# *nab*-Paclitaxel versus Docetaxel for the First-line Treatment of Metastatic Breast Cancer

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## Abstract

Taxane-based treatment regimens are standard first-line therapies for metastatic breast cancer (MBC). The clinical benefit of solvent-based taxanes, including solvent-based paclitaxel and docetaxel, in MBC has been established in large randomized clinical trials. Docetaxel has demonstrated greater efficacy versus solvent-based paclitaxel in at least one trial, but both solvent-based paclitaxel and docetaxel are associated with undesirable dose-limiting toxicities, including neutropenia, sensory neuropathy, and hypersensitivity reactions. *nab*-Paclitaxel, an albumin-bound form of paclitaxel, was developed to improve the therapeutic index of taxane treatment. This review summarizes preclinical experiments and clinical data from MBC trials comparing *nab*-paclitaxel with docetaxel. In preclinical studies, *nab*-paclitaxel more effectively suppressed tumor growth than docetaxel (80 versus 29 % inhibition) in breast cancer tumor xenograft models and was associated with less toxicity. Clinical studies confirmed these findings and reported a better therapeutic index with *nab*-paclitaxel than docetaxel. As such, the clinical experience with *nab*-paclitaxel supports its role as an important advance in the treatment of MBC with taxane-based regimens.

## Keywords

Albumin, *nab*-paclitaxel, docetaxel, taxane, metastatic breast cancer

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Taxane-based treatment regimens are standard first-line therapies for metastatic breast cancer (MBC),[1] the second most common cause of cancer deaths among women in the US.[2] Currently, two solvent-based taxanes, solvent-based paclitaxel and docetaxel, as well as albumin-bound paclitaxel (*nab*-paclitaxel), a novel solvent-free formulation of paclitaxel, are available for use as single agents or components of multi-agent regimens for the treatment of MBC.[1] A meta-analysis of randomized trials in MBC comparing taxane-containing therapies versus nontaxane-containing therapies revealed a statistically significant longer overall survival (OS) among patients receiving taxane-containing regimens, supporting the key role that taxanes play in MBC treatment.[3]

The potent anticancer activity of taxanes stems from their capacity to inhibit microtubule dynamics by binding directly to b-tubulin subunits (see *Figure 1*). In doing so, taxanes promote microtubule polymerization, inhibit microtubule depolymerization, and enhance microtubule stability.[4,5] When taxanes bind to microtubules, these normally dynamic structures form highly organized microtubule bundles and become dysfunctional. Consequently, taxanes induce cell death by disrupting mitotic spindle formation during the G2 and M phases of the cell cycle.[4,6] Despite sharing this similar mechanism of action, the formulations of solvent-based paclitaxel, docetaxel and *nab*-paclitaxel differ; this may explain some of the differences in their efficacy and safety profiles.

This article describes the clinical experience to date with solvent-based taxanes from large pivotal phase III trials of patients with MBC with a particular emphasis on the toxicity challenges associated with these agents. The rationale for the development of *nab*-paclitaxel and its unique mechanism of delivery are also described. Finally, preclinical and clinical studies of *nab*-paclitaxel and docetaxel in MBC are reviewed.

## History of Taxane Development

### Solvent-based Paclitaxel

Paclitaxel was discovered as a result of a large-scale effort by the National Cancer Institute to identify plant extracts with antitumor properties in the 1960s.[5] In a landmark publication in 1971, Wani et al. described paclitaxel being isolated from the bark of the *Taxus brevifolia* tree and initial preclinical studies that revealed its potent preclinical anticancer activity.[7]

As paclitaxel is extremely hydrophobic, it is difficult to solubilize. Its insolubility, together with the potential difficulties in harvesting a limited natural resource, nearly thwarted the clinical development of paclitaxel.[5,8] Eventually, Cremophor® EL (CrEL), a polyoxyethylated castor oil, combined with dehydrated alcohol, United States Pharmacopeia (USP), emerged as a promising vehicle for paclitaxel delivery and remains in the formulation of solvent-based paclitaxel available commercially.[8,9]

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**Table 1: Relative Efficacy Values in Xenograft Models Treated with *nab*-Paclitaxel versus Docetaxel**

| | *nab*-Paclitaxel Dose | Docetaxel Dose | Relative Efficacy Ratio |
|---|---|---|---|
| MX-1 (breast) | 15 mg/kg | 15 mg/kg | 2.9 |
| MDA-MB-231 (breast) | 120 mg/kg | 15 mg/kg | Not reported* |
| MDA-MD-231/hER2+ | 120 mg/kg | 15 mg/kg | 0.4 |
| LX-1 (lung) | 120 mg/kg | 15 mg/kg | 27.8 |
| hT29 (colon) | 120 mg/kg | 15 mg/kg | 2.3 |
| PC3 (prostate) | 120 mg/kg | 15 mg/kg | 1.0 |

**The ratio could not be determined because all mice in the* nab*-paclitaxel group achieved a complete response by day 31. hER2 = human epidermal growth factor receptor-2.*

**Table 2: Cross-trial Comparison of Anthracycline-exposed Patients in Phase III Trials that Led to US Food and Drug Administration Approval—Efficacy**

| | Registration Trial for Docetaxel 100 mg/m$^2$ Every 3 Weeks (n=203) | Registration Trial for *nab*-Paclitaxel 260 mg/m$^2$ Every 3 Weeks (n=176)* |
|---|---|---|
| ORR (%) | 30 | 34 |
| TTP, median (weeks) | 19.0 | 22.8 |
| OS, median (months) | 11.4 | 14.9 |

**For the intent-to-treat population of this arm (n=229). ORR = overall response rate; OS = overall survival; TTP = time to tumor progression.*

**Table 3: Cross-trial Comparison of Anthracycline-exposed Patients in Phase III Trials that Led to US Food and Drug Administration Approval—Safety**

| Treatment-related Grade 3/4 Adverse Events (%) | Registration Trial for Docetaxel 100 mg/m$^2$ Every 3 Weeks (n=203) | Registration Trial for *nab*-Paclitaxel 260 mg/m$^2$ Every 3 Weeks (n=176) |
|---|---|---|
| Hematologic | | |
| Neutropenia | 93.1 | 33.0 |
| Febrile neutropenia | 9.0 | 1.7 |
| Thrombocytopenia | 4.1 | 0.6 |
| Infection without neutropenia | 11.0 | 3.4 |
| Nonhematologic | | |
| Sensory neuropathy | 5.0 | 9.1 |
| Fatigue | Not applicable | 4.5 |
| Asthenia | 16.0 | 0 |
| Stomatitis | 9.0 | 2.3 |
| Diarrhea | 7.5 | 0 |

It was reported in early trials of solvent-based paclitaxel that the taxanes had similar efficacy to anthracyclines, the standard of care for MBC at the time. Compared with anthracyclines in the first-line setting, solvent-based paclitaxel at its now indicated dose (175 mg/m$^2$ via a 3 hour intravenous infusion every 3 weeks) and doxorubicin elicited mostly similar efficacy outcomes, including OS.[10,11] Given these findings, solvent-based paclitaxel was approved to treat previously untreated MBC in 1994.[12]

Despite the promising clinical activity described above, it became clear that treatment with solvent-based paclitaxel exposed patients to peripheral neuropathy, hypersensitivity reactions, and neutropenia.[9,13] Hypersensitivity reactions have been independently attributed to CrEL.[8,14] The mechanism underlying CrEL-triggered hypersensitivity reactions is most likely related to its induction of histamine release and complement activation.[8,14] Peripheral neuropathy has also been directly attributed to CrEL.[8]

Although the dose of paclitaxel approved by the US Food and Drug Administration (FDA) is 175 mg/m$^2$ every three weeks,[9] researchers have sought in clinical trials to optimize paclitaxel dosing by administering a lower dose every week.[15,16] Doing so would theoretically maintain the efficacy of but reduce the toxicities associated with paclitaxel. Overall, weekly paclitaxel doses ranging from 80–175 mg/m$^2$ resulted in overall response rates (ORRs) of 22–78% in previously treated and untreated patients with MBC.[15] Furthermore, a continuous weekly 80 mg/m$^2$ dose significantly improved OS relative to the 175 mg/m$^2$ every three weeks dose (hazard ratio [HR]=1.28,

**Table 4: Summary of Efficacy Data from a Randomized Phase II Trial Comparing First-line *nab*-Paclitaxel at Different Doses versus Docetaxel in Patients with Metastatic Breast Cancer**

| Investigator-assessed Efficacy | *nab*-Paclitaxel | | | Docetaxel | p Value* | Hazard Ratio |
|---|---|---|---|---|---|---|
| | 300 mg/m$^2$ q3w (n=76) A | 100 mg/m$^2$ qw 3/4 (n=76) B | 150 mg/m$^2$ qw 3/4 (n=74) C | 100 mg/m$^2$ q3w (n=74) D | | |
| ORR,[41] n (%) | 35 (46) | 48 (63) | 55 (74) | 29 (39) | Overall: <0.001**<br>C versus D: <0.001<br>B versus D: 0.002<br>A versus B: 0.024<br>A versus C: 0.002 | NA |
| PFS,[41] median (months) | 10.9 | 7.5 | 14.6 | 7.8 | Overall: 0.008***<br>C versus D: 0.012<br>C versus B: 0.001 | C versus D: 0.568<br>C versus B: 0.507 |
| OS,[42] median (months) | 22.7 | 22.2 | 33.8 | 26.6 | Overall: 0.047***<br>C versus B: 0.008<br>C versus D: NA | C versus B: 0.575<br>C versus D: 0.688 |

**The ratio could not be determined because all mice in the* nab*-paclitaxel group achieved a complete response by day 31. hER2 = human epidermal growth factor receptor-2; ORR = overall response rate; OS = overall survival; TTP = time to tumor progression..*

95% confidence interval [CI] 1.06–1.54; p=0.0092) in a phase III MBC study.[16] The most common toxicities associated with the weekly schedule have been reported to be neutropenia and neuropathy.[15]

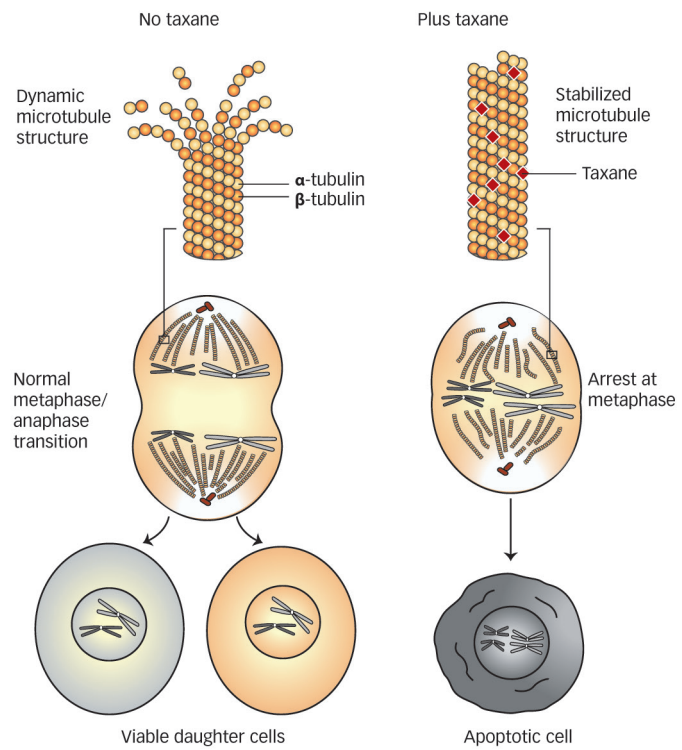
In addition to inducing hypersensitivity reactions and contributing to the risk for peripheral neuropathy in some patients,[8] CrEL also limits the pharmacokinetics of solvent-based paclitaxel.[17–21] When administered via a 3-hour intravenous infusion, solvent-based paclitaxel exhibits a nonlinear increase in systemic exposure with rising doses of drug.[17,20,21] Such disproportionate increases in paclitaxel exposure have been attributed to the capacity of CrEL to form micelles that encapsulate the active drug, as well as other drugs administered with it.[19–21] In doing so, CrEL reduces levels of paclitaxel available for cell partitioning and its rate of elimination.[19,21] Consequently, CrEL limits the therapeutic index of solvent-based paclitaxel by nonselectively increasing the systemic exposure to paclitaxel.[17–21] Taken together, the toxicities and limiting pharmacokinetics of solvent-based paclitaxel leave room for additional therapies with improved efficacy and tolerability profiles.

## Docetaxel

Docetaxel, a semisynthetic analog of paclitaxel, was developed in an effort to overcome the challenges associated with harvesting sufficient amounts of a natural resource for cancer research relative to the starting material originally required for paclitaxel.[4] Of paclitaxel analogs examined, docetaxel had the most promising antitumor activity, owing to its potent inhibition of microtubule dynamics.[22]

Similar to paclitaxel, docetaxel is difficult to solubilize. Rather than using CrEL as a vehicle though, docetaxel is formulated with polysorbate 80 (Tween® 80). Tween is similar to CrEL in that it is also thought to form micelle-like structures, which influence docetaxel pharmacokinetics.[8] In its Tween-based form, the FDA conditionally approved docetaxel in 1996 for patients with MBC who had progressed or relapsed after anthracycline-based chemotherapy.[23] Similar to paclitaxel, docetaxel was compared with anthracyclines in its early clinical trials. TAX 304 is the pivotal phase

**Figure 1: Mechanism of Action of Taxanes**




III trial that led to its full approval in this setting.[12] A total of 392 patients with MBC progressing after anthracycline-based chemotherapy were randomized to either docetaxel at a dose of 100 mg/m$^2$ every 3 weeks or a combination regimen of mitomycin plus vinblastine, a salvage regimen that was widely used at the time the trial was designed.[24]

Docetaxel achieved a significantly higher ORR (30.0 versus 11.6 %; p<0.0001) and median OS (11.4 versus 8.7 months; p=0.0097) relative to the mitomycin plus vinblastine regimen, solidifying its place in MBC

management. The most clinically significant adverse event (AE) reported in this pivotal trial was severe neutropenia.[24]

Docetaxel was also compared with anthracyclines in patients with anthracycline-naive MBC in the TAX 303 pivotal trial.[23,25] In this trial, 326 patients with MBC previously treated with alkylating agents received docetaxel at a dose of 100 mg/m$^2$ or doxorubicin at 75 mg/m$^2$ administered every 3 weeks. Although all clinical event outcomes favored docetaxel, only the ORR was statistically superior for docetaxel versus doxorubicin (47.8 versus 33.3 %; p=0.008). Overall, hematologic toxicities were more common with doxorubicin, whereas diarrhea, nail and skin disorders, and neurotoxicity were more common with docetaxel.[25] With the positive results from TAX 303, the indication for docetaxel in MBC was broadened to include use after non-anthracycline-based chemotherapy.[23,25]

Docetaxel was directly compared with solvent-based paclitaxel in a phase III trial (n=449) in patients with MBC who had progressed on a previous anthracycline-containing regimen.[26] Docetaxel was superior to solvent-based paclitaxel in terms of time to progression (5.7 versus 3.6 months, HR=1.64; 95 % CI 1.33–2.02; p<0.0001) and median OS (15.4 versus 12.7 months, HR=1.41; 95 % CI 1.15–1.73; p=0.03). However, compared with solvent-based paclitaxel, docetaxel was associated with a higher incidence of neutropenia (95.9 versus 83.3 %; p<0.0001), grade 3/4 neutropenia (93.3 versus 54.5 %; p<0.0001), febrile neutropenia (14.9 versus 1.8 %; p<0.001), anemia (77.0 versus 61.3 %; p<0.0001), and thrombocytopenia (52.3 versus 31.5 %; p=0.0006), as well as nonhematologic AEs like asthenia, peripheral edema, nausea, stomatitis, diarrhea, infection, peripheral neuropathy, skin disorders, and vomiting.[26] Thus, some gain in efficacy was offset with a higher degree of toxicity.

In an effort to examine whether alternative dosing schedules might improve the therapeutic index of docetaxel, a phase III study was conducted to compare the recommended every-3-week schedule versus weekly dosing in patients with MBC.[27] Similar to weekly dosing with paclitaxel, weekly docetaxel dosing theoretically reduces toxicities while preserving this taxane's efficacy. However, ORRs were numerically lower with weekly docetaxel dosing than dosing every three weeks (20.3 % [95 % CI 11.0–32.8 %] versus 35.6 % [95 % CI 23.6–49.1 %], respectively). No differences in progression-free survival (PFS) or OS were noted between treatment arms in this study. Compared with the every-3-week regimen, weekly docetaxel caused less neutropenia, febrile neutropenia, fatigue, myalgia, and neuropathy but more nausea, vomiting, epiphora, and effusions.[27]

## *nab*-Paclitaxel

The toxicities associated with both solvent-based paclitaxel and docetaxel combined with the encouraging efficacy of both taxanes for the treatment of MBC brought about a desire to improve the therapeutic index of taxane therapy. *nab*-Paclitaxel was developed in an effort to meet this desire.[28–32] Formulation of *nab*-paclitaxel results in 130 nm-sized particles composed of paclitaxel and albumin.[31] Using albumin to carry paclitaxel dispenses with the need to use chemical solvents (i.e. CrEL or Tween 80) that are otherwise necessary to create an injectable solution. *nab*-Paclitaxel was designed to improve on the tolerability concerns associated with solvent-based taxanes, such as hypersensitivity, peripheral neuropathy, and neutropenia.[28–32]

Currently, *nab*-paclitaxel is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior to receiving *nab*-paclitaxel, patients should have received an anthracycline unless clinically contraindicated, according to its package insert.[33] The preclinical and clinical trials that led to its approval in 2005, as well as the similarities and differences between the safety and efficacy of *nab*-paclitaxel and docetaxel, are the focus of the rest of this article.

## Preclinical and Pharmacokinetic Studies

Preclinical studies helped elucidate the unique mechanism of delivery of *nab*-paclitaxel. In early mouse tumor xenograft models, *nab*-paclitaxel appeared to deliver higher concentrations of cytotoxin to tumors than solvent-based paclitaxel.[28] In doing so, it was less toxic to mice than solvent-based paclitaxel. Furthermore, increased antitumor activity was observed with *nab*-paclitaxel, as evidenced by its prolongation of time to recurrence and tumor doubling time, as well as decreased tumor volume after treatment.[28]

Supporting the enhanced antitumor activity observed with *nab*-paclitaxel compared with solvent-based paclitaxel were findings from a pharmacokinetic study, which indicated that the disposition of paclitaxel depends on its formulation.[34] Fourteen patients received at least one cycle of solvent-based paclitaxel and one cycle of *nab*-paclitaxel. Although total drug exposure did not differ between the two formulations (p=0.72), exposure to unbound paclitaxel was significantly higher after *nab*-paclitaxel than after solvent-based paclitaxel. Higher systemic exposure was thought to be a function of the increased free drug fraction (0.063±0.021 versus 0.024±0.009; p<0.001), which likely drives drug uptake by malignant cells. These findings may at least in part explain the preclinical finding of greater antitumor activity with *nab*-paclitaxel than solvent-based paclitaxel.[34]

Research into the exact mechanism of delivery of *nab*-paclitaxel is ongoing; however, it is hypothesized that *nab*-paclitaxel may take advantage of albumin-mediated transport to reach tumors.[35] Albumin crosses endothelial cell membranes by binding with high affinity to the 60 kDa glycoprotein (gp60) cell surface receptors, triggering caveolae formation, which is then followed by internalization of vesicles into endothelial cells.[36] Vesicles cross the cells and fuse with the opposite membrane, releasing their contents into the subendothelial space.[36] Albumin-bound paclitaxel and free paclitaxel may also reach the subendothelial space by the enhanced permeation and retention (EPR) effect.[37,38] In the case of tumors, the subendothelial space may represent the tumor interstitium. Once in the tumor interstitium, albumin-binding proteins, such as secreted protein acidic and rich in cysteine (SPARC), are hypothesized to retain albumin-bound paclitaxel in the tumor interstitial space.[29,31,32,35,39] It has been hypothesized that *nab*-paclitaxel may leverage the interaction between SPARC and albumin to accumulate in the tumor microenvironment (see *Figure 2*).[35]

The antitumor activity and tolerability of *nab*-paclitaxel have been compared with those of docetaxel in preclinical studies using mouse xenograft models created by implanting athymic mice with breast cancer cells from human tumors.[29] For assessment of tumor growth or regression, tumor diameters and tumor volume over time were measured. Suppression of tumor growth was defined as the percent decrease in tumor volume in treated versus control mice at the time of euthanasia.

*nab*-Paclitaxel was found to have a higher maximum tolerated dose of >120 mg/kg, whereas the maximum tolerated dose of docetaxel was 15 mg/kg. However, when each drug was administered at a dose of 15 mg/kg, *nab*-paclitaxel more effectively suppressed tumor growth (80 versus 29 % inhibition) in mice implanted with human breast cancer MX-1 cells.[29] Doubling times in mice receiving *nab*-paclitaxel also appeared longer versus those receiving docetaxel for the majority of cell lines tested. Furthermore, *nab*-paclitaxel brought about a greater decrease in tumor volume versus docetaxel (see *Table 1* for relative efficacy values [ratios of tumor volumes at fixed time periods]). Thus, *nab*-paclitaxel demonstrated greater antitumor activity compared with docetaxel in the majority of cancer models tested in this study.[29]

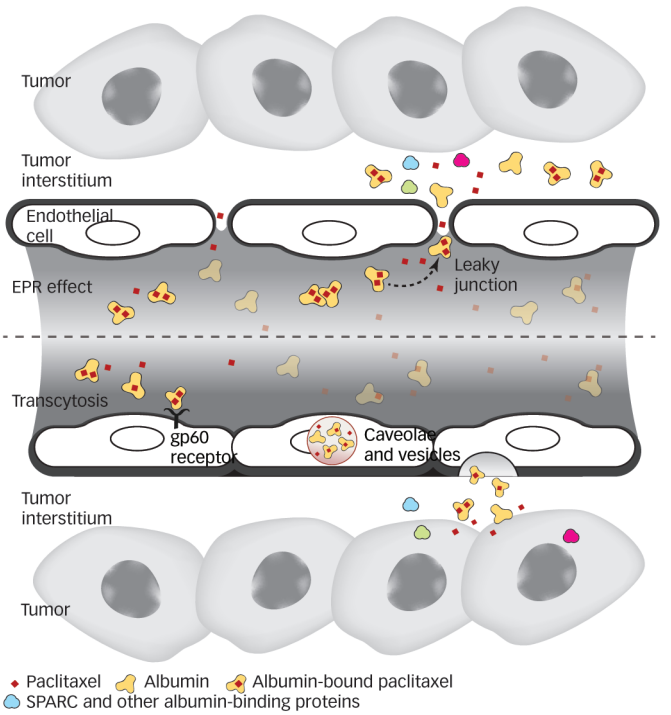
## Comparing *nab*-Paclitaxel with Docetaxel in Clinical Trials

One means for evaluation of the safety and efficacy of *nab*-paclitaxel relative to docetaxel is to examine the data from registration trials for each agent. In its pivotal phase III clinical trial, *nab*-paclitaxel was compared with solvent-based paclitaxel in 454 patients with MBC.[30] Patients received either *nab*-paclitaxel 260 mg/m$^2$ (without premedication) given as a 30-minute infusion every 3 weeks or solvent-based paclitaxel 175 mg/m$^2$ with premedication given as a 3-hour infusion every 3 weeks. *nab*-Paclitaxel produced a significantly higher ORR (33 versus 19 %; p=0.001, primary endpoint) and a longer median time to progression (23.0 versus 16.9 weeks; p=0.006) compared with solvent-based paclitaxel. Although not significant, median OS was also greater with *nab*-paclitaxel than solvent-based paclitaxel (65.0 versus 55.7 weeks, respectively; p=0.374).[30] The rate of grade 4 neutropenia was lower with *nab*-paclitaxel than solvent-based paclitaxel, but the incidence of grade 3 neuropathy was higher. No severe hypersensitivity reactions occurred with *nab*-paclitaxel, even in the absence of premedication. The results of this trial led to the approval of *nab*-paclitaxel for the treatment of MBC in 2005.[12]

*Tables 2* and *3* highlight the findings from the registration trials of *nab*-paclitaxel and docetaxel. The patient populations selected for this comparison were quite similar; for comparison's sake, these tables are restricted only to patients who were exposed to anthracycline treatment.[24,30,40] The results shown in *Tables 2* and *3*, including a higher ORR (34 versus 30 %) and longer median OS (14.9 versus 8.7 months), would seem to suggest that *nab*-paclitaxel may achieve a favorable therapeutic index versus docetaxel; however, such comparisons are best made in head-to-head trials.

*nab*-Paclitaxel and docetaxel have been directly compared in a randomized phase II trial.[41] In light of encouraging research efforts comparing weekly dosing of first-generation taxanes with every-3-week dosing, weekly *nab*-paclitaxel was compared with *nab*-paclitaxel administered every 3 weeks and with docetaxel administered every 3 weeks in MBC. In this study, three doses of *nab*-paclitaxel (300 mg/m$^2$ every 3 weeks, 150 mg/m$^2$ weekly, and 100 mg/m$^2$ weekly) were compared with docetaxel at a dose of 100 mg/m$^2$ every 3 weeks in 302 patients with previously untreated MBC. Significantly higher investigator-assessed ORRs were achieved with *nab*-paclitaxel at doses of 100 mg/m$^2$ and 150 mg/m$^2$ weekly versus docetaxel (63, 74, and 39 %, respectively; overall p<0.001, 150 mg/m$^2$ versus docetaxel; p<0.001; 100 mg/m$^2$ versus docetaxel; p=0.002).[41] The ORR of *nab*-paclitaxel at 300 mg/m$^2$ every 3 weeks was 46 %. The 150 mg/m$^2$ dose of *nab*-paclitaxel significantly prolonged median PFS (by investigator assessment) compared with docetaxel (14.6 versus 7.8 months, respectively; p=0.012), whereas the PFS values for the 100 and 300 mg/m$^2$ doses of *nab*-paclitaxel were 7.5 and 10.9 months, respectively. Furthermore, a follow-up publication also demonstrated a trend towards improved median OS with *nab*-paclitaxel relative to docetaxel (see *Table 4*), again underscoring the benefits of *nab*-paclitaxel over first-generation taxanes in MBC.[42]

## Figure 2: *nab*-Paclitaxel Accumulation in Tumor Tissues




EPR, enhanced permeation and retention; gp60, 60-kDa glycoprotein; SPARC, secreted protein acidic and rich in cysteine

The most common treatment-emergent AEs reported with weekly *nab*-paclitaxel and every-3-week docetaxel noted after the initial analysis of the phase II trial were neutropenia, alopecia, neuropathy, fatigue, and arthralgia (see *Table 5*).[42] Grade 4 neutropenia was less frequent in all *nab*-paclitaxel arms than in the docetaxel arm. Grade 3 fatigue was also less common in patients receiving *nab*-paclitaxel (no cases of grade 4 fatigue in any arm).The incidence of grade 3 sensory neuropathy was highest with *nab*-paclitaxel 150 mg/m$^2$ (no cases of grade 4 sensory neuropathy in any arm). The highest rate of dose reductions occurred in the *nab*-paclitaxel 150 mg/m$^2$ weekly arm (47 %) versus 18 and 20 % in the 100 mg/m$^2$ weekly and 300 mg/m$^2$ every-3-week *nab*-paclitaxel arms, respectively, and 30 % in the docetaxel arm.[42] The treatment arm with the best AE profile proved to be weekly *nab*-paclitaxel 100 mg/m$^2$, which had the lowest rates of grade 4 neutropenia and grade 3 sensory neuropathy and fatigue. Overall, the results of this study demonstrated that weekly schedules of *nab*-paclitaxel may have a better therapeutic index than docetaxel.[41,42]

## Discussion and Conclusions

Based on the preclinical studies and clinical trial data reviewed here, *nab*-paclitaxel represents a novel delivery platform for taxanes to reach tumors and preferentially accumulate near malignant cells. Because

**Table 5: Summary of Safety Data from a Randomized Phase II Trial Comparing First-line *nab*-Paclitaxel at Different Doses versus Docetaxel in Patients with Metastatic Breast Cancer[42]**

| Safety | *nab*-Paclitaxel | | | Docetaxel | Overall p Value |
|---|---|---|---|---|---|
| | 300 mg/m² q3w (n=76) A | 100 mg/m² qw 3/4 (n=76) B | 150 mg/m² qw 3/4 (n=74) C | 100 mg/m² q3w (n=74) D | |
| Neutropenia,*n (%) | | | | | |
| Grade 3 | 28 (37) | 15 (20) | 26 (35) | 14 (19) | <0.001*** |
| Grade 4 | 5 (7) | 4 (5) | 7 (9) | 54 (75)** | |
| Mean nadir ± SD (x $10^9$/L) | 1.21±1.00 | 1.51±0.96 | 1.11±0.63 | 0.38±0.34 | |
| Grade 3 sensory neuropathy, n (%) | 16 (21) | 7 (9) | 16 (22) | 9 (12) | 0.083*** |
| Grade 3 fatigue, n (%) | 4 (5) | 0 | 3 (4) | 14 (19) | <0.001*** |
| Time to onset of sensory neuropathy,§ median (days) | 151 | 189 | 162 | 176 | 0.454◊ |
| Time to improvement of sensory neuropathy, median (days) | 22 | 22 | 20 | 41 | 0.154◊ |

**Febrile neutropenia occurred in 1 % of patients in each* nab*-paclitaxel arm and 8 % of patients in the docetaxel arm. **The docetaxel arm produced higher rates of grade 4 neutropenia versus each* nab*-paclitaxel arm (p<0.001 for each comparison). ***Based on the Fisher exact test. § Grade 3 sensory neuropathy. ◊ Based on log-rank test. ¶ Improvement to grade ≤2. MBC = metastatic breast cancer; q3w = every 3 weeks; qw 3/4 = first 3 of 4 weeks; SD = standard deviation.*

both docetaxel and *nab*-paclitaxel arose from efforts to improve on the therapeutic index of taxane treatment after solvent-based paclitaxel was developed, the comparison of these two agents is logical. *nab*-Paclitaxel appears to be better tolerated and more efficacious than docetaxel in the comparative data available to date.[41,42] In addition, administration of *nab*-paclitaxel does not require any premedication for potential hypersensitivity reactions, making it the more convenient option for most patients.[23,33]

*nab*-Paclitaxel demonstrated greater ORR, PFS, OS, and tolerability than docetaxel in patients with MBC.[41,42] This trial suggested that weekly administration may be the ideal schedule for *nab*-paclitaxel.[41,42] The 150 mg/m² weekly dose was associated with greater efficacy but also a higher rate of dose reductions due to toxicity versus the 100 mg/m² weekly dose, suggesting a need for further evaluation of dose in the weekly schedule.[42] Preliminary results from a phase III trial conducted by the Cancer and Leukemia Group B (CALGB) comparing *nab*-paclitaxel ± bevacizumab (n=271) or ixabepilone ± bevacizumab (n=245) with solvent-based paclitaxel ± bevacizumab (n=283) for the first-line treatment of MBC were presented at the 2012 Annual Symposium of the American Society of Clinical Oncology.[43] Ninety-eight percent of enrolled patients received bevacizumab. The difference in median PFS for *nab*-paclitaxel ± bevacizumab versus solvent-based paclitaxel ± bevacizumab was not statistically significant (9.2 versus 10.6 months, respectively, HR=1.19 [95% CI 0.96–1.49]; p=0.12) based on an interim analysis conducted at a time-point less than half way through the study. Notably, 45% of patients receiving *nab*-paclitaxel ± bevacizumab underwent dose reductions by cycle 3 versus 15% of patients receiving solvent-based paclitaxel ± bevacizumab. This compares with the 47% of patients receiving *nab*-paclitaxel monotherapy at 150 mg/m² who required dose reductions in the previously described trial versus docetaxel.[42] In addition, the CALGB trial showed that by cycle 5, a higher percentage of patients had discontinued *nab*-paclitaxel versus solvent-based paclitaxel (>45 versus <30 %). Consistent with the higher rates of dose reductions and discontinuations, patients receiving *nab*-paclitaxel ± bevacizumab in the CALGB trial experienced more grade ≥3 hematologic (51 versus 21 %; p<0.0001) and nonhematologic (60 versus 44 %; p=0.0002) AEs compared with patients receiving solvent-based paclitaxel ± bevacizumab.[43] These results may suggest that the 150 mg/m² dose of *nab*-paclitaxel was too high; the CALGB trial represents the first time this dose of *nab*-paclitaxel was administered in a phase III trial in the US. Future research may determine that dose should be tailored to patients based on specific characteristics, such as performance status, tumor burden, and pre-existing conditions like neutropenia and peripheral neuropathy.

Although not addressed by this review, guidelines for early-stage breast cancer also recommend solvent-based paclitaxel and docetaxel as preferred agents in the adjuvant setting.[1] Combination therapies with category one recommendations include the following: docetaxel, doxorubicin, and cyclophosphamide (TAC); doxorubicin and cyclophosphamide followed by solvent-based paclitaxel (AC→T); and docetaxel and cyclophosphamide (TC). A randomized phase III trial (n=4,950) compared the efficacy and safety of adjuvant therapy consisting of AC followed by either solvent-based paclitaxel or docetaxel.[44] Patients received four cycles of AC therapy every three weeks (q3w) and then received four cycles of either docetaxel at 100 mg/m² or solvent-based paclitaxel at 175 mg/m² q3w or 12 cycles of docetaxel at 35 mg/m² or solvent-based paclitaxel at 80 mg/m² weekly. Compared with the standard q3w solvent-based paclitaxel arm, the three experimental arms demonstrated longer OSs with HRs of 1.32 for weekly solvent-based paclitaxel (98.3% CI 1.02–1.72; p=0.01), 1.13 for q3w docetaxel (98.3% CI 0.88–1.46; p=0.25), and 1.02 for weekly docetaxel (98.3% CI 0.80–1.32; p=0.80). Grade 3/4 AEs occurred in 28 % of patients receiving weekly solvent-based paclitaxel, 30% of patients receiving q3w solvent-based paclitaxel, 45% of patients receiving weekly docetaxel, and 71% of patients receiving q3w docetaxel. These OS and tolerability results would seem to support the use of weekly paclitaxel over the other groups in this adjuvant treatment paradigm.

Given the clinical activity that *nab*-paclitaxel has thus far demonstrated relative to docetaxel and paclitaxel in the MBC setting, it may be feasible to investigate *nab*-paclitaxel as an adjuvant therapy as well. Indeed,

encouraging findings from a few clinical trials support such a role for *nab*-paclitaxel in early-stage breast cancer.[45,46] In a pilot study, 29 women with high-risk, operable breast cancer received dose-dense AC followed by dose-dense *nab*-paclitaxel (260 mg/m$^2$ every 2 weeks).[46] Overall, most AEs were consistent with earlier trials that examined dose-dense AC followed by dose-dense solvent-based paclitaxel. However, most patients in the pilot study did not require prophylactic pegfilgrastim, whereas those in the trial with standard paclitaxel did.[46] Grade 2/3 peripheral neuropathy was common with *nab*-paclitaxel but resolved after the trial in most patients.[46] Based on these findings, the study authors concluded that dose-dense AC followed by dose-dense *nab*-paclitaxel is feasible in early-stage breast cancer.[46]

A separate phase II study examined a similar regimen, albeit with the addition of bevacizumab, in early-stage breast cancer.[45] A total of 197 patients with early-stage breast cancer were randomized to receive dose dense AC followed by dose-dense *nab*-paclitaxel (260 mg/m$^2$ every 2 weeks plus bevacizumab or dose-dense AC followed by solvent-based paclitaxel (175 mg/m$^2$ every 2 weeks) plus bevacizumab. The majority of patients in both arms completed all four cycles of planned therapy. Compared with patients receiving solvent-based paclitaxel, those given *nab*-paclitaxel received 44% more of the study drug during the trial. Percentages of AC and bevacizumab received by each treatment arm did not significantly differ. All study participants experienced at least one treatment-related AE, with the most common being fatigue, sensory neuropathy, leukopenia, anemia, nausea, and alopecia in both arms. Notably, no differences in grade ≥3 taxane-associated AEs were reported between treatment arms, suggesting that *nab*-paclitaxel is as feasible as solvent-based paclitaxel in this setting; however, no efficacy values were reported in this study.[45]

In conclusion, taxanes remain a cornerstone of MBC treatment. *nab*-Paclitaxel was developed to improve the therapeutic index of taxanes, and results from clinical trials to date suggest that this goal has been achieved, while maintaining or increasing efficacy. Both preclinical and clinical data support the continued development of *nab*-paclitaxel in MBC. Furthermore, ongoing trials in early-stage breast cancer are attempting to further explore the role of *nab*-paclitaxel, with encouraging early results. Large randomized phase III trials will be necessary to further define the role of *nab*-paclitaxel for the treatment of early-stage breast cancer. ■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