Published in final edited form as:

Clin Breast Cancer. 2014 August ; 14(4): 228–234. doi:10.1016/j.clbc.2014.02.005.

Phase II Trial of Neoadjuvant Weekly Nanoparticle Albumin-Bound Paclitaxel, Carboplatin, and Biweekly Bevacizumab Therapy in Women With Clinical Stage II or III HER2-Negative Breast Cancer

Ewa Mrózek¹, Rachel Layman¹, Bhuvaneswari Ramaswamy¹, Maryam Lustberg¹, Andrea Vecchione², Michael V. Knopp³, and Charles L. Shapiro¹

¹Division of Medical Oncology, The Ohio State University Medical Center, Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH

²Department of Molecular Virology, Immunology, and Medical Genetics, College of Medicine and Comprehensive Cancer Center, The Ohio State University, Columbus, OH

³Division of Imaging Science, Department of Radiology, The Ohio State University, Columbus, OH

Abstract

This phase II trial tested the rate of pathologic complete response (pCR) achieved by women with stage II–III human epidermal growth factor receptor 2-negative (HER2-negative) breast cancer (BC) treated with neo-adjuvant nanoparticle albumin-bound paclitaxel (nab-P), carboplatin and bevacizumab. The rate of pCR was 18%, all pCRs were observed in patients with triple negative BC.

Background—We hypothesized that adding bevacizumab to neoadjuvant chemotherapy (NCT) with nab-P and carboplatin would increase the rates of pCR in BC patients and that early changes in tumor vascularity imaged by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) would predict pCR.

Methods—Thirty-three women with clinical stage II or III HER2-negative BC received nab-P 100 mg/m² and carboplatin area under the curve = 2 on days 1, 8, and 15 in combination with bevacizumab 10 mg/kg on days 1 and 15 administered every 28 days.

Results—Six patients (18%) achieved pCR, all pCRs occurred in triple-negative BC (TNBC) (pCR = 50% for TNBC). At the end of cycle 2, the changes in relative angiogenic volume were significantly different between responders and non-responders ($P = .001$). The major toxicity of this NCT was myelosuppression.

© 2014 Elsevier Inc. All rights reserved.

Address for correspondence: Ewa Mrózek, MD, Division of Medical Oncology, The Ohio State University, B 424 Starling-Loving, 320 West 10th Ave, Columbus, OH, 43210, ewa.mrozek@osumc.edu.

The authors have stated that they have no additional conflicts of interest.

Disclosure

The work was supported in part by grants from Celgene and from Genentech. This article was presented in part at the American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, June 4–8, 2010.

Conclusion—NCT with weekly nab-P, carboplatin, and biweekly bevacizumab resulted in a pCR rate that was neither superior to the historical data with anthracycline- or taxane-containing NCT nor to carboplatin and taxane combinations in patients with HER2-negative BC. In patients with TNBC, the observed pCR rate was 50%. The early changes in the relative angiogenic volume imaged by DCE-MRI could predict pCR.

Keywords

Carboplatin; Human epidermal growth factor receptor–negative breast cancer; Nanoparticle albumin-bound paclitaxel; Neoadjuvant chemotherapy; Pathologic complete response

Introduction

Neoadjuvant chemotherapy (NCT) provides an opportunity to assess clinical, image-guided, and pathologic tumor response.^{1–4} Several neoadjuvant trials have shown that a pathologic complete response (pCR) correlates well with favorable long-term outcomes and may be a surrogate marker for survival.^{5–7} Whereas anthracycline-based regimens were extensively evaluated in the neoadjuvant setting, there is need to evaluate non–anthracycline-containing NCT regimens. Analyses of 8 large, randomized adjuvant trials comparing anthracycline- with non–anthracycline-chemotherapy regimens showed that mainly women with human epidermal growth factor receptor–positive (HER2⁺) breast cancer derived an incremental benefit from anthracycline use.⁸ Furthermore, retrospective analyses of adjuvant trials suggest that non–anthracycline chemotherapy may be particularly effective in the adjuvant treatment of triple-negative cancers.^{9,10} In search of non–anthracycline regimens, the DNA-damaging platinum drugs in combination with taxanes gained interest.¹¹ The combination of paclitaxel and carboplatin was active in the metastatic and neoadjuvant settings of breast cancer therapy.^{12–15} NCT with a combination of weekly paclitaxel and carboplatin resulted in pCR rates that were similar or better than those of anthracycline-based NCT with acceptable side effects.^{12,13}

Nanoparticle albumin-bound paclitaxel (nab-P) was developed to avoid hypersensitivity reactions associated with the polyethoxylated castor oil (Cremophor) vehicle in solvent-based paclitaxel. In addition, preclinical models suggested that nab-P may reach the tumor micro-environment more efficiently than solvent-based paclitaxel via caveolae-mediated transcytosis.¹⁶ Clinical studies have demonstrated superior efficacy and safety of weekly nab-P compared with that of paclitaxel or docetaxel in the treatment of metastatic breast cancer.^{17,18} Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF) A, when added to anthracycline-and-taxane–based neoadjuvant chemotherapy, significantly increased the rate of pCR.^{19,20} We hypothesized that NCT with weekly nab-P, carboplatin, and bevacizumab would be worthy of further study if the target pCR rate was at least 30%, which is not inferior to the historical data with anthracycline and taxane NCT.

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) detects breast cancer by demonstrating contrast enhancement associated with tumor angiogenesis.²¹ The NCT provides opportunity for prospective assessment whether DCE-MRI can serve as an earlier and more accurate marker of tumor response than anatomic imaging or clinical breast

examination. We hypothesized that the early changes in tumor vascularity imaged by DCE-MRI would predict the pCR.

The eucine zipper, putative tumor suppressor 1 (LZTS1) protein has been implicated in cell-cycle control through its interaction with the Cdk1/cyclinB1 complex.²² The LZTS1 expression was significantly reduced or absent in a series of 340 invasive breast carcinomas compared with that in normal breast tissue. Lower levels of LZTS1 correlated with high histologic grade, lymph node metastasis, and poor prognosis.²³ We analyzed LZTS1 expression by immunohistochemistry (IHC) in pre-NCT breast biopsies to evaluate whether LZTS1 could be a predictive marker for response to the NCT regimen used in our study.

Patients and Methods

Patient Population

Eligible patients had histologically proven invasive breast cancer and were judged by the multidisciplinary team to be candidates for neo-adjuvant chemotherapy. The participants were required to have clinical stage II or III breast cancer with clinically or radiographically measurable residual tumor after core biopsy. Women with HER2⁺ breast cancer were excluded. Other eligibility criteria included Eastern Cooperative Oncology Group (ECOG) Performance Status 1; age ≥ 18 years; absolute neutrophil count (ANC) > 1500 cells/dL; hemoglobin > 9 g/dL; platelet count > 100,000 cells/dL; creatinine < 1.5 × upper limit of normal (ULN); an adequate liver function with aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 2.5 × ULN, alkaline phosphatase < 2.5 × ULN, and bilirubin < ULN; left ventricular ejection fraction measurement by echocardiogram or multigated acquisition scan (MUGA) that was greater than the institutional lower limit of normal (LLN). All participants provided written consent before initiation of treatment. The study was approved by the human institutional review board, and all patients signed informed consent.

Treatment Design

This was a single-institution, single-arm phase II NCT trial of weekly nab-P 100 mg/m² over 30 minutes and carboplatin area under the curve (AUC) 2, as calculated by the Calvert formula, over 30 minutes in combination with bevacizumab. The bevacizumab at the dose of 10 mg/kg was administered on days 1 and 15 of each 28-day cycle for 5 cycles only. The sixth cycle of NCT was administered without bevacizumab, to allow for at least an 8-week break between the last dose of bevacizumab and the time of definite breast surgery. On day 1 of each cycle, the treatment was delayed for ANC < 1500 cells/dL or platelet count < 100,000 cells/dL. On day 8 or day 15 of each cycle, the treatment was held if ANC was < 1000 cells/dL or platelet count was < 75,000 cells/dL. For febrile neutropenia or grade 4 neutropenia lasting for > 7 days, filgrastim was added. When febrile neutropenia or grade 4 neutropenia reoccurred despite treatment with filgrastim, the dose of carboplatin was reduced to AUC 1.5 for all subsequent weekly doses. The dose of carboplatin was also reduced to AUC 1.5 for grade 3 or 4 thrombocytopenia. The dose of nab-P was reduced to 80 mg/m² for grade 3 peripheral neuropathy. Chemotherapy was suspended for other grade 3 or greater nonhematologic toxicities, till they resolved to grade 2.

DCE-MRI

DCE-MRI was performed before NCT, after 2 cycles of therapy and prior to the definitive surgery with a 6-timepoint, 3-dimensional sagittal bilateral dynamic vibrant sequence on a Signa 1.5 T clinical scanner (GE, Fairfield, CT). Gadopentetate dimeglumine (Magnevist, Bayer HealthCare, Leverkusen, Germany) was used as the contrast agent. An experienced radiologist who was blinded to clinical information reviewed the magnetic resonance images with the assistance of a computer-aided design system (CADstream, Confirma, Kirkland, WA).

Surgery

The type of breast surgery performed after NCT was left to the discretion of the surgeon and patient. Definitive surgery occurred approximately 4 to 5 weeks after the completion of NCT and approximately 9 weeks from the last dose of bevacizumab.

Adjuvant Chemotherapy

All patients were to receive 6 months of adjuvant bevacizumab at 15 mg/kg intravenously (I.V.) every 3 weeks. The use of anthracycline-containing adjuvant chemotherapy or radiation therapy was left to the treating physician's judgment. If the patient was treated with an adjuvant anthracycline-containing regimen, then bevacizumab was administered 3 weeks after completing the anthracycline regimen. All patients with hormone receptor-positive breast cancer received endocrine therapy.

LZTS1 Immunohistochemistry

Pre-NCT core biopsy specimens were assayed by immunohisto-chemistry (IHC), using an anti-LZTS1 antibody. Following depar-affinization and antigen retrieval in citrate buffer (0.01 M sodium citrate [pH 7]), all sections were immunostained overnight at room temperature with a 1:1000 dilution of the anti-LZTS1 antibody. The primary antibody was omitted and replaced with preimmune serum in the negative control. Sections were reacted with biotinylated anti-rabbit antibody and streptavidin-biotin-peroxidase (Histostain-SP Kit, Life Technologies, Thermo Fisher Scientific, Waltham, MA). Diaminobenzidine (DAB) was used as a chromogene substrate. Finally, sections were washed in distilled water and weakly counterstained with Harry's modified hematoxylin. All sections were examined independently of knowledge of pCR. The protein expression was scored by the staining index. The staining index for each tumor was calculated by multiplying the intensity of staining by the percent of cell staining. Intensity of staining was scored on the majority of stained cells. The following scoring system was used in the analysis: 0, no staining; 1+, weak-to-moderate staining; 2+, moderate-to-strong staining; 3+, strong staining.

Study Endpoints

The trial had 2 primary endpoints: (1) the rate of pCR, defined as the absence of viable invasive tumor cells in the surgical breast specimen and axillary lymph nodes and (2) the side effects of the treatment regimen. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (<http://ctep.cancer.gov/protocol>). Patients with residual ductal carcinoma in situ (DCIS) or isolated

tumor cells (ITCs) in the breast or in a single axillary node (N0i⁺) were also considered to have achieved a pCR. Minimal residual disease (MRD) was defined as a residual invasive disease of ≤ 0.5 cm (ypT1a).

The secondary objectives of the study were (1) to evaluate whether early changes in tumor vascularity imaged by DCE-MRI could correlate with pathologic response; (2) to assess whether expression of LZTS1 in pre-NCT breast biopsy could predict sensitivity or resistance to NCT; (3) to evaluate the feasibility and toxicity of 6-month therapy with single-agent bevacizumab in the adjuvant setting.

Statistical Analysis

A Fleming single-stage phase II trial design (with $P_0 = .1$, $\alpha = 0.05$, and $\beta = 0.10$) indicated that a sample size of 33 patients was needed to demonstrate the true pCR probability or target pCR rate of 30% or greater (P_1). With 33 patients treated, we were able to estimate the frequency of pCR with a 95% confidence interval of not greater than 17%. All patients who received at least 1 cycle of bevacizumab, nab-P, and carboplatin were included in the intent-to-treat (ITT) population.

Results

Patients

Patient and disease characteristics are presented in Table 1. In all, 33 patients with clinical stage II or III HER2-negative (HER2⁻) breast cancer were enrolled in the study. The majority of women were premenopausal, with a median age of 48 years (range, 28–74 years). A total of 12 patients (36%) had triple-negative breast cancer (TNBC). All but 1 patient had axillary lymph node evaluation before the NCT. Evidence of LN involvement, based on core biopsy or sentinel lymph node biopsy, was observed in 19 (57%) patients.

Treatment Summary

Table 2 provides a summary of received systemic treatment. Of 33 patients, 24 (76%) received all 6 cycles of neoadjuvant chemotherapy with delays and some missed doses; however, only 3 patients (9%) received all 18 planned infusions without delays. One patient received 5 cycles of neoadjuvant chemotherapy, and when she recovered from prolonged neutropenia after cycle 5, she proceeded with the breast surgery. The remaining 8 patients (24%) received 4 or fewer cycles of NCT. The primary reason for not completing all 6 cycles was prolonged myelosuppression ($n = 6$), wound infection ($n = 1$), or disease progression ($n = 1$). Twenty patients (61%) received 6 months of adjuvant bevacizumab therapy. Adjuvant bevacizumab was withheld from 2 patients because of postsurgical healing complications at the site of breast surgery. Eight patients (24%) received postsurgical adjuvant chemotherapy with 4 cycles of doxorubicin and cyclophosphamide (AC).

Toxicity

Table 3 describes hematologic adverse events observed during neoadjuvant chemotherapy. Although there was only 1 grade 4 hematologic toxicity (thrombocytopenia), almost 70% of

patients developed grade 3 neutropenia at some point of therapy. Thus, myelosuppression was responsible for the noncompletion of neoadjuvant therapy and for delays in administration of treatment in the majority of patients. There was only 1 episode of grade 3 neutropenic fever.

Table 4 describes the most common nonhematologic toxicities observed during neoadjuvant chemotherapy. The only grade 4 adverse event was skin necrosis at the site of nab-P extravasation that required skin grafting. The most common grade 3 nonhematologic toxicities were fatigue, reported in 7 patients (21%), and peripheral neuropathy, reported in 2 patients (6%). Common grade 2 toxicities included fatigue, insomnia, headaches, arthralgia, diarrhea, constipation, and neuropathy. Among 20 patients (61%) who received 6 months of adjuvant bevacizumab therapy, there was 1 patient with grade 3 hypersensitivity reaction (3%), 2 patients with grade 3 hypertension (6%), and 1 patient with grade 3 infection at the mastectomy site (3%) with normal ANC.

Efficacy

The overall rate of pCR in 33 patients enrolled in the study was 18%. All 6 patients who achieved pCR had TNBC Table 5. Thus, in the subgroup of 12 patients with TNBC, the rate of pCR was 50%. Microscopic residual disease was found in 3 patients (9%).

DCE-MRI

Relative angiogenic volume (AV) was defined as the ratio of AV to the geometric volume of the tumor in the breast. Relative AV was measurable in 20 of the 28 evaluable patients. One patient was excluded because DCE-MRI was not conducted after cycle 2. One patient was identified as an outlier because her target tumor completely dissolved by the time of the pathologic analysis, but she had positive nodes. Because DCE-MRI is not a node-sensitive technique, she was excluded. The other 6 patients were excluded because of poor signal enhancement that caused significant underestimation of tumor volume after NCT. The DCE-MRI showed that at the end of cycle 2, the relative AV decreased from $65\% \pm 18\%$ in baseline DCE-MRI to $40\% \pm 33\%$ in patients with pCR and MRD. The changes in relative AV were significantly different between responders and nonresponders ($P = .001$) (Fig. 1).

LZTS1 Expression

Each patient had 2 core biopsies collected from the breast tumor prior to NCT. However, at the time of IHC analysis of the research core biopsies, 6 patients (18%) did not have evaluable cancer in collected samples. Of those patients, 1 had TNBC. Therefore, LZTS1 expression in breast cancer cells collected prior to NCT was assessed in 27 patients (82%) (Table 6). There was no apparent correlation between response to NCT and LZTS1 protein expression.

Discussion

This phase II trial showed that NCT with a weekly schedule of nab-P and carboplatin and twice per week bevacizumab resulted in a pCR of 18% in women with clinical stage II or III HER2⁻ breast cancer. Among 12 (36%) patients with TNBC, the pCR rate was 50%. We

acknowledge the limitations of our study, given the lack of a control arm and the relatively small sample size. Although the current trial did not meet the primary endpoint for efficacy, it supported the hypothesis that this regimen might be effective in the subpopulation of patients with TNBC.

Comparing results among NCT studies is difficult because of differences in the duration of treatment, patient populations, and definitions of pCR. Table 7^{14,15,25,30,31} presents results of current, mostly small, single-institution and single-arm studies of the combination of taxanes and carboplatin in NCT. A phase II study of NCT in 107 patients with tumor characteristics similar to those of the current trial and a similar definition of pCR showed that 4 cycles of weekly paclitaxel and carboplatin achieved pCR rate of 19.4%, and the pCR rate in patients with TNBC was 33%.¹⁵ Results of our study suggest that the addition of 2 more cycles of chemotherapy, or the substitution of paclitaxel with nab-P, or the addition of bevacizumab to cytotoxic chemotherapy might not improve the pCR rate in the general population of HER2⁻ breast cancer patients. However, for patients with TNBC, a longer course of NCT might increase the rate of pCR, as suggested by our study and a Brown University Oncology Group study, in which 6 cycles of NCT with carboplatin and paclitaxel generated pCR rates of 50% and 67%, respectively.¹⁴ The GeparQuinto study (GBG 44) showed that the addition of bevacizumab to neoadjuvant anthracycline- and taxane-based chemotherapy in TNBC significantly increases pCR rates.²⁴ In agreement with our findings, a multicenter phase II trial of bevacizumab combined with docetaxel–carboplatin in NCT of TNBC resulted in an encouraging pCR rate of 42% in 45 patients.²⁵

The current trial revealed a higher-than-expected incidence of myelosuppression. This toxicity could be attributed to the addition of bevacizumab to the weekly schedule of carboplatin. The rationale for the weekly, as opposed to every-3-week, schedule of carboplatin therapy was based on trials in breast and ovarian cancer showing that weekly administration was associated with less myelosuppression.^{26,27} An additional argument for using a weekly schedule of carboplatin and nab-P was evidence from the Cancer and Leukemia Group B (CALGB) 9741 trial demonstrating that dose density and intensity play an important role in breast cancer chemotherapy in the adjuvant setting.²⁸

Bevacizumab-related postoperative wound complications are of concern in the neoadjuvant setting. Recent data suggest that neo-adjuvant bevacizumab may be associated with an increased risk of major postoperative complications.²⁹ We observed 3 instances (9%) of wound-healing complications during NCT, with 1 patient having grade 2 delayed wound healing after breast surgery, 1 having delayed wound healing after the removal of an infected Medi-port, and 1 patient developing skin necrosis at the site of nab-P extravasation that required skin grafting. This rate of complications was similar to those reported in other neoadjuvant trials with bevacizumab. We did not observe any wound-healing problems during 6 months of adjuvant bevacizumab therapy.

Our trial showed that it is feasible to administer 6 months of adjuvant bevacizumab therapy. Among 20 patients who received 6 months of adjuvant bevacizumab, we observed 1 grade 3 hypersensitivity reaction, 2 grade 3 hypertension, and 1 grade 3 infection at the mastectomy site with normal ANC.

DCE-MRI of the breast has been proposed to have a role in predicting final pathologic response when undertaken early during NCT of breast cancer.³⁰ Multiple MRI parameters, including changes in uni- or bidimensional tumor size, 3-dimensional volume, quantitative dynamic contrast measurements, early contrast uptake, and descriptive patterns of tumor reduction, were measured in different studies. Heterogeneity across evaluated MRI parameters, differences in the definition of pCR, and a small number of patients preclude comparison of those studies. Our study suggests that early changes in a relative AV imaged by DCE-MRI after 2 cycles of NCT were able to distinguish responders from nonresponders at completion of treatment.

Analysis of LZTS1 expression by IHC showed that 9 of 11 patients with evaluable TNBC (82%) (all grade 3 tumors) had moderate-to-strong expression of LZTS1, in contrast to 50% of evaluable patients with hormone-responsive breast cancer. We could not make a correlation between expression of LZTS1 and pCR because of a small number of evaluable patients.

Conclusion

In conclusion, our study shows that NCT with weekly nab-P and carboplatin and twice per week bevacizumab resulted in a pCR rate that was superior neither to the historical data with anthracycline/taxane-containing NCT nor to carboplatin and taxane combinations in patients with HER2⁻ breast cancer. However, the 50% rate of pCR observed in the subpopulation of patients with TNBC makes this combination worthy of further evaluation. In addition, our study suggests that early changes in the relative AV imaged by DCE-MRI could predict pCR.

Clinical Practice Points

- The NCT allows assessing clinical, image-guided and pathologic tumor response. While anthracycline-based regimens were extensively evaluated in the neoadjuvant setting, there is less data on non-anthracycline NCT regimens.
- Since a pCR may be a surrogate marker for survival, we examined the pCR rate in response to NCT with weekly Nab-P, carboplatin and bevacizumab in patients with stage II–III HER2 negative breast cancer.
- The current study shows that above NCT resulted in pCR rate that was neither superior to the historical data with anthracycline/taxane-containing NCT nor to carboplatin/taxane combinations in patients with HER2 negative breast cancer. However, in a subpopulation of patients with TNBC the observed pCR rate was 50%.
- Our study suggests that early changes in the relative AV imaged by DCE-MRI could predict pCR.
- The current trial revealed higher than expected incidence of myelosuppression, possibly due to the addition of bevacizumab to weekly instead of every 3 week schedule of carboplatin.

- Our results provide further support for the benefit of non-anthracycline NCT in TNBC.

Acknowledgments

The authors thank all of the patients who participated in this trial as well as the dedicated nurses, nurse practitioners, and staff of The Ohio State University Comprehensive Cancer Center Clinical Trials Office.

References

1. Bear HD, Anderson S, Smith RE, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol.* 2006; 24:2019–27. [PubMed: 16606972]
2. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol.* 1998; 16:2672–85. [PubMed: 9704717]
3. van der Hage JA, van der Velde CJ, Julien JP, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. *J Clin Oncol.* 2001; 19:4224–37. [PubMed: 11709566]
4. Wolff AC, Berry D, Carey LA, et al. Research issues affecting preoperative systemic therapy for operable breast cancer. *J Clin Oncol.* 2008; 26:806–13. [PubMed: 18258990]
5. Pierga JY, Mouret E, Laurence V, et al. Prognostic factors for survival after neo-adjuvant chemotherapy in operable breast cancer: the role of clinical response. *Eur J Cancer.* 2003; 39:1089–96. [PubMed: 12736108]
6. Debled M, Mauriac L. Neoadjuvant chemotherapy: are we barking up the right tree? *Ann Oncol.* 2010; 21:675–9. [PubMed: 20338876]
7. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol.* 2012; 30:1796–804. [PubMed: 22508812]
8. Gennari A, Sormani MP, Pronzato P, et al. *HER2* status and efficacy of adjuvant anthracyclines in early breast cancer: a pooled analysis of randomized trials. *J Natl Cancer Inst.* 2008; 100:14–20. [PubMed: 18159072]
9. Conforti R, Boulet T, Tomasic G, et al. Breast cancer molecular subclassification and estrogen receptor expression to predict efficacy of adjuvant anthracyclines-based chemotherapy: a biomarker study from two randomized trials. *Ann Oncol.* 2007; 18:1477–83. [PubMed: 17515403]
10. Colleoni M, Cole BF, Viale G, et al. Classical cyclophosphamide, methotrexate, and fluorouracil chemotherapy is more effective in triple-negative, node-negative breast cancer: results from two randomized trials of adjuvant chemoendocrine therapy for node-negative breast cancer. *J Clin Oncol.* 2010; 28:2966–73. [PubMed: 20458051]
11. Gelmon K, Dent R, Mackey JR, et al. Targeting triple-negative breast cancer: optimising therapeutic outcomes. *Ann Oncol.* 2012; 23:2223–34. [PubMed: 22517820]
12. Loesch D, Robert N, Asmar L, et al. Phase II multicenter trial of a weekly paclitaxel and carboplatin regimen in patients with advanced breast cancer. *J Clin Oncol.* 2002; 20:3857–64. [PubMed: 12228205]
13. Estevez LG, Gradishar WJ. Evidence-based use of neoadjuvant taxane in operable and inoperable breast cancer. *Clin Cancer Res.* 2004; 10:3249–61. [PubMed: 15161677]
14. Sikov WM, Dizon DS, Stenger R, et al. Frequent pathologic complete responses in aggressive stages II to III breast cancers with every-4-week Carboplatin and weekly Paclitaxel with or without trastuzumab: a Brown University Oncology Group Study. *J Clin Oncol.* 2009; 27:4693–700. [PubMed: 19720916]
15. Chen XS, Nie XQ, Chen CM, et al. Weekly paclitaxel plus carboplatin is an effective non-anthracycline-containing regimen as neoadjuvant chemotherapy for breast cancer. *Ann Oncol.* 2010; 21:961–7. [PubMed: 20211870]

16. Desai N, Trieu V, Yao Z, et al. Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. *Clin Cancer Res.* 2006; 12:1317–24. [PubMed: 16489089]
17. Ibrahim NK, Samuels B, Page R, et al. Multicenter phase II trial of ABI-007, an albumin-bound paclitaxel, in women with metastatic breast cancer. *J Clin Oncol.* 2005; 23:6019–26. [PubMed: 16135470]
18. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil–based paclitaxel in women with breast cancer. *J Clin Oncol.* 2005; 23:7794–803. [PubMed: 16172456]
19. Bear HD, Tang G, Rastogi P, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. *N Engl J Med.* 2012; 366:310–20. [PubMed: 22276821]
20. von Minckwitz G, Eidtmann H, Rezai M. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. *N Engl J Med.* 2012; 366:299–309. [PubMed: 22276820]
21. Arlinghaus LR, Li X, Levy M, et al. Current and future trends in magnetic resonance imaging assessments of the response of breast tumors to neoadjuvant chemotherapy. *J Oncol.* 2010; 2010 pii: 919620.
22. Vecchione A, Croce CM, Baldassarre G. *Fez1/Lzts1* a new mitotic regulator implicated in cancer development. *Cell Div.* 2007; 2:24. [PubMed: 17718912]
23. Wang XX, Zhu Z, Su D, et al. Down-regulation of leucine zipper putative tumor suppressor 1 is associated with poor prognosis, increased cell motility and invasion, and epithelial-to-mesenchymal transition characteristics in human breast carcinoma. *Hum Pathol.* 2011; 42:1410–9. [PubMed: 21419475]
24. Gerber B, Loibl S, Eidtmann H, et al. Neoadjuvant bevacizumab and anthracycline-taxane-based chemotherapy in 678 triple-negative primary breast cancers; results from the geparquinto study (GBG 44). *Ann Oncol.* 2013; 24:2978–84. [PubMed: 24136883]
25. Kim HR, Jung KH, Im SA, et al. Multicentre phase II trial of bevacizumab combined with docetaxel-carboplatin for the neoadjuvant treatment of triple-negative breast cancer (KCSG BR-0905). *Ann Oncol.* 2013; 24:1485–90. [PubMed: 23380385]
26. Perez EA, Suman VJ, Rowland KM, et al. Two concurrent phase II trials of paclitaxel/carboplatin/trastuzumab (weekly or every-3-week schedule) as first-line therapy in women with HER2-overexpressing metastatic breast cancer: NCCTG study 983252. *Clin Breast Cancer.* 2005; 6:425–32. [PubMed: 16381626]
27. Wu CH, Yang CH, Lee JN, et al. Weekly and monthly regimens of paclitaxel and carboplatin in the management of advanced ovarian cancer. A preliminary report on side effects. *Int J Gynecol Cancer.* 2001; 11:295–9. [PubMed: 11520368]
28. Citron ML, Berry DA, Cirincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol.* 2003; 21:1431–9. [PubMed: 12668651]
29. Golshan M, Garber JE, Gelman R, et al. Does neoadjuvant bevacizumab increase surgical complications in breast surgery? *Ann Surg Oncol.* 2011; 18:733–7. [PubMed: 20882415]
30. Marinovich ML, Sardanelli F, Ciatto S, et al. Early prediction of pathologic response to neoadjuvant therapy in breast cancer: systematic review of the accuracy of MRI. *Breast.* 2012; 21:669–77. [PubMed: 22863284]
31. Roy V, Pockaj BA, Allred JB, et al. A Phase II trial of docetaxel and carboplatin administered every 2 weeks as preoperative therapy for stage II or III breast cancer: NCCTG study N0338. *Am J Clin Oncol.* 2013; 36:540–4. [PubMed: 22868240]
32. Chang HR, Glaspy J, Allison MA, et al. Differential response of triple-negative breast cancer to a docetaxel and carboplatin-based neoadjuvant treatment. *Cancer.* 2010; 116:4227–37. [PubMed: 20549829]

Figure 1.

Post-Neoadjuvant Chemotherapy Drop in Relative Angiogenic Volume for the Triple-Negative (n = 10) and Non-Triple-Negative Breast Cancer Patients (n = 10)

Relative angiogenic volume = (V_{Angio}/V_{Geo}).

Abbreviations: ER = estrogen receptor; PR = progesterone receptor; V_{Angio} = angiogenic volume; V_{Geo} = geometric volume.

Table 1**Main Patient and Tumor Characteristics**

Characteristic	Patients, No. (%)
Median age (range), years	48 (28–74)
Race	
White	30 (91)
African-American	2 (6)
Asian	1 (3)
Menopausal status	
Premenopausal	21 (64)
Postmenopausal	12 (36)
Receptor status (all HER2/neu negative)	
Triple negative	12 (36)
ER and PR positive	21 (64)
Axillary lymph node status before NCT	
Positive by core biopsy	15 (45)
Positive by SLNB	4 (12)
Negative by core biopsy	5 (15)
Negative by SLNB	8 (24)
Not evaluated	1 (3)

Abbreviations: ER = estrogen receptor; HER2/neu = human epidermal growth factor receptor 2; NCT = neoadjuvant chemotherapy; PR = progesterone receptor, SLNB = sentinel lymph node biopsy.

Table 2

Summary of Systemic Treatment Received by 33 Patients

Systemic Treatment	Patients, No. (%)
Neoadjuvant chemotherapy	
Received all 18 planned infusions without delays	3 (9)
Received all 18 infusions with delays	4 (12)
Received all cycles with missed doses and delays	17 (52)
Received 5 cycles	1 (3)
Received 4 cycles	2 (6)
Received 3 cycles	2 (6)
Received 2 cycles	4 (12)
Adjuvant chemotherapy	
Doxorubicin and cyclophosphamide	8 (24)
Bevacizumab	20 (61)

Table 3

Hematologic Toxicities Observed During Neoadjuvant Chemotherapy in 33 Patients

Hematologic Toxicity	Patients, No. (%)		
	Grade 2	Grade 3	Grade 4
Leukopenia	19 (58)	7 (21)	0 (0)
Anemia	15 (45)	1 (3)	0 (0)
Thrombocytopenia	11 (33)	2 (6)	1 (3)
Neutropenia	6 (18)	23 (70)	0 (0)
Neutropenic fever	0 (0)	1 (3)	0 (0)

Table 4

Nonhematologic Toxicities Observed in 33 Patients During Neoadjuvant Chemotherapy

Toxicity	Patients, No. (%)		
	Grade 2	Grade 3	Grade 4
Wound complications	2 ^a	1 ^b	1 ^c
Fatigue	21	7	0
Nausea	7	1	0
Infection with normal ANC	7	1	0
Peripheral neuropathy	6	2	0
Constipation	7	1	0
Hypertension	5	1	0
Depressed mood	5	1	0
Syncope	0	1	0
Insomnia	12	0	0
Headache	12	0	0
Arthralgia	10	0	0
Diarrhea	6	0	0
Mucositis	4	0	0

Abbreviations: ANC = absolute neutrophil count; nab-P = nanoparticle albumin-bound paclitaxel.

^aDelayed wound healing after breast surgery.^bDelayed wound healing after removal of infected Medi-port.^cSkin necrosis at the site of nab-P extravasation.

Table 5

The Rate of Complete Pathologic Response

Subtype of Breast Cancer	Patients, Total No.	Patients With pCR, No. (%)
Triple negative	12	6 (50)
ER ⁺ /PR ⁺	21	0 (0)

Abbreviations: ER = estrogen receptor; pCR = pathologic complete response; PR = pro-gesterone receptor.

Table 6

Expression of LZTS1 in 27 Patients With Evaluable Core Biopsies

	LZTS1 Expression			
	0	+1	+2	+3
Patients with TNBC n = 11	2	0	3	6
Patients with pCR n = 5	2	0	2	1
Patients with hormone-responsive BC n = 16	6	2	2	6

Abbreviations: BC = breast cancer; pCR = pathologic complete response; TNBC = triple-negative breast cancer.

Table 7

Current Neoadjuvant Chemotherapy Studies With Platinum or Taxane

Chemotherapy	Patients, Total no.	Patients, No. With TNBC	Patients With pCR, %/Total Patients With TNBC, %	pCR Definition
Weekly paclitaxel, carboplatin AUC6 every 4 weeks for 16 weeks ¹⁴	54	12	45/67	pCR in breast and axilla
Weekly paclitaxel, weekly carboplatin AUC2 for 4 cycles ¹⁵	107	24	19.4/33	pCR in breast and axilla
Docetaxel and carboplatin AUC6 every 2 weeks for 4 cycles ³¹	57	9	16/44	pCR in breast and axilla
Docetaxel and carboplatin AUC6 every 3 weeks for 4 cycles ³²	74	11	27/55	pCR in breast
Docetaxel, carboplatin AUC5 and bevacizumab every 3 weeks for 6 cycles ²⁵	45	45	42/42	pCR in breast and axilla

Abbreviations: AUC = area under the curve; pCR = pathologic complete response; TNBC = triple-negative breast cancer.