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ORIGINAL REPORT

Phase III Study of Gemcitabine Plus Docetaxel Compared With Capecitabine Plus Docetaxel for Anthracycline-Pretreated Patients With Metastatic Breast Cancer

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ABSTRACT

Purpose
Patients with metastatic breast cancer who are pretreated with anthracyclines frequently receive taxane-based combinations. This phase III study compared the efficacy and safety of gemcitabine-docetaxel (GD) with capecitabine-docetaxel (CD) in advanced breast cancer.

Patients and Methods
Patients were randomly assigned to GD (G 1,000 mg/m^2 days 1 and 8; D 75 mg/m^2 day 1) or CD (C 1,250 mg/m^2 twice daily days 1 through 14; D 75 mg/m^2 day 1) every 21 days. Comparison of progression-free survival (PFS) was the primary objective.

Results
Patient characteristics were balanced between arms (N = 305). Median PFS was 8.05 months (95% CI, 6.60 to 8.71) for GD and 7.98 (95% CI, 6.93 to 8.77) for CD (log-rank $P = .121$). Overall response rate (ORR) was 32% in both arms, and overall survival (OS) was not different between arms ($P = .983$). Time to treatment failure (TTF; defined as discontinuation, progressive disease, death as a result of any cause, or the start of a new anticancer therapy) was superior in the GD arm ($P = .059$). Hematologic toxicity was similar in both arms, except for grades 3 to 4 leukopenia (GD, 78%; CD, 66%; $P = .025$) and transfusions (GD, 17%; CD, 7%; $P = .0051$). Grades 3 to 4 diarrhea, mucositis, and hand-and-foot syndrome were significantly higher in the CD arm. Fewer patients in the GD arm discontinued because of drug-related adverse events (13% *v* 27% in CD; $P = .002$).

Conclusion
No difference was observed between GD and CD arms in PFS, ORR, and OS. TTF was longer in the GD arm. These findings, combined with a nonhematologic toxicity profile that favors GD over approved doses of CD, suggest that gemcitabine may be a better option than capecitabine in combination with docetaxel in this clinical setting.

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INTRODUCTION

Despite advances in the clinical management of breast cancer, patients who experience relapse and develop distant metastasis have a median life expectancy of 2 to 3 years.[1-3] New treatments are needed to prolong survival, control symptoms, and minimize toxicity.

Anthracyclines are widely used as front-line treatment,[4] but concerns regarding cardiotoxicity limit their use in subsequent lines of therapy. Recently, other drugs have been identified for the treatment of metastatic breast cancer (MBC). Docetaxel has achieved response rates up to 48% and median survival times up to 16.0 months.[5-7] Single agents gemcitabine and capecitabine have also shown efficacy.[8-10]

A recent Cochrane review showed that combination regimens significantly improved tumor response and time to disease progression compared with single-agent chemotherapy, with a modest improvement in overall survival (OS).[11] Drugs with distinct mechanisms of action and nonoverlapping toxicities, such as gemcitabine and capecitabine, are being explored in combination regimens to additionally improve efficacy. Recently, both drugs demonstrated superior efficacy in combination with taxanes.[12,13] Docetaxel-capecitabine was superior to docetaxel, although nonhematologic toxicities were significantly higher.[12] Leonard et al[14] suggested that

the toxicity of the combination may be better managed without compromising efficacy by allowing dosing flexibility. However, these data, obtained from a retrospective subgroup analysis, have not been tested in a prospective clinical trial. In a separate study,[13] gemcitabine-paclitaxel was found to have better efficacy than paclitaxel without a clinically meaningful increase in toxicity.

Gemcitabine has demonstrated synergy with docetaxel in vitro and in vivo.[15,16] Capecitabine also has shown synergy with docetaxel in preclinical models.[17] The observed synergy has translated into promising efficacy and manageable toxicities in clinical trials, even in heavily pretreated patients.[12, 18-29]

We designed a phase III trial to compare gemcitabine plus docetaxel (GD) versus capecitabine plus docetaxel (CD) in patients with locally advanced breast cancer or MBC. The primary objective was to compare progression-free survival (PFS) between treatments. Secondary objectives included determination of OS, overall response rate (ORR), time-to-treatment failure (TTF), toxicity, and quality of life (QoL).

PATIENTS AND METHODS

Eligibility Criteria

Patients 18 years of age and older with a histologic or cytologic diagnosis of locally advanced breast cancer or MBC were eligible if they had measurable disease per Response Evaluation Criteria in Solid Tumors; Karnofsky performance status (KPS) $\geq$ 70; adequate bone marrow, liver, and renal function; and an estimated life expectancy $\geq$ 12 weeks. Treatment with one prior anthracycline regimen (neo/adjuvant or first-line metastatic setting) was required. Taxane pretreatment was permitted in the neo/adjuvant setting if completed 6 months or more before enrollment. Hormonal therapy or immunotherapy must have been terminated before enrollment; prior radiation therapy was permitted if less than 25% of the bone marrow was treated and and if it was completed 4 weeks or more before enrollment.

Ineligibility criteria included the following: inflammatory breast disease; brain metastasis; second primary malignancy; serious concomitant illness; peripheral neuropathy National Cancer Institute Common Toxicity Criteria grade 2 or higher; or cardiac abnormalities.

Study Design and Treatment Plan

In this international, multicenter, phase III trial, patients randomly received gemcitabine (1,000 mg/m^2 30-minute intravenous [IV] infusion) on days 1 and 8 (GD arm) or oral capecitabine (1,250 mg/m^2 twice daily) on days 1 through 14 (CD arm). In both arms, docetaxel (75 mg/m^2 60-minute IV infusion) was given on day 1 before gemcitabine or capecitabine. Doses were based on labeling guidelines for capecitabine and on phase II results for gemcitabine.[18,19] Cycles were repeated every 21 days until disease progression or unacceptable toxicity occurred.

Stratification factors were first- or second-line metastatic treatment, visceral metastases, KPS, and prior adjuvant taxane therapy.

Written informed consent was obtained according to local institutional guidelines. The study was conducted in accordance with the Declaration of Helsinki and the applicable guidelines on good clinical practice.

Dose Modifications

Before day 1 of each cycle, patients had to have an adequate absolute neutrophil count and platelet count. All nonhematologic toxicities (except alopecia and grades 2 to 3 nausea and vomiting) must have subsided to grade 1 or less. Patients were discontinued if 8 weeks or longer were required for recovery. Patients who required a dose reduction on day 1 continued on the reduced dose. Treatment was discontinued in any patient with two prior dose reductions who experienced a toxicity that caused a third dose reduction.

For both docetaxel and gemcitabine, patients with grade 4 neutropenia (which lasted $>$ 5 days or with fever $\geq$ 38.5°C) or grade 4 thrombocytopenia received 75% of the dose. Patients who experienced thrombocytopenia with bleeding requiring transfusion received 50% of the dose. For most grade 3 or 4 nonhematologic toxicities (except grade 3 nausea and vomiting), treatment was delayed until the toxicity resolved to grade 1 and was resumed at 75%.

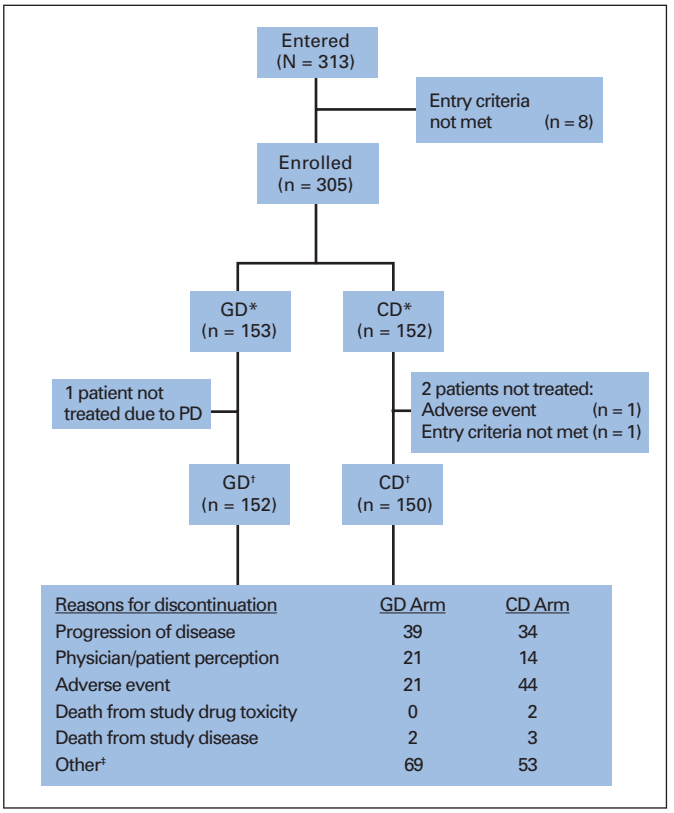
For peripheral neuropathy, docetaxel was reduced to 75% for grade 2, was delayed and then resumed at 50% for grade 3, and was discontinued for grade 4. Docetaxel was omitted for bilirubin greater than 1.0 upper limit of normal (ULN), and alkaline phosphatase greater than 5.0 ULN, or alkaline phosphatase $\geq$ 1.0 ULN, and an increase in transaminases. Patients were discontinued for grades 3 to 4 fluid retention or grade 4 anaphylaxis.

Day 8 gemcitabine was omitted for platelets less than 50,000 $\times$ 10^6/L or for an absolute neutrophil count less than 500 $\times$ 10^6/L. For grades 3 to 4 nonhematologic toxicities, the dose was either reduced or omitted, depending on the toxicity and physician's decision.

Capecitabine therapy was interrupted at the first or second occurrence of a grade 2 or 3 toxicity and was restarted at 100%, 75%, or 50% (depending on the grade and frequency of the toxicity) when the toxicity decreased to grade 1. For occurrence of grade 4 toxicity, treatment was discontinued or interrupted until toxicity resolved or decreased to grade 1, and treatment was restarted at 50%. In patients with baseline creatinine clearances of 30 to 50 mL/min, the dose was reduced to 75%. Dose omissions of capecitabine were not replaced or restored.

Baseline and Treatment Assessments

Medical history and physical examinations, KPS evaluations, and tumor measurements of palpable or visible lesions were done at baseline and before every cycle. Radiologic assessments were performed at baseline and were repeated after every third cycle. The same method used at baseline was used



Reasons for discontinuation	GD Arm	CD Arm
Progression of disease	39	34
Physician/patient perception	21	14
Adverse event	21	44
Death from study drug toxicity	0	2
Death from study disease	2	3
Other‡	69	53

Fig 1. CONSORT flow diagram. (*) Patients included in the final analyses of survival and secondary efficacy variables per intent-to-treat principle. (†) Patients treated and therefore included in the safety analysis. (‡) Includes protocol violation, satisfactory response, entry criteria not met, death unrelated to disease or study drug, lost to follow-up, or unable to contact patient. GD, gemcitabine-docetaxel; CD, capecitabine-docetaxel; PD, progressive disease.

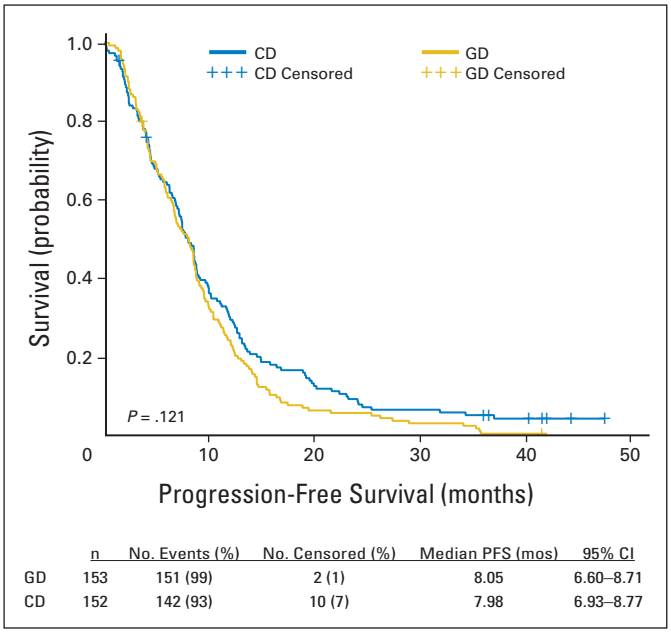
consistently for tumor assessment. Confirmation of response was performed 3 weeks or more after the first evidence of response. Radiologic assessment occurred every 9 weeks thereafter. Poststudy assessments included tumor measurement and KPS evaluation after 30 days. Long-term follow-up included radiologic assessments every 4 months until progressive disease (PD) occurred and every 6 months thereafter until death.

PFS was defined as the time from the date of random assignment to the first date of documented progression or death as a result of any cause. PFS was censored at the date of the last follow-up visit for patients who were still alive and progression free. Best response (ie, complete plus partial response) was assessed by using Response Evaluation Criteria in Solid Tumors. Duration of response (DOR) was defined as the time from the date when the measurement criteria were met for complete or partial response (whichever occurred first) until the date of the first observed PD or death as a result of any cause. TTF was defined as the time from the date of random assignment to the date of the first of the following events: discontinuation, PD, death as a result of any cause, or the start of a new anticancer therapy. OS was defined as the time from the date of random assignment to the date

Table 1. Patient Baseline Characteristics and Prior Therapy

Characteristic	Treatment Arm			
	GD (n = 153)		CD (n = 152)	
	No.	%	No.	%
Age, years				
Median	56		53	
Range	26-76		30-78	
KPS				
< 80	11	7	9	6
≥ 80	142	93	143	94
Median	90		90	
Range	70-100		70-100	
Stage of disease				
Locally advanced	6	4	4	3
Metastatic	147	96	148	97
No. of metastatic sites				
1	27	18	30	20
2	52	34	51	34
≥ 3	74	48	71	47
Type of metastatic site				
Visceral	129	84	133	88
Lung	62	41	66	43
Liver	96	63	98	64
Nonvisceral	24	16	19	13
Bone	68	44	76	50
HR status				
Positive	105	69	110	72
Negative	36	24	27	18
Unknown	12	8	15	10
HER-2 status				
Positive	28	18	24	16
Negative	75	49	70	46
Unknown	50	33	58	38
Prior therapy				
Chemotherapy				
Adjuvant/neoadjuvant*	96	63	101†	66
Locally advanced/metastatic	36	24	31	20
Both	21	14	19	13
Taxane	18	12	15	10
Hormonal therapy	107	70	98	64
Prior radiotherapy	128	84	120	79
Disease-free interval, months				
First-line patients				
Median	28.3		28.8	
Range	1-174		2-236	
Second-line patients				
Median	7.8		6.9	
Range	1-54		0-184	

Abbreviations: GD, gemcitabine-docetaxel; CD, capecitabine-docetaxel; KPS, Karnofsky performance status; HR, hormone receptor; HER-2, human epidermal growth factor receptor 2.
*First-line patient population.
†One patient did not receive prior chemotherapy.



	n	No. Events (%)	No. Censored (%)	Median PFS (mos)	95% CI
GD	153	151 (99)	2 (1)	8.05	6.60–8.71
CD	152	142 (93)	10 (7)	7.98	6.93–8.77

Fig 2. Progression-free survival. GD, gemcitabine-docetaxel; CD, capecitabine-docetaxel; PFS, progression-free survival.

of death as a result of any cause. OS was censored at the date of the last follow-up visit for patients who were still alive.

Toxicity was graded according to National Cancer Institute Common Toxicity Criteria version 2.0. Hand-foot syndrome was graded 1 to 3.[30] QoL was assessed by using the Rotterdam Symptom checklist at baseline and on day 1 of each cycle.

Statistical Methods

If a median PFS improvement from 6 months in CD (as previously reported[12]) to 8.2 months in GD is assumed, a total of 250 progressions or deaths were required to achieve a power of 80% (with the use of a log-rank test and a two-sided 10% significance level). Three hundred patients were required for enrollment over 24 months, and an additional 12 months of follow-up were planned for after the last patient was enrolled.

Time-to-event end points were calculated by using Kaplan-Meier estimates and were compared between arms by using the log-rank test at a two-sided 10% significance level (ie, $P < .1$ to demonstrate statistical significance). Comparisons of response rates were conducted with Pearson's χ^2 test.

An earlier analysis was conducted at 259 PFS events.[25] Because the analysis was considered final for the primary objective, no adjustment for multiplicity was considered for the updated PFS analysis presented here.

RESULTS

Patient Characteristics

A total of 305 women were enrolled (GD, n = 153; CD, n = 152) from October 2002 to March 2004 in 49 institutions in six European countries (Fig 1). Baseline characteristics were balanced between arms (Table 1). The median age was 55 years (range, 26 to 78 years). Forty-eight percent of patients had three or more disease sites, and 86% had visceral disease. Sixty-five percent and 35% of the patients received treatment as first and second line, respectively; 11% received prior taxanes.

Dose Administration

A total of 875 and 758 cycles were administered in the GD and CD arms, respectively, and median administration was six cycles in both arms. Median relative dose intensities (RDIs) were 68.3% (range, 30.7% to 95.6%) for gemcitabine and 57.5% (range, 0% to 102%) for capecitabine. The median RDI for docetaxel was 88.8% in both arms (range, 45.9% to 106.7% in GD and 57.8% to 100.9% in CD). In the GD arm, 13%, 14%, and 6% of gemcitabine doses and 7%, less than 1%, and 9% of docetaxel doses were reduced, omitted, or delayed, respectively. Most of the gemcitabine dose reductions and omissions occurred on day 8. In the CD arm, 11% of docetaxel doses were reduced, less than 1% was omitted, and 9% were delayed. Twenty-nine percent of cycles had one or more capecitabine dose reduction, 34% had one or more dose omissions, and 8% had one or more dose delays. Neutropenia was the most common reason for dose adjustment in both arms.

Table 2. Summary of Post-Study Chemotherapy

No. and Type of Chemotherapy*	Before Progression				After Progression			
	GD (n = 153)		CD (n = 152)		GD (n = 153)		CD (n = 152)	
	No.	%	No.	%	No.	%	No.	%
≥ 1 chemotherapy	16	10	39	26	102	67	91	60
Anthracycline	1	1	1	1	30	20	25	16
Capecitabine	4	3	15	10	68	44	15	10
Cyclophosphamide	1	1	0	0	7	5	9	6
Docetaxel	7	5	23	15	14	9	13	9
Etoposide	0	0	1	1	9	6	10	7
Fluorouracil	0	0	2	1	20	13	10	7
Gemcitabine	2	1	2	1	6	4	29	19
Methotrexate	0	0	2	1	13	8	11	7
Mitomycin	0	0	2	1	17	11	19	13
Paclitaxel	2	1	1	1	21	14	24	16
Trastuzumab	1	1	1	1	14	9	8	5
Vinorelbine	2	1	4	3	50	33	63	41

Abbreviations: GD, gemcitabine-docetaxel; CD, capecitabine-docetaxel.
*Patients may have had more than one type of chemotherapy.

Efficacy

Efficacy data for the intent-to-treat population (N = 305) are consistent with the previous analysis.[25] No significant difference in PFS was seen between the two treatment arms (log-rank $P = .121$; hazard ratio, 1.20; 95% CI, 0.96 to 1.50), and the median was 8.05 months (95% CI, 6.60 to 8.71) for GD and 7.98 months (95% CI, 6.93 to 8.77) for CD (Fig 2). The 12-month PFS rate was 23.72% (95% CI, 17.31% to 30.73%) and 29.61% (95% CI, 22.50% to 37.05%) for GD and CD, respectively. Significantly more patients in the CD arm received poststudy chemotherapy before progression (26% *v* 10%; Table 2); however, the greater number of patients did not favor the CD PFS estimates, as shown by a sensitivity analysis performed after patients who received chemotherapy before progression were censored. Median PFS for the first-line (n = 198) and second-line (n = 107) patient populations, respectively, were 8.51 months (95% CI, 6.83 to 9.49) and 6.60 months (95% CI, 5.09 to 8.41) for GD and were 7.69 months (95% CI, 6.41 to 9.59) and 8.51 months (95% CI, 6.70 to 9.79) for CD.

TTF significantly favored the GD arm (log-rank $P = .059$), and the median TTF was 4.24 months (95% CI, 4.11 to 4.44) for GD and 4.07 months (95% CI, 3.81 to 4.24) for CD. This difference was particularly noticeable within the first 4 months (Fig 3A).

The best ORR was 32% in both arms (Table 3). DOR was significantly higher for CD (log-rank $P = .047$).

OS was not significantly different between arms (log-rank $P = .983$). Median OS was 19.29 months (95% CI, 15.57 to 23.59) for GD compared with 21.45 months (95% CI, 17.12 to 24.94) for CD (Fig 3B). The 12-month survival rates were 70.98% (95% CI, 62.94% to 77.59%) and 70.56% (95% CI, 62.54% to 77.18%) for GD and CD, respectively.

Seventy-one percent of patients in the GD arm and 73% in the CD arm received poststudy chemotherapy (Table 2); 10% in the GD and 26% in the CD arm received it before progression; capecitabine and docetaxel were used most frequently. Chemotherapy received after progression was similar in the two arms, with the exception of capecitabine, gemcitabine, and vinorelbine.

Safety

All patients who received at least one dose were assessable for safety (n = 302). Three patients did not receive treatment (one in the GD arm and two in the CD arm; Table 4).

Grades 3 to 4 hematologic toxicity were not significantly different in the two arms except for grades 3 to 4 leukopenia (GD, 78%; CD, 66%; $P = .025$). There were no statistically significant differences in grades 3 to 4 neutropenia (GD, 84%; CD, 79%; $P = .456$) and febrile neutropenia/neutropenic sepsis (GD, 9%; CD, 14%; $P = .134$). Seventeen percent and 7% of patients required transfusions in the GD and CD arms, respectively ($P = .0051$), but there were no differences in grades 3 to 4 anemia ($P = .1036$). Erythropoietin and granulocyte colony-stimulating factor were administered to 18% and 30% of patients, respectively, in the GD arm and to 7% and 25%, respectively, in the CD arm. Day 8 hematologic data were not available from 13% of cycles (31% of patients) in the CD arm compared with 3% of cycles (16% of patients) in the GD arm.

Several grades 3 to 4 nonhematologic toxicities were significantly higher in the CD arm. These were diarrhea (8% *v* 18%; $P = .009$), hand-foot syndrome (0% *v* 26%; $P < .001$), and mucositis (4% *v* 15%; $P < .001$).

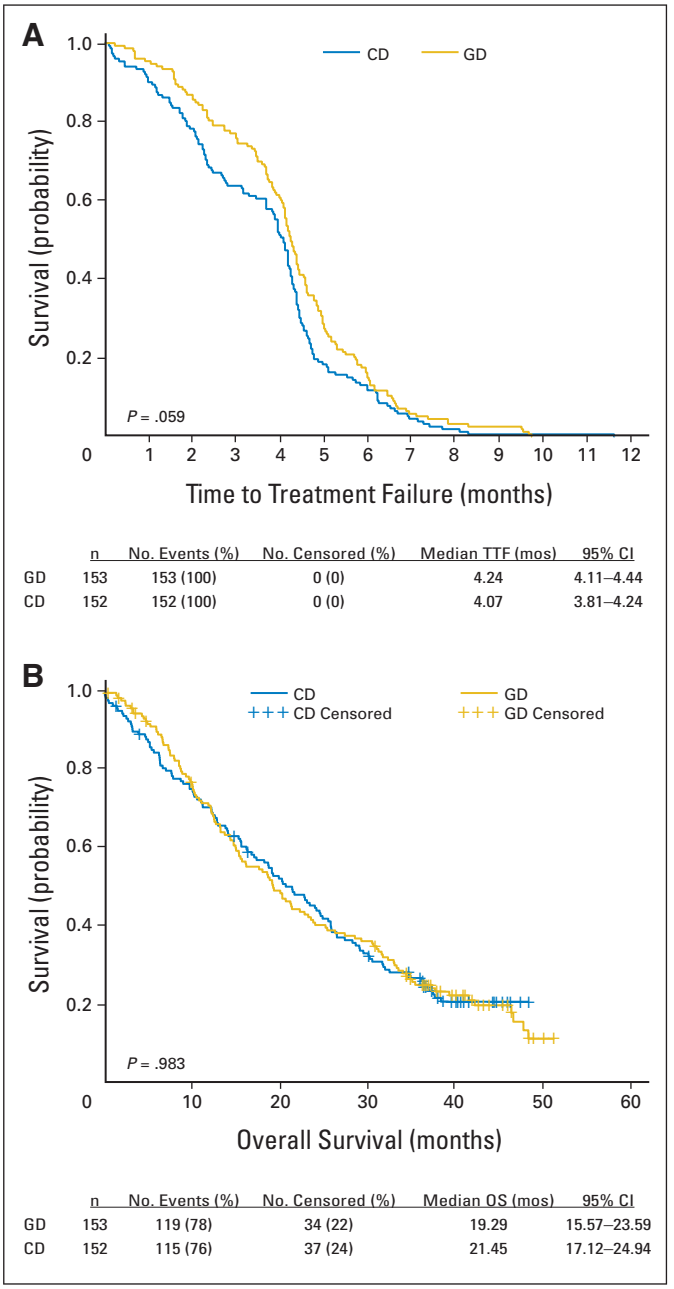


Fig 3. (A) Time to treatment failure (TTF). (B) Overall survival (OS). GD, gemcitabine-docetaxel; CD, capecitabine-docetaxel.

Fewer patients in the GD arm discontinued treatment as a result of drug-related adverse events (13% *v* 27%, respectively; $P = .002$). Hand-foot syndrome (9%) and neutropenia (5%) were the most common reasons for discontinuations in the CD arm. Eleven percent and 19% of discontinuations as a result of adverse events occurred within the first five cycles of treatment in the GD and CD arms, respectively ($P = .045$).

Nine patients died within 30 days or less of study completion (five in the CD arm and four in the GD arm). Two patients in the CD arm

Table 3. Best Overall Response

Response	Treatment Arm: GD (n = 153) No.	GD (n = 153) %	CD (n = 152) No.	CD (n = 152) %	χ^2 *P*
Overall	49	32	48	32	.931
95% CI	24.6 to 39.4		24.2 to 39.0		
Complete	7	5	4	3	—
Partial	42	27	44	29	—
Overall in first-line population	41*	43	30†‡	29	.051
95% CI	32.8 to 52.6		20.6 to 38.3		
Overall in second-line population	8§	14	18‖	36	.008
95% CI	5.0 to 23.1		22.7 to 49.3		
Median duration, months	7.75		9.07		.047¶
95% CI	6.64 to 9.20		7.23 to 10.61		
Stable disease	75	49	61	40	—
Progressive disease	20	13	22	14	—
Unknown	9	6	21	14	—

Abbreviations: GD, gemcitabine-docetaxel; CD, capecitabine-docetaxel.
*Total No. of patients = 96.
†Total No. of patients = 102.
‡Includes one patient who did not receive prior adjuvant/neoadjuvant chemotherapy.
§Total No. of patients = 57.
‖Total No. of patients = 50.
¶Log-rank *P* value.

died as a result of drug-related pneumonia and paralytic ileus; two patients in the GD arm died as a result of non–drug-related heart failure and respiratory failure. The remaining five patients died as a result of PD.

QoL was not different between treatments arms. There was no decrease in the overall valuation of life in either arm. Additional data will be presented in a separate publication.

DISCUSSION

Better disease control relative to toxicity and QoL is the treatment goal in MBC. Despite better OS observed with CD compared with docetaxel monotherapy in a previous phase III trial,[12] CD is not commonly used because of poor tolerability. This phase III study showed

Table 4. NCI-CTC Toxicities

Toxicity	Toxicity Grade by Treatment Arm: GD (n = 152) 1-2 No.	GD 1-2 %	GD 3 No.	GD 3 %	GD 4 No.	GD 4 %	CD (n = 150) 1-2 No.	CD 1-2 %	CD 3 No.	CD 3 %	CD 4 No.	CD 4 %
Hematologic*												
Anemia	141	93	4	3	4	3	133	89	1	1	1	1
Neutropenia	20	13	54	36	73	48	20	13	39	26	79	53
Febrile neutropenia/neutropenic sepsis	NA	NA	8	5	5	3	NA	NA	10	7	11	7
Thrombocytopenia	87	57	9	6	5	3	64	43	4	3	2	1
Leukopenia†	31	20	87	57	31	20	45	30	66	44	33	22
Nonhematologic												
ALT/AST	101	66	14	9	0	0	80	53	7	5	0	0
Diarrhea†	47	31	11	7	1	1	62	41	25	17	2	1
Nausea/vomiting	70	46	10	7	0	0	78	52	6	4	0	0
Mucositis†	67	44	6	4	0	0	72	48	18	12	5	3
Asthenia	45	30	11	7	0	0	31	21	16	11	0	0
Alopecia	103	68	NA	NA	NA	NA	87	58	NA	NA	NA	NA
Hand and foot syndrome†	2	1	0	0	0	0	45	30	39	26	0	0

NOTE. Includes grades 3 to 4 toxicities (except alopecia) observed in 5% or more of patients.
Abbreviations: NCI-CTC, National Cancer Institute Common Toxicity Criteria; GD, gemcitabine-docetaxel; CD, capecitabine-docetaxel; NA, not applicable.
*In the GD arm, 17% of patients required transfusions compared with 7% in the CD arm ($P = .0051$).
†Grades 3 to 4 toxicities were significantly different between the two arms ($P < .05$).

no statistically significant differences in PFS, ORR, or OS between the GD and CD arms; however, GD had a better nonhematologic toxicity profile. TTF was superior for GD, and DOR was superior for CD.

No statistically significant difference was observed in PFS ($P = .121$). Both arms achieved a median PFS that approached 8.2 months, which was the previously assumed PFS for GD. It is important to note that the PFS observed with CD was higher than expected on the basis of data reported in the study by O'Shaughnessy et al.[12] However, patients included in that study had received more prior treatments than patients in this study.

DOR was longer in the CD arm, which may be explained, in part, by the poststudy chemotherapy received before progression. Types of poststudy chemotherapy were similar in the two arms, with the exception of capecitabine and gemcitabine and, unexpectedly, vinorelbine and taxanes (Table 2), which may have impacted OS.

We did not observe a difference in PFS; however, the GD regimen was better tolerated. Although TTF (all discontinuations) was superior for GD, this was based on a 10% probability of error, which is not conventionally used in comparative phase III trials. The difference was particularly noticeable during the first 4 months, during which 19% of patients in the CD arm versus 11% in the GD arm discontinued treatment as a result of adverse events.

CD was associated with a significantly higher incidence of grades 3 to 4 diarrhea, hand-foot syndrome, and mucositis compared with GD. These toxicities are consistent with those observed in the trial reported by O'Shaughnessy et al[12] (CD, same dose), which were the only data available at the time we initiated our study. More recently, several reports have shown that combinations of taxanes and capecitabine at lower doses (ie, 1,650 mg/m^2) have relatively lower toxicity.[14,31-33] These combinations appear effective, but they have not been compared with the standard approved doses in phase III trials. More patients reported leukopenia in the GD arm without a difference in neutropenia or febrile neutropenia. The transfusion rate was higher than expected in the GD arm, given previous data,[13,20-24,27,29] but there was no difference in anemia. These differences in hematologic toxicity may be explained by fewer patients in the CD arm with day 8 hematologic data.

The better tolerability of GD is also evident in the higher RDI achieved with gemcitabine and in the fewer discontinuations as a result of adverse events (ie, twice as many patients in the CD arm). Additionally, more than twice the number of patients in the CD arm received poststudy chemotherapy before progression, most likely because of a higher number of early discontinuations.

Addition of gemcitabine did not add to the known toxicity profile of docetaxel, similar to the gemcitabine-paclitaxel combination.[12,13,34,35] Moreover, docetaxel activity appears schedule independent,[36] in contrast to paclitaxel.[37,38] The 3-week docetaxel regimen chosen in this trial is preferred and is more frequently used in clinical practice because of the ease of administration and patient management.

An active, synergistic combination, such as GD, that does not produce a decrease in QoL may offer an alternative to sequential single-agent treatment after the use of anthracyclines in the adjuvant setting, especially in patients who have visceral metastasis or disease-related symptoms. Additionally, 46% of patients in the GD arm received capecitabine poststudy. Thus, GD may offer an opportunity for the sequential use of capecitabine, which is preferred as a single agent in clinical practice for long-term MBC treatment.

In conclusion, the efficacy results for GD are consistent with previous phase II trials, which confirms that GD is active and well tolerated in MBC.[18,20-23,27] These results are in the range of those reported for other active regimens in MBC.[12,13,39,40] Both GD and CD were similar with regard to PFS, ORR, and OS. However, a longer TTF and a more favorable nonhematologic toxicity profile suggest that GD was better tolerated than CD when CD was given at approved doses in patients with MBC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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