Combined Targeted Therapies for First-line Treatment of Metastatic Triple Negative Breast Cancer—A Phase II Trial of Weekly Nab-Paclitaxel and Bevacizumab Followed by Maintenance Targeted Therapy With Bevacizumab and Erlotinib

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Abstract

Chemotherapy remains the mainstay of metastatic triple negative breast cancer treatment; however, angiogenesis and epidermal growth factor receptor are potential targets. The present phase II clinical trial of nab-paclitaxel and bevacizumab, followed by maintenance therapy with bevacizumab and erlotinib, demonstrated progression-free survival similar to that with other regimens. Most patients experienced a partial response and received maintenance therapy, resulting in a significant break from cytotoxic chemotherapy.

Introduction: Angiogenesis and epidermal growth factor receptor signaling are potential therapeutic targets in triple negative breast cancer (TNBC). We hypothesized that targeting these critical pathways would prolong progression-free survival with first-line therapy for metastatic TNBC. **Patients and Methods:** We conducted a phase II trial of nab-paclitaxel and bevacizumab, followed by maintenance therapy with bevacizumab and erlotinib, for patients with metastatic TNBC. During induction, the patients received nab-paclitaxel 100 mg/m^2 intravenously (days 1, 8, and 15) and bevacizumab 10 mg/kg intravenously (days 1 and 15) every 28 days for 6 cycles. Patients free of progression at 24 weeks received maintenance therapy with bevacizumab 10 mg/kg intravenously every 2 weeks and oral erlotinib 150 mg/d until disease progression. The primary endpoint was progression-free survival (PFS). The secondary endpoints were best overall response, overall survival (OS), and adverse events. We explored the measurement of circulating tumor cells as a prognostic marker. **Results:** A total of 55 evaluable patients were enrolled. The median PFS and OS for the cohort was 9.1 months (95% confidence interval, 7.2-11.1) and 18.1 months (95% confidence interval, 15.6-21.7), respectively. Of the 53 patients with measurable disease, 39 (74%) had experienced a partial response and 10 (19%) had stable disease using the Response Evaluation Criteria In Solid Tumors. The most common toxicities were uncomplicated neutropenia, fatigue, and neuropathy. Decreased circulating tumor cells from baseline to the first assessment correlated with longer PFS and OS. **Conclusion:** Nab-paclitaxel and bevacizumab, followed by maintenance targeted therapy with bevacizumab and erlotinib, resulted in PFS similar to that of other trials. Most patients

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experienced a partial response (74%). Most patients received maintenance therapy (55%), providing a break from cytotoxic chemotherapy.

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Introduction

Breast cancer is the second leading cause of cancer-related death in women, with an estimated 40,920 deaths in 2018 alone.[1] It has been widely recognized that patients with breast cancer that expresses the basaloid or "triple negative" phenotype (estrogen receptor-negative, progesterone receptor-negative, and human epidermal growth factor receptor 2 [HER2] without overexpression) have a particularly aggressive form of the disease with characteristics that include younger age of onset, advanced stage at diagnosis, and a high rate of metastasis.[1-6] During the past decade, better molecular characterization of triple negative breast cancer (TNBC) has led to the development of new treatment strategies, including DNA damaging agents, poly-ADP ribose polymerase inhibitors, androgen receptor blockade, and, most recently, immunotherapy.[7,8] Despite these advances, no targeted therapies have been approved for sporadic TNBC. Thus, the mainstay of treatment has remained cytotoxic chemotherapy, highlighting the need for more effective treatment options.

Angiogenesis appears to have a central role in the progression of breast cancer and, therefore, has been studied as a potential targeted therapy for the treatment of metastatic TNBC.[3,9] The Eastern Cooperative Oncology Group (ECOG) 2100 trial showed that the combination of paclitaxel and bevacizumab was associated with a significant improvement in progression-free survival (PFS) for patients with HER2$^-$ disease (11.4 months with paclitaxel and bevacizumab vs. 6.11 months for paclitaxel alone; hazard ratio, 0.51; $P < .0001$), leading to Food and Drug Administration approval in 2008.[10] During subsequent years, numerous trials were performed of bevacizumab combined with other agents, which showed only marginal improvements for PFS.[11] The use of bevacizumab has, in part, been hampered by the lack of validated prognostic or predictive biomarkers of response. Variations in circulating tumor cells (CTCs) and circulating endothelial cells (CECs) are promising surrogate markers; however, this has yet to be implemented as a clinical tool for predicting the response to targeted therapies.[12,13]

Another common alteration in TNBC is the overexpression of epidermal growth factor receptor (EGFR).[14-16] Overexpression of EGFR has been associated with chemotherapy resistance, large tumor size, and poor prognosis.[17,18] Many anti-EGFR therapies have been in use for cancer treatment, including non–small-cell lung cancer and colorectal cancer. EGFR is another attractive target for TNBC treatment.[19-21] We hypothesized that leveraging these pathways in combination (bevacizumab targeting angiogenesis and erlotinib directed against EGFR) might offer a novel treatment strategy for patients with metastatic TNBC and, importantly, provide a treatment option that would spare patients from the toxicity of uninterrupted cytotoxic chemotherapy. We also hypothesized that decreases in the CTCs might predict for a longer interval to disease progression and increases in apoptotic CECs might be predictive of a response to chemotherapy and bevacizumab.

The most commonly studied agents in combination with bevacizumab have been taxanes. Nab-pclitaxel has demonstrated activity in metastatic breast cancer similar to other taxanes.[22] Additionally, when administered weekly, nab-paclitaxel itself appears to be antiangiogenic.[23,24] In contrast, erlotinib combined with chemotherapy appeared to be deleterious for patients with non–small-cell lung cancer. A sequential approach has, therefore, been preferred, with chemotherapy, followed by the small molecule inhibitor.[25] In the present study, we report the safety and efficacy for an "induction phase" of nab-paclitaxel and bevacizumab, followed by a "maintenance phase" with targeted therapies alone of bevacizumab and erlotinib for patients with advanced TNBC and the effect of this treatment on the CTC and CEC levels.

Patients and Methods

Patient Eligibility

The eligibility criteria were histologically confirmed invasive TNBC (estrogen receptor-negative, ≤10%; progesterone receptor-negative, ≤10%; and HER2$^-$ using immunohistochemistry or fluorescence in situ hybridization) and first-line therapy for metastatic disease. The additional eligibility criteria included measurable disease using Response Evaluation Criteria In Solid Tumors (RECIST) or nonmeasurable disease with an increasing serum cancer antigen 15-3 or cancer antigen 27.29 or carcinoembryonic antigen level documented by 2 consecutive measurements taken ≥14 days apart, adequate organ function, no pregnancy, and no contraindications to bevacizumab.

Patients who had developed recurrent disease within 12 months after completion of adjuvant chemotherapy containing a weekly taxane were excluded. In addition, patients were excluded if they had active, untreated central nervous system metastases. Additional exclusion criteria are listed in Supplemental Table 1 (available in the online version). All patients provided written informed consent before undergoing any study-related procedures. The present trial was registered at ClinicalTrials.gov (ClinicalTrials.gov identifier, NCT0073340).

Drug Administration

For the induction phase, the patients were treated with nab-paclitaxel 100 mg/m^2 on days 1, 8, 15, and 21 and bevacizumab 10 mg/kg intravenously on days 1 and 15 for 24 weeks (28-day cycles for 6 cycles). In January 2014, the nab-paclitaxel schedule was modified to 100 mg/m^2 intravenously on days 1, 8, and 15 every 28 days to improve tolerance. Eighteen patients were enrolled after this modification. Those patients who were free of progression at 24 weeks

began maintenance therapy with bevacizumab 10 mg/kg intravenously every 2 weeks and oral erlotinib 150 mg/d until progression with radiographic assessments every 8 weeks (Figure 1).

Toxicity

The patients were evaluated for adverse events at each study visit for the duration of their participation in the trial and for 30 days after discontinuation. Vital signs, including blood pressure, were checked before inclusion in the study, every 2 weeks during the induction phase and maintenance, and during follow-up. Toxicity notation and laboratory studies (complete blood count with absolute neutrophil count, platelet count, metabolic panel, serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase, alkaline phosphatase, and bilirubin) were evaluated before study inclusion, monthly during induction and maintenance, and during follow-up. Urinalysis with protein and creatinine was performed before the study, every 8 weeks during treatment, and in follow-up. For treatment-related toxicity and adverse event reporting, the study used the National Cancer Institute Common Terminology Criteria, version 3.0 (available at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Doses were adjusted or delayed in accordance with the protocol and the system showing the greatest degree of treatment-related toxicity. Data on adverse events that met severity grade $\geq$2 were collected and reported.

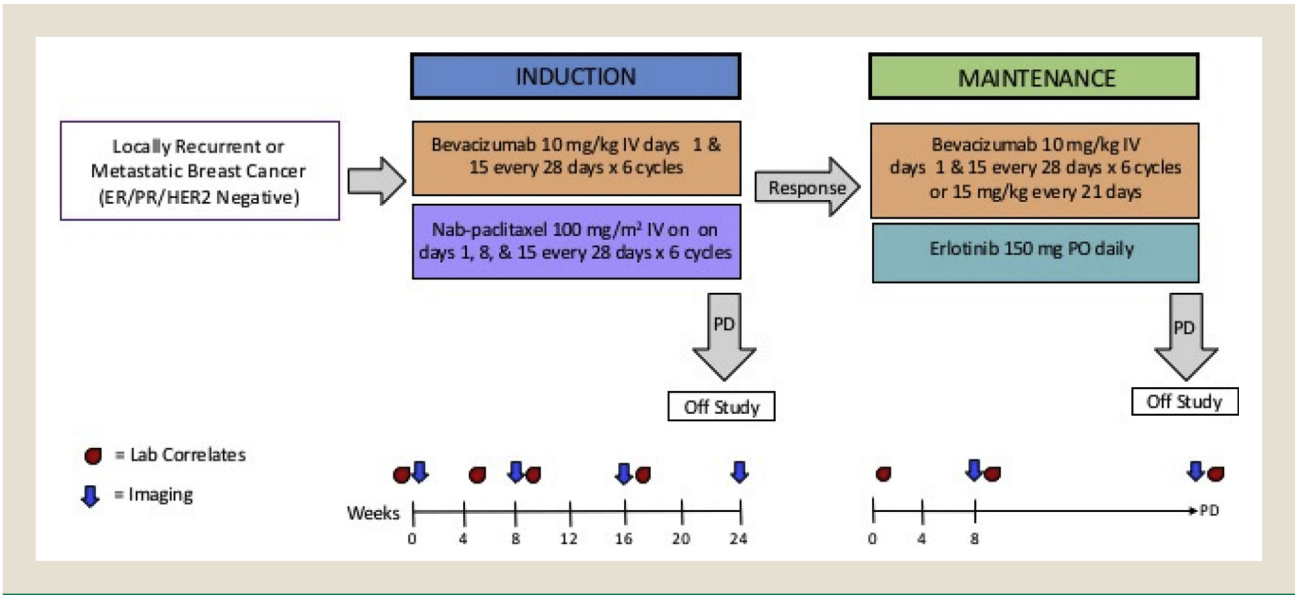
Clinical Response

The primary endpoint was PFS, which was defined as the interval from the date of registration to the date of the first documentation of progression, symptomatic deterioration, or death from any cause. Secondary endpoints included best overall response for patients with measurable disease, overall survival (OS), and safety and toxicity. Changes in the levels of the CTCs and CECs as potential predictors of treatment response were included as exploratory endpoints. Patients were evaluated with baseline staging scans performed before inclusion in the study, every 8 weeks during induction and maintenance therapy, and during the follow-up period. The response was evaluated among patients with measurable disease using RECIST, version 1.1, with a central review performed. The patients provided written informed consent, and a review of the medical records was performed to confirm the date of death and last follow-up visit.

CTC and CEC Counts

Two whole blood samples (1 for CTC and 1 for CEC analysis) were collected using CellSave tubes at each specified evaluation point. Samples were collected before the initiation of the study treatment (baseline), at weeks 5, 9, and 17 of induction with nab-paclitaxel and bevacizumab treatment, and at weeks 1 and 9 of maintenance treatment with bevacizumab and erlotinib. All samples were obtained before the infusion of chemotherapy or before the patient had taken the first of oral therapy for that interval. The protocol was later modified to include collection at the time of progression. For patients who had not had a sample collected at the time of progression, the value of the sample collected closest to the time of progression was assigned for the purposes of the data analysis. After collection, the tubes were inverted a minimum of 8 times to ensure proper mixing of the additives and were stored at ambient temperature (10°-30°C). The standardized CellSearch technique was used, which has been well documented in the reported data. The CTCs expressing the epithelial cell adhesion molecule were stained with 4,2-diamidino-2-phenylindole dihydrochloride (positive), cytokeratin 8, 18, and 19 (positive), and CD45 (negative). CECs expressing CD146 were stained with

Figure 1 Schema for a Phase II Trial of Induction Therapy With Nab-Paclitaxel and Bevacizumab Followed by Maintenance Targeted Therapy With Bevacizumab and Erlotinib (ClinicalTrials.gov Identifier, NCT0073340)



Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IV = intravenously; Lab = laboratory; PD = progressive disease; PO = orally; PR = progesterone receptor.

4,2-diamidino-2-phenylindole dihydrochloride (positive), CD105 (positive), and CD45 (negative). CTC and CEC morphology was confirmed in all cases.[12,26,27]

Statistical Analysis

The study was planned for a sample size of 59 patients, with 80% power to detect a median PFS of 13 months as superior to a historical control of 8 months with the combination of chemotherapy and bevacizumab.[10] Descriptive statistics, such as the frequency and percentage for categorical variables and the mean, median, range, and standard deviation for continuous variables, were calculated for the patient and disease characteristics, treatment completion, reason for discontinuation, and CTC/CEC measurements. The Kaplan-Meier method was used to estimate the PFS and OS, with censoring at the date of the last tumor assessment (PFS) or date of the last follow-up visit (OS). The median intervals (95% and 90% confidence intervals [CIs]) for PFS and OS were estimated from the Kaplan-Meier curves. The log-rank test was used to assess the survival differences among the subgroups (eg, interval from diagnosis to metastasis >3 years vs. ≤3 years). Grade 3-4 toxicities were summarized by the induction and maintenance phase and the number of subjects and number of events (Supplemental Table 2; available in the online version).

Results

Patient and Disease Characteristics

From April 2009 through January 2016, 59 patients (safety population) were enrolled from the academic center and community network oncology practices and initiated study therapy. Four of these patients failed to complete a single cycle of induction treatment and were not included in the efficacy analysis because their progression was thought to be related to a failure in the initial disease assessment rather than to treatment failure.

Of the 55 patients included in the efficacy population, 53 (96%) had measurable disease and were included in the analysis of the best overall response. The patient characteristics are summarized in Table 1. All patients enrolled were women, and the average age at registration was 54.9 years (range, 33-83 years). Most patients had a high functional status at registration, with an ECOG score of 0 or 1 (51 patients; 92.8%). The tumor characteristics were recorded from the metastatic biopsy findings (if available) or breast primary tumor findings. Of the 59 patients, 41 (75.5%) had received previous (neoadjuvant or adjuvant) chemotherapy and 14 (24.5%) were chemotherapy naive.

Table 1 Patient Characteristics

Characteristic	Overall (n = 55)
Race	
Native American or Alaskan native	2 (3.64)
Asian	1 (1.82)
Black or African American	2 (3.64)
White or Caucasian	47 (85.5)
Other or multiple	1 (1.82)
Unknown	2 (3.64)
Ethnicity	
Hispanic or Latino	6 (10.9)
Not Hispanic	47 (85.5)
Unknown	2 (3.64)
Stage at diagnosis	
I	6 (10.9)
II	22 (40)
III	12 (21.8)
IV	9 (16.4)
Unknown, <IV	6 (10.9)
Histologic type at diagnosis	
Ductal	47 (85.5)
Lobular	1 (1.82)
Unknown	7 (12.7)
ECOG score at registration	
0	37 (67.3)
1	14 (25.5)
2	1 (1.82)
Unknown	3 (5.45)
Conversion to TNBC from other histologic type	
Yes	11 (20.0)
No	42 (76.4)
Unknown	2 (3.6)
Previous chemotherapy	
Yes	41 (74.5)
No	14 (25.5)
Treatment site	
UWMC/SCCA	26 (47.2)
Other[a]	11 (20.0)
WVC	8 (14.5)
CCC	4 (7.27)
PAMC	3 (5.45)
SCCA-EH	3 (5.45)

Data presented as n (%).
Abbreviations: CCC = Cascade Cancer Center; ECOG = Eastern Cooperative Oncology Group; PAMC = Providence Alaska Medical Center; SCCA = Seattle Cancer Care Alliance; SCCA-EH = Seattle Cancer Care Alliance at EvergreenHealth; TNBC = triple negative breast cancer; UWMC = University of Washington Medical Center; WVC = Wenatchee Valley Clinic.
[a]Including Bend Memorial Clinic (n = 2), Bozeman Deaconess Cancer Center (n = 2), Columbia Basin Hematology Oncology (n = 2), Group Health Cooperative (n = 1), Kadlec Clinic Hematology and Oncology (n = 1), Katmai Oncology Group (n = 1), Skagit Valley Hospital (n = 1), and Spokane Valley Cancer Center (n = 1).

Toxicity Profile

During induction, 58 toxicity events of grade ≥3 that were definitely or probably related to treatment were reported using Common Terminology Criteria for Adverse Events, version 3.0. In addition, 9 grade ≥3 events occurred during maintenance that were definitely or probably related to treatment. Grade 3 or 4 toxicities with ≥2 events are listed in Table 2. During induction, these events occurred in 27 of the 59 patients. During maintenance, these events occurred in 7 of 30 patients. Toxicities that were considered possibly related to treatment are reported in Supplemental Table 3 (available in the online version). The most common toxicities during the induction phase were neutropenia (n = 15), fatigue (n = 11), neuropathy (n = 7), and leukopenia (n = 5). The most common toxicity during the maintenance phase was rash (n = 3). No grade 5 toxicities were reported. The grade 3 and 4 toxicities

Table 2 Toxicity

Grade 3/4 Toxicity	Induction (n = 59)	Maintenance (n = 30)
Anemia	2 (3.4)	0 (0)
Dehydration	2 (3.4)	1 (3.3)
Fatigue	11 (18.6)	1 (3.3)
Lymphopenia	5 (8.5)	1 (3.3)
Nail changes	2 (3.4)	0 (0)
Nausea/vomiting	2 (3.4)	0 (0)
Neuropathy	7 (11.9)	0 (0)
Neutropenia	15 (25.4)	0 (0)
Pain	2 (3.4)	1 (3.3)
Rash	0 (0)	3 (10.0)

Data presented as n (%).
Grade 3-4 toxicities definitely or probably related to the study drugs with ≥2 events reported using National Cancer Institute Common Terminology Criteria, version 3.0; no grade 5 toxicities developed.

reported were similar to those in other reports evaluating these agents, and we did not observe any new or unexpected toxicities.

Of the 55 patients, 34 (62%) completed induction therapy, some with dose modifications or holds (Table 3). Thirty of these patients received maintenance therapy for 29 to 564 days (mean, 198 days). Four patients completed induction but did not subsequently receive maintenance therapy (3 because of progression and 1 by patient choice owing to toxicity). The most common reasons for dose modifications or holds related to toxicity during induction included neutropenia (n = 9), neuropathy (n = 7), fatigue (n = 3), and leukopenia (n = 3). The most common reasons for dose modifications or holds during maintenance related to toxicity included neuropathy (n = 6), fatigue (n = 5), neutropenia (n = 4), and diarrhea (n = 4). Other reasons for dose modifications or holds included anorexia, liver function test result abnormalities, constipation, rash, anemia, hypertension, hemorrhage, hypotension, infection, muscle weakness, syncope, muscle weakness, nausea/vomiting, dehydration, and weight loss.

Of the 55 patients, 4 (7%) discontinued treatment because of toxicity in accordance with the protocol guidelines, 6 patients (11%) discontinued study treatment by choice, 1 patient (2%) discontinued treatment due to physician recommendation, and 4 (7%) discontinued study treatment for other reasons. The remaining 40 patients were removed from the study because of progressive disease (13 patients during the induction phase and 27 patients during the maintenance phase). Most patients who removed themselves from the study by choice cited quality of life concerns and toxicity as the primary reasons. The adverse effects resulting in termination of study treatment included anorexia, dehydration, fatigue, infection, leukocytosis, nausea/vomiting, neuropathy, neutropenia, constipation, and diarrhea. One patient experience grade 3 congestive heart failure during the maintenance phase (month 16). No serious adverse events related to study therapy were observed.

Table 3 Summary of Patient Disposition and Reasons for Study Discontinuation in Efficacy Cohort (n = 55)

Treatment Summary	n (%)
Completed induction without dose modification	11 (20)
Completed induction with dose modifications or holds	23 (42)
Removed from study during induction phase	21 (38)
Reason for discontinuation	
Progressive disease	40 (73)
Physician recommendation	1 (2)
Toxicity	4 (7)
Patient choice	6 (11)
Other	4 (7)

Survival Data

The median PFS for the efficacy cohort was 9.1 months (95% CI, 7.2-11.1; 90% CI, 7.3-9.6), and the median OS was 18.1 months (95% CI, 15.6-21.7; 90% CI, 16.3-21.3; Figures 2 and 3). No significant difference was seen in patients who had had a prolonged interval from the initial diagnosis to metastasis (defined as >3 years) for either PFS or OS ($P = .3$ and $P = .47$, respectively; Supplemental Figures 1 and 2; available in the online version). Additionally, no significant difference was seen in patients who converted to triple negative status from another histopathologic status during the course of their disease for either PFS or OS ($P = .28$ and $P = .55$, respectively; Supplemental Figures 3 and 4; available in the online version).

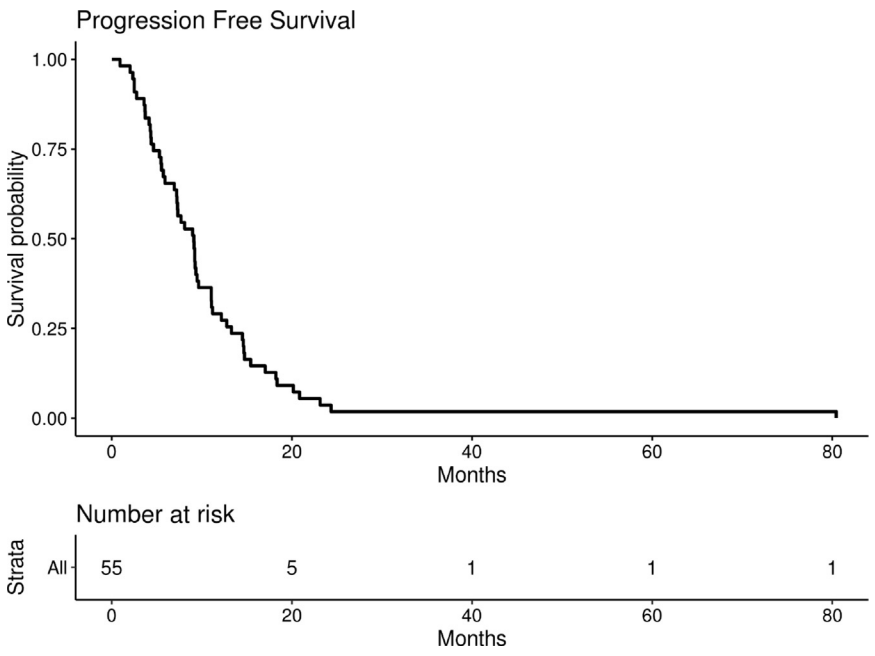
Of the 53 patients with measurable disease, 39 (74%) experienced a partial response and 10 (19%) had stable disease using the RECIST (Figure 4). Two patients had no response (0%) and were designated as having baseline status. The response was unknown for 4 patients. No patients experienced a complete response. The greatest decrease (in the sum of the longest diameter of the target lesion) was 87%. The PFS for this patient was 469 days, and the OS was 907 days. This patient had had stage IIA disease at diagnosis but had not received previous systemic chemotherapy.

Three patients had long-term disease control and had received treatment for a long duration with 613, 660, and 740 days between enrollment and the development of progression. The corresponding duration of the maintenance period for these patients was 441, 476, and 564 days. The corresponding best response using the RECIST for these patients was −77%, −60%, and −66% and the corresponding OS duration was 1022 days (patient still living at the last follow-up visit), 1156, and 1692 days. One patient had metastatic disease at diagnosis and was chemotherapy naive. The other 2 patients had had stage 1 and stage IIa disease and had previously received chemotherapy.

CTC/CEC Levels

During the course of the trial, CTC and CEC samples were collected from patients at prespecified points to determine their potential as predictors of the response to treatment as an exploratory endpoint. The number of CTCs, when averaged at each measurement point, showed a general decreasing trend during the course of treatment, although the sample size was not consistent (Figure 5). The number of CECs did not substantially change during the course of treatment, although, similarly, the sample size varied (Figure 5). In accordance with the results from the Southwestern

Figure 2 Progression-free Survival for Efficacy Cohort (n = 55). Median Progression-free Survival was 9.1 Months (95% Confidence Interval, 7.2-11.1; 90% Confidence Interval, 7.3-9.6)



Oncology Group 0500 trial, PFS and OS were analyzed using the CTC levels at baseline and after 1 cycle of induction chemotherapy (week 5).[28] Three patients from the trial had not had either a baseline or first follow-up CTC level collected and were excluded from the analysis. Of the 51 patients with CTCs evaluated at both evaluation points, 28 (55%) did not have elevated CTCs at baseline

Figure 3 Overall Survival for 55 Patients With Measurable and Evaluable Disease. Median Overall Survival was 18.1 Months (95% Confidence Interval, 15.6-21.7; 90% Confidence Interval, 16.3-21.3)

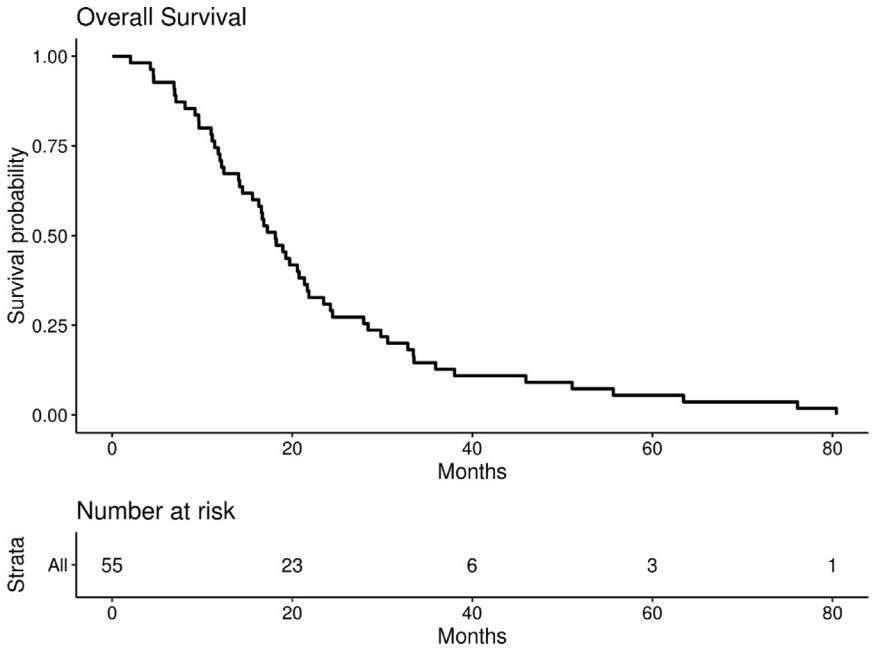
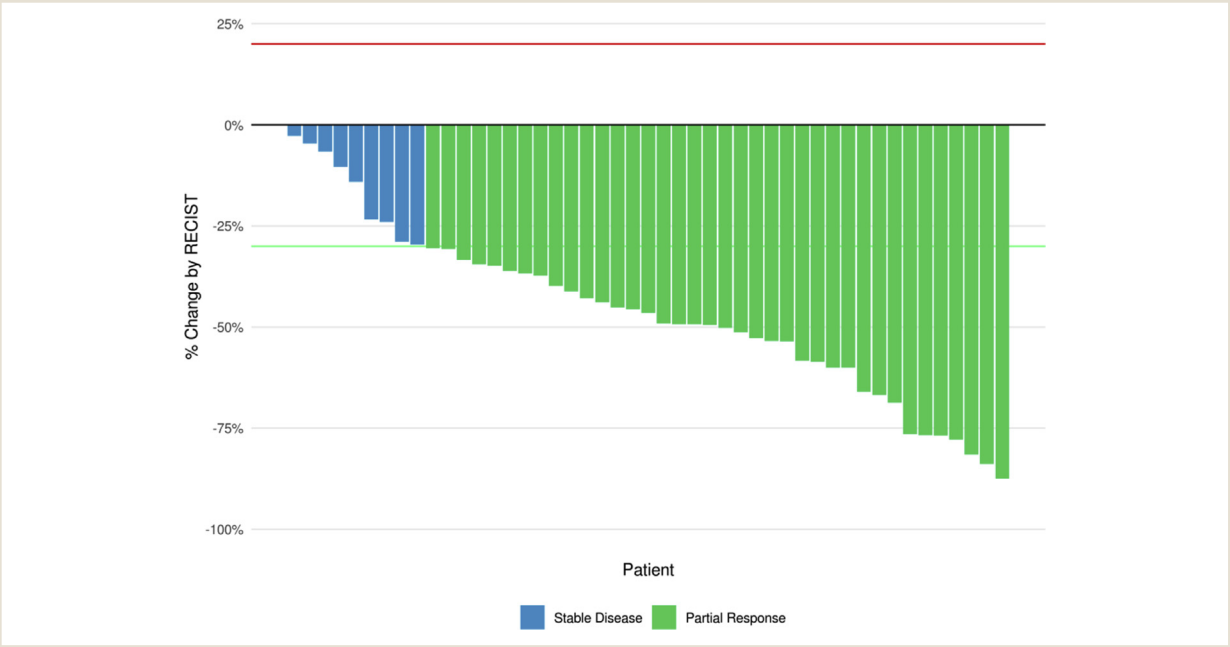


Figure 4 Best Response According to Response Evaluation Criteria In Solid Tumors (RECIST), Version 1.1 (Percentage of Change in the Sum of the Longest Diameters of all Target Lesions Compared With Baseline) for Patients With Measurable Disease and Follow-up Assessment (n = 47)



(with elevated CTCs defined as ≥5 CTCs per 7.5 mL of whole blood[28]; Figure 6; arm A). Of the 23 patients with elevated CTCs at baseline, 16 (70%) had CTC levels that were no longer elevated after 5 weeks of chemotherapy (arm B) and 7 (30%) had persistent CTC elevation (arm C). CTC status was associated with both PFS ($P = .0037$) and OS ($P = .0019$), with a clear disadvantage seen for patients in arm C. The median PFS was 9.3, 7.9, and 2.8 months for arms A, B, and C and the median OS was 19.5, 20.7, and 9.6 months, respectively (Figure 6). All 3 of the patients with an exceptional response were in arm A, as was the patient with a best response of −87%.

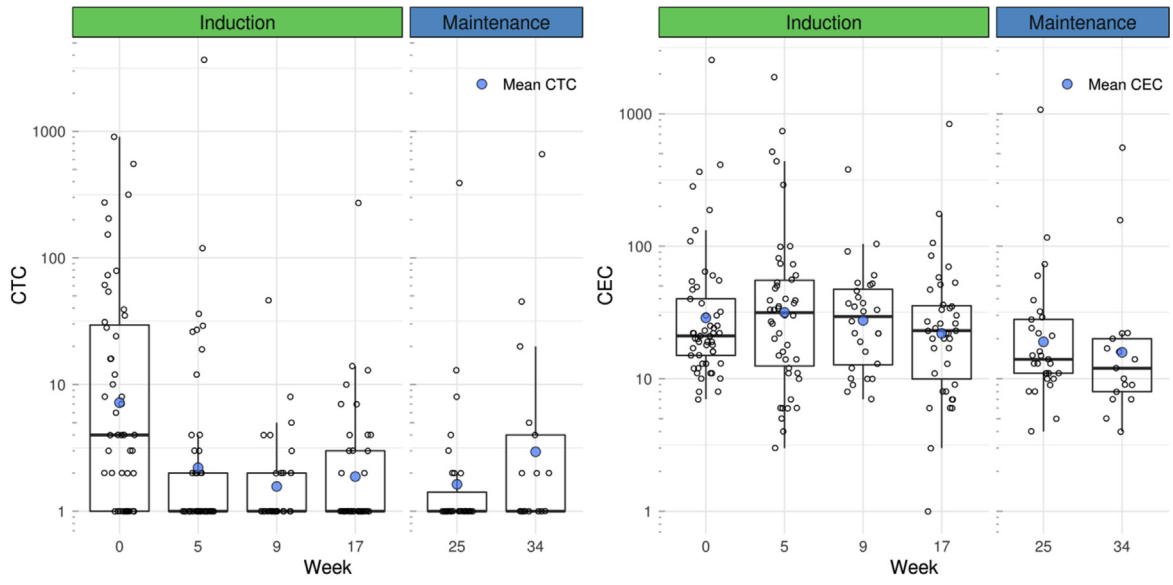
Discussion

Overall, we found that nab-paclitaxel and bevacizumab, followed by maintenance targeted therapy with bevacizumab and erlotinib, was well tolerated as first-line therapy for metastatic TNBC. The observed median PFS (9.1 months; 95% CI, 7.2-11.1) did not meet the prespecified criteria of interest, which had been defined as a 60% increase in the median PFS from 8 to 13 months. The PFS observed in the present trial was similar to that reported by other trials, which have studied the use of bevacizumab for metastatic TNBC.[11] We hypothesized that patients with a longer interval to progression to metastatic disease after the initial diagnosis and patients whose disease had converted to TNBC might have had more favorable disease and, therefore, an improved response. However, no difference in PFS or OS was observed among these subtypes. Although the PFS did not meet the prespecified endpoint, 30 patients were able to be treated with noncytotoxic maintenance therapy for 29 to 564 days (average, 198 days), providing a substantial break from chemotherapy. The toxicity during the maintenance period was less, with minimal grade 3 and 4 reactions. Manageable rash was the most common toxicity during maintenance therapy. In addition, 3 patients had an exceptional response, with 613, 660, and 740 days, respectively, between enrollment and disease progression. Additionally, most patients had a partial response using the RECIST (39; 74%), and the best response using the RECIST was 87%.

Most toxicities were neutropenia, leukopenia, fatigue, and neuropathy, which most commonly occurred during the induction phase. During the study, 4 patients were removed because of toxicity and 5 patients were removed by patient choice, with all but 1 citing quality of life concerns or side effects. A total of 23 patients (42%) required dose modifications or a hold during the course of treatment. However, no grade 5 toxicities occurred, and the toxicities that were observed were similar to other reports of bevacizumab, nab-paclitaxel, and erlotinib. Overall, the treatment combination was found to be safe and well tolerated.

Since the promising results of the ECOG 2100 trial, numerous other studies have evaluated bevacizumab for early-stage breast cancer in both adjuvant and neoadjuvant settings and in advanced breast cancer. Comparable to our findings, these studies have also shown only modest improvements in PFS, with no significant changes in OS.[29,30] A systematic review of bevacizumab use for breast cancer by Kümler et al[11] in 2014 evaluated 14 phase III trials, which unanimously showed an increased response rate and PFS, but no OS benefit in any trial. Several groups of investigators have also conducted studies to target EGFR in breast cancer, especially TNBC, because EGFR is commonly overexpressed in TNBC. However, the results have been similarly disappointing.[19,20] Two trials have specifically evaluated combination therapy with

Figure 5 Mean, Median, and Range for Circulating Tumor Cell (CTC) and Circulating Endothelial Cell (CEC) Measurements During the Course of Treatment



	log_{10} CTC Mean (SD)	log_{10} CTC Median	log_{10} CTC Range	N (CTC)	log_{10} CEC Mean (SD)	log_{10} CEC Median	log_{10} CEC Range	N (CEC)
Baseline	0.857 (0.854)	0.602	0.000-2.957	51	1.458 (0.491)	1.322	0.845-3.408	53
Induction wk 5	0.344 (0.693)	0.000	0.000-3.565	51	1.499 (0.604)	1.498	0.477-3.279	46
Induction wk 9	0.195 (0.363)	0.000	0.000-1.663	33	1.439 (0.394)	1.468	0.845-2.581	28
Induction wk 17	0.274 (0.495)	0.000	0.000-2.433	41	1.341 (0.509)	1.362	0.000-2.921	39
Maintenance wk 1	0.213 (0.524)	0.000	0.000-2.591	31	1.278 (0.470)	1.146	0.602-3.031	29
Maintenance wk 9	0.469 (0.781)	0.000	0.000-2.820	17	1.199 (0.534)	1.079	0.602-2.746	17
Progression	0.531 (0.756)	0.301	0.000-3.565	55	1.332 (0.574)	1.217	0.000-3.279	54

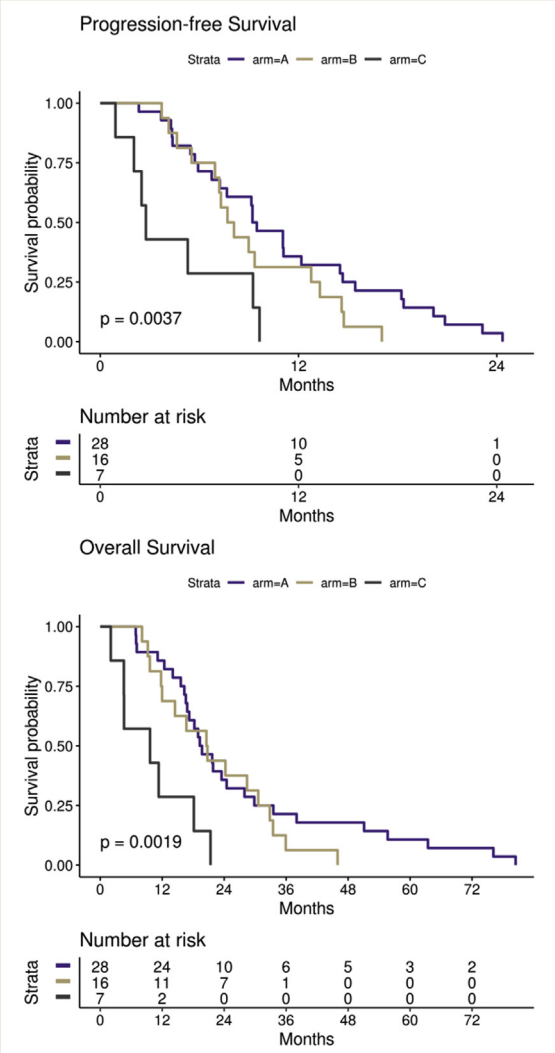
Abbreviation: SD = standard deviation.

bevacizumab and erlotinib. A trial reported by Dickler et al[31] studied erlotinib combined with bevacizumab in patients with metastatic breast cancer, who had previously received chemotherapy and identified no statistically significant differences in the median time to progression (11 weeks; 95% CI, 8-18 weeks). Another study by Montagna et al[32] investigated metronomic chemotherapy combined with bevacizumab and erlotinib for patients with metastatic breast cancer and found a response rate of 62%, PFS of 9.6 months, and OS of 24 months. However, in contrast to our study, most patients (55%) were chemotherapy naive.

Several explanations have been offered for the persistent failure of these therapies despite the known roles of their targets in metastatic breast cancer. The lack of proper patient selection and resistance mechanisms to antiangiogenic therapy have likely contributed to bevacizumab's inability to improve OS. For example, fibroblast growth factor receptor is mutated in ≤10% of breast cancers but is not routinely assayed and could be driving angiogenesis independently of vascular endothelial growth factor (VEGF).[33,34]

Additional possibilities exist for the failure of EGFR inhibition in breast cancer. Studies have suggested that EGFR is involved in regulating the epithelial−mesenchymal transition, migration, and tumor invasion and, therefore, might be more useful in preventing metastasis rather than producing tumor shrinkage owing to cell proliferation.[19,35] Because our study focused on patients with known metastatic disease, it might have been too late in the patients' course to capture this benefit. Additionally, at the time the present study was designed, erlotinib administered concurrently with chemotherapy appeared deleterious. However, a recent study by Lee et al[36] has suggested that EGFR-targeted therapy might enhance the sensitivity of TNBC cells to cytotoxic therapy. The chemotherapy-sensitizing benefits of erlotinib would have also been lost during that trial because it was administered during the maintenance, rather than the induction, phase with nab-paclitaxel. Similar to bevacizumab, resistance via alternative signaling pathways likely contributes to failure of erlotinib treatment. In addition, EGFR is known to interact with other tyrosine kinases such as

Figure 6 Progression-free Survival and Overall Survival in Patients With Metastatic Triple Negative Breast Cancer Stratified by Circulating Tumor Cell (CTC) Levels at Baseline and First Follow-up Visit After 5 Weeks of Treatment With Induction Nab-Paclitaxel and Bevacizumab. Arm A Represents Patients With No CTC Elevation at Baseline (Defined as <5 CTCs per 7.5 mL of Whole Blood; n = 28). Arm B Represents Patients With Elevated CTC Levels at Baseline (Defined as ≥5 CTCs per 7.5 mL of Whole Blood but <5 CTCs per 7.5 mL of Whole Blood at the First Follow-up Visit; n = 16). Arm C Represents Patients With Elevated CTCs at Baseline (≥5 CTCs per 7.5 mL of Whole Blood that Remained Elevated at the First Follow-up Visit; n = 7)



c-MET and insulin-like growth factor-1 receptor, which could be involved in resistance.[37] Finally, in contrast to malignancies such as non–small-cell lung cancer, most cases of TNBC exhibit overexpression of EGFR rather than activating mutations; thus, they are not exclusively dependent on EGFR signaling for their survival.[20] Several studies have sought to identify activating mutations in EGFR in breast cancer because these patients might receive improved benefit from tyrosine kinase inhibitors such as erlotinib. However, the results have been controversial, and activating mutations in TNBC appear to be extremely rare.[20,38]

Although the clinical value of anti-VEGF– and anti-EGFR–targeted therapies remains in dispute for TNBC, biomarkers are needed to identify patient subsets that might benefit from these agents. Currently, no biomarkers are available to predict which patients will be most likely to respond to EGFR inhibitors; in addition, the level of EGFR expression has not been predictive of response.[19,31]

For bevacizumab, some evidence has shown that the CEC and/or CTC levels might be independent predictors of responsive. No study has considered the combined predictive value of the CTC and/or CEC levels. Other biomarkers such as VEGF-A have also not been shown to be predictive of the response.[39] Although the available data regarding CECs have been inconsistent regarding the utility of this measure, in part owing to numerous technical differences,[12,13,40] some study results support their continued evaluation. For example, using the same CellSearch platform used in the present study, Bidard et al[12] found that increased CEC counts were associated with an improved time to progression (threshold, 20 CECs/4 mL; $P < .01$). Calleri et al[40] also found that higher baseline CEC levels were associated with an increased interval to progression ($P = .021$). Also, in their study, the CEC levels were markedly reduced at progression ($P = .0002$).[40] In our study, we did not find a substantial change in the number of CECs during treatment, and the CEC levels did not correlate with the response to treatment, although the analysis was limited because of missing samples.

The results for CTCs have been more promising. Cristofanilli et al[41] showed that the number of CTCs before treatment is an independent predictor of PFS and OS in patients with metastatic breast cancer. In the Southwestern Oncology Group 0500 trial, Smerage et al[28] showed that patients with metastatic breast cancer who had increased CTCs at baseline (defined as ≥5 per 7.5 mL of whole blood) that persisted after 21 days of first-line chemotherapy had a significantly worse prognosis compared with those with either a treatment response or without elevated CTCs at baseline. Our study did find a general downward trend in the number of CTCs during treatment. Similar to the study by Smerage et al,[28] our trial showed that patients with elevated CTCs at baseline that had remained elevated at the first follow-up evaluation after 5 weeks of induction therapy (arm C) experienced significantly worse PFS and OS compared with patients either without elevated CTCs at baseline (arm A) or with CTC levels that were no longer elevated at the first follow-up examination (arm B). All the patients with an exceptional response to study treatment were in arm A. Although no biomarker has yet been implemented clinically, these data highlight the promise of using biomarkers to identify which patients will respond best to certain therapies, including targeted agents.

Conclusion

Induction therapy with nab-paclitaxel and bevacizumab, followed by maintenance therapy with bevacizumab and erlotinib, was found to be safe and well tolerated. However, the efficacy was limited. Although the present study did not show a significant increase in PFS or OS, most patients had a partial response and received a substantial break from chemotherapy toxicity. Several

patients with an exceptional response continued with maintenance therapy for well over 1 year and, therefore, experienced a significant break from cytotoxic chemotherapy. Our findings add to the increasing body of evidence that challenges the use of both bevacizumab and erlotinib for TBNC treatment. However, because studies have shown some degree of tumor response for bevacizumab, it remains a part of the discussion for TBNC treatment strategies.[42] In addition, with the advent of immunotherapy, interest in the possibility of combination strategies has been renewed. For both bevacizumab and erlotinib, failure to identify those patients more likely to benefit from anti-VEGF and anti-EGFR therapy has hindered the development of these drugs for breast cancer. To date, no biomarker has been identified to reliably follow the patient response to bevacizumab or erlotinib. The survival of patients with advanced TNBC remains poor, underscoring the need for novel therapies and the need to identify which patients will benefit from these treatments.[43]

Clinical Practice Points

- TNBC remains an aggressive subtype with a poor prognosis and, despite extensive clinical research, the mainstay of treatment remains cytotoxic chemotherapy.[43]
- Angiogenesis and overexpression of EGFR have both been identified as potential targets in TNBC.[3,14,16]
- The present phase II clinical trial showed that induction therapy with nab-paclitaxel and bevacizumab, followed by maintenance targeted therapy with bevacizumab and erlotinib, was safe and well tolerated for patients with metastatic TNBC.
- Although the PFS did not meet the prespecified criterion of interest, it was similar to that reported in comparable trials.
- Additionally, most patients had a partial response using the RECIST, and most had received maintenance therapy, providing a break from cytotoxic chemotherapy.
- Several of our patients experienced an exceptional response and were able to continue maintenance therapy for well over 1 year, highlighting the need for biomarkers to better identify which patients will benefit from these targeted therapies.
- CTC levels were found to be prognostic, with patients with persistently elevated CTCs after 1 cycle of induction chemotherapy having a significantly worse prognosis compared with those with either a decrease in CTCs after cycle 1 of induction therapy or without elevated CTCs at baseline.

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Disclosure

The authors declare that they have no competing interests.

Supplemental Data

The supplemental data accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2018.12.008.

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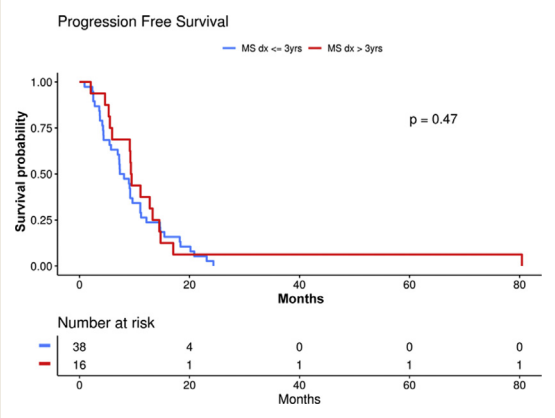
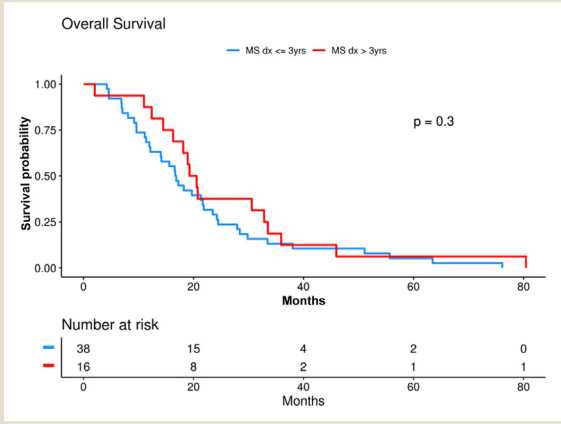
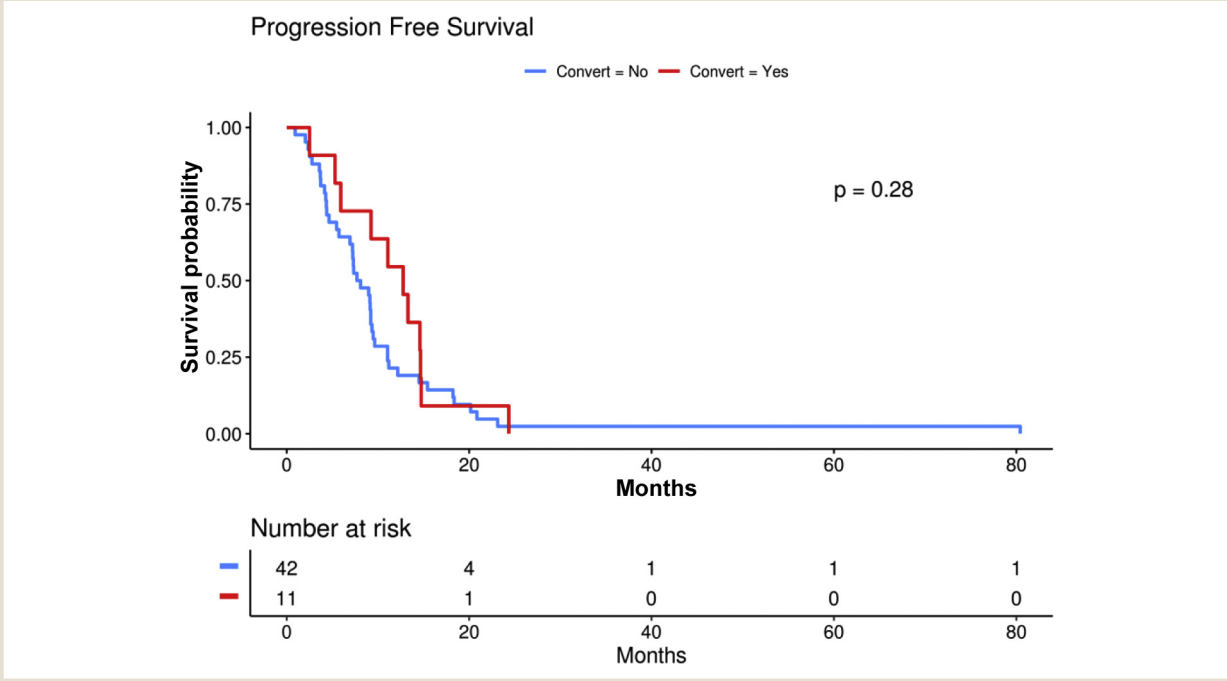
Supplemental Figure 1 Differences in Progression-free Survival Stratified by the Interval to Metastasis, Defined as >3 or <3 Years ($P = .47$). MS dx, metastasis diagnosis



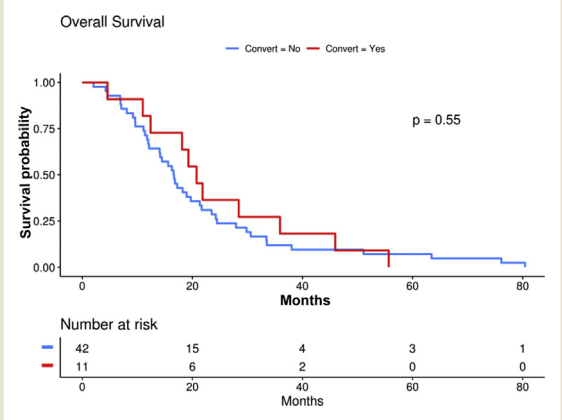
Supplemental Figure 2 Differences in Overall Survival Stratified by the Interval to Metastasis, Defined as >3 or <3 Years ($P = .3$). MS dx, metastasis diagnosis



Supplemental Figure 3 Differences in Progression-free Survival Stratified by whether patients had Presented With Triple negative Breast Cancer or Their Disease had Converted (Convert) From Another Subtype ($P = .28$)



Supplemental Figure 4 Differences in Overall Survival Stratified by whether patients had Presented With Triple negative Breast Cancer or Their Disease had Converted (Convert) From Another Subtype ($P = .55$)



Supplemental Table 1 Exclusion Criteria

Recurrent disease within 12 months after completion of adjuvant chemotherapy containing a weekly taxane
Active, untreated central nervous system metastases
Pre-existing nephritic syndrome
Serious concurrent medical or psychiatric illness
Inadequately controlled hypertension (defined as systolic blood pressure >150 and/or diastolic blood pressure >100 mm Hg with antihypertensive medication)
New York Heart Association grade ≥II congestive heart failure or significant vascular disease
Symptomatic peripheral vascular disease
Bleeding diathesis or coagulopathy
Major surgery within 28 days before enrollment and/or anticipated during the study period
Minor surgery within 7 days before enrollment
Serious nonhealing wounds or bone fractures
Proteinuria at screening (defined as urine protein/creatinine ratio >1.0 or urine dipstick with ≥2 proteinuria)
Any of the following within 6 months before study enrollment: myocardial infarction, unstable angina, stroke, transient ischemic attack, abdominal fistula, gastrointestinal perforation, intra-abdominal abscess

Supplemental Table 2 All Grade 3/4 Toxicities Definitely or Probably Related to Treatment

Grade 3/4 Toxicities	Induction (n = 59)	Maintenance (n = 30)
Allergic reaction	1 (1.7)	0 (0)
Anemia	2 (3.4)	0 (0)
Anorexia	0 (0)	1 (3.3)
Constipation	1 (1.7)	0 (0)
Dehydration	2 (3.4)	1 (3.3)
Dermatology, other	1 (1.7)	0 (0)
Diarrhea	1 (1.7)	0 (0)
Fatigue	11 (18.6)	1 (3.3)
Hemorrhage	1 (1.7)	0 (0)
Hypertension	1 (1.7)	0 (0)
Infection	1 (1.7)	0 (0)
Liver function test abnormality	0 (0)	1 (3.3)
Lymphopenia	5 (8.5)	1 (3.3)
Muscle weakness	1 (1.7)	0 (0)
Nail changes	2 (3.3)	0 (0)
Nausea/vomiting	2 (3.3)	0 (0)
Neuropathy	7 (11.9)	0 (0)
Neutropenia	15 (25.4)	0 (0)
Pain	2 (3.3)	1 (3.3)
Patient odor	1 (1.7)	0 (0)
Proteinuria	1 (1.7)	0 (0)
Rash	0 (0)	3 (10.0)
Syncope	1 (1.7)	0 (0)

Data presented as n (%).
Toxicities either definitely or probably related to study drugs reported using National Cancer Institute Common Terminology Criteria, version 3.0; no grade 5 toxicities developed.

Supplemental Table 3 Grade 3/4 Toxicities Possibly Related to Treatment

Grade 3/4 Toxicities	Induction (n = 59)	Maintenance (n = 30)
Anorexia	1 (1.7)	0 (0)
Congestive heart failure	0 (0)	1 (3.3)
Constitutional, other	1 (1.7)	0 (0)
Dysphagia	1 (1.7)	0 (0)
Fatigue	3 (5.1)	0 (0)
Hemorrhage	1 (1.7)	0 (0)
Hyperglycemia	1 (1.7)	0 (0)
Hypertension	1 (1.7)	0 (0)
Hyponatremia	2 (3.3)	0 (0)
Hypophosphatemia	1(1.7)	0 (0)
Hypoxia	1 (1.7)	0 (0)
Infection	0 (0)	2 (6.6)
Neutropenia	0 (0)	1 (3.3)
Pain	1 (1.7)	1 (3.3)
Rash	0 (0)	1 (3.3)
Thrombocytopenia	2 (3.3)	0 (0)
Thrombosis	2 (3.3)	0 (0)

Data presented as n (%).
Toxicities either definitely or probably related to study drugs reported using National Cancer Institute Common Terminology Criteria, version 3.0; no grade 5 toxicities developed.