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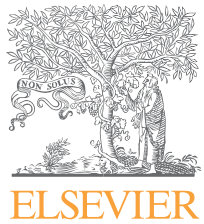

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The role of *nab*™-paclitaxel in managing metastatic breast cancer: a report of three cases

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ABSTRACT

Options for the treatment of metastatic breast cancer (MBC) continue to grow with the advent of signal transduction modulators, new cytotoxics, and new formulations of standard agents. These developments are welcome as a means of further extending progression-free and overall survival, and as a way of allowing us to tailor therapy to characteristics of the individual patient such as the molecular biology of their tumour, treatment history, and performance status. Targeting drug delivery to the tumour is a promising means of increasing the therapeutic index of highly active agents such as the taxanes, and nanoparticle albumin-bound (*nab*) paclitaxel is one such advance. This paper reviews the clinical trial background for *nab*-paclitaxel and three individual cases in which its use was judged especially appropriate. These include a patient with prior exposure to anthracycline and docetaxel needing second-line treatment for MBC, a patient requiring first-line treatment following adjuvant anthracycline, and a patient in whom flexible dosing was a potential advantage.

1. Introduction

The treatment of metastatic breast cancer (MBC) remains an extremely challenging area of oncology. The clinician must balance the likelihood of benefit against the risk of adverse events while taking into account the particular circumstances of the patient. The daily reality of the clinic is that trial data and formal indications provide only one source of guidance: individual experience (and perhaps still the "art of medicine") continue to have a role. The treatment decisions in the three cases outlined here represent the judgment of the clinicians involved. As others might have reached different conclusions, the considerations which led the clinicians to arrive at the decisions they made are discussed in detail.

The advent of novel therapies for MBC has led to significantly prolonged disease-free and overall survival (OS). In this setting, taxanes have been shown to be the most active single agents.[1] Due to their hydrophobic nature, however, the conventional taxanes paclitaxel and docetaxel require solubilization in detergent-like solvents such as Cremophor EL. These solvents are associated with toxicities, notably hypersensitivity reactions, neuropathy and haematotoxicity.[2] Novel nanoparticle albumin-bound or "*nab*" technology allows the coupling of hydrophobic drugs such as paclitaxel to albumin, the natural carrier in the body for hydrophobic molecules including fatty acids, hormones and vitamins. Besides avoiding adverse events associated with detergent-like solvents, *nab*-technology allows higher concentrations of active drug to be achieved in tumour tissues.[3]

2. *nab*-Paclitaxel versus Cremophor-solvent based paclitaxel

The superiority of *nab*-paclitaxel over solvent-based paclitaxel in clinical outcome was demonstrated in a phase III trial.[4] In this study, 454 patients with MBC were

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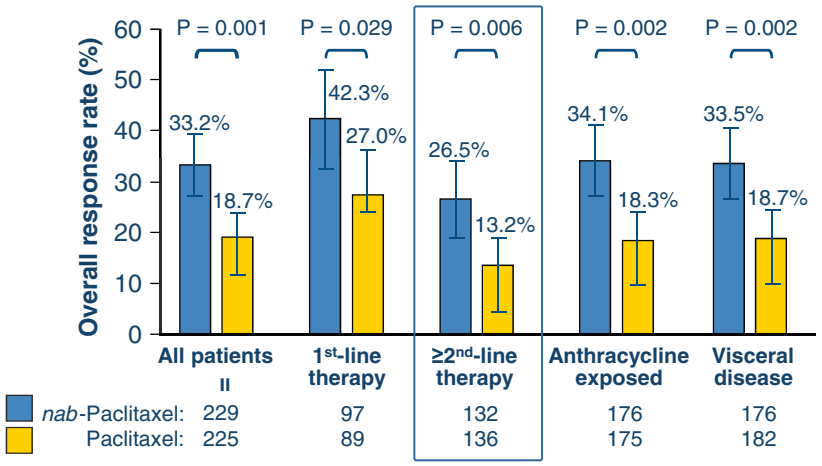

Fig. 1 – Overall response rates in the total population studied and in relevant sub-populations receiving *nab*-paclitaxel vs standard paclitaxel for the treatment of MBC.[4] Bars indicate 95% confidence intervals.

Table 1 – Non-haematological toxicities reported in patients with MBC receiving *nab*-paclitaxel or standard paclitaxel[4]

Adverse event	*nab*-Paclitaxel (n = 229)			Paclitaxel (n = 225)			P-value
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	
Hypersensitivity (%)	<1	0	0	0	1	0	0.150
Flushing (%)	<1	0	0	5	0	0	<0.001
Sensory neuropathy (%)	20	10	0	10	2	0	<0.001
Fatigue (%)	13	8	<1	16	3	<1	0.062
Myalgias (%)	12	7	0	15	2	0	0.567
Vomiting (%)	4	3	<1	4	1	0	0.022
Edema (%)	2	0	0	<1	<1	0	0.851

Table 2 – Haematological toxicities (grade 3 and 4) reported in patients with MBC receiving *nab*-paclitaxel or standard paclitaxel[4]

Hematologic toxicity	*nab*-Paclitaxel (n = 229)		Paclitaxel (n = 225)		P-value
	Grade 3	Grade 4	Grade 3	Grade 4	
Neutropenia (%)	25	9	32	22	<0.001
Thrombocytopenia (%)	<1	0	<1	0	0.290
Anaemia (%)	<1	<1	0	<1	0.279
Febrile neutropenia (%)	<1	<1	<1	0	0.491
Septic deaths (%)	0	0	0	0	–

randomised to *nab*-paclitaxel (260 mg/m^2) or standard paclitaxel (175 mg/m^2) every 3 weeks. Patients receiving *nab*-paclitaxel had a significantly higher objective response rate (ORR) than those treated with standard paclitaxel (ORR 33% vs 19% respectively, P = 0.001; Fig. 1) and significantly longer time to tumour progression (23.0 weeks vs 16.9 weeks respectively, P = 0.006).

In addition, a significant survival difference in favour of *nab*-paclitaxel was evident among patients receiving second-line or greater treatment (who formed the majority of those studied). In this group, patients assigned to *nab*-paclitaxel and standard paclitaxel had a median OS of 56.4 weeks and 46.7 weeks respectively (P = 0.024).

Regarding toxicity (Table 1), no grade 3 or 4 hypersensitivity reactions were observed in patients receiving *nab*-paclitaxel. Although grade 3 sensory neuropathy was more frequent in the *nab*-paclitaxel group than in those treated with the conventional formulation (10% vs 2%, respectively; P < 0.001), dose interruption and reduction resulted in a rapid improvement of grade (median time 22 days) and resumption of treatment.

Concerning haematological toxicity, grade 4 neutropenia was less frequent with *nab*-paclitaxel than with paclitaxel (9% vs 22%, respectively; P < 0.001), despite the 49% higher dose of paclitaxel administered (Table 2).

Based on this study, *nab*-paclitaxel monotherapy is indicated in Europe for the treatment of MBC in patients

who have failed first-line treatment for metastatic disease and for whom standard anthracycline-containing therapy is not indicated.

3. Weekly and q 3 week schedules of *nab*-paclitaxel versus docetaxel q 3 weeks

Recently, a phase II randomised trial compared the clinical outcome of three different schedules of *nab*-paclitaxel (*nab*-paclitaxel 300 mg/m^2 every 3 weeks, *nab*-paclitaxel 100 or 150 mg/m^2 weekly for three weeks followed by a week off drug) and that of docetaxel 100 mg/m^2 every 3 weeks.[5] Weekly schedules of *nab*-paclitaxel were more effective than giving the drug q3w ($P < 0.001$) (Fig. 2). Weekly *nab*-paclitaxel (150 mg/m^2) achieved significantly longer progression-free survival (PFS) than docetaxel by independent radiological assessment (12.9 vs 7.5 months, respectively; $P = 0.0065$).

Although ORR with weekly 150 mg/m^2 *nab*-paclitaxel (49%) and 100 mg/m^2 paclitaxel (45%) was higher than that with docetaxel (35%), these differences were not statistically significant. Regarding toxicity, grade 4 neutropenia was less frequent in the weekly *nab*-paclitaxel (150 mg/m^2) than in the docetaxel arm (9% vs 75% respectively). Grade 3 fatigue was more frequent in the docetaxel arm (19% vs 3%). Although the frequency of grade 3 neuropathy was similar for these two arms, patients in the weekly *nab*-paclitaxel arm (150 mg/m^2) demonstrated significantly faster improvement and could more rapidly resume treatment than those with docetaxel-induced toxicity (19 vs 37 days, respectively) (Fig. 3).

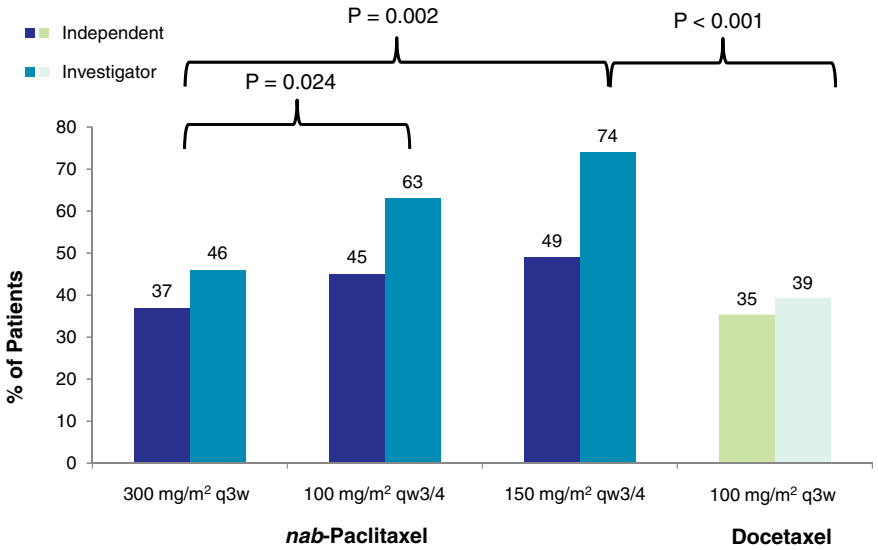

Fig. 2 – Overall response rates in patients with MBC receiving different doses or schedules of *nab*-paclitaxel vs docetaxel. [5]

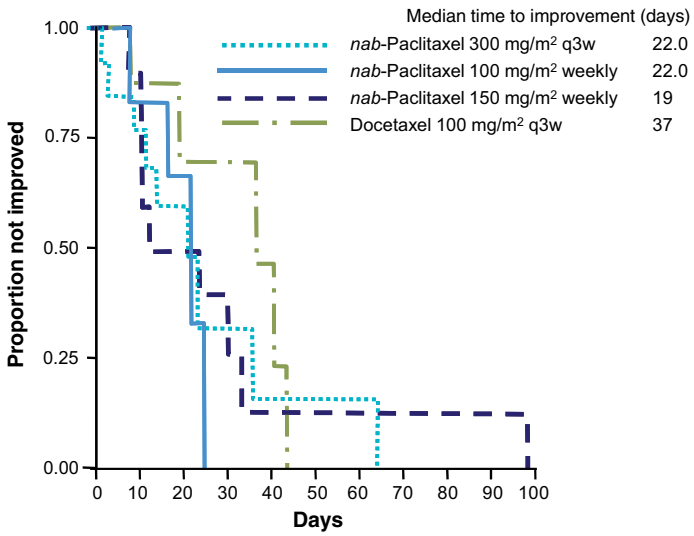

Fig. 3 – Improvement of neuropathy over time in patients with MBC receiving different doses or schedules of *nab*-paclitaxel vs docetaxel. [5]

These data demonstrate a better clinical outcome for weekly *nab*-paclitaxel when compared to docetaxel in first-line MBC patients. The greater efficacy, improved toxicity profile, absence of premedication and shorter administration times (30 minutes vs 3 hours) make *nab*-paclitaxel a good alternative in a wide range of MBC patients.

4. Case studies

The three cases that follow illustrate a range of potential applications for *nab*-paclitaxel which seek to exploit the favourable therapeutic index achieved by the avoidance of solvent co-administration and the presence of albumin-based drug targeting.

4.1. *Case 1: Taxane-pretreated patient*

A 62-year-old woman with no comorbidities presented with an invasive ductal adenocarcinoma grade 3 (1.8 cm) with lymph node infiltration (5/15). The tumour was ER and PgR positive (40% and 20% respectively) and negative for HER2 by immunohistochemistry (IHC). The patient had breast-conserving surgery. She was given standard adjuvant treatment with FEC-75 ×6, followed by 5 years' tamoxifen. The disease recurred with supraclavicular lymph nodes evident after 4 years on tamoxifen and she was treated with docetaxel 100 mg/m^2 q3w for 6 cycles. A partial tumour response was achieved but the patient developed fatigue and was maintained on letrozole therapy. Four months after docetaxel treatment the patient presented with prolonged fatigue and weight loss (ECOG performance score = 2). CT scans revealed four liver metastases, the largest being 3.5 cm, and two lung metastases.

In this context, the options were considered to be:

(i) polychemotherapy (paclitaxel + either capecitabine or gemcitabine, or capecitabine plus vinorelbine);
(ii) single-agent chemotherapy (CT), the options in a taxane-pretreated patient being capecitabine, vinorelbine, rechallenge with liposomal doxorubicin, or *nab*-paclitaxel); or
(iii) chemotherapy (capecitabine or *nab*-paclitaxel) plus bevacizumab.

Although the patient had high-risk disease (large liver lesions and a short disease-free interval), the fact that she had had prior treatment with anthracyclines and taxanes, and fatigue and a poor ECOG performance score suggested she was not fit enough for polychemotherapy.

Her treatment history remained relevant to choice of single agent chemotherapy. In 2007, Blum et al. reported a study of *nab*-paclitaxel in patients who had developed progressive disease despite taxane therapy for MBC or who had relapsed within a year of taxane-containing adjuvant treatment.[6] Among 75 patients given 125 mg/m^2 *nab*-paclitaxel, the disease control rate was 45% in those previously treated with conventional paclitaxel and 46% in those with prior exposure to docetaxel. In the wider population studied in this trial (which also included 106 patients treated with 100 mg/m^2 *nab*-paclitaxel), patients with disease control lasting sixteen weeks or more showed the same survival benefit as confirmed responders.

As noted above, the phase III study of Gradishar et al. demonstrated that single-agent *nab*-paclitaxel offers anthracycline-pretreated patients the possibility of response.[4] *nab*-Paclitaxel monotherapy is therefore clearly active in patients such as the woman whose case is being considered, who had had both an adjuvant anthracycline and then docetaxel for MBC, and does so with acceptable toxicity. This was the treatment option chosen.

However, consideration should also be give to the possibility of combining chemotherapy with bevacizumab in taxane-refractory patients. Capecitabine with or without bevacizumab was evaluated in a randomised phase III study.[7] This trial involved 462 MBC patients previously treated with an anthracycline and a taxane. Patients were randomised to receive capecitabine (2500 mg/m^2/d) twice daily on days 1 through 14 every 3 weeks, with or without bevacizumab (15 mg/kg) on day 1. Combination therapy significantly increased the response rate compared with capecitabine alone (19.8% vs 9.1%; P = 0.001), but the rate of response was still disappointingly low; and there was no improvement in either PFS (4.86 vs 4.17 months; hazard ratio [HR] = 0.98) or OS (15.1 vs 14.5 months). Nor was any benefit observed in quality of life. Capecitabine plus bevacizumab combination therapy is not an encouraging option for this patient.

The combination *nab*-paclitaxel/bevacizumab was evaluated in a retrospective analysis involving 40 patients pretreated with a minimum of two different regimens (prior anthracyclines, n = 34; prior taxanes, n = 35).[8] Patients received *nab*-paclitaxel (80–125 mg/m^2 on days 1, 8, and 15 of a 28-day cycle, or 170–200 mg/m^2 every 14 days) plus bevacizumab 10 mg/kg every 14 days. Of patients with measurable disease (n = 33), almost half responded to combination therapy (ORR, 48.5%); 3 patients showed complete responses (9.0%) and 13 showed partial response (39.4%), while 5 had stable disease (Table 3).

Time to progression for responders was 103 days for the group receiving treatment every 2 weeks and 148 days for the group receiving weekly treatment. In terms of toxicity, no grade 4 adverse events occurred. Neuropathy, anaemia, fatigue, pain, and hypertension were the most common complaints, but the combination of *nab*-paclitaxel with bevacizumab was generally well tolerated and would probably also have been an option in this patient, despite her relatively poor performance status. This combination would be an appropriate candidate for

Table 3 – Efficacy results in patients with MBC receiving a treatment combining *nab*-paclitaxel with bevacizumab [8]

nab-Paclitaxel + bevacizumab	n (%)
Overall response rate	16 (48.5)
Complete response	3 (9.0)
Partial response	13 (39.4)
Stable disease	5 (15.2)
Progressive disease	12 (36.4)

randomised study to confirm its efficacy and safety in high-risk MBC patients with HER2-negative symptomatic disease unfit for polychemotherapy.

4.2. Case 2: A patient needing first-line treatment for MBC after prior adjuvant anthracycline exposure

In April 2007, a 60-year-old woman had breast surgery and axillary lymphadenectomy. The patient presented with an invasive ductal adenocarcinoma (2.5 cm, grade 3) with lymph node infiltration (3/20). The tumour had a relatively low expression of ER (30%) and PgR (10%) and was negative for HER2 by IHC. In May 2007, she started 6 courses of anthracycline-based adjuvant treatment (FEC-100) and radiotherapy. Since September 2007 the patient has been maintained on an adjuvant aromatase inhibitor. In September 2009, she presented with shortness of breath and cough. Radiological workup was ordered. CT scan of the chest showed multiple but small bilateral nodules and right hilar lymphadenopathy. Abdominal CT and bone scan were negative. PET-CT showed areas of high uptake in the lung and nodes. The patient had a relatively good ECOG performance score of 1 and her only comorbidity was hypertension controlled by an ACE inhibitor.

The treatment options considered were the following:

(i) second-line endocrine therapy (ET);
(ii) CT (single agent or polychemotherapy); or
(iii) the combination of chemotherapy plus bevacizumab.

ET was rejected because the patient had progressed while on an adjuvant aromatase inhibitor and because she was symptomatic, even if only mildly so. However, ET could be considered as maintenance therapy after completion of CT.

Polychemotherapy is indicated for patients in whom a rapid shrinkage of tumour is required, i.e., for those presenting with rapidly progressive, life threatening, highly symptomatic disease and massive visceral involvement. This patient had small tumours and was only mildly symptomatic. Polychemotherapy was therefore not considered a good option and single-agent chemotherapy was the chosen course.

In the setting of MBC, single agent taxane therapy is the standard first-line treatment for patients with previous exposure to anthracycline-based adjuvant CT. [1]

A remaining question is whether there is a case for adding bevacizumab to first-line, single-agent CT in MBC. Three independent randomised trials have addressed this issue. The consistent finding is that the addition of bevacizumab improves both response rates and PFS. [9–11] CT plus bevacizumab should therefore be considered an effective treatment strategy for first-line treatment of MBC. A second question is which agent to use as the cytotoxic element of the combination.

As shown in Table 4, three of the combination therapies involved a taxane: weekly paclitaxel in the case of ECOG 2100 [9]; three-weekly docetaxel in the case of AVADO [10,11] and, when a taxane regimen was chosen

Table 4 – Overview of clinical studies in which bevacizumab is added to standard chemotherapy regimens for MBC

	E2100 [9]		AVADO [10,11]		RIBBON-1 [12]			
					Capecitabine		A/T	
Placebo (Pl) controlled	No		Yes		Yes		Yes	
Chemotherapy	Weekly paclitaxel (P)		q3w docetaxel (D)		Capecitabine (C)		q3w docetaxel/*nab*-P /FAC/EC/FEC	
Dose of bevacizumab (B), mg/kg	10 q2w		7.5/15 q3w		15 q3w		15 q3w	
	P	P+B	D+Pl	D+B	C+Pl	C+B	A/T+Pl	A/T+B
ORR, %	25.2	49.2	44.4	55.2/63.1	23.6	35.4	37.9	51.3
PFS, months	5.9	11.8	8.0	8.7/8.8	5.7	8.6	8.0	9.2
HR	0.60, P < 0.0001		0.79/0.72, P = 0.318/0.0099		0.69, P = 0.0002		0.64, P < 0.0001	
OS, months	25.2	26.7	NR	NR	21.2	29	23.8	25.2
HR	0.88, P = 0.16		0.92 or 0.68		0.85, P = 0.27		1.03, P = 0.83	

Table 5 – Overview of studies in which different combination chemotherapy regimens are administered as first-line treatment for MBC [9,10,12,15–18]

Regimen	ORR, %	OS, mo	Reference
Docetaxel + gemcitabine	33	15.8	O'Shaughnessy et al. [15]
Docetaxel + capecitabine	32	14.5	O'Shaughnessy et al. [16]
Paclitaxel + doxorubicin	47	22.0	Sledge et al. [17]
Paclitaxel + capecitabine	51	29.9	Gradishar et al. [18]
Paclitaxel + bevacizumab	37	27	Miller et al. [9]
Capecitabine + bevacizumab (RIBBON-1)	35.4	29.0	Robert et al. [12]
Docetaxel + bevacizumab (AVADO)	63.1	NR	Miles et al. [10]

in RIBBON-1, either docetaxel or *nab*-paclitaxel. [12] At ASCO 2009, preliminary data presented by Conlin et al. showed overall response rates of over 40% in patients treated with bevacizumab plus *nab*-paclitaxel given at either 260 mg/m^2 every three weeks or 130 mg/m^2 weekly. [13]

Clinical trials comparing *nab*-paclitaxel against Cremophor-based paclitaxel or against docetaxel in the setting of MBC, including first-line treatment, are reviewed above and elsewhere in this issue. [14] In summary, however, *nab*-paclitaxel was associated with superior clinical outcome, in terms both of efficacy and toxicity. [4,5] Combination therapy consisting of bevacizumab plus *nab*-paclitaxel is therefore a good treatment strategy for this patient.

4.3. *Case 3: Flexible scheduling with nab-paclitaxel following relapse after adjuvant chemotherapy*

In June 2006, a 65-year-old woman diagnosed with an invasive ductal breast carcinoma underwent mastectomy and axillary dissection. The carcinoma was 2.1 cm, grade 3 with lymph node infiltration (2/12) and was negative for ER (0%), PgR (0%) and HER2 by FISH. The patient had well-controlled diabetes and no other comorbidities. Given her triple negative disease she received adjuvant chemotherapy consisting of 3 cycles of FEC-100 followed by 3 cycles of docetaxel. Two and half years later, the patient presented with fatigue and slight bone pain in the left hip. She was also diagnosed with arterial hypertension that was not optimally controlled. Imaging confirmed lung and liver metastases but liver and renal function were normal and her ECOG score was 1.

The treatment options considered for this patient were:

(i) polychemotherapy (i.e., paclitaxel plus capecitabine, paclitaxel plus gemcitabine, capecitabine plus vinorelbine);
(ii) single-agent chemotherapy: anthracycline or taxane (qw or q3w) or other single agents such as capecitabine, liposomal doxorubicin, vinorelbine, gemcitabine, *nab*-paclitaxel; or
(iii) combination therapy.

Regarding polychemotherapy in first-line MBC, regimens involving docetaxel and paclitaxel have response rates ranging from 30% to 50% and median OS ranging from 14 to 30 months (Table 5).

When a cytotoxic is combined with bevacizumab, the overall response rates reach 63% and median overall survival can exceed two years. Deciding on the best treatment approach for this elderly woman with MBC requires a careful balancing of efficacy and toxicity. The toxicity level of a given regimen depends on the precise combination used. For docetaxel-based regimens, neutropenia and other haematological toxicities are frequent while non-haematological toxicities (diarrhoea, fatigue and hand–foot syndrome) depend largely on the combination partner chosen. Paclitaxel regimens have less haematological toxicity and more neurological toxicities; and in combination with capecitabine fatigue becomes more frequent. Bevacizumab-containing therapies have been associated with variable rates of neutropenia and neutropenic sepsis, with almost no febrile neutropenia except in combination with docetaxel. The most frequent non-haematological toxicities are hypertension, proteinuria and (at low incidence) deep vein thrombosis.

The efficacy of the solvent-based taxanes differs between docetaxel and paclitaxel and, in the case of the latter, according to schedule. Weekly paclitaxel is superior to q3w administration in response rate (42% vs 29%) and time to disease progression (9 vs 5 months). [19] Comparison between 3-weekly docetaxel and 3-weekly paclitaxel shows that the docetaxel regimen is superior in time to disease progression (5.7 vs 3.6 months) and overall survival (15.4 vs 12.7 months). [20]

With a wide choice of first-line agents available, the decision on which to use is also influenced by an individual patient's particular circumstances. In this instance, possible relevant factors include the presence of liver and lung metastases, diabetes, arterial hypertension, fatigue, slight bone pain and good performance status.

nab-Paclitaxel, an agent that offers an opportunity of optimizing clinical outcome in many patients, can be administered in 3 different schedules. This gives flexibility in terms of management which is greater than that offered by the standard of care of docetaxel

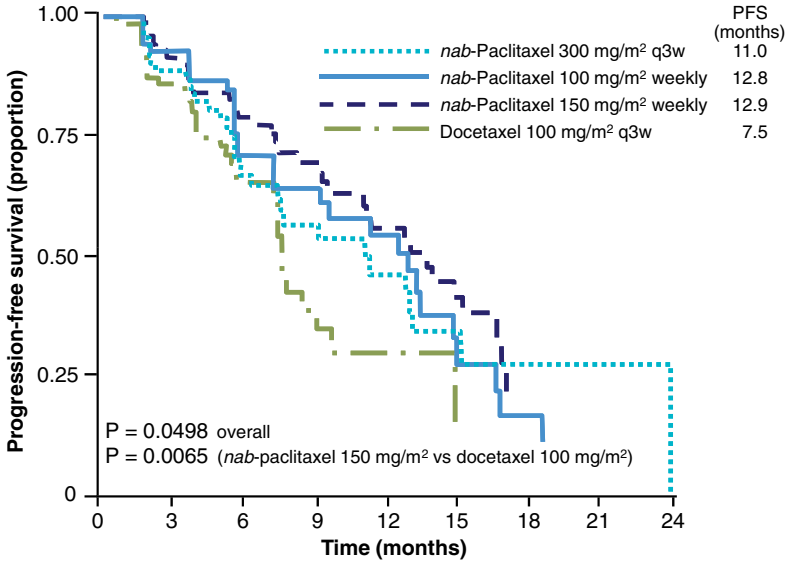

Fig. 4 – Progression-free survival curves (by Independent Review) and median PFS values in patients with MBC receiving different doses or schedules *nab*-paclitaxel vs docetaxel. [5]

100 mg/m² every 3 weeks. There are also data, reviewed above, suggesting that 100 and 150 mg/m² weekly *nab*-paclitaxel regimens are superior to the standard docetaxel regimen in overall response (Fig. 2) and disease control rate (Fig. 4). [5]

Time to disease progression was almost 13 months in weekly *nab*-paclitaxel regimens compared to 7.5 months for docetaxel (Fig. 4). Furthermore, as already noteded, weekly *nab*-paclitaxel as single agent has a favourable safety profile. Together with several other agents, monotherapy with *nab*-paclitaxel is recognized by expert groups such as the German AGO as a valid treatment option for first-line MBC in patients previously exposed to anthracyclines. Taking into account the good performance status of this patient and the fact that she had lung and liver metastases, 150 mg/m² weekly *nab*-paclitaxel was the treatment of choice.

5. Conflict of interest statement

Dr Davidson received honoraria from Abraxis Bioscience.

6. Role of the funding source

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