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CLINICAL TRIAL

Ixabepilone plus capecitabine in metastatic breast cancer patients with reduced performance status previously treated with anthracyclines and taxanes: a pooled analysis by performance status of efficacy and safety data from 2 phase III studies

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Abstract Patients with metastatic breast cancer (MBC) previously treated with anthracyclines and taxanes often have decreased performance status secondary to extensive tumor involvement. Here, we report the pooled analysis of efficacy and safety data from two similarly designed phase III studies to provide a more precise estimate of benefit of ixabepilone plus capecitabine in MBC patients with Karnofsky's performance status (KPS) 70–80. Across the studies, anthracycline/taxane-pretreated MBC patients were randomized to receive ixabepilone plus capecitabine or capecitabine alone. Individual patient data for KPS 70–80 subset ($n = 606$) or KPS 90–100 subset ($n = 1349$) from the two studies were pooled by treatment. Analysis included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and safety. In patients with reduced performance status (KPS 70–80), ixabepilone plus capecitabine was associated with improvements in OS (median: 12.3 vs. 9.5 months; HR, 0.75; $P = 0.0015$), PFS (median: 4.6 vs. 3.1 months; HR, 0.76; $P = 0.0021$) and ORR (35 vs. 19%) over capecitabine alone. Corresponding results in patients with high performance status (KPS 90–100) were median OS of 16.7 versus 16.2 months (HR, 0.98; $P = 0.8111$), median PFS of 6.0 versus 4.4 months (HR, 0.58; $P = 0.0009$), and ORR of 45 versus 28%. The safety profile of combination therapy was similar between the subgroups. Ixabepilone plus capecitabine appeared to show superior efficacy compared to capecitabine alone in MBC patients previously treated with anthracyclines and taxanes, regardless of performance status, with a possible OS benefit favoring KPS 70–80 patients (ClinicalTrials.gov identifiers: NCT00080301 and NCT00082433).

Keywords Ixabepilone plus capecitabine · Metastatic breast cancer · Taxane resistance · Karnofsky's performance status · Subset analysis · Overall survival

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Introduction

Breast cancer, a leading cause of morbidity and mortality among women, is estimated to have afflicted 1.3 million women and claimed 465,000 lives worldwide in 2007 [1].

One in every three women initially diagnosed with breast cancer eventually develops locally advanced or metastatic disease [2, 3]. Despite recent advances in treatment, the median survival for patients with metastatic breast cancer (MBC) remains 2–3 years [2, 3]. Chemotherapeutic regimens containing taxanes and anthracyclines are the current standard of care for hormone-refractory MBC, and are being used earlier in the course of the disease with increasing frequency [2–4]. Sequential single-agent therapies including capecitabine, gemcitabine, and vinorelbine are preferred to combination regimens for MBC progressing after anthracyclines and taxanes, with capecitabine being the only approved monotherapy [5–9]. While these agents exhibit antitumor activity in this patient population, none showed a survival benefit either alone or in combination with other drugs [8, 9]. The prognosis is particularly unfavorable for patients with a reduced performance status who are typically more symptomatic and less responsive to treatment than those with a good performance status [10–16]. Patients with Karnofsky's index of performance status (KPS) 70 are unable to carry on normal activity, and patients with KPS 80 are capable of doing normal activity and have some symptoms. In contrast, patients with KPS 90 are able to carry on normal activity and have minor signs or symptoms while patients with KPS 100 have no signs or symptoms of disease. New treatments are needed for patients who progress after anthracyclines and taxanes, particularly for those with a reduced performance status.

Ixabepilone, the first drug in a new class of microtubule stabilizing agents known as epothilones [17–19], showed clinical efficacy in patients with MBC resistant to or pretreated with taxanes and/or anthracyclines [20–22] as well as in patients who progressed after treatment with taxanes, anthracyclines, and capecitabine [23]. Consistent with the synergistic antitumor activity between ixabepilone and capecitabine in preclinical studies [19], two large randomized phase III trials in anthracycline- and taxane-pretreated MBC patients demonstrated that the addition of ixabepilone to capecitabine significantly improved progression-free survival (PFS) and objective response rate (ORR) over capecitabine alone, although no difference in overall survival (OS) was observed [24, 25]. Ixabepilone is approved in several countries including the United States as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients after failure of anthracyclines, taxanes, and capecitabine, or in combination with capecitabine for the treatment of metastatic or locally advanced breast cancer in patients after failure of anthracyclines and taxanes [26, 27].

Since performance status is a well established indicator of prognosis and treatment efficacy [10, 11, 14–16], original protocols in the above phase III studies stipulated the analysis of many subsets including those with KPS 70–80 and KPS 90–100. Similar study designs and patient characteristics between the two studies allowed the pooling of individual patient data in each subgroup for more precise estimates of efficacy. This report presents subset analyses performed on these two KPS subgroups in individual studies as well as on patients pooled from the two studies. Our present results represent the largest dataset addressing the response of symptomatic KPS 70–80 patients to specific chemotherapy regimens.

Methods

Patients

A total of 1,973 patients was enrolled across the two international, randomized, open-label, phase III studies: 752 patients in the anthracycline/taxane (A/T)-resistant study and 1,221 in the A/T-pretreated study. Patient eligibility criteria and treatment status for both studies were described [24, 25]. Briefly, women 18 years or older with metastatic breast cancer pretreated with or resistant to anthracyclines and taxanes were eligible. Taxane resistance was defined as tumor progression during treatment or within 4 months of last dose in the metastatic setting, or recurrence within 12 months in the neoadjuvant or adjuvant setting. Taxane resistance and measurable disease were mandatory for the A/T-resistant study, but not for the A/T-pretreated study. Up to three prior lines of chemotherapy in the A/T-resistant study and up to two prior lines in the A/T-pretreated study were allowed. Entry criteria in each study required a KPS score of 70 or higher. KPS was assessed by treating physicians prior to randomization.

Studies were conducted in accordance with the declaration of Helsinki and related amendments. The protocol was approved by the institutional review boards of participating institutions, and all patients provided written informed consent before enrollment.

Treatment

In both studies, patients were randomly assigned to receive, in a 21-day cycle, either ixabepilone 40 mg/m^2 as a 3-h intravenous infusion on day 1, plus oral capecitabine 1,000 mg/m^2 twice daily on days 1 through 14, or oral capecitabine alone 1,250 mg/m^2 twice daily on days 1 through 14. Treatment was continued until disease progression, death or unacceptable toxicity. Doses were reduced, delayed, or discontinued based on tolerability as described [24, 25]. Patients were allowed to receive additional therapy after discontinuation of study treatments.

Efficacy measurements

The endpoints in each study were PFS, OS, and ORR. The primary endpoints were PFS in the A/T-resistant study and OS in the A/T-pretreated study. The secondary endpoints were OS and ORR in the A/T-resistant study, and PFS and ORR in the A/T-pretreated study. In the A/T-pretreated study, the analysis of PFS and ORR was prospectively limited to patients with measurable disease at baseline. This was due to the limitations in assessing progression in patients with non-measurable disease and less frequent tumor assessments. ORR and PFS were assessed for all randomized patients in the A/T-resistant study and for randomized patients with measurable disease in the A/T-pretreated study, whereas OS data were assessed for all randomized patients in both studies. PFS and ORR data were assessed by both investigators and Independent Radiology Review Committee in the A/T-resistant study, and only by investigators in the A/T-pretreated study. In the A/T-resistant study, results from investigator assessments were consistent with those from Independent Radiology Review [24]. To ensure consistency, only investigator-assessed data are presented in this report. The data for OS were matured with greater than 75% of patients having deaths reported. Patients who were alive at the time of the analysis had a median follow-up of approximately 2 years.

Safety assessment

All patients who received study drug were evaluated for safety. Adverse events and laboratory abnormalities were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.

Data analysis

In each study, the KPS 70–80 subgroup consisted of patients with a KPS score of either 70 or 80, while the KPS 90–100 subgroup included patients with a KPS score of either 90 or 100. Individual patient data in each subgroup from the two studies were pooled. Data analysis for each subgroup was performed on pooled patients as well as on patients in individual studies. PFS, OS, and median time of resolution of peripheral neuropathy were estimated using Kaplan–Meier product limit method. Cox proportional hazards models, stratified by study, were used to calculate hazard ratios (HR) for PFS and OS. All P values were two-sided. KPS was not a stratification factor at randomization in either of the studies. Nominal log-rank P values presented here were not adjusted for multiple comparisons, and should be interpreted with caution.

Results

Patient baseline characteristics

Of 1,955 patients with KPS scores of 70 to 100 across the two studies, 31% ($N = 606$) were pooled into the KPS 70–80 and 69% ($N = 1349$) into the KPS 90–100 subgroup. Baseline patient characteristics in each pooled subgroup were well matched between the two treatment arms (Table 1). Patient age, adjuvant treatment, visceral disease, and tumor receptor status were similar between the two subgroups. Nearly 70% of patients in each subgroup were taxane resistant, and all patients were previously treated with anthracyclines and taxanes. However, more patients in the KPS 70–80 subgroup than in the KPS 90–100 subgroup received two or more prior metastatic regimens (35 vs. 25%) or had 2 or more metastatic organ sites (56 vs. 45%). Ten percent of the KPS 70–80 subgroup and 17% of the KPS 90–100 subgroup received study therapy as first-line treatment for metastatic disease. Most of the remaining patients in both subgroups (81–89%) received study therapy as second- or third-line treatment.

Efficacy in patients with KPS 70–80

In pooled patients with KPS 70–80, the addition of ixabepilone to capecitabine increased the median PFS by 1.5 months over capecitabine alone (4.6 vs. 3.1 months) with a 24% reduction of the estimated risk of disease progression (HR, 0.76; $P = 0.0021$) (Table 2; Fig. 1a). Consistent improvements in PFS were observed in the KPS 70–80 patients in the A/T-resistant study (4.2 vs. 2.7 months; HR, 0.78) and the A/T-pretreated study (5.6 vs. 3.9 months; HR, 0.74).

In the pooled KPS 70–80 subgroup, the combination increased ORR substantially over capecitabine alone (35 vs. 19%). Consistent ORR increases with the combination compared to capecitabine alone were seen in the KPS 70–80 patients in both A/T-resistant (36 vs. 16%) and A/T-pretreated (37 vs. 25%) studies (Table 2).

In the pooled KPS 70–80 subgroup, the median OS with ixabepilone plus capecitabine was 12.3 and 2.8 months longer than that seen with capecitabine alone (9.5 months) (Table 2; Fig. 1b). This survival benefit was associated with a HR of 0.75, corresponding to a 25% reduction of the estimated risk of death ($P = 0.0015$). The survival curves were separated early and maintained the separation over time (Fig. 1b). The 12-month survival rate was 50% with the combination and 40% with capecitabine alone. Consistent with the pooled results, the OS differences between the two regimens in KPS 70–80 patients were 2.3 months (HR, 0.75) in the A/T-resistant study and 2.7 months (HR, 0.76) in the A/T-pretreated study (Table 2).

Table 1 Baseline patient characteristics of pooled KPS subgroups

Characteristics	KPS 70–80		KPS 90–100	
	Ixa + Cape $N = 314$	Cape $N = 292$	Ixa + Cape $N = 659$	Cape $N = 690$
Age, years				
Median	54	54	53	53
Range	26–78	25–79	23–77	24–81
Prior neoadjuvant/adjuvant, %				
0	27	27	24	25
1	69	69	71	72
2	4	3	5	3
Prior metastatic regimens, %				
0	9	12	18	16
1	55	55	57	60
2	34	30	24	23
≥3	2	3	1	1
Taxane resistant, %	68	72	69	65
Extent of disease, %				
≥2 disease sites	55	56	46	43
Visceral disease (liver and/or lung)	71	72	70	70
Receptor status, %				
HER2+	10	15	17	16
HER2−/unknown	90	85	83	84
ER+	54	49	52	53
ER−/other	46	51	48	47
Triple negative (ER−, PR−, HER2−)	20	24	22	23

KPS Karnofsky's performance score, *Ixa* ixabepilone, *Cape* capecitabine, *HER2* epidermal growth factor receptor-2, *ER* estrogen receptor, *PR* progesterone receptor

Table 2 Efficacy of ixabepilone plus capecitabine versus capecitabine alone in KPS 70–80 patients

Response	Patient population					
	Pooled		A/T-resistant		A/T-pretreated	
	Ixa + Cape	Cape	Ixa + Cape	Cape	Ixa + Cape	Cape
Progression-free survival[a]						
No. of patients	268	257	119	136	149	121
Median, months	4.6	3.1	4.2	2.7	5.6	3.9
95% CI	4.2–5.6	2.7–3.9	3.3–4.7	1.7–3.3	4.3–6.8	2.8–4.8
Hazard ratio	0.76		0.78		0.74	
95% CI	0.64–0.90		0.6–1.0		0.58–0.95	
Log-rank P[b]	0.0021		NC		NC	
Tumor response[a]						
No. of patients	268	257	119	136	142	115
ORR	35	19	36.0	16.0	37.0	25.0
95% CI	30–42	15–25	28–45	10–24	29–46	18–34
Overall survival[c]						
No. of patients	314	292	119	136	195	156
Median, months	12.3	9.5	10.1	7.8	14.0	11.3
95% CI	10.5–14.0	7.9–11.1	7.6–12.2	5.8–9.4	11.6–15.6	9.1–13.6
Hazard ratio	0.75		0.75		0.76	
95% CI	0.63–0.90		0.58–0.98		0.60–0.96	
Log-rank P[b]	0.0015		NC		NC	

KPS Karnofsky's performance score, *A/T* anthracycline and taxane, *Ixa* ixabepilone, *Cape* capecitabine, *NC* not calculated

[a] Computed using investigator assessment data on all randomized patients in the A/T-resistant study and on patients randomized to measurable disease stratum in the A/T-pretreated study, [b] Not adjusted for multiple comparisons, [c] Computed using investigator assessment data on all randomized patients in the A/T-resistant and A/T-pretreated studies

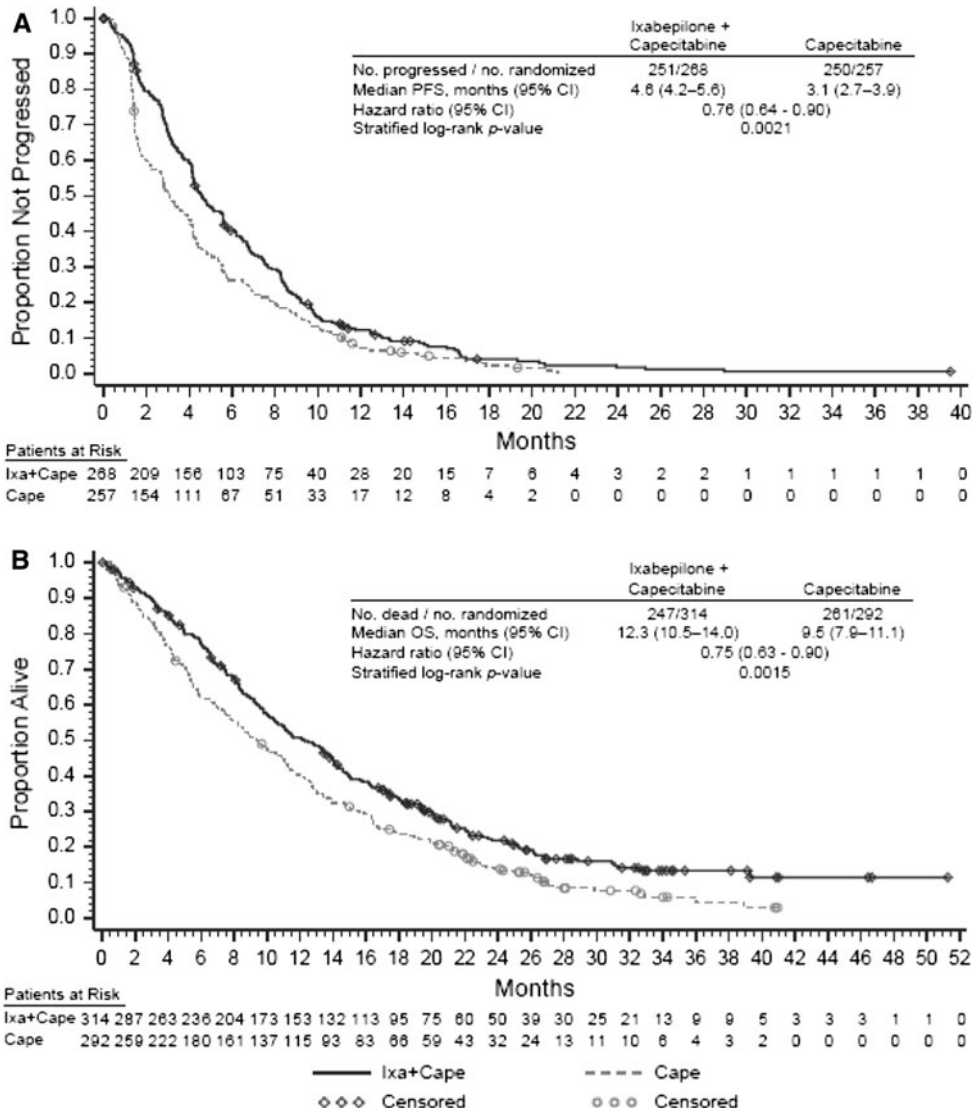

Fig. 1 Kaplan–Meier analysis of progression-free survival (**a**) and overall survival (**b**) in Pooled KPS 70–80 Patients. For progression-free survival analysis, patients who neither progressed nor died were censored on the date of last assessment. For overall survival analysis, patients who had not died or were lost to follow-up were censored on the last date they were known to have been alive. *Ixa* ixabepilone, *Cape* capecitabine

Efficacy in patients with KPS 90–100

Improvements in PFS and ORR were similar between the two subgroups. In the pooled KPS 90–100 subgroup, the combination prolonged median PFS by 1.6 months over capecitabine alone (6.0 vs. 4.4 months) with a 42% reduction of the estimated risk of disease progression (HR, 0.58; $P = 0.0009$) (Table 3; Fig. 2a). Consistent improvements in PFS were observed in the KPS 90–100 patients across individual studies (Table 3).

Consistent increases in ORR with the combination compared to capecitabine alone were observed in the pooled KPS 90–100 patients (45 vs. 28%) and in the KPS 90–100 patients across individual studies (Table 3).

Across both arm, the median OS values were higher in the KPS 90–100 subgroup were longer than the KPS 70–80 subgroup (Table 3; Fig. 2b). No difference in OS was seen between the treatment arms in the pooled KPS 90–100 subgroup (HR, 0.98; $P = 0.8111$), or in the KPS 90–100 patients in individual studies (Table 3).

Safety

Both subgroups experienced increased toxicity with the combination, reflecting the known side effects of the individual agents (Table 4). Myelosuppression was common in the combination arm with virtually identical profiles between the two subgroups. The most frequent grade 3–4 events were leukopenia (60–61%) and neutropenia (70–72%) with a 5–8% incidence of febrile neutropenia. Anemia and thrombocytopenia were mostly grade 1–2 in both treatment arms.

The pattern and frequency of non-hematologic adverse events were similar between the two subgroups. The two most frequent grade 3–4 non-hematologic adverse events were peripheral neuropathy (combination arm) and hand-

Table 3 Efficacy of ixabepilone plus capecitabine versus capecitabine alone in KPS 90–100 patients

Response	Patient population					
	Pooled		A/T-resistant		A/T-pretreated	
	Ixa + Cape	Cape	Ixa + Cape	Cape	Ixa + Cape	Cape
Progression-free survival[a]						
No. of patients	576	594	253	237	323	357
Median, months	6.0	4.4	5.6	4.2	6.3	5.3
95% CI	5.6–6.6	4.2–5.3	4.8–6.6	3.8–4.6	5.6–7.2	4.2–5.6
Hazard ratio	0.82		0.81		0.83	
95% CI	0.73–0.92		0.67–0.97		0.71–0.96	
Log-rank P[b]	0.0009		NC		NC	
Tumor response[a]						
No. of patients	576	594	253	237	314	345
ORR	45	28	45.0	27.0	46.0	30.0
95% CI	41–49	24–32	39–52	21–33	41–52	25–35
Overall survival[c]						
No. of patients	659	690	253	237	406	453
Median, months	16.7	16.2	14.1	14.1	18.1	17.9
95% CI	14.6–17.9	14.9–17.8	12.4–15.3	11.8–16.1	16.3–19.8	15.9–20.2
Hazard ratio	0.98		1.01		0.97	
95% CI	0.87–1.12		0.83–1.22		0.82–1.14	
Log-rank P[b]	0.8111		NC		NC	

KPS Karnofsky's performance score, *A/T* anthracycline and taxane, *Ixa* ixabepilone, *Cape* capecitabine, *NC* not calculated

[a] Computed using investigator assessment data on all randomized patients in the A/T-resistant study and on patients randomized to measurable disease stratum in the A/T-pretreated study, [b] Not adjusted for multiple comparisons, [c] Computed using investigator assessment data on all randomized patients in the A/T-resistant and A/T-pretreated studies

foot syndrome (combination and capecitabine alone arms). The rates of grade 3–4 hand-foot syndrome, a known side-effect of capecitabine, were similar between the combination (15%) and capecitabine (16%) arms among KPS 70–80 patients, as well as among KPS 90–100 patients (22 and 20%, respectively). Peripheral neuropathy in patients receiving the combination occurred with similar frequencies for both KPS 70–80 (all grades, 64%) and KPS 90–100 (all grades, 68%), and was predominantly sensory and mostly grade 1–2. Grade 3–4 sensory neuropathy occurred in 22% of KPS 70–80 patients including 1.6% grade 4 events ($n = 5$) and in 22% of KPS 90–100 patients including 0.3% grade 4 events ($n = 2$). In patients treated with the combination, 6 deaths (1.9%) in the KPS 70–80 subgroup and 8 (1.2%) in the KPS 90–100 subgroup were attributed to the treatment. The corresponding numbers in patients treated with capecitabine alone were 1 (0.3%) and 3 (0.4%), respectively.

The rates of resolution of grade 3–4 neuropathy to baseline or grade 1 following dose reduction, interruption, or discontinuation were high for both KPS 70–80 (81%) and KPS 90–100 (90%). The resolution occurred rapidly with median times of 7.3 weeks (95% CI, 5.0–10.0) for KPS 70–80 and 5.6 weeks (95% CI, 4.9–7.1) for KPS 90–100.

Pooled KPS 70–80 patients received a median of 5 cycles in the combination arm, and a median of 4 cycles in the capecitabine arm while the pooled KPS 90–100 subgroup received a median of 6 cycles in each treatment arm (Table 5). Adverse events were generally managed by dose modifications. Proportions of patients on combination therapy requiring a dose reduction of at least one agent were similar between KPS 70–80 (62%) and KPS 90–100 (64%), as were for patients on capecitabine alone (35 and 43%, respectively) (Table 5). In the combination arm, dose reductions due to peripheral neuropathy were also similar between KPS 70–80 (17%) and KPS 90–100 (18%).

At the time of the analysis, all patients except one KPS 70–80 and 3 KPS 90–100 patients were off-treatment. The reasons for treatment discontinuation were similar between the two KPS subgroups with progressive disease/relapse being the main reason (Table 4).

Subsequent therapy

In the pooled KPS 70–80 subset, 70% of patients in the combination arm and 67% in the capecitabine arm received subsequent therapy whereas 83% of the KPS 90–100

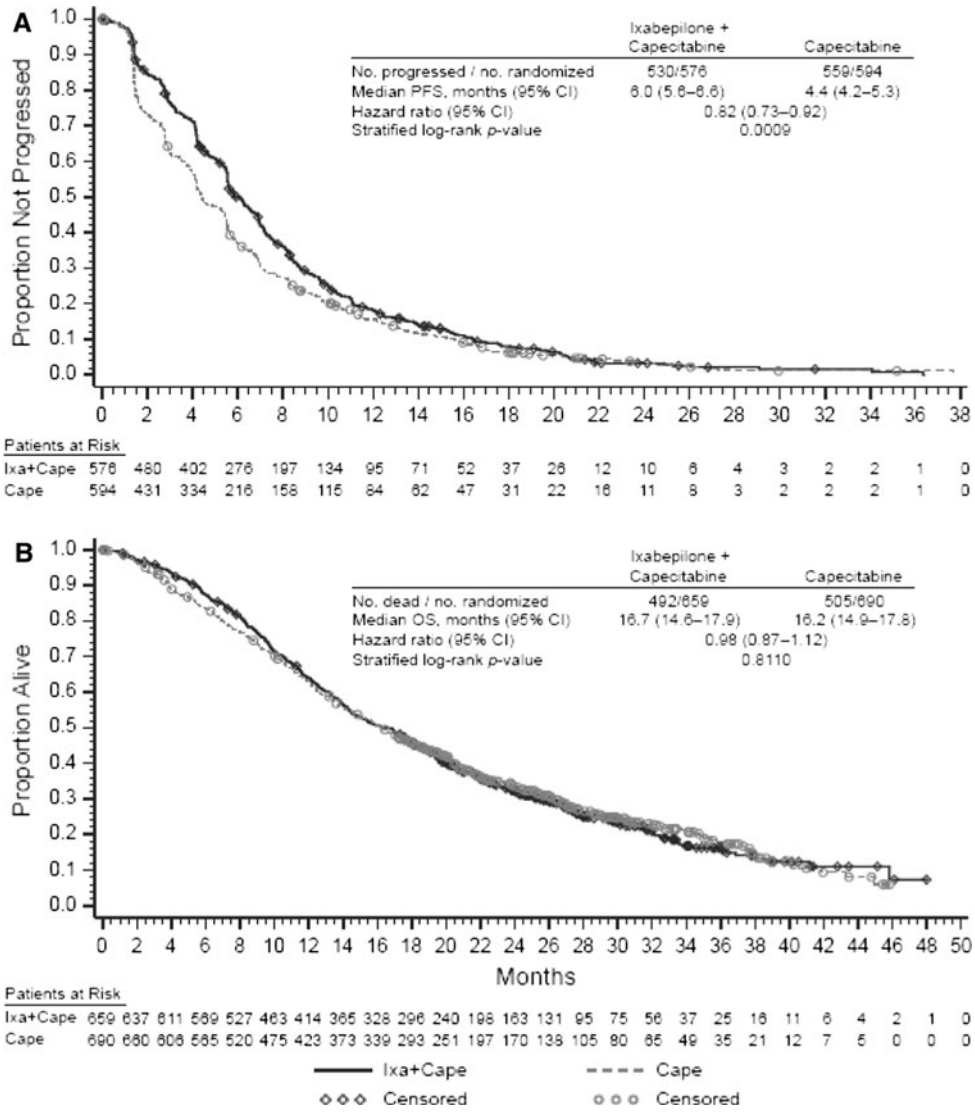

Fig. 2 Kaplan–Meier analysis of progression-free survival (**a**) and overall survival (**b**) in Pooled KPS 90–100 Patients. For progression-free survival analysis, patients who neither progressed nor died were censored on the date of last assessment. For overall survival analysis, patients who had not died or were lost to follow-up were censored on the last date they were known to have been alive. *Ixa* ixabepilone, *Cape* capecitabine

patients in each arm received subsequent therapy (Table 6). The rates of subsequent taxane use in the combination and capecitabine alone arms were lower for the KPS 70–80 patients (13 and 18%, respectively) than for the KPS 90–100 patients (18 and 26%, respectively).

Discussion

The subset analyses presented here suggest that, in MBC patients previously treated with anthracyclines and taxanes who are symptomatic with KPS 70–80, the addition of ixabepilone to capecitabine improves PFS, OS, and ORR over capecitabine alone in each of the two studies. These improvements are confirmed by the analysis of pooled data from 606 patients with KPS 70–80. In this pooled population, the combination increased median OS by 2.8 months with a 25% reduction in the risk of death ($P = 0.0015$), suggesting a clinically meaningful OS benefit.

Although the present analyses were aimed at comparing the efficacy of the two treatment modalities in each of the two KPS subgroups, and not between the subgroups, they revealed some differences in treatment effect between the subgroups. For instance, OS and PFS observed in each treatment arm were lower in patients with KPS 70–80 than in those with KPS 90–100, a finding consistent with the prognostic value of performance status. Notably, despite clinically meaningful improvements in PFS and ORR in the KPS 90–100 subgroup by the addition of ixabepilone to capecitabine, there was no difference in OS between the treatments. These results for KPS 90–100, like those for KPS 70–80, were consistently seen across A/T-resistant and A/T-pretreated studies and the pooled patients. Additionally, both A/T-resistant and A/T-pretreated studies demonstrated consistent benefit in PFS and ORR across several other subsets of sufficient size [24, 25].

It is unclear why the OS difference was observed for KPS 70–80 and not for KPS 90–100. Both subgroups were

Table 4 Selected adverse events and treatment discontinuation in pooled KPS subgroups

Event	KPS 70–80				KPS 90–100			
	Ixa + Cape $N = 310$		Cape $N = 288$		Ixa + Cape $N = 647$		Cape $N = 679$	
	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4
Hematologic adverse event, %[a]								
Neutropenia	91	71	41	11	91	72	48	9
Leukopenia	95	60	52	7	93	61	58	7
Anemia	93	11	76	7	88	5	67	3
Thrombo-cytopenia	62	9	32	6	55	6	31	2
Febrile neutropenia	8	8	1	1	5	5	<1	<1
Non-hematologic adverse event, %								
Any PN	64	23	16	1	68	24	20	1
Sensory PN	62	22	15	0	67	22	20	1
Motor PN	14	5	1	1	11	4	1	0
HFS	60	15	56	16	67	22	70	20
Fatigue	37	11	19	5	44	11	23	2
Diarrhea	41	7	39	9	44	6	39	9
Myalgia	23	5	2	0	29	6	3	<1
Anthralgia	16	3	3	<1	18	3	1	0
Stomatitis	17	2	9	1	20	2	12	1
Toxic death, %	1.9		0.3		1.2		0.4	
Treatment discontinuation, %								
Total	100		99.7		99.7		99.9	
Key reasons								
PD/relapse	50.8		64.8		51.5		70.2	
Drug toxicity	23.2		8.0		26.7		9.7	
Patient request	9.6		4.5		7.1		4.3	
Physician choice	6.4		5.9		6.8		7.7	
Death	2.3		5.6		2.0		1.5	

KPS Karnofsky's performance score, *A/T* anthracycline and taxane, *Ixa* ixabepilone, *Cape* capecitabine, *PN* peripheral neuropathy, *HFS* hand-foot syndrome, *PD* progressive disease

[a] In the KPS 70–80 subgroup, $n = 305$ in the Ixa + Cape arm and $n = 284$ in the Cape only arm

not different in median age, taxane resistance, and receptor status. However, patients with KPS 70–80 had more extensive prior chemotherapy and higher burden of baseline disease than those with KPS 90–100, factors likely to have contributed to the reduced performance status at baseline. Although improvements in ORR were similar between the two subgroups, it may be speculated that cytoreduction induced by ixabepilone is more beneficial in the setting of high disease burden. Additional therapy subsequent to completion of study treatment was received by more patients with KPS 90–100 (83%) than with KPS 70–80 (67–70%) and might have obscured the OS difference in the KPS 90–100 subgroup. The potential negative impact of post-study therapy on detecting OS differences even in earlier stages of the disease is illustrated by the failure to demonstrate a survival advantage in six of eight randomized trials evaluating anthracycline–taxane combinations for the first-line treatment of MBC [28]. It is also possible that, because of poor prognosis, patients with KPS 70–80 derived little or no OS benefit from subsequent therapy.

No chemotherapy has, heretofore, demonstrated an OS improvement in MBC patients whose tumors have progressed after anthracyclines and taxanes. In A/T-resistant and A/T-pretreated studies, statistically significant increases in PFS and ORR in the overall population were associated with OS improvements that did not reach statistical significance [24, 25]. Three other phase III randomized studies evaluating combination regimens bevacizumab plus capecitabine [29], lapatinib plus capecitabine [30], and gemcitabine plus vinorelbine [31] in anthracycline- and taxane-pretreated MBC patients reported to date failed to show a difference in OS. None of these three studies addressed patient subsets based on performance status.

Table 5 Dose exposure and reduction in pooled KPS subgroups

	KPS 70–80			KPS 90–100		
	Ixa + Cape		Cape	Ixa + Cape		Cape
Exposure						
No. of patients	310		288	647		679
Median no. of cycles	5.0		4.0	6.0		6.0
Range	1–44		1–43	1–39		1–50
Dose reduction[a]						
No. of patients	280		249	611		628
At least one reduction, %	62.1		35.3	64.0		42.7
Reason for first reduction, %						
Reduced agents	Ixa	Cape	Cape	Ixa	Cape	Cape
Hematologic toxicity	17.5	1.4	1.6	14.6	3.6	1.3
Peripheral neuropathy	17.1	0	0	18.2	0	0
Other non-hematologic toxicity	14.3	37.1	32.1	13.7	41.2	39.5

KPS Karnofsky's performance score, *Ixa* ixabepilone, *Cape* capecitabine

[a] Computed on patients who received at least two courses of study therapy and who had at least one drug from the combination regimen reduced once during the treatment

Table 6 Subsequent therapy in pooled KPS subsets

Therapy	Percentage of patients			
	KPS 70–80		KPS 90–100	
	Ixa + Cape $N = 314$	Cape $N = 292$	Ixa + Cape $N = 659$	Cape $N = 690$
Any therapy	70	67	83	83
Chemotherapy	56	56	67	74
Paclitaxel	7	14	11	17
Docetaxel	6	5	7	9

KPS Karnofsky's performance score, *Ixa* ixabepilone, *Cape* capecitabine

However, a recent phase III study comparing taxane-based regimens as first-line therapy for MBC previously treated with adjuvant anthracyclines demonstrated a significant OS difference between weekly paclitaxel and 3-weekly paclitaxel plus carboplatin in favor of weekly paclitaxel for patients with European Cooperative Oncology Group-performance status (ECOG-PS) of 1 (HR = 0.50, $P = 0.007$), but not for those with ECOG-PS of 0 (HR = 0.99, $P = 0.96$) [32]. These results combined with our current findings suggest that MBC patients with a reduced performance status may experience an OS benefit from certain combination regimens.

The present OS findings based on a reasonably large number of patients, while compelling, should be considered hypothesis-generating, because of the limitations associated with the present analyses. First, these are retrospective subset analyses; although analyses of subsets characterized by KPS scores were stipulated in the original study protocols, no formal statistical comparisons adjusted for multiplicity were planned. Second, the data were pooled from the studies with OS being the primary endpoint in one and a secondary endpoint in the other. However, OS results in the pooled patients were consistent with those in patients from individual studies. Third, although the patient populations from the two studies were generally similar, the differences did exist in terms of disease burden and prior chemotherapy. Fourth, while investigator-assessed data in patients with measurable disease were used for PFS and ORR analyses, the OS analysis included all randomized patients. Finally, patients were not stratified by KPS scores at randomization and *P* values showing statistical significance were not adjusted for multiplicity, thus warranting caution in interpretation.

Addition of ixabepilone to capecitabine increased toxicity in a manner reflective of known toxicities of the individual agents in both KPS subgroups. Combination therapies are considered to put patients with a reduced performance status at a greater risk of toxicity [5, 6]. It is, therefore, notable that the safety profile of ixabepilone combination in KPS 70–80 patients was virtually identical to that in KPS 90–100 patients in terms of patterns, frequencies, severity, and manageability. While the median number of treatment courses for the combination was lower for KPS 70–80 (5 cycles) than for KPS 90–100 (6 cycles), both subgroups had similar dose reduction and treatment discontinuation due to toxicity. Grade 3–4 neuropathy was moderately high (22%). Notably, resolution of grade 3–4 neuropathy appeared to have occurred at a lower rate (81 vs. 90%) and took longer (median resolution time of 7.3 vs. 5.6 weeks) in KPS 70–80 patients compared to those with KPS 90–100. Death due to toxicity from the combination treatment seemed to have occurred more frequently in patients with KPS 70–80 than in those with KPS 90–100 (1.9 vs. 1.2%). Of note, both studies excluded patients with grade 2 or higher alanine aminotransferase, aspartate aminotransferase, and bilirubin levels because of an association between baseline-elevated liver enzymes and toxicity [24, 25]. Therefore, these results may not necessarily reflect safety findings in all patients with reduced performance.

The patient population represented by KPS 70–80 patients described here needs more effective therapies, because of high tumor burden, short survival, and limited treatment options. The present results suggest that the KPS 70–80 patients with progressive disease after anthracyclines and taxanes may experience a meaningful clinical benefit from the addition of ixabepilone to capecitabine and support the hypothesis that this combination may prolong OS in this population. These results provide a rationale for

investigating this combination in prospectively designed trials in MBC patients who are refractory to anthracyclines and taxanes and have a reduced performance status.

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Conflicts of interest Henri Roche, Pierfranco Conte, and Joseph Sparano have served as consultants for and received honoraria from Bristol-Myers Squibb; Edith A. Perez and Binghe Xu have nothing to declare; Jacek Jassem has served as a consultant for Bristol-Myers Squibb**;** Ronald Peck and Thomas Kelleher are employees of Bristol-Myers Squibb and own shares of Bristol-Myers Squibb stock**;** Gabriel N. Hortobagyi has served as a consultant for Bristol-Myers Squibb, Novartis, and Sanofi-Aventis, and received research funding from Novartis.

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