nab™-Paclitaxel: A Targeted Chemotherapy to Improve Outcomes in Metastatic Breast Cancer

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ABSTRACT

Nanoparticle albumin-bound (nab™)-paclitaxel is a novel formulation of paclitaxel that does not require the synthetic solvent carrier used with other taxanes. It exploits the natural properties of albumin to increase uptake and accumulation of paclitaxel in the tumor through gp60-mediated endothelial transcytosis, and interaction with the albumin-binding protein SPARC (secreted protein, acidic and rich in cysteine). Preclinical models have shown that nab-paclitaxel has greater antitumor activity than solvent-based paclitaxel and docetaxel, leading to the clinical testing of nab-paclitaxel.

A large phase III randomized controlled trial demonstrated the superior efficacy and favorable safety profile of nab-paclitaxel compared with solvent-based paclitaxel in patients with metastatic breast cancer (MBC). Based on these findings, nab-paclitaxel has now received regulatory approval in 37 countries, including Australia, China and South Korea in the Asia Pacific region. nab-Paclitaxel is currently licensed for the treatment of MBC after failure of anthracycline therapy, and is given as a 30 min intravenous infusion without corticosteroid or antihistamine premedication. Also, because it is free of solvents, there is no need for special infusion sets with nab-paclitaxel.

Thus, nab-paclitaxel is not just another taxane but is a targeted chemotherapy that represents a new treatment advance for women with MBC. An extensive clinical development program is now ongoing for nab-paclitaxel in a range of tumor types, including MBC, and it is hoped that this will establish the true role of this novel anticancer therapy.

Keywords: nab-paclitaxel, albumin, metastatic breast cancer, chemotherapy, solvent-based paclitaxel, targeted therapy, Cremophor EL, taxane

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INTRODUCTION

The taxanes paclitaxel and docetaxel are among the most active drugs in the treatment of metastatic breast cancer (MBC), and are established as the standard of care, either as monotherapy or in combination with other cytotoxic agents.1 However, despite their clinical activity in MBC, the use of taxanes is often limited by significant toxicities, including hypersensitivity reactions, neuropathy, and neutropenia, which can complicate treatment and diminish quality of life.

The hydrophobic nature and poor water solubility of taxanes mandate the concomitant use of synthetic solvents for their solubilization and delivery. Paclitaxel is formulated with polyoxyethylated castor oil (Cremophor® EL), while docetaxel requires a combination of polysorbate 80 (Tween® 80) and ethanol to allow parenteral administration. These solvents may be responsible for some of the toxicities associated with taxanes, particularly hypersensitivity and neurotoxicity.3,4 Cremophor EL also leaches plasticizers from polyvinyl chloride bags and infusion sets, which can result in severe, and sometimes fatal, hypersensitivity reactions.3,4 Special intravenous tubing is therefore required for taxane administration in order to reduce the risk of hypersensitivity reactions. In addition, premedication with corticosteroids and antihistamines is also required to limit the severity of any arising hypersensitivity reactions.

Solvents may also affect the efficacy of conventional taxane formulations. Cremophor EL has been shown to entrap paclitaxel through formation of micelles in plasma, preventing the drug from reaching tumor sites and resulting in reduced intratumoral concentrations of the active drug.5,7–9 Micelle formation may explain the lack of dose–response seen with solvent-based paclitaxel, as it limits the potential benefit of increased dose.7 Dose escalation of solvent-based paclitaxel does not improve outcomes, and is associated with increased toxicity.9

These limitations of solvent-based taxanes have prompted research efforts to improve their therapeutic index by creating solvent-free formulations, such as liposomal encapsulated paclitaxel, paclitaxel vitamin E emulsion and a polymer microsphere formulation of paclitaxel.10 The first successful attempt to formulate a solvent-free taxane has been the development of nanoparticle albumin-bound (nab™)-paclitaxel (Abraxane®, Abraxis BioScience, Los Angeles, CA, USA). The nab platform exploits the natural properties of albumin to increase drug delivery to the tumor and eliminates the need for solvents.11 nab-Paclitaxel

nab-Paclitaxel is a novel formulation of paclitaxel that consists of nanometer-range particles of paclitaxel bound...
to human serum albumin. The albumin-bound paclitaxel particles have an average size of 130 nm (Figure 1). nab-Paclitaxel exploits the role of albumin as the natural carrier of hydrophobic molecules in humans to increase delivery of paclitaxel to tumor cells, thereby removing the necessity for synthetic solvents. The albumin moiety of nab-paclitaxel binds to the specific albumin cell surface receptor (gp60) on the endothelial cell membrane. This activates caveolin-1, a major component of membrane vesicles, resulting in receptor-mediated internalization of the albumin–drug complex into caveolae, with subsequent transcytosis and delivery of drug to the tumor cells. The leaky junctions associated with tumor vasculature also facilitate the entry and accumulation of nab-paclitaxel into the tumor microvessels, although this is now believed to be a minor component of the transport relative to the gp60-based mechanism.

The uptake and accumulation of nab-paclitaxel in the tumor interstitium may be enhanced through the interaction of albumin with SPARC (secreted protein, acidic and rich in cysteine). SPARC is overexpressed in many tumor types, including breast cancer, and its overexpression is associated with poorer outcomes in patients with breast cancer. Preclinical studies using the SPARC-positive MX-1 breast cancer xenograft model showed that nab-paclitaxel achieved a 33% higher intratumoral paclitaxel concentration compared with equivalent doses of solvent-based paclitaxel. Other studies in patients with head and neck cancer demonstrated a correlation between high SPARC expression and response to nab-paclitaxel, suggesting a possible role for SPARC as a biomarker for nab-paclitaxel effectiveness.

In preclinical models, nab-paclitaxel has been shown to have greater antitumor activity than solvent-based paclitaxel and doxetaxel in multiple tumor types, including breast xenografts. In a dose-finding study in mice, nab-paclitaxel was significantly less toxic than solvent-based paclitaxel: the LD₅₀ values for nab-paclitaxel and solvent-based paclitaxel were 47 and 30 mg/kg/day, respectively. The maximum tolerated doses (MTDs) were 30 and 13.4 mg/kg/day for nab-paclitaxel and solvent-based paclitaxel, respectively; these doses induced a 4% mortality rate in treated mice and were considered equitoxic.

The possible mechanisms of increased intratumoral paclitaxel accumulation were examined in vitro using human umbilical vascular endothelial cells treated with fluorescent-labeled nab-paclitaxel and solvent-based paclitaxel. Endothelial binding of nab-paclitaxel was found to be 9.9-fold higher than solvent-based paclitaxel, and transcytosis across endothelial cells was 4.2-fold higher with nab-paclitaxel than with solvent-based paclitaxel. Endothelial transcytosis of nab-paclitaxel was blocked by methyl β-cycloextrin, a known inhibitor of caveolar-mediated transport. Cremophor EL inhibited binding of paclitaxel to the endothelial cells and to albumin in a dose-dependent manner, highlighting the negative effect this solvent may have on intratumoral delivery of paclitaxel. The absence of Cremophor EL, and the enhanced endothelial binding and transcytosis of nab-paclitaxel, may explain in part its greater antitumor activity when compared with solvent-based paclitaxel.

The encouraging antitumor activity and reduced toxicity reported in preclinical studies led to the progression of nab-paclitaxel into clinical development.

CLINICAL DEVELOPMENT OF nab-PACLITAXEL

The efficacy and safety of nab-paclitaxel was established in a phase III randomized, controlled trial. Based on the findings from this study, nab-paclitaxel has received regulatory approval in 37 countries, including Australia, China, and South Korea in the Asia Pacific region. nab-Paclitaxel is currently licensed for the treatment of MBC after failure of anthracycline therapy, and is given as a 30 min intravenous infusion without premedication. Also, because it is free of solvents, there is no need for special infusion sets with nab-paclitaxel.

There is an extensive clinical development program ongoing for nab-paclitaxel in a range of tumor types, including MBC. This will evaluate the efficacy and safety of nab-paclitaxel as a single agent and in combination with various other agents commonly used in MBC and other tumor types.

Early Clinical Development of nab-Paclitaxel

The toxicity profile, MTD, and pharmacokinetics of nab-paclitaxel administered every 3 weeks (q3w) were examined in a phase I study involving 19 patients with advanced solid tumors. nab-Paclitaxel was administered as a 30 min infusion without premedication. Doses ranged from 135 to 375 mg/m². No hypersensitivity reactions occurred, despite the absence of premedication. The MTD was determined to be 300 mg/m², almost
50% higher than the recommended dose of paclitaxel (175 mg/m² q3w). Dose-limiting toxicities included sensory neuropathy, stomatitis and superficial keratopathy. Linear pharmacokinetics were observed with nab-paclitaxel over the clinically relevant dose range of 135 to 300 mg/m², suggesting that a dose increase over this range may improve efficacy.

The MTD and pharmacokinetics of nab-paclitaxel administered weekly were also examined. In this phase I study, 39 patients with advanced nonhematologic malignancies received nab-paclitaxel at doses of 80 to 200 mg/m² weekly for 3 weeks in each monthly cycle. The drug was administered as a 30 min infusion without premedication. After the first cohort was enrolled, patients at subsequent dose levels were enrolled into 1 of 2 cohorts, 'lightly' or 'heavily' pretreated, based on the extent of prior chemotherapy. MTDs were 100 and 150 mg/m² for heavily and lightly pretreated patients, respectively. The dose-limiting toxicities were grade 4 neutropenia in heavily pretreated patients, and grade 3 peripheral neuropathy in lightly pretreated patients. Pharmacokinetics were linear over the dose range studied. These findings indicate that nab-paclitaxel could be administered weekly as a 30 min infusion without premedication.

Figure 2. Overall response rates phase III comparative trial of nab-paclitaxel versus solvent-based paclitaxel.

Phase III Trial of nab-Paclitaxel Versus Solvent-Based Paclitaxel

An international, randomized phase III trial directly compared the antitumor activity and safety of nab-paclitaxel with solvent-based paclitaxel in patients with MBC. The study was conducted at 70 sites in 5 countries (Canada, Russia, Ukraine, UK, and the USA). A total of 460 patients with measurable MBC were enrolled into the study and randomly assigned (1:1) to treatment q3w with either nab-paclitaxel at a dose of 260 mg/m² intravenously over 30 min without premedication, or solvent-based paclitaxel at its licensed dose of 175 mg/m² intravenously over 3 h with corticosteroid and antihistamine premedication. The dose of nab-paclitaxel used in this study was lower than the MTD used in the phase II study, and was selected so that nab-paclitaxel would not be more toxic than solvent-based paclitaxel at 175 mg/m².

Of the 460 patients enrolled, 83% were postmenopausal, 76% had more than 3 metastatic lesions, 86% had received prior chemotherapy and 59% had progressed following first-line treatment for metastatic disease. Approximately half of the patients in each treatment group received at least 6 treatment cycles. The paclitaxel dose intensity delivered was 49% higher in patients in the nab-paclitaxel group than in the solvent-based paclitaxel group (mean [standard deviation], 85.13 [3.118] mg/m² vs 57.02 [3.008] mg/m² per week, respectively). Solvent-based paclitaxel was administered with premedication in 99% of cycles, whereas nab-paclitaxel was administered without premedication in 95% of cycles.

Treatment with nab-paclitaxel was associated with a significant improvement in response rate (primary end point) compared with solvent-based paclitaxel (33% vs 19%; P=0.001; Figure 2). The superiority of nab-paclitaxel was also observed across the subgroups analyzed, including patients who received nab-paclitaxel as first-line therapy (42% vs 27%; P=0.029), and those who received it as second-line therapy or greater (27% vs 13%; P=0.006; Figure 2). Median TTP (secondary end point) was significantly longer with nab-paclitaxel than with solvent-based paclitaxel for all patients (23.0 vs 16.9 weeks; hazard ratio [HR]=0.75; P=0.006),
and among those receiving second-line therapy or greater (20.9 vs 16.1 weeks; HR=0.73; \( P=0.020 \)). Although not significantly different, there was a trend for greater median overall survival (secondary end point) among all patients treated with nab-paclitaxel compared with solvent-based paclitaxel (65.0 vs 55.7 weeks; \( P=0.374 \); Figure 3A). A significant difference was observed in patients who received nab-paclitaxel as second-line or greater therapy (56.4 vs 46.7 weeks; \( P=0.024 \); Figure 3B).

Treatment compliance was high in both groups, with 96% of patients in the nab-paclitaxel group receiving 90% of the protocol-specified dose, and 94% in the solvent-based paclitaxel group receiving 90% of the protocol-specified dose. Drug-related discontinuations, reductions and dose delays were also infrequent (3% to 7%) in both groups.

Despite the 49% higher dose of paclitaxel administered to patients in the nab-paclitaxel group, grade 4 neutropenia was significantly less common in this group than in the solvent-based paclitaxel group (9% vs 22%, respectively; \( P<0.001 \)), suggesting that the solvent (Cremophor EL) may have contributed to this toxicity. As expected with a higher dose of paclitaxel, grade 3 sensory neuropathy was more common with nab-paclitaxel (10% vs 2%; \( P<0.001 \)). This was easily managed with treatment interruption and dose reduction, and rapidly improved to grade 2 or 1 in a median of 22 days (Figure 4). No severe (grade 3 or 4) hypersensitivity reactions occurred in patients treated with nab-paclitaxel, despite the absence of routine premedication and the shorter infusion time compared with solvent-based paclitaxel. Conversely, 5 patients in the solvent-based paclitaxel group experienced grade 3 hypersensitivity reactions, despite standard premedication.

Comparable efficacy results were reported in a phase III trial involving 210 Chinese patients with MBC. \(^{22}\) As in the Gradishar et al. \(^{18}\) study, patients were randomized 1:1 to receive either nab-paclitaxel 260 mg/m\(^2\) intravenously over 30 min q3w with no premedication, or solvent-based paclitaxel 175 mg/m\(^2\) intravenously over 3 h q3w with standard premedication. The ORR was significantly higher in the nab-paclitaxel group than in the solvent-based paclitaxel group (54% vs 29%, respectively; \( P<0.001 \)). This advantage was maintained in the subgroups who received nab-paclitaxel as first-line therapy (56% vs 29%, \( P<0.001 \)), and in the group with no prior anthracycline exposure (61% vs 21%, \( P=0.001 \)). Median TTP (nab-paclitaxel vs solvent-based paclitaxel, 7.6 months vs 6.2 months; \( P=0.078 \)) and median progression-free survival (PFS) (7.6 months vs 6.2 months; \( P=0.118 \)) were higher in the nab-paclitaxel group, although the differences were not statistically significant. The most common toxicities reported were alopecia and peripheral neuropathy; both occurred with similar frequency in the 2 groups. Thus, results from phase III studies establish the efficacy and safety of nab-paclitaxel 260 mg/m\(^2\) administered q3w in patients with MBC.

**nab-Paclitaxel Once Weekly Administration**

Recent data show that weekly solvent-based paclitaxel is more effective than q3w administration. \(^{23}\) This finding, along with results demonstrating efficacy of nab-paclitaxel in first-line patients, \(^{18}\) and superior efficacy versus docetaxel in preclinical models, \(^{17}\) provided the rationale for evaluating weekly nab-paclitaxel in first-line MBC.

A randomized phase II study compared the efficacy and safety of 3 regimens of nab-paclitaxel with docetaxel for first-line therapy in patients with MBC. \(^{24}\) In this 4 arm study, 300 patients with previously untreated MBC were randomized to receive nab-paclitaxel 300 mg/m\(^2\)
nab-–Paclitaxel: A Targeted Chemotherapy to Improve Outcomes in Metastatic Breast Cancer

q3w (n=76), nab-paclitaxel 100 or 150 mg/m² weekly for 3 of every 4 weeks (n=76 and 74, respectively), or docetaxel 100 mg/m² q3w (n=74). nab-Paclitaxel was administered intravenously over 30 min without premedication, while docetaxel was given over 60 min after oral corticosteroids. The lower-dose nab-paclitaxel arms were compared with the higher-dose arm, and all nab-paclitaxel arms were compared with docetaxel.

Most (75%) of the patients enrolled were postmenopausal, and 43% had received prior adjuvant or neoadjuvant chemotherapy. Weekly nab-paclitaxel schedules of 100 and 150 mg/m² produced higher response rates compared with the q3w schedule. Response rates were higher in all nab-paclitaxel regimens compared with docetaxel, and these differences were significant in both weekly nab-paclitaxel groups compared with docetaxel (Figure 5). In terms of disease control (complete response + partial response + stable disease for ≥16 weeks), the rates were significantly higher in both weekly nab-paclitaxel arms compared with docetaxel (Figure 6). Median PFS was significantly longer with nab-paclitaxel 150 mg/m² than with docetaxel (14.6 vs 7.8 months, respectively; HR=0.57; P=0.012; Figure 7). Although median PFS was also longer with nab-paclitaxel 300 mg/m² than with docetaxel, this did not reach statistical significance. OS data were not mature at the time of data cut-off for this publication.

Regarding toxicity, all nab-paclitaxel arms were associated with lower rates of grade 3/4 neutropenia, grade 3/4 fatigue, and febrile neutropenia compared with docetaxel. The incidence of grade 4 neutropenia was higher with docetaxel than with nab-paclitaxel (5%, 9%, 5%, and 75% for nab-paclitaxel 100 mg/m² weekly, nab-paclitaxel 150 mg/m² weekly, nab-paclitaxel 300 mg/m² q3w, and docetaxel 100 mg/m² q3w, respectively). Peripheral neuropathy occurred with similar frequency in all treatment arms. However, median time to improvement in grade 3 peripheral neuropathy was shorter with nab-paclitaxel (22, 22, and 19 days for 300 mg/m² q3w, 100 mg/m² weekly, and 150 mg/m² weekly, respectively) than with docetaxel (37 days).
These results therefore strongly suggest superior efficacy and safety of weekly nab-paclitaxel therapy over docetaxel in first-line MBC, with the nab-paclitaxel weekly dose of 150 mg/m² appearing to be the most effective.

**CLINICAL IMPLICATIONS OF USING nabh-PACLITAXEL IN MBC**

From the clinical studies described above, the use of the nab platform may overcome the limitations and adverse consequences of synthetic solvents, resulting in improved efficacy without increasing toxicity. Compared with solvent-based paclitaxel, higher doses of nab-paclitaxel can be administered over a shorter infusion time (30 min vs 3 h) without the need for special tubing or premedication.

In the pivotal phase III study, treatment with nab-paclitaxel resulted in superior efficacy in terms of response rates and TTP when compared with solvent-based paclitaxel. A survival benefit was also seen in patients receiving second-line or greater therapy. nab-Paclitaxel treatment was also associated with an improved safety profile compared with solvent-based paclitaxel, with a significantly lower incidence of hematologic toxicities despite the higher paclitaxel dose administered in nab-paclitaxel. The risk of hypersensitivity reactions was reduced with nab-paclitaxel, despite the shorter infusion times compared with solvent-based paclitaxel and the absence of premedication.

The phase III and phase II data reported support the use of single-agent nab-paclitaxel 260 mg/m² as a valuable treatment option for MBC. Moreover, additional medications such as corticosteroids, which may be associated with unpleasant side effects, are not needed.

**ONGOING CLINICAL DEVELOPMENT OF nabh-PACLITAXEL IN MBC AND FUTURE DIRECTION**

The positive efficacy data for nab-paclitaxel coupled with a more favorable tolerability profile compared with solvent-based taxanes has led to the initiation of an extensive clinical development program for nab-paclitaxel in various tumor types, including MBC. A key phase III study in patients with MBC is the Cancer and Leukemia Group B/North Central Cancer Treatment Group (CALGB/NCCGT) study.

**The CALGB/NCCGT Study**

The Eastern Cooperative Oncology Group 2100 study demonstrated that adding bevacizumab to paclitaxel for the first-line treatment of MBC leads to significant improvements in response rate and PFS. Based on these results, the CALGB/NCCGT 40,502 randomized phase III study will compare weekly regimens of solvent-based paclitaxel, nab-paclitaxel, and ixabepilone, all combined with bevacizumab in first-line therapy for MBC (Figure 8 [ClinicalTrials.gov identifier: NCT00785291; accessed February 27, 2009]). The study will recruit 900 patients with locally recurrent or metastatic breast cancer. Days 1, 8, and 15 q28d; CEC, circulating endothelial cells; CTC, circulating tumor cells; n=900.
nab™-Paclitaxel: A Targeted Chemotherapy to Improve Outcomes in Metastatic Breast Cancer

progression-free at 12 months, and OS. Serum and tumor biomarkers (caveolin-1 and SPARC), along with circulating tumor and endothelial cells, will be measured to assess their possible role as predictive markers of response. This will be a US-based study.

nab-Paclitaxel in Triple-Negative Breast Cancer

The expression of caveolin-1, a structural component of caveolae in breast cancer, is associated with triple-negative breast cancer.27 As nab-paclitaxel is transported from the circulation to the tumor site via albumin-receptor mediated transcytosis, which involves caveolin-1,27 it is possible that patients with the triple-negative phenotype may respond particularly well to this novel drug. In addition, expression of SPARC, which has been shown to correlate with tumor response to nab-paclitaxel,13,14 is higher in triple-negative breast cancer.27 However, to date, only a few nab-paclitaxel studies have included small numbers of patients with triple-negative breast cancer.28–30 As such, there are currently no data available on the correlation between the triple-negative phenotype, SPARC expression and/or response to nab-paclitaxel, although some studies are planned.

SUMMARY

nab-Paclitaxel is a novel paclitaxel formulation that does not require the synthetic solvents used with other taxanes. It is approved for the treatment of MBC and is the first nanotechnology-based drug on the market. The nab platform exploits the properties of albumin to facilitate uptake of drug directly into the tumor cells via the gp60 receptor-mediated pathway, resulting in increased antitumor activity and reduced toxicity compared with solvent-based paclitaxel. The advantages of the nab platform are borne out by the results from clinical studies with nab-paclitaxel, which support the superior efficacy and safety of nab-paclitaxel compared with solvent-based paclitaxel and docetaxel. Thus, nab-paclitaxel is not just another taxane, but is a targeted chemotherapy which exploits albumin-based transport mechanisms such as gp60 transcytosis across tumor endothelial cells and binding of tumoral SPARC. This nanotechnology-based drug represents a new treatment advance for women with MBC.

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