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North Central Cancer Treatment Group (NCCTG) N0537: Phase II Trial of VEGF-Trap in Patients With Metastatic Breast Cancer Previously Treated With an Anthracycline and/or a Taxane

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Abstract

Introduction—Angiogenesis is an established target for the treatment of MBC. Aflibercept (VEGF-Trap) is a humanized fusion protein, which binds VEGF-A, VEGF-B, and PIGF-1 and -2.

Patients and Methods—A 2-stage phase II study with primary end points of confirmed tumor response and 6-month progression-free survival (PFS). If either end point was promising after the initial 21 patients, an additional 20 patients would be enrolled. Measurable disease, <2 previous chemotherapy treatments, previous anthracycline or taxane therapy, and Eastern Cooperative Oncology Group performance status of 0 or 1 were required. Aflibercept was given at a dose of 4 mg/kg intravenous every 14 days.

Results—Twenty-one patients were enrolled; 71% had visceral disease, 57% were estrogen receptor negative, 19% had $HER2^+$ disease with previous trastuzumab treatment, and 33% had 2 previous chemotherapy regimens. Partial response rate was 4.8% (95% confidence interval [CI], 0.1%–23.8%) and 6-month PFS was 9.5% (95% CI, 1.2%–30.4%). Neither primary end point met efficacy goals and the study was terminated. A median of 3 cycles was given. Median PFS was 2.4 months. Common grade 3 or 4 adverse events were hypertension (33%), fatigue (19%), dyspnea (14%), and headache (14%). Two cases of severe left ventricular dysfunction were noted.

Conclusions—Aflibercept did not meet efficacy goals in patients previously treated with MBC. Toxicity was as expected for anti-VEGF therapy.

Keywords

Angiogenesis; Cooperative group; Monoclonal antibody; Breast cancer

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Disclosures
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Introduction

Treatment for metastatic breast cancer (MBC) has evolved in the past 20 years because of the discovery of new and better tolerated therapies. Survival of patients with MBC has improved, with median survival now ranging between 18 and 30 months, and 5-year survival between 23% and 30%.[1–3] However, MBC remains incurable, and breast cancer remains the second leading cause of cancer-related mortality in women. Thus, newer and better approaches and therapies are needed. Modulation of angiogenesis is 1 of such approaches.

Angiogenesis is an important biological process for many cancers, including breast cancer. Vascular endothelial growth factor (VEGF) ligands, and their binding to VEGF receptors 1 and 2, play a dominant role in the process of angiogenesis.[4,5] VEGF ligands are involved in vascular permeability, migration, and mitogenesis of endothelial cells, as well as maintenance of newly formed blood vessels. In fact, inhibition of VEGF and its receptors is a validated target for cancer therapy and research.

Bevacizumab, a monoclonal antibody against circulating VEGF-A and B, was the first angiogenesis inhibitor to consistently demonstrate anticancer activity in breast cancer,[6] and is currently approved for the treatment of several human malignancies.[7] Single agent activity in MBC is quite modest, with response rates in 9% and disease stabilization in 17% of patients.[6] Bevacizumab has been combined in multiple clinical trials with chemotherapeutic drugs, particularly taxanes, and has consistently shown a significant prolongation in disease-free survival.[7–9] However, to date, no prolongation of median overall survival (OS) has been demonstrated, although patient numbers and crossover in most of the trials have limited power to rigorously answer this question.[10]

Other agents that work by inhibition of angiogenic mechanisms include small molecule tyrosine kinase inhibitors (TKIs), such as sunitinib, sorafenib, vandetanib, pazopanib, and axitinib, which inhibit downstream signaling of the VEGF receptor. Several of these agents have been tested as single agents, as well as in combination with chemotherapeutic drugs, in MBC. Again, like bevacizumab, single agent activity has been generally poor,[11–13] and other than modest improvements in progression-free survival (PFS), to date, no improvement in OS has been demonstrated.

Aflibercept is a recombinantly produced fusion protein entirely composed of human protein sequences.[14] It binds circulating VEGF-A and VEGF-B ligands, just like bevacizumab, but in addition, binds to other key circulating proteins involved in angiogenesis, such as placental growth permeability factors PIGF-1 and 2.[14] In addition, aflibercept binds VEGF-A with a much higher affinity than bevacizumab, and has a considerably longer half-life. Given the above advantages of aflibercept, the demonstrated safety of aflibercept in phase I clinical trials[15,16] and the importance of angiogenesis in breast cancer, we developed a phase II clinical trial to test and efficacy and safety of aflibercept in patients with MBC.

Patients and Methods

Patient Eligibility

Men and women ≥ 18 years old were eligible if they had histologically or cytologically confirmed adenocarcinoma of the breast, clinical evidence of MBC, and measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST v1.0). Additional eligibility requirements included normal basic hematologic values, urinary protein-to-creatinine ratio of <1, Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy of > 3 months, and ≤ 2 previoous chemotherapy regimens for MBC. Unlimited previous

hormone therapies were allowed, and patients with $HER2^+$ disease must have had previous trastuzumab therapy (concurrent treatment with trastuzumab was not allowed). Patients were excluded if they had bone-only disease, leptomeningeal disease, or brain metastasis, pleural effusions, ascites, previous treatment with bevacizumab, or clinically significant cardiovascular disease.

Study Design and Treatment

The North Central Cancer Treatment Group (NCCTG) study N0537 was a prospective, multicenter, 2-stage, phase II study of single agent aflibercept in patients with MBC. Patients were treated with aflibercept 4 mg/kg intravenous every 14 days until disease progression, unacceptable toxicity, or voluntary withdrawal from the study. Up to 2 dose modifications were allowed per patient for toxicity.

Evaluation of Response and Toxicity

Evaluation of response was performed every 8 weeks. Criteria for response and progression were based on RECIST v1.0. Evaluation for toxicity was based on the National Cancer Institute Common Terminology Criteria for Adverse Events (v3.0). Toxicities were evaluated with every visit. Blood pressure was monitored weekly during the first cycle, and before every infusion of aflibercept thereafter.

Statistical Analysis

The primary end point of this trial was dual in nature. That is, the study was designed to simultaneously assess the confirmed tumor response rate and 6-month PFS rate. A 2-stage Simon design was chosen to test that the true confirmed tumor response rate in the given patient population was at most 5% and the true 6-month PFS rate was at most 15% versus the alternative that the true confirmed tumor response rate was at least 20% or the true 6-month PFS rate was at least 35%. The chosen design had a .12 significance level and at least 90% power if the true confirmed tumor response rate was at least 20% or the true 6-month PFS rate was at least 35%. Stage 1 would enroll 21 patients, and if sufficient activity was seen, an additional 20 patients were to be enrolled for a total planned enrollment of 41 patients. Secondary end points included PFS, OS, duration of response (DOR), and the adverse event profile. The distributions of PFS, OS, and DOR were estimated using the Kaplan-Meier method. Simple descriptive statistics were used to summarize the adverse event profile and patient characteristics at enrollment.

Results

Enrollment and Patient Characteristics

Twenty-one women were enrolled during the first stage of the study between January 2007 and March 2008. No patients were found to be ineligible and all enrolled women were included in the analysis. Table 1 lists the baseline characteristics of the study population. Average age was 58 (range, 34 –75). Nine patients (43%) had estrogen receptor-positive tumors, and 4 patients (19%) had $HER2^+$ tumors.

Treatment

A median of 3 treatment cycles (range, 1–15) was given. All 21 women have discontinued treatment. Reasons for discontinuation are disease progression (n = 12; 57%), adverse events (AE) (n = 7; 33%), and refusal of further treatment (n = 2; 10%).

Primary End Point

Tumor measurement data were available in all 21 women. Overall, 1 patient (4.8%; 95% confidence interval [CI], 0.1%–23.8%) achieved a confirmed tumor partial response (PR). There were no complete responders. Two women (9.5%; 95% CI, 1.2%–30.4%) were taking the study treatment and free of progression at 6 months. Two additional women were not taking the treatment and free of progression at 6 months (1 received 1 cycle of treatment and the other received 6 cycles of treatment; both discontinued the study because of AE). Because the data did not reveal either enough confirmed responders or enough women that were taking the study treatment and progression-free at 6 months further enrollment was terminated per study design.

Progression-Free Survival, OS, and Duration of Response

The median PFS was 2.7 months (95% CI, 1.8 –5.0 months; Figure 1A). Three women (14%) remain alive at last follow-up with a median OS of 12.7 months (95% CI, 6.7–31.1 months; Figure 1B). The lone confirmed responder maintained her PR for 4.6 months before progressing and discontinuing study after 12 cycles of treatment.

Adverse Events and Treatment Tolerability

Data on AE were available for all 21 women. Overall 16 women (76%) experienced a grade 3 or higher AE of which 4 women (19%) experienced a grade 4 adverse event (Table 2). The most common (occurring in ≥ 10% of women) grade 3 or 4 nonhematologic AE were hypertension (33%), fatigue (19%), dyspnea (14%), and headache (14%). Only 1 patient (5%) developed grade 4 hematologic toxicity (thrombocytopenia).

Of the 93 cycles of administered treatment, 8 (9%) were at a reduced dose. These reductions occurred in 3 women and were all because of hypertension. Additionally 6 cycles (6%) were delayed. These delays occurred in 5 women and were because of hypertension (2 women, 1 cycle each), proteinuria (1 woman, 2 cycles), pulmonary toxicity (1 woman, 1 cycle), and delay in drug shipment (1 woman, 1 cycle).

Discussion

The NCCTG N0537 study evaluated the clinical efficacy and safety of single agent aflibercept. Only 1 patient exhibited a PR and 2 patients were in the study and free of progression at 6 months. At the interim analysis the study did not meet the efficacy criteria for continuation, indicating that single agent aflibercept does not have sufficient single agent activity to warrant further study in this patient population.

The single agent activity of aflibercept in our trial is consistent with the generally low single agent activity that has been demonstrated with other angiogenesis inhibitors. Bevacizumab, a recombinant, humanized, anti-VEGF monoclonal antibody, was shown to have a single agent activity of 9.3% (7 out of 75 patients) in terms of response rates, when tested in a patient population similar to our study.[6] Sunitinib, a multitargeted TKI has shown a response rate of 11% (7 out of 64 patients) in similar patients.[11] Sorafenib and vandetanib, both multitargeted TKIs, have shown a response rate of 0% in 23 and 46 patients, respectively.[17,18] Pazopanib has shown a response in 1 of 20 patients studied (5%).[19] However, this single agent activity might not totally affect the ability of these agents to have a role as part of combination strategies for patients with several malignancies, including breast cancer.

These observations have led to combination studies of angiogenesis inhibitors with chemotherapeutics. A meta-analysis of 3 phase III studies (E2100, AVADO [Avastin Plus

Docetaxel Chemotherapy], RIBBON [Regimens in Bevacizumab for Breast Oncology]-1) have shown that the addition of bevacizumab to taxanes, anthracyclines, or capecitabine consistently improve PFS from 6.7 to 9.2 months and response rates from 32% to 49% in the first-line metastatic setting.[10] In addition, 1 phase III study (RIBBON-2) showed that combining bevacizumab with multiple chemotherapeutics in the second-line setting improves PFS from 5.1 to 7.2 months and response rates from 30% to 40%.[20] However, despite the promising activity of these combinations, none have shown an overall survival benefit to date. For example, the meta-analysis of phase III studies showed that adding bevacizumab to chemotherapy in the first-line setting has no OS advantage (hazard ratio, 0.97; CI, 0.86 –1.08).[10] Similarly, TKIs have also been combined with chemotherapeutic agents in multiple trials.[21–23] None of the trials, however, have demonstrated an OS advantage.

There are several possible reasons for the failure to observe OS differences when angiogenesis agents were used for the treatment of breast cancer. Crossover to the investigational arm was allowed in some of the trials in addition to the possible use of antiangiogenesis agents in subsequent lines of therapy. Moreover, patients with MBC have a better prognosis than those with many other aggressive malignancies, with median survival typically between 2 and 3 years. As a result of this long postprogression survival, patients are treated, typically, with many lines of subsequent therapies, and this has been shown to make an OS effect difficult to observe.[24,25] Finally, in subsequent lines of therapy, the heterogeneity characterizing early MBC is replaced with a more homogeneous population of patients who have generally responded to previous lines of therapy. This ‘selection’ of patients could introduce a bias against the patients who would potentially have benefited from antiangiogenesis therapy, but have developed tumor progression and died. Unfortunately, to date, no biomarker for angiogenesis therapy has been identified to help select patients who would specifically benefit from such therapy, although, preliminary data from AVADO and other studies suggest that serum levels of VEGF and VEGFR2 deserve further evaluation.[26]

The toxicity observed with aflibercept in our study was significant, however was in keeping with the toxicity observed by other antiangiogenesis therapies. Hypertension was the most common observed grade 3 adverse event in our study and is a frequently observed side effect of antiangiogenesis therapies. Guidelines for the monitoring and early treatment of hypertension in patients taking antiangiogenesis therapies have been published by the National Cancer Institute.[27] Two events of left ventricular dysfunction were observed, and other severe complications seen with antiangiogenesis therapies, such as bowel perforation, fistula formations, and wound complications, were not seen in our small study.

Conclusion

Aflibercept, a VEGF-Trap, showed an adverse event profile similar to other antiangiogenesis therapies and it seems to lack sufficient single agent activity to warrant further testing as a single agent in patients with MBC. Considering the theoretic advantages that aflibercept has when compared with bevacizumab, such as the potent binding to VEGF-A ligand, and the additional binding to permeability factors PIGF-1 and 2, further studies of aflibercept in combination therapies with chemotherapeutic agents should be conducted. Though such combination studies are under way in multiple cancer types, particularly in metastatic colorectal cancer in which an improvement in OS has been demonstrated in the second-line setting (VELOUR; Aflibercept Versus Placebo in Combination With Irinotecan and 5-FU in the Treatment of Patients With Metastatic Colorectal Cancer After Failure of an Oxaliplatin Based Regimen trial), we are not aware of such ongoing studies to date for patients with breast cancer.

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References

1. Gennari A, Conte P, Rosso R, et al. Survival of metastatic breast carcinoma patients over a 20-year period: a retrospective analysis based on individual patient data from six consecutive studies. Cancer. 2005; 104:1742–50. [PubMed: 16149088]
2. Dawood S, Broglio K, Buzdar AU, et al. Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. J Clin Oncol. 2010; 28:92–8. [PubMed: 19933921]
3. Desantis C, Siegel R, Bandi P, et al. Breast cancer statistics, 2011. CA Cancer J Clin. 2011; 61:409–18. [PubMed: 21969133]
4. Ferrara N. Role of vascular endothelial growth factor in physiologic and pathologic angiogenesis: therapeutic implications. Semin Oncol. 2002; 29:10–4. [PubMed: 12516033]
5. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003; 9:669–76. [PubMed: 12778165]
6. Cobleigh MA, Langmuir VK, Sledge GW, et al. A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. Semin Oncol. 2003; 30:117–24. [PubMed: 14613032]
7. Van Meter ME, Kim ES. Bevacizumab: current updates in treatment. Curr Opin Oncol. 2010; 22:586–91. [PubMed: 20811277]
8. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007; 357:2666–76. [PubMed: 18160686]
9. Robert NJ, Dieras V, Glaspy J, et al. Ribbon-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol. 2010; 29:1252–60. [PubMed: 21383283]
10. O'Shaughnessy J, Miles D, Gray RJ, et al. A meta-analysis of overall survival data from three randomized trials of bevacizumab (BV) and first-line chemotherapy as treatment for patients with metastatic breast cancer (MBC). J Clin Oncol. 2010; 28(15 Suppl):1005. [PubMed: 20100960]
11. Burstein HJ, Elias AD, Rugo HS, et al. Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2008; 26:1810–6. [PubMed: 18347007]
12. Perez EA, Spano JP. Current and emerging targeted therapies for metastatic breast cancer. Cancer. 2012; 118:3014–25. [PubMed: 22006669]
13. Bianchi G, Loibl S, Zamagni C, et al. Phase II multicenter, uncontrolled trial of sorafenib in patients with metastatic breast cancer. Anticancer Drugs. 2009; 20:616–24. [PubMed: 19739318]
14. Holash J, Davis S, Papadopoulos N, et al. VEGF-Trap: a VEGF blocker with potent antitumor effects. Proc Natl Acad Sci U S A. 2002; 99:11393–8. [PubMed: 12177445]
15. Tew WP, Gordon M, Murren J, et al. Phase 1 study of aflibercept administered subcutaneously to patients with advanced solid tumors. Clin Cancer Res. 2010; 16:358–66. [PubMed: 20028764]

16. Lockhart AC, Rothenberg ML, Dupont J, et al. Phase I study of intravenous vascular endothelial growth factor trap, aflibercept, in patients with advanced solid tumors. J Clin Oncol. 2010; 28:207–14. [PubMed: 19949018]

17. Miller KD, Trigo JM, Wheeler C, et al. A multicenter phase II trial of ZD6474, a vascular endothelial growth factor receptor-2 and epidermal growth factor receptor tyrosine kinase inhibitor, in patients with previously treated metastatic breast cancer. Clin Cancer Res. 2005; 11:3369–76. [PubMed: 15867237]

18. Moreno-Aspitia A, Morton RF, Hillman DW, et al. Phase II trial of sorafenib in patients with metastatic breast cancer previously exposed to anthracyclines or taxanes: North Central Cancer Treatment Group and Mayo Clinic Trial N0336. J Clin Oncol. 2009; 27:11–5. [PubMed: 19047293]

19. Taylor SK, Chia S, Dent S, et al. A phase II study of pazopanib in patients with recurrent or metastatic invasive breast carcinoma: a trial of the Princess Margaret Hospital phase II consortium. Oncologist. 2010; 15:810–8. [PubMed: 20682606]

20. Brufsky AM, Hurvitz S, Perez E, et al. Ribbon-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol. 2011; 29:4286–93. [PubMed: 21990397]

21. Rugo HS, Stopeck AT, Joy AA, et al. Randomized, placebo-controlled, double-blind, phase II study of axitinib plus docetaxel versus docetaxel plus placebo in patients with metastatic breast cancer. J Clin Oncol. 2011; 29:2459–65. [PubMed: 21555686]

22. Bergh J, Greil R, Voytko N, et al. Sunitinib (SU) in combination with docetaxel (D) versus D alone for the first-line treatment of advanced breast cancer (ABC). J Clin Oncol. 2010; 28(Suppl 18s):Abstract LBA1010.

23. Gradishar WJ, Dalenc F, Kaklamani VG, et al. Multivariate analysis (MVA) of progression-free survival (PFS) in two phase IIb, multinational, double-blind, randomized, placebo (PL)-controlled trials evaluating sorafenib (SOR) plus standard chemotherapy in patients (pts) with HER2-negative locally advanced or metastatic breast cancer (BC). J Clin Oncol. 2010; 28(Suppl 15s):Abstract 1073.

24. Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst. 2009; 101:1642–9. [PubMed: 19903805]

25. Saad ED, Katz A, Buyse M. Overall survival and post-progression survival in advanced breast cancer: a review of recent randomized clinical trials. J Clin Oncol. 2010; 28:1958–62. [PubMed: 20194852]

26. Miles DW, deHaas SL, Dirix L, et al. Plasma biomarker analysis in the AVADO phase III randomized study of first-line bevacizumab + docetaxel in patients with human epidermal growth factor receptor (HER) 2-negative metastatic breast cancer. Cancer Res. 2010; 70(24 suppl):Abstract P2-16-04.

27. Maitland ML, Bakris GL, Black HR, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. J Natl Cancer Inst. 2010; 102:596–604. [PubMed: 20351338]

Clinical Practice Points

- Angiogenesis is an established target for the treatment of MBC.
- Aflibercept (VEGF-Trap) is a novel humanized fusion protein, which binds VEGF-A, VEGF-B, and PIGF-1 and -2.
- This phase II study is the first study assessing the single agent activity and safety of aflibercept in patients with metastatic breast cancer.
- Aflibercept was safe and the side effect profile was similar to other antiangiogenesis treatments such as bevacizumab.
- Aflibercept treatment failed to demonstrate sufficient single agent activity in patients with pretreated metastatic breast cancer.
- Considering the known role of angiogenesis in the progression of breast cancer, and the theoretic advantages of aflibercept treatment when compared with bevacizumab, such as binding of PIGF-1 and PIGF-2, binding of VEGF-A with a much higher affinity than bevacizumab, and considerable longer half-life, further efforts for study of aflibercept, in this patient population, should continue, and focus on combination strategies with other therapeutic agents.

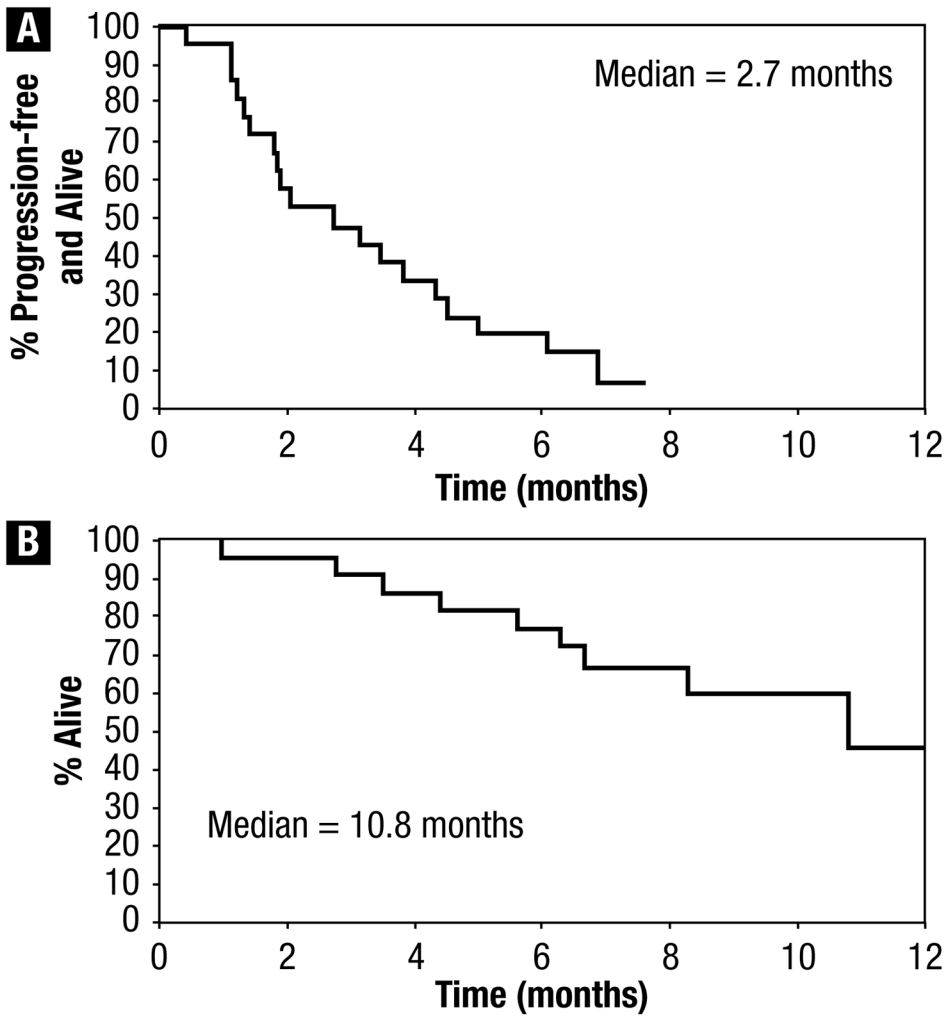

Figure 1.
Kaplan-Meier Plots for (A) Progression-Free Survival (n = 19 events) and (B) Overall Survival (n = 9 events)

Table 1

Baseline Characteristics

Characteristic	n	%
Median Age (Range)	58 (34–75)	
Sex, Female	21	100.0
ECOG Performance Score		
0	14	66.7
1	7	33.3
Nottingham Grade		
Well	1	4.8
Moderate	3	14.3
Poor	11	52.3
Unknown/not reported	6	28.6
Dominant Disease		
Visceral	15	71.4
Nonvisceral	6	28.6
History of Hypertension		
Yes	6	28.6
No	15	71.4
Race		
White	18	85.7
Black or African American	1	4.8
Asian	1	4.8
American Indian or Alaska native	1	4.8
ER Result		
Positive	9	42.9
Negative	12	57.1
PR Result		
Positive	5	23.8
Negative	16	76.2
HER2 Result		
Positive	4	19.1
Negative	14	66.7
HER2 testing not done	3	14.3
Previous (*Neo*) Adjuvant Chemotherapy		
Yes	13	61.9
No	8	38.1
Previous Chemotherapy Regimens, n		
0	3	14.3
1	11	52.4

Characteristic	n	%
2	7	33.3
Previous Hormonal Therapy		
Yes	9	42.9
No	12	57.1
Previous Trastuzumab		
Yes	5	23.8
No	16	76.2
Prior Anthracyclines		
Yes	15	71.4
No	6	28.6

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; PR = partial response.

Table 2

Severe Toxicities

Adverse Event	Grade 3		Grade 4	
	n	%	n	%
Hypertension	6	28.6	1	4.8
Fatigue	4	19.0	0	0.0
Dyspnea	1	4.8	2	9.5
Pain	6	28.6	0	0.0
Arthralgia	1	4.8	0	0.0
Diarrhea—No Colostomy	1	4.8	0	0.0
Anorexia	1	4.8	0	0.0
Proteinuria	1	4.8	0	0.0
Left Ventricular Failure	1	4.8	1	4.8