

Randomized Trial of Standard Adjuvant Chemotherapy Regimens Versus Capecitabine in Older Women With Early Breast Cancer: 10-Year Update of the CALGB 49907 Trial

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PURPOSE Older women with breast cancer remain under-represented in clinical trials. The Cancer and Leukemia Group B 49907 trial focused on women age 65 years and older. We previously reported the primary analysis after a median follow-up of 2.4 years. Standard adjuvant chemotherapy showed significant improvements in recurrence-free survival (RFS) and overall survival compared with capecitabine. We now update results at a median follow-up of 11.4 years.

PATIENTS AND METHODS Patients age 65 years or older with early breast cancer were randomly assigned to either standard adjuvant chemotherapy (physician's choice of either cyclophosphamide, methotrexate, and fluorouracil or cyclophosphamide and doxorubicin) or capecitabine. An adaptive Bayesian design was used to determine sample size and test noninferiority of capecitabine. The primary end point was RFS.

RESULTS The design stopped accrual with 633 patients at its first sample size assessment. RFS remains significantly longer for patients treated with standard chemotherapy. At 10 years, in patients treated with standard chemotherapy versus capecitabine, the RFS rates were 56% and 50%, respectively (hazard ratio [HR], 0.80; $P = .03$); breast cancer-specific survival rates were 88% and 82%, respectively (HR, 0.62; $P = .03$); and overall survival rates were 62% and 56%, respectively (HR, 0.84; $P = .16$). With longer follow-up, standard chemotherapy remains superior to capecitabine among hormone receptor-negative patients (HR, 0.66; $P = .02$), but not among hormone receptor-positive patients (HR, 0.89; $P = .43$). Overall, 43.9% of patients have died (13.1% from breast cancer, 16.4% from causes other than breast cancer, and 14.1% from unknown causes). Second nonbreast cancers occurred in 14.1% of patients.

CONCLUSION With longer follow-up, RFS remains superior for standard adjuvant chemotherapy versus capecitabine, especially in patients with hormone receptor-negative disease. Competing risks in this older population dilute overall survival benefits.

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INTRODUCTION

Increasing age is the major risk factor for breast cancer.¹ The average age at diagnosis of breast cancer in the United States is now 62 years, and the majority of women who die of breast cancer are age 65 years and older.¹ Despite major advances over the past 30 years in prolonging breast cancer survival for women of all ages, there is some evidence that breast cancer-specific survival (BCSS) remains lowest in older women.² The reasons for this are unclear, but most compelling is the

underuse of adjuvant systemic therapy in these older patients.^{3,4}

In 2009, the Cancer and Leukemia Group B (now part of the Alliance for Clinical Trials in Oncology) reported initial results of a randomized trial specifically designed for women with early-stage breast cancer age 65 years and older that compared standard chemotherapy (physician's choice of cyclophosphamide, methotrexate, and fluorouracil [CMF] or doxorubicin and cyclophosphamide [AC]) with capecitabine.⁵ Previous large trials had shown that CMF and AC resulted in

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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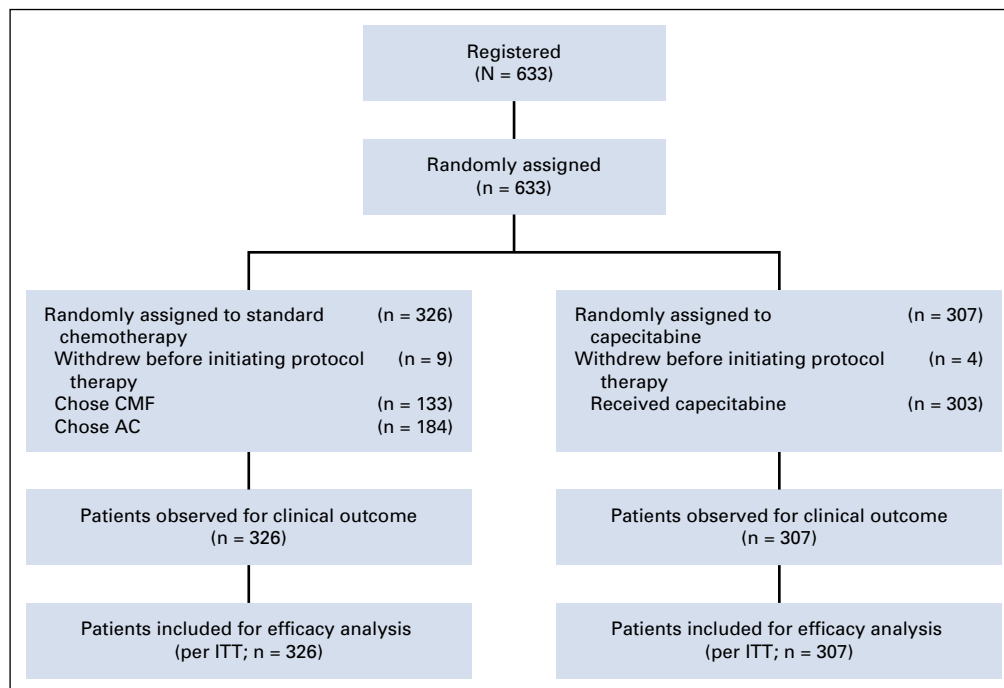


FIG 1. CONSORT diagram for Alliance/Cancer and Leukemia Group B 49907 trial. AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and fluorouracil; ITT, intent-to-treat analysis.

similar outcomes in the adjuvant setting.^{6,7} In metastatic breast cancer, capecitabine had been shown to be associated with response rates approximating 30%⁸ and, in one randomized phase II trial, showed similar activity to CMF.⁹

Our trial was designed to show recurrence-free survival (RFS) noninferiority of capecitabine and used a novel Bayesian adaptive design. After enrolling 600 patients, the probability that with longer follow-up capecitabine was highly likely to be noninferior met a prespecified cutoff value, and enrollment was discontinued. The final sample size was 633 patients. At the time of the earlier publication, the median follow-up time was 2.4 years, and the maximum follow-up time was 5.6 years. The estimated 3-year RFS rate was 85% in the standard chemotherapy group compared with 68% in the capecitabine group, and the overall survival (OS) rates were 91% and 86%, respectively; both differences were statistically significant. Because of the limited follow-up in our earlier report, we now assess the risks and benefits of treatment after a median follow-up time of 11.4 years. In addition, we calculate BCSS and report on the causes of death and the frequency of second new cancers.

PATIENTS AND METHODS

Patients

Eligibility criteria required that patients be age 65 years or older with operable, histologically confirmed adenocarcinoma of the breast. Performance status had to be 0 to 2 (National Cancer Institute criteria). Patients were ineligible if they had another active malignancy with a risk of relapse of greater than 30%. Complete details on eligibility criteria

have been previously published⁵ and can also be found in the Data Supplement.

Random Assignment and Study Treatment

All patients were required to give written informed consent meeting all state, federal, and institutional guidelines. Eligible patients were randomly assigned in a one-to-one ratio to either standard chemotherapy or capecitabine. Standard chemotherapy consisted of either CMF (cyclophosphamide 100 mg/m² orally on days 1 to 14 and methotrexate 40 mg/m² and fluorouracil 600 mg/m² on days 1 and 8 intravenously; cycles were repeated every 28 days for six cycles) or AC (doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² intravenously on day 1; cycles were repeated every 21 days for four cycles). For patients randomly assigned to standard chemotherapy, the physician and patient selected either CMF or AC. Patients randomly assigned to capecitabine received a dosage of 2,000 mg/m² per day for 14 consecutive days every 3 weeks for six cycles. Doses were based on actual body weight, and there were no dose limits. For all regimens, toxicity assessment and dose modifications were based on standard National Cancer Institute Common Terminology Criteria for Adverse Events criteria (version 3.0)¹⁰ and were clearly defined in the protocol.

Statistical Design

The study was designed as a noninferiority trial comparing capecitabine with standard chemotherapy and used a unique adaptive Bayesian design.¹¹ The primary end point was RFS, as defined by Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials criteria.¹² RFS events included local recurrence, distant

TABLE 1. Baseline Patient Characteristics

Characteristic	No. of Patients (%)	
	CMF or AC (n = 326)	Capecitabine (n = 307)
Age, years		
65-69	110 (34)	108 (35)
70-79	204 (63)	185 (60)
≥ 80	12 (4)	14 (5)
Performance status		
0 or 1 (fully active or minimal symptoms)	317 (97)	295 (96)
2 (symptoms, but active > 50% of the time)	9 (3)	12 (4)
Race		
White	277 (85)	261 (85)
Other	46 (14)	37 (12)
Missing data	3 (1)	9 (3)
Tumor size, cm		
≤ 2	159 (49)	120 (39)
> 2 - ≤ 5	147 (45)	169 (55)
> 5	18 (6)	17 (6)
Missing data	2 (< 1)	0 (0)
No. of positive lymph nodes		
0	90 (28)	95 (31)
1-3	180 (55)	157 (51)
4-9	39 (12)	42 (14)
≥ 10	13 (4)	9 (3)
Missing data	4 (1)	4 (1)
Tumor grade		
Low	46 (14)	36 (12)
Intermediate	124 (38)	132 (43)
High	131 (40)	127 (41)
Missing data	25 (8)	12 (4)
Hormone receptor status		
Negative	106 (33)	97 (32)
Positive	219 (67)	210 (68)
Missing data	1 (< 1)	0 (0)
ER and PR status		
ER negative, PR negative	106 (33)	97 (32)
ER positive, PR negative	40 (12)	54 (18)
ER negative, PR positive	6 (2)	5 (2)
ER positive, PR positive	172 (53)	150 (49)
Missing data	2 (1)	1 (< 1)
HER2 status		
Positive	39 (12)	37 (12)
Negative	275 (84)	254 (83)
Unknown	12 (4)	16 (5)

(continued in next column)

TABLE 1. Baseline Patient Characteristics (continued)

Characteristic	No. of Patients (%)	
	CMF or AC (n = 326)	Capecitabine (n = 307)
ER, PR, and HER2 status		
ER or PR positive, HER2 negative	196 (60)	177 (58)
ER, PR, and HER2 negative (triple-negative)	78 (24)	76 (25)
Type of surgery		
Lumpectomy and breast irradiation	152 (47)	136 (44)
Mastectomy	172 (53)	169 (55)
Missing data	2 (< 1)	2 (< 1)
Axillary evaluation		
Sentinel node biopsy only	64 (20)	67 (22)
Axillary dissection only	115 (35)	100 (33)
Both sentinel node biopsy and axillary dissection	142 (44)	136 (44)
Neither sentinel node biopsy nor axillary dissection	4 (1)	3 (< 1)
Missing data	1 (< 1)	1 (< 1)

Abbreviations: AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and fluorouracil; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

metastasis, or death as a result of any cause. The trial assumed a 5-year RFS of 60% for standard chemotherapy, and capecitabine was considered to be noninferior if its 5-year RFS was 53% or higher. The planned sample size was 600 to 1,800 patients. Interim monitoring was devised for both futility and noninferiority on the basis of Bayesian predictive probabilities assuming non-informative prior distributions. Interim analyses were scheduled to occur when 600, 900, 1,200, and 1,500 patients had been enrolled; randomization was not adaptive. Further details on our selection of trial sample sizes have been previously published.⁵ OS was a secondary end point.

In this report, we also analyzed BCSS, defined as time from registration until death as a result of breast cancer. This end point was not prespecified in the protocol, and these analyses are exploratory because the cause of death was not completely ascertained in a large number of patients. For BCSS, deaths as a result of causes other than breast cancer or from unknown causes were censored at the time death occurred. All efficacy analyses were based on the intent-to-treat principle and included all patients who were randomly assigned. The reverse Kaplan-Meier method was used to estimate the extent of clinical follow-up maturity.¹³ Kaplan-Meier curves were used to estimate RFS, OS, and BCSS.¹⁴ Cox proportional hazards models were used to compare

treatment effects between arms, adjusting for tumor size, lymph node status, hormone receptor status, age, and race. These long-term outcome comparisons were not preplanned in the original protocol, which used a Bayesian adaptive design. The *P* values presented here are descriptive only. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies.

RESULTS

Study Conduct

This long-term outcome analysis is based on data available as of December 31, 2017. The trial opened for accrual on September 15, 2001, and was closed on December 29, 2006, after 633 patients had been entered. Six hundred patients were accrued as of November 2006, and the first planned analysis concluded that the probability that capecitabine would be noninferior to standard chemotherapy met our preplanned criteria for futility. The median follow-up time for RFS was 11.4 years (95% CI, 11.2 to 11.6 years).

Patient Characteristics

Three hundred twenty-six patients were randomly assigned to the standard treatment arm, and 307 patients were assigned to the capecitabine arm (Fig 1). Nine patients in the standard treatment arm never received treatment,

leaving 317 patients who were treated (184 patients with AC and 133 patients with CMF). Patient characteristics are listed in Table 1. Approximately two thirds of the patients were age 70 years and older, and approximately 5% were age 80 years and older. Almost all patients had excellent performance status (ambulatory and without any symptoms), and the majority of patients were white (85%). More than half of patients had tumors larger than 2 cm, and more than two thirds of patients had positive lymph nodes. Two thirds of patients were hormone receptor positive, and approximately 12% were human epidermal growth factor receptor 2 positive.

RFS, OS, and BCSS

For the entire cohort, the 10-year RFS, OS, and BCSS rates were 52.7% (95% CI, 48.8% to 57%), 59.2% (95% CI, 55.3% to 63.4%), and 85.4% (95% CI, 82.4% to 88.5%), respectively (Appendix Table A1 and Appendix Figs A1 to A3, online only). Table 2 compares RFS events and OS events between our initial report and this update. Approximately half of all patients now have an RFS event, and approximately 44% have died. Estimated 10-year RFS rates are 55.7% (95% CI, 50.2% to 61.7) and 49.7% (95% CI, 44.1% to 56%) for standard chemotherapy and capecitabine, respectively (Fig 2). The Kaplan-Meier curves for RFS and OS seem to cross toward the later period of follow-up (Fig 2; *P* = .05 and *P* = .02 for the test of non-proportionality for RFS and OS, respectively). The non-proportionality for end points that involve non-breast cancer-specific death is not surprising given other competing causes of death in this elderly population. In the

TABLE 2. Recurrence-Free and Overall Survival Events

Event or Patient Status	No. of Patients (%)			
	2009*		2018	
	CMF or AC (n = 326)	Capecitabine (n = 307)	CMF or AC (n = 326)	Capecitabine (n = 307)
Recurrence-free survival				
Alive without relapse	291 (89.3)	247 (80.5)	171 (52)	146 (48)
Total events	35 (10.7)	60 (19.5)	155 (48)	161 (52)
Local recurrence only	5 (1.5)	19 (6.2)	17 (5)	28 (9)
Distant metastases	15 (4.6)	24 (7.8)	41 (13)	44 (14)
Died without relapse	15 (4.6)	17 (5.5)	97 (30)	89 (29)
Overall survival				
Alive	302 (93)	269 (88)	187 (57)	168 (55)
Total deaths	24 (7.4)	38 (12.4)	139 (43)	139 (45)
Cause of death				
Breast cancer	8 (2.5)	18 (5.9)	34 (10)	49 (16)
Breast cancer treatment	0 (0)	2 (0.7)	0	2 (0.7)
Cause other than breast cancer	12 (3.3)	14 (4.6)	56 (17)	48 (16)
Unknown	4 (0.8)	4 (1.3)	49 (15)	40 (13)

Abbreviations: AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and fluorouracil.

*Data from initial publication.⁵

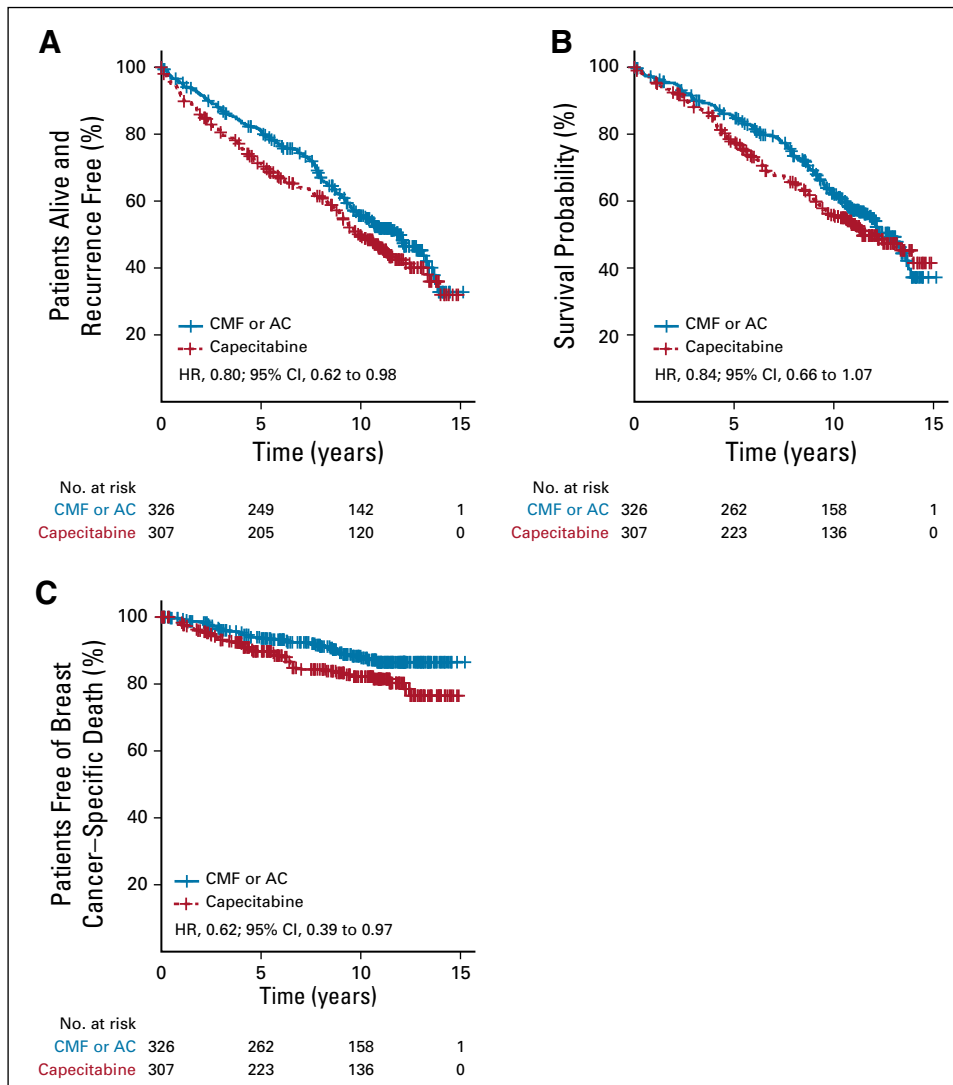


FIG 2. Kaplan-Meier plots for (A) recurrence-free survival, (B) overall survival, and (C) breast cancer-specific survival by treatment arm. AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and fluorouracil; HR, hazard ratio.

multivariable analysis (Table 3), RFS, BCSS, and OS favored patients treated with standard therapy (RFS: hazard ratio [HR], 0.80; 95% CI, 0.62 to 0.98; $P = .03$; BCSS: HR, 0.62; 95% CI, 0.39 to 0.97; $P = .03$; OS: HR, 0.84; 95% CI, 0.66 to 1.07; $P = .16$). As expected and similar to our earlier report, larger tumor size, a greater number of positive nodes, and negative hormone receptor status were associated with significantly poorer outcomes, whereas race was not. Of interest, multivariable analysis also found that patients age 70 years and older had significantly poorer prognosis compared with those age 65 to 69 years. Because death from any cause is considered an RFS event and because increasing age is associated with shorter life expectancy, these findings are not unexpected. Of note, almost two thirds of RFS events were a result of deaths without relapse and were similar in both treatment groups.

At the time of this update, 43.9% of patients have died (13.1% from breast cancer, 16.4% from non-breast cancer causes, and 14.1% from unknown causes). Second

new cancers occurred in 14.7% of patients (16.9% of patients who received standard therapy v 12.4% of patients who received capecitabine). Breast cancer accounted for 10% and 16% of all deaths in patients treated with standard therapy versus capecitabine, respectively ($P = .045$), whereas deaths not attributable to breast cancer were reported for 17% and 16% of patients treated with standard therapy versus capecitabine, respectively. In approximately 14% of all patients, the cause of death was unknown. Only two deaths, both in the capecitabine arm, were definitely related to treatment.

Before the development of this trial, the potential benefits of chemotherapy for patients with hormone receptor-positive versus hormone receptor-negative tumors were not well defined. In an unplanned subset analysis done for our initial report, a statistically significant interaction between treatment and receptor status was noted for both RFS and OS, and the benefits of standard chemotherapy were confined to patients with hormone receptor-negative tumors. In this

TABLE 3. Multivariable Analysis of Treatment Effect Adjusting for Baseline Characteristics for All ITT Patients

Variable	Recurrence-Free Survival		Overall Survival		Breast Cancer-Specific Survival	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Treatment						
Capecitabine	1 (Ref)	.0312	1 (Ref)	.1629	1 (Ref)	.0348
CMF or AC	0.80 (0.62 to 0.98)		0.84 (0.66 to 1.07)		0.62 (0.39 to 0.97)	
Age group, years						
65-69	1 (Ref)	< .001	1 (Ref)	< .001	1 (Ref)	.0359
≥ 70	1.57 (1.21 to 2.04)		1.85 (1.39 to 2.48)		1.82 (1.04 to 3.18)	
Race						
White	1 (Ref)	.6112	1 (Ref)	.7344	1 (Ref)	.664
Other	1.09 (0.79 to 1.50)		0.94 (0.66 to 1.34)		1.14 (0.63 to 2.08)	
Tumor size, cm						
≤ 2	1 (Ref)	.004	1 (Ref)	< .001	1 (Ref)	.0011
> 2	1.41 (1.12 to 1.79)		1.56 (1.21 to 2.01)		2.39 (1.41 to 4.03)	
No. of positive lymph nodes						
0	1 (Ref)	< .001	1 (Ref)	< .001	1 (Ref)	< .001
1-3	1.76 (1.31 to 2.36)		1.73 (1.27 to 2.38)		1.95 (1.02 to 3.72)	
≥ 4	2.18 (1.54 to 3.08)		2.35 (1.63 to 3.39)		5.02 (2.63 to 9.60)	
Hormone receptor status						
Positive	1 (Ref)	< .001	1 (Ref)	< .001	1 (Ref)	.003
Negative	1.69 (1.32 to 2.16)		1.73 (1.33 to 2.25)		2.02 (1.27 to 3.20)	

NOTE. Patients with any missing covariates were excluded from the analysis.

Abbreviations: AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and fluorouracil; HR, hazard ratio; ITT, intent-to-treat; Ref, reference.

follow-up analysis, RFS remains significantly better for patients with hormone receptor–negative tumors treated with standard chemotherapy compared with capecitabine (HR, 0.66; 95% CI, 0.46 to 0.95; $P = .02$), but this benefit was not observed among patients with hormone receptor–positive tumors (HR, 0.89; 95% CI, 0.68 to 1.18; $P = .43$; Fig 3). The interaction test between treatment and hormone receptor status for RFS yielded a nominal $P = .15$, possibly as a result of the limited statistical power available for interaction tests.¹⁵ For OS and BCSS, the treatment difference did not reach statistical significance in either hormone receptor subgroup, likely because of the limited power in these subgroup analyses. Nevertheless, there was a visual trend toward greater magnitude of efficacy with standard chemotherapy among patients with hormone receptor–negative tumors.

In this update, we specifically analyzed data from the 154 patients with triple-negative breast cancer in an exploratory analysis (Appendix Table A2 to A4 and Appendix Figs A4 to A6, online only). Similar to hormone receptor–negative patients, RFS was significantly improved for patients with triple-negative breast cancer treated with standard chemotherapy (HR, 0.61; 95% CI, 0.39 to 0.95; $P = .03$). However, no significant difference was noted between the

two arms for OS (HR, 0.71; 95% CI, 0.45 to 1.14; $P = .15$) or BCSS (HR, 0.56; 95% CI, 0.25 to 1.25; $P = .16$).

Toxicity and Second Cancers

Toxicity data have been previously published.⁵ Two patients on capecitabine had drug-related deaths. With longer follow-up, 89 (14.1%) of 633 patients have developed new second primary cancers, 55 patients (16.9%) in the standard therapy group and 38 patients (12.4%) in the capecitabine group ($P = .12$; Table 4). At this time, death attributed to congestive heart failure (six patients) or cardiomyopathy (three patients) has been noted for seven patients treated with standard therapy (AC, $n = 5$; CMF, $n = 2$) and two patients treated with capecitabine (one patient with congestive heart failure and one with cardiomyopathy). Myelodysplasia was reported in two patients (one patient treated with capecitabine and one treated with standard therapy). Acute myelogenous leukemia was reported in one patient receiving standard therapy.

DISCUSSION

Initial results of this trial showed that standard chemotherapy with CMF or AC resulted in superior RFS compared with capecitabine in older women with early-stage breast cancer. Now with longer follow-up, standard chemotherapy

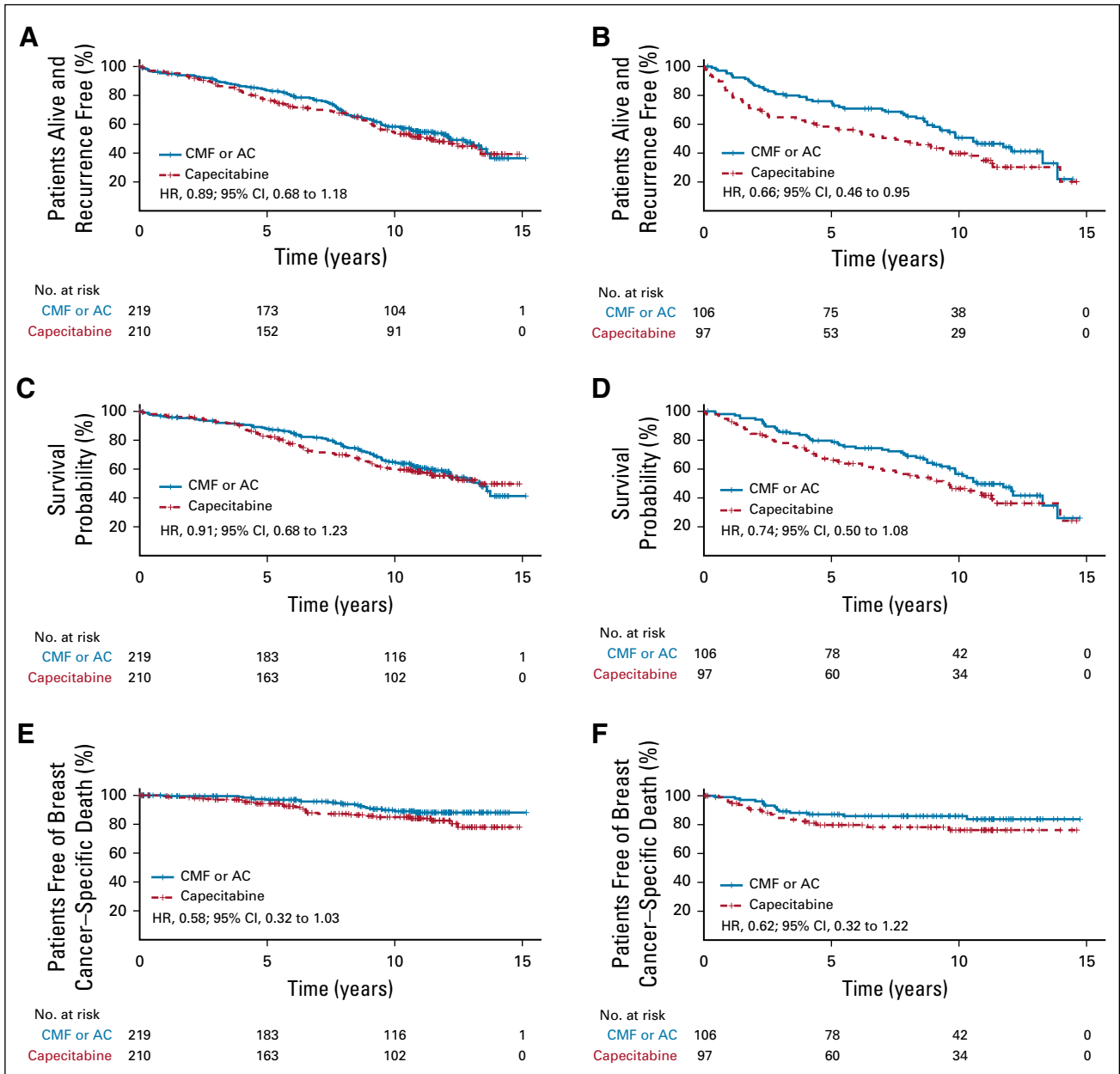


FIG 3. Kaplan-Meier plots for recurrence-free survival in patients with (A) hormone receptor–positive and (B) hormone receptor–negative tumors, overall survival in patients with (C) hormone receptor–positive and (D) hormone receptor–negative tumors, and breast cancer–specific survival in patients with (E) hormone receptor–positive and (F) hormone receptor–negative tumors by treatment arm. AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and fluorouracil; HR, hazard ratio.

remains significantly superior to capecitabine for RFS and BCSS but not OS. Similar to our earlier report, the major benefit of standard chemotherapy was seen in RFS among patients with hormone receptor–negative disease. A difference in the rate of metastatic disease among treatment groups is no longer apparent, with most of the breast cancer relapse differences being a result of local regional recurrence. The reason for the lack of a significant survival difference after longer follow-up is likely a result of the large number of deaths from non–breast cancer causes in this older population, diluting the

benefits of adjuvant treatment.¹⁶ Now with 11.4 years of follow-up, the majority of the 278 deaths in this trial were a result of causes other than breast cancer (104 deaths; 37.4%) or unknown causes (89 deaths; 32.0%). Only 85 of the total deaths (30.6%) were caused by breast cancer (including two treatment-related deaths on capecitabine). Although it is uncertain how many of the deaths from unknown causes were a result of breast cancer, these data underscore the importance of competing causes of mortality in this older population. This is especially important because in this trial and most clinical

TABLE 4. New Second Primary Cancers

Second Cancer	No. of Patients (%)		
	CMF or AC (n = 58)	Capecitabine (n = 38)	Total (N = 96)
Solid tumor	24 (41)	14 (37)	38 (40)
GI	7 (12)	2 (5)	9 (9)
Genitourinary	2 (3)	3 (8)	5 (5)
Gynecologic	6 (10)	2 (5)	8 (8)
Other	7 (12)	7 (18)	14 (15)
Breast	8 (14)	6 (16)	14 (15)
Invasive	5 (9)	3 (8)	8 (8)
DCIS/LCIS	3 (5)	3 (8)	6 (6)
Skin	6 (10)	6 (16)	12 (13)
Blood	9 (16)	5 (13)	14 (15)
Lymphoma	3 (5)	1 (3)	4 (4)
Myeloma	1 (2)	2 (5)	2 (2)
Myelodysplasia	2 (3)	1 (3)	3 (3)
AML	2 (3)	0 (0)	2 (2)
CLL	0 (0)	1 (3)	1 (1)
CML	1 (2)	0 (0)	1 (1)
Unknown	11 (19)	7 (18)	18 (19)

NOTE. Among the 89 patients who developed a second cancer, there were 96 cancer occurrences in total. Six patients had multiple secondary cancer events, all on the cyclophosphamide, methotrexate, and fluorouracil (CMF) or doxorubicin and cyclophosphamide (AC) arm.

Abbreviations: AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; DCIS, ductal cancer in situ; LCIS, lobular cancer in situ.

trials, older patients are likely to be healthier than the older population at large.

As reported previously, toxicity was seen in the majority of patients. Only 62% of patients completed all six planned cycles of CMF, but 80% completed six planned cycles of capecitabine, and 92% completed four cycles of AC therapy. With further follow-up, death attributed to congestive heart failure or cardiomyopathy has been noted for seven patients treated with standard therapy (AC, n = 5; CMF, n = 2) and two treated with capecitabine. Myelodysplasia and acute myelogenous leukemia were seen in only three patients.

This trial remains among the few focused on the role of adjuvant chemotherapy in older women with breast cancer. Since the publication of our initial results in 2009, few additional randomized trials focused on this population have been performed. Two trials compared capecitabine with a nonchemotherapy control group. One randomized trial compared ibandronate with or without capecitabine in 1,358 older patients with moderate- or high-risk early breast cancer and showed no benefit for capecitabine.¹⁷ A second case-control study compared 104 older patients given adjuvant capecitabine with a similar untreated control

group of 147 patients.¹⁸ Considering the negative outcome from our trial and the larger trial by von Minckwitz et al,¹⁷ we do not believe that capecitabine alone has a role in the adjuvant treatment of older women with breast cancer.

Clinical trials in older patients remain sparse. A randomized trial of CMF or weekly docetaxel in 302 patients age 65 to 69 years showed no difference in outcome after a median follow-up of almost 6 years.¹⁹ A second trial randomly assigned 198 nonfrail patients age 65 years and older to epirubicin and cyclophosphamide followed by CMF versus six cycles of nanoparticle albumin-bound paclitaxel and capecitabine.²⁰ There was no difference in survival among the treatment groups at 2 years of follow-up. Two phase II trials have focused on specific regimens such as docetaxel and cyclophosphamide^{21,22} and liposomal doxorubicin and taxanes, but convincing outcome data were lacking.²³ Unfortunately, in a meta-analysis reported in 2012 of 100,000 women in 123 randomized trials, only a small percentage of patients age 70 years and older were treated, limiting our knowledge about the benefits of many newer state-of-the-art regimens in older patients.²⁴ Accrual of older patients to groundbreaking adjuvant chemotherapy trials remains a major problem.

We have learned much about adjuvant therapy since the initial development and publication of our study. First, many of the patients enrolled in our trial would not currently be recommended to receive chemotherapy, especially many node-negative patients in whom genetic-based assays would likely suggest no benefit.^{25,26} In addition, although CMF and AC result in similar outcomes,^{6,7} the majority of lower risk patients receiving chemotherapy today are treated with docetaxel and cyclophosphamide, a combination that is superior to AC (and CMF) and that showed similar benefits for patients older and younger than 65 years.²⁷ The use of geriatric assessment to help select older patients for chemotherapy treatment has also proven to be of great value²⁸ because performance status misses many areas of vulnerability in older patients²⁹ and geriatric assessment can inform the choice of interventions in addition to allowing one to accurately predict life expectancy³⁰ and toxicity.^{31,32}

In addition to commonly defined clinical trial outcomes including RFS, OS, BCSS, and toxicity, this trial incorporated prospectively collected ancillary data (Data Supplement) on a number of geriatric-related domains. This has resulted in numerous publications exploring the effects of the chemotherapy regimens used in our trial on quality of life,³³ adherence to oral chemotherapy,^{34,35} self-reported cognitive function,³⁶ lymphedema and musculoskeletal events,³⁷ and functional decline.³⁸ Pretreatment data were also used to assess the effects of comorbidity,³⁹ social support,⁴⁰ renal function,⁴¹ patient preferences to receive chemotherapy,⁴² and selected covariates⁴³ on patient outcomes. In addition, we developed a companion trial (ClinicalTrials.gov identifier: [NCT00068328](https://clinicaltrials.gov/ct2/show/study/NCT00068328)) for

patients who declined participation in the Cancer and Leukemia Group B 49907 trial (Alliance) that ran simultaneously and that compared treatment and other outcomes with the treatment groups in our study.⁴⁴ These assessments related to quality of life and function and the need for supportive care during treatment are key to discussing treatment recommendations with patients. Another unique aspect of our trial was the use of an adaptive Bayesian statistical design that allowed us to determine noninferiority with a smaller sample size while retaining the robustness of the treatment comparisons. Such adaptive designs should be considered for future trials designed specifically for older patients to facilitate accrual. The

majority of patients who die of breast cancer in the United States are age 65 years and older, and our data and those of others indicate that chemotherapy can improve outcomes in this older age group. An online calculator validated in older patients can also help define the benefits of chemotherapy in patients with different tumor phenotypes.⁴⁵ Optimally, we must increase the number of older patients in cancer clinical trials to have accurate data on outcomes, especially toxicity, for newer agents. Efforts are being made to overcome the age bias associated with offering older patients trial participation,^{46,47} but trials designed specifically for older patients and that include serial geriatric assessments are needed.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Randomized Trial of Standard Adjuvant Chemotherapy Regimens Versus Capecitabine in Older Women With Early Breast Cancer: 10-Year Update of the CALGB 49907 Trial**

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APPENDIX

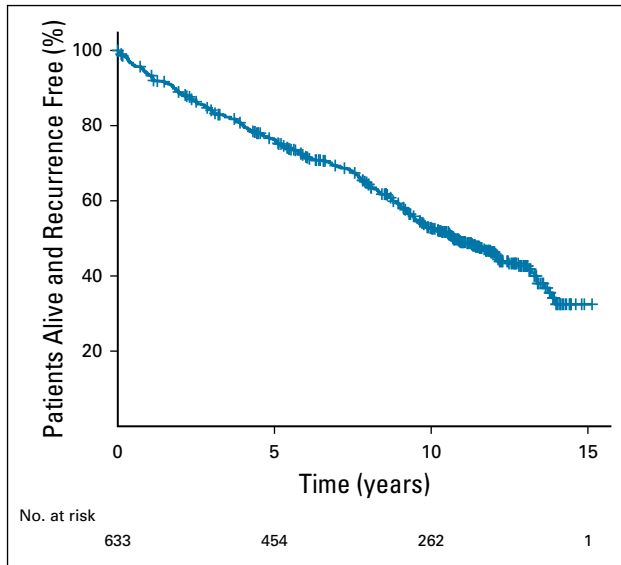


FIG A1. Relapse-free survival for all patients.

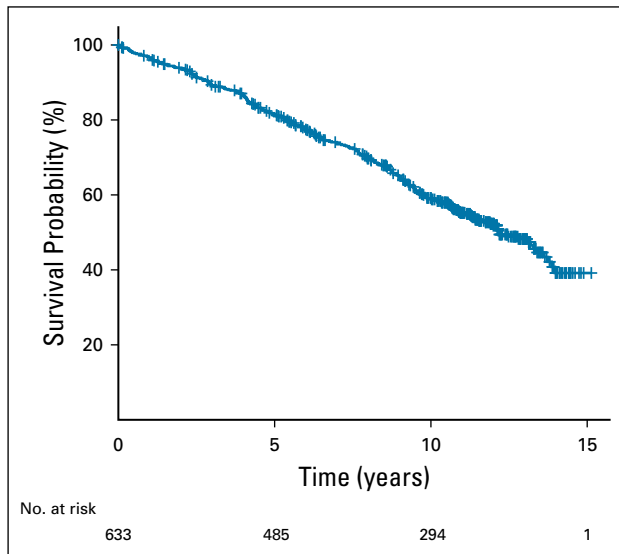


FIG A2. Overall survival for all patients.

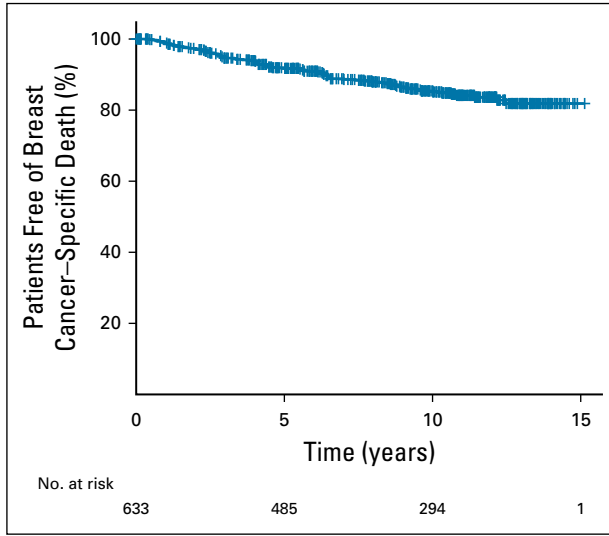


FIG A3. Breast cancer-specific survival for all patients.

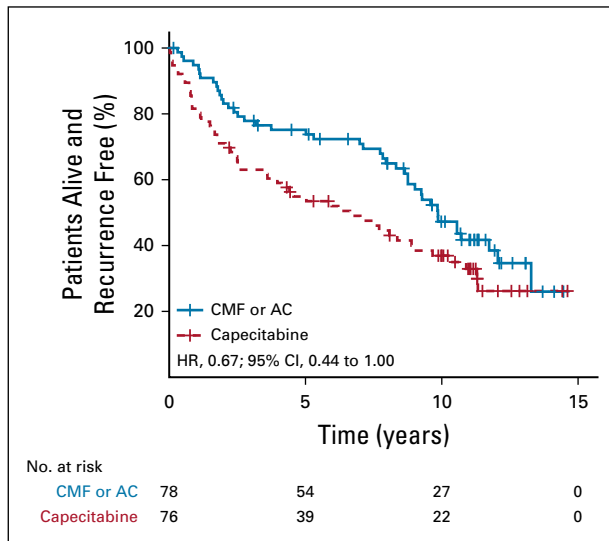


FIG A4. Kaplan-Meier plots for recurrence-free survival in patients with triple-negative breast cancer. AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and fluorouracil; HR, hazard ratio.

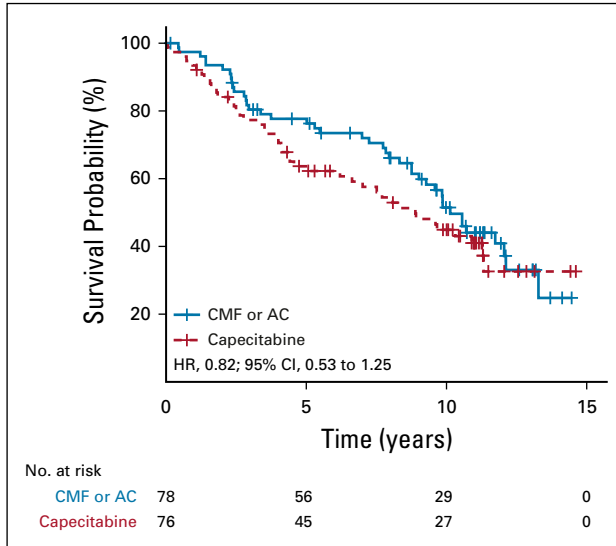


FIG A5. Kaplan-Meier plots for overall survival in patients with triple-negative breast cancer. AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and fluorouracil; HR, hazard ratio.

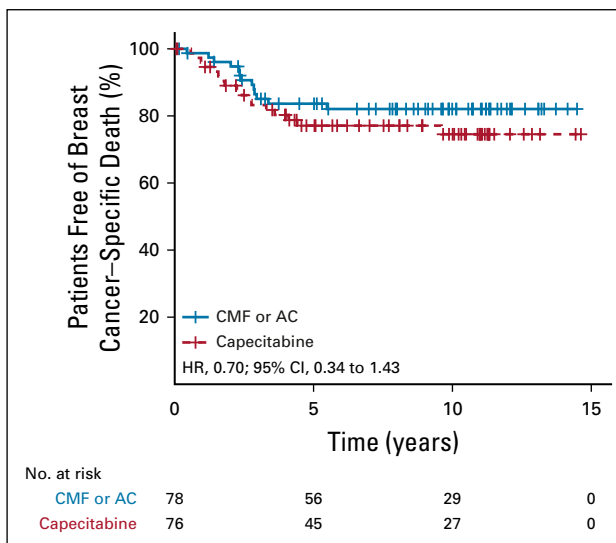


FIG A6. Kaplan-Meier plots for breast cancer-specific survival in patients with triple-negative breast cancer. AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and fluorouracil; HR, hazard ratio.

TABLE A1. RFS, OS, and BCSS Estimates at 5 and 10 Years

Kaplan-Meier Estimates for All ITT Patients	Median (years; 95% CI)	5-Year Estimate (%; 95% CI)	10-Year Estimate (%; 95% CI)
RFS	10.7 (9.7 to 12.1)	76.3 (73.0 to 79.7)	52.7 (48.8 to 57.0)
OS	12.2 (11.3 to 13.6)	81.6 (78.6 to 84.7)	59.2 (55.3 to 63.4)
BCSS	NA	91.7 (89.5 to 94.0)	85.4 (82.4 to 88.5)

NOTE. Median follow-up times were 11.4 years (95% CI, 11.2 to 11.6 years) for relapse-free survival (RFS), 11.4 years (95% CI, 11.3 to 11.7 years) for overall survival (OS), and 10.5 years (95% CI, 10.0 to 10.8 years) for breast cancer–specific survival (BCSS).

Abbreviations: NA, not available; ITT, intent to treat.

TABLE A2. Characteristics of Patients With Triple-Negative Breast Cancer

Characteristic	No. of Patients (%)		P (Fisher's exact test)
	CMF or AC (n = 78)	Capecitabine (n = 76)	
Age group, years			.10
65-69	14 (18)	25 (33)	
70-79	57 (73)	45 (59)	
≥ 80	7 (9)	6 (8)	
Performance score			1.00
0 or 1 (fully active or minimal symptoms)	75 (96)	73 (96)	
2 (symptoms, but active > 50% of the time)	9 (4)	3 (4)	
Race or ethnic group			.65
White	67 (86)	62 (82)	
Other race	10 (1)	12 (3)	
Missing data	1 (13)	2 (16)	
Tumor size, cm			.24
≤ 2	39 (49)	30 (39)	
> 2 to ≤ 5	36 (45)	45 (55)	
> 5	3 (6)	1 (6)	
No. of positive lymph nodes			.55
0	37 (47)	36 (47)	
1-3	30 (38)	25 (33)	
4-9	8 (10)	12 (16)	
≥ 10	1 (1)	0 (0)	
Missing data	2 (3)	3 (1)	
Tumor grade			.28
Low	3 (4)	0 (0)	
Intermediate	17 (22)	19 (25)	
High	49 (63)	54 (71)	
Missing data	9 (12)	3 (4)	
Type of surgery			.42
Lumpectomy and breast irradiation	36 (47)	41 (54)	
Mastectomy	42 (53)	35 (46)	

(continued on following page)

TABLE A2. Characteristics of Patients With Triple-Negative Breast Cancer (continued)

Characteristic	No. of Patients (%)		P (Fisher's exact test)
	CMF or AC (n = 78)	Capecitabine (n = 76)	
Axillary evaluation			.93
Sentinel node biopsy only	22 (28)	23 (30)	
Axillary dissection only	29 (37)	25 (33)	
Both sentinel node biopsy and axillary dissection	26 (33)	27 (36)	
Neither sentinel node biopsy nor axillary dissection	1 (1)	1 (< 1)	

Abbreviations: AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and fluorouracil.

TABLE A3. Kaplan-Meier Estimates for Patients with Triple-Negative Breast Cancer

Outcome	Median (years; 95% CI)	5-Year Estimate (%; 95% CI)	10-Year Estimate (%; 95% CI)
RFS	8.9 (7.7 to 10.6)	65.1 (63.7 to 78.4)	42.2 (34.7 to 51.3)
OS	9.8 (8.8 to 11.3)	70.7 (78.6 to 84.7)	48.2 (40.5 to 57.4)
BCSS	NA	80.4 (74.2 to 87.2)	78.4 (71.7 to 85.7)

Abbreviations: BCSS, breast cancer–specific survival; NA, not available; OS, overall survival; RFS, relapse-free survival.

TABLE A4. Multivariable Cox Proportional Hazards Models for Patients With Triple-Negative Breast Cancer (N = 154)

Variable	Relapse-Free Survival		Overall Survival		Breast Cancer-Specific Survival	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Treatment						
Capecitabine	1 (Ref)	.0296	1 (Ref)	.1533	1 (Ref)	.1564
CMF or AC	0.61 (0.39 to 0.95)		0.71 (0.45 to 1.14)		0.56 (0.25 to 1.25)	
Age group, years						
65-69	1 (Ref)	.1693	1 (Ref)	.0654	1 (Ref)	.1338
≥ 70	1.49 (0.84 to 2.63)		1.84 (0.96 to 3.54)		3.18 (0.70 to 14.41)	
Race						
White	1 (Ref)	.9565	1 (Ref)	.9290	1 (Ref)	.7445
Other	1.02 (0.55 to 1.88)		1.03 (0.54 to 1.96)		0.82 (0.24 to 2.75)	
Tumor size, cm						
≤ 2	1 (Ref)	.4112	1 (Ref)	.2303	1 (Ref)	.7334
> 2	1.20 (0.77 to 1.87)		1.33 (0.83 to 2.12)		1.15 (0.52 to 2.54)	
No. of positive lymph nodes						
0	1 (Ref)	.0089	1 (Ref)	< .001	1 (Ref)	.0028
1-3	1.89 (1.17 to 3.06)		2.32 (1.38 to 3.88)		5.00 (1.62 to 15.44)	
≥ 4	2.30 (1.24 to 4.29)		3.16 (1.64 to 6.05)		8.03 (2.42 to 26.68)	

Abbreviations: AC, doxorubicin and cyclophosphamide; CMF, cyclophosphamide, methotrexate, and fluorouracil; HR, hazard ratio; Ref, reference.