# Efficacy of Very-Low-Dose Capecitabine in Metastatic Breast Cancer

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## Abstract

**Background:** The FDA-approved dosage of capecitabine, 1250 mg/m$^2$ twice daily, is often associated with treatment-limiting toxicities. Clinical experience and published reports suggest that lower starting dosages of capecitabine can be as effective as the approved dosage. In this retrospective analysis we compared the efficacy of significantly lower dosages of capecitabine with the FDA-approved dosage, using previously published results as comparators.

**Patients and Methods:** We performed a retrospective cohort analysis of patients treated at University of Southern California hospitals who received capecitabine as the first, second, or third line of chemotherapy for metastatic or unresectable locally advanced breast cancer to determine the progression-free survival (PFS) associated with low starting dosages.

**Results:** Patients (n = 84) received a median capecitabine dosage of 565 mg/m$^2$ twice daily, mostly administered as a flat dosage (not adjusted for body surface area) of 1000 mg twice daily. The median PFS among patients with measurable disease (n = 62; 74% of patients) was 4.1 months (95% confidence interval, 2.9-5.7), which was similar to the median PFS values (4.4 months; 4.2 months) for single-agent capecitabine reported in the 2 major trials with similar eligibility criteria. Furthermore, only 2 patients (2.4%) discontinued capecitabine due to toxicity, supporting our hypothesis that starting treatment at low dosages minimizes side effects while preserving efficacy.

**Conclusions:** Our results provide evidence that very low dosages of capecitabine are efficacious in treating metastatic breast cancer. Large-scale randomized, controlled trials testing lower starting dosages of capecitabine are necessary in order to firmly establish an optimally effective and well-tolerated dosage.

**Key words:** Capecitabine, chemotherapy, metastatic breast cancer, drug toxicity, dose intensity

## Introduction

Breast cancer causes approximately 40,000 deaths annually in the United States.[1] The majority of these deaths occur in women with metastatic breast cancer (MBC), reflecting the incurability of MBC and the need for improved treatment. Currently, treatment for MBC is palliative and involves balancing improvement in cancer symptoms and delay of progression against side effects of therapy.[2]

Capecitabine is an orally administered prodrug of 5-fluorouracil (5-FU) that is activated to 5-FU preferentially in tumor tissue due to increased expression of thymidine phosphorylase in tumor tissue, which contributes to the drug's specificity and action against tumor cell proliferation.[3] Capecitabine was first approved for MBC in 1998 in patients pretreated with anthracyclines and taxanes. It was later approved in combination with docetaxel after the combination resulted in improved overall survival (OS) when compared with docetaxel alone.[4,5] Since then, capecitabine has come into wide use in MBC and is now approved both as monotherapy and in combination with docetaxel.[6]

Capecitabine was approved for use at a starting dosage of 1250 mg/m$^2$ twice daily, with a dosing schedule of 14 days on followed by 7 days off despite frequent treatment-limiting toxicities, primarily hand-and-foot syndrome, stomatitis, and diarrhea at this dosage. These side effects are typically managed by dosage reduction or starting at a lower dosage despite a lack of evidence from phase 3 randomized clinical trials to validate the efficacy of these lower dosages.

Since the approval of capecitabine, moderate dosage reductions have been studied, either retrospectively[7,8] or in small prospective trials[9-11] in order to assess both the efficacy and frequency of adverse effects (AEs) associated with lower dosages. Other studies have examined the efficacy of dosages of capecitabine as low as 825 mg/m$^2$ twice daily,[12] suggesting that this dosage is no less efficacious than the full dosage. Altering the treatment schedule has also been investigated as a method of reducing drug-associated toxicity. The administration of capecitabine via "continuous" dosing (without a 7-day rest period) using dosages as low as 650 mg/m$^2$ twice daily was recently shown to be superior in both tolerability and efficacy to classical cyclophospha-

mide, methotrexate, and fluorouracil as first-line chemotherapy for MBC.[13] Another series of studies demonstrated tolerability of a 7-days-on, 7-days-off "dose-dense" regimen of capecitabine,[14] as well as efficacy of this alternate schedule in combination with lapatinib[15] or bevacizumab[16] that was comparable to results of prior trials using the traditional 14-days-on, 7-days-off schedule.

The question of dosing is further complicated by the fact that fluoropyrimidine pharmacokinetics vary significantly between patients[17] and demographic groups,[18] such that precise dosing based on body surface area (BSA) may be unnecessary. The concept that variations in thymidine phosphorylase polymorphisms may explain differences in patients' responses to the drug in both tumor and extratumoral tissues was proposed by Kaufmann et al[9] as a rationale for the observed correlation between the development of hand-foot syndrome with time to progression (TTP) on capecitabine therapy. These findings provide hope that in the future, more objective measures will be used to individualize treatment and dosing regimens. Currently, however, selection of patients for treatment with capecitabine and modifications in dosing rely heavily on clinical judgment. The lack of consensus on an appropriate starting dosage of capecitabine has resulted in the use of myriad different dosing regimens and schedules in recent phase 1 and 2 clinical trials, many of which have been shown to be comparable in efficacy to standard dosing. Additionally, several retrospective studies have determined that lower dosages of capecitabine possess efficacy comparable to that of the full dosage, with less significant toxicity.[7,8]

At the University of Southern California (USC) hospitals, defined as Los Angeles County (LAC) + USC Medical Center and USC Norris Comprehensive Cancer Center, capecitabine is routinely prescribed at dosages as low as 600 mg/m$^2$ twice daily, with a majority of patients receiving a flat dosage (not adjusted for BSA) of 1000 mg twice daily, lower than previously published series. In addition to the existing evidence of efficacy of lower dosages of capecitabine, the rationale for this practice is that the use of lower dosages facilitates patient adherence to treatment, as providers at the LAC+USC Medical Center often encounter challenges with compliance and observation of follow-up appointments among the underserved patient population treated at this hospital.

We sought to compare outcomes of patients at the USC hospitals who were treated with very low dosages with published trials using standard FDA-approved dosing. A secondary aim was to identify clinical predictors of PFS, including dosage of capecitabine, within our cohort. In order to best approximate the clinical population treated with capecitabine, we chose comparator studies that included patients with MBC treated with this agent in up to 3 lines of therapy.[19,20]

## Patients and Methods

### *Patients*

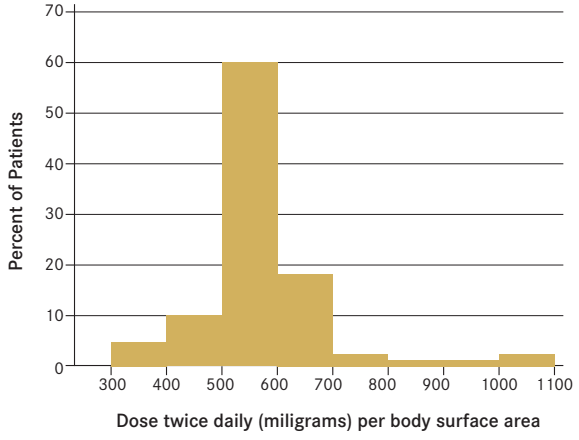
Under an institutional review board-approved protocol, we used electronic medical records (EMRs), pharmacy records, and care providers' patient lists to identify patients with MBC or unresectable locally advanced breast cancer. Patient demographic, clinical, pathologic, and outcome data were gathered from EMRs and coded to protect patient privacy. We selected subjects who had received capecitabine as a single agent or with trastuzumab for HER2-positive cases, as the first, second, or third line of chemotherapy in the metastatic setting from January 2006 to March 2011. Our decision to include patients treated with trastuzumab reflects the fact that the use of trastuzumab is now widely accepted as the standard of care for patients with HER2-positive disease, along with the fact that our comparator studies did not exclude trastuzumab-treated patients. Patients who received capecitabine with lapatinib were excluded because lapatinib treatment requires a modified starting dose of capecitabine and was not represented in the comparator studies. Patients with measurable or nonmeasurable disease were eligible, although only patients with measurable disease on the basis of radiology reports and physical examination were included in the comparison of outcomes with published trials that used standard FDA-approved dosing.

### *Outcome Assessments*

Our study was conducted as a retrospective cohort analysis of the medical records of eligible patients. The primary endpoint was progression-free survival (PFS), defined as the duration in time between date capecitabine treatment started and date of progression, with patients who did not have progression censored at the last follow-up date. We followed the principle of intent to treat (ITT), in that patients were not censored because of deviation from the intended capecitabine treatment. Progression was defined clinically and based upon evidence from radiology reports and physical examination. Included in this definition of progression was the decision by the treating physician to initiate palliative radiation therapy, due to the fact that such decisions often reflect refractoriness to the current chemotherapy regimen and overall disease progression. Formal tumor assessment using the Response Evaluation Criteria in Solid Tumors (RECIST) was not done.

The primary aim of this study was a comparison of median PFS for USC patients with measurable disease with the reported median PFS in published trials that used standard FDA-approved dosing. Our major secondary aim was a comparison of PFS between patients in this cohort who had measurable disease and those who had nonmeasurable disease. Additional analyses were performed to explore the relationship between PFS and various clinical and tumor characteristics in all patients (both patients with and without measurable disease).

**FIGURE 1.** Distribution of Capecitabine Dosage Per Body Surface Area




Distribution of capecitabine dosage per body surface area in this cohort. Range, 305-1057 mg/m$^2$ twice daily; median dosage, 565 mg/m$^2$ twice daily; standard deviation = 115 mg/m$^2$ twice daily

BSA indicates body surface area; PFS, progression-free survival.

*Statistical Analysis*

Analysis of PFS in relation to patient and disease characteristics was based on the log rank test, product-limit estimator, and univariate and multivariate Cox regression analysis.[21] Patient or disease characteristic variables were each examined for their relationship with PFS, adjusting for whether or not a patient had measurable disease. Variables examined included treating site (LAC+USC Medical Center or Norris Comprehensive Cancer Center), race/ethnicity, age at initial diagnosis of breast cancer, age at initiation of capecitabine treatment, biomarker status (estrogen receptor [ER], progesterone receptor [PR], and HER2), prior treatment with anthracycline or taxane, line of administration of capecitabine therapy (1, 2, or 3), disease-free interval (DFI; defined as time between initial histological diagnosis of breast cancer and diagnosis of metastatic disease), concurrent administration of trastuzumab with capecitabine, the number of metastatic disease sites, presence of visceral disease, and capecitabine dose per BSA. The variables that were associated with PFS at $P \leq .20$ after controlling for measurable disease status were then included in a multivariate Cox regression model, and a backward stepwise model selection method was used to select a final model by successively dropping nonsignificant variables from the model and refitting reduced models until all remaining variables were statistically significant at 0.20.[22] Statistical analyses were performed using Stata Statistical Software (version 11.0; StataCorp LP, College Station, TX).

## Results

*Patient Characteristics*

We identified a total of 84 eligible patients who were treated with capecitabine alone or with trastuzumab between January 2006 and March 2011. Patient and disease characteristics are shown in **Table 1**. With the exception of the ethnic composition, baseline demographics and prognostic indicators including age, receptor status, DFI, and prior therapies were comparable between both hospital cohorts and those in the 2 major randomized controlled trials[19,20] that serve as our comparators. Notably, 49% of patients were Hispanic, reflecting the large proportion of patients of this ethnicity seen at the USC hospitals. Sixty-two (74%) patients had measurable disease and 16 (19%) had nonmeasurable disease. For the remaining 6 (7%) patients, measurability could not be ascertained. Twenty-four percent of patients had HER2-positive disease; 75% of these patients received trastuzumab concurrently. Of the HER2-negative cases, 76% had hormone receptor (HR; ER or PR) –positive tumors and 24% had triple-negative tumors. Seventy-five percent of patients had received some prior chemotherapy in any setting before receiving capecitabine, while 25% of patients were chemotherapy-naïve. Overall, 70% of patients had been pretreated with an anthracycline, a taxane, or both. The majority of patients in our study (77%) received capecitabine as the first line; 17% received capecitabine as second-line, and 6% of patients received capecitabine as the third-line chemotherapy in the metastatic setting. Overall, our cohort was well matched to those in the chosen phase 3 comparator studies.

*Capecitabine Exposure*

All 84 patients in our study received capecitabine at dosages significantly lower than the dosage approved by the FDA (1250 mg/m$^2$ twice daily) or reported in the literature.[8-10,12] Our use of flat dosing, rather than according to BSA, introduced some heterogeneity in dosage per BSA received by the patients in this cohort. The median starting dosage was 565 mg/m$^2$ twice daily, with a standard deviation of 115 mg/m$^2$ twice daily and a range of 305 mg/m$^2$ to 1057 mg/m$^2$ twice daily (**Figure 1**). Since we typically used a flat-dosing method, the majority of our patients (n = 72; 86%) received an absolute dosage of 1000 mg twice daily. Of the remaining 12 patients, 1 (1%) received 500 mg twice daily, 4 (5%) received 750 mg twice daily, and 7 (8%) received 1500 mg twice daily. The median absolute dosage was 1017 mg twice daily, with a standard deviation of 163 mg twice daily. Two-thirds of our patients received capecitabine at dosages under 600 mg/m$^2$ twice daily, less than half of the FDA-approved dosage of 1250 mg/m$^2$ twice daily.

*Efficacy of Capecitabine Therapy*

Of the 84 patients in our study, a total of 64 patients had disease progression during capecitabine treatment, including 52 patients who progressed on capecitabine as determined clinically by the

**TABLE 1.** Patient and Disease Characteristics

| Variable | Total (N = 84) | % |
|---|---|---|
| **Measurable Disease** | | |
| No | 16 | 21% |
| Yes | 62 | 79% |
| Unknown | 6 | |
| **Hospital** | | |
| Los Angeles County Hospital (LAC+USC) | 46 | 55% |
| Norris Comprehensive Cancer Center | 38 | 45% |
| **Race/Ethnicity** | | |
| Hispanic | 39 | 49% |
| White (non-Hispanic) | 31 | 39% |
| Asian/Pacific Islander | 6 | 7% |
| African/African American | 4 | 5% |
| Unknown | 4 | |
| **Age at Diagnosis of Breast Cancer** | | |
| Mean, median (range) | 49 years, 48 years (22-85 years) | |
| <50 years | 47 | 56% |
| ≥50 years | 37 | 44% |
| **Age at Initiation of Capecitabine** | | |
| Mean, median (range) | 55 years, 55 years (24-88 years) | |
| <50 years | 36 | 43% |
| ≥50 years | 48 | 57% |
| **Tumor Biomarkers Subtype** | | |
| HER 2-, ER+ or PR + | 49 | 58% |
| HER 2-, ER -, PR - | 15 | 18% |
| HER 2+ | 20 | 24% |
| **Prior Chemotherapy (neoadjuvant, adjuvant, or metastatic setting)** | | |
| No | 21 | 25% |
| Yes | 63 | 75% |
| **Pretreatment With Anthracyline/Taxane** | | |
| Anthracycline only | 9 | 11% |
| Taxane only | 9 | 11% |
| Both | 39 | 48% |
| Neither | 25 | 30% |
| Unknown | 2 | 31% |
| **Prior Hormonal Therapy (adjuvant or metastatic setting)** | | |
| No | 26 | |
| Yes | 58 | 69% |

| Variable | Total (N = 84) | % |
|---|---|---|
| **Disease-Free Interval** | | |
| Mean, median (range) | 3.9 years, 2.6 years (0-14.8 years) | |
| 0 (stage IV disease at presentation) | 16 | 19% |
| <1 year | 6 | 7% |
| ≥1 year and <2 years | 11 | 13% |
| ≥2 years and <5 years | 23 | 28% |
| >5 years | 28 | 33% |
| **Capecitabine: Line of Chemotherapy in Metastatic Setting** | | |
| 1 | 65 | 77% |
| 2 | 14 | 17% |
| 3 | 5 | 6% |
| **Trastuzumab Administered With Capecitabine** | | |
| No | 68 | 82% |
| Yes | 15 | 18% |
| Unknown | 1 | |
| **Number of Disease Sites at Start of Capecitabine Therapy** | | |
| 1-2 | 42 | 51% |
| >2 | 40 | 49% |
| Unknown | 2 | |
| **Visceral Disease** | | |
| No | 27 | 33% |
| Yes | 56 | 67% |
| Unknown | 1 | |
| **Brain Metastases** | | |
| No | 74 | 89% |
| Yes | 9 | 11% |
| Unknown | 1 | |
| **Bone Disease Only** | | |
| No | 74 | 89% |
| Yes | 9 | 11% |
| Unknown | 1 | |
| **Body Surface Area (BSA)** | | |
| Mean, median (range) | 1.8 $m^2$, 1.8 $m^2$ (1.3 $m^2$-2.4 $m^2$) | |

BSA indicates body surface area; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

treating physician, 7 patients who commenced radiation therapy while taking capecitabine, 2 patients who progressed after finishing capecitabine with no intervening antineoplastic therapy, and 4 patients who progressed on the subsequent therapy, as we used an ITT approach with progression as the desired outcome variable. Of these 4 patients, 2 discontinued capecitabine due to toxicity. Of the 20 patients who did not have disease progression, 10 patients did not progress as of the end of our study period and 10 were lost to follow-up. Median follow-up in these 20 patients was 5.3 months (range, 0.5-56 months). Baseline patient and tumor characteristics are shown in **Table 1**.

Since the 2 major published randomized trials examining the efficacy of single-agent capecitabine both restricted their analyses of PFS to patients with measurable disease,[19,20] we also determined median PFS for patients in our cohort with measurable disease. Median PFS for patients with measurable disease was 4.1 months (95% confidence interval [CI], 2.9-5.7; **Figure 2A**, dashed line), which is similar to the median PFS values of 4.4 months (95% CI, 4.1-5.4; n = 480)[19] and 4.2 months (95% CI, 3.8-4.5; n = 377)[20] previously reported. A total of 55 patients with measurable disease received flat dosages of capecitabine of 1000 mg twice daily. Median PFS in these patients was 4.1 months (95% CI, 2.8-5.7 months), which was almost identical to the median PFS for all patients with measurable disease.

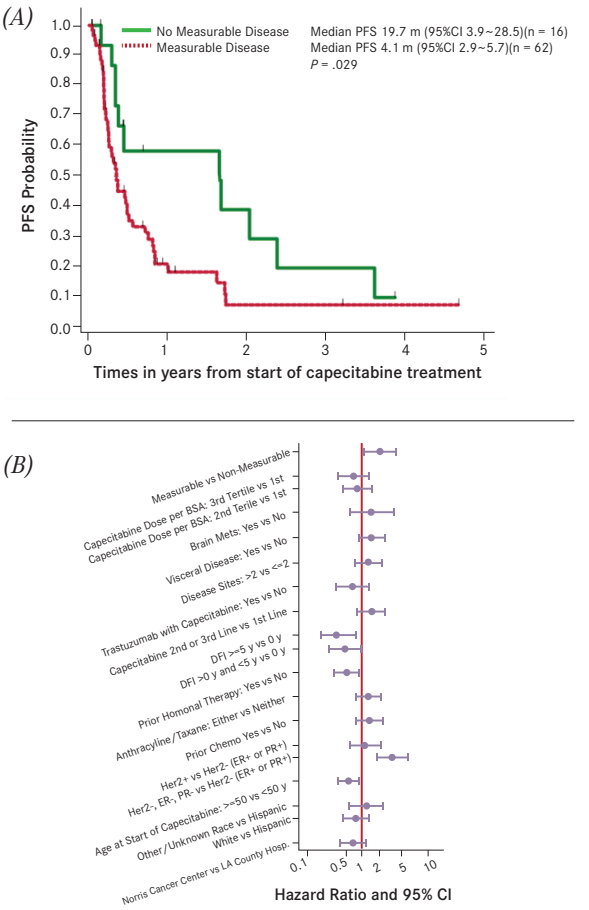
Since a secondary aim was to compare PFS between patients in this cohort with and without measurable disease, we also determined PFS for patients with nonmeasurable disease. These patients had a significantly longer PFS than patients with measurable disease (19.7 months; 95% CI, 3.9-28.5; **Figure 2A**, solid line).

The relationship between median PFS and each patient and disease characteristic variable was examined, and the hazard ratios for progression for each variable, with associated 95% CI, are shown in **Figure 2B**.

For the remaining analyses, we included both measurable and nonmeasurable cases. Patients were stratified based on measurable disease status, and the relationship between PFS and each patient and disease characteristic variable known to influence disease progression was examined. Stratifying by measurable disease status, univariate analyses showed that factors associated with PFS at $P \leq .05$ included biomarker status, DFI, age at initiation of capecitabine therapy, and prior hormonal therapy. Specifically, triple-negative (ER-, PR-, HER2-) status was associated with a lower PFS, as was shorter DFI. Concurrent administration of trastuzumab produced a trend toward increased PFS ($P = .12$). Patients with measurable disease who did not receive trastuzumab concurrently with capecitabine had a median PFS of 3.7 months (95% CI, 2.8-5.7; n = 51). Multivariate Cox regression analyses showed that besides measurable disease status, biomarker status and DFI were significantly associated with PFS at $P \leq .05$ independent from other factors, and receiving trastuzumab concurrently with capecitabine was marginally associated with PFS ($P = .077$). Odds ratios for progression based on these factors are shown in **Table 2**. Kaplan-Meier curves for these independently associated factors are depicted in **Figure 3**.

Demographic factors not independently associated with PFS at the significance level of 0.20 included race and age at initial diagnosis of breast cancer. Notably, within the range of low dosages administered to this cohort, dosage of capecitabine was not independently associated with PFS at $P = .20$, with all three dosage tertiles demonstrating similar median PFS (**Figure 4**). Other treatment-related factors not independently associated with PFS at $P = .20$ included history of administration of any prior chemo-

**FIGURE 2.** Kaplan-Meier Curve Showing PFS




Kaplan-Meier curve showing PFS for patients with and without measurable disease; (B) PFS hazard ratios and associated 95% CIs for subset analyses.

BSA indicates body surface area; DFI, disease-free interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

therapy, history of administration of anthracyclines or taxanes, and line of therapy of capecitabine in the metastatic setting (1, 2, or 3; **Figures 5A, B**, and **C**). The median PFS was 3.7 months (95% CI, 2.5-5.5; n = 46) for patients with measurable disease who were previously treated with either anthracyclines or taxanes, which was similar to the PFS value of 4.1 months determined for all patients with measurable disease.

Finally, for the 4 patients who progressed on the next therapy after capecitabine was terminated without progression, censoring these patients at the time capecitabine was stopped did not alter the median PFS among patients with measurable disease.

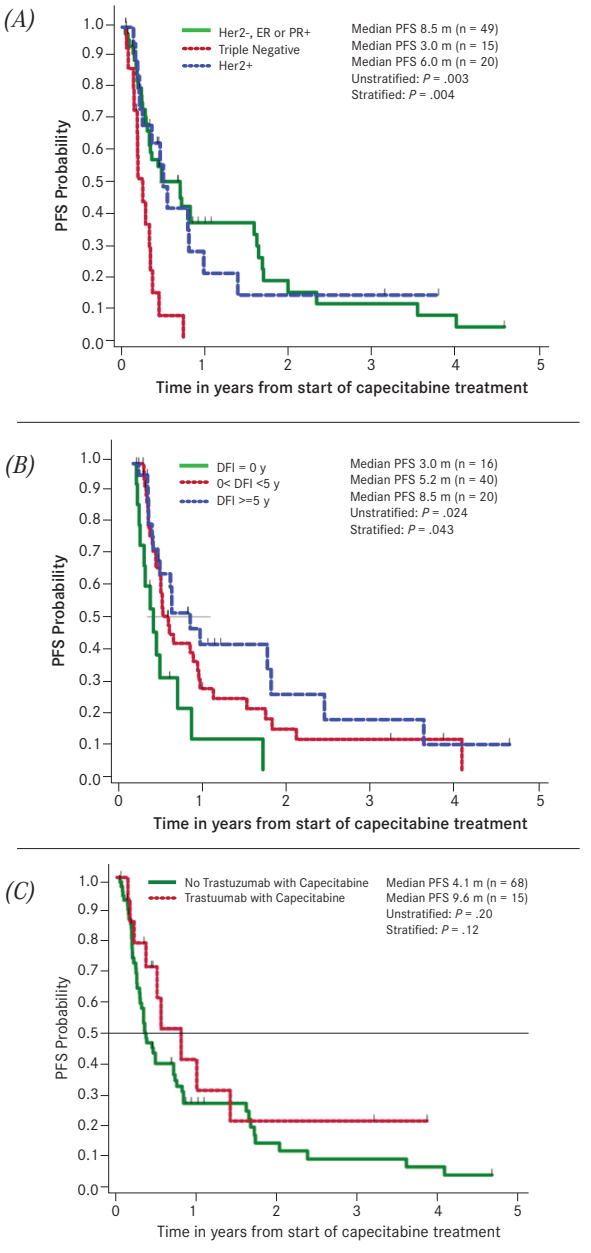
## Discussion

Our retrospective analysis suggests that the administration of low starting dosages of capecitabine is as effective in the treatment of MBC as the full FDA-approved dosage. Although it is well established that the FDA-approved dosage of capecitabine is associated with frequent and treatment-limiting toxicities, little or no efficacy data from phase 3 randomized, controlled trials exist to support the administration of capecitabine at lower dosages.

Here, we report data demonstrating efficacy of capecitabine in MBC at significantly lower starting dosages (median dosage of 565 mg/m$^2$ twice daily, or 1130 mg/m$^2$ daily) than any values previously reported in the literature.[7-13] We first presented our results at the 2012 meeting of the American Society of Clinical Oncology.[23] Since that time, Ambros et al[24] have published a similar study that replicated our results. This study was a retrospective analysis of 86 patients treated at a single breast-focused oncology practice with a fixed low dosage of capecitabine monotherapy for HER2-negative MBC. The authors concluded that a flat dosage of 1000 mg twice daily (median starting dosage of 633.5 mg/m$^2$ twice daily, or about half the FDA-approved dosage of 1250 mg/m$^2$ twice daily) had a similar clinical benefit rate, as determined by objective response rate and TTP, to the full dosage based on a historical comparison of 12 prior trials involving 1949 patients. These results reinforce the results of our study and strengthen our recommendation for a prospective randomized, controlled trial evaluating the efficacy of low dosages of capecitabine as single-agent therapy, or in combinations that have shown benefit over single-agent therapy.

Since patients typically received a flat dosage of capecitabine of 1000 mg twice daily, there was some heterogeneity of dosage per BSA within this cohort. However, we observed no differences in PFS between any of the 3 strata of dosages per BSA, which lends support to the evidence that precise dosing based on BSA may be unnecessary, as has been suggested by others.[25] Furthermore, only 2 patients in our study (2.4%) discontinued capecitabine due to toxicity. Previous clinical trials reported rates of discontinuation due to toxicity of 11%[20] and 11.9%[26] for capecitabine dosages of 1250 mg/m$^2$ and 1000 mg/m$^2$ twice daily, respectively. Though this analysis does not allow for formal statistical

**FIGURE 3.** Factors That Significantly Influenced PFS




Factors that significantly influenced PFS on capecitabine therapy in patients with and without measurable disease. (A) tumor biomarker status; (B) DFI; and (C) concurrent trastuzumab administration. For all figures, unstratified *P* value refers to *P* value in univariate analysis; stratified *P* value refers to *P* value after controlling for measurable disease status.

DFI indicates disease-free interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PFS, progression-free survival; PR, progesterone receptor.

**TABLE 2.** Variables Independently Associated With PFS

| | | Median PFS (95% CI, months) | Univariate | | Multivariate[b] | |
|---|---|---|---|---|---|---|
| **Variable** | **n** | | **HR (95% CI)** | ***P*** | **HR (95% CI)** | ***P*** |
| **Measurable Disease** | | | | | | |
| No | 16 | 19.7 (3.9-28.5) | Reference | .029 | Reference | |
| Yes | 62 | 4.1 (2.9-5.7) | 2.0 (1.03-4.0) | | 1.7 (0.84-3.4) | .12 |
| Unknown | 6 | | | | | |
| **Age at Initiation of Capecitabine[a]** | | | | | | |
| <50 years | 36 | 4.0 (2.2-5.7) | Reference | | Eliminated | |
| ≥50 years | 48 | 6.0 (3.9-9.9) | 0.58 (0.34-0.97) | .040 | | |
| **Biomarker Subtypes[a]** | | | | .004[c] | | .009[c] |
| HER2 -, ER+ or PR+ | 49 | 8.5 (3.9-19.3) | Reference | | Reference | |
| HER2 -, ER -, PR - | 15 | 3.0 (1.6-4.1) | 3.2 (1.6-6.3) | | 3.3 (1.6-7.2) | |
| HER2 + | 20 | 6.0 (2.5-11.9) | 0.94 (0.50-1.8) | | 2.6 (0.79-8.3) | |
| **Prior Hormonal Therapy[a]** | | | | | | |
| No | 26 | 3.9 (2.2-4.4) | Reference | | Eliminated | |
| Yes | 58 | 6.6 (4.0-9.9) | 0.57 (0.33-0.97) | .042 | | |
| **Disease-Free Interval[a]** | | | | .043[c] | | .028[c] |
| 0 years | 16 | 3.0 (0.88-6.6) | Reference | | Reference | |
| >0 years, <5 years | 40 | 5.2 (3.4-9.6) | 0.53 (0.27-1.03) | | 0.41 (0.20-0.83) | |
| ≥5 years | 28 | 8.5 (3.7-20.5) | 0.37 (0.18-0.79) | | 0.36 (0.16-0.79) | |
| **Trastuzumab With Capecitabine[a]** | | | | | | |
| No | 68 | 4.1 (3.3-8.5) | Reference | | Reference | |
| Yes | 15 | 9.6 (2.5-16.9) | 0.58 (0.29-1.2) | 0.12 | 0.30 (0.09-1.03) | 0.077 |
| Unknown | 1 | | | | | |
| Overall | 84 | 5.2 (3.7-8.5) | | | | |

[a]For these variables, the univariate analysis was stratified based on whether or not a patient had measurable disease. Only variables that were associated with PFS at $P \leq .20$ after controlling for measurable disease status are presented in Table 2.
[b]Variables in Table 2 were included in a multivariate Cox regression model, and the stepwise backward selection procedure was used to eliminate any variable that was not significant at $P \leq .20$.
[c]Overall *P* value.

ER indicates estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; PFS, progression-free survival; PR, progesterone receptor.

testing, this result suggests that the dosages administered to the USC cohort are associated with less treatment-limiting toxicity than dosages previously reported. This result becomes even more significant in light of evidence that observed compliance with capecitabine treatment is relatively low,[27] and that reducing toxicity associated with capecitabine improves adherence to the treatment regimen.[28]

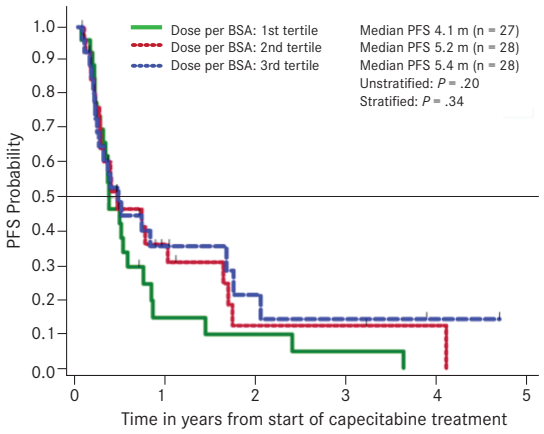
The major prognostic indicators in this study were related to patient characteristics rather than treatment. After controlling for measurable disease status, HR status was the strongest prognostic indicator, with triple-negative status associated with lower PFS than HR-positive, HER2-negative tumors ($P = .004$). Disease-free interval was also an independent prognostic indicator, with all 3 groups (DFI = 0; DFI 0-5 years; and DFI >5

years) associated with statistically significant differences in PFS ($P$ = .043). These findings are consistent with prior studies regarding prognostic indicators in MBC.[29] Several patient-related variables typically associated with lower PFS, including more than 2 disease sites, presence of visceral disease, and presence of central nervous system disease, were not found to be significant prognostic indicators in our analysis.

The initial trials leading to the approval of capecitabine enrolled patients defined as resistant to anthracycline[3] or taxane[4] chemotherapy, as did our comparator studies,[19,20] which compared the efficacy of capecitabine alone against capecitabine plus ixabepilone. Other trials have examined the efficacy of capecitabine as first-line chemotherapy for MBC, demonstrating superiority over cyclophosphamide, methotrexate, and 5-fluorouracil, albeit with respect to OS and not PFS in the case of the larger trial,[13] possibly due to post-progression therapy.[13,29] These findings have helped to establish first-line capecitabine therapy as a standard of care in MBC. Our study reflects these evolving patterns of capecitabine administration, including 77% of patients who received capecitabine as the first line and 23% who received capecitabine as second- or third-line chemotherapy in the metastatic setting. Notably, neither line of treatment of capecitabine therapy nor prior administration of anthracyclines or taxanes were significant predictors of PFS, suggesting that low starting dosages of capecitabine are efficacious both as first-line chemotherapy and in patients who have been more heavily pretreated in the metastatic setting.

Our results support the equal efficacy of low-dose capecitabine among patients with measurable disease, but also suggest that the responses of patients without measurable disease may be fundamentally different. To maximize comparability with previous studies, patients without measurable disease were excluded from our primary analysis of PFS. However, we determined that measurability of disease was a significant predictor of PFS for patients in our cohort, as patients with measurable disease had a median PFS of 4.1 months and patients without measurable disease had a median PFS of 19.7 months. For various reasons, patients without measurable disease have typically been excluded from analysis in clinical trials, and as a result, less information is available regarding their responses to treatment. Nevertheless, these patients represent a sizeable, and thus clinically important, subset of patients with MBC. A large proportion of our patients (and MBC patients in general) without measurable disease had metastases in bone only, and it is known that bone-only tumors are more likely to be HR-positive and possess other less aggressive tumor characteristics.[30,31] Additionally, there is evidence that patients with bone-only disease or disease that is otherwise not measurable may be a biologically distinct subgroup of patients, and therefore should be analyzed separately.[32] Our study emphasizes the need for further research on patients without measurable disease in order to facilitate the delivery of informed, evidence-based care for this subset of patients.

**FIGURE 4.** PFS For Patients In Each Dosage Tertile



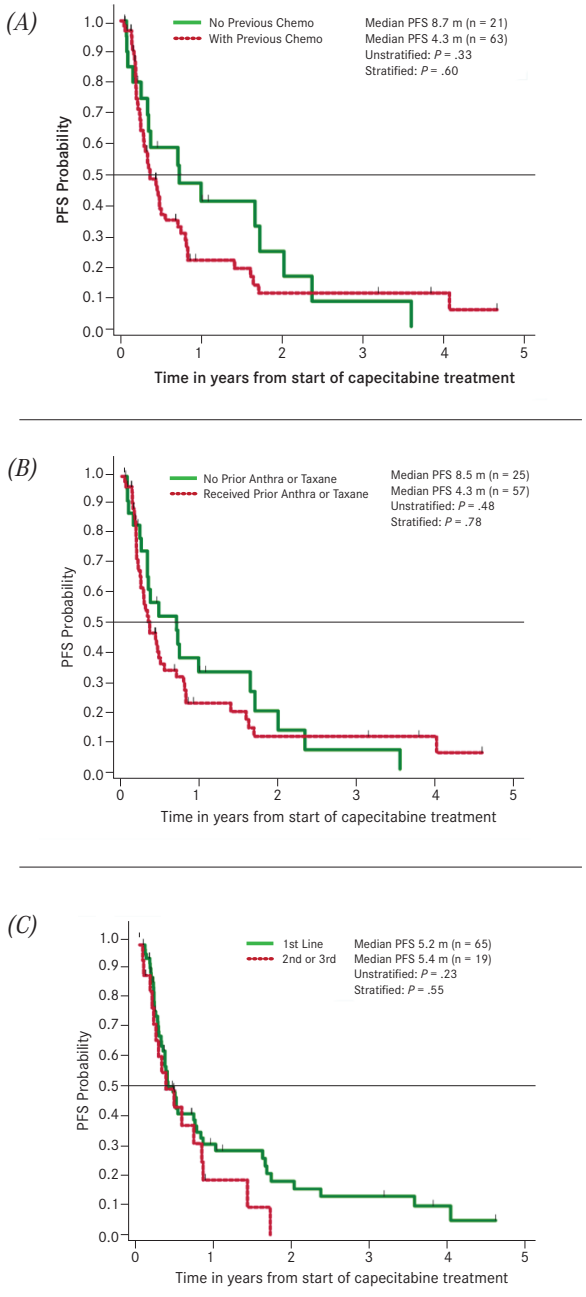

PFS for patients in each dosage tertile. 1st tertile: 305-536 mg/m$^2$; 2nd tertile: 536.5-593 mg/m$^2$; 3rd tertile: >593 mg/m$^2$ (doses administered twice daily).

BSA indicates body surface area; PFS, progression-free survival.

Our results also provide preliminary data on responses to capecitabine in a cohort with a significant proportion of Hispanic patients. Little, if any, of the prior work on capecitabine has reported data on responses among Hispanic patients, but there is evidence that disease characteristics and responses to treatment may be different in Hispanics than in other ethnic groups.[33,34] Though we did not observe a difference in PFS on capecitabine therapy between Hispanic and non-Hispanic patients, we were unable to gather data on the frequency of various treatment-related AEs. It is possible that pharmacogenomics and other factors differ between patients of different ethnicities, and more studies in ethnic subsets are needed.

This study presents evidence that capecitabine is effective at significantly lower starting dosages than previously appreciated, and supports decisions by clinicians to initiate treatment at lower dosages than the one approved by the FDA. The main limitation of our study is its retrospective nature. As such, we were unable to collect information on dosage reductions or the frequency of various drug toxicities. While this cohort was heterogeneous in lines of therapy and prior treatments received, these factors were not significant predictors of PFS. Additionally, although we were able to quantify PFS, we were unable to use formal RECIST criteria to evaluate tumor responses, and as a result were unable to separate the nonprogressors into complete responders, partial responders, and stable disease, and to perform a more in-depth analysis based on those parameters. For these reasons, a random-

**FIGURE 5.** Treatment-Related Factors Not Significantly Associated With PFS




Treatment-related factors not significantly associated with PFS on capecitabine therapy. (A) History of any prior chemotherapy; (B) prior administration of anthracycline or taxane therapy; and (C) line of therapy of capecitabine in the metastatic setting.

PFS indicates progression-free survival.

ized phase 3 trial examining capecitabine dosing is necessary in order to confirm these results.

## Conclusions

In the 13 years since the approval of capecitabine by the FDA, there has been mounting evidence that lowering the starting dosage can reduce drug-associated toxicity without compromising antitumor efficacy.[7-9,11,26] Our report adds to this evidence, and along with a subsequent report[24] supports a prospective phase 3 randomized clinical trial of the FDA-approved dosage of capecitabine against one or several lower starting dosages, coupled with appropriate pharmacogenomics studies, in order to optimize the benefit-to-toxicity ratio of this agent. Future studies should also address the question of dosing method, as our results suggest that similar outcomes can be achieved regardless of whether patients are given flat dosages or dosed based on BSA. Updating the guidelines governing the use of capecitabine based on more definitive studies would have important implications for clinicians and patients, as a milder toxicity profile may improve compliance by patients and lead to longer disease control with fewer discontinuations due to toxicity.

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