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Nanoparticle albumin-bound (*nab*™)-paclitaxel: improving efficacy and tolerability by targeted drug delivery in metastatic breast cancer

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ABSTRACT

Breast cancer deaths in western countries are falling due to screening and adjuvant therapy, but the treatment of metastatic breast cancer (MBC) has not shown comparable advances. The most active single agents are taxanes, which extend both disease-free and overall survival. However, opportunities remain for improving outcome. Nanoparticle technology is proving a valuable addition to the pharmaceutical armamentarium, particularly in oncology. Its use to bind paclitaxel to human albumin (nanoparticle albumin-bound paclitaxel; *nab*-paclitaxel; Abraxane®) ensures solubility of the taxane without the use of solvents and minimizes the risk of hypersensitivity reactions without premedication. The homogeneous colloidal suspension created allows rapid dispersal of unbound drug and linear pharmacokinetics. Albumin-mediated transport of paclitaxel across the endothelium facilitates uptake of drug, and a degree of tumour selectivity is achieved by the albumin-binding propensity of SPARC (Secreted Protein Acidic Rich in Cysteine), a substance expressed on and around many breast tumours. Clinical trials in first- and second-line MBC show that *nab*-paclitaxel is both more effective than solvent-based taxanes and associated with less severe neutropenia. Sensory neuropathy occurs but improves rapidly when compared with that caused by conventional taxanes. A clinical development programme is investigating *nab*-paclitaxel in the adjuvant and neoadjuvant settings. The low incidence of neutropenia makes *nab*-paclitaxel a good candidate for combination with other cytotoxics. It is also being assessed when given with biologic agents such as trastuzumab and bevacizumab.

1. Introduction

While the incidence of breast cancer has been increasing in countries with majority Caucasian populations, mortality from the disease has generally shown a steady decrease with time.[1] Analysis of data from European cancer registries showed that the age-adjusted five year survival rate for women diagnosed with breast cancer in the period 2000–2002 was 79%.[2] Improvements in survival have been attributed in roughly equal measure to earlier detection through mammography and to a reduction in the rate of recurrence of early breast cancer (EBC) achieved by adjuvant endocrine therapy and chemotherapy.[3]

In the setting of metastatic breast cancer (MBC), undoubted progress has been made in prolonging

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progression-free survival (PFS) and overall survival (OS). The addition of trastuzumab to chemotherapy for patients with HER2-positive disease was a major advance, resulting in significantly improved response rates, time to progression and OS.[4] More recently, the addition of lapatinib to letrozole in hormone receptor and HER2-positive tumours has confirmed the value of multi-targeted treatment.[5] There is also considerable promise in anti-angiogenic agents, and the combination of bevacizumab with paclitaxel or docetaxel has been shown to delay progression when compared with the taxane alone.[6,7] However, for women who present with locally advanced or disseminated breast cancer, or who develop metastases despite the multimodality management of EBC, life expectancy remains severely limited and the prospect of cure remote.

In the individual patient, choice of therapy for MBC is influenced by factors including the hormonal and HER2 status of the tumour and the nature of any prior adjuvant therapy, patients' performance status and visceral involvement. Where chemotherapy is indicated, which will typically be the case in patients with tumours which are hormone-receptor negative or refractory to endocrine therapy, the twin cornerstones of treatment are still the anthracyclines and the taxanes.[8] Also used are the anti-metabolites capecitabine, gemcitabine, and the vinca alkaloid vinorelbine. Although recent guidelines from the National Comprehensive Cancer Network and the European Society of Medical Oncology state that polychemotherapy is not superior to the sequential use of single agents in terms of overall survival, the use of cytotoxics in combination may be preferred in life-threatening and symptomatic disease because of the higher likelihood of response.[8,9]

MBC remains essentially a palliative setting, and the aim is one of maximising anti-tumour efficacy without compromising quality of life by the burden of toxicity. In this context, any development which improves the therapeutic index of a well-established therapy is likely to be welcome. Nanoparticle albumin-bound (*nab*) paclitaxel, which harnesses a natural protein delivery system to increase drug targeting to the tumour cell, is one such development. Drug uptake is also associated with SPARC (secreted protein acidic and rich in cysteine), a substance overexpressed in many breast tumours.[10] SPARC positivity may therefore constitute a biomarker predictive of response to *nab*-paclitaxel and hence assist in the tailoring of therapy to the characteristics of the individual patient.

2. Rationale behind the development of *nab*-paclitaxel

The approval in 1994 of the microtubule stabilising agent paclitaxel and in 1999 of docetaxel opened a new era in the treatment of MBC.[11] Paclitaxel had proved active in patients with disease resistant to or relapsing after treatment with anthracyclines, the then gold-standard of treatment, leading to trial of taxanes alone and in combination in a range of MBC settings.[12,13] Docetaxel proved superior to doxorubicin in patients previously treated with alkylating agents, and superior to mitomycin plus vinblastine in patients progressing after anthracycline-containing chemotherapy.[14,15]

The question of whether docetaxel was superior to paclitaxel was addressed by Jones et al., who randomised patients who had progressed on anthracycline-containing chemotherapy to either paclitaxel 175 mg/m^2 or docetaxel 100 mg/m^2, both given every three weeks.[16] Docetaxel-treated patients had a significantly higher response rate and longer median time to progression and OS. However, over the period this study was being conducted, a variety of different paclitaxel doses and schedules became widespread, and patterns of docetaxel use also became more varied (though to a lesser extent than with paclitaxel). These developments were aimed at increasing efficacy but also at reducing the burden of toxicity and the necessity for dose reduction and delay, which continue to be a problem in a palliative setting where many patients are elderly and of poor performance status.

Changes in dose and schedule mean that it remains difficult to judge how paclitaxel and docetaxel stand relative to each other in terms of efficacy. The position is made more complicated by the emergence of new cytotoxics as potential partners for combination chemotherapy and, in the case of paclitaxel, by the development of an entirely novel formulation made possible by nanoparticle technology.

3. Nanoparticle technology

Due to its complex structure of hydrocarbon radicals, paclitaxel is hydrophobic. The traditional way around this problem has been to use detergent-like substances as solvents. However, these substances, notably Cremophor EL (polyoxyethylated castor oil), are themselves associated with toxicity, including peripheral neuropathy and hypersensitivity reactions.[17] It is therefore routine to give steroids and anti-histamines prior to infusion. Furthermore, use of Cremophor may decrease the fraction of paclitaxel which is in its unbound, pharmacologically active form.[18] Coupling paclitaxel to human albumin offers a novel means of converting an insoluble drug into an injectable form without associated increase in toxicity.[19] *nab*-Paclitaxel is the first uniquely nanoparticle-based pharmaceutical product to be approved and marketed.

The coupling process results in a colloidal suspension of particles consisting of a hydrophobic core towards

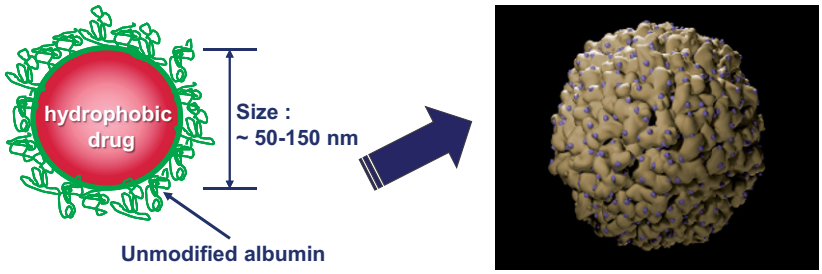

Fig. 1 – The insoluble drug is transformed into injectable nanoparticle form using human albumin.

which the drug moiety faces, because of lack of solubility, surrounded by a hydrophilic exterior created by the negatively-charged amino acids in unmodified human serum albumin (Fig. 1). The particles are physically stable and have a reproducible, narrow range of diameter (50–150 nm) around a mean value of 130 nm.[20] Their negatively charged albumin surfaces repel each other, allowing the particles to remain in homogeneous suspension and avoiding flocculation.

A consequence of the product's physical characteristics is that pharmacokinetics are linear: the AUC of *nab*-paclitaxel increases predictably with dose over the range 135 to 300 mg/m^2.[21] This contrasts with the parabolic pharmacokinetics seen after the one- or three-hour infusion of standard paclitaxel. The solvent vehicle results in entrapment of drug in large micelles in the circulation from which the drug cannot escape by simple diffusion.[22,23] This leads to an unpredictable relationship between dose, efficacy and risk of toxicity. In the case of *nab*-paclitaxel, however, the nanoparticles dissociate within 30 to 45 seconds of injection into their constituent albumin molecules which circulate rapidly around the body with their bound paclitaxel attached.

3.1. *The active role of albumin*[24,25]

Albumin is the body's natural carrier of hydrophobic molecules and the means by which fatty acids, hormones and the fat-soluble vitamins are transported. Albumin binding to the glycoprotein receptor gp60 on endothelial cells results in activation of caveolin-1 and the transcytosis of intact nanoparticles across the cell membrane (see Fig. 2). (Transcytosis differs from endocytosis in that the contents of the vesicles are not digested.) The success of anticancer chemotherapy depends on delivering active agent to the tumour cell. In the case of *nab*-paclitaxel, this is achieved by using the body's own mechanism for delivering proteins to cells.

In addition to the active albumin-mediated transport of drug into tumour cells, a degree of tumour-selective targeting is provided by SPARC, a protein which modulates the interaction of cells with the extracellular matrix.[26] SPARC binds albumin with an affinity almost as great as that of gp60 and is over-expressed in many cancers.[27] Although associated with tumours, SPARC is not tumour-specific since it is found in normal tissues, especially during embryonic development.[28] Increased levels of SPARC (osteonectin) are associated with tissue and bone remodelling and hyperproliferation, but a pronounced increase in expression is seen with malignant transformation. In this setting, SPARC mediates the switch from E-cadherin to N-cadherin expression, resulting in enhanced cell migration and invasion. In association with the integrins, SPARC may be involved in the process of metastasis. It is therefore not surprising that retrospective studies have found that high levels of SPARC are associated with poor prognosis in several tumours including those of the head and neck, and non-small cell lung and breast cancers.[29–31] SPARC is present on the surface of MX-1 human mammary carcinoma cells.[32] It is thought that the SPARC-mediated concentration of paclitaxel-carrying albumin molecules in the vicinity of tumour cells could lead to locally high levels of drug release, and so selective apoptosis (Fig. 2).

4. Experience with *nab*-paclitaxel

4.1. *Preclinical and phase I*

The expected lower toxicity of *nab*-paclitaxel compared with standard, Cremophor paclitaxel was demonstrated in mice: the LD50 for *nab*-paclitaxel was 47 mg/kg, and that for Cremophor-paclitaxel 30 mg/kg.[33] In these tumour-bearing animals, exposure to *nab*-paclitaxel produced more complete regressions and longer survival than exposure to equitoxic doses of standard paclitaxel. Consistent with the reduced toxicity seen in the mouse model, the maximum tolerated dose (MTD) of *nab*-paclitaxel in man, at 300 mg/m^2 every three weeks, is higher than the 175 mg/m^2 MTD for Cremophor-paclitaxel.[21] No hypersensitivity reactions were observed in this study.

In a further phase I study, *nab*-paclitaxel was given weekly for three weeks, followed by one week without drug.[34] The MTDs for heavily- and lightly-pretreated patients were 100 and 150 mg/m^2 respectively. Partial responses were seen in five patients, all of whom had been treated previously with solvent-based taxanes.

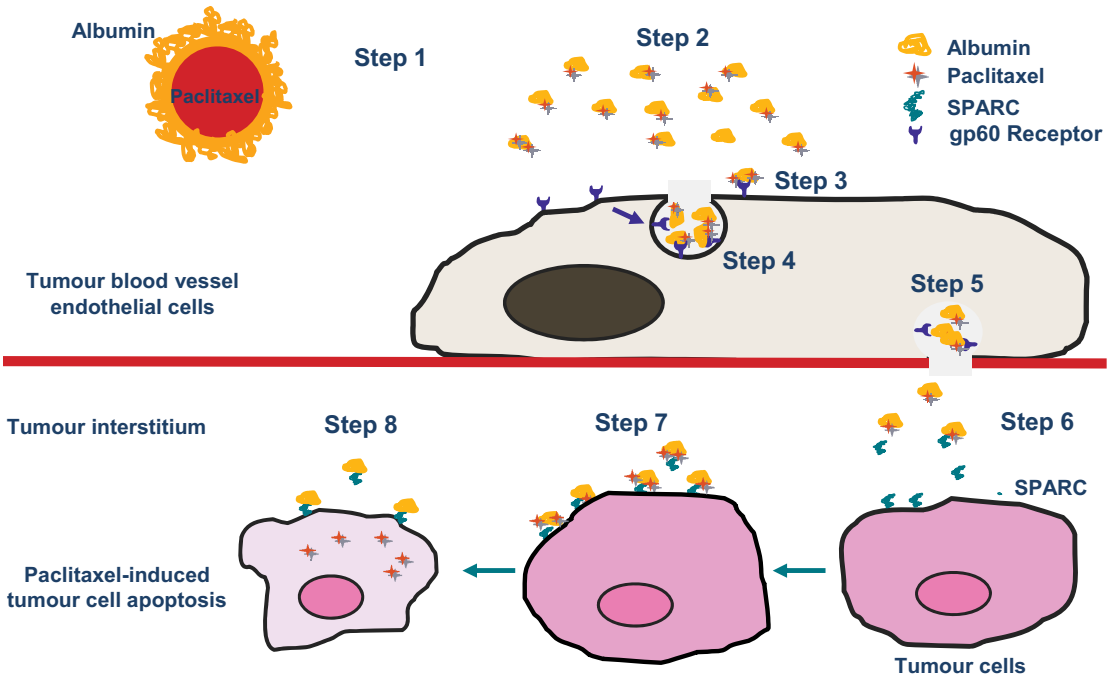

Fig. 2 – The *nab*-technology platform as a means of connecting two endogenous albumin pathways in order to target and improve drug delivery. Step 1: injection of *nab*-paclitaxel into blood vessels; Step 2: suspended in the blood, *nab*-paclitaxel dissociates into individual particles; Step 3: because it is associated with albumin, *nab*-paclitaxel binds to gp60 receptors present on the endothelial cells of tumour blood vessels; Step 4: binding of albumin to gp60 activates caveolin-1 which creates vesicles (caveolae) in the endothelial cell wall; these caveolae fill with *nab*-paclitaxel and migrate across the cytoplasm; Steps 5&6: caveolae deposit their contents into the interstitium of the tumour, where *nab*-paclitaxel binds to SPARC; Step 7: accumulation of *nab*-paclitaxel via SPARC at tumour cell membranes; Step 8: diffusion of paclitaxel into the intracellular compartment and subsequent induction of cell death.

4.2. *Phase II study in MBC*

Given the encouraging phase I experience, a phase II study was undertaken in 63 MBC patients using the three-weekly 300 mg/m^2 regimen of *nab*-paclitaxel without premedication.[35] Patients had not received taxanes within the previous six months; 59% had prior exposure to anthracyclines. A median of six cycles of *nab*-paclitaxel were administered; dose intensity was well maintained and only 7% of treatment cycles were delayed. An overall response rate (ORR) of 48% was obtained (64% in patients without prior chemotherapy for MBC, but 41% even in those exposed to anthracyclines). Median time to progression (TTP) was 26.6 weeks and OS 63.6 weeks. Grade 4 neutropenia was seen in 24% of patients, and 5% experienced febrile neutropenia. There were no cases of grade 4 sensory neuropathy, and an 11% rate of grade 3 toxicity.

4.3. *Phase III comparison against solvent-based paclitaxel*

In a pivotal phase III trial, 460 women with MBC were randomised to receive either 175 mg/m^2 standard, solvent-based intravenous (iv) paclitaxel over three hours q 3 weeks or 260 mg/m^2 *nab*-paclitaxel iv over thirty minutes, again q 3 weeks.[36] Solvent-based paclitaxel (but not *nab*-paclitaxel) was given with dexamethasone and anti-histamine premedication. Patients had no prior exposure to taxanes for metastatic disease but were stratified for prior treatment with anthracyclines.

For the study population as a whole, the ORR was 33.2% with *nab*-paclitaxel, significantly higher than the 18.7% with standard paclitaxel ($P = 0.001$) (Fig. 3); and *nab*-paclitaxel treated patients had a significantly longer median time to progression (TTP 23.0 vs 16.9 weeks, $P = 0.006$). Overall survival was somewhat longer among *nab*-paclitaxel treated patients (median OS of 65.0 weeks vs 55.7 weeks in patients treated with conventional paclitaxel).

Among patients previously exposed to anthracyclines (in either the adjuvant or metastatic settings) the ORR with *nab*-paclitaxel was 34.1% and that with solvent-based paclitaxel 18.3% ($P = 0.002$).[37] Among patients with prior anthracycline treatment for metastatic disease only, the response rates were 27.0% and 13.8% respectively. Patients previously treated with anthracyclines – whether in both adjuvant and metastatic settings or for metastatic disease alone – also experienced longer TTP and longer OS when treated with *nab*-paclitaxel than when given the conventional formulation. Thus *nab*-paclitaxel treated patients with prior

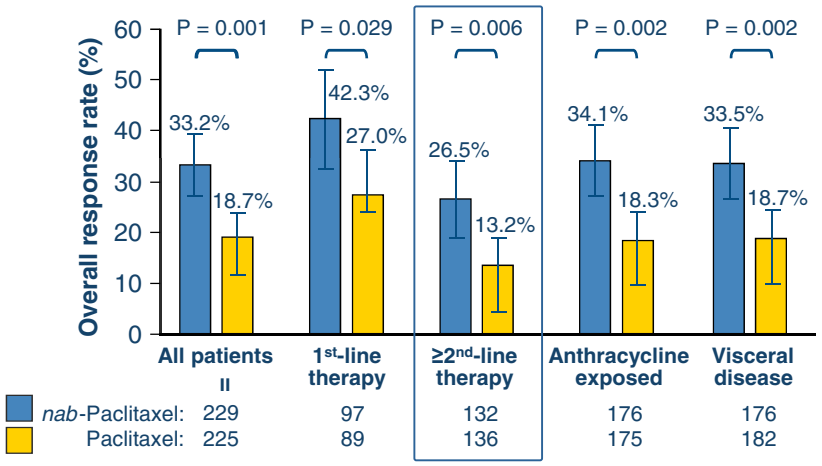

Fig. 3 – Overall response rates in the total population studied and in relevant subpopulations receiving *nab*-paclitaxel vs standard paclitaxel. [36,37] **Bars indicate 95% confidence intervals.**

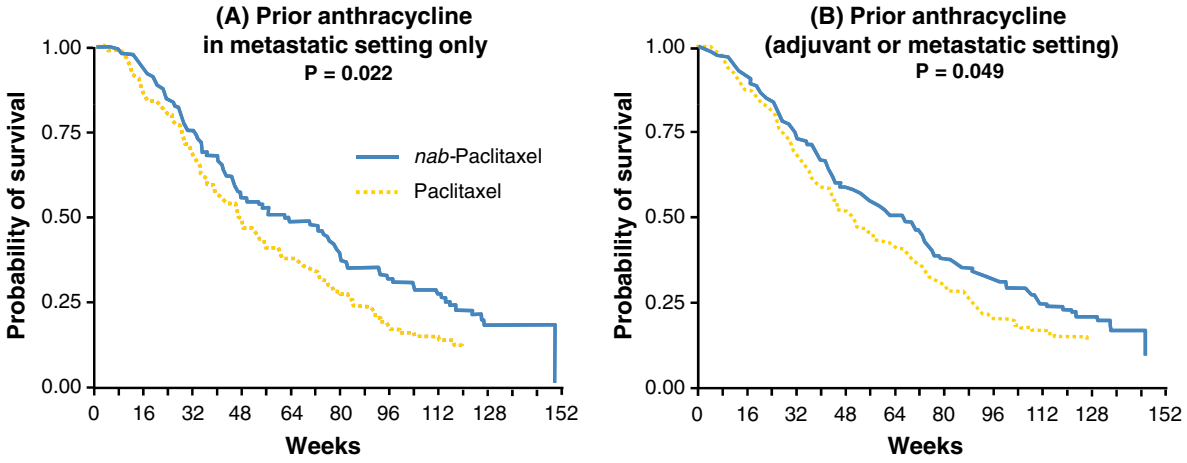

Fig. 4 – *nab*-Paclitaxel significantly extended median OS compared with standard paclitaxel in anthracycline-exposed patients: (A) only metastatic anthracycline therapy; (B) adjuvant/metastatic anthracycline therapy. [37]

anthracycline exposure (at any stage) had a median TTP of 23.0 weeks. In this category of patients, the TTP with standard paclitaxel was 16.6 weeks (P = 0.004). Among patients with anthracycline exposure confined to the metastatic setting, the TTPs were 21.0 and 15.7 months respectively (P = 0.011). Patients with prior anthracycline treatment for MBC survived a median of 46.7 weeks when treated with solvent-based paclitaxel and 56.4 weeks when treated with *nab*-paclitaxel (P = 0.022) (Fig. 4). Among those with anthracycline exposure for either EBC or MBC, the corresponding figures were 65.0 and 52.4 months respectively (P = 0.049).

For the majority of the patients enrolled (n = 268), the drug given during the trial represented at least their second line of treatment for MBC. [36] Among these patients with prior chemotherapy, randomization to *nab*-paclitaxel conferred a significantly greater likelihood of response (ORR 26.5% vs 13.2% with standard paclitaxel, P = 0.006). In this large group of patients, *nab*-paclitaxel was also associated with significantly improved overall survival (median OS with *nab*-paclitaxel 56.4 vs 46.7 weeks with standard paclitaxel, P = 0.024; Fig. 5).

Sensory neuropathy of grade 3 (there was no neuropathy at grade 4) was experienced by 10% of *nab*-paclitaxel patients and by 2% of those treated with the standard formulation (P < 0.001). However, patients in the *nab*-paclitaxel arm received an average paclitaxel dose intensity 49% greater than that received by patients in the standard paclitaxel group. Moreover, in the case of treatment with *nab*-paclitaxel, the neuropathy improved to a lower grade within a median of 22 days. This compared with a median of 79 days on conventional paclitaxel. [38]

Compared with standard paclitaxel, rates of neutropenia were significantly lower among patients assigned to the albumin-bound form (Grade 3 in 25% vs 31%; Grade 4 in 9% vs 22%; P < 0.001). Rates of grade 4 febrile neutropenia, thrombocytopenia and anaemia were <1% overall.

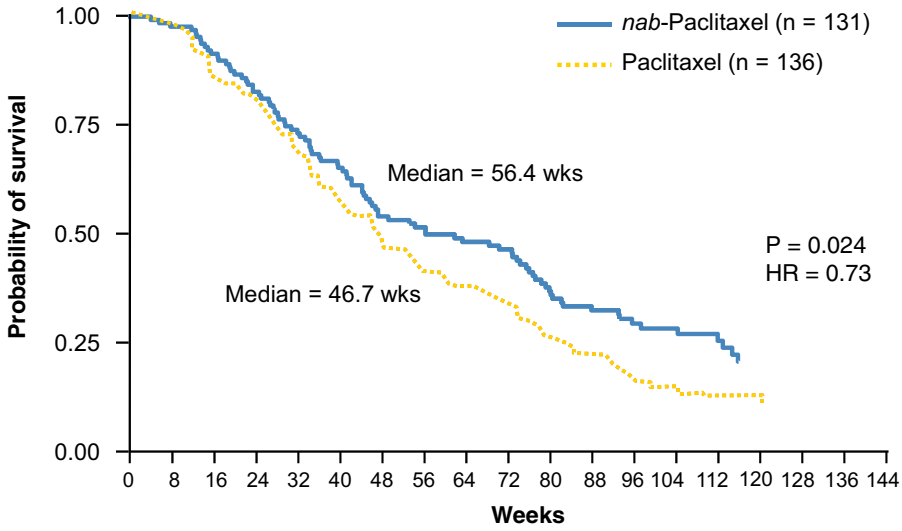

Fig. 5 – Overall survival rates in patients receiving at least second-line treatment for MBC in the pivotal phase III study of *nab*-paclitaxel vs standard paclitaxel.

4.4. Experience in heavily pre-treated MBC patients

The potential of *nab*-paclitaxel has been extended by further clinical work in heavily pre-treated, taxane-refractory patients.[39] In the study by Blum et al., *nab*-paclitaxel was given initially to 106 patients at a dose of 100 mg/m^2 weekly for three weeks, followed by a week off drug. An ORR was seen in 16% of patients, and a further 26% had disease control. In the subgroup of 34 patients with prior docetaxel treatment, the ORR rate was an encouraging 21%, and the rate of stable disease 32% (so that 53% had clinical benefit). The ORR was 7% and the disease control rate 21% (i.e. clinical benefit in 28%) even among the 29 patients who had been previously treated with both paclitaxel and docetaxel.

Given the acceptable tolerability profile of *nab*-paclitaxel, the dose of drug was increased to 125 mg/m^2 (on the same four-weekly cycle) in a further 75 patients. In this cohort, the ORR was 14% and the rate of disease control 37%. Aggregating data from both cohorts, the survival curve for patients experiencing stable disease for 16 weeks or longer overlapped that of patients with a confirmed response. Grade 4 neutropenia and leucopenia 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.

4.5. Comparison against docetaxel

As would be expected given a drug of proven value second line, controlled clinical study of *nab*-paclitaxel in the first-line setting is being extended. Recently, *nab*-paclitaxel has been compared with docetaxel in a four-arm randomised phase II trial involving 300 evaluable patients treated first line for MBC.[40] The control arm was the standard regimen of 100 mg/m^2 docetaxel q 3 weeks (q3w). The experimental arms were *nab*-paclitaxel 300 mg/m^2 q3w, and two arms in which *nab*-paclitaxel was given weekly according to a cycle of three weeks on/one week off (qw3/4) at either 100 or 150 mg/m^2.

ORRs confirmed by independent review were 49% in patients receiving *nab*-paclitaxel 150 mg/m^2 qw3/4 and 35% in those treated with weekly 100 mg/m^2 docetaxel. Independently assessed rates of disease control were 80% in the *nab*-paclitaxel group and 58% among patients receiving docetaxel (Fig. 6). Also of importance was the significantly longer period of PFS among patients receiving *nab*-paclitaxel 150 mg/m^2 qw3/4 when compared with those on the standard regimen of docetaxel (median PFS according to independent review 12.9 vs 7.5 months, P = 0.0065; Fig. 7).

In this study, the incidence of sensory neuropathy was comparable across treatment arms, although rates of improvement were notably faster following *nab*-paclitaxel-induced neuropathy than in docetaxel-treated patients experiencing the same toxicity (median time to improvement 19–22 days vs 37 days). Severe neutropenia, however, was markedly less frequent with *nab*-paclitaxel: across the three *nab*-paclitaxel arms, the rate of grade 4 neutropenia ranged from 5% to 9% and the rate among docetaxel-treated patients was fully 75%. Episodes of febrile neutropenia also occurred significantly more frequently in the docetaxel group (8% vs 1% in each *nab*-paclitaxel arm). The rate of grade 3 fatigue was also substantially higher among docetaxel-treated patients (19% vs 0–5% in the *nab*-paclitaxel arms). There were no cases of grade 4 fatigue.

The better PFS with weekly *nab*-paclitaxel, coupled with the more favourable toxicity profile, suggest that this agent is an appropriate alternative to the widely used regimen of q 3 weekly docetaxel 100 mg.

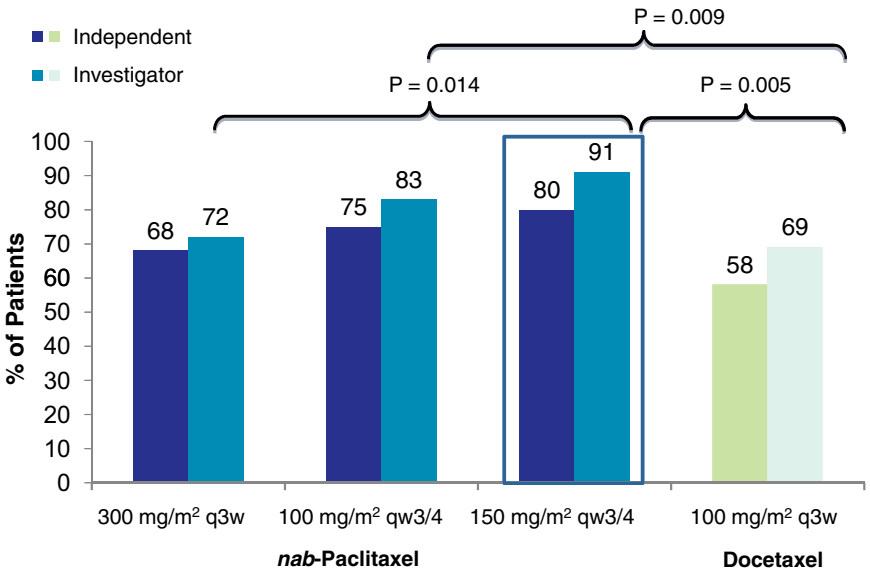

Fig. 6 – Disease control rates in patients with MBC receiving different doses or schedules of *nab*-paclitaxel vs docetaxel. [40]

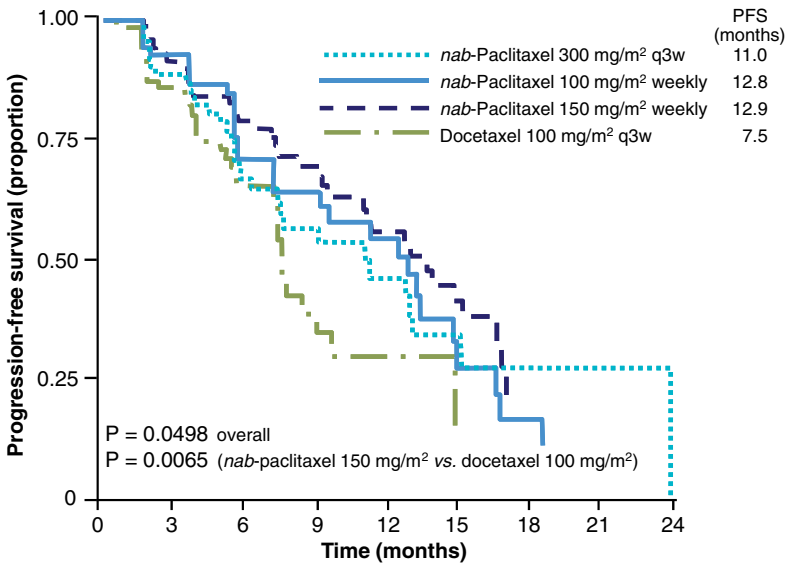

Fig. 7 – Progression-free survival rates in patients administered 3 different dose schedules of *nab*-paclitaxel or the standard docetaxel dose (results by independent review [40]**).**

4.6. nab-Paclitaxel combined with other chemotherapy agents

Experience of *nab*-paclitaxel in combination with other agents is also being gathered. A study of a q 3 weekly cycle of *nab*-paclitaxel 125 mg/m^2 (days 1 and 8) plus capecitabine 825 mg/m^2 bid (days 1 and 14) first line in MBC has recently reported an ORR of 60.9%. [41] In HER2-negative MBC patients, the combination of 125 mg/m^2 *nab*-paclitaxel with 1000 mg/m^2 gemcitabine (both drugs given on days 1, 8 and 15 every 21 days) achieved an ORR of 50% and median PFS of 7.9 months in previously untreated patients. [42] Median OS has not yet been reached. Only one of the fifty patients treated in this phase II study developed febrile neutropenia.

4.7. nab-Paclitaxel in combination with targeted therapy

nab-Paclitaxel 125 mg/m^2 (given on days 1, 8 and 15, q4w) has been combined with bevacizumab 10 mg/kg (on days 1 and 15) in 45 HER2-negative patients with previously untreated MBC. [43] The ORR was 33% and median PFS 7.4 months. In a similar patient population, triple therapy with *nab*-paclitaxel plus gemcitabine and bevacizumab achieved an ORR of 52% (n = 23). [44] In HER2-positive patients, *nab*-paclitaxel has been combined with trastuzumab and carboplatin. [45] Among 32 patients studied, the ORR was 54% and median PFS an encouraging 15.9 months.

4.8. Early stage and locally advanced breast cancer

While the adjuvant chemotherapy of EBC leads to significant reduction in the risk of disease recurrence, this is achieved at the cost of appreciable toxicity.[46] Among the potential adverse events are taxane-related neutropenia and delayed anthracycline-related cardiovascular side effects, including congestive heart failure.[47,48] There is therefore considerable interest in ongoing studies that integrate *nab*-paclitaxel into neo-adjuvant or adjuvant regimens such as doxorubicin plus cyclophosphamide (AC) and AC plus bevacizumab.[49]

In the randomised phase II/III (ICE II) study, members of the German Breast Group are randomising patients aged 65 years and over to the investigator's choice of standard adjuvant chemotherapy (either epirubicin plus cyclophosphamide or cyclophospamide plus methotrexate plus 5-fluorouracil) or to an investigational regimen consisting of *nab*-paclitaxel plus capecitabine.[50]

There also remains an unmet need for the more effective treatment of locally advanced breast cancer. Robidoux et al. studied 66 treatment-naive women who received 100 mg/m^2 *nab*-paclitaxel weekly for twelve weeks followed by four cycles of 5-fluorouracil plus epirubicin plus cyclophosphamide (and trastuzumab in the case of HER2-positive disease).[51] In this neoadjuvant setting, the addition of *nab*-paclitaxel to chemotherapy contributed minimal additional toxicity. Pathological complete response (pCR) rates of up to 67% were obtained in HER2-positive and ER/PgR-negative patients. Almost without exception, patients achieving a pCR had tumours positive for SPARC. This suggests this substance, while associated with poor prognosis in general, may more specifically be a valuable indicator of likely response to a targeted agent such as *nab*-paclitaxel.

5. Discussion

The taxanes have brought significant clinical gains and enjoy a well established place in the management of MBC. However, these gains, though statistically significant, are clinically modest: the majority of patients with advanced disease have only very limited prospects of enjoying lengthy periods without disease progression. Treatment with conventional taxanes is also associated with substantial toxicities, notably neutropenia and motor and sensory neuropathies. Attempts to improve the risk/benefit ratio by adjusting dose and schedule have not resolved these problems. In this setting, innovative approaches to treatment are welcome.

Efforts at tumour cell targeting run in parallel with those aimed at tailoring therapy to the individual patient. Biomarkers which predict the likelihood of therapeutic benefit are not new: in breast cancer, hormone receptor status is the archetype, and the aim of achieving targeted therapy has been considerably advanced by the measurement of HER2 status to determine the appropriateness of treatment with trastuzumab or other anti-HER2 therapies.

In this context, the relationship between SPARC status and likelihood of response to neo-adjuvant *nab*-paclitaxel is interesting. Compared with HER2, the SPARC molecule is heterogeneous (it is more a family of proteins than a single entity). So too is its pattern of expression, which varies between the primary tumour and metastases, and from one metastasis to another. It must also be noted that the suggestion of a correlation between response and SPARC status is based on retrospective analysis. In an attempt to prospectively evaluate the relationship, a co-operative group trial involving the CALGB 40502 and NCCTG is assessing tumour tissue for SPARC and tubulin mutations in patients randomised to paclitaxel, *nab*-paclitaxel or ixabepilone followed by bevacizumab. Serial serum measurements will also assess the potential of circulating caveolin-1 as a biomarker.

In conclusion, we are increasingly realizing the aim of tumour-directed therapy. One aspect of this is the use of novel antibody or small-molecule agents designed to inhibit abnormal mechanisms of growth-signalling within and around the cancer cell. However, there remains a need to increase the efficacy and tolerability of conventional cytotoxic agents with a proven record in achieving tumour regression and prolonging disease-free and overall survival. Paclitaxel is one such agent. The use of albumin-bound nanoparticles to more effectively ensure its uptake by tumour cells, as well as to reduce solvent-associated toxicities, is another aspect of therapeutic targeting. The evidence reviewed above suggests this novel technology is achieving its aim of improving the therapeutic index of this well-established agent for the benefit of breast cancer patients.

6. Conflict of interest statement

Dr Cortes received honoraria from Roche and from Abraxis Bioscience.

7. Role of funding source

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