

***nab*-Paclitaxel for first-line treatment of patients with metastatic breast cancer and poor prognostic factors: a retrospective analysis**

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Abstract Nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) has demonstrated clinical benefit in metastatic breast cancer (MBC) in a randomized phase III trial versus paclitaxel (CA012; $N = 454$) and in a randomized phase II trial versus docetaxel (CA024; $N = 300$). This retrospective analysis examines whether patients with poor prognostic factors demonstrate similar outcomes to the intent-to-treat (ITT) populations in these trials. This retrospective analysis evaluated the efficacy and safety of previously untreated patients with MBC with the following poor prognostic factors: visceral dominant metastases and short disease-free interval (DFI; ≤ 2 years). In CA012 ($n = 186$ first-line patients), *nab*-paclitaxel demonstrated a significantly higher overall response rate (ORR) versus paclitaxel in patients with visceral dominant metastases (42 vs. 23 %; $P = 0.022$), whereas the higher ORR for *nab*-paclitaxel in patients with a short DFI (43 vs. 33 %; $P = \text{NS}$) was not statistically significant. In CA024, a significantly higher

ORR for *nab*-paclitaxel 150 mg/m² versus docetaxel was observed in patients with visceral dominant metastases (76 vs. 37 %; $P < 0.001$). No significant differences in ORR were observed in patients with a short DFI. Although progression-free survival (PFS) and overall survival showed trends similar to ORR, statistical significance was only achieved for comparisons of PFS in patients with visceral dominant metastases in CA024 (13.1 months for *nab*-paclitaxel 150 mg/m² vs. 7.8 months for docetaxel [$P = 0.019$] and 7.5 months for *nab*-paclitaxel 100 mg/m² [$P = 0.010$]). Safety results were similar to previous reports of the ITT populations. *nab*-Paclitaxel demonstrated similar efficacy in patients with poor prognostic factors as in the ITT populations of these two trials. In each trial, ORR was significantly higher for *nab*-paclitaxel versus the comparator taxane among patients with visceral dominant metastases.

Keywords *nab*-Paclitaxel · Visceral disease · Metastatic breast cancer · Taxanes

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Introduction

Breast cancer has the highest incidence and second-highest mortality rate of any cancer in women worldwide [1]. Only lung cancer kills more women each year [1]. Although breast cancer mortality has declined over the last two decades [1, 2], approximately 30 % of women initially diagnosed with an earlier stage of breast cancer will develop metastatic disease, which remains essentially incurable [3]. Therefore, treatments that provide clinical benefit among these patients will continue to be sought. Although the 5-year survival rate for patients diagnosed with metastatic breast cancer (MBC) remains less than

25 % [2], a number of factors predict poor survival, including previous adjuvant chemotherapy, estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status, short disease-free interval (DFI), the number of metastatic lesions, site(s) of recurrence, and visceral involvement [4–8].

Taxanes have proven to be one of the most active classes of antitumor agents for MBC [3]. The evolution of taxane approval for the treatment of MBC began with paclitaxel in 1994, continued with docetaxel (Taxotere) in 1996, and most recently included nanoparticle albumin-bound (*nab*-) paclitaxel (Abraxane) in 2005 [9]. The activity of taxane monotherapy in patients with MBC who have one or more poor prognostic factors has been well documented, both in the first-line setting and in the context of progressive/resistant disease [10–12].

nab-Paclitaxel was developed to take advantage of the antitumor activity of paclitaxel while decreasing or eliminating the toxicities typically associated with the solvent (Cremophor® EL) used to administer the most common formulation of paclitaxel [13–15]. Results from the phase III trial ($N = 454$) that led to the approval of *nab*-paclitaxel demonstrated that *nab*-paclitaxel at 260 mg/m² every 3 weeks (q3w) achieved a higher overall response rate (ORR; 33 vs. 19 %; $P = 0.001$) and a longer time to tumor progression (23.0 vs. 16.9 weeks; HR 0.75; $P = 0.006$) compared with paclitaxel at 175 mg/m² q3w in patients with MBC who were treated in the \geq first-line setting [14]. Among patients who received \geq second-line treatment for MBC, the median overall survival (OS) for *nab*-paclitaxel was significantly greater than that of paclitaxel (56.4 vs. 46.7 weeks; $P = 0.024$). Grade 4 neutropenia was less frequent among patients who received *nab*-paclitaxel (9 vs. 22 %; $P < 0.001$), but grade 3 sensory neuropathy occurred at a higher rate (10 vs. 2 %; $P < 0.001$).

In order to evaluate the activity of *nab*-paclitaxel in a first-line MBC population and explore whether a weekly schedule might offer favorable clinical outcomes relative to the approved q3w schedule, a randomized phase II trial ($N = 300$) was conducted [16]. Patients received one of the following treatments: *nab*-paclitaxel 300 mg/m² q3w, 100 mg/m² the first 3 of 4 weeks (qw 3/4), or 150 mg/m² qw 3/4 or docetaxel at 100 mg/m² q3w. This study demonstrated superior efficacy and safety of weekly *nab*-paclitaxel compared with docetaxel. *nab*-Paclitaxel 150 mg/m² qw 3/4 had the highest investigator-assessed ORR (74 vs. 46 % for *nab*-paclitaxel 300 mg/m² q3w [$P = 0.002$], 63 % for *nab*-paclitaxel 100 mg/m² qw 3/4 [P not statistically significant, NS], and 39 % for docetaxel [$P < 0.001$]). *nab*-Paclitaxel 150 mg/m² qw 3/4 also demonstrated the longest investigator-assessed progression-free survival (PFS; 14.6 vs. 10.9 months for *nab*-paclitaxel 300 mg/m² q3w [$P = \text{NS}$], 7.5 months for *nab*-paclitaxel 100 mg/m²

qw 3/4 [$P = 0.001$], and 7.8 months for docetaxel [$P = 0.012$]). Patients who received *nab*-paclitaxel at 150 mg/m² qw 3/4 also had the longest median OS (overall $P = 0.047$): 33.8 months vs. 27.7, 22.2, and 26.6 months in patients who received *nab*-paclitaxel 300 mg/m² q3w, 100 mg/m² qw 3/4, and docetaxel, respectively [17]. The 100 mg/m² *nab*-paclitaxel arm exhibited the best safety profile with the lowest rates of grade ≥ 3 neutropenia (25 vs. 43–45 % in the other *nab*-paclitaxel arms and 92 % in the docetaxel arm), sensory neuropathy (8 vs. 14–17 % in the other *nab*-paclitaxel arms and 12 % in the docetaxel arm), and fatigue (0 vs. 3–5 % in the other *nab*-paclitaxel arms and 19 % in the docetaxel arm).

The objective of this analysis was to examine the efficacy and safety of *nab*-paclitaxel versus paclitaxel and docetaxel in patients with poor prognostic factors. As such, we performed a post hoc analysis of patients who received first-line treatment in the two randomized trials described above to determine whether the efficacy and safety of *nab*-paclitaxel were maintained across patient subgroups defined by DFI or visceral dominant metastases.

Methods

Patients

The patient populations for the two trials were analyzed separately due to differences in treatment and patient eligibility. In both trials, patients ≥ 18 years old with pathologically confirmed MBC, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 , and adequate hematologic, hepatic, and renal function were included. For the phase III CA012 trial, patients who had received docetaxel or paclitaxel in the adjuvant setting were permitted if ≥ 1 year had passed since completion of that therapy [14]. Patients in the phase II CA024 study had not received prior chemotherapy for metastatic disease, but patients who had received chemotherapy in the neoadjuvant or adjuvant setting were permitted if ≥ 1 year had passed since completion of that therapy [16]. Patients with preexisting sensory neuropathy of grade ≥ 1 were excluded from CA012, whereas patients in CA024 were permitted to enroll with grade ≤ 1 sensory neuropathy.

Study design and assessments

This is a retrospective analysis of patients from the randomized, multicenter phase III trial (CA012) and a randomized, multicenter phase II trial (CA024). For detailed information on the trial designs, see Gradishar et al. [14, 16], respectively. Although patients enrolled in CA012 could have received chemotherapy for metastatic disease if the

treatment did not contain solvent-based paclitaxel or docetaxel, this analysis only includes those patients who had not received prior chemotherapy for metastatic disease. Trial CA024 included only patients who received first-line treatment. Within each of the six treatment arms among the two studies, patients were subdivided into the following subgroups for this analysis: patients with visceral dominant metastases and patients with a short DFI (≤ 2 years).

The primary efficacy endpoint for both studies was ORR, defined as complete response + partial response. Responses were assessed by the trial investigators using Response Evaluation Criteria in Solid Tumors [18]. Other efficacy endpoints in this analysis included median OS and PFS. The safety endpoints included in this analysis were treatment-related adverse events, including sensory neuropathy, neutropenia, and fatigue. Hematologic toxicity was reported on the basis of central laboratory data.

In the CA012 trial, patients received either *nab*-paclitaxel at 260 mg/m² q3w or paclitaxel at 175 mg/m² q3w. In the CA024 trial, patients received docetaxel at 100 mg/m² q3w or *nab*-paclitaxel at 300 mg/m² q3w, 100 mg/m² qw 3/4, or 150 mg/m² qw 3/4.

Statistical methods

The statistical analyses for the two trials were carried out separately as it was not appropriate to combine patient populations. Descriptive statistics were used to calculate the ORRs and 95 % binomial confidence intervals. Median OS and PFS values were calculated using Kaplan–Meier methods. For CA012, the median PFS represented the time from first dose to disease progression or death, and the median OS represented the time from first dose to death. For CA024, the median PFS represented the time from patient randomization to disease progression or death, and the median OS represented the time from patient randomization to death. Tumor shrinkage was calculated as the percent change in size from baseline of the target lesion to the smallest post-baseline measurement.

Results

Patients

The CA012 trial included 97 and 89 patients who received first-line therapy in the *nab*-paclitaxel and paclitaxel treatment arms, respectively. The numbers of patients per treatment arm in the intent-to-treat (ITT) population of CA024 ranged from 74 to 76. Baseline characteristics within each trial for the given patient subgroups were well balanced (Table 1).

Efficacy

Overall response rate

In the CA012 trial, ORR results for each poor prognostic factor subset were similar to the results from the general ITT population (Fig. 1). The ORR was higher with *nab*-paclitaxel versus paclitaxel in patients with visceral dominant disease (42 vs. 23 %; $P = 0.022$) and short DFI (43 vs. 33 %; $P = 0.417$). Similarly, ORR values among patients with poor prognostic factors in trial CA024 also corresponded to the trends in the ITT population. In both subsets, patients who received *nab*-paclitaxel on a qw 3/4 schedule exhibited higher ORRs compared with patients who received docetaxel (Fig. 1). Although comparisons within the short DFI subgroups failed to reach statistical significance, comparisons among patients with visceral dominant lesions did demonstrate significant differences for ORR.

The mean maximum percent tumor shrinkage was also calculated for all patients in this analysis. Waterfall plots of tumor shrinkage for study CA012 are shown in Fig. 2 as a patient-by-patient overlay of treatment groups from the least tumor shrinkage to the most tumor shrinkage. Among patients with visceral dominant metastases (Fig. 2A), the mean maximum percent tumor shrinkage was 37.4 % in the *nab*-paclitaxel arm versus 19.9 % in the paclitaxel arm ($P = 0.006$). The difference in mean percent tumor shrinkage among patients with a short DFI was not statistically significant (Fig. 2B; 39.9 % for *nab*-paclitaxel vs. 25.4 % for paclitaxel; $P = 0.096$). The tumor shrinkage data for study CA024 are shown in Supplemental Figs. 1 (visceral dominant metastases) and 2 (short DFI). For patients with visceral dominant metastases, patients who received *nab*-paclitaxel 300 mg/m² q3w, 100 mg/m² qw 3/4, and 150 mg/m² qw 3/4 had mean maximum percent tumor shrinkages of 35.5 %, 47.5 %, and 57.1 %, respectively, versus 37.0 % for the docetaxel group. For patients with a short DFI, patients who received *nab*-paclitaxel 300 mg/m² q3w, 100 mg/m² qw 3/4, and 150 mg/m² qw 3/4 had mean maximum percent tumor shrinkages of 36.2 %, 48.1 %, and 56.1 %, respectively, versus 32.6 % for the docetaxel group. None of the differences for study CA024 were statistically significant.

Progression-free survival

In trial CA012, PFS values in both poor prognostic factor subsets favored the *nab*-paclitaxel arm, although the differences were not statistically significant (Table 2). Trial CA024 also showed PFS trends among the patient subsets that reflected those of the ITT population. Comparisons of PFS in patients with visceral dominant metastases revealed

Table 1 Baseline patient characteristics

Trial/treatment	<i>n</i>	Age (years), mean	White race, <i>n</i> (%)	Body weight (kg), mean	ECOG PS ≤1, <i>n</i> (%)	ECOG PS 2, <i>n</i> (%)	Post-menopausal, <i>n</i> (%)
Visceral dominant metastasis							
CA012							
<i>nab</i> -P 260 mg/m ² q3w	74	52.2	70 (95)	72.4	68 (92)	6 (8)	52 (70)
P 175 mg/m ² q3w	64	53.0	60 (94)	71.5	63 (98)	1 (2)	45 (70)
CA024							
<i>nab</i> -P 300 mg/m ² q3w	61	51.6	59 (97)	73.2	55 (90)	6 (10)	39 (64)
<i>nab</i> -P 100 mg/m ² qw 3/4	60	55.6	59 (98)	71.8	56 (93)	4 (7)	50 (83)
<i>nab</i> -P 150 mg/m ² qw 3/4	59	53.8	59 (100)	76.1	55 (93)	4 (7)	45 (76)
Doc 100 mg/m ² q3w	67	56.2	67 (100)	75.9	65 (97)	2 (3)	57 (85)
Short DFI							
CA012							
<i>nab</i> -P 260 mg/m ² q3w	42	50.8	42 (100)	72.4	39 (93)	3 (7)	31 (74)
P 175 mg/m ² q3w	30	52.3	30 (100)	70.0	30 (100)	0	21 (70)
CA024							
<i>nab</i> -P 300 mg/m ² q3w	20	49.5	20 (100)	73.2	18 (90)	2 (10)	13 (65)
<i>nab</i> -P 100 mg/m ² qw 3/4	21	51.4	21 (100)	75.7	21 (100)	0	17 (81)
<i>nab</i> -P 150 mg/m ² qw 3/4	14	52.2	14 (100)	80.1	12 (86)	2 (14)	9 (64)
Doc 100 mg/m ² q3w	19	51.5	19 (100)	84.5	19 (100)	0	14 (74)

DFI disease-free interval, *nab*-P *nab*-paclitaxel, *Doc* docetaxel, *ECOG PS* Eastern Cooperative Oncology Group performance status, *P* paclitaxel, *q3w* every 3 weeks, *qw 3/4* the first 3 of 4 weeks

statistically significant differences between *nab*-paclitaxel 150 mg/m² qw 3/4 and docetaxel and between both qw 3/4 *nab*-paclitaxel treatment groups. In both prognostic factor subsets, the *nab*-paclitaxel 150 mg/m² qw 3/4 treatment arm showed the longest PFS values (13.1 and 14.1 months in the visceral dominant metastases and short DFI groups, respectively).

Overall survival

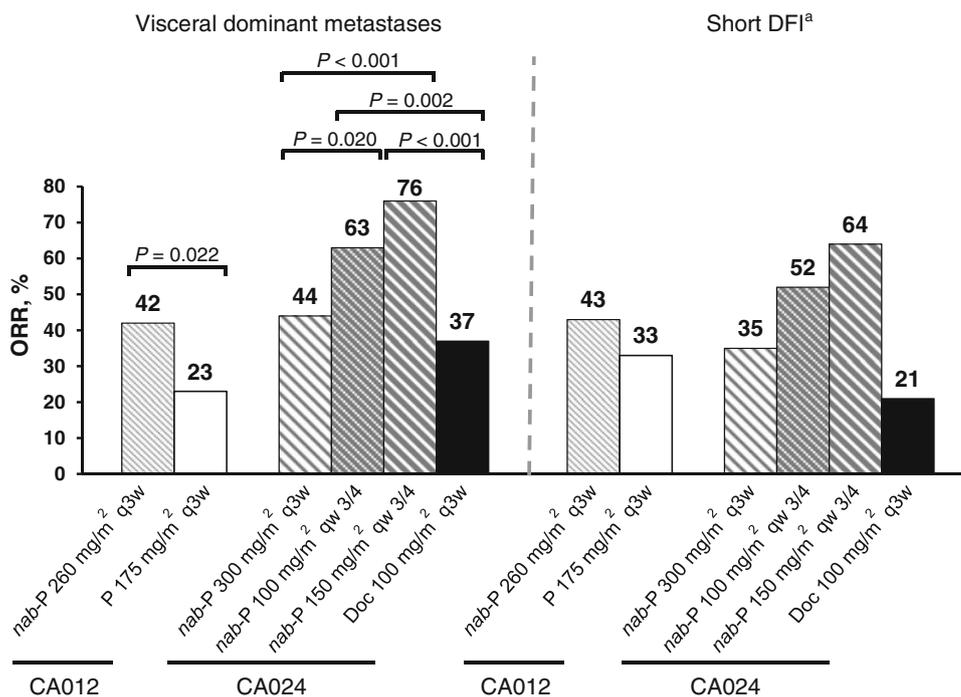
In this subset analysis, no comparisons for median OS reached statistical significance. In CA012, median OS was numerically higher with *nab*-paclitaxel versus paclitaxel in each of the subgroups (Table 3). Trial CA024 once again demonstrated similar trends in each patient subgroup compared with the ITT population. In patients with visceral dominant lesions, OS was numerically highest in patients who received *nab*-paclitaxel 150 mg/m² qw 3/4, while in patients with a short DFI, the OS was numerically highest with *nab*-paclitaxel 100 mg/m² qw 3/4.

Treatment exposure

As the administered dose of *nab*-paclitaxel in the CA012 trial was higher than that of paclitaxel, patients in that

treatment arm received a higher median cumulative dose (1,560 mg/m² for patients in both subgroups who received *nab*-paclitaxel vs. 962.5 mg/m² for patients in both subgroups who received paclitaxel) and a higher dose intensity (86.6 mg/m²/week for patients with visceral dominant metastases who received *nab*-paclitaxel and 85.3 mg/m²/week for patients with a short DFI who received *nab*-paclitaxel vs. 58.3 mg/m²/week for patients in both subgroups who received paclitaxel). Treatment delays and dose reductions occurred at similar frequencies between the two treatment arms across both prognostic subgroups. Patients in the *nab*-paclitaxel arm received a median of 6 cycles of treatment in both groups versus 5.5 for patients in the paclitaxel arm in both groups. The average dose intensities among the two patient subgroups for the *nab*-paclitaxel arms in trial CA024 ranged from 99.5 to 100 mg/m²/week in the 300 mg/m² arm, 73.7–75 mg/m²/week in the 100 mg/m² arm, and 98.7–103.1 mg/m²/week in the 150 mg/m² arm. The median number of cycles received was highest for the *nab*-paclitaxel 150 mg/m² qw 3/4 arm among patients with visceral dominant metastases (9 vs. 8 in the other arms), but among patients with a short DFI, patients in the *nab*-paclitaxel 100 mg/m² qw 3/4 arm received the highest number of cycles (8 vs. 6–7 in the other arms). Among the poor prognostic factor subgroups

Fig. 1 Overall response rate. *DFI* disease-free interval, *Doc* docetaxel, *nab-P* nab-paclitaxel, *ORR* overall response rate, *P* paclitaxel, *qw 3/4* every 3 weeks, *qw 3/4* the first 3 of 4 weeks



^a For the short DFI subgroup, no statistically significant differences were found between treatment arms within either trial. *P* values from study CA012 were calculated by Cochran-Mantel-Haenszel (CMH) test. *P* values from study CA024 were calculated by CMH test, stratified by study site.

in trial CA024, the highest rate of dose reductions took place in the *nab*-paclitaxel 150 mg/m² qw 3/4 arm (44 and 50 % among patients with visceral dominant metastases and a short DFI, respectively), followed by docetaxel (30 and 26 %, respectively), and the two other *nab*-paclitaxel arms, which showed similar rates of dose reductions among the patient subgroups (14–18 %).

Safety

Tables 4 and 5 show the all-grade adverse events and the grade ≥ 3 adverse events, respectively, for the patients with poor prognostic factors in both trials. Safety results across the patient subgroups for trial CA012 were similar to the ITT population: grade 3/4 neutropenia was more frequent for paclitaxel in the poor prognostic factor subgroups, whereas sensory neuropathy and fatigue were both more frequent for *nab*-paclitaxel (Table 5). In trial CA024, rates of grade 3/4 adverse events in the patient subgroups very closely matched those of the ITT populations (Table 5). Accordingly, patients in each treatment arm had similar frequencies of specific adverse events for each poor prognostic factor subgroup. In the two subgroups, the rates of grade 3/4 neutropenia and fatigue were highest for the docetaxel group and lowest in the *nab*-paclitaxel 100 mg/m² qw 3/4 group (no cases of grade 3/4 fatigue were reported in either qw 3/4 *nab*-paclitaxel arm). The *nab*-paclitaxel 100 mg/m² qw 3/4 dose also

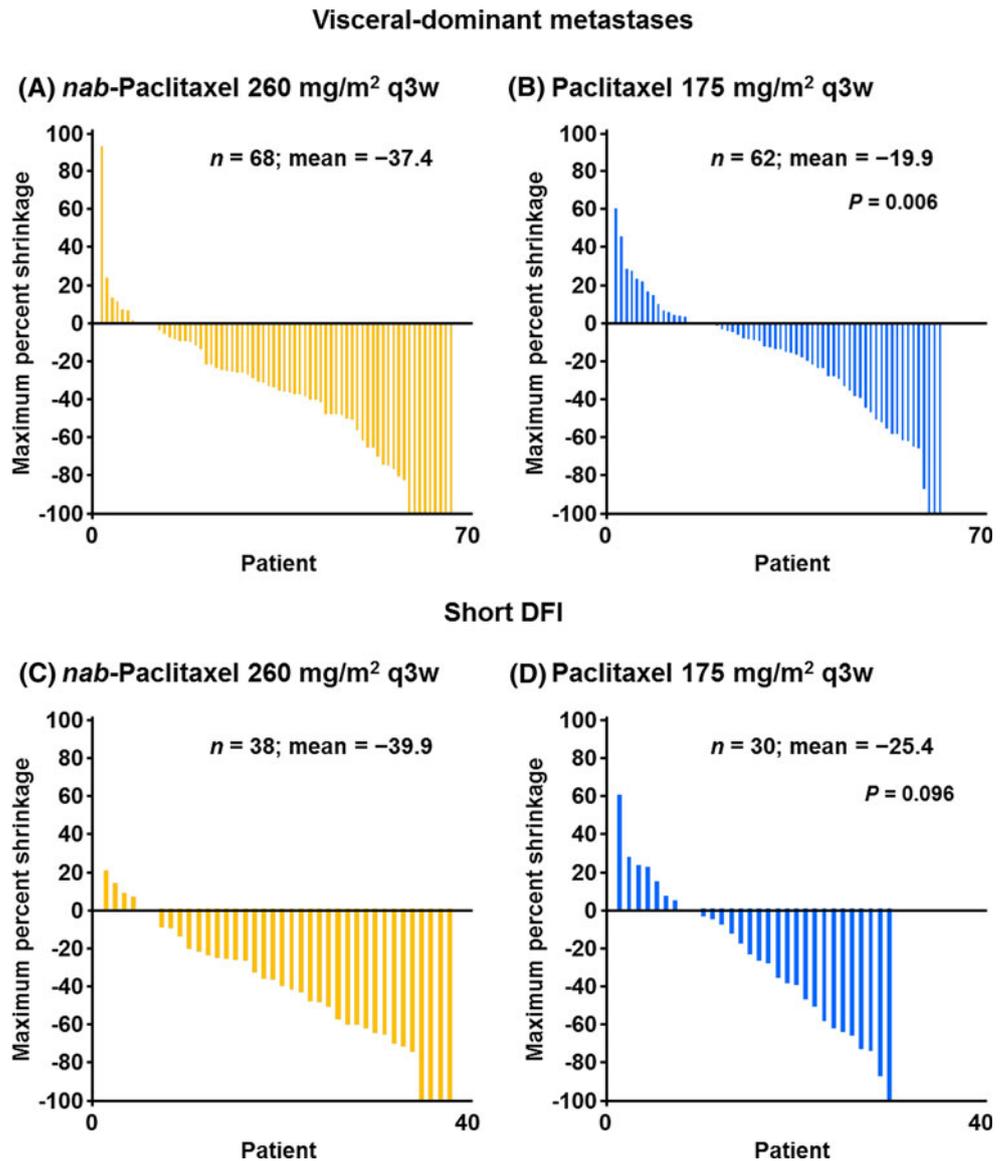
produced the lowest rate of grade ≥ 3 sensory neuropathy in each prognostic factor subgroup.

Discussion

The results of this analysis indicate that the treatment benefits observed for *nab*-paclitaxel versus paclitaxel in the ITT populations of a randomized phase III trial and versus docetaxel in a randomized phase II trial also apply to patients with poor prognostic factors. In general, ORR, OS, PFS, safety, and treatment exposure were similar for each treatment arm among patients with visceral dominant metastases and patients with a short DFI. For trial CA012, the difference in ORR reached statistical significance in the subset of patients with visceral dominant metastases. In CA024, both qw 3/4 *nab*-paclitaxel arms exhibited higher ORRs versus docetaxel in the visceral dominant metastasis subgroup. The differences in ORR and the trends in median PFS and OS suggest that *nab*-paclitaxel provides clinical benefit to patients with virulent MBC who received first-line treatment.

This retrospective analysis was limited by two key factors. First, the patient subsets examined in this retrospective study were not large enough to allow statistical significance for some of the differences in efficacy outcomes, despite similar magnitudes of differences in

Fig. 2 Mean maximum percent tumor shrinkage in study CA012. *DFI* disease-free interval, *q3w* every 3 weeks



absolute terms relative to the ITT populations of the two clinical trials. In addition, certain patient data, such as ER status, progesterone receptor status, and HER2 status were not collected in these trials.

A separate retrospective analysis examined patients ≥ 65 years old in these two studies [19]. It should be noted that for CA024, the numbers of patients ≥ 65 years old among the different treatment arms ranged from only 9 to 19. Nevertheless, that report reflected a common theme with the results of this study: the efficacy benefits of *nab*-paclitaxel relative to the other taxanes in these two trials were consistent among patient subgroups. Indeed, the ORR values for patients ≥ 65 years old in trial CA012 were 27 % for *nab*-paclitaxel versus 19 % for paclitaxel, and median PFS values were 5.6 and 3.5 months, respectively.

Among patients ≥ 65 years old in CA024, ORR values were 22 % in the *nab*-paclitaxel 300 mg/m² q3w group and 60–64 % in the qw 3/4 treatment groups versus 32 % in the docetaxel group. PFS values for all three *nab*-paclitaxel arms were longer than those for the docetaxel arm (9.2–18.9 vs. 8.5 months).

A recent presentation at the 2012 annual meeting of the American Society of Clinical Oncology gave results of a large phase III trial conducted by the Cancer and Leukemia Group B (CALGB) comparing three regimens for the first-line treatment of MBC: *nab*-paclitaxel \pm bevacizumab ($n = 271$), paclitaxel \pm bevacizumab ($n = 283$), and ixabepilone \pm bevacizumab ($n = 245$) [20]. Although the trial protocol was amended to make bevacizumab use optional, 98 % of patients received it. The dose selected for

Table 2 Investigator-assessed PFS

Trial/treatment	PFS (months), median			
	Visceral dominant metastasis		Short DFI	
	<i>n</i>	PFS (95 % CI)	<i>n</i>	PFS (95 % CI)
Study CA012				
<i>nab</i> -P 260 mg/m ² q3w	74	5.6 (4.3–7.2)	42	5.0 (3.6–6.6)
P 175 mg/m ² q3w	64	3.8 (3.5–5.1)	30	3.5 (2.7–5.1)
HR (95 % CI)		0.717 (0.483–1.063)		0.729 (0.437–1.215)
<i>P</i> values ^a		0.094		0.220
Study CA024				
<i>nab</i> -P 300 mg/m ² q3w (A)	61	10.9 (7.6–13.8)	20	7.4 (2.4–10.3)
<i>nab</i> -P 100 mg/m ² qw 3/4 (B)	60	7.5 (7.2–9.3)	21	7.3 (7.2–9.3)
<i>nab</i> -P 150 mg/m ² qw 3/4 (C)	59	13.1 (9.8–17.7)	14	14.1 (6.2–18.4)
Doc 100 mg/m ² q3w (D)	67	7.8 (5.8–10.3)	19	5.5 (3.1–10.3)
HR ^b		C versus D: 0.600		All NS
		B versus C: 1.731		
<i>P</i> values ^{a,b}		Overall: 0.049		All NS
		C versus D: 0.019		
		B versus C: 0.010		

CI confidence interval, DFI disease-free interval, Doc docetaxel, HR hazard ratio, *nab*-P *nab*-paclitaxel, NS not statistically significant, P paclitaxel, PFS progression-free survival, q3w every 3 weeks, qw 3/4 the first 3 of 4 weeks

^a *P* values from log-rank test

^b For study CA024, only significant results shown

Table 3 Overall survival

Trial/treatment	OS (months), median			
	Visceral dominant metastasis		Short DFI	
	<i>n</i>	OS (95 % CI)	<i>n</i>	OS (95 % CI)
Study CA012				
<i>nab</i> -P 260 mg/m ² q3w	74	15.1 (11.5–19.0)	42	14.6 (10.7–18.1)
P 175 mg/m ² q3w	64	14.2 (11.8–22.5)	30	11.7 (8.8–18.3)
HR (95 % CI)		1.251 (0.841–1.859)		0.942 (0.567–1.565)
<i>P</i> values ^a		0.268		0.819
Study CA024				
<i>nab</i> -P 300 mg/m ² q3w	61	27.7 (20.5–38.9)	20	16.6 (12.1–22.0)
<i>nab</i> -P 100 mg/m ² qw 3/4	60	19.6 (14.5–26.0)	21	19.1 (13.2–28.1)
<i>nab</i> -P 150 mg/m ² qw 3/4	59	32.1 (23.9–40.6)	14	18.6 (10.6–>37.5)
Doc 100 mg/m ² q3w	67	21.4 (18.0–31.3)	19	14.4 (11.4–18.0)
<i>P</i> values		All NS		All NS

CI confidence interval, DFI disease-free interval, Doc docetaxel, HR hazard ratio, *nab*-P *nab*-paclitaxel, NS not statistically significant, OS overall survival, P paclitaxel, q3w every 3 weeks, qw 3/4 the first 3 of 4 weeks

^a Values from log-rank test

nab-paclitaxel in this trial was 150 mg/m² qw 3/4, marking the first time that a dose this high has been used in a phase III trial. Preliminary results from the trial suggest that the survival outcomes were similar with *nab*-paclitaxel and paclitaxel when given with bevacizumab; however, higher rates of dose reduction and discontinuation in the *nab*-paclitaxel arm suggest suboptimal delivery of the 150 mg/m² dose of *nab*-paclitaxel when given in combination with bevacizumab. The preliminary findings of the CALGB study do not address a comparison of *nab*-paclitaxel versus paclitaxel outside of the combination with bevacizumab in

patients with virulent MBC. Thus, further research may be required to determine the optimal weekly dose of *nab*-paclitaxel.

The results of this analysis of patients with visceral dominant metastases and a short DFI suggest that *nab*-paclitaxel exhibits substantial clinical activity in patients with virulent MBC. The efficacy of *nab*-paclitaxel versus paclitaxel and docetaxel in these two trials suggests that a phase III trial prospectively examining the effect of *nab*-paclitaxel in patients with poor prognostic factors may be warranted.

Table 4 All-grade toxicity

	Adverse events, <i>n</i> (%)	<i>n</i>	Neutropenia	Sensory neuropathy	Fatigue
Visceral dominant metastasis					
CA012					
<i>nab</i> -P 260 mg/m ² q3w		74	56 (76)	51 (69)	37 (50)
P 175 mg/m ² q3w		64	51 (80)	37 (58)	31 (48)
CA024					
<i>nab</i> -P 300 mg/m ² q3w		61 ^a	55 (92)	49 (80)	23 (38)
<i>nab</i> -P 100 mg/m ² qw 3/4		60	48 (80)	38 (63)	20 (33)
<i>nab</i> -P 150 mg/m ² qw 3/4		59	53 (90)	49 (83)	28 (47)
Doc 100 mg/m ² q3w		67 ^b	65 (100)	44 (66)	39 (58)
Short DFI					
CA012					
<i>nab</i> -P 260 mg/m ² q3w		42	30 (71)	30 (71)	20 (48)
P 175 mg/m ² q3w		30	28 (93)	16 (53)	15 (50)
CA024					
<i>nab</i> -P 300 mg/m ² q3w		20 ^c	17 (89)	14 (70)	9 (45)
<i>nab</i> -P 100 mg/m ² qw 3/4		21	17 (81)	15 (71)	6 (29)
<i>nab</i> -P 150 mg/m ² qw 3/4		14	14 (100)	11 (79)	4 (29)
Doc 100 mg/m ² q3w		19	19 (100)	15 (79)	9 (47)

DFI disease-free interval, Doc docetaxel, *nab*-P *nab*-paclitaxel, P paclitaxel, q3w every 3 weeks, qw 3/4 the first 3 of 4 weeks

^a 60 Patients evaluable for neutropenia

^b 65 Patients evaluable for neutropenia

^c 19 Patients evaluable for neutropenia

Table 5 Grade ≥ 3 toxicity

	Adverse events, <i>n</i> (%)	<i>n</i>	Neutropenia	Sensory neuropathy	Fatigue
Visceral dominant metastasis					
CA012					
<i>nab</i> -P 260 mg/m ² q3w		74	29 (39)	9 (12)	11 (15)
P 175 mg/m ² q3w		64	37 (58)	3 (5)	1 (2)
CA024					
<i>nab</i> -P 300 mg/m ² q3w		61 ^a	27 (45)	11 (18)	3 (5)
<i>nab</i> -P 100 mg/m ² qw 3/4		60	15 (25)	5 (8)	0
<i>nab</i> -P 150 mg/m ² qw 3/4		59	25 (42)	13 (22)	3 (5)
Doc 100 mg/m ² q3w		67 ^b	61 (94)	8 (12)	13 (19)
Short DFI					
CA012					
<i>nab</i> -P 260 mg/m ² q3w		42	10 (24)	4 (10)	5 (12)
P 175 mg/m ² q3w		30	20 (67)	0	1 (3)
CA024					
<i>nab</i> -P 300 mg/m ² q3w		20 ^c	8 (42)	4 (20)	1 (5)
<i>nab</i> -P 100 mg/m ² qw 3/4		21	3 (14)	1 (5)	0
<i>nab</i> -P 150 mg/m ² qw 3/4		14	6 (43)	3 (21)	0
Doc 100 mg/m ² q3w		19	19 (100)	2 (11)	4 (21)

DFI disease-free interval, Doc docetaxel, *nab*-P *nab*-paclitaxel, P paclitaxel, q3w every 3 weeks, qw 3/4 the first 3 of 4 weeks

^a 60 Patients evaluable for neutropenia

^b 65 Patients evaluable for neutropenia

^c 19 Patients evaluable for neutropenia

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Celgene Corporation, Jose Iglesias—Former employee and stockholder of Celgene Corporation. William Gradishar had no conflicts of interest to disclose.

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