Targeted chemotherapy with nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) in metastatic breast cancer: which benefit for which patients?

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Abstract: The therapeutic goals in metastatic breast cancer (MBC) remain palliative in nature, aimed at controlling symptoms, improving or maintaining quality of life and prolonging survival. The advent of new drugs and new formulations of standard agents has led to better outcomes in patients with advanced or metastatic disease. These developments have also allowed a tailored therapeutic approach, in which the molecular biology of the tumour, the treatment history, and patient attitudes are taken into account in the decision-making process. Targeting drug delivery to the tumour is a promising mean of increasing the therapeutic index of highly active agents such as the taxanes, and nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel), the first nanotechnology-based drug developed in cancer treatment, is one such advance. Data from randomized trials support the efficacy of single-agent *nab*-paclitaxel as first-line and further treatment lines in MBC at the registered 3-weekly schedule of 260 mg/m^2, but emerging evidence suggests its activity as a weekly regimen or combined with other agents in various clinical scenarios. Thus, *nab*-paclitaxel seems to offer flexibility in terms of dosing schedules, allowing physicians to tailor the dose according to different clinical situations. This paper reviews the clinical trial background for *nab*-paclitaxel in MBC, focusing on specific 'difficult-to-treat' patient populations, such as taxane-pretreated or elderly women, as well as those with triple-negative, HER2-positive and poor-prognostic-factors disease. Moving beyond evidence-based information, 'real life' available experiences are also discussed with the aim of providing an update for daily clinical practice.

Keywords: metastatic breast cancer, *nab*-paclitaxel, taxanes

Introduction

Despite advances in screening and treatment, breast cancer remains a leading cause of death among women worldwide. More than 30% of patients presenting localized disease will eventually recur, and 5-year survival for advanced disease is less than 25% [Siegel *et al.* 2014]. In the setting of metastatic breast cancer (MBC), undoubted progress has been made in improving clinical outcomes such that many patients now live with secondary disease for many years [Andre *et al.* 2004; Giordano *et al.* 2004; Dawood *et al.* 2008]. It is likely the greatest improvement to be related to the development and widespread availability of modern systemic therapies for MBC,

including combinations with targeted biological agents in different breast cancer subtypes, with proven efficacy in increasing response rate, progression-free survival (PFS) and overall survival (OS) [O'Shaughnessy, 2005; Gennari *et al.* 2005; Chia *et al.* 2007; Mauri *et al.* 2008; Dawood *et al.* 2010]. Currently, taxanes are considered the most effective cytotoxic drugs for the treatment of MBC, both in monotherapy and combination schedules, with a proven survival benefit compared with the use of other types of chemotherapy. Paclitaxel and docetaxel, the two most commonly used taxanes against breast cancer, are the agents of choice in patients progressing after anthracycline-containing chemotherapy according to the

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most recent international guidelines [Ghersi *et al.* 2003; Cardoso *et al.* 2014]. These two agents were both registered as 3-weekly (q3w) regimens, but different doses and schedules were subsequently tested aiming at increasing efficacy and at reducing the burden of treatment-related toxicity. Weekly (qw) paclitaxel 80 mg/m^2 and q3w docetaxel 75–100 mg/m^2 are considered the gold standard in anthracycline-pretreated MBC patients, based on results of randomized clinical trials [Jones *et al.* 2005]. In a phase III study by the Hellenic Cooperative Oncology Group, patients receiving qw single-agent solvent-based paclitaxel 80 mg/m^2 as first-line therapy for MBC had better median OS (41 months) than those randomized to q3w solvent-based paclitaxel combined with carboplatin (30 months) or q3w docetaxel combined with gemcitabine (27 months); patients with HER2-overexpressing tumours (30% of the whole population) also received trastuzumab [Fountzilas *et al.* 2009]. Another phase III trial reported better ORR, TTP and OS for MBC patients undergoing first- or second-line therapy with qw paclitaxel versus those randomized to q3w dosing; again, in that study approximately 40% of patients also received trastuzumab [Seidman *et al.* 2008]. Finally, two phase III studies have shown no difference in PFS or OS for weekly docetaxel compared with other regimens for MBC [Palmeri *et al.* 2013], with an ORR of 20% for single-agent docetaxel as first- or second-line treatment [Rivera *et al.* 2008]. Despite their clinical activity, the use of taxanes is often limited by significant toxicities observed in treated patients, most notably hypersensitivity reactions and peripheral neuropathy, and so remains a major challenge. The taxane side effects have been associated with the need for synthetic solvents because of the agents' hydrophobicity [polyoxyethylated castor oil (Cremophor: BASF- The chemical company. Ludwigshafen, Germany) for paclitaxel and polysorbat 80 (Tween 80: CRODA Americas LLC. Wilmington, Delaware, US) for docetaxel], but they also alter their pharmacokinetic profiles. Premedication with corticosteroids and antihistamines before taxane administration is mandatory but causes additional side effects [Weiss *et al.* 1999; Sparreboom *et al.* 1999; ten Tije *et al.* 2003].

Nanoparticle albumin-bound paclitaxel (*nab*-paclitaxel) is a solvent-free colloidal suspension of paclitaxel and human serum albumin that exploits the physiological transport of albumin from the bloodstream *via* the endothelium of the blood vessels. The nanoparticle drug delivery system eliminates the need for toxic solvents such as cremophor through binding of paclitaxel to albumin, thus reducing the limitations of paclitaxel dosing and affecting overall drug efficacy [Henderson and Bathia, 2007]. The proposed mechanisms through which this is achieved are: (1) active transport across endothelial cells *via* the gp60/caveolin-1 receptor pathway; and (2) active binding of albumin-paclitaxel complexes by SPARC (secreted protein acid and rich in cysteine) [Desai, 2007; Cortes and Saura, 2010]. This system may also allow better delivery of drug to the tumour microenvironment, thus it is associated with more linear pharmacokinetics. *Nab*-paclitaxel has shown good clinical results in first- and further-line therapy of patients with MBC [Gradishar *et al.* 2005, 2009, 2012], as well as in taxane-pretreated disease [Blum *et al.* 2007]. It is registered as monotherapy with a recommended dose of 260 mg/m^2 every 3 weeks for the treatment of patients with MBC who have failed a first-line treatment of metastatic disease and for whom a standard anthracycline-containing therapy is not indicated [EMA, 2008]. Clinical evidence is today available for the registered q3w regimen and for alternative qw schedules, in combination regimens with other cytotoxic or targeted agents [Megerdichian *et al.* 2014; Viùdez *et al.* 2014].

This paper summarizes the data and the authors' views of the expected benefits of *nab*-paclitaxel use in the treatment of different MBC patient populations in clinical practice, based on the review and discussion of available results from both clinical trials and real-life experiences.

Clinical development of *nab*-paclitaxel in breast cancer patients

Three phase I studies have established the pharmacokinetics and toxicity profiles of qw and q3w regimens of *nab*-paclitaxel, showing that the drug demonstrates linear pharmacokinetics across the clinically relevant dose range (80–300 mg/m^2) and is associated with a significantly greater fraction of unbound drug compared with conventional paclitaxel. The recommended doses are between 300 mg/m^2 q3w and 100 mg/m^2 (in heavily pretreated patients) or 150 mg/m^2 (in lightly pretreated patients) for the qw schedule. In these studies, the dose-limiting toxicity was established on the basis of occurrence of grade 4 neutropenia and grade 3 neuropathy, without colony-stimulating factor administration or

premedication; no hypersensitivity was observed. Findings from these early studies also showed that *nab*-paclitaxel demonstrates dose-dependent antitumour activity, with a higher maximum-tolerated dose achieved compared with conventional paclitaxel [Ibrahim *et al.* 2002; Nyman *et al.* 2005; Gardner *et al.* 2008]. Such attractive characteristics of *nab*-paclitaxel in phase I studies allowed the development of a phase II trial on 63 women with MBC, 59% of whom had prior exposure to anthracyclines. An objective response rate (ORR) of 48% was achieved (41% in the pretreated patients, 64% in those chemotherapy-naïve for the metastatic disease); median time to progression (TTP) and overall survival (OS) were 26.6 and 62.6 weeks, respectively [Ibrahim *et al.* 2005].

The efficacy and safety of *nab*-paclitaxel in the first- and second-line treatment of MBC was demonstrated in a large randomized phase III trial comparing q3w *nab*-paclitaxel 260 mg/m^2 and q3w solvent-based paclitaxel 175 mg/m^2. That study showed a statistically significant superiority of *nab*-paclitaxel in terms of ORR (33% *versus* 19%, $p = 0.001$; 42% *versus* 27% in the first-line setting) and PFS (23 *versus* 16.9 weeks, $p = 0.006$); a trend in favour of *nab*-paclitaxel for OS was also observed (65.0 *versus* 55.7 months, $p = 0.046$). Patients randomized in the *nab*-paclitaxel arm had a lower incidence of grade 4 neutropenia (9% *versus* 22%, $p = 0.046$) with hypersensitivity reactions being less than 1%, although they did not receive premedication; grade 3 sensory neuropathy was increased with *nab*-paclitaxel to a rate of 10% compared with 2% of standard formulation ($p < 0.01$), with a median time of improvement to a lower grade of 22 and 79 days, respectively [Gradishar *et al.* 2005]. The results from the pivotal phase III study led to the regulatory approval of *nab*-paclitaxel for the treatment of MBC by the Food and Drug Administration, USA, in 2005 and by the European Medicines Agency, Europe, in 2008.

The next logical step in the clinical development of *nab*-paclitaxel was the investigation of a qw schedule. A large, randomized, open-label, multi-centre phase II study was designed to directly compare the safety and activity of weekly (100 or 150 mg/m^2) and q3w *nab*-paclitaxel (300 mg/m^2) and docetaxel (100 mg/m^2) in 300 women with previously untreated MBC. Findings from this study showed that qw dosing of *nab*-paclitaxel was associated with a similar tolerability profile to q3w dosing, with no unexpected toxicities

reported. The incidence of significant adverse events was significantly higher in the docetaxel group and similarly low across the three *nab*-paclitaxel groups: grade 4 neutropenia occurred in 5%, 9%, 7% and 75% of patients for *nab*-paclitaxel 100 mg/m^2 qw, 150 mg/m^2 qw and 300 mg/m^2 q3w, and docetaxel 100 mg/m^2, respectively, $p < 0.001$; and grade 3 fatigue was reported in 0%, 4%, 5% and 19%, respectively; $p < 0.001$ [Gradishar *et al.* 2009]. In terms of efficacy, either dose of *nab*-paclitaxel was superior compared with docetaxel in terms of ORR and PFS as first-line treatment for MBC. According to the independent assessment, compared with the other treatment groups, the 150 mg/m^2 qw regimen was associated with a numerically greater ORR (49% *versus* 35% and 45%, $p = 0.224$) and a significantly longer PFS (12.9 *versus* 7, at 5 and 12.8 months, $p = 0.0498$). These data therefore suggest that *nab*-paclitaxel 150 mg/m^2 qw has a superior therapeutic index compared with q3w dosing for the first-line treatment of women with MBC. Indeed, the median OS reported for this dosing regimen of 33.8 months is impressive and rarely seen in this setting [Gradishar *et al.* 2009, 2012].

Experience of *nab*-paclitaxel in managing MBC is growing and data concerning the combination with other cytotoxic or molecularly targeted agents are also being gathered. The sections that follow illustrate a range of clinical applications for *nab*-paclitaxel in specific 'difficult-to-treat' patient populations, moving beyond evidence-based information to the 'real life' available experiences, with the aim of providing an update for daily clinical practice.

Nab-paclitaxel in taxane-pretreated metastatic breast cancer patients

A major challenge associated with effective MBC management is prior exposure to anthracycline with or without taxane therapy, both of which are being used increasingly in the neoadjuvant and adjuvant settings, particularly in high-risk patients.

Indeed, previous treatment with conventional taxanes in earlier or advanced stages of disease has a significant impact on subsequent treatment selection in MBC since it may limit available options for many patients. Despite current lack of standard of care, a considerable proportion of these women receives multiple lines of treatment for metastatic disease, including taxane

rechallenge, according to previous efficacy and tolerance, with results that justify this practice [Roché and Vahdat, 2011; Planchat *et al.* 2011; Palumbo *et al.* 2013; Cardoso *et al.* 2014]. However, very few data are available outlining outcomes after this pragmatic approach in MBC [Palmieri *et al.* 2010; Toulmonde *et al.* 2012; Andreupoulou and Sparano, 2013]. In clinical practice, the introduction of liposomal anthracyclines offers an opportunity for anthracycline rechallange in MBC, whereas taxane rechallange may be possible by selecting a different taxane, using an alternative regimen of the same agent or selecting paclitaxel albumin [Palmieri *et al.* 2010]. The first suggestion that *nab*-paclitaxel does not demonstrate absolute cross-resistance with first-generation taxanes is derived from a phase II study on 181 MBC patients, whose disease progressed despite conventional taxane therapy. In this trial, taxane failure was defined as metastatic disease progression during taxane therapy or relapse within 12 months of adjuvant taxane therapy. Patients with a median of three prior chemotherapies (range 0–14) including paclitaxel, docetaxel, or both, were treated with qw *nab*-paclitaxel at 100 mg/m^2 (*n* = 106) and in a second cohort at 125 mg/m^2 (*n* = 75) on days 1, 8, and 15 q4w. Overall ORR was 14% and 16%, disease control rate 26% and 36%, median PFS 3.0 and 3.5 months, and median OS 9.1 and 9.2 months, respectively. Among women given 125 mg/m^2 *nab*-paclitaxel, the disease control rate was 45% in those treated with conventional paclitaxel and 46% in those with prior exposure to docetaxel; in the whole population median survival was similar for responding patients and those with disease stabilization of no less than 16 weeks. Patients received a median of 15.2 doses in the 100 mg/m^2 cohort and 13.1 doses in the 125 mg/m^2 cohort corresponding to median cumulative doses of 900.5 and 1125 mg/m^2, respectively. *Nab*-paclitaxel was well tolerated in the whole population: grade 4 leukopenia and neutropenia were seen in fewer than 5% of patients; and 15 of the 23 patients who stopped treatment because of peripheral neuropathy were able to restart the drug at a reduced dose [Blum *et al.* 2007].

The potential of *nab*-paclitaxel in heavily pretreated, taxane-refractory patients has been confirmed in subsequent real-life experiences (Table 1). First, a retrospective analysis included 43 patients with MBC from Ottawa Hospital Cancer Center, pretreated for metastatic disease (median three lines, range 1–6) and exposed to taxanes in the adjuvant or metastatic settings. *Nab*-paclitaxel was given in a q3w schedule to 46.5% of patients and in a qw schedule to 44.2%. The results of the analysis seemed to favour the qw regimen, since patients receiving it displayed reduced toxicity (27.3% dose reduction *versus* 61.9%), increased clinical benefit rate (76.2% *versus* 57.1%) and OS (13.6 *versus* 10.8 months, *p* = 0.033) compared with the q3w regimen. Details are provided regarding sensitive neuropathy, the most common adverse event, which occurred in 41.9% of the treated patients (all grades), while grade 3 neuropathy was observed in 11.6% of cases. Regardless of the schedule of administration, women who experienced clinical benefit lived significantly longer than those who did not achieve it (17.3 *versus* 7.7 months, *p* < 0.001) [Dent *et al.* 2013]. A subsequent study enrolled 138 MBC patients across five cancer centres in British Columbia from 2007 to 2011. In this retrospective analysis, pretreatment with taxanes in the adjuvant setting was observed in 24% of patients; likely because of the presence of more adverse prognostic factors at diagnosis, this group had a significantly shorter time to relapse (2.7 *versus* 4.5 years) compared with women not exposed to taxanes. *Nab*-paclitaxel was administered in the setting of second to eighth line of treatment, mostly in the q3w regimen (83.6%). The number of cycles given for the overall cohort was 4.4 (range 0.3–13), with the median number of cycles being greater when the drug was prescribed as first or second line of treatment (median 5 cycles *versus* 3.7 cycles for anything more than third line). Despite the earlier relapse of taxane-exposed patients *versus* nonexposed, no statistically significant differences were noticed in the median time to treatment failure for *nab*-paclitaxel (96 *versus* 73.5 days, *p* = 0.58) and dose reduction rate (20% *versus* 27.2%, *p* = 0.43) [Lohmann *et al.* 2013]. Two additional reports on smaller patient populations confirm that most MBC patients treated in the routine clinical practice with the qw or q3w *nab*-paclitaxel schedule achieve a clinical benefit, in advanced lines of treatment too [Aigner *et al.* 2013; Singh *et al.* 2014]. Authors of a recently reported multicentre experience aimed to analyse the patterns of treatment and outcome of 215 consecutive women receiving *nab*-paclitaxel for their MBC at nine Italian institutions, with analysis focusing on potential predictive or prognostic factors for treatment response and disease outcome. In this 'real life' study, 145 patients (cohort A) received the 260 mg/m^2 q3w schedule (78 in second line, 46 in third and 21 in anything

Table 1. *Nab*-paclitaxel in taxane-pretreated MBC.

Reference, *Study type*	Total/evaluable pts, Median age [range]	*Nab*-P schedule	Prior CT lines for MBC	Treatment response	Median PFS	Median OS	Highest reported toxicities [%]
Blum *et al.* [2007], Prospective phase II	106/106 53 years [34–76] 75/75 53 years [34–74]	100 mg/m² on day 1, 8, 15 q4w 125 mg/m² on day 1, 8, 15 q4w	Median 3 (range 0–7) Median 3 (range 1–14)	ORR: 14% PR: 14% DCR: 26% ORR 16% CR 1%; PR 15% DCR: 37%	3 months 3.5 months	9.2 months 9.1 months	Gr. 3–4 neutropenia: 7% Gr.3 sensory neuropathy: 8% Gr. 3 fatigue: 5% Gr. 3 nausea/vomiting: 7% Gr. 3–4 neutropenia: 32% Gr.3 sensory neuropathy: 19% Gr. 3 fatigue: 12% Gr. 3 nausea/vomiting: 4%
Dent *et al.* [2013], Retrospective analysis	22/21 57 years [34–74] 21/21 57 years [34–74]	260 mg/m² on day 1 q3w 100 mg/m² on day 1, 8, 15 q4w	Median 3 (range 1–6)	ORR: 4.7% PR: 4.7% CBR: 76.2% ORR: 14.2% PR: 14.2% CBR: 57.1%	n.r.	13.6 months 10.8 months	Gr.3 sensory neuropathy: 11.6% Gr. 2 fatigue: 9.3% Gr. 3 myalgia: 2.3% Gr. 3 dyspnea: 2.3% Gr. 3 mucositis: 2.3%
Lohmann *et al.* [2013], Retrospective analysis	138/122 30 pts taxane-treated in the adjuvant setting	260 mg/m² on day 1 q3w [102 pts] 100 mg/m² on day 1, 8, 15 q4w or every 2 weeks	Median 2 (range 1–8)	n.r.	TTF: 84 days (range 0–1176)	n.r.	Dose reductions due to toxicity: 20% in taxane-pretreated *versus* 27.2% in the no taxane pretreated group
Aigner *et al.* [2013], Retrospective analysis	36/31 60 years [39–79]	150 mg/m² on day 1, 8, 15 q4w	Median 1 (range 0–10)	ORR: 9.7% PR: 9.7% DCR: 64.5%	7.5 months	14.2 months	Gr. 4 neutropenia: 7.7% Gr. 3 fatigue: 27.8% Gr.3 dyspnea: 5.6% Gr.3 rash: 5.6% Gr.3 polineuropathy: 2.8%
Singh *et al.* [2014], Retrospective analysis	43/14 58 years [39–70]	260 mg/m² on day 1 q3w	Median 3 (range 0–6)	ORR: 42.8% CR: 7.1% PR: 35.7% CBR: 78%	26.6 weeks	63.6 weeks	Gr. 4 neutropenia: 1.8% Gr. 3 sensory neuropathy: 5.8% Gr. 3 anemia: 1.9%
Palumbo *et al.* [2015 b], Prospective phase II	52/52 53 years [33–71]	260 mg/m² on day 1 q3w	One only prior line in all patients	ORR: 48.1 CR: 13.5% PR: 34.6% CBR: 76.9%	8.9 months	not reached yet	Gr.3 sensory neuropathy: 14.3% Gr. 4 neutropenia: 7.14%
Fabi *et al.* [2015], Prospective phase II	42/42 48 years [21–80]	260 mg/m² on day 1 q3w (10 pts) 125 mg/m² weekly (32 pts)	4 lines in 12% of pts	ORR: 23.8% CR: 2.4% PR: 21.4% DCR: 50%	4.6 months	1 year OS rate: 53.8%	Gr.3–4 peripheral neuropathy: 12% Gr. 3–4 neutropenia: 70% Gr. 3–4 fatigue: 13%

MBC, metastatic breast cancer; CT, chemotherapy; PFS, progression-free survival; pts, patients; OS, overall survival; CR, complete response; PR, partial response; DCR, disease control rate; CBR, clinical benefit rate; TTF, time to treatment failure; n.r., not reported.

more than fourth) and 70 (cohort B) the 125 mg/m^2 qw regimen (25 in second line, 18 in third and 27 in anything more than fourth). Visceral involvement was present in 67% of patients, with three or more metastatic sites in 43%, while 68% and 65% of patients were pretreated with taxane-based chemotherapy in the adjuvant or metastatic settings, respectively. Statistical analysis showed no predictive or prognostic value of the evaluated variables [disease-free interval (DFI), tumour subtype, site and number of metastases, previous taxane-based chemotherapy, prior lines of treatment for metastatic disease, dosing schedules], while the line of chemotherapy significantly affected both the probability of response (61% ORR in second line *versus* 38% in more than three lines; $p < 0.05$) and outcome (PFS 12.6 *versus* 4.9 months, respectively; $p = 0.03$). In the subgroup analysis, an age under 65 years, DFI up to 24 months, triple-negative subtype and predominant visceral disease were significantly correlated with higher ORR and longer PFS in cohort A, while in cohort B older patients with no visceral involvement and as many as two metastatic sites had the better outcome ($p = 0.04$) [Palumbo *et al.* 2015a]. The question of whether *nab*-paclitaxel could be a good chance in taxane pretreated MBC patients has been specifically addressed in an additional, recently completed trial by our Group. This single-arm, multicentre, prospective study was undertaken to assess the activity, safety and impact on quality of life (QoL) of q3w 260 mg/m^2 *nab*-paclitaxel as second-line chemotherapy in women who at the time of disease relapse had already received the most active agents in the adjuvant or metastatic settings (i.e. conventional taxanes). The activity of q3w *nab*-paclitaxel observed in our study was higher than that previously reported in taxane-pretreated MBC patients [Blum *et al.* 2007; Dent *et al.* 2013; Lohmann *et al.* 2013], but cross-comparison of results is difficult because of the different characteristics of enrolled patients. We reported an ORR of 48%, including 13% complete responses, in 52 evaluable patients: 13 out of 24 women (54%) previously given paclitaxel/bevacizumab or docetaxel/capecitabine as first-line treatment for the metastatic disease obtained an objective response. Overall, 77% of patients had a clinical benefit from their second-line treatment with *nab*-paclitaxel, since 19 stable diseases lasting more than 6 months were observed. The median PFS was 8.9 months (range 5–21+ months), the median OS has not yet been reached. The treatment-related toxicities were expected and

manageable, with good patient compliance and preserved QoL in patients given long-term treatment. A short time to response was also noted, with 98% of responder patients achieving maximum response by cycle 3 (median 70 days, range 52–86 days) [Palumbo *et al.* 2015b]. An additional mono-institutional phase II trial evaluated *nab*-paclitaxel according to the weekly or 3-weekly schedule on 42 taxane-pretreated women. As expected in a heavily pretreated population, lower ORR and more significant toxicity were observed [Fabi *et al.* 2015].

Nab-paclitaxel in HER2-positive metastatic breast cancer

Treatment options and outcomes for HER2-positive (HER2+) MBC have improved significantly over the past decade with the availability of several agents targeting the HER2 pathway, including trastuzumab, lapatinib, pertuzumab, and more recently trastuzumab emtansine [Mustacchi *et al.* 2015]. In early as well as advanced disease, synergy between chemotherapy and HER2-directed therapy has improved PFS and OS, compared with chemotherapy alone [Balduzzi *et al.* 2014]. The better therapeutic index of *nab*-paclitaxel compared with traditional taxanes makes it an attractive choice for evaluation as part of combination regimens with HER2-directed therapy. In Table 2, the results of the studies concerning the use of *nab*-paclitaxel in patients with HER2+ disease are described. The combination of qw *nab*-paclitaxel administered at 125 mg/m^2 on days 1, 8 and 15 of a 28-day cycle plus concurrent trastuzumab (loading dose 4 mg/kg, than 2 mg/kg qw) as first-line treatment was evaluated in a phase II study on 72 MBC patients [50 HER2 negative (HER2−) and 22 HER2+]. The ORR was 38.1% in HER2− patients and 52.4% in HER2+ patients. Median PFS was 12.8 and 18.7 months and median OS 27.3 and 36.8 months, respectively. The most commonly observed toxicities were mild or moderate, and grade 3 sensory neuropathy that occurred in only six patients (8%) [Mirtsching *et al.* 2011]. Another multicentre phase II trial in 33 patients with HER2+ MBC evaluated the efficacy and safety of qw *nab*-paclitaxel (100 mg/m^2 on days 1, 8 and 15) in combination with carboplatin [area under the curve (AUC) = 2 on days 1, 8 and 15 in the first set of 13 patients and AUC = 6 on day 1 of a 28-day cycle on the latter set of 19 patients] and qw trastuzumab (2 mg/kg after a loading dose of 4 mg/kg). The ORR was 62.5%, clinical benefit rate

Table 2. *Nab*-paclitaxel in HER2-positive MBC.

Reference, study type	Total/evaluable pts Median age (range)	Treatment regimen	Previous treatment	Treatment response	Median PFS	Median OS	Highest reported toxicities (%)
Conlin *et al.* [2010], Multicentre phase II	32/32 52 years (29–76)	*Nab*-P, 100 mg/m2 + CBDCA AUC = 2, on day 1, 8, 15 q4w (13 pts) or AUC = 6 q4w (19 pts) + Trastuzumab 4mg/Kg (loading dose) then 2mg/Kg qw	Previous neo-adjuvant CT: 44% Taxane-based CT: 34%	ORR: 62.5% CR: 9% PR: 53% CBR: 81%	16.6 months	n.r.	Gr. 4 neutropenia: 9% Gr. 3 sensory neuropathy: 3% Gr. 3 fatigue: 16%
Mirtsching *et al.* [2011], Multicentre phase II	72/64 63.5 years (41–90) • 21 pts HER2-+ disease	*Nab*-P, 125 mg/m² on day 1, 8, 15 q4w + Trastuzumab 4mg/Kg (loading dose) then 2mg/Kg qw	Adjuvant CT: 68% Taxane-based CT: 20.8% Adjuvant Trastuzumab: 2.7%	ORR: 42.2% CR: 7.8% PR: 34.3% CBR: 68.8% • HER2+ population: ORR: 52.4% CR: 14.2% PR: 38.0% CBR: 71.4%	14.5 months (range 1–49.3) • HER2+ population: 18.7 months	29 months (range 1–49.3) • HER2+ population: 36.8 months	Gr. 3 neutropenia: 11.1% Gr. 3 sensory neuropathy: 8.3% Gr. 3 fatigue: 6.9% Gr. 3 pain: 15.2% Gr. 4 cardiac event: 1.3%
Yardley *et al.* [2013], Single-arm multicentre phase II	55/55	*Nab*-P, 100 mg/m² on day 1, 8, 15 q4w + Lapatinib 1000 mg orally once daily on a continuous basis	Neo-adjuvant CT: 57% First line: 25%	ORR: 53% PR: 47% CR: 7% SD: 17%	39.7 weeks	Not reached	Gr. 3 diarrhea: 20% Gr. 3 neutropenia: 22% Gr. 4 events (diarrhea, nausea, fatigue, febrile neutropenia, and hypokalemia): 8%

MBC, metastatic breast cancer; CR, complete response; PR, partial response; CT, chemotherapy; CBR, clinical benefit rate; n.r., not reported; SD, stable disease; PFS, progression free survival; OS, overall survival; pts, patients.

81% and median PFS 16.6 months. Grade 4 neutropenia was observed in 9% of patients, with one case of febrile neutropenia, while the frequency of peripheral neuropathy was 13% for grade 3 and 3% for grade 4 toxicity [Conlin *et al.* 2010]. More recently, efficacy and safety of qw *nab*-paclitaxel (100 mg/m² on days 1, 8 and 15 every 28 days) plus lapatinib (1000 mg/daily continuously) were evaluated in an open-label, single-arm multicentre phase II study in 55 women with HER2+ MBC who had received no more than one prior chemotherapy for metastatic disease. The ORR was 53%, with 47% partial responses, 7% complete responses, and 17% stable disease. The median estimated of investigator-assessed PFS was 39.7 weeks, with a median time to response of 7.8 weeks. The median duration of response and median TTP were 48.7 and 41 weeks, respectively. Grade 3 neutropenia occurred in 22% of cases, and five patients (8%) experienced grade 4 adverse events (diarrhoea, nausea, fatigue, febrile neutropenia, and hypokalaemia) [Yardley *et al.* 2013].

Nab-paclitaxel in selected populations

A consistent proportion of patients are underrepresented across the clinical trials due to the relative rarity of their pathological condition (triple-negative breast cancer), the unfavourable clinical course (patients with extensive visceral or brain metastases, short disease-free interval), or their intrinsic frailty (elderly patients). In Table 3 we summarize the results of *nab*-paclitaxel use in these selected populations.

Triple-negative metastatic breast cancer

Triple-negative breast cancer (TNBC) (lacking overexpression of HER2 and expression of estrogen and progesterone receptors) remains a difficult-to-treat biological subtype due to a lack of response to hormonal and HER2-targeted agents coupled with an aggressive disease course [Dent *et al.* 2007; Oakman *et al.* 2010]. Clearly, there is a need for better therapeutic options in women with metastatic TNBC, ideally in the form of target agents, although the heterogeneity within the disease has made achieving this goal more complex [Davis *et al.* 2014]. To date, only one trial has been completed and published in which a TNBC-exclusive population was treated with *nab*-paclitaxel. In this multicentre phase II study, 34 women received first-line chemotherapy with *nab*-paclitaxel (100 mg/m² on days 1, 8 and 15)

plus carboplatin (AUC = 2 on days 1, 8 and 15) and bevacizumab (10 mg/kg on days 1–15 of a 28-day cycle). An ORR of 85% was reached, with a clinical benefit rate of 94%. The median PFS was 9.2 months. Treatment was well tolerated, with grade 3–4 neutropenia and thrombocytopenia in 53% and 18% of cases, respectively, and one case of febrile neutropenia; in addition, one of each of grade 3 and grade 4 thrombotic events were observed [Hamilton *et al.* 2013]. In a previous single-centre, open-label phase II study, 30 women with HER2− MBC, including 13 TNBC, received gemcitabine 1500 mg/m², *nab*-paclitaxel 150 mg/m², and bevacizumab 10 mg/kg on days 1 and 15 of a 28-day cycle. Median PFS was 10.4 months (95% CI, 5.6–15.2 months). The ORR in 29 evaluable patients was 75.9%, comprising eight (27.6%) complete and 14 (48.3%) partial responses; five patients had stable disease and only two patients (6.9%) had progressive disease as their best response. The clinical benefit rate was 93.1% (27/29) in the overall group and 84.6% in the triple-negative cohort (11/13); median PFS was 10.4 months with 18-month survival rate of 77.2%. Interestingly, no significant difference in PFS and OS values was observed between patients with TNBC and those with hormone receptor-positive disease, suggesting a high degree of activity for the regimen in the TNBC population. Safety data were not reported separately for the TNBC subgroup, with 8/29 patients (27.6%) patients experiencing grade 3 or 4 toxicity [Lobo *et al.* 2010]. Finally, a randomized phase III trial by the Cancer and Leukemia Group B (Trial CALGB 40502) compared qw paclitaxel 90 mg/m² given the first 3 of 4 weeks (qw3/4) plus bevacizumab 10 mg/kg every 2 weeks (q2w) *versus nab*-paclitaxel 150 mg/m² qw3/4 plus bevacizumab 10 mg/kg q2w or ixabepilone 16 mg/kg qw3/4 plus bevacizumab 10 mg/kg q2w. Median PFS was similar in the 272 women receiving paclitaxel and in the 263 women given *nab*-paclitaxel [11 *versus* 9.3 months, respectively; hazard ratio (HR) 1.20, *p* = 0.054]; in the subset of TNBC patients HR was 0.86, *p* = 0.43. Again, safety data were not reported separately for the TNBC subgroup, but high rates of serious adverse events were observed in the *nab*-paclitaxel plus bevacizumab arm, with grade 3 or above neurotoxicity in 26% and grade 3 or above haematological toxicity in 55% of patients, respectively; dose reductions were required in 45% of patients by cycle three and discontinuation by cycle five in more than 40% of patients [Rugo *et al.* 2015].

Table 3. *Nab*-paclitaxel in 'special' populations (triple negative breast cancer, aggressive disease, elderly patients).

Reference, Study type	Total/evaluable pts Median age (range)	Treatment regimen	Previous treatment	Treatment response	Median PFS	Median OS	Highest reported toxicities (%)
Nab-paclitaxel in triple negative breast cancer							
Hamilton et al. [2013], Multicentre phase II	38/34 50 years (30–76) • 34/34 pts with TNBC, first line setting	Nab-P, 100 mg/m² on day 1, 8, 15 q4w + Carboplatin AUC 2 on day 1, 8, 15 q4w + Bevacizumab 10 mg/kg on day 1–15 q4w	Adjuvant CT 77% Taxane-containing therapy 62%	ORR: 85% CR: 17.7% PR: 67.7% CBR: 94%	9.2 months (range 7.8–25.1)	n.r.	Gr. 3–4 neutropenia: 53% Gr. 3–4 thrombocytopenia: 18% Gr. 3 sensory neuropathy: 6%
Lobo et al. [2010], Single centre phase II	30/29 • 13/30 pts with TNBC, first line setting	Nab-P, 150 mg/m² on day 1, 15 q4w + Gemcitabine 1500 mg/m² on day 1, 15 q4w + Bevacizumab 10 mg/kg on day 1–15 q4w	Adjuvant CT 37.9%	ORR: 75.9% CR: 27.6% PR: 48.3% PD: 6.9% SD: 17.2% CBR: 93.1% (84.6% for TNBC)	10.4 months (range 5.6–15.2) 18-months • 10.6% in TNBC; • 25.0% for HR+	18-month OS rate: 82.5% for TNBC 18-months OS rate: 77.2% for HR+	Gr. 3 toxicity in 27.6% (port-a-cath infections, leukopenia, peripheral neuropathy, seizure/syncope, shortness of breath, cardiac tamponade, thrombocytopenia) A single case of neutropenia fever
Rugo et al. [2015], Multicentre phase III	799/783 57 years • 25% with TNBC, first line setting	Bevacizumab 10 mg/kg on day 1–15 q4w + Arm A paclitaxel 90 mg/m² on day 1, 8, 15 q4w Arm B Nab-P, 150 mg/m² on day 1, 8, 15 q4w Arm C Ixabepilone 16 mg/m2 on day 1, 8, 15 q4w	44% treated with taxane as adjuvant therapy	ORR (A) 38% ORR (B) 34% ORR (C) 27% (p = 0.0038 for inferiority to arm A)	TNBC A: 7.4 months B: 6.5 months C: 5.6 months (p = 0.02 for inferiority to arm A)	Whole population: A: 27.4 months B: 23.5 months C: 23.6 months (p = 0.027 for inferiority to arm A)	Gr. ≥3 hematologic: A: 22% B: 55% C: 12% Gr. ≥3 nonhematologic A: 49% B: 65% C: 58%

(Continued)

Table 3. (Continued)

Nab-paclitaxel in aggressive breast cancer

Reference, Study type	Total/evaluable pts Median age (range)	Treatment regimen	Previous treatment	Treatment response	Median PFS	Median OS	Highest reported toxicities (%)
O'Shaughnessy et al. [2013], Retrospective analysis of phase II (CA024) and phase III (CA012) trials	Visceral dominant disease CA012 n = 138 CA024 n = 247 Short DFI CA012 n = 72 CA024 n = 74	CA012 (A) *Nab*-P, 260 mg/m² q3w (B) paclitaxel 175 mg/m² q3w. CA024 (A) docetaxel 100 mg/m² q3w or (B) *Nab*-P, 300 mg/m2 q3w or (C) *Nab*-P, 100 mg/m² 1, 8, 15 q4w or (D) *Nab*-P, 150 mg/m² 1, 8, 15 q4w	First line setting	Visceral dominant CA012 A: 42% B: 23% CA024 A: 44% B: 63% C: 76% D: 37% Short DFI CA012 A: 43% B: 33% CA024 A: 35% B: 52% C: 64% D: 21%	Visceral dominant CA012 A: 5.6 months B: 3.8 months CA024 A: 10.9 months B: 7.5 months C: 13.1 months D: 7.8 months Short DFI CA012 A: 5.0 months B: 3.5 months CA024 A: 7.4 months B: 7.3 months C: 14.1 months D: 5.5 months	Visceral dominant CA012 A: 15.1 months B: 14.2 months CA024 A: 27.7 months B: 19.6 months C: 32.1 months D: 21.4 months Short DFI CA012 A: 14.6 months B: 11.7 months CA024 A: 16.6 months B: 19.1 months C: 18.6 months D: 14.4 months	• Treatment delays and dose reductions similar frequencies between the two treatment arms and across both prognostic subgroups • Gr 3/4 neutropenia more frequent for paclitaxel in the poor prognostic factor subgroups, • sensory neuropathy and fatigue more frequent for *nab*-paclitaxel
Seidman et al. [2013], Randomized phase II trial	Visceral dominant disease 212/208 Median age 59 (Arm A) and 56 years (Arm B, C).	Bevacizumab 10 mg/kg on day 1–15 q4w + Arm A *nab*-paclitaxel 260 mg/m² on day 1, q3w Arm B *nab*-paclitaxel 260 mg/m² on day 1, q2w Arm C *nab*-paclitaxel 130 mg/m² on day 1, 8, 15 q3w	First line setting	ORR (A) 45% ORR (B) 39% ORR (C) 46% (p = 0.465)	A: 7.6 months B: 5.8 months C: 9.0 months (p = 0.166)	A: 19.8 months B: 18.9 months C: 24.6 months (p = 0.335 for inferiority to arm A)	Treatment limiting peripheral neurotoxicity: A: 19% B: 43% C: 27%

Table 3. (Continued)

Reference, Study type	Total/evaluable pts Median age (range)	Treatment regimen	Previous treatment	Treatment response	Median PFS	Median OS	Highest reported toxicities (%)
Nab-paclitaxel in elderly patients							
Aapro *et al.* [2011], *Post hoc* analysis of phase III [CA012] and phase II [CA024] studies	• CA012 *n* = 454 [62/62] over 65) • CA024 *n* = 300[52/52] over 65)	CA012 (A) *nab*-paclitaxel 260 mg/m² q3w (B) paclitaxel 175 mg/m² q3w CA024 (A) docetaxel 100 mg/m² q3w or (B) *nab*-paclitaxel 300 mg/m2 q3w or (C) *nab*-paclitaxel 100 mg/m² 1, 8, 15 q4w or (D) *nab*-paclitaxel 150 mg/m² 1, 8, 15 q4w	CA012 Neo/Adj, metastatic in 80% of pts CA024 Neo/Adj, metastatic in 1/3 of pts	ORR CA012 A: 27% B: 19% CA024 A: 32% B: 22% C: 64% D: 60%	CA012 A: 5.6 months B: 3.5 months CA024 A: 8.5 months B: 13.8 months C: 9.2 months D: 18.9 months	CA012 A: 17.6 months B: 12.8 months CA024 A: 21.2 months B: 19.9 months C: 21.7 months D: 20.7 months	CA012 • Gr 3 sensory neuropathy 17% vs 0 • Gr 3–4 neutropenia 35% vs 65% CA024 • Gr 3 sensory neuropathy 16% vs 11% vs 21% vs 20% • Gr 4 neutropenia 7% to 22% in the *nab*-paclitaxel arms; 34% with solvent-based paclitaxel or and 74% docetaxel

MBC, metastatic breast cancer; TNBC, triple negative breast cancer; CT, chemotherapy; CR, complete response; PR, partial response; DCR, disease control rate; CBR, clinical benefit rate; pts, patients; PD, progressive disease; SD, stable disease.

A randomized phase II trial is currently under way [Forero-Torres *et al.* 2011], in which 60 patients with TNBC will receive qw *nab*-paclitaxel for 3 consecutive weeks with or without tigatuzumab, a novel humanized monoclonal antibody that demonstrated strong *in vitro* and *in vivo* activity against basal-like breast cancer cells, which was enhanced by chemotherapeutics such as paclitaxel [Forero-Torres *et al.* 2010]. Finally, the randomized phase II-III tnAcity study is evaluating the activity of *nab*-paclitaxel in combination with gemcitabine or carboplatin *versus* gemcitabine plus carboplatin in patients with metastatic TNBC to verify the usefulness of *nab*-paclitaxel as part of doublet chemotherapy in this setting [ClinicalTrials.gov identifier: NCT01881230].

Aggressive metastatic breast cancer

Although aggressive MBC has not been formally defined, several clinical and molecular features have been identified that are associated with poor prognosis [Sorlie *et al.* 2001; Bauer *et al.* 2007]. In addition to the triple-negative phenotype, women who present with a higher number of metastatic sites, visceral-dominant disease and shorter DFI are considered affected with 'aggressive' MBC. For these patients, fast-acting and effective chemotherapy is warranted, but there is a lack of clear guidance regarding the most appropriate regimen to choose. To examine the efficacy and safety of *nab*-paclitaxel *versus* paclitaxel and docetaxel in patients with poor prognostic factors, a *post hoc* analysis of women who received *nab*-paclitaxel for first-line treatment in the two randomized phase III and phase II trials CA012 and CA024 [Gradishar *et al.* 2005, 2009] was undertaken, aiming to determine whether the efficacy and safety of *nab*-paclitaxel were maintained across patient subgroups defined by DFI or visceral-dominant metastases. Overall, the efficacy and safety results of the poor prognostic factor subgroups were similar to those of the intention-to-treat (ITT) populations. In the phase III study, patients with visceral-dominant disease achieved a higher ORR (42% *versus* 23%, *p* = 0.022) and a longer PFS and OS, although differences in these outcome values were not statistically significant. Among patients who had a DFI of less than 2 years, ORR, PFS, and OS were also in favour of *nab*-paclitaxel, again without statistical significance, likely because of the small number of patients in these groups. The poor prognostic factor subset analysis of the phase II trial also demonstrated similar results to those of the ITT

populations: patients with visceral-dominant metastases treated in the qw3/4 arms achieved higher ORRs compared with docetaxel (63% and 76% for the 100 mg/m² and 150 mg/m² groups, respectively, *versus* 37% for the docetaxel arm; *p* = 0.002 and <0.001, respectively). The paclitaxel 150 mg/m² arm also demonstrated a longer PFS *versus* the docetaxel arm (13.1 *versus* 7.8 months, *p* = 0.019) and a not statistically significant better OS (32.1 *versus* 21.4 months). The subgroups of patients in the retrospective analysis showed similar safety results as the ITT populations: in both the trials, patients with markers of poor prognosis who received *nab*-paclitaxel experienced a lower incidence of grade 3 neutropenia and higher incidence of sensorial neuropathy [O'Shaughnessy *et al.* 2013]. An additional subgroup analysis retrospectively explored efficacy in women with poor prognostic factors enrolled in a phase II trial in which three regimens of *nab*-paclitaxel plus bevacizumab were tested as first-line treatment for HER2− MBC. No differences were found in the efficacy or safety in patients with visceral-dominant disease or DFI up to 2 years compared with the ITT populations. In a pooled treatment-arm analysis, the prevalence of three or more toxicities was similar in both groups: sensory neuropathy (44%), fatigue (24%), and neutropenia (22% for patients with short DFI and 19% in those with visceral-predominant disease) [Seidman *et al.* 2013].

Taken together, these data suggest that *nab*-paclitaxel exhibits substantial clinical activity in patients with virulent MBC. Ongoing research will further define the optimal *nab*-paclitaxel regimens for patients with different types of aggressive MBC, as at present, the available data do not clearly support the superiority of one schedule over another [Ciruelos and Jackisch, 2014; Gluck, 2014].

Elderly patients with metastatic breast cancer

Effective treatment of elderly patients with MBC represents an additional critical issue to clinicians: older women are typically under-represented in clinical trials because they are presumed to be at higher risk for therapy-induced adverse events, due to age and potential comorbid conditions [Jolly *et al.* 2012]. Indeed, studies indicate that body clearance of chemotherapeutic agents or their formulation vehicles may be altered by age, so patients older than 65 years are likely to metabolize chemotherapeutic agents more slowly,

or differently, than younger women, resulting in higher drug-exposure levels and more severe side effects [John *et al.* 2003; Markopoulos and van de Water, 2012]. In a study comparing a single 1-hour infusion of solvent-based paclitaxel at 80 mg/m^2 in patients 70 years old or above with MBC *versus* 100 mg/m^2 in patients less than 70 years old, the older women had reduced unbound (active) paclitaxel clearance, with concomitant increased paclitaxel bioavailability of the drug [Smorenburg *et al.* 2003]. This effect was thought to be related, in part, to the surprisingly faster clearance of Cremophor EL observed in the older patients, which may be the result of elevated circulating enzyme levels in the elderly; similar to those with moderate to severe hepatic dysfunction [Nannan Panday *et al.* 1999; John *et al.* 2003; Wasil and Lichtman, 2005]. A prospective trial by the Cancer and Leukemia Group B (CALGB 9762) demonstrated age-related differences in the pharmacokinetics of paclitaxel but no significant adverse sequelae in terms of infections and hospitalization. However, this trial analysed only the first cycle of treatment and cumulative toxicity was not assessed [Lichtman *et al.* 2006]. An increased cardiovascular toxicity was reported in a prospective study of qw paclitaxel in 46 elderly patients with MBC; the baseline geriatric assessment predicted a lower probability of response and survival but not of toxicity [Del Mastro *et al.* 2005]. More extensive data have recently been reported by a combined analysis on 1048 elderly women included in two randomized trials evaluating the efficacy and toxicity of paclitaxel in older MBC patients. In this analysis, treatment activity was similar among the age groups (<55 years, 45%; 55–64 years, 29%; ≥65 years, 26%), but an increased incidence of paclitaxel-related toxicities was observed in the elderly population. Specifically, grade 3 or above leucopenia, granulocytopenia, anorexia, bilirubin elevation and neurotoxicity increased linearly with age; patients over 65 years receiving second-line therapy had the shortest time to neurotoxicity [Lichtman *et al.* 2012].

A subgroup analysis by age of data from the pivotal phase III study indicated that *nab*-paclitaxel is associated with improved clinical benefit in both younger (<65 years) and older (≥65 years) patients with MBC compared with conventional paclitaxel. ORR was greater for *nab*-paclitaxel than for standard paclitaxel in patients 65 years old or above (27% *versus* 19%, respectively), but the results did not reach statistical significance

because of the small number of patients in this subset. For the elderly population, the incidence of the following adverse events were notably lower in the *nab*-paclitaxel group than in the standard paclitaxel group: neutropenia (23% *versus* 59%, respectively), leukopenia (10% *versus* 31%, respectively), nausea (20% *versus* 38%, respectively), hyperglycaemia (0% *versus* 19%, respectively) and flushing (0% *versus* 16%, respectively) [Gradishar *et al.* 2005]. Corroborating these findings, a *post hoc* analysis of two randomized trials [Gradishar *et al.* 2005, 2009] investigated the safety and efficacy of qw and q3w *nab*-paclitaxel in older patients with MBC compared with q3w solvent-based paclitaxel and docetaxel. Among the total treatment population in the two studies, 114 (15%) were aged 65 years or above (phase II, *n* = 52; phase III, *n* = 62) and all were included in the analysis. In the phase II trial, ORRs were 22%, 64% and 60% for *nab*-paclitaxel dosed at 300 mg/m^2 q3w, 100 mg/m^2 qw and 150 mg/m^2 qw, respectively, and 32% for docetaxel. The advantage of qw dosing observed for ORR was also observed for the disease control rate (DCR): 53%, 56%, 86%, and 90%, respectively. Median PFS times were 13.8, 9.2, 18.9, and 8.5 months, respectively; the median OS times were 19.9, 21.7 and 20.7 months, respectively, for older women treated with *nab*-paclitaxel dosed at 300 mg/m^2 q3w, 100 mg/m^2 qw and 150 mg/m^2 qw, respectively, and 21.2 months for patients treated with docetaxel [Gradishar *et al.* 2009]. When examined across studies, the ORRs for *nab*-paclitaxel dosed at 260 and 300 mg/m^2 q3w, and 100 and 150 mg/m^2 qw were 27%, 22%, 64% and 60%, respectively, suggesting that weekly dosing results in higher antitumour activity than q3w dosing in these older patients. In the phase III study, treatment outcomes were also examined according to line of therapy: women receiving first-line therapy had higher ORR and longer PFS than those receiving second-line treatment (50% *versus* 14% and 6.7 *versus* 2.1 months). The DCR and the median PFS were higher for those treated with 260 mg/m^2 q3w *nab*-paclitaxel than for 175 mg/m^2 q3w solvent-based paclitaxel (53% *versus* 41% and 5.6 *versus* 3.5 months, respectively). For older patients treated with *nab*-paclitaxel, median OS was 17.6 *versus* 12.8 months of those receiving conventional paclitaxel [Gradishar *et al.* 2005]. Across both studies, dose reductions and delays appeared to be more frequent for qw *nab*-paclitaxel than for q3w solvent-based paclitaxel or docetaxel in this older population: in the phase II study patients who received at least 90%

of the intended dose were 57% and 40% for qw 100 and 150 mg/m², respectively, *versus* 67% and 74% for q3w *nab*-paclitaxel dosing or docetaxel. In the phase III study, all patients treated with *nab*-paclitaxel and 97% of those treated with solvent-based paclitaxel received at least 90% of the intended dosage. Nevertheless, the mean cumulative dose of paclitaxel was higher for the qw *nab*-paclitaxel regimens than that observed for the q3w *nab*-paclitaxel regimens. In general, grade 3 and 4 treatment-related adverse events were similar for the elderly patients compared with results from all patients in the two studies. In the phase II trial, the incidence of grade 3 sensory neuropathy was similar for qw *nab*-paclitaxel (20–21%) and q3w docetaxel (16%) and lower for q3w *nab*-paclitaxel (11%); in the phase III study, 17% of women had grade 3 sensory neuropathy [Aapro *et al.* 2011].

The age-related changes in *nab*-paclitaxel pharmacokinetics and pharmacodynamics have been investigated in a recently reported prospective study on 40 women who received the drug at the dose of 100 mg/m² weekly for 3 weeks followed by a 1-week break as first- or second-line chemotherapy. The treatment was well tolerated across all the age groups: statistical analyses showed a borderline positive association between age and 24-hour AUC, but no differences were noted for pharmacodynamic variables (grade 3 toxicity, dose reductions or dose omissions) based on age, while a significant association was found between chemotherapy toxicity risk-score category and presence of grade 3 toxicity [Hurria *et al.* 2015].

The safety and efficacy of paclitaxel albumin in elderly patients is also being explored in a prospective, multicentre, randomized phase II–III study in which elderly patients with an increased risk of relapse of primary breast cancer are randomized to receive adjuvant therapy with either standard therapy (four cycles of epirubicin/cyclophosphamide or six cycles of cyclophosphamide/methotrexate/ fluorouracil) or six cycles of *nab*-paclitaxel (100 mg/m² on days 1, 8 and 15 q22) plus capecitabine (2000 mg/m² on days 1–14 q22) [Von Minckwitz *et al.* 2010].

Discussion

Although the outcome of women with MBC is slowly but steadily improving, with median OS increased from 18 to 28 months in recent years [Gennari *et al.* 2011; Dawood *et al.* 2008, 2010], the therapeutic goals in the metastatic setting remain palliative in nature, aimed at controlling symptoms, improving or maintaining QoL and prolonging survival, while carefully balancing treatment efficacy and toxicity [Chung and Carlson 2003; Smith, 2006; Jones, 2008]. For patients in whom chemotherapy is recommended, the choice between a single agent or a combination regimen, and the selection of a specific therapy, should take into account several factors in an effort to individualize therapy as much as possible. Despite more than 40 years of clinical research, treatment choice beyond the first line in MBC is not an easy task in terms of drug selection and combination, since the majority of patients will have been exposed to paclitaxel (alone, or with docetaxel) at the time of disease relapse. There is little evidence from available data that major differences exist among the commonly used taxane-based regimens, and the issue of sequential *versus* combined first-line approach in the metastatic setting remains an unresolved question. It is our opinion that taxanes will likely continue to be used in earlier lines of therapy, whereas eribulin and ixabepilone may be more appropriate for later lines of treatment. [Fossati *et al.* 1998; Cardoso *et al.* 2014; Sachdev and Jahanzeb, 2015]. The introduction of *nab*-paclitaxel opened a novel scenario in the treatment of MBC and now we have more options available to look towards the possibility of tailoring taxane-based therapy in the decision-making process. The challenge to pick the adequate dose for the individual patient will depend on the therapeutic ratio of the different possible regimens. In clinical practice, for *nab*-paclitaxel, this is linked to the probability of sensory neuropathy. In the clinical trials reviewed in this review article, the incidence of grade 3 neuropathy ranges from 10% for the q3w schedule up to 14% for the qw 150 mg/m², 6–12% for the qw 125 g/m², and 0–8% for the qw 100 mg/m² regimen in first line [Gradishar *et al.* 2005, 2009, 2012]. For patients receiving the q3w 260 mg/m² regimen as second-line treatment, following taxane-based chemotherapy in the adjuvant or metastatic setting, the incidence was 6% [Palumbo *et al.* 2015b], while in heavily taxane-pretreated patients, the incidence was 19% for the 125 mg/m² qw schedule and 8% for the 100 mg/m² schedule [Blum *et al.* 2007]. Even lower incidence has been reported in the published real-life experiences [Aigner *et al.* 2013; Dent *et al.* 2013; Lohmann *et al.* 2013; Palumbo *et al.* 2015a; Singh *et al.* 2014], and grade 4

sensory neuropathy did not occur with any of the studied *nab*-paclitaxel regimens.

As elegantly highlighted in a recent editorial [Kudlowitx and Muggia, 2014], further investigation is required to better manage this difficult-to-quantify toxicity, since data in MBC are rather equivocal at present time. Numerous studies for the management of neuropathy exist, but there is a need for more prospective trials to assess patient-reported neuropathy and validated predictors of drug-related neurotoxicity [Ohno *et al.* 2014; Rivera and Cianfrocca, 2015]. The severity, time on onset and improvement in neuropathy are important considerations for patient management. While the rate of grade 3 or more neuropathy with taxanes has been shown to be dose and schedule dependent, time to improvement to anything up to grade 1 is typically shorter with *nab*-paclitaxel than for other taxanes in MBC patients.

For clinicians, the time to reversibility of neuropathy appears to be an additional important variable to be considered when choosing the dose and schedule of *nab*-paclitaxel in treating MBC patients. The hereby reviewed data confirm that sensorial neuropathy occurs late in the course of treatment with both the qw and q3w schedules, also in taxane-pretreated patients, and adequate management by dose reductions or treatment delays allows to maintain an adequate dose-intensity of the drug [Gradishar *et al.* 2005, 2009, 2012; Blum *et al.* 2007; Von Minckwitz *et al.* 2013; Palumbo *et al.* 2015a, 2015b].

Although the introduction of *nab*-paclitaxel represents a significant advance in taxane therapy, further work is required to fully establish its role in the management of MBC. Indeed, since it was approved, research efforts have continued to evaluate alternative dosing regimens of *nab*-paclitaxel and to explore its use as part of combination therapy. The true question remains if *nab*-paclitaxel can be used now in any setting where paclitaxel was previously used. Obviously, the comparison of the two agents in all these setting would require many years of research and a substantial number of patients enrolled in prospective, randomized studies.

Additional strategies to optimize *nab*-paclitaxel-based therapy in MBC include evaluating response to treatment according to specific patient and tumour characteristics. In this view, it would be useful to consider the role of potential predictive markers of efficacy when administering *nab*-paclitaxel for the treatment of MBC patients. For example, SPARC expression and its interaction with albumin is suggested to be the reason for enhanced uptake and intratumoural accumulation, indicating a possible role for SPARC as a biomarker for *nab*-paclitaxel effectiveness [Desai 2007; Trieu *et al.* 2007]. Also, in a recently reported analysis of tumour tissue of 667 patients from the neoadjuvant GeparTrio trial, high SPARC expression was associated with a higher chance of achieving a pathological complete remission after taxane-based chemotherapy, especially in the triple-negative subgroup, suggesting that *nab*-paclitaxel may be particularly effective in this biological subtype [Lindner *et al.* 2015]. However, available data also suggest that SPARC expression varies according to tumour histology and grade [Watkins *et al.* 2005; Desai *et al.* 2008]. Similarly, a strong association between caveolin-1 expression and breast carcinomas with a basal-like phenotype has been reported, suggesting that the utilization of the gp60/caveolin-1 pathway as a means to deliver cytotoxic therapy may be particularly lucrative in some breast cancer subtypes [Pinilla *et al.* 2006; Savage *et al.* 2007] and that patients with higher caveolin-1 expression, such as those with a basal-like phenotype, may derive greater benefit from *nab*-paclitaxel [Altundag *et al.* 2006]. On the other hand, retrospective and real-life data showed a significantly higher ORR in patients with visceral-dominant metastases treated with *nab*-paclitaxel compared with solvent-based paclitaxel [O'Shaughnessy *et al.* 2013; Palumbo *et al.* 2015a, 2015b]. Thus, disease-related factors such as visceral-dominant metastases may be clinical predictive markers of treatment response. It appears clear that further investigation in the context of prospective, controlled clinical trials should be performed to evaluate and validate the role of both biological and clinical factors as markers of efficacy for *nab*-paclitaxel.

On the basis of the available literature data, we attempt to underline some key points that, in our opinion, could be useful for clinical practice.

1. *Nab*-paclitaxel has been shown to be active and well tolerated in taxane-pretreated MBC patients, producing encouraging ORR and PFS values without the concern of significant toxicity. Such an approach represents a valid therapeutic option for the

treatment of that increasing population of women who at the time of disease relapse have already received the most active agents in the adjuvant or metastatic settings, that is, conventional taxanes.

2. The good tolerability profile and encouraging preliminary efficacy data suggest that *nab*-paclitaxel could be a valid option for the management of women with HER2+ MBC. Since the role of targeted agents for the treatment of breast cancer continues to evolve, combination of *nab*-paclitaxel with newer biologically targeted agents have yet to be evaluated in ongoing and future clinical trials. In particular, the lack of a statistically significant advantage of *nab*-paclitaxel over paclitaxel reported in the neoadjuvant setting in this specific subgroup deserves further investigation [Untch *et al.* 2016].

3. The available studies of *nab*-paclitaxel-containing regimens for metastatic TNBC demonstrate promising efficacy data, such as an ORR of 34–85% [Lobo *et al.* 2010; Hamilton *et al.* 2013; Rugo *et al.* 2015], but future research is needed to answer questions as to the overall effectiveness and the ideal *nab*-paclitaxel regimen in this challenging setting. Subset analysis of randomized trials and recently reported real-world experiences also support the use of single-agent *nab*-paclitaxel for women with other disease features associated with poor prognostic factors, as visceral-dominant metastases and DFI of no less than 2 years.

4. The improved safety and efficacy profile of *nab*-paclitaxel compared with conventional taxanes suggests that the drug may be particularly useful in older patients. Specifically, the 150 mg/m^2 qw for 3 weeks followed by one week of rest *nab*-paclitaxel could be the optimal schedule in patients aged at least 65 years, since it resulted in 60% ORR and 21 months of median OS along with no significant serious adverse events [Biganzoli *et al.* 2009; Aapro *et al.* 2011]. Since the increased risk of neurotoxicity in elders remains a critical issue, older patients should be closely monitored for this event to minimize complications, and assessment of neuropathy in elders should include evaluation of functional decline and falls.

Finally, in an attempt to answer the question 'which schedule for which patients?' the following issues could help physicians to select the optimal dosing schedule according to the different patient profiles and clinical situations:

1. For women with aggressive disease, in which fast-acting and effective chemotherapy is essential, the q3w 260 mg/m^2 or the qw 150 mg/m^2 schedule could be the preferred regimens, also in taxane-pretreated patients. Findings from the randomized phase II and III studies and subsequent exploratory analyses all indicate that single agent *nab*-paclitaxel is associated with a rapid tumour response, even in patients whose tumours are characterized by poor prognostic factors. [Gradishar *et al.* 2005, 2009; O'Shaughnessy *et al.* 2013] These findings appear of importance in the practical management of MBC patients, since tumour response to chemotherapy can lead to restoration of organ function, symptom relief and improvement in patient QoL. In addition, retrospective and real-life data also suggest that patients achieving a complete or partial response on treatment with *nab*-paclitaxel appeared to live longer than those who did not, and this trend was seen across various patient subgroups [Dent *et al.* 2013; Lohmann *et al.* 2013; Palumbo *et al.* 2015 b]. However, whether tumour response could be indicative of a survival benefit with *nab*-paclitaxel is unknown, and the role of surrogate endpoints to predict OS benefit to chemotherapy remains an unresolved question.

2. For patients with slowly progressing disease who may benefit from longer treatment or for patients whose key objective of therapy is to maintain QoL, the 100–125 mg/m^2 qw schedule of *nab*-paclitaxel might be the preferred choice, considering that in this setting obtaining prolonged stabilization of disease can provide the same clinical advantage as exhibiting an objective response. Because of its favourable toxicity profile, the qw schedule also appears to be an attractive option for elderly patients as well as for combination regimens with other cytotoxic or targeted agents, allowing the physicians to monitor treatment closely and to react promptly to the onset of side effects such as neuropathy.

This concept is being explored further in the ongoing SNAP (schedules of *nab*-paclitaxel in metastatic breast cancer) study [ClinicalTrials. gov identifier: NCT01746225].

Conclusion

Several questions about *nab*-paclitaxel in the management of MBC are still pending, such as the optimal dose and treatment schedule in first and further lines of therapy, which risk population subgroups will benefit most, and whether it is possible to reverse prior resistance to taxanes with *nab*-paclitaxel. The answers to these questions should come from trials that are currently ongoing or those already planned for the near future. All in all, efficacy and safety data from both clinical trials and real-life experiences along with a more convenient administration confirm that the drug is an optimal treatment option for those 'difficult-to treat' MBC populations that represent a challenge in the routine clinical practice, enabling the continuous offering of safer, tailor-made approach.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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