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Pilot Trial of Preoperative (Neoadjuvant) Letrozole in Combination With Bevacizumab in Postmenopausal Women With Newly Diagnosed Estrogen Receptor–or Progesterone Receptor–Positive Breast Cancer

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Abstract

Introduction—Tumor content or expression of vascular endothelial growth factor (VEGF) is associated with impaired efficacy of antiestrogen adjuvant therapy. We designed a pilot study to assess the feasibility and short-term efficacy of neoadjuvant letrozole and bevacizumab (anti-VEGF) in postmenopausal women with stage II and III estrogen receptor/progesterone receptor–positive breast cancer.

Patients and Methods—Patients were treated with a neoadjuvant regimen of letrozole orally 2.5 mg/day and bevacizumab intravenously 15 mg/kg every 3 weeks for a total of 24 weeks before the surgical treatment of their breast cancer. Patients were followed for toxicity at 3-week intervals, and tumor assessment (a physical examination and ultrasound) was performed at 6-week intervals. Positron emission tomography (PET) scans were performed before therapy and 6 weeks after the initiation of therapy.

Results—Twenty-five evaluable patients were treated. The regimen was well-tolerated, except in 2 patients who were taken off the study for difficulties controlling their hypertension. An objective clinical response occurred in 17 of 25 patients (68%), including 16% complete responses (CRs) and 52% partial responses. The 4 patients with clinical CRs manifested pathologic CRs in their breasts (16%), although 1 patient had residual tumor cells in her axillary nodes. Eight of 25

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patients (32%) attained stage 0 or 1 status. The PET scan response at 6 weeks correlated with clinical CRs and breast pathologic CRs at 24 weeks ($P < .0036$).

Conclusion—Combination neoadjuvant therapy with letrozole and bevacizumab was well-tolerated and resulted in impressive clinical and pathologic responses. The Translational Breast Cancer Research Consortium has an ongoing randomized phase II trial of this regimen in this patient population.

Keywords

Antiangiogenesis; Monoclonal antibody; Sentinel lymph node biopsy; Tamoxifen; VEGF

Introduction

Preoperative (neoadjuvant) and postoperative adjuvant therapies of stage II or III breast cancer yield comparable efficacy.¹ However, neoadjuvant therapy is often the chosen strategy, because it provides useful response observations that may aid in decision-making, and provides an enhanced opportunity for breast-conserving surgery.^{2,3} The majority of patients who are candidates for adjuvant therapy are postmenopausal women whose tumors express estrogen receptor (ER) and/or progesterone receptors (PgR). As a group, they exhibit a much lower frequency of attaining pathologic complete remission (pCR) from neoadjuvant chemotherapy compared with women whose tumors are ER-negative.² The attainment of pCR identifies patients with excellent prognoses,⁴ and is often used as an intermediate marker for the comparison of different neoadjuvant chemotherapy regimens.^{5,6} The use of neoadjuvant antiestrogen therapy for patients with ER-positive tumors rarely achieves pCR, with frequencies of $< 1\%$ in the 2 largest trials.⁷ Recently, the pathologic attainment of stage 0 or 1 (0/1) status after neoadjuvant therapy was reported to identify an antiestrogen neoadjuvant-treated population with excellent prognoses.⁷ Direct comparisons of chemotherapy versus antiestrogen neoadjuvant therapy trials in patients with ER-positive tumors are limited.^{8,9}

Recent clinical trials reported that patients treated with neoadjuvant aromatase inhibitors demonstrate longer progression-free survival than those treated with tamoxifen, but no difference was evident in overall survival (OS).^{10,11} Thus, a need exists for novel strategies to enhance antiestrogen neoadjuvant treatment. Preclinical^{12,13} and clinical^{14,15} studies support the concept that vascular endothelial growth factor (VEGF) content or expression in breast tumors impairs the efficacy of antiestrogen therapy. A study from our Breast Cancer Specialized Programs of Research Excellence (SPORE) demonstrated that the expression of VEGF at the Michigan Cancer Foundation – 7 (MCF-7; ER/PgR-positive) breast tumor xenografts imparts tamoxifen resistance, increased tumor growth rates, and enhanced metastatic potential.¹³ The authors concluded that this finding was likely a paracrine effect, and that the inhibition of VEGF may well enhance antiestrogen therapy. The present report describes the results of a pilot neoadjuvant trial using antiestrogen therapy (letrozole) combined with an anti-VEGF monoclonal antibody (bevacizumab) in postmenopausal women with stage II or III ER-positive tumors.

Patients and Methods

Study Design

This was an open-label single-arm pilot study of the combination of letrozole (2.5 mg orally daily) and intravenous bevacizumab (15 mg/kg every 3 weeks) in postmenopausal women with ER-positive and/or PgR-positive newly diagnosed breast cancer, with tumors staged at T2-T3, N0-2, and M0. The tumors had to exhibit at least 10% nuclear staining for ER and/or PgR. No dose modifications were allowed. Patients were treated for 24 weeks before surgery unless they were withdrawn earlier from the study because of progressive disease, an adverse event that resulted in a treatment delay of ≥ 3 weeks, or patient/investigator request. A sentinel lymph node (SLN) biopsy was performed before the initiation of therapy on patients with normal results of an axillary lymph node physical evaluation and imaging. The initiation of therapy with bevacizumab was delayed 2 weeks after an SLN biopsy. Patients were allowed to begin letrozole immediately after an SLN biopsy. Patients with palpable lymph nodes or abnormal nodes on imaging underwent fine-needle aspiration of their nodes to confirm the presence of tumor involvement. Patients with positive lymph nodes before therapy underwent axillary lymph node dissection at the time of definitive surgery.

Patients were evaluated for response every 6 weeks. Those patients with an objective response or stable disease (as determined by physical evaluation and ultrasound), according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, continued their therapy, with restaging every 6 weeks for a total of 24 weeks or until progression was evident.

Surgery was scheduled for approximately 6 months after the date the patient received her first treatment, with an interval of at least 4 weeks between the last dose of bevacizumab and the patient's operation. Patients were considered to have completed the study after receiving 6 months of treatment and definitive surgery. The treatment of patients after surgery was based on the investigator's discretion. However, all patients are being followed for the development of local recurrence, distant metastasis, and survival for 5 years after surgery.

Study Population

Patients manifested measurable breast disease according to clinical examination, mammography, or ultrasound. Adequate hematologic, renal, and liver function and a life expectancy of at least 6 months were also required. All patients provided written, informed consent, and institutional review board approval was obtained. Patients were required to demonstrate controlled blood pressure (< 150/90 mm Hg) and a normal ejection fraction according to a multigated acquisition (MUGA) scan or an echocardiogram. Exclusion criteria comprised uncontrolled endocrine or cardiac disease, bilateral or inflammatory breast cancer, distant metastases, major surgical procedures within 28 days before the initiation of therapy, minor surgical procedures within 7 days before the initiation of therapy, a history of abdominal fistulagastrointestinal perforation–intra-abdominal abscess, or other malignant diseases (except for treated in situ cervical carcinoma or adequately treated basal cell or squamous cell carcinoma of the skin). The co-administration of other

cancer treatments was not allowed, and hormone replacement therapy had to be discontinued at least 2 weeks before initiation of the study.

Study Assessments

Study-specific screening evaluations were performed within 8 weeks before initiating therapy. Screening evaluations included a complete medical history, demographics, weight and height, a complete physical examination, vital signs, and performance status. Tumor stage was determined by measuring the primary breast lesion and the axillary lymph nodes (if applicable) by physical examination, mammogram, and breast ultrasound. In addition, ER and PgR status, an SLN biopsy (when required), a positron emission tomography (PET) scan and bone scan (to rule out metastatic disease), a MUGA scan or echocardiogram, and a urine protein/creatinine ratio were also obtained for purposes of screening.

A physical examination, vital signs, and performance status were assessed every 3 weeks. Tumor assessment for objective response was performed using ultrasound every 6 weeks, according to the RECIST criteria. Evaluations of adverse events and concomitant medications/therapies were also assessed every 3 weeks. A PET scan was obtained 6 weeks after initiating therapy. A urine protein/creatinine ratio was obtained before every administration of bevacizumab. At 24 weeks, ultrasound, mammography, urine protein/creatinine ratio, and assessment for surgery were performed.

PET Scan Studies

Routine whole-body PET and computed tomography (CT) scans were performed 55–60 minutes after an intravenous injection of fluorine-18 fluorodeoxyglucose on patients with fasting serum glucose measurements of < 200 mg/dL, using a GE Discovery LS scanner (General Electric; Fairfield, CT). Measurements of standard uptake values (SUV) were performed, with regions of interest drawn to calculate the maximal activity (SUVmax) on any area of activity above background level. A decrease in SUVmax of ≥ 20% was considered a positive response, ie, a significant decrease in SUVmax.¹⁶

Study Objectives

This was a pilot study to assess the feasibility (safety) of the regimen, and to assess evidence of antitumor efficacy, using the criteria for objective responses and intermediate endpoint pathologic responses. Objective responses were defined as complete response (CR) or partial response (PR), as determined by RECIST criteria, where response categories include CR, PR, stable disease (SD), and progressive disease (PD). The intermediate endpoint pathologic response criteria included: (1) a pathologic complete response (pCR) in the breast or in the breast and nodes, presenting no evidence of residual invasive tumor in the breast or axillary lymph nodes (residual carcinoma in situ was allowed); and (2) the attainment of tumor stage 0 or I.⁷ The latter criterion refers to downstaging patients to pathologic stage 0 (T-0, N-0) or stage I (T-1, N-0). The safety and tolerability of the combination therapy were determined according to the occurrence of adverse events, assessed at 3-week intervals. The severity of adverse events was graded according to the National Cancer Institute's Common Toxicity Criteria (version 3.0). A secondary endpoint involved whether changes in the results of a PET scan after 6 weeks of therapy correlated with the 24-week response data.

Statistical Analysis

We selected an accrual of 25 evaluable patients to provide a reasonable standard error of less than 10% for rates of objective response, pCR, and the attainment of stage 0/1 status.⁷ Patients were considered evaluable if they had received at least 1 dose of therapy (on day 1 of treatment). Twenty-six patients provided signed, informed consent, but patient 17 manifested a transient neurologic event before the initiation of therapy and was not categorized as evaluable. The statistical analysis of this trial was descriptive. Means or medians are provided for continuous variables, and frequencies or percentages are provided for binary variables. Two-sided 95% confidence intervals (CIs) were calculated using the Blyth-Still-Casella exact test. The χ^2 statistical method was used to evaluate the association between improvements in PET scan results and efficacy endpoints. Patient follow-up was calculated from the date of initial therapy to April 1, 2009.

Results

Patient Demographics

A total of 26 patients gave signed, informed consent, but patient 17 received no therapy. Thus, 25 patients were evaluable in terms of toxicity and response. Patients' (Table 1) ages ranged from 54 to 79 years of age (median age, 62 years), and all had an Eastern Cooperative Oncology Group performance status of 0. Tumor pathology included 6 invasive lobular, 14 invasive ductal, and 6 invasive mammary carcinomas. Fifteen patients demonstrated lymph node involvement (N1 or N2), and their clinical stages comprised II A (n = 10), II B (n = 13), III A (n = 2), and III B (n = 1).

Toxicity

The side effects of therapy included those that were expected according to the side-effect profiles of the 2 therapeutic agents (Table 2). The most common side effect was hypertension, which occurred in 19 of 25 patients (76%), and was readily controlled except in 2 patients, who were taken off the study because of grade 3 toxicity (Table 2). Grade 1 proteinuria occurred in 2 patients (8%), and 3 patients (12%) manifested grade 1 elevations of transaminase. In terms of bleeding or thrombosis, 1 patient exhibited grade 2 gastrointestinal bleeding associated with diverticulitis, and 1 patient exhibited a grade 1 occlusion of her vascular port. Other side effects were typical of letrozole therapy, including joint and musculoskeletal pain, hot flashes, vaginal dryness and bleeding, and dry skin. Two severe adverse events were thought to be unrelated to therapy, ie, 1 episode of cholecystitis (cholelithiasis), and 1 episode of acute renal failure. No surgical problems were evident regarding wound healing, thrombotic events, or unusual bleeding associated with surgical treatment of the breast.

Antitumor Efficacy

As listed in Table 1, 17 of 25 (68%; 95% CI, 47%–84%) evaluable patients yielded objective responses according to ultrasound RECIST criteria, including 4 CRs (16%) and 13 PRs (52%). Stable disease occurred in 4 patients (16%), and 2 patients (8%) manifested PD (patients 14 and 21) at 16 and 9 weeks, respectively. Pathologic findings after 24 weeks of

therapy are also given in Table 1. Four of 25 patients (16%; 95% CI, 6%–35%) had pCRs in their breasts. These were the same 4 patients with CRs according to ultrasound criteria. One of these 4 (patient 26) with a pCR of the breast presented with residual tumor cells in her axillary nodes, and thus the pCR status for breast/lymph node was 3/25 (12%; 95% CI, 3%–30%). In addition, 8 of 25 patients (32%; 95% CI, 16%–53%) attained stage 0/1 status after neoadjuvant therapy. As indicated in Table 1, 2 of 15 patients with preoperative lymph node tumor involvement manifested negative lymph nodes at the time of surgical therapy. These included patient 3, who was graded T-2, N-1, and who achieved pCR after therapy, and patient 22, who changed from T-2, N-1 to T-1, N-0 at surgery. Of 21 patients who completed 24 weeks of therapy, 8 underwent breast-conserving surgery (38%) and 13 received modified radical mastectomies (62%).

Nine of 25 patients demonstrated objective improvements in their PET scan evaluations after 6 weeks of therapy, including all 4 patients who achieved pCR in their breast resections. Minimal, if any, reductions in tumor size had occurred (according to ultrasound measurements) at the time of PET scan (after 6 weeks of therapy). A strong association was evident between improvements in PET scan results and clinical CR and breast pCR status ($P = .0036$). No other correlations of PET scan results were evident in terms of clinical or pathologic outcomes.

Patient Follow-up

Of the evaluable patients, 1 (patient 16) was lost to follow-up after the completion of therapy. The 2 patients taken off the study because of toxicity (patients 5 and 6) readily recovered from their toxicity. Patient 5 was treated with neoadjuvant combination chemotherapy and postoperative radiation therapy, and demonstrated no evidence of disease (NED) recurrence at 37 months of follow-up. Patient 6 received single-agent letrozole neoadjuvant therapy and surgery, and also presented NED at 29 months. The median follow-up for the remaining 22 patients was 33 months as of April 1, 2009. The 2 patients with progressive disease (patients 14 and 21) received neoadjuvant combination chemotherapy. One of them (patient 21) had a relapse of systemic disease at 35 months, and the other (patient 14) presented NED at 29 months. The 4 patients with SD received adjuvant combination chemotherapy. One of them (patient 10) had a relapse with systemic disease at 25 months, and the others presented NED at 29–37 months. The remaining 16 patients, all of whom had objective clinical responses, have had no disease relapses after follow-ups of 27–45 months. Seven of those 16 received adjuvant chemotherapy (mainly patients with positive lymph nodes at surgery), and all are scheduled to continue their letrozole for 5 years. Eight of 13 patients treated with mastectomy received adjuvant radiation therapy. Thus, 2 of 24 evaluable patients (8%) with adequate follow-up have had a disease relapse after a 33-month median follow-up.

Discussion

Several clinical studies support the concept that the breast tumor content and expression of VEGF in patients with ER-positive or PgR-positive tumors limit the efficacy of tamoxifen in the adjuvant¹⁵ or metastatic setting.¹⁷ These observations led our Breast Cancer SPORE to

examine the effects of VEGF expression in MCF-7 cells in vitro and in vivo.¹³ The expression of VEGF at levels comparable to those seen in human breast cancer resulted in enhanced tumor growth rate and the development of tamoxifen resistance in orthotopic xenogeneic (MCF-7) murine models. The tumors formed by VEGF-secreting MCF-7 cells were also shown to express substantial stromal induction and metastatic potential.¹³

These observations led to the development of this pilot trial of letrozole plus bevacizumab (anti-VEGF) neoadjuvant therapy to determine the feasibility of this approach in regard to safety and affect on surgical treatment, and to assess any preliminary signs of efficacy. In terms of the intermediate endpoints of neoadjuvant therapy, considerable emphasis has been placed on pCR outcomes, which identify patients with excellent prognoses (> 95% 5-year relapse-free survival). However, pCR outcomes are uncommon (< 1%) in large hormonal neoadjuvant trials.^{7,18} This finding led Ellis et al to propose an alternative pathologic criterion of efficacy, that is, the attainment of stage 0 or 1 pathologic stage at surgery.⁷ In the P024 Hormonal Neoadjuvant Trial, 30 of 205 (15%) patients attained stage 0/1 status. After a median follow-up of 61 months, this population was projected to manifest 100% 5-year relapse-free survival. The majority of patients (85%) remained at stage 2/3 status, and had a 30% 5-year incidence of relapse.⁷

Our experience in this pilot neoadjuvant trial indicated that the regimen was well-tolerated, with a side-effect profile reflective of the known side effects of bevacizumab and letrozole. We found no adverse effects in regard to surgery, with 38% of patients undergoing breast-conserving procedures. The efficacy analysis was impressive, with a 68% objective response rate, including 4 patients with clinical CRs that were also breast pCRs (16%). One of these breast pCRs had residual tumor cells in the regional nodes, such that the pCR rate in breast and nodes was 12%. Further, 8 of 25 patients (32%) attained stage 0/1 status. Although this experience was limited by the modest number of patients (n = 25), the results are encouraging compared with hormonal neoadjuvant trials (pCR, < 1%), and comparable to combination chemotherapy neoadjuvant trials for ER/PgR-positive patient populations.

The 6-week PET scan “response” (improvement) was significantly correlated with clinical CR and breast pCR at 24 weeks ($P = .0036$). This technique may provide an early sign of efficacy, but this observation needs confirmation in larger numbers of patients. The experience of combining VEGF inhibition with antiestrogen treatment of breast cancer is quite limited. We believe that this is the first report of such a combination in neoadjuvant therapy for ER/PgR-positive postmenopausal women. A safety and feasibility study of bevacizumab plus letrozole for second-line therapy in ER/PgR-positive metastatic breast cancer was well-tolerated, with 3 of 43 patients producing a PR.¹⁹ Torrisi et al reported on a combination of bevacizumab, letrozole, and chemotherapy as neoadjuvant therapy in ER/PgR-positive breast cancer patients, and reported an objective clinical response rate of 86% in 36 evaluable patients, although no patient achieved a pCR.²⁰ Interestingly, 69% of these patients were premenopausal, and received gonadotropin-releasing hormone (GnRH) analogue (triptorelin) therapy before the initiation of letrozole.

The strategy of using antiangiogenesis in the treatment of patients with cancer has undergone recent review and reanalysis²¹ in regard to animal model studies.^{22,23} Those

studies suggested that antiangiogenesis strategies under certain conditions could lead to enhanced progression and invasion, and accelerated metastases. The animal models and treatment regimens were not similar to those in the adjuvant (or neoadjuvant) therapy of breast cancer. Further, the animal studies used receptor TK inhibitors and/or monoclonal antibodies to VEGF receptor-2, which are associated with hypoxia-driven elevated levels of circulating VEGF. Presumably, these hypoxia-driven VEGF levels would be associated with the enhancement of VEGF's many effects on tumor cells and the tumor microenvironment.^{24,25} In contrast, the use of bevacizumab for antiangiogenesis is associated with no functional (free) circulating VEGF.²⁶ Extended follow-ups of patients in this trial and other adjuvant trials will help clarify the role of antiangiogenesis in the treatment of human cancer.

Conclusion

The results of this 25-patient pilot trial of neoadjuvant bevacizumab plus letrozole in postmenopausal women with ER/PgR-positive tumors demonstrated the feasibility and safety of this treatment strategy. The clinical and pathologic intermediate endpoints were impressive for a relatively nontoxic therapy. A formal, randomized, phase II trial of this therapy is ongoing at the Translational Breast Cancer Research Consortium. This strategy may exert an important affect on therapeutic options in this patient population.

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Table 1

Patient Demographics and Treatment Response

Patient	Age, Years	Diagnosis ^a	Pretherapy		Clinical Objective Response ^c (% Decrease)	Surgical Pathology		
			Tumor Size	Node Status ^b		Tumor Size, cm	Node Status ^d	Stage 0/1
1	62	IDC ER ⁺ /PgR ⁺	T2	N-0	PR (83%)	2.0	NA ^b	Yes
2	62	IMC ER ⁺ /PgR ⁺	T3	N-1	PR (81%)	1.5	2/14	–
3	72	IDC ER ⁺ /PgR ⁺	T2	N-1	CR	0	0/8	Yes
4	77	IDC ER ⁺ /PgR ⁺	T2	N-0	PR (84%)	1.1	NA	Yes
5	62	IDC ER ⁺ /PgR ⁺	T2	N-0	Toxicity	–	–	–
6	71	ILC ER ⁺ /PgR [–]	T2	N-1	Toxicity	–	–	–
7	79	IDC ER ⁺ /PgR ⁺	T2	N-1	PR (59%)	5	1/7	–
8	56	ILC ER ⁺ /PgR ⁺	T2	N-0	PR (79%)	2.7	NA	–
9	61	ILC ER ⁺ /PgR ⁺	T3	N-1	SD(O)	4.2	2/18	–
10	75	ILC ER ⁺ /PgR ⁺	T2	N-1	SD(O)	2.1	20/29	–
11	61	IDC ER ⁺ /PgR ⁺	T2	N-0	PR (98%)	1.5	NA	Yes
12	59	IMC ER ⁺ /PgR ⁺	T2	N-1	PR (45%)	6.5	4/9	–
13	56	IDC ER ⁺ /PgR ⁺	T2	N-1	PR (48%)	3	1/11	–
14	65	IMC ER ⁺ /PgR ⁺	T2	N-0	PD	–	–	–
15	63	ILC ER ⁺ /PgR ⁺	T2	N-0	PR (93%)	1.6	NA	Yes
16	65	IDC ER ⁺ /PgR ⁺	T2	N-1	PR (84%)	4.8	1/12	–
17	72	IMC ER ⁺ /PgR ⁺	T2	N-1	N/A	–	–	–
18	64	IDC ER ⁺ /PgR ⁺	T3	N-2	PR (42%)	3.5	1/9	–
19	74	IDC ER ⁺ /PgR ⁺	T2	N-0	CR	0	NA	Yes
20	57	IDC ER ⁺ /PgR ⁺	T2	N-1	SD	5	8/15	–
21	57	IDC ER ⁺ /PgR ⁺	T2	N-0	PD	–	–	–
22	54	IMC ER ⁺ /PgR [–]	T2	N-1	PR (84%)	1.2	0/7	Yes
23	65	IDC ER ⁺ /PgR ⁺	T2	N-1	PR (45%)	3	1/10	–
24	64	ILC ER ⁺ /PgR ⁺	T2	N-1	SD	6	4/9	–
25	60	IMC ER ⁺ /PgR ⁺	T2	N-0	CR	0	NA	Yes
26	54	IDC ER ⁺ /PgR ⁺	T2	N-1	CR	0	3/7	–

Abbreviations: ER = estrogen receptor; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; IMC = invasive mammary carcinoma; NA = not available; PD = progressive disease; PgR = progesterone receptor; PR = partial response; SD = stable disease; SLN = sentinel lymph node

^aPathology and ER/PgR status.

^bPre-therapy N-0 patients (SLN-negative) did not undergo lymphadenectomies. Stages N-1 and N-2 were documented to exhibit positive tumor involvement according to fine-needle aspiration or SLN biopsy.

^cBased on tumor ultrasound measurements.

^dNode Status is given as number of tumor involved nodes/number of nodes examined.

Table 2

Adverse Events During Trial

Adverse Event	NCI-CTC Grade	Number of Patients
Hypertension	3	7
Hypertension	2	7
Hypertension	1	5
Joint Pain	2	4
Joint Pain	1	5
Muscle/Bone Pain	2	3
Muscle/Bone Pain	1	3
Fatigue	2	4
Fatigue	1	6
Hot Flashes	3	1
Hot Flashes	2	2
Hot Flashes	1	4
Proteinuria	1	2
Anorexia	2	1
Anorexia	1	4
Vaginal Dryness	2	1
Vaginal Bleeding	1	1
Skin Dryness	2	1
Skin Dryness	1	3
Urinary Tract Infection	2	2
Increased AST/ALT	1	3
Numbness	1	2
Cough	1	3
Port Occlusion	1	1
Gastrointestinal Bleeding/Diverticulitis	2	1
Diarrhea	1	1
Insomnia	1	1
Hypomagnesemia	1	1
Hypocalcemia	1	1

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; NCI-CTC = National Cancer Institute Common Toxicity Criteria, version 3.0