the response rate by the RECIST criteria. The median number of treatment cycles for this study was 10.5 (2-12). Seven patients achieved CR (35%) and nine patients



Year	0	1	2	3	4	5
Week	0	52	104	156	208	260
cumulative events	0	13	18	-	-	-
remaining cases	20	7	2	-	-	-

Year	0	1	2	3	4	5
Week	0	52	104	156	208	260
cumulative events	0	10	15	18	18	-
remaining cases	20	10	5	2	2	-

Figure 1. *Kaplan-Meier survival curves for progression-free rate (A) and overall survival rate (B).*

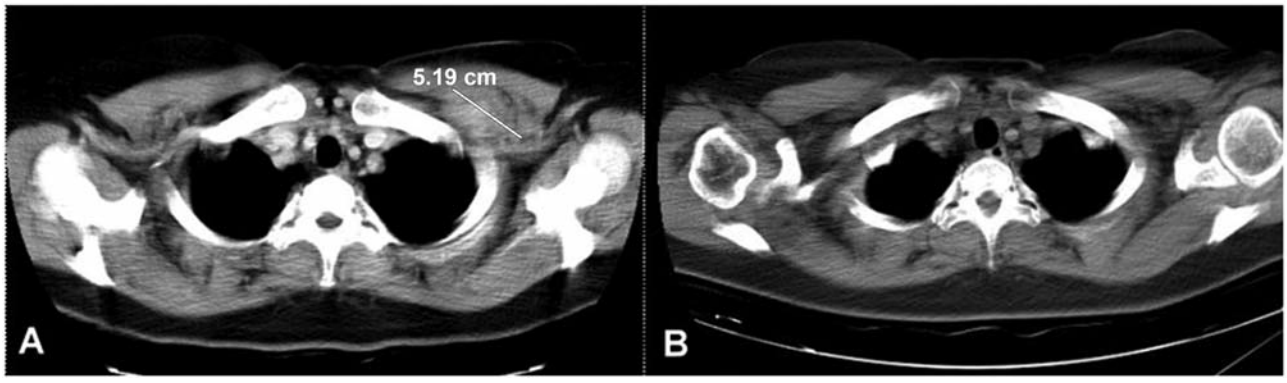


Figure 2. *A female patient aged 45 years had a HER2-negative invasive ductal breast carcinoma, with metastases in the chest wall and neck lymph nodes. After receiving 12 cycles of bevacizumab plus docetaxel plus cisplatin, she had a complete response. A: Before treatment, computed tomography (CT) scan in November 2006, showing a tumor mass of size 5.19 cm; B: after treatment, CT scan in March 2007, showing resolved tumor.*

achieved PR (45%). The response rate was 16/20 (80%). Results are presented in Table III.

Time-to-progression: The median time to progression is presented in Figure 1A. For the patient group overall, the median time-to-progression was 28.0 weeks [95% confidence interval (CI) for the median=14.6-41.1 weeks]. The median time-to-progression for the 10 patients who completed all 12 cycles of treatment was 64.0 weeks (95% CI=51.9-76.1 weeks).

Overall survival: The median overall survival time for the whole patient group was 52.0 weeks (95% CI for the median=35.9-68.1 weeks). The median overall survival time for the 10 patients who completed all 12 cycles of treatment was 80.0 weeks (95% CI=19.0-140.4). Presented in Figure 2, one week after treatment, one patient showed marked improvement in bilateral lung metastases.

Discussion

The present phase II pilot study was designed and conducted to assess the safety and efficacy of bevacizumab combined with docetaxel plus cisplatin in the treatment of patients with advanced HER2-negative breast cancer. Several clinical trials

have presented strong data that bevacizumab can significantly improve the efficacy of taxane-based chemotherapeutic compounds for advanced breast cancer without significantly altering toxicity profiles (19-25).

In this study, we observed that 16 out of 20 (80%) patients exhibited PR or CR to bevacizumab in combination with docataxel plus cisplatin. Patients who successfully completed the 12-cycle bi-weekly treatment exhibited a median time-to-progression of 64.0 weeks, and an overall survival rate of 80.0 weeks. One patient, as illustrated in Figure 2 with multiple metastases, actually showed a dramatic improvement one week after treatment. We also noted that patients with liver-only metastasis had a strong, non-significant, trend for improved treatment response and longer survival compared to patients with multiple sites of metastasis (data not shown).

There were two main reasons we adopted a bi-weekly 12-cycle treatment schedule. Firstly, patients with metastatic diseases are usually unable to tolerate chemotherapy for long periods of time. We felt that a treatment regimen that only lasted six months was the optimal treatment schedule to reduce unneeded stress for these patients. Secondly, bevacizumab is very expensive, and its cost-effectiveness is often debated by the oncology community (26-29). We felt that if this study could show that a 12-cycle treatment schedule provided good efficacy against advanced breast cancer metastases, the cost-effectiveness might be more optimal for patients and insurance coverage (8, 11, 26-29).

In 2011, the US Food and Drug Administration (FDA) rescinded its approval of bevacizumab (Avastin®) use for the treatment of advanced HER2-negative breast cancer metastasis, citing large safety risks with minimal benefit; however this decision is highly debatable (26, 30). It is true that many studies involving adjunct bevacizumab treatment failed to show improved overall survival compared to chemotherapy-alone in patients with metastatic HER2-negative breast cancer. According to Miles *et al*. however, bevacizumab combined with docetaxel increases the objective response rate and the progression-free survival rate in advanced HER2-negative metastatic breast cancer when compared to docetaxel-alone, without significantly affecting toxicity (24, 25). The incidence of high-grade neutropenia, a common side-effect of docetaxel, was also relatively low in their trial, which is in contrast to our results.

Although, in the present study, we used a concentration that was half the commonly administered dose for docetaxel and cisplatin, we observed a high incidence of grade 3 neutropenia. Since it is postulated that bevacizumab can enhance the cytotoxic activity of chemotherapy compounds, it is possible that an additive effect of bevacizumab could also enhance docetaxel and cisplatin-related side-effects. This would also explain the reasonably high incidence of sensory neuropathy, a side-effect common with both docetaxel and cisplatin; however, since many other clinical trials showed that bevacizumab does not alter toxicity profiles, other possibilities may also apply (25). It is very possible that what we observed is indeed the combined toxicity profile of all three compounds (bevacizumab, docetaxel, cisplatin), but it is also very likely that due to a small patient subset (n=20) from a single research hospital, the toxicity profile in our study was skewed. This is a potential risk assessment that will need to be addressed with future multicenter clinical studies. Even with these side-effects, our results in this pilot study strongly support the therapeutic benefits of 12 cycles of bevacizumab in combination with docetaxel plus cisplatin against advanced HER2-negative breast cancer.

There are a few limitations to this study. As mentioned previously, the small nature of this pilot study may not fully address the efficacy and safety of bevacizumab in combination with docetaxel plus cisplatin in a wider patient population. Moreover, by not comparing the effects of bevacizumab in combination with docetaxel plus cisplatin with patients receiving docetaxel plus cisplatin-alone, we cannot truly address the actual adjunct effect of bevacizumab on chemotherapy, including differences in progression-free survival or overall survival rates. By conducting an extensive multicenter phase II trial with a much larger patient subset that compares bevacizumab with docetaxel plus cisplatin treatment to docetaxel plus cisplatin-alone, we will be able to achieve a much more effective and robust understanding of the therapeutic benefit and toxicity profile for bevacizumab in advanced HER2-negative metastatic breast cancer.

In this study, bevacizumab in combination with docetaxel plus cisplatin led to a high response rate in patients with advanced HER2-negative metastatic breast cancer. The median time-to-progression for patients that completed the 12 cycles of treatment was 64 weeks and the overall survival was 80 weeks. Our data, supported from previously published studies, indicate that if bevacizumab can remain cost-effective, it will play an important role as an adjunct treatment option, in combination with conventional chemotherapy for HER2-negative metastatic breast cancer.

Conflicts of Interest

The Authors report no conflicts of interest in regard to this study.

References

1 Miller KD, Sweeney CJ and Sledge GW Jr.: Redefining the target: Chemotherapeutics as antiangiogenics. J Clin Oncol *19*: 1195-1206, 2001.

2 Moy B and Goss PE: Lapatinib: Current Status and Future Directions in Breast Cancer. Oncologist *11*: 1047-1057, 2006.

3 Chu E: Bevacizumab targeted therapy. Validation of angiogenesis as a key target for advanced colorectal cancer. Clin Colorectal Cancer *4*: 16, 2004.

4 Eniu A: Integrating biological agents into systemic therapy of breast cancer: trastuzumab, lapatinib, bevacizumab. J B.U.On. Suppl *1*: S119-126, 2007.
5 Caprioni F and Fornarini G: Bevacizumab in the treatment of metastatic colorectal cancer. Future Oncol *3*: 141-148, 2007.
6 Jubb AM, Hurwitz HI, Bai W, Holmgren EB, Tobin P, Guerrero AS, Kabbinavar F, Holden SN, Novotny WF, Frantz GD, Hillan KJ and Koeppen H: Impact of vascular endothelial growth factor-A expression, thrombospondin-2 expression, and microvessel density on the treatment effect of bevacizumab in metastatic colorectal cancer. J Clinl Oncol *24*: 217-227, 2006.
7 Schaller G, Fuchs I, Gonsch T, Weber J, Kleine-Tebbe A, Klare P, Hindenburg HJ, Lakner V, Hinke A and Bangemann N: Phase II Study of Capecitabine Plus Trastuzumab in Human Epidermal Growth Factor Receptor 2 Overexpressing Metastatic Breast Cancer Pretreated With Anthracyclines or Taxanes. J Clin Oncol *25*: 3246-3250, 2007.
8 Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J and Norton L: Use of Chemotherapy plus a Monoclonal Antibody against HER2 for Metastatic Breast Cancer That Overexpresses HER2. N Engl J Med *344*: 783-792, 2001.
9 Koukourakis GV: Has bevacizumab (Avastin) given extra therapeutic gain in metastatic colorectal cancer and malignant brain gliomas? Systematic review answering this question. Recent Pat Inflamm Allergy Drug Discov *6*: 70-77, 2012.
10 Planchard D: Bevacizumab in non-small-cell lung cancer: a review. Expert Rev Anticancer Ther *11(8)*: 1163-1179, 2011.
11 Syrigos KN, Karapanagiotou E, Boura P, Manegold C, Harrington K: Bevacizumab-induced hypertension: pathogenesis and management. BioDrugs *25(3)*: 159-169, 2011.
12 Emmanouilides C, Pegram M, Robinson R, Hecht R, Kabbinavar F and Isacoff W: Anti-VEGF antibody bevacizumab (Avastin) with 5FU/LV as third line treatment for colorectal cancer. Tech Coloproctol *8(Suppl 1)*: s50-52, 2004.
13 Ferrara N, Hillan KJ and Novotny W: Bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy. Biochem Biophys Res Commun *333*: 328-335, 2005.
14 Cobleigh MA, Langmuir VK, Sledge GW, Miller KD, Haney L, Novotny WF, Reimann JD and Vassel A: A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. Semin Oncol *30(5 Suppl 16)*: 117-124, 2003.
15 Link JS, Waisman JR, Nguyen B and Jacobs CL: Bevacizumab and albumin-bound paclitaxel treatment in metastatic breast cancer. Clin Breast Cancer *7*: 779-783, 2007.
16 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS and Rubinstein L: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst *92*: 205-216, 2000.
17 Therneau T and Grambsch P: Modeling Survival Data: Extending the Cox Model. New York: Springer, 2000.
18 Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0. Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, 2003.
19 von Minckwitz G, Eidtmann H, Loibl S, Blohmer JU, Costa SD, Fasching PA, Kreienberg R, Hilfrich J, Gerber B, Hanusch C, Fehm T, Strumberg D, Solbach C, Nekljudova V, Untch M; German Breast Group and Arbeitsgemeinschaft Gynäkologische Onkologie-Brust investigators: Integrating bevacizumab, everolimus, and lapatinib into current neoadjuvant chemotherapy regimen for primary breast cancer. Safety results of the GeparQuinto trial. Ann Oncol *22(2)*: 301-306, 2011.
20 Miller KD: A phase III trial of paclitaxel versus paclitaxel/bevacizumab for metastatic breast cancer. Clin Breast Cancer *3*: 421-422, 2003.
21 Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, Dickler M, Overmoyer BA, Reimann JD, Sing AP, Langmuir V and Rugo HS: Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol *23*: 792-799, 2005.
22 Miller KD, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D and Davidson NE: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med *357*: 2666-2676, 2007.
23 Xu BH, Jiang ZF, Shen ZZ, Guan ZZ, Chen ZD, Cheng Y, Zheng H, Jiang J, Wang XJ, Tong ZS, Qin SK, Luo Y, Yao M, Wang LW and He J: Safety and efficacy of first-line bevacizumab combined with taxane therapy in Chinese patients with HER2-negative locally recurrent or metastatic breast cancer: findings from the ATHENA study. Chin Med J (Engl) *125(5)*: 764-769, 2012.
24 Mayer EL, Lin NU and Burstein HJ: Novel approaches to advanced breast cancer. bevacizumab and lapatinib. J Natl Compr Canc Netw *5*: 314-323, 2007.
25 Goldfarb SB, Hudis C and Dickler MN: Bevacizumab in metastatic breast cancer: when may it be used? Ther Adv Med Oncol *3(2)*: 85-93, 2011.
26 Miles DW, Chan A, Dirix LY, Corte's J, Pivot X, Tomczak P, Delozier T, Sohn JH, Provencher L, Puglisi F, Harbeck N, Steger GG, Schneeweiss A, Wardley AM, Chlistalla A and Romieu G: 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(20)*: 3239-3247, 2010.
27 Montero AJ, Escobar M, Lopes G, Glück S and Vogel C: Bevacizumab in the treatment of metastatic breast cancer: friend or foe? Curr Oncol Rep *14*: 1-11, 2012.
28 Chu TB, Liu TC, Chen CS, Tsai YW and Chiu WT: Household out-of-pocket medical expenditures and national health insurance in Taiwan: income and regional inequality. BMC Health Serv Res *5*: 60, 2005.
29 Dedes KJ, Matter-Walstra K, Schwenkglenks M, Pestalozzi BC, Fink D, Brauchli P and Szucs TD: Bevacizumab in combination with paclitaxel for HER-2 negative metastatic breast cancer: an economic evaluation. Eur J Cancer *45(8)*: 1397-1406, 2009.
30 D'Agostino RB Sr: Changing end points in breast-cancer drug approval – the Avastin story. N Engl J Med *14: 365(2)*: e2, 2011.

Received September 17, 2012
Revised October 23, 2012
Accepted October 24, 2012