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Phase II Trial of Simple Oral Therapy with Capecitabine and Cyclophosphamide in Patients with Metastatic Breast Cancer: SWOG S0430

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Key Words. Metastatic breast cancer • Capecitabine • Cyclophosphamide • Oral therapy

LEARNING OBJECTIVES:

After completing this course, the reader will be able to:

1. Compare outcomes in patients treated with capecitabine plus CPA with those of capecitabine monotherapy and combination therapy with bevacizumab, sorafenib, or ixabepilone.

2. Identify patients for whom single-agent capecitabine is recommended.

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ABSTRACT

Background. Interest in oral agents for the treatment of metastatic breast cancer (MBC) has increased because many patients prefer oral to i.v. regimens. We evaluated a simple oral combination of capecitabine with cyclophosphamide (CPA) for MBC.

Methods. The trial was designed to determine whether or

not combination therapy would achieve a 42% response rate (RR) using the Response Evaluation Criteria in Solid Tumors (RECIST) in MBC. Patients with two or fewer prior chemotherapy regimens for MBC were eligible. Those with estrogen receptor–positive MBC had to have progressed on endocrine therapy. Patients had measurable disease or elevated mucin (MUC)-1 antigen and received CPA, 100 mg daily on days 1–14, and capecitabine, 1,500 mg twice daily on days 8–21, in 21-day cycles.

Results. In 96 eligible patients, the median progression-free survival (PFS) interval was 5.9 months (95% confidence interval [CI], 3.7–8.0 months) and median overall survival (OS) time was 18.8 months (95% CI, 13.1–22.0 months). The RR was 36% (95% CI, 26%–48%) in 80 patients with measurable disease. The MUC-1 antigen RR was 33% (95% CI, 20%–48%), occurring in 15 of 46 patients with elevated MUC-1 antigen. Toxicity was mild, with no treatment-related deaths.

Conclusions. PFS, OS, and RR outcomes with capecitabine plus CPA compare favorably with those of capecitabine monotherapy and combination therapy with bevacizumab, sorafenib, or ixabepilone. The addition of these other agents to capecitabine does not improve OS time in MBC patients, and this single-arm study does not suggest that the addition of CPA to capecitabine has this potential in an unselected MBC population. When OS prolongation is the goal, clinicians should choose single-agent capecitabine. *The Oncologist* 2012;17:179–187

INTRODUCTION

There is continued interest in oral agents for the treatment of metastatic breast cancer (MBC) patients, particularly because these patients report a preference for oral, home-based therapy over i.v., office- or clinic-based regimens [1]. However, patients are generally not willing to sacrifice efficacy for an oral therapy over an i.v. therapy [2], nor are they likely to prefer an oral regimen if the toxicity is higher [3]. With these parameters in mind, we endeavored to develop a well-tolerated, efficacious, all-oral combination chemotherapy regimen for the treatment of MBC patients.

There are two independent scientific justifications for combination therapy with capecitabine, an approved oral agent in breast cancer, with cyclophosphamide (CPA). First, there is hypothesized synergy between capecitabine and CPA. Capecitabine is an oral prodrug of 5-fluorouracil (5-FU). Capecitabine is converted to 5-FU preferentially in tumors, by a three-step process ending with the enzyme thymidine phosphorylase (TP) [4]. Both preclinical and clinical studies have shown that TP expression in cancers is increased by administration of a number of chemotherapy agents, including CPA [5, 6]. Preclinical xenograft breast tumor models have demonstrated synergistic inhibition of tumor growth with capecitabine in combination with CPA [7].

The second scientific rationale is based on the continuous scheduling of capecitabine and CPA used in this trial. Metronomic chemotherapy is the frequent administration of cytotoxic drugs at doses that are low enough to avoid dose-limiting adverse effects, which would otherwise require rest periods [8]. Metronomic therapy may target tumor cells indirectly by inhibiting angiogenesis and vasculogenesis through continuous exposure of the more slowly proliferating tumor endothelial cells to cytotoxic therapy [9]. Metronomic scheduling of well-tolerated doses of CPA and capecitabine may take advantage of a synergistic cytotoxic interaction between the drugs, as well as provide a potential antiangiogenic effect, with less toxicity than with alternative regimens.

We hypothesized that elderly patients may particularly benefit from an all-oral, metronomic approach to treatment. Weekly i.v. taxane therapy has been evaluated as a gentler and better tolerated therapy in this population [10, 11]. Barriers to this treatment could include problems with i.v. access in elderly individuals and transportation issues for weekly administration. An all-oral combination therapy that provides greater patient benefit than existing single-agent oral or i.v. therapies would represent a significant clinical advance and potentially a cost savings [12].

This study piloted the use of the serum mucin (MUC)-1 antigens CA 27–29 and CA 15–3 as surrogate markers of response in a SWOG clinical trial. It has been shown that a 50% decline in serum prostate-specific antigen (PSA) in prostate cancer patients is a statistically significant factor associated with survival, and thus PSA has been proposed as a useful surrogate endpoint to be used in phase II chemotherapy trials in prostate cancer patients, whose disease is often bone predominant and poorly measurable [13, 14]. Likewise, a 50% decline in CA-125 in ovarian cancer patients was strongly correlated with response rates (RRs) using standard criteria, and response definitions based on a 50% or 75% decrease in CA-125 level accurately predicted which drugs in phase II trials for relapsed ovarian cancer were active and justified further investigation [15]. In breast cancer, the MUC-1–associated antigens CA 27–29 and CA 15–3 may represent a similar situation [16–18]. These antigens are closely related and give comparable assay results [19]. Moreover, a >20% reduction in MUC-1 antigen levels suggested a longer time to progression in pretreatment marker-positive patients [19].

Despite numerous studies documenting the utility of MUC-1 antigens in monitoring response in clinical practice, the use of change in MUC-1 antigen levels as a surrogate endpoint in the design of phase II trials has been limited, perhaps because of some inherent limitations. First, MUC-1 antigens are elevated in only ~70% of patients with documented metastatic disease, and more often in bone- and visceral-predominant disease than in soft tissue disease. The kinetics of MUC-1 antigens are such that early measurement may be misleading, because up to one third of responding patients may have an initial increase in levels at 15 days and 30 days, followed by a return to baseline levels at 60 days [20–22]. Additionally, hand–foot syndrome, pulmonary fibrosis, hepatic toxicity, and gastrointestinal inflammation may be associated with false elevations in MUC-1 antigens [23].

Despite these limitations, MUC-1 antigens have the poten-

tial to serve as tools for estimating treatment response in patients with metastatic disease not measurable radiographically. In the area of breast cancer, a significant subset of patients suffers from bone-predominant disease that is nonmeasurable using the Response Evaluation Criteria in Solid Tumors (RECIST), thus making them ineligible for many clinical trials. We planned to use the experience gained in this trial to guide future trial designs of SWOG.

MATERIALS AND METHODS

Patient Eligibility

This prospective clinical trial (ClinicalTrials.gov identifier, NCT00107276) was conducted by SWOG, a federally funded clinical trials cooperative group. Patients aged ≥18 years with MBC and zero, one, or two prior chemotherapy regimens for metastatic disease were eligible to participate. Patients with estrogen receptor (ER)$^+$ MBC must have progressed on at least one endocrine therapy in the metastatic setting. RECIST-measurable disease was not required for all patients; however, in the absence of measurable disease, patients were required to have a MUC-1 antigen level (either CA 15–3 or CA 27–29) over two times the upper limit of normal (>2× ULN) and a MUC-1 antigen level documented to have increased by 1.5× prior to registration. Patients with symptomatic brain or central nervous system (CNS) metastases were excluded, although treated CNS metastatic disease was allowed if radiation therapy had been completed at least 8 weeks previously. Prior capecitabine or oral CPA therapy and concurrent antineoplastic therapy (radiation, chemotherapy, immunotherapy, biological therapy, hormonal therapy) were not allowed, with the exception of bisphosphonates. Other eligibility criteria were: a Zubrod performance status score of 0–2, adequate renal function (creatinine clearance >40 mL/minute by the Cockcroft and Gault formula), the ability to take oral medications, no prior unanticipated severe reaction to fluoropyrimidine therapy, no known sensitivity to 5-FU, and no known dihydropyrimidine dehydrogenase deficiency. Patients requiring full-dose anticoagulation with warfarin were excluded because of the interaction between warfarin and capecitabine. The study protocol was approved by the institutional review boards at participating institutions. Patients were informed of the investigational nature of the study and provided written informed consent in accordance with institutional and federal guidelines, including informed consent regarding the banking of whole blood and serum specimens to explore relevant molecular parameters.

Study Treatment

CPA (100 mg) was given on days 1–14, with capecitabine (1,500 mg twice daily) beginning on day 8 and continuing to day 21 (total of 14 days), on a 21-day schedule. This alternating schedule was designed to exploit the hypothesized induction of TP by CPA. Flat dosing of the oral agents was used in view of published data indicating that the clearance of both drugs is independent of body surface area [24, 25]. Patients with a lower creatinine clearance (40–50 mL/minute) were started at capecitabine dose level −1 (1,000 mg twice daily). The CPA dose was based on a phase III clinical trial evaluating a similar combination [26]. Chemotherapy was given for eight cycles. Treatment beyond eight cycles was at the discretion of the treating physician.

The continuous therapy was interrupted in cases of toxicity, and treatment was resumed once the toxicity had resolved as specified for that calendar day, with dose adjustment as required. CPA was held if the absolute neutrophil count was <1,000/mm^3, if the platelet count was <75,000/μL, or for any nonhematological grade 3 or 4 toxicity attributable to the drug. Dosing of capecitabine was interrupted for hand–foot syndrome, diarrhea, or mucositis grade ≥2 that developed at any time while the patient was receiving the drug, and the dose was subsequently reduced for grade 3–4 toxicity or for grade 2 toxicity that occurred twice. Dose levels of capecitabine were: level 0, 1,500 mg twice daily; level −1, 1,000 mg twice daily; level −2, 500 mg in the morning and 1,000 mg in the evening; and level −3, 500 mg twice daily. Dose escalations were not allowed. If a dose reduction was mandated by toxicity, dose re-escalation was not allowed even if the toxicity resolved. Use of filgrastim was not allowed, but erythropoietin was allowed at the discretion of the treating physician.

Study Assessments

Baseline evaluation included a history and physical examination, weight measurement, assessment of performance status, CBC and differential, and measurement of serum bilirubin, serum glutamic oraloacetic transaminase or serum glutamic pyruvic transaminase, alkaline phosphatase, creatinine, calcium, potassium, and sodium levels. For patients without measurable disease, MUC-1 antigen elevation (CA 15–3 or CA 27–29) was required for study eligibility. Patients were requested to provide a baseline serum and whole blood sample for banking for future correlative studies. Baseline imaging was performed as required by location of metastases, including a physical examination, computed tomography scan of the chest, abdomen, and pelvis, bone scan, and x-rays. Response to treatment was evaluated at the beginning of odd-numbered treatment cycles using the RECIST (version 1.0). MUC-1 antigen was measured each cycle. Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

Statistical Analysis

The objectives of this trial were to: (a) evaluate the RRs (complete response [CR] and partial response [PR], confirmed and unconfirmed) to combination simple oral therapy with CPA and capecitabine in the subset of patients with measurable disease, (b) estimate progression-free survival (PFS) and overall survival (OS) outcomes, (c) evaluate the toxicity of this drug combination, (d) explore the use of MUC-1 antigens (CA 27–29 or CA 15–3) as surrogates for clinical benefit in patients with nonmeasurable disease, and (e) establish a serum and whole blood specimen bank for MBC for future correlative studies.

We planned to enroll 96 patients in a single stage over 4

years with 2 years of follow-up after the last enrollment. Because response in patients aged ≥65 years was of special interest, a subset analysis was prospectively planned for this age group.

Efficacy was evaluated using the proportion of responders to treatment, defined as those with a CR or PR. We assumed that 75% of the patients would have measurable disease using the RECIST. We anticipated a 25% RR with single-agent standard treatment. The combined CPA and capecitabine therapy would be of interest if the RR was 42%. Assuming a significance level of $\alpha = 0.05$ (one sided) and 72 patients with measurable disease, the power to detect this difference would be 92% overall. If 47 patients aged ≥65 years were enrolled, then the power would be 80% to detect an absolute 17% higher RR.

Analyses of PFS and OS outcomes were performed using Kaplan–Meier analysis. The PFS interval was defined as the difference between the registration date and date of progression or death resulting from any cause, or the last follow-up date if progression or death was not observed. The OS duration was the time from registration to death resulting from any cause, or the last follow-up date in censored individuals. If the median OS time was ~12 months with standard treatment, then a longer median OS time of 16 months could be detected with 90% power and $\alpha = 0.05$ (one sided).

The trial's objectives included an exploration of the use of MUC-1 antigens (CA 27–29 or CA 15–3) as surrogates for clinical benefit in patients with nonmeasurable disease, and the trial had prespecified definitions for MUC-1 response determination. The set of patients analyzed for overall MUC-1 antigen response was all patients with a baseline CA 27–29 or CA 15–3 level >2× ULN. Only MUC-1 values recorded during the treatment period were included in the assessment of MUC-1 response. An initial spike in a MUC-1 antigen level did not change the baseline comparator, nor did MUC-1 antigen elevation determine progression if the patient did not clinically progress. A MUC-1 antigen PR (mPR) was defined as a >50% decline in MUC-1 antigen compared with baseline that persisted for ≥21 days. A MUC-1 antigen CR (mCR) was defined as a decrease in a MUC-1 antigen level into the normal range that persisted for ≥21 days. MUC-1 antigen progressive disease (mPD) was defined as an increase in a MUC-1 antigen level >50% as the best response. MUC-1 antigen stable disease (mSD) was a MUC-1 antigen response that did not fit any of the above categories. The overall MUC-1 antigen RR (mRR) was defined as the number of patients with mCR or mPR divided by the number of patients with an elevated baseline MUC-1 antigen level. Patients without a MUC-1 antigen response assessment were considered to have not responded when calculating the mRR. The overall mRR (mCR or mPR) is provided with an exact 95% two-sided confidence interval (CI) using standard methods based on the binomial distribution. As a supplemental analysis, the rate of disease control (mCR, mPR, or mSD) was summarized in the same way as the overall mRR.

RESULTS

Between August 15, 2005 and September 1, 2007, 112 patients were registered from 26 institutions. Patient characteristics are summarized in Table 1. Sixteen patients were ineligible. Reasons for ineligibility included: no measurable disease and MUC-1 antigen ineligible (10 patients), ER$^+$ disease but no prior endocrine therapy (four patients), and too many prior chemotherapies (two patients).

Eighty eligible patients had measurable disease at baseline. Six patients with inadequate or delinquent disease assessments were assumed to be nonresponders for the purpose of RR estimation. There were 29 responses (four CRs and 25 PRs) among the 80 patients with measurable disease, for an RR of 36% (95% CI, 26%–48%) (Table 2). The RRs for patients with zero, one, and two prior metastatic chemotherapy regimens were 32%, 40%, and 45%, respectively (Table 3).

Evaluation of efficacy in the elderly population was of specific interest in this study. Twenty-five patients aged ≥65 years had measurable disease, and the RR in this subgroup was significantly lower than that observed in the younger population, estimated at 16% (95% CI, 5%–36%; $p = .013$) (Table 3). When SD is included, the clinical benefit rate (CBR) was 68% overall, with little difference between women aged <65 years (69%) and those aged ≥65 years (64%) ($p = .80$).

Ninety-six eligible patients with follow-up data were evaluated for survival endpoints. Ninety-two of the 96 experienced PD or death. Seventy-nine deaths were recorded among the 92 patients. The median PFS interval was 5.9 months (95% CI, 3.7–8.0 months) and the median OS time was 18.8 months (95% CI, 13.1–22.0 months) (Fig. 1). For patients with zero, one, or two prior metastatic chemotherapy regimens, the median PFS intervals were 6.4 months, 6.3 months, and 4.1 months, respectively. The median OS times for patients with zero, one, or two prior chemotherapy regimens were 24.1 months, 17.3 months, and 8.6 months, respectively. Tests for trend confirmed that PFS and OS times decreased with increasing number of previous regimens ($p = .012$ and $p < .001$, respectively). For patients aged ≥65 years and <65 years, the median PFS intervals were 2.9 months and 7.0 months (not significant [NS]), respectively. The median OS times for patients aged ≥65 years and <65 years were 17.3 months and 19.9 months (NS).

Ninety-five patients were evaluated for adverse events and, overall, the treatment was associated with low toxicity (Table 4). One patient with no toxicity assessments done prior to progression was not evaluable for toxicity assessment. There were no treatment-related deaths reported. Four patients experienced grade 4 toxicities: lymphopenia (three cases) and thrombosis/embolism (one case). Thirty-three patients experienced grade 3 toxicities as the maximum degree, including leukopenia (15 patients); hand–foot syndrome (seven patients); and fatigue, diarrhea, and dehydration (two patients each).

Of the 96 eligible patients, two did not have MUC-1 testing prior to treatment initiation. Of the remaining 94 patients, 46 (49%) had MUC-1 values >2× ULN at baseline. Four of the 46 (9%) had sustained subsequent normal MUC-1 values during treatment, thus meeting the definition of mCR. An additional 11 patients (24%) had a 50% reduction in MUC-1 level from baseline and were categorized as mPR. Eleven had an increase >50% from baseline and were categorized as mPD. An

Table 1. Patient characteristics at baseline

Characteristic	*n* of patients	%
n enrolled	112	
n eligible	96	
Age, yrs (median = 59)		
34–49	22	23
50–64	44	46
65–88	30	31
Menopausal status		
Premenopausal	18	19
Postmenopausal	78	81
Metastatic site[a]		
Bone	53	55
Lung	44	46
Liver	38	40
Lymph nodes	26	27
Pleura	11	11
Other	48	50
n of metastatic sites		
1	25	26
2	30	31
≥3	41	43
Tumor hormone receptor status		
ER$^+$PgR$^+$	45	48
ER$^+$PgR$^-$	11	12
ER$^-$PgR$^+$	2	2
ER$^-$PgR$^-$	36	38
Missing	2	
HER-2/*neu* status		
Absent	7	7
Negative	78	82
Positive	6	6
Equivocal	4	4
Prior adjuvant therapy		
None	26	27
CT	30	31
HT	9	9
CT + HT	31	32
Prior therapy for metastatic disease		
None	17	18
CT	21	22
HT	36	37
CT + HT	22	23
n of prior metastatic CT regimens		
0	53	55
1	30	31
2	13	14

[a]Multiple sites possible.
Abbreviations: CT, chemotherapy; ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; HT, hormone therapy; PgR, progesterone receptor.

Table 2. Response for measurable patients

Response Evaluation Criteria in Solid Tumors	*n*	%
Complete response	4	5%
Partial response	25	31%
Stable disease/no response	25	31%
Progressive disease	18	23%
Symptomatic deterioration	2	3%
Assessment inadequate	6	8%
Total	80	100%

Table 3. Response rates for measurable patients by prior therapy, ER status, and age subgroup

	n	Responses	Response rate	95% CI
All patients	80	29	36%	26%–48%
n of prior chemotherapy regimens for metastatic disease				
0	44	14	32%	19%–48%
1	25	10	40%	21%–61%
2	11	5	45%	17%–77%
ER status				
Positive	41	17	41%	26%–58%
Negative	38	12	32%	17%–49%
Missing	1			
Age subgroup				
≥65 yrs	25	4	16%[a]	5%–36%
<65 yrs	55	25	45%[a]	32%–59%

[a]Significant difference, *p* = .013.
Abbreviations: CI, confidence interval; ER, estrogen receptor.

additional four patients (9%) with initial abnormal values did not have a follow-up MUC-1 assessment during treatment and, thus, were categorized as nonresponders. The remaining 16 patients (35%) did not meet any of the aforementioned criteria and were categorized as mSD. Therefore, the mRR (mCR and mPR) among those with elevated initial MUC-1 values was 33% (15 of 46) with a 95% CI of 20%–48%. If those with mSD are included, the MUC-1 antigen CBR is 67% (31 of 46), with a 95% CI of 52%–80%.

Thirty patients had disease measurable by both methods. Ten of 30 were responders as evaluated using the RECIST, nine of 30 had a response using MUC-1 assessment, and seven of 30 patients had a response using both methods (Fig. 2). The
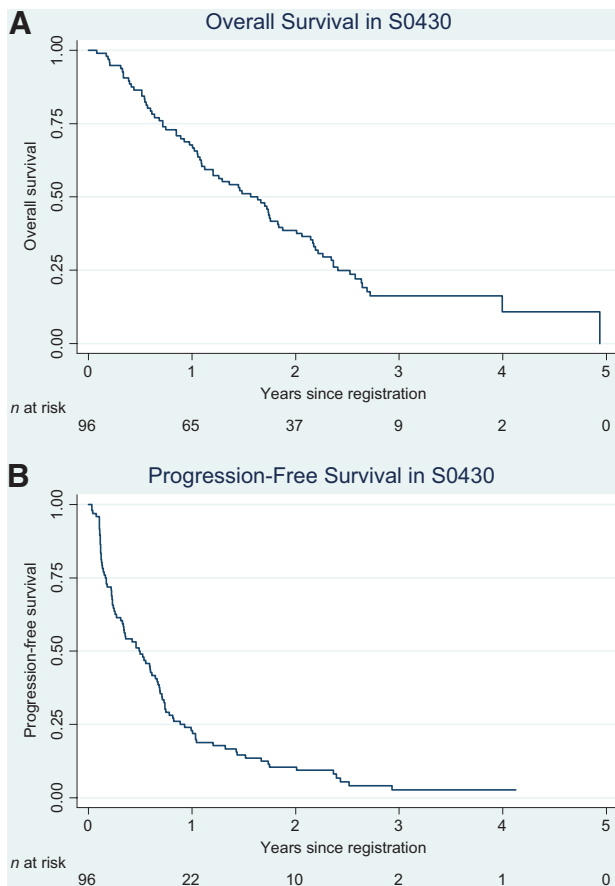
Figure 1. Overall survival (**A**) and progression-free survival (**B**) outcomes in the Southwest Oncology Group S0430 trial.

two patients who had a response using MUC-1 assessment but not using the RECIST had SD per the RECIST.

The MUC-1 values of all 16 patients with nonmeasurable disease were elevated at baseline as part of the requirement for eligibility. Six of these 16 patients had bone as the only site of disease, and 13 of these 16 patients had at least one bone metastasis. Six of these 16 were responders (two with mCR and four with mPR) using the MUC-1 criteria, giving an mRR of 38% (95% CI, 15%–65%). Six more had mSD, and the remaining four patients had mPD using the MUC-1 criteria. The mRR in RECIST-measurable patients was 30% (nine of 30) with a 95% CI of 15%–49%. Overall, the RRs in the MUC-1 subsets were similar to the RECIST RRs (Fig. 2).

DISCUSSION

In this trial of combination capecitabine and CPA in MBC patients treated with two or fewer prior chemotherapy regimens, the primary RR, PFS, and OS outcomes compare favorably with those from historical reports of single-agent capecitabine. Toxicity was mild, with few serious adverse events reported in a multicenter setting that included both academic and community-based practices.

The protocol-defined historical comparator was a 25% RR. Published single-agent capecitabine phase II studies have documented RRs of 15%–28% [27–30], and recent randomized

studies using capecitabine as the control arm have similarly shown RRs with single-agent capecitabine of 14%–31% [16, 18, 19]. In combination with oral CPA, we observed a 36% RR overall, but note that this did not reach our goal of a 42% RR. It is, however, consistent with the 36% RR observed with concurrent capecitabine–CPA therapy recently published by Tanaka et al. [31].

The regimen had a disappointing RR in the elderly. However, CBRs were comparable between age groups because SD was more often recorded in the elderly. The PFS interval was shorter in older women, but the difference was not statistically significant.

Closer review of the data does not provide further explanation of the low RR in the elderly. The older women tended to have more ER+ and progesterone receptor–positive disease and were treated with fewer previous regimens for metastatic disease. Dose delays and modifications were not obviously more common in elderly patients, but it should be noted that the study was not designed to look for a difference in these factors. Overall, these results suggest a somewhat lesser activity of this chemotherapy in elderly patients, but advocate that elderly patients may still receive clinical benefit.

The patient population in this study included both pre-treated and chemotherapy-naïve patients, and reflects a typical MBC population. Our results have implications for clinical trial design for MBC. First, these data do not support the routine exclusion of MBC patients who have had prior chemotherapy regimens from phase II clinical trials in which the RECIST RR is the primary endpoint, because there was little difference in the RR between the subsets of pretreated and chemotherapy-naïve patients. Furthermore, these data emphasize the sensitivity of survival outcomes to the number of prior chemotherapy regimens and highlight the importance of stratifying or controlling for these factors when survival outcomes are primary.

The 16 patients enrolled with nonmeasurable disease are of specific interest to determine whether MUC-1 antigen positivity should satisfy an eligibility criterion in future SWOG studies. In this trial, 13 of 16 patients had bony disease, and in six of 16, bone was the only site of disease. The mRR in those 16 patients was comparable with the RECIST RR in the measurable population of patients. Furthermore, there was good concordance between RECIST response and MUC-1 response in patients measurable by both methods. Overall, these data encourage further investigation of mRR as a surrogate marker of efficacy in patients with bone-predominant breast cancer, in whom the disease is poorly measurable radiographically. Continuing use of MUC-1 antigen positivity as an eligibility criterion in SWOG studies will provide an opportunity for this clinically relevant patient population to be included in early-phase clinical trials designed to look for signals of treatment efficacy.

It is interesting to consider this regimen in the context of other possible capecitabine combinations. Several recently reported randomized trials have examined capecitabine alone versus in combination with other therapies: with bevacizumab, an i.v. monoclonal antibody directed against vascular endothelial growth factor (VEGF) in first-line and second-line treatment for advanced breast cancer [32, 33]; with sorafenib, an

Table 4. Number of patients with a given type and grade of adverse event

Adverse event	Unknown	Grade					
		0	1	2	3	4	5
Antidiuretic hormone	0	94	0	0	1	0	0
Alanine aminotransferase	0	89	4	1	1	0	0
Alkaline phosphatase	0	85	8	1	1	0	0
Dehydration	0	92	0	1	2	0	0
Diarrhea	0	66	25	2	2	0	0
Dyspnea	0	87	7	0	1	0	0
Fatigue	0	38	35	20	2	0	0
Febrile neutropenia	0	94	0	0	1	0	0
Hand–foot syndrome	0	58	14	16	7	0	0
Hemoglobin	0	57	24	13	1	0	0
Hypokalemia	0	89	5	0	1	0	0
Hyponatremia	0	89	5	0	1	0	0
Leukocytopenia	0	52	17	11	15	0	0
Lymphopenia	0	74	2	6	10	3	0
Mood alteration: depression	0	90	2	2	1	0	0
Nausea	1	43	42	8	1	0	0
Neutropenia	0	66	8	14	7	0	0
Thrombocytopenia	0	82	11	1	1	0	0
Pruritus	0	94	0	0	1	0	0
Rash	0	91	3	0	1	0	0
Thrombosis/embolism	0	93	0	0	1	1	0
Weight loss	0	88	6	0	1	0	0
Maximum grade any adverse event	1	6	17	34	33	4	0

Adverse events unlikely or not related to treatment and those with maximal grade 2 were excluded.
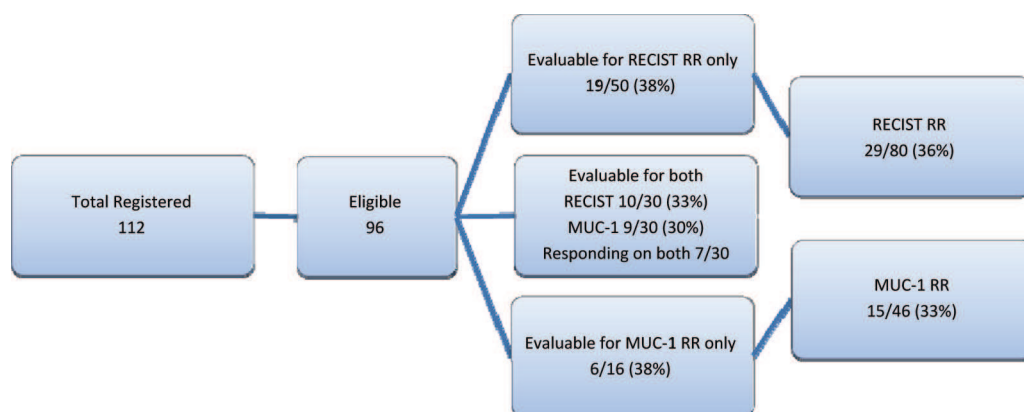

Figure 2. Response rate (RR) by the Response Evaluation Criteria in Solid Tumors (RECIST) and mucin (MUC)-1 criteria.

oral tyrosine kinase inhibitor with many targets, including VEGF, in first-, second-, and third-line therapy of advanced breast cancer [34]; and with ixabepilone, a newly approved epothilone cytotoxic in the setting of prior anthracycline and taxane therapy [35]. The clinical data from these studies, as published or presented recently at major oncology meetings, are summarized Table 5. The RR, PFS, and OS results with CPA and capecitabine appear to be similar to those with combinations of capecitabine with bevacizumab, sorafenib, and ixabepilone, taking into consideration the prior number of therapies and proportion of ER$^+$ versus ER$^-$ patients. However, intertrial comparisons must be interpreted with caution be-

Table 5. Results of combination capecitabine regimen trials

	Robert et al. [32]	Brufsky et al. [33]	Thomas et al. [35]	Baselga et al. [34]	S0430
Capecitabine combined with	Placebo/bevacizumab	Placebo/bevacizumab	Control/ixabepilone	Placebo/sorafenib	CPA
n of patients	206/409	47/97	377/375	114/115	96
n of prior chemotherapy regimens					
0	100%	Excluded	9%/7%	54%/43%	55%
1	Excluded	100%	49%/48%	45%/57%	31%
2	Excluded	Excluded	37%/41%	Excluded	14%
3	Excluded	Excluded	6%/5%	Excluded	Excluded
ER$^+$ or PgR$^+$	NR	NR	49%/47%	68%/77%	62%
ER$^-$ PR$^-$			26%/24%	29%/17%	38%
HER-2$^-$ Unknown ER			11%/13%	3%/6%	1%
Response	23.6%/35.4%	NR	14%/35%	30.7%/38.3%	36%
PFS (mos)	5.7/8.6	4.1/6.9	4.2/5.8	4.1/6.4	5.9

Abbreviations: CPA, cyclophosphamide; ER, estrogen receptor; HER-2, human epidermal growth factor receptor 2; NR, not reported; PFS, progression-free survival; PgR, progesterone receptor.

cause there are often significant differences in the clinical trial populations.

CONCLUSION

Randomized trials have failed to show that the addition of bevacizumab, sorafenib, or ixabepilone to capecitabine as a single agent leads to longer OS times in MBC patients. Nor do our results suggest that the addition of CPA to capecitabine has this potential in an unselected MBC population. Therefore, we conclude that single-agent capecitabine should continue to be used in patients without immediately life-threatening or highly symptomatic disease.

Combination chemotherapy regimens in breast cancer typically are associated with higher RRs and longer PFS times than with single-agent regimens, but they have failed to produce an OS benefit compared with single-agent sequential therapy. Despite this fact, we continue to be informed of trial results that pit combination capecitabine therapies against single-agent capecitabine therapy. We propose that any expensive or less convenient capecitabine combination regimen in routine use based on such trial results should be tested against another combination regimen. The SWOG all-oral regimen would be of interest in randomized comparative effectiveness studies to better evaluate costs, quality of life, and the preferences of MBC patients and their caregivers.

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