Published in final edited form as:

Clin Breast Cancer. 2015 October ; 15(5): 325–331. doi:10.1016/j.clbc.2015.03.004.

Phase II randomized study of ixabepilone vs. observation in patients with significant residual disease after neoadjuvant systemic therapy for HER2-negative breast cancer

Ana M Gonzalez-Angulo^{1,2}, Xiudong Lei³, Richardo H Alvarez¹, Majorie C Green⁴, James L Murray¹, Vicente Valero¹, Kimberly B Koenig¹, Nuhad K Ibrahim¹, Jennifer K Litton¹, Lakshmy Nair¹, Savitri Krishnamurthy⁵, Gabriel N Hortobagyi¹, and Funda Meric-Bernstam^{6,7}

¹Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcomb e Boulevard, Houston, TX 77030, USA

²Department of Systems Biology, The University of Texas MD Anderson Cancer Center, 1515 Holcomb e Boulevard, Houston, TX 77030, USA

³Department of Biostatistics, The University of Texas MD Anderson Cancer Center, 1515 Holcomb e Boulevard, Houston, TX 77030, USA

⁴Genentech, 1 DNA Way, South San Francisco, CA 94080, USA

⁵Department of Pathology, The University of Texas MD Anderson Cancer Center, 1515 Holcomb e Boulevard, Houston, TX 77030, USA

⁶Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, 1515 Holcomb e Boulevard, Houston, TX 77030, USA

⁷Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcomb e Boulevard, Houston, TX 77030, USA

Abstract

Background—Residual disease (RD) after neoadjuvant chemotherapy (NST) carries an increased risk for recurrence. Ixabepilone has activity in anthracycline/taxane resistant breast cancer. We explored adjuvant ixabepilone in patients with significant RD HER2-negative breast cancer.

Methods—A Phase II study in patients with residual cancer burden (RCB-II or RCB-III) randomized to ixabepilone vs. observation was conducted. CTCs were measured at baseline, at 9

Correspondence: Funda Meric-Bernstam, M.D., Division of Cancer Medicine and Surgery, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 455, Houston, TX 77030-4009, USA; Tel: (713) 794-1226; Fax: (713) 563-0566; fmeric@mdanderson.org.

DISCLOSURES

AMG, JKL and have research support and have served as advisors for Bristol Myers Squibb.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

and at 18 weeks. Survival probabilities were estimated by Kaplan-Meier product limit. Toxicities were reported as proportions in the ixabepilone arm.

Results—Accrual was stopped due to ixabepilone toxicity. Sixty-seven patients were registered, 43 randomized, 19 received ixabepilone and 24 went to observation. One patient (9.1%) in the observation arm vs. 2 patients (18.2%) in the ixabepilone arm had CTCs at 18 weeks ($P=1.0$). Three-year RFS and OS were 94% and 82%, and 100% and 79% in the observation and ixabepilone arms ($P=0.35$ and 0.18), respectively. Most common adverse events (AEs) included fatigue, pain, neuropathy, constipation, nausea, rash, anorexia, and diarrhea. Serious AEs included pain (63.2%), fatigue and neuropathy (31.6% each).

Conclusion—Adjuvant ixabepilone in patients with significant RD after NST was difficult to administer due to AEs. It did not change the presence of CTC or affect survival outcomes.
NCT00877500

Keywords

Residual disease; neoadjuvant systemic therapy; circulating tumor cells; ixabepilone

INTRODUCTION

Neoadjuvant systemic therapy (NST), a standard approach to treat women with locally advanced and inflammatory breast cancer, is increasingly being used in patients with earlier stage disease. It is associated with a number of advantages, including down staging of tumors and in-vivo assessment of chemo-sensitivity. Furthermore, attaining a pathological complete response (pCR) following NST has been shown to be a surrogate marker for improved long-term outcome.^{1–8} On the other hand, patients with residual breast cancer after NST are at increased risk for recurrence and may have therapy-resistant disease. A retrospective study from our institution demonstrated a significant survival benefit for patients who achieved pCR vs. no pCR, and was observed regardless of hormone receptor (HR) status.⁷ NST with conventional anthracycline and/or taxane-containing regimens results in pCR in up to 30% of patients.^{4, 9–12} Although the standard of care for patients with residual invasive disease after NST includes completion of loco-regional therapies and addition of adjuvant endocrine therapy and/or trastuzumab based on receptor status, no further therapy is recommended. This is based on the lack of molecular or clinical data demonstrating benefit from additional therapy. While it is generally held that a definition of pCR should include patients without residual invasive carcinoma in the breast and lymph nodes (ypT0N0), investigators at our institution developed the residual cancer burden (RCB) as a continuous index combining pathologic measurements of the primary tumor and nodal metastases. Index cutoff points were identified. Patients with minimal RD (RCB-I) carried the same prognosis as those with pCR (RCB-0), and patients with extensive RD (RCB-III) had poor prognosis, regardless of hormone receptor status or adjuvant endocrine therapy.⁸

The significance of detectable circulating tumor cells (CTCs) after completion of NST is unknown. However, a study from our institution determined that in non-metastatic patients the presence of one or more CTCs predicts early recurrence and decreased overall survival in chemo-naïve patients.¹³

The epothilones are agents that stabilize microtubule dynamics leading to apoptotic cell death. They were developed to overcome tumor resistance mechanisms. Ixabepilone, a semisynthetic analog of epothilone B, was specifically designed to provide enhanced antitumor activity relative to other antineoplastic agents. In an international Phase III study designed to compare ixabepilone plus capecitabine with capecitabine alone in anthracycline-pretreated or -resistant and taxane-resistant locally advanced MBC, the addition of ixabepilone to capecitabine resulted in significant improvement in progression-free survival.¹⁴ In this study, we aimed to evaluate the presence of CTCs at the time of surgery and after ixabepilone therapy, and to explore if the addition of adjuvant ixabepilone improved survival outcomes in patients that have significant RD HER2-negative breast cancer after NST.

PATIENTS AND METHODS

This was a phase II randomized trial conducted at MD Anderson Cancer Center (MDACC). Eligible patients had confirmed RCB-II or RCB-III HER2-negative breast cancer after standard anthracycline/taxane-based NST, and adequate organ function. Patients who had other invasive malignancies within the previous 5 years, pre-existing peripheral neuropathy > grade 1, or evidence of distant metastasis were excluded. All patients signed informed consent approved by the MDACC institutional review board. Patients were stratified by HR status and randomly assigned, 1:1 to ixabepilone (40mg/m² IV every 3 weeks for 6 cycles) vs. observation. Ixabepilone premedication consisted on dexamethasone 20 mg IV, diphenhydramine 50mg IV and famotidine 20mg IV 30–45 minutes prior to infusion. CTCs were collected at baseline, at 9 weeks and at 18 weeks of therapy/observation. NCI Common Toxicity Criteria (CTCAE) Version 3.0 was used for toxicity and adverse event reporting. Ixabepilone was reduced by 20% if the patient experienced either grade 3 non-hematologic toxicity or grade 2 neuropathy.

Toxicity assessments were done every three weeks for 18 weeks while receiving ixabepilone. Treatment was discontinued if unacceptable toxicity or exacerbation of underlying disease developed. Treatment was also discontinued for any grade 4 toxicity, treatment interruption for >21 days, or if toxicity reoccurred after dose reduction. Patients were followed as per current standards after the 18 weeks of protocol therapy (every three months for the first two years, and every six months for the following three years). A patient was considered to have completed therapy if they completed at least 4 cycles. Endocrine therapy for HR-positive disease was started at week 9, and radiotherapy was given per institutional guidelines before ixabepilone therapy.

The primary objective was to examine the difference in CTCs at 18 weeks between those who underwent Ixabepilone therapy and those who were simply observed. A CTCs was defined as the presence of any identified tumor cell per 7.5 ml of whole blood by CellSearch[®] system. The proportion of patients with CTCs was expected to be approximately 20% at the time of surgery. In order to detect a decrease from 30%, which is expected in the observation group at 18 weeks, to 10% in the ixabepilone group at 18 weeks, 58 patients were needed in each group when using an alpha of 0.10 and 80% power. Data was analyzed as intent-to-treat (ITT) and included patients who had consented to the

protocol and were randomized into either of the two arms. Data was also analyzed as per-protocol excluding patients who withdrew consent from the observation arm after randomization. Patient characteristics and CTCs at 18 weeks were compared using the Fisher's exact test. Survival probabilities were estimated non-parametrically using the Kaplan-Meier product limit method. Cox proportional hazards regression models were used to model recurrence-free survival (RFS) and overall survival (OS) as a function of treatment group. Statistical analyses were carried out using SAS 9.2 (SAS Institute, Cary, NC) and S-Plus 7.0 (Insightful Corporation, Seattle, WA).

RESULTS

The trial was designed to randomize 116 patients. However, due to significant toxicities in the ixabepilone arm, the Data and Safety Monitoring Committee recommended to close the study early. Sixty-seven patients were registered, 16 patients were screen failures, 8 patients withdrew consent before randomization, and 8 patients from the observation group withdrew consent after randomization. Thus the ITT analysis included a total of 43 patients (24 in the observation arm and 19 patients in the ixabepilone arm), and the per-protocol analysis included 35 patients (16 in the observation arm, and 19 in the ixabepilone arm) (Figure 1).

Table 1 presents the patient and clinical characteristics between the two arms on the ITT analysis. Median age was 48 years old (range, 23–64 years). There was no statistically significant difference regarding any of the patient and clinical characteristics assuring correct randomization. Half of the patients were younger than 50 years, 70% had HR-positive disease and RCB-III disease, and 16% had residual inflammatory breast cancer.

Table 2 shows the CTC measurement at baseline, at 9 weeks and at 18 weeks in the per-protocol analysis. At 18 weeks, there were 5 patients in the observation arm and 8 patients in the ixabepilone arm that missed CTC collections. After excluding patients with missing CTC measurements, there was 1 patient (9.1%) in the observation arm versus 2 patients (18.2%) in the ixabepilone arm who had at least 1 CTC ($P=1.0$) at 18 weeks. As a sensitivity analysis by treating all missing CTC at 18 weeks as failures (at least 1 CTC), the p-value for comparison was 0.37.

Patients randomized to ixabepilone received a median of 6 cycles (range: 1–6) of treatment. Two patients only received 2 cycles, and 11 patients received the full 6 cycles. Eight patients discontinued therapy, seven of them after a dose reduction, six due to grade 3 toxicities and one to grade 4 toxicities all attributed to ixabepilone. Table 3 summarizes the ixabepilone-related adverse events (AEs). Most common AEs included fatigue (84.2%), pain, neuropathy, constipation, nausea (78.9% each), rash and anorexia (68.4% each), and diarrhea (63.2%). Serious AEs included pain (63.2%), fatigue and neuropathy (31.6% each). One patient reported grade 4 pain and grade 4 neuropathy that required hospitalization and did not resolve after six months of aggressive supportive care.

Median follow-up among all patients was 48 months (range, 16 – 66 months). At the time of this exploratory survival per-protocol analysis, 5 patients (14.2%) had died (4 in the ixabepilone arm and 1 in the observation arm), and 7 (20%) had experienced a recurrence (4

in the ixabepilone arm, and 3 in the Observation arm). Three-year RFS and OS for all patients were 88% and 89%, respectively. Three-year RFS estimates were 94% and 82% in the observation and ixabepilone arms ($P=0.35$), respectively. Three-year OS estimates were 100% and 79% in the observation and ixabepilone arms ($P=0.18$), respectively. Figure 2 shows the survival curves for RFS and OS by study arm. Multivariable Cox proportional hazards models for RFS and OS adjusted for randomization group, and breast cancer subtype showed no significant impact of ixabepilone use on RFS ($P=0.47$) or OS ($P=0.99$) (Data not shown).

DISCUSSION

Residual disease after NST with anthracyclines and taxanes for breast cancer is considered to demonstrate resistance to standard chemotherapy. Current standard of care therefore is no further systemic chemotherapy, as no effective drugs in this setting have yet been identified. Investigators have looked at the role of CTCs in metastatic breast cancer. They found that the presence of 5 or more CTCs/7.5ml of blood was an independent predictor of outcome.¹⁵ Further, elevated CTCs at any time during therapy was an accurate indication of subsequent rapid disease progression and mortality.¹⁶ Several groups have collected blood samples before and after NST in patients with locally advanced breast cancer using the CellSearch® system for evaluation of CTCs. Pierga et al investigated pre- and post-NST blood samples from 118 patients. While the persistence of CTCs at the end of NST was not correlated with primary tumor response, the presence of CTCs was an independent prognostic factor for shorter distant metastasis-free interval ($P=0.017$).¹⁷ Riethdorf et al. evaluated blood samples of 287 patients from the German multicenter GeparQuattro study and demonstrated that >1 CTC was present before NST in 22% of patients, whereas after chemotherapy only 10% had persistent CTCs ($P=0.002$).¹⁸ A total of 15% initially CTC-positive cases were CTC-negative after chemotherapy, whereas 8% of cases became CTC-positive after chemotherapy. Survival data are not yet published for this trial. The prognostic value of CTCs before adjuvant chemotherapy was studied in the German multicenter SUCCESS-trial. CTCs were enumerated in 2,026 breast cancer patients with node-positive or high risk node-negative disease using the CellSearch® system. CTCs were detected in 22% of patients after primary tumor resection.¹⁹ At a median follow-up of 35 months, presence of CTCs before systemic treatment predicted poor disease-free survival ($P<0.0001$), and OS ($P=0.0002$).

To date, there is no available data of the significance of CTCs in RD after NST. In this study we studied the presence of any CTC (1 or more) at baseline and at two other time points. In this small cohort, ixabepilone did not have an effect on the presence of CTCs at the end of therapy. A larger cohort of patients should be studied to answer this question and more importantly, to determine if eradication of CTCs with an adjuvant intervention would correlate with therapy efficacy.

Running clinical trials in the RD setting has been difficult and without encouraging results. A large randomized multicenter study lead by the Translational Breast Cancer Research Consortium looking at the role of adjuvant anti-angiogenesis therapy and non-pharmacologic intervention in this setting had to close due to slow accrual (NCT00925652).

The German Breast Group recently presented the results of the NATAN (Neo-Adjuvant Trial Add-on) trial using postneoadjuvant treatment with zoledronate in patients with RD after anthracyclines/taxane-based NST. They found no effect of this intervention in survival outcomes with an event rate of 50% of the expected at the time of analysis.²⁰

We chose ixabepilone based on the data supporting its activity in anthracycline/taxane resistant metastatic breast cancer. We found that adjuvant ixabepilone was difficult to tolerate, and that in the exploratory analysis of this small cohort, there was no effect on survival outcomes.

Although the AEs reported in our studies are consistent with ixabepilone therapy,¹⁴ the frequency and grade were higher than expected for single agent therapy,²¹ and could be explained by the fact that all patients had recently completed 24 weeks of anthracycline and taxane-based NST, surgery and radiotherapy with almost no therapy-free interval.

CONCLUSIONS

Both the toxicity and lack of efficacy of ixabepilone intervention support the need to identify markers better able to discriminate the different prognostic categories, and underlying biology to help identify more efficacious interventions in the future.²² An excellent example is the recently completed trial to evaluate the role of adjuvant cisplatin and rucaparib in patients with residual triple-negative breast cancer and *BRCA* mutations (NCT01074970). Further studies including those targeting the immune checkpoints are under development. Using RD in order to pre-identify those at highest risk of recurrence may be an important clinical trial model in the future. For those patients who obtain a pCR, adding more therapy is unlikely to significantly impact outcomes, yet finding those at highest risk of recurrence with high RCB and evaluating an intervention would subject only those patients at highest risk to more exposures, while allowing the biology of the RD potentially to help dictate the best treatment strategy.

Acknowledgments

FUNDING

This work was supported in part by Komen for the Cure Catalytic Award KG090341 (AMG), Komen for the Cure Grant SAC 100004 (AMG), American Cancer Society Research Scholar Grant 121329-RSG-11-187-01-TBG (AMG), The Commonwealth Foundation for Cancer Research (AMG), and Bristol Myers Squibb (New York, NY).

References

1. Feldman LD, Hortobagyi GN, Buzdar AU, et al. Pathological assessment of response to induction chemotherapy in breast cancer. *Cancer Res.* 1986; 46:2578–2581. [PubMed: 3697997]
2. Sataloff DM, Mason BA, Prestipino AJ, et al. Pathologic response to induction chemotherapy in locally advanced carcinoma of the breast: a determinant of outcome. *J Am Coll Surg.* 1995; 180:297–306. [PubMed: 7874340]
3. 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; 16:2672–2685. [PubMed: 9704717]
4. Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol.* 1999; 17:460–469. [PubMed: 10080586]

5. Wolmark, N.; Wang, J.; Mamounas, E., et al. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. *J Natl Cancer Inst Monogr.* 2001. <http://www.ncbi.nlm.nih.gov/pubmed/11773300:96-102>
6. 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; 24:2019–2027. [PubMed: 16606972]
7. Guarneri V, Broglio K, Kau SW, et al. Prognostic value of pathologic complete response after primary chemotherapy in relation to hormone receptor status and other factors. *J Clin Oncol.* 2006; 24:1037–1044. [PubMed: 16505422]
8. Symmans WF, Peintinger F, Hatzis C, et al. Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy. *J Clin Oncol.* 2007; 25:4414–4422. [PubMed: 17785706]
9. O'Regan RM, Von Roenn JH, Carlson RW, et al. Final results of a phase II trial of preoperative TAC (docetaxel/doxorubicin/cyclophosphamide) in stage III breast cancer. *Clin Breast Cancer.* 2005; 6:163–168. [PubMed: 16001995]
10. Stearns V, Singh B, Tsangaris T, et al. A prospective randomized pilot study to evaluate predictors of response in serial core biopsies to single agent neoadjuvant doxorubicin or paclitaxel for patients with locally advanced breast cancer. *Clin Cancer Res.* 2003; 9:124–133. [PubMed: 12538460]
11. Colleoni M, Viale G, Zahrieh D, et al. Chemotherapy is more effective in patients with breast cancer not expressing steroid hormone receptors: a study of preoperative treatment. *Clin Cancer Res.* 2004; 10:6622–6628. [PubMed: 15475452]
12. Chevallier B, Roche H, Olivier JP, et al. Inflammatory breast cancer. Pilot study of intensive induction chemotherapy (FEC-HD) results in a high histologic response rate. *Am J Clin Oncol.* 1993; 16:223–228. [PubMed: 8338056]
13. Lucci A, Hall CS, Lodhi AK, et al. Circulating tumour cells in non-metastatic breast cancer: a prospective study. *Lancet Oncol.* 2012; 13:688–695. [PubMed: 22677156]
14. Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol.* 2007; 25:5210–5217. [PubMed: 17968020]
15. Cristofanilli M, Budd GT, Ellis MJ, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. *N Engl J Med.* 2004; 351:781–791. [PubMed: 15317891]
16. Hayes DF, Cristofanilli M, Budd GT, et al. Circulating tumor cells at each follow-up time point during therapy of metastatic breast cancer patients predict progression-free and overall survival. *Clin Cancer Res.* 2006; 12:4218–4224. [PubMed: 16857794]
17. Pierga JY, Bidard FC, Mathiot C, et al. Circulating tumor cell detection predicts early metastatic relapse after neoadjuvant chemotherapy in large operable and locally advanced breast cancer in a phase II randomized trial. *Clin Cancer Res.* 2008; 14:7004–7010. [PubMed: 18980996]
18. Riethdorf S, Muller V, Zhang L, et al. Detection and HER2 expression of circulating tumor cells: prospective monitoring in breast cancer patients treated in the neoadjuvant GeparQuattro trial. *Clin Cancer Res.* 2010; 16:2634–2645. [PubMed: 20406831]
19. BKR, CS, UA, et al. Use of circulating tumor cells (CTC) in peripheral blood of breast cancer patients before and after adjuvant chemotherapy to predict risk for relapse: The SUCCESS trial. *J Clin Oncol.* 2010; 28(suppl):abstr 1003.
20. von Minckwitz G, Rezai M, Eidtmann H, et al. Abstract S5-05: Postneoadjuvant treatment with zoledronate in patients with tumor residuals after anthracyclines-taxane-based chemotherapy for primary breast cancer – The phase III NATAN study (GBG 36/ABCSG XX). *Cancer Research.* 2013; 73:S5–05.
21. Smith JW 2nd, Vukelja S, Rabe A, et al. Phase II randomized trial of weekly and every-3-week ixabepilone in metastatic breast cancer patients. *Breast Cancer Res Treat.* 2013; 142:381–388. [PubMed: 24166282]
22. Gonzalez-Angulo AM, Liu S, Chen H, et al. Functional proteomics characterization of residual breast cancer after neoadjuvant systemic chemotherapy. *Ann Oncol.* 2013; 24:909–916. [PubMed: 23139263]

Clinical Practice Points

- Residual disease after neoadjuvant chemotherapy carries a high risk for recurrence.
- Adjuvant ixabepilone is difficult to administer due to AEs in patients with significant RD after NST; and in this small study adjuvant ixabepilone did not affect survival outcomes. Less toxic, personalized adjuvant therapy are needed to improve outcomes in patients with RD after chemotherapy.
- Adjuvant ixabepilone did not change the presence of circulating cells. Further study is needed to the role of CTCs and other circulating biomarkers as pharmacodynamic markers of response.

Figure 1.
Patient enrollment and disposition

Figure 2.
Recurrence-free survival (A) and overall survival (B) estimates per-protocol analysis

Table 1**Patient and Tumor Characteristics**

All Patients (N = 43)										Observation (N = 24)		Ixabepilone (N = 19)		P-value*
	N		N	%	N	%	N	%						
Age, years														
Age ≤ 50	23		14	58.3	9	47.4								
Age > 50	20		10	41.7	10	52.6							0.47	
Race/Ethnicity														
White	30		18	75.0	12	63.2								
Black	5		2	8.3	3	15.8								
Hispanic	7		3	12.5	4	21.1								
Other	1		1	4.2	0	0.0							0.66	
Pathologic Stage														
I	2		2	8.7	0	0.0								
II	12		7	30.4	5	26.3								
III	28		14	60.9	14	73.7							0.50	
Histology														
Ductal	38		20	83.3	18	94.7								
Other	5		4	16.7	1	5.3							0.36	
Nuclear Grade														
1	1		1	4.3	0	0.0								
2	14		9	39.1	5	26.3								
3	27		13	56.5	14	73.7							0.51	
Subtype														
Hormone receptor-positive	29		18	75.0	11	61.1								
Triple negative	13		6	25.0	7	38.9							0.33	
Lymphovascular Invasion														
Negative	25		15	62.5	10	52.6								
Positive	18		9	37.5	9	47.4							0.51	
IBC														
No	36		19	79.2	17	89.5								

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

	All Patients (N = 43)		Observation (N = 24)		Ixabepilone (N = 19)		P-value*
	N		N	%	N	%	
Yes	7		5	20.8	2	10.5	0.44
RCB							
II	12		9	39.1	3	15.8	
III	30		14	60.9	16	84.2	0.17
Radiation							
No	2		2	9.5	0	0.0	
Yes	37		19	90.5	18	100.0	0.49

RCB = residual cancer burden; IBC = inflammatory breast cancer.

* Fisher's exact p-value.

Table 2

Circulating tumor cells measurements by per-protocol analysis

All Patients (N = 35)			Observation (N = 16)		Ixabepilone (N = 19)	
	N (%)	N	%	N	%	P-value*
CTC at baseline						
Absence	23(71.9%)	11	73.3	12	70.6	
Presence	9(28.1%)	4	26.7	5	29.4	1.0
CTC at 9 weeks						
Absence	20(64.5%)	8	53.3	12	75.0	
Presence	11(35.5%)	7	46.7	4	25.0	0.27
CTC at 18 weeks						
Absence	19(86.4%)	10	90.9	9	81.8	
Presence	3(13.6%)	1	9.1	2	18.2	1.0
Sensitivity analysis (treating missing CTC as "presence")						
CTC at 9 weeks						
Absence	20(57.1%)	8	50.0	12	63.2	
Presence	15(42.9%)	8	50.0	7	36.8	0.43
CTC at 18 weeks						
Absence	19(54.3%)	10	62.5	9	47.4	
Presence	16(45.7%)	6	37.5	10	52.6	0.37

CTC = circulating tumor cells;

* Fisher's exact p-value.

Table 3

Ixabepilone-related adverse events

	Ixabepilone (N = 19)		
Toxicity	Grade	N	%
Anemia	All 3-4	2 2	10.5 10.5
Anorexia	All 3-4	13 1	68.4 5.3
Constipation	All 3-4	15 3	78.9 15.8
Cough	All 3-4	4 0	21.1 0.0
Dehydration	All 3-4	1 0	5.3 0.0
Diarrhea	All 3-4	12 2	63.2 10.5
Dizziness	All 3-4	2 0	10.5 0.0
Dyspnea	All 3-4	2 0	10.5 0.0
Edema	All 3-4	4 0	21.1 0.0
Epiphora	All 3-4	6 1	31.6 5.3
Fatigue	All 3-4	16 6	84.2 31.6
Fever	All 3-4	4 0	21.1 0.0
Headache	All 3-4	3 1	15.8 5.3
Infection	All 3-4	4 0	21.1 0.0
Mucositis	All 3-4	6 0	31.6 0.0
Nail change	All 3-4	3 0	15.8 0.0
Nausea	All 3-4	15 1	78.9 5.3
Neuropathy	All 3-4	15 6	78.9 31.6
Neutropenia	All 3-4	2 1	10.5 5.3
Pain	All 3-4	15 12	78.9 63.2
Rash	All 3-4	13 1	68.4 5.5
Transaminases	All 3-4	1 0	5.3 0.0
Thrombocytopenia	All 3-4	1 0	5.3 0.0

	Ixabepilone (N = 19)		
Toxicity	Grade	N	%
Vomiting	All	11	57.9
	3-4	1	5.3

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript