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Breast Cancer

A Pooled Analysis of Gemcitabine Plus Docetaxel Versus Capecitabine Plus Docetaxel in Metastatic Breast Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Gemcitabine • Docetaxel • Capecitabine • Metastatic breast cancer • Pooled analysis

ABSTRACT

Introduction. In two randomized phase III trials of patients with metastatic breast cancer (MBC), gemcitabine-docetaxel (GD) and capecitabine-docetaxel (CD) had similar efficacy, but distinct safety profiles.

Methods. Data from two GD versus CD studies were pooled; overall survival (OS), progression-free survival (PFS), and overall response rate (ORR) were determined. Cox proportional hazards models identified prognostic factors associated with improved OS and PFS. Using a multivariate prognostic model incorporating identified adverse prognostic factors, we grouped MBC patients into low-, intermediate-, and high-risk categories. Hazard ratios (HRs) of GD over CD for OS and PFS were determined for subsets of patients.

Results. Baseline demographics of the pooled population were mostly well balanced. In the pooled population, there were no significant differences between GD versus CD for OS (HR = 1.02; $p = .824$), PFS (HR = 1.15; $p = .079$), and ORR ($p = .526$). In the pooled crossover population, there were trends toward improved OS (HR = 0.82; $p = .171$) and PFS (HR = 0.93; $p = .557$) with GD. Several prognostic factors (including prior adjuvant taxane) for improved OS or PFS were identified; however, there were no significant interactions between treatment arms and prognostic factors for PFS or OS, except number of metastatic sites. In the prognostic model, median OS and PFS were numerically lower in the high-risk group versus the intermediate- and low-risk groups.

Conclusion. This analysis confirms the lack of efficacy difference between GD and CD in the pooled population, crossover population, and almost all subpopulations. Several prognostic factors were associated with improved outcomes in the pooled population. ***The Oncologist*** 2014;19:443–452

Implications for Practice: In two randomized phase III trials of metastatic breast cancer patients, gemcitabine-docetaxel and capecitabine-docetaxel had similar efficacy, but distinct safety profiles. This pooled analysis confirmed the lack of efficacy difference between gemcitabine-docetaxel and capecitabine-docetaxel in the pooled population, the pooled crossover population, and almost all examined subpopulations. This analysis also identified several prognostic factors (Eastern Cooperative Oncology Group performance status, estrogen receptor status, prior adjuvant taxane, and number of metastatic sites) that were associated with both improved overall survival and progression-free survival in the overall pooled population. The choice of regimen should be guided by the clinical characteristics and tolerance to toxicities of the individual patient while considering the approved indications of the drugs.

INTRODUCTION

Globally, female breast cancer accounted for 23% of total cancer cases and 14% of cancer deaths in 2008, making this the most frequently diagnosed cancer and the leading cause of cancer death among females [1]. Despite advances in treatment, the long-term prognosis for women with metastatic breast cancer (MBC) is poor [2, 3]. In these patients, systemic chemotherapy can prolong survival and improve quality of life [4, 5]. However, new and better treatment options are needed to improve outcomes. In addition, the best use of existing agents has yet to be determined.

Several agents, including gemcitabine, docetaxel, and capecitabine, have single-agent activity in advanced breast cancer [6–8]. Relative to single-agent therapy, combinations can significantly improve time to progression (TTP) and response, with a small increase in overall survival (OS) [9]. However, it is unclear whether combinations are more effective than the same agents administered sequentially [10]. In addition, combination therapy is usually associated with increased toxicity [9, 10].

In order to improve outcomes and minimize toxicity, treatments have combined drugs with distinct mechanisms

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of action (and sometimes synergistic activity) and partially nonoverlapping toxicities. When combined with taxanes, both gemcitabine and capecitabine have superior efficacy relative to taxane monotherapy [11, 12]. Gemcitabine-paclitaxel was associated with improved OS, TTP, and response relative to paclitaxel monotherapy and had manageable toxicity [11]. This regimen is now indicated in the U.S. for treatment of patients with MBC who have relapsed following anthracycline-based adjuvant/neoadjuvant chemotherapy unless clinically contraindicated [13] and has similar indications in the European Union and China [14, 15]. Likewise, the combination of capecitabine and docetaxel (capecitabine-docetaxel) was associated with improved OS, TTP, and response relative to docetaxel monotherapy [12] and is approved for use in the United States, European Union, and China [16–18].

Because of the synergy of gemcitabine and docetaxel in vitro [19], the combination of gemcitabine and docetaxel (gemcitabine-docetaxel) was explored in patients with MBC. This doublet was tested in nonrandomized clinical trials and demonstrated activity and tolerability [20–28].

More recently, gemcitabine-docetaxel and capecitabine-docetaxel were compared in two randomized phase III trials of patients with MBC [29, 30]. One of these trials had a planned crossover to the alternate single agent [30]. In these phase III trials, gemcitabine-docetaxel had similar efficacy to capecitabine-docetaxel, but the toxicity profile of the regimens differed. Here, we performed a pooled analysis of these phase III trials to confirm the efficacy of gemcitabine-docetaxel versus capecitabine-docetaxel in MBC patients, and to identify subsets of patients who may derive the most benefit from each regimen.

Materials and Methods

Patients

In total, 780 patients were enrolled in the two international randomized phase III trials. Both studies enrolled patients ≥18 years old with histologically or cytologically confirmed MBC [29, 30].

In the Chan et al. trial (NCT00191438), patients had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) [31] and a Karnofsky performance status ≥70 [29]. Treatment with one prior anthracycline regimen in the neoadjuvant/adjuvant or first-line metastatic setting was required. Prior taxane treatment was permitted in the neoadjuvant/adjuvant setting if completed 6 months before enrollment.

In the Seidman et al. trial (NCT00191152), patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1 and measurable or nonmeasurable disease. Patients may have completed neoadjuvant or adjuvant taxane therapy ≥6 months before enrollment [30]. Prior anthracycline, hormone, or immunotherapy, and no more than one prior line of chemotherapy for MBC were allowed. Patients who received prior taxane therapy for MBC were excluded.

In both trials, patients provided written informed consent according to local guidelines. The studies were conducted per the principles of Good Clinical Practice and the Declaration of Helsinki.

Treatment

Patients were randomized to receive either gemcitabine-docetaxel or capecitabine-docetaxel [29, 30]. In the Chan trial, patients assigned to gemcitabine-docetaxel received gemcitabine (1,000 mg/m^2 30-minute i.v. infusion) on days 1 and 8 and docetaxel (75 mg/m^2 60-minute i.v. infusion) on day 1 [29]. Patients assigned to capecitabine-docetaxel received oral capecitabine (1,250 mg/m^2 twice daily) on days 1 through 14 and docetaxel (75 mg/m^2 60-minute i.v. infusion) on day 1. The capecitabine dose was based on the label [16]. Cycles were repeated every 21 days until progressive disease or unacceptable toxicity.

In the Seidman trial, patients assigned to gemcitabine-docetaxel received gemcitabine (1,000 mg/m^2 30-minute i.v. infusion) on days 1 and 8 and docetaxel (75 mg/m^2 60-minute i.v. infusion) on day 1 [30]. Patients assigned to capecitabine-docetaxel received oral capecitabine (1,000 mg/m^2 twice daily) on days 1 through 14 and docetaxel (75 mg/m^2 60-minute i.v. infusion) on day 1. Cycles were repeated every 21 days until disease progression. The capecitabine dose was reduced because of the high incidence of diarrhea and hand-foot syndrome that was observed in the earlier Chan trial [29]. Patients who progressed on induction gemcitabine-docetaxel or capecitabine-docetaxel received single-agent capecitabine or gemcitabine, respectively (using the induction doses and schedules) within 4 weeks of documented progressive disease.

Dose reductions were described in the original reports [29, 30].

Efficacy Evaluations

In the Chan trial, the primary endpoint was progression-free survival (PFS); secondary endpoints were OS, overall response rate (ORR), time-to-treatment failure, safety, and quality of life [29]. In the Seidman trial, the primary endpoint was TTP; secondary endpoints were ORR, OS, and safety. Time-to-treatment failure was added as a post hoc analysis [30]. Tumor responses were evaluated using RECIST 1.0 criteria [31] every third cycle. Confirmatory scans were performed at least 3 weeks after the first evidence of response [29, 30].

Statistical Analyses

Patient-level data from two individual studies were pooled for analyses. OS was calculated from the date of randomization until death from any cause or censored at last known alive date. PFS was calculated from the date of randomization until first date of documented progression or death from any cause or censored last follow-up visit for patients who were still alive and progression-free. OS and PFS were estimated using the Kaplan-Meier product limit method [32]. Cox proportional hazards models [33] and log-rank tests, stratified by study, were used to calculate hazard ratios (HRs) and to compare survival curves of the two treatment arms for OS and PFS. Pooled ORR (defined as the proportion of patients with a best overall response of complete response [CR] or partial response [PR]) and disease control rate (DCR, defined as the proportion of patients with a best overall response of CR, PR, or stable disease) were also calculated in the two treatment arms and compared using the Cochran-Mantel-Haenszel test stratified by study. Potential prognostic factors were identified initially by searching available baseline variables that significantly

influenced OS or PFS at a level of $p < .05$ in the univariate analyses, and then were included in the multivariate analyses using stepwise Cox proportional hazards modeling for OS or PFS. Factors with p values $<.05$ in the multivariate analyses were considered statistically significant and prognostic. All p values were two-sided and were not adjusted for multiplicity. Caution should be used when interpreting these p values.

The crossover population consisted of patients who received induction gemcitabine-docetaxel and then, upon progression, crossed over to capecitabine, and patients who received induction capecitabine-docetaxel and then, upon progression, crossed over to gemcitabine. Induction PFS was estimated for all crossover patients from the time of randomization to the date of first progressive disease or death from any cause, whichever occurred first.

Results

Patient Demographics

Table 1 shows the baseline demographics for the pooled population. From the Chan trial, 305 patients (153 gemcitabine-docetaxel; 152 capecitabine-docetaxel) were randomized [29]; from the Seidman trial, 475 patients (239 gemcitabine-docetaxel induction phase; 236 capecitabine-docetaxel induction phase) were randomized [30]. A minority of patients received prior chemotherapy for MBC (20.9% gemcitabine-docetaxel; 19.1% capecitabine-docetaxel). The arms were well balanced, with the possible exceptions of crossover status and progesterone receptor status. HER2 status was not available in the Seidman trial [30] and prior use of trastuzumab was unknown in both trials.

Efficacy

Pooled Efficacy of Gemcitabine-Docetaxel Versus Capecitabine-Docetaxel

In the pooled population, OS for patients randomized to gemcitabine-docetaxel versus capecitabine-docetaxel was not statistically different (stratified log-rank $p = .824$, HR $= 1.02$, 95% CI, 0.86–1.20; median 21.5 months vs. 22.0 months) (Fig. 1A). In the pooled population, PFS for patients randomized to gemcitabine-docetaxel versus capecitabine-docetaxel was not statistically different (stratified log-rank $p = .079$, HR $= 1.15$, 95% CI, 0.98–1.35; median 8.5 months vs. 8.5 months) (Fig. 1B).

In the pooled population, the ORR was 32.1% (95% CI, 27.5–37.0) for gemcitabine-docetaxel and 34.3% (95% CI, 29.6–39.2) for capecitabine-docetaxel (Cochran-Mantel-Haenszel $p = .526$). The DCR (CR + PR + stable disease) was 56.6% (95% CI, 51.6–61.6) for gemcitabine-docetaxel and 57.5 (95% CI, 52.4–62.4) for capecitabine-docetaxel (Cochran-Mantel-Haenszel $p = .781$).

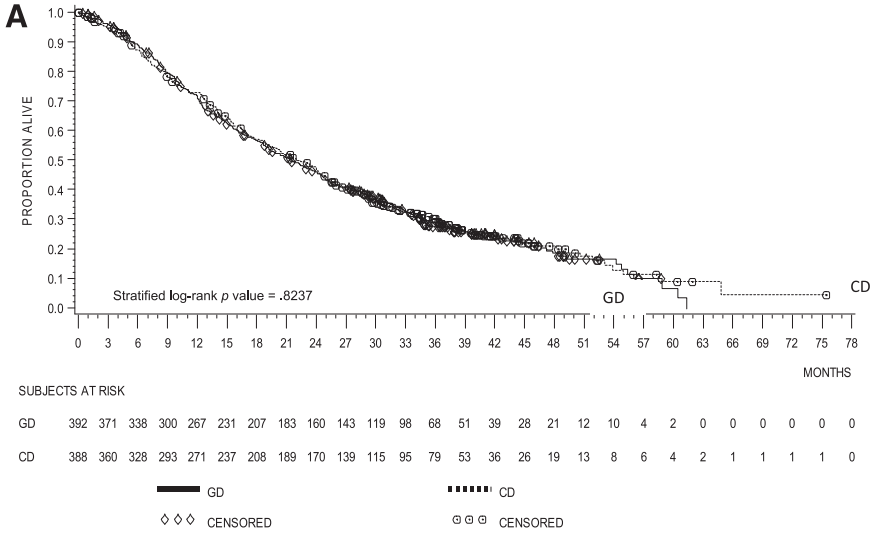
Pooled Efficacy of Crossover Population

In the pooled crossover population, although there was a trend favoring gemcitabine-docetaxel, the difference in OS among patients initially receiving gemcitabine-docetaxel versus capecitabine-docetaxel was not statistically significant (unstratified log-rank $p = .171$, HR $= 0.82$, 95% CI, 0.62–1.09; median 25.5 months vs. 23.5 months) (Fig. 2A). Likewise, there

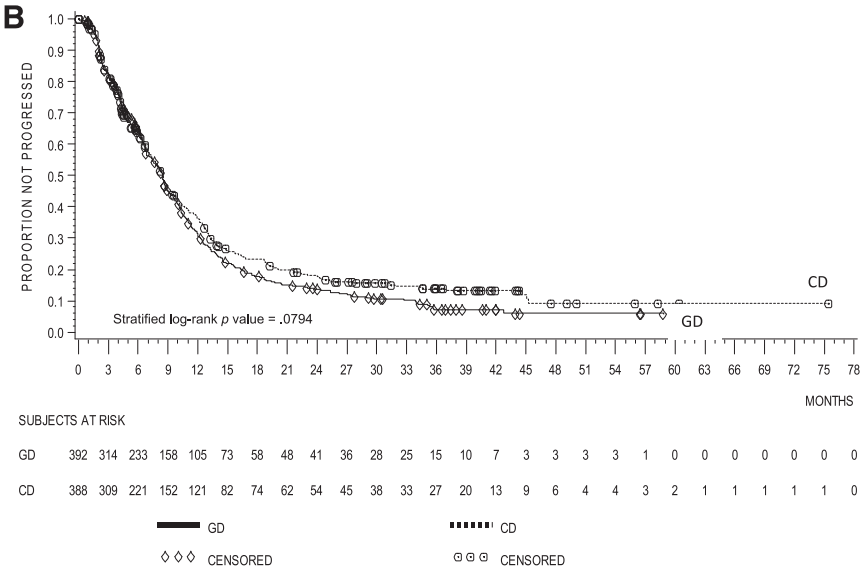
Table 1. Baseline demographics of pooled population

Demographic	Gemcitabine-docetaxel ($n = 392$)	Capecitabine-docetaxel ($n = 388$)
Median age (range), yr	57 (26–81)	54 (27–82)
Age, *n* (%)		
≤65	313 (79.8)	326 (84.0)
>65	79 (20.2)	62 (16.0)
Median time since diagnosis (range), yr	2.7 (0.01–29.4)	2.6 (0.003–21.3)
Race, *n* (%)		
Asian	28 (7.1)	33 (8.5)
Black	24 (6.1)	13 (3.4)
Caucasian	312 (79.6)	306 (78.9)
Hispanic	26 (6.6)	36 (9.3)
Other	2 (0.5)	0
Eastern Cooperative Oncology Group performance status, *n* (%)		
0	239 (61.0)	233 (60.1)
1	138 (35.2)	141 (36.3)
2	11 (2.8)	9 (2.3)
Missing	4 (1.0)	5 (1.3)
Estrogen receptor status, *n* (%)		
Positive	233 (59.4)	238 (61.3)
Negative	136 (34.7)	119 (30.7)
Intermediate/unknown	23 (5.9)	31 (8.0)
Progesterone receptor status, *n* (%)		
Positive	171 (43.6)	196 (50.5)
Negative	172 (43.9)	147 (37.9)
Intermediate/unknown	49 (12.5)	45 (11.6)
Number of metastatic sites, *n* (%)		
1	65 (16.6)	63 (16.2)
2	86 (21.9)	88 (22.7)
≥3	240 (61.2)	235 (60.6)
Missing	1 (0.3)	2 (0.5)
Prior surgery, *n* (%)		
Yes	365 (93.1)	345 (88.9)
No	26 (6.6)	43 (11.1)
Missing	1 (0.3)	0
Prior radiotherapy, *n* (%)		
Yes	142 (36.2)	136 (35.1)
No	250 (63.8)	252 (64.9)
Prior chemotherapy for metastatic breast cancer, *n* (%)		
Yes	82 (20.9)	74 (19.1)
No	308 (78.6)	311 (80.2)
Missing	2 (0.5)	3 (0.8)
Prior adjuvant taxane use, *n* (%)		
Yes	63 (16.1)	61 (15.7)
No[a]	329 (83.9)	327 (84.3)
Crossover status, *n* (%)		
Yes	149 (38.0)	111 (28.6)
No	243 (62.0)	277 (71.4)

[a]In the pooled analysis, patients with an unknown taxane status were considered to have received no prior taxanes.



Group	# Deaths/ # Randomized	Median (95% CI)	HR (95% CI)
GD	283/392	21.5 (18.7–24.4)	--
CD	279/388	22.0 (19.2–24.6)	--
GD over CD	--	--	1.02 (0.86–1.20)



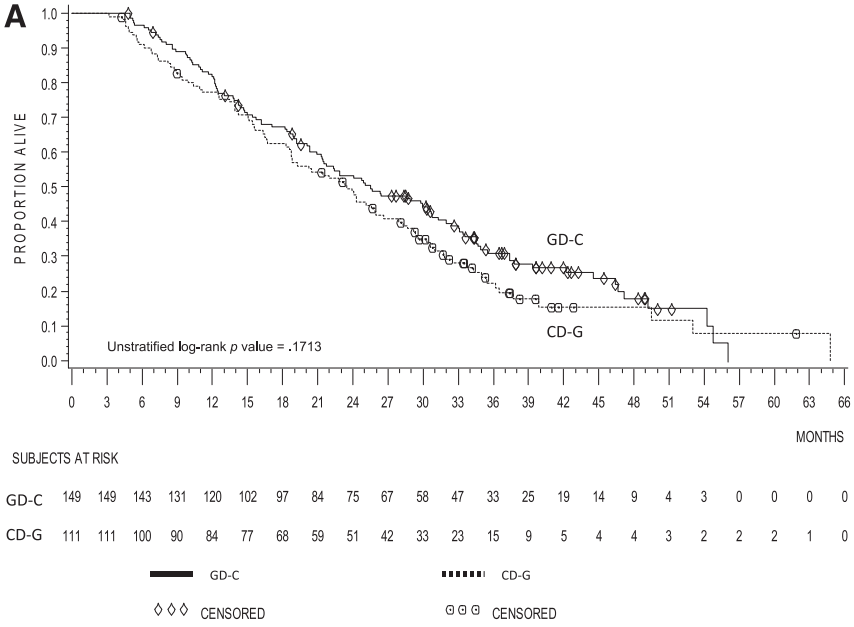
Group	# Progressed/ # Randomized	Median (95% CI)	HR (95% CI)
GD	328/392	8.5 (7.5–9.0)	--
CD	301/388	8.5 (7.4–9.1)	--
GD over CD	--	--	1.15 (0.98–1.35)

Figure 1. Kaplan-Meier curves of the pooled population. **(A):** Overall survival. **(B):** Progression-free survival.
Abbreviations: CD, capecitabine-docetaxel; CI, confidence interval; GD, gemcitabine-docetaxel; HR, hazard ratio.

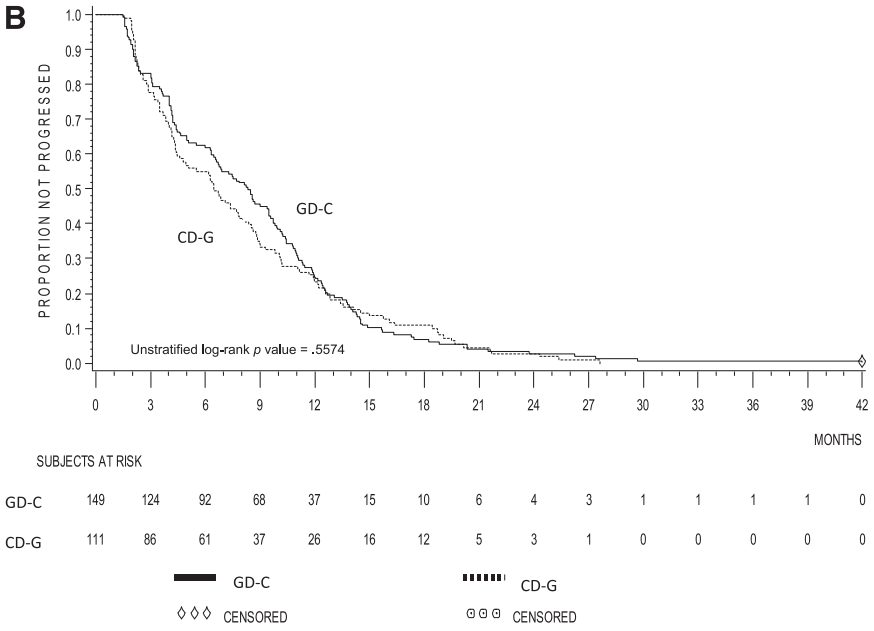
was a trend toward improved PFS of the induction phase with gemcitabine-docetaxel, but the difference in PFS in the pooled crossover population receiving gemcitabine-docetaxel versus capecitabine-docetaxel was not statistically significant (unstratified log-rank $p = .557$, HR = 0.93, 95% CI, 0.73–1.19; 8.3 months vs. 6.5 months) (Fig. 2B).

Prognostic Factors

Using a univariate Cox proportional hazards model, we found that several potential prognostic factors were associated with improved OS or PFS at a significance level of $p < .05$ (Table 2). For OS, these were race, ECOG PS, estrogen receptor status, progesterone receptor status, prior surgery, prior



Group	# Deaths/ # Randomized	Median (95% CI)	HR (95% CI)
GD-C	109/149	25.5 (21.4–30.8)	--
CD-G	87/111	23.5 (18.7–26.6)	--
GD-C over CD-G	--	--	0.82 (0.62–1.09)



Group	# Progressed/ # Randomized	Median (95% CI)	HR (95% CI)
GD-C	148/149	8.3 (6.6–9.6)	--
CD-G	111/111	6.5 (4.4–8.1)	--
GD-C over CD-G	--	--	0.93 (0.73–1.19)

Figure 2. Kaplan-Meier curves of the crossover subpopulation within the pooled population. **(A):** Overall survival. **(B):** Progression-free survival.

Abbreviations: CD-G, capecitabine-docetaxel crossed over to gemcitabine; CI, confidence interval; GD-C, gemcitabine-docetaxel crossed over to capecitabine; HR, hazard ratio.

Table 2. Prognostic factors for pooled overall survival and progression-free survival (univariate analysis)

	Overall survival		Progression-free survival	
Factor	**HR (95% CI)**	***p*[a]**	**HR (95% CI)**	***p*[a]**
Age (≤65 vs. >65)	0.912 (0.737–1.129)	.397	0.850 (0.691–1.046)	.124
Race (nonwhite vs. white)	0.765 (0.599–0.976)	.031	0.923 (0.743–1.147)	.471
ECOG PS (0 vs. >0)	0.573 (0.479–0.684)	<.001	0.702 (0.593–0.831)	<.001
ERS (positive vs. negative)	0.613 (0.513–0.733)	<.001	0.579 (0.488–0.686)	<.001
PRS (positive vs. negative)	0.725 (0.608–0.866)	<.001	0.685 (0.578–0.810)	<.001
Prior surgery (no vs. yes)	0.680 (0.486–0.952)	.025	1.043 (0.779–1.398)	.777
Prior radiotherapy (no vs. yes)	0.690 (0.550–0.866)	.001	0.831 (0.668–1.035)	.098
Prior adjuvant taxane (no vs. yes)	0.686 (0.553–0.850)	<.001	0.764 (0.616–0.947)	.014
Time since diagnosis (<median vs. ≥median)	0.870 (0.732–1.034)	.115	0.773 (0.655–0.911)	.002
Number of metastatic sites (1–2 vs. >2)	0.643 (0.538–0.768)	<.001	0.756 (0.640–0.892)	<.001
Prior chemotherapy for MBC (no vs. yes)	0.818 (0.665–1.007)	.059	0.925 (0.761–1.125)	.435

[a]*p* values were generated using Wald tests.
Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ERS, estrogen receptor status; HR, hazard ratio; MBC, metastatic breast cancer; PRS, progesterone receptor status.

Table 3. Prognostic factors for pooled overall survival and progression-free survival (multivariate analysis)

	Overall survival		Progression-free survival	
Factor	**HR (95% CI)**	***p*[a]**	**HR (95% CI)**	***p*[a]**
Race (nonwhite vs. white)	0.716 (0.552–0.930)	.012	NA	NA
ECOG PS (0 vs. >0)	0.561 (0.462–0.681)	<.001	0.739 (0.612–0.893)	.002
ERS (positive vs. negative)	0.618 (0.513–0.745)	<.001	0.569 (0.475–0.681)	<.001
Prior radiotherapy (no vs. yes)	0.761 (0.590–0.981)	.035	NA	NA
Prior adjuvant taxane (no vs. yes)	0.657 (0.517–0.834)	<.001	0.672 (0.533–0.846)	<.001
Number of metastatic sites (1–2 vs. >2)	0.621 (0.511–0.754)	<.001	0.788 (0.655–0.948)	.011

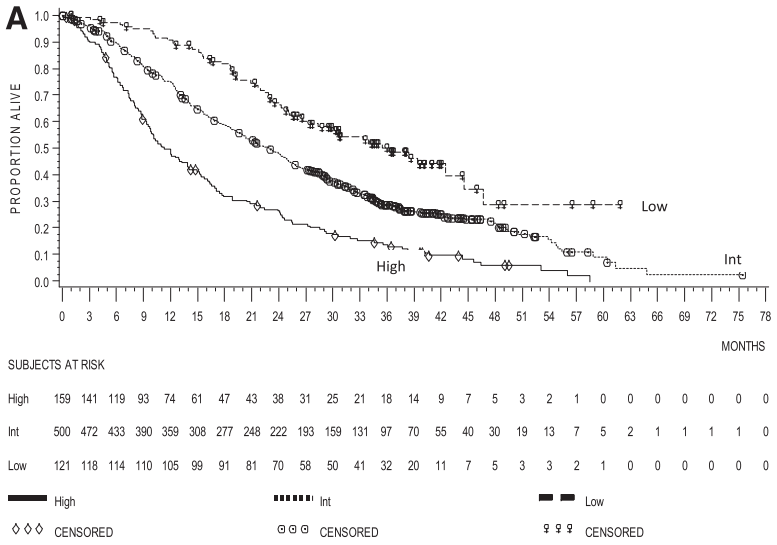
[a]*p* values were generated using Wald tests.
Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ERS, estrogen receptor status; HR, hazard ratio; NA, not assessed.

radiotherapy, prior adjuvant taxane, and number of metastatic sites; for PFS, these were ECOG PS, estrogen receptor status, progesterone receptor status, prior adjuvant taxane, time since diagnosis, and number of metastatic sites. These factors were chosen for further multivariate analysis using the stepwise multivariate Cox proportional hazards modeling. As a result, race, ECOG PS, estrogen receptor status, prior radiotherapy, prior adjuvant taxane, and number of metastatic sites were significant at $p < .05$ for OS, and ECOG PS, estrogen receptor status, prior adjuvant taxane, and number of metastatic sites were significant at $p < .05$ for PFS (Table 3).

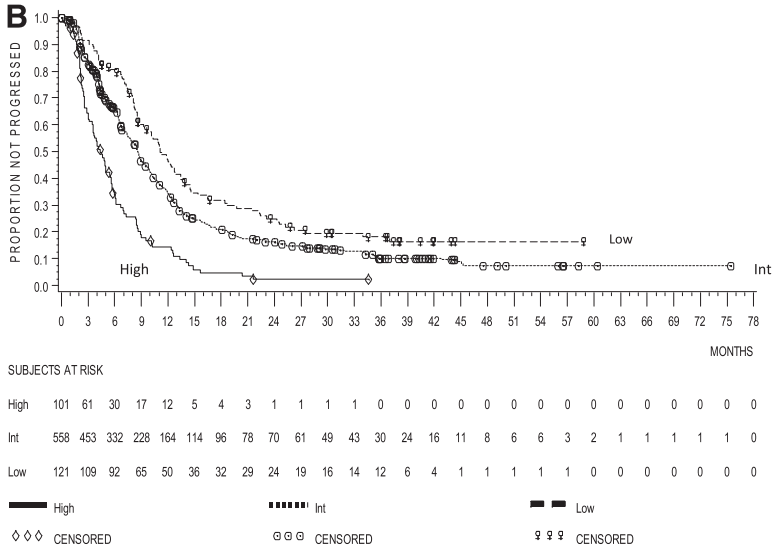
A multivariate prognostic model was constructed by incorporating all identified adverse prognostic factors. The prognostic factors were grouped according to the criteria shown in supplemental online Table 1. For OS, the low-risk group ($n = 121$) had none or one negative prognostic factor, the intermediate-risk group ($n = 500$) had two or three negative prognostic factors, and the high-risk group ($n = 159$) had four to six negative prognostic factors; for PFS, the low-risk group ($n = 121$) had no negative prognostic factors, the intermediate-risk group ($n = 558$) had one or two negative prognostic factors, and the high-risk group ($n = 101$) had three or four negative prognostic factors. The median OS was 11.3 (95% CI, 9.5–14.1) months in the high-risk group, 22.9 (95% CI, 20.3–24.9) months in the intermediate-risk group, and 36.5 (95% CI, 27.5–44.5) months in the low-risk group (Fig. 3A). The median PFS was 4.4 (95% CI, 3.5–5.5) months in the high-risk group, 8.6 (95% CI, 7.8–9.2) months in the intermediate-risk group, and 11.2 (95% CI, 9.3–13.4) months in the low-risk group (Fig. 3B). In all risk groups, the *p* value was <.001 using a stratified log-rank test.

Subgroup Analyses for Prognostic Factors

Figure 4A shows the subgroup analysis for OS. Although there were trends toward a more favorable OS with capecitabine-docetaxel in some subgroups (nonwhite race, ECOG PS >0, estrogen receptor negative, prior radiotherapy, prior taxane usage, one or two metastatic sites, and high-risk group), no interaction tests were statistically significant at the $p = .05$ level (*p* values not shown), suggesting that there is no heterogeneity of treatment effects across the levels of the prognostic factors and two treatment arms. Also, in most subgroups, there were trends toward a more favorable PFS with capecitabine-docetaxel (Fig. 4B). However, with the exception of a possible interaction between metastatic sites and treatment arms (favored capecitabine-docetaxel in patients with one or two vs. more than two metastatic sites;



Group	# Deaths/ # Randomized	Median (95% CI)
High-risk	142/159	11.3 (9.5–14.1)
Intermediate-risk	362/500	22.9 (20.3–24.9)
Low-risk	58/121	36.5 (27.5–44.5)



Group	# Progressed/ # Randomized	Median (95% CI)
High-risk	91/101	4.4 (3.5–5.5)
Intermediate-risk	448/558	8.6 (7.8–9.2)
Low-risk	90/121	11.2 (9.3–13.4)

Figure 3. Kaplan-Meier curves of the risk groups. **(A):** Overall survival. **(B):** Progression-free survival. The stratified log-rank test for both overall survival and progression-free survival risk groups was $p < .001$.

Abbreviations: CI, confidence interval; Int, intermediate.

$p = .026$), interaction tests for other prognostic factors were not statistically significant (p values not shown).

Discussion

Despite improvements in outcomes for patients with MBC, the optimal use of existing chemotherapeutic agents continues to be debated. Gemcitabine and capecitabine in combination with taxanes are routinely used in first-line MBC patients who received prior anthracyclines, but the optimal use of these combinations is unknown. This pooled analysis of two international phase III trials that compared gemcitabine-docetaxel with capecitabine-docetaxel [29, 30]

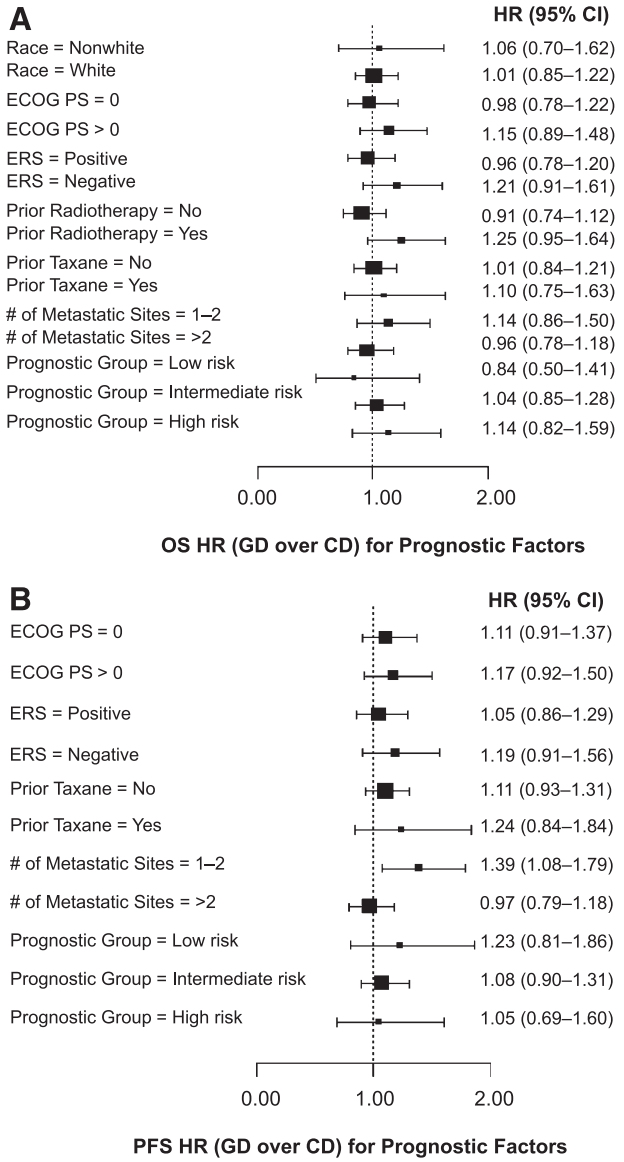


Figure 4. Forest plots. Subgroups were identified using a multivariate Cox model. Squares indicate point estimates; horizontal lines indicate 95% CIs. **(A):** Overall survival. **(B):** Progression-free survival. HR >1 favors CD; HR <1 favors GD. For PFS, Wald $p = .026$ for treatment arm and number of metastatic sites.

Abbreviations: CD, capecitabine-docetaxel; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ERS, estrogen receptor status; GD, gemcitabine-docetaxel; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

was performed to provide guidance for the best use of these agents.

Results obtained with the pooled population confirm the lack of efficacy difference between gemcitabine-docetaxel and capecitabine-docetaxel that had been previously reported for the individual phase III trials [29, 30]. In the pooled population, there were no between-arms differences in OS (HR = 1.02), PFS (HR = 1.15), or ORR ($p = .526$). The median OS (21.5 months) and median PFS (8.5 months) reported here for the pooled gemcitabine-docetaxel arm are at least equivalent to those obtained for the gemcitabine-paclitaxel combination in the registration trial (OS = 18.6 months; TTP = 6.14 months), whereas the ORR for gemcitabine-docetaxel in the pooled population (32.1%) seems lower than that in the registration trial (41.4%) [11]. Here, the capecitabine-docetaxel combination (median OS = 22.0 months; median PFS = 8.5 months) outperformed itself relative to the registration trial (median OS = 14.5 months; median TTP = 6.1 months) [12]. However, patients in the capecitabine registration trial [12] received more prior treatments than patients in the pooled population [29, 30].

Because there was no efficacy difference between gemcitabine-docetaxel and capecitabine-docetaxel in the pooled population, it was of interest to identify subsets of patients that may benefit the most from these regimens. Our data also show that although there were trends toward improved OS and PFS with gemcitabine-docetaxel in the pooled crossover population, the differences between gemcitabine-docetaxel and capecitabine-docetaxel were not statistically significant. A possible explanation is that capecitabine was better tolerated as a single agent than when combined with docetaxel. This is supported by the toxicity profiles of the Chan and Seidman trials; both trials had high rates of toxicity-related discontinuations in the capecitabine-docetaxel arms compared with the gemcitabine-docetaxel arms (Seidman = 28.4% vs. 18.0%; Chan = 27% vs. 13% in the induction phases) [29, 30]. However, this was a post hoc subset analysis, and the usual caveats regarding subset analyses should be noted [34]. It should also be noted that in the crossover population, data for secondary progression (e.g., from crossover to further progression) were not collected in the Chan trial [29], so the induction PFS in the crossover population should be viewed with caution. Given the limitations of this subset analysis, the trends toward improved OS and PFS with gemcitabine-docetaxel suggest that gemcitabine-docetaxel followed by capecitabine might be a preferred sequence option for certain MBC patients and may warrant further evaluation. However, it should be noted that gemcitabine in combination with docetaxel is currently not approved in the U.S., European Union, or China for the treatment of MBC.

Although several prognostic factors were associated with improved outcomes in the overall pooled population, there were no interactions in OS or PFS between gemcitabine-docetaxel and capecitabine-docetaxel and any of the tested prognostic factors, with the possible exception of longer PFS in the capecitabine-docetaxel arm in the subgroup of patients with one or two sites of metastases. This suggests that there is no evidence of benefiting more in either regimen within each level of prognostic factors. Using risk factors identified in a multivariate prognostic model, we categorized patients into low-, intermediate-, and high-risk groups. The high-risk group had worse outcomes (OS and PFS) than the other risk groups. However, no statistically significant interaction was found between treatment arms and risk groups.

These data show that prior adjuvant taxane was a prognostic factor for both OS and PFS. However, it should be noted that in the Seidman trial [30], a large proportion of patients had an unknown adjuvant taxane status (67.8% gemcitabine-docetaxel; 69.5% capecitabine-docetaxel). For the purpose of the pooled analysis, patients with an unknown taxane status were considered to have received no prior adjuvant taxane, but it is possible that this assumption was incorrect for some

patients. Another potential issue with this analysis is that, in the Chan trial, enrolled patients were required to have received one prior anthracycline regimen [29], whereas the Seidman trial did not have this requirement, so a significant proportion of patients had not been exposed to anthracyclines (approximately 42%) [30]. Finally, it should be noted that patients with prior exposure to adjuvant taxanes may acquire drug resistance to taxanes. Thus, non–cross-resistant regimens should be evaluated in those patients toward optimization.

Finally, it should be noted that, with the exception of capecitabine, the drug doses and schedules were identical in the parent trials. The Chan trial used the approved capecitabine dose (1,250 mg/m^2), whereas the Seidman trial used a reduced dose (1,000 mg/m^2) [29, 30]. When used as a component of capecitabine-docetaxel or as monotherapy, the capecitabine dose can be reduced without compromising TTP or OS [35]. Therefore, the efficacy results should not have been affected by using pooled data from the previously described trials [29, 30].

Because the reduced capecitabine dose is associated with a decreased incidence of treatment-related adverse events, particularly hand-foot syndrome, diarrhea, and stomatitis [35], it would not have been appropriate to perform a safety analysis on the pooled population. Nonetheless, based on the parent trials, it is known that gemcitabine-docetaxel and capecitabine-docetaxel have different toxicity profiles; capecitabine-docetaxel is generally associated with higher incidences of grade 3-4 gastrointestinal toxicity, hand-foot syndrome, and mucositis, and gemcitabine-docetaxel is generally associated with more grade 3-4 fatigue, elevated liver enzymes, neutropenia, leukopenia, and thrombocytopenia [29, 30]. Despite these differences, toxicity-related discontinuations in the capecitabine-docetaxel arm (28.4%) were significantly greater ($p = .009$) than in the gemcitabine-docetaxel arm (18.0%) in the Seidman trial [30], which is consistent with toxicity-related discontinuations observed in the Chan trial (capecitabine-docetaxel = 27%; gemcitabine-docetaxel = 13%) [29].

Conclusion

Results from this analysis confirm the lack of efficacy difference between gemcitabine-docetaxel and capecitabine-docetaxel in the pooled population. In addition, there are no efficacy differences between regimens in the crossover population, as well as in almost all examined subpopulations. Several prognostic factors, such as ECOG PS, estrogen receptor status, prior adjuvant taxane, and number of metastatic sites, were associated with both improved OS and PFS in the overall pooled population. The choice of regimen should be guided by the clinical characteristics and tolerance to toxicities of the individual patient.

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