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REVIEW

Safety and Efficacy of *nab*-Paclitaxel in the Treatment of Patients with Breast Cancer

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Abstract: Taxanes are highly active chemotherapeutic agents in the treatment of early-stage and metastatic breast cancer. Novel formulations have been developed to improve efficacy and decrease toxicity associated with these cytotoxic agents. *nab*-paclitaxel is a solvent free, albumin-bound 130-nanometer particle formulation of paclitaxel (Abraxane®, Abraxis Bioscience), which was developed to avoid toxicities of the Cremophor vehicle used in solvent-based paclitaxel. In a phase III clinical trial, *nab*-paclitaxel demonstrated higher response rates, better safety and side-effect profile compared to conventional paclitaxel, and improved survival in patients receiving it as second line therapy. Higher doses can be administered over a shorter infusion time without the need for special infusion sets or pre-medications. It is now approved in the US for treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant therapy, where prior therapy included an anthracycline. Recently, several phase II studies have suggested a role for *nab*-paclitaxel as a single agent and in combination with other agents for first-line treatment of metastatic breast cancer.

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

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Introduction

Taxanes (eg, paclitaxel, docetaxel) and anthracyclines (eg, doxorubicin, epirubicin) remain among the most active and widely used chemotherapy agents in breast cancer, both in adjuvant and metastatic settings.[1–3] A recent meta-analyses of 13 randomized clinical trials showed a significant improvement of disease-free and overall survival (OS) rates in high-risk early stage breast cancer with chemotherapy regimens incorporating combination of taxanes and anthracyclines.[4] However, approximately 25%–30% of early stage breast cancers will recur. There is an imperative need for agents that not only overcome resistance but also have a favorable toxicity profile. The solvents used for dissolving hydrophobic molecules, paclitaxel and docetaxel are known to be associated with significant risk of hypersensitivity reactions and neuropathy and also impair drug delivery to the tumor, limiting their clinical effectiveness.[5,6]

With the advent of nanotechnology, a novel formulation of solvent free 130-*n*anometer *a*lbumin-*b*ound paclitaxel (*nab*-paclitaxel, Abraxane®, Abraxis Bioscience) was developed for use as a colloidal suspension intravenously. Based on the pivotal phase III clinical trial results, *nab*-paclitaxel was approved in the United States by US Food and Drug Administration (FDA) in January 2005 and in Europe by European Medicines Agency (EMEA) in January 2008 for use in patients with metastatic breast cancer (MBC) who have failed combination chemotherapy or relapse within 6 months of adjuvant therapy where prior therapy included an anthracycline.

This article provides a review of pharmacology, safety and efficacy profile of *nab*-paclitaxel, and evaluates its benefit in treatment of breast cancer.

Side-Effects and Drawbacks of Solvent-Based Taxanes

Taxanes bind to the interior surface of β-microtubule chain and enhance tubulin polymerization, thereby stabilizing microtubules. This inhibits mitosis, motility and intracellular transport within (cancer) cells, leading to apoptotic cell death. Taxanes also block anti-apoptotic effects of BCL-2 gene family, induce *TP*53 gene activation with resultant mitotic arrest leading to cell death.[7]

Paclitaxel was first approved in 1992 for clinical use. It is a naturally occurring diterpinoid product extracted from bark of pacific yew. Docetaxel, another taxane, which was approved by FDA for clinical use in 2004, is a semi-synthetic esterified product of 10-deacetyl baccatin III extracted from needles of European yew. Both paclitaxel and docetaxel are highly hydrophobic. Cremaphor EL (CrEL), a non-ionic surfactant poly-oxy-ethylated castor oil mixed 1:1 with dehydrated ethanol was recognized to be the most feasible option to solubilize paclitaxel for intravenous administration. Likewise, the solvent used for Docetaxel is another poly-oxy-ethylated surfactant, polysorbate-80.[6] Being biologically and pharmacologically active, these solvents are associated with several major side effects such as hypersensitivity reactions and neuropathies. They also impair tumor penetration, limiting the clinical effectiveness of solvent-based taxanes.[5,6] CrEL-paclitaxel formulation needs special infusion set to minimize exposure to di(2-ethylhexyl)phthalate (DHEP), which may be leached from standard polyvinyl chloride sets. Prolonged infusion times and premedications with corticosteroids and antihistamine agents are required to reduce hypersensitivity reactions. However, minor reactions still occur in about 40% of all patients receiving solvent-based taxanes and nearly 3% develop potentially life-threatening reactions.[6] CrEL is also shown to cause neutropenia and prolonged peripheral neuropathy related to axonal degeneration. Fluid retention, a toxicity commonly seen with docetaxel has been attributed in part due to alteration of membrane fluidity by polysorbate-80.[6,8] Formation of large polar micelles of CrEL-paclitaxel in the plasma compartment can cause entrapment of the drug leading to non-linear pharmacokinetics.[5] This alters the pharmaco-dymanic characteristics of the solubilized drug resulting in a substantial increase in systemic exposure with concomitantly reduced systemic clearance placing patients at risk for severe systemic toxicities. This drug entrapment phenomenon which decreases the duration of drug exposure partly explains why the attempts to improve efficacy of CrEL-paclitaxel by utilizing doses higher than the standard-of-care dose (175 mg/m^2 over 3 hours every 3 weeks) have been unsuccessful.[9] More frequent dosing (such as weekly administration) which may lead to increased duration of exposure, has demonstrated improved efficacy in both adjuvant/neoadjuvant and metastatic settings.[10]

To address these limitations of solvent-based taxanes and to improve their therapeutic index, various solvent-free formulations and delivery systems such as liposomal encapsulated paclitaxel, paclitaxel vitamin E emulsion and polymer microsphere formulation of paclitaxel were investigated but with limited success.[6,8] First successful attempt to formulate a solvent-free taxane has been the development of *nab*-paclitaxel. The nano-particle protein platform utilizes the natural properties of albumin to increase drug delivery to the tumor and eliminates the need for solvents.

Nanomedicine and *nab*-Technology

Nanomedicine is the medical application of molecular *nab*-technology, a new area of science that involves working with small scale materials and devices that are at the nanometer level (10^{-9} of a meter). A few examples of the development by this discipline include liposomes, dendrimers, super paramagnetic nanoparticles and polymer-based platforms.[11] Albumin has a number of features that make it an ideal drug delivery system. It is a natural carrier of endogenous hydrophobic molecules such as vitamins, hormones and other water-insoluble plasma substances that are bound in a reversible non-covalent manner. Albumin plays an important role in endothelial transcytosis of protein-bound and unbound plasma constituents mainly by binding to a cell-surface 60 kDa glycoprotein receptor (gp60) on the endothelial cell membrane. This leads to activation of caveolin-1, a major component of membrane vesicles, resulting in receptor mediated internalization of the albumin-drug complex into caveolae (small invaginations of plasma membrane). Subsequently, caveolae transports the albumin-drug conjugate to the extracellular space, including the tumor interstitium. SPARC (*secreted protein, acidic and rich in cysteine*), which is believed to be selectively secreted by the tumors, binds to albumin-drug complex with the resultant release of the drug in the vicinity of tumor cells.[11,12]

Preclinical and Clinical Evaluation of *nab*-Paclitaxel

Comparative intratumoral and antitumoral activity of *nab*-paclitaxel has been demonstrated to be greater than CrEL-paclitaxel and docetaxel in multiple tumor types using preclinical models.[12,13] Desai et al[13] using radiolabeled paclitaxel in mice with xenografts, showed that *nab*-paclitaxel was significantly less toxic; LD_{50} (lethal dose, 50%) values and maximum tolerated dose (MTD) for *nab*-paclitaxel and CrEL-paclitaxel were 47 and 30 mg/kg/day, and 30 and 13.4 mg/kg/day, respectively. At equal doses, intratumoral paclitaxel accumulation was found to be 33% higher for *nab*-paclitaxel. In live human umbilical vascular endothelial cells (HUVEC), endothelial binding and transport across the endothelial cell monolayer was significantly higher (9.9 fold and 4.2 fold respectively) with *nab*-paclitaxel and this difference was abrogated by methyl β-cyclodextrin, a known inhibitor of endothelial gp60 receptor and caveolar-mediated transport.[13] Zhou et al recently reported similar antitumoral responses with *nab*-paclitaxel in hepatocelluar carcinoma (HCC) cell lines.[14] In a panel of HCC cell lines studied, *nab*-paclitaxel showed an effective IC_{50} dose at 15-fold lower than paclitaxel or docetaxel alone, and ~450-fold less compared to doxorubicin. SPARC, a type of caveolin-1 has a sequence homology with gp60, leads to its binding to albumin. It is over expressed in several tumor types including breast cancer. This interaction between SPARC and albumin has been suggested to be the reason for enhanced uptake and intra-tumoral accumulation, and also a possible role for SPARC as a bio-marker for *nab*-paclitaxel effectiveness.[12] These data provided the preclinical evidence to advance the drug to clinical studies.

Phase 1 and Pharmacokinetic Studies

Three different dose schedules of *nab*-paclitaxel have been evaluated in Phase I and pharmacokinetics studies. In a study by Ibrahim et al,[15] 19 patients with advanced solid tumors received *nab*-paclitaxel as a 30 minute infusion given every 3 weeks without premedication using doses from 135 to 375 mg/m^2. No infusion related acute hypersensitivity reactions were noted during the drug administration. Hematological toxicity was mild and not cumulative. At the highest dose studied (level 3, 375 mg/m^2), dose-limiting toxicity occurred in 3 of 6 patients and consisted of sensory neuropathy (3 patients), stomatitis (2 patients) and superficial keratopathy (2 patients). The MTD was determined to be 300 mg/m^2, substantially higher than the typical dose used with CrEL-paclitaxel. Pharmacokinetic analyses revealed whole blood

paclitaxel concentrations and area under the curve (AUC) values to increase linearly over the dose range of 135–300 mg/m^2 unlike the non-linear kinetics of solvent-based paclitaxel.

In another phase 1 trial reported by Nyman et al,[16] 39 patients with advanced non-hematological malignancies received *nab*-paclitaxel without premedication at a dose levels from 80 to 200 mg/m^2 as a 30-minute infusion once a week for 3 weeks in each monthly cycle. One third of patients received ≥6 cycles. After enrollment of the first cohort, patients were enrolled into 1 of 2 cohorts, 'lightly' and 'heavily' pretreated based on the extent of prior exposure to chemotherapy. MTDs for these two cohorts were 150 mg/m^2 and 100 mg/m^2; dose-limiting toxicities were grade 3 peripheral neuropathy and grade 4 neutropenia respectively. The pharmacokinetics was again noted to be linear and there were no dose-dependant changes in plasma clearance. Partial response (PR) was observed in patients previously treated with CrEL-paclitaxel.

A randomized cross over study comparing the pharmacokinetics of *nab*-paclitaxel and CrEL-paclitaxel was reported by Gardner et al.[17] Seventeen patients with locally advanced or metastatic solid tumors that were likely to be responsive to taxanes were randomized to receive *nab*-paclitaxel (260 mg/m^2 as a 30-minute infusion) or CrEL-paclitaxel (175 mg/m^2 as a 3 hour infusion). Patients crossed over to the alternate treatment after 1st cycle. Thereafter, patients received treatments with 260 mg/m^2 of *nab*-paclitaxel every 3 weeks. Pharmacokinetic studies were carried out for the first cycle of CrEL-paclitaxel and the first two cycles of *nab*-paclitaxel. The total drug exposure was comparable between the two formulations and the mean fraction of unbound paclitaxel was significantly higher with *nab*-paclitaxel compared to CrEL-paclitaxel (0.063 ± 0.021 vs. 0.024 ± 0.009; $P < 0.001$). This study purports that systemic exposure to unbound paclitaxel would lead to increased tumoral uptake thereby resulting in an augmented anti-tumor efficacy compared to CrEL-paclitaxel.

In a phase 1 study of three different schedules of *nab*-paclitaxel in combination with carboplatin,[18] 41 heavily pretreated patients with advanced solid tumors received *nab*-paclitaxel and carboplatin AUC of 6 on day 1. Group A received *nab*-paclitaxel at doses ranging from 220 to 340 mg/m^2 on day 1 every

21 days; group B received *nab*-paclitaxel at 100 or 125 mg/m^2 on days 1, 8, and 15 every 28 days; and group C received *nab*-paclitaxel 125 or 150 mg/m^2 on days 1 and 8 every 21 days. MTD of *nab*-paclitaxel in combination with carboplatin was 300, 100, and 125 mg/m^2 in groups A, B, and C, respectively with myelosuppression was the primary dose limiting toxicity in all the groups.

In a recent phase 1 study reported by Chien et al,[19] vascular-priming chemosensitization with 2-day pulse of high dose lapatinib followed by weekly infusion of 100 mg/m^2 *nab*-paclitaxel treatment was investigated in 25 patients with advanced solid tumors. 72% of these patients were previously taxane-refractory. Maximum tolerated dose of lapatinib was defined as 5250 mg/day in divided doses. The dose-limiting toxicities were grade 3 vomiting and grade 4 neutropenia. 65% of evaluable patients had a partial or stable response on this therapy.

Phase II Studies

Based on the results of phase 1 study,[15] Ibrahim et al investigated *nab*-paclitaxel in a multicenter phase II study to evaluate safety and antitumor activity in patients with MBC.[20] 63 women with confirmed and measurable MBC received 300 mg/m^2 of *nab*-paclitaxel over 30 minutes every 3 weeks. 48 patients had received prior chemotherapy; 39 patients had received no prior treatment for metastatic disease. Median number of treatments was 6 cycles. Overall response rate (ORR), which was the primary end point of the study, was 48% for all patients and 64% for those receiving *nab*-paclitaxel as first line treatment. Median time to progression (TTP) was 26.6 weeks and median OS was 63.6 weeks. No severe hypersensitivity reactions were reported despite lack of premedication. Toxicities noted were typical of paclitaxel and included grade 4 neutropenia (24%) and grade 3 sensory neuropathy (11%) and grade 4 febrile neutropenia (5%).

Blum et al[21] reported the benefit of weekly *nab*-paclitaxel in patients with MBC whose disease had failed conventional taxane treatment. Taxane failure was defined as metastatic disease progression during taxane therapy or relapse within 12 months of adjuvant taxane therapy. Patients received 100 mg/m^2 (n = 106) or 125 mg/m^2 (n = 75) on days 1, 8, and 15 of 28 day cycle. Response rates were 14% and 16% for the 100 mg/m^2 and 125 mg/m^2 cohorts, respectively with

Table 1. nab-PACLITAXEL: AT A GLANCE[37]

***nab*-PACLITAXEL: AT A GLANCE[37]**
Mechanism of action
Antimicrotubule agent, promote microtubules assembly from tubulin dimers and stabilize microtubules to prevent depolymerization. This stability causes inhibition of the normal dynamic reorganization of the microtubules which is necessary for important interphase and mitotic functions in the cells
Dosing and administration
260 mg/m^2 Intravenous infusion over 30 minutes once every 3 weeks
Pharmacokinetics
Distribution: Extensive extra-vascular distribution and/or tissue binding; does not penetrate blood brain barrier Protein binding: 89% to 98% Metabolism: Hepatic; P450 (CYP2C8 and CYP3A4) Excretion: Fecal (20%); renal (4%) Elimination half life: 27 hours
Side effects
Common: Cardiovascular: abnormal EKG (60%), edema (10%) Dermatologic: alopecia (90%) Gastrointestinal: diarrhea (27%), nausea (30%), Vomiting (18%) Hematologic: Anemia (33%), Neutropenia, (any grade, 80%) Hepatic: raised transaminases (39%), raised alkaline phosphatase (36%) Neurologic: asthenia/myalgia/fatigue (47%), sensory neuropathy (any grade, 71%) Ophthalmic: visual disturbance (13%) Renal: raised serum creatinine (11%) Respiratory: dyspnea (12%) Serious: Cardiovascular: cardiac arrest, cerebrovascular accident, supraventricular tachycardia, transient ischemic attack (3%) Hematologic: severe anemia (1%), bleeding (2%), febrile neutropenia (2%), neutropenia, grade 4 (9%), severe thrombocytopenia (<1%) Neurologic: severe sensory neuropathy (10%)
Special precaution
Paclitaxel has been shown to be clastogenic, teratogenic and fetotoxic and should not be used in pregnancy. Men should be advised not to father a child while receiving treatment. It is not known if paclitaxel is excreted in human milk; however, it is recommended that nursing should be discontinued during therapy
Synonyms
ABI-007, albumin-bound paclitaxel
Trade name
ABRAXANE (Abraxis Bioscience)

an additional 12% and 21% of patients, respectively, having stable disease (SD) for ≥16 weeks. Median progression-free survival (PFS) (3 vs. 3.5 months) and median survival (9.2 vs. 9.1 months) were similar for the two dose cohorts; Survival was similar for responding patients and those with SD. No severe hypersensitivity reactions were reported and grade 4 neutropenia occurred in less than 5% of patients.

Mirtsching et al recently reported the efficacy and safety of weekly *nab*-paclitaxel as a first-line therapy of MBC.[22] *nab*-paclitaxel (125 mg/m^2) was administered by 30-minute intravenous infusion weekly for 3 of 4 weeks. Patients whose tumors overexpressed HER2 also received trastuzumab. 72 patients were enrolled; 22 patients had HER2+ breast cancer. The ORR was 42.2%; 5 patients had a CR and 22 patients had a PR. Additionally, 17 patients experienced SD, providing a disease control rate (CR + PR + SD) of 68.8%. Patients with HER2+ disease had an ORR of 52.4%; the ORR was 38.1% in the HER2- population. Median PFS was 14.5 months and survival rates at 1 year and 2 years were 69% and 62%, respectively. The most commonly observed toxicities were pain (64%), fatigue (58%), sensory neuropathy (54%), infection (46%), nausea (38%), alopecia (33%), and anemia (33%). The investigators concluded that

weekly *nab*-paclitaxel had a favorable safety profile and was well tolerated as a first-line treatment for MBC including patients with HER2+ disease.

Roy et al,[23] reported a multicenter phase II study of weekly *nab*-paclitaxel in combination with gemcitabine in patients with MBC. In this open-label, one-stage trial, 50 patients with previously untreated MBC were treated with 125 mg/m² of *nab*-paclitaxel and 1000 mg/m² of gemcitabine on days 1 and 8 of a 21 day cycle until disease progression. 40 patients (80%) had visceral involvement and 30 patients (60%) had ≥3 sites of metastases. ORR was 50% (4 complete responses, 8%; 21 partial responses, 42%). Median PFS was 7.9 months. PFS and OS at 6 months was 60% and 92% respectively. Neutropenia was the most common toxicity (grade 3: 43%, grade 4: 12%). Grade 3–4 neuropathy was noted in only 4 patients (8%).

Gradishar et al[24] reported a randomized multicenter phase II study comparing *nab*-paclitaxel with docetaxel as first line treatment in patients with MBC. 300 previously untreated MBC patients were randomized to 3 different *nab*-paclitaxel treatment schedules—300 mg/m² every 3 weeks (n = 76), 150 mg/m² weekly (n = 74) and 100 mg/m² weekly (n = 76). Docetaxel dose was 100 mg/m² once every 3 weeks (n = 74). 43% of patients had received prior adjuvant or neoadjuvant chemotherapy. 150 mg/m² weekly *nab*-paclitaxel demonstrated significantly longer PFS than docetaxel (12.5 vs. 7.5 months). On the basis of independent radiologist review, both 150 mg/m² (49%) and 100 mg/m² (45%) weekly *nab*-paclitaxel demonstrated a higher ORR than docetaxel (35%), but this did not reach statistical significance. This trend was supported by statistically significant investigator ORR for both weekly *nab*-paclitaxel doses versus docetaxel. Every 3 weekly *nab*-paclitaxel versus docetaxel was not different in terms of ORR or PFS. Grade 3/4 fatigue, neutropenia and febrile neutropenia were less frequent in all *nab*-paclitaxel arms and the frequency and grade of peripheral neuropathy was similar in all treatment groups but this resolved more rapidly after treatment withdrawal with *nab*-paclitaxel compared with patients who received docetaxel.

Robert et al in a pilot study reported the safety of sequential adjuvant dose-dense (every-2-week) doxorubicin (A) plus cyclophasphamide (C) followed by dose-dense *nab*-paclitaxel for early-stage breast cancer.[25]

Women with high risk breast cancer (T1-3, N1-2, or N0 disease with tumors that were >2 cm) were enrolled and received four cycles of dose-dense A (60 mg/m²) plus C (600 mg/m²) with peg-filgrastim, followed by dose-dense *nab*-paclitaxel (260 mg/m²) with peg-filgrastim given as needed. Endpoints were adverse events (AEs), including myelosuppression. 30 patients received four cycles of dose-dense AC with no unanticipated AEs, one withdrew after AC therapy. Of 29 women who began *nab*-paclitaxel therapy, 27 received all 4 doses (mean cumulative dose, 959 mg/m²); one discontinued *nab*-paclitaxel after 2 doses due to unacceptable AEs. 4 patients had a grade 3 *nab*-paclitaxel related neuropathy (no grade 4 event). Of 29 patients, 34% received peg-filgrastim during *nab*-paclitaxel therapy and 31% had a *nab*-paclitaxel treatment delay, mainly due to hematologic toxicity. Based on Kaplan–Meier probability estimates, the percentage of patients having ≤1 grade neuropathy at the end of treatment, 2, and 8 months after treatment were 59, 79, and 97%. The authors concluded that administering adjuvant dose-dense AC followed by 260 mg/m2 dose-dense *nab*-paclitaxel was feasible in women with early-stage BC, with manageable AEs. Most patients had ≤1 grade neuropathy 2 months after treatment completion.

nab-paclitaxel administered sequentially with anthracycline has also been evaluated in a neoadjuvant setting for locally advanced breast cancer (LABC) in a phase II study by Robidoux et al[26] 66 patients with LABC but without prior treatment and regardless of hormone receptor or HER2 status were treated with *nab*-paclitaxel weekly for 12 weeks followed by 5-fluorouracil, epirubicin and cyclophosphamide (FEC) every 3 weeks for 4 cycles. Trastuzumab was allowed in HER2-positive (HER2+) patients. Sixty-three patients completed 4 cycles of albumin-bound paclitaxel following which 58 completed 4 cycles FEC. 17 of 19 HER2+ patients received trastuzumab. Pathologic complete response (pCR), the primary objective of the study, was 29% (19 of 65). For the HER2+ subset, the pCR was 58% (11 of 19). Both *nab*-paclitaxel and FEC were well tolerated. The most significant toxicities were grade 2/3 neuropathy (16%) with *nab*-paclitaxel and grade 3/4 febrile neutropenia (7%) with FEC.

These studies suggest that *nab*-paclitaxel alone or in combination with other therapeutic agents has

a significant activity in patients with breast cancer, including those previously treated with taxanes and/or anthracyclines,. These studies are summarized in Table 2. Because of its efficacy, ease of administration and a favorable toxicity profile, *nab*-paclitaxel is currently being evaluated in combination with other cytotoxic or targeted agents in breast cancer and other solid tumors (Table 3).

Phase III Studies

Based on the favorable phase I and phase II data, *nab*-paclitaxel's antitumor efficacy and safety was compared to CrEL- paclitaxel in a pivotal, multi-national randomized phase III trial conducted at 70 sites in 5 countries.[27] Of the 460 women with MBC enrolled in the study, 454 were randomized to 3-weekly cycles of either *nab*-paclitaxel at a dose of 260 mg/m^2 intravenously over 30 minutes without premedition (n = 229) or CrEL-paclitaxel at a dose of 175 mg/m^2 intravenously over 3 hours with corticosteroid and antihistamine premedications (n = 225). The large majority of patients had more than three metastatic lesions (76%), visceral disease (79%), prior chemotherapy (86%), and progression after first-line therapy for metastatic disease (59%). About half of the patients in each group received at least 6 cycles of treatment. Actual delivered paclitaxel dose-intensity was 49% higher in the *nab*-paclitaxel group than in the CrEL-paclitaxel group (85.13 vs. 57.02 mg/m^2/week). *nab*-paclitaxel demonstrated significantly higher response rates compared with CrEL-paclitaxel (33% vs. 19%, *P* = 0.001). Patients who received *nab*-paclitaxel as first line and second line or greater treatment had an ORR of 42% and 27% compared to 27% and 13% with CrE-paclitaxel, respectively. TTP was also significantly longer with *nab*-paclitaxel for all patients (23 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* = 0.02). There was no significant difference in median OS among all patients between the *nab*-paclitaxel and CrEL-paclitaxel groups (65 vs. 55.7 weeks; *P* = 0.374); however in the patients who received *nab*-paclitaxel as second-line or greater therapy had a significantly longer OS (56.4 vs. 46.7 weeks; HR = 0.73; *P* = 0.024). The incidence of grade 4 neutropenia was lower in *nab*-paclitaxel group compared to CrEL-paclitaxel group (9% vs. 22%) despite a 49% higher paclitaxel dose. Febrile neutropenia was uncommon (<2%), and the incidence did not differ between the two study arms. Interestingly, grade 3 sensory neuropathy was more common in *nab*-paclitaxel arm than in the CrEL-paclitaxel arm (10% vs. 2%) but was easily managed and improved rapidly to grade 1–2 in a median of 22 days. No severe hypersensitivity reactions occurred with *nab*-paclitaxel despite the absence of premedication and shorter administration time.

Similar results were reported from a phase III trial comparing *nab*-paclitaxel with CrEL-paclitaxel in 210 Chinese patients with MBC.[28] Patients were equally randomized to receive either *nab*-paclitaxel 260 mg/m^2 over 30 min every 3 weeks with no premedication or CrEL-paclitaxel 175 mg/m^2 over 3 hours every 3 weeks with standard premedication. ORR was 52% in the *nab*-paclitaxel group and 27% in the CrEL-paclitaxel group (*P* < 0.001). Median TTP (7.6 months vs. 5.7 months; p = 0.03) and median PFS

Table 2. Summary table of Phase II Clinical trial results.

Study	N	ORR	Median PFS (months)	Median survival	Ref
Phase II studies assessing the activity of *nab*-paclitaxel in metastatic breast cancer					
Ibrahim et al	63	48% (all patients) 64% (first line treatment)	6.2*	14.6 months	20
Blum et al	181	14% (100 mg/m^2) 16% (125 mg/m^2)	3 (100 mg/m^2) 3.5 (125 mg/m^2)	9.2 months	21
Roy et al**	50	50%	7.9	NR	23
Gradishar et al	300	45% (100 mg/m^2/q week) 49% (150 mg/m^2/q week) 37% (300 mg/m^2/q 3 weeks)	12.8 (100 mg/m^2/q week) 12.9 (150 mg/m^2/q week) 11 (300 mg/m^2/q 3 weeks)	NR	24

Notes: *Time to progression; **in combination with gemcitabine.
Abbreviations: ORR, overall response rate; PFS, progression-free survival; NR, not reached.

Table 3. On-going Phase II clinical trials in breast cancer with *nab*-paclitaxel.

Study identifier	Stage and specifiers	Combination	Sequence	Start date	Primary endpoint
nab-Paclitaxel in breast cancer: active phase II trials[36]					
NCT00397761	Locally advanced	Capecitabine	Neoadjuvant	Nov-06	pCR
NCT00456846	Metastatic	Single agent *nab*-paclitaxel	First line	Feb-08	Toxicity and response
NCT00470548	Metastatic breast cancer and other advanced solid tumors	Pemetrexed	Second line	May-07	Safety and efficacy
NCT00472693	Metastatic, triple negative breast cancer	Bevacizumab	Second line	May-07	PFS
NCT00479674	Metastatic, triple negative breast cancer	Carboplatin and bevacizumab	First or second line	May-07	Safety and efficacy
NCT00503750	Locally advanced, HER2 positive	Trastuzumab, vinorelbine	Neoadjuvant	May-07	pCR
NCT00609791	Metastatic	Single agent *nab*-paclitaxel	First or second line	Feb-08	pK and toxicity
NCT00616967	Locally advanced	Carboplatin, vorinostat	Neoadjuvant	Feb-08	pCR
NCT00617942	Locally advanced, HER2+	Carboplatin, trastuzumab	Neoadjuvant	Feb-08	pCR
NCT00617942	Locally advanced, HER2+	Carboplatin, trastuzumab	Neoadjuvant	Feb-08	pCR
NCT00618657	Locally advanced	Carboplatin and trastuzumab or bevacizumab	Neoadjuvant	Feb-08	PFS
NCT00629499	Locally advanced	Cyclophosphamide	Adjuvant	Feb-08	Feasibility and toxicity
NCT00654836	Locally recurrent or metastatic	Carboplatin, bevacizumab	First line	Apr-08	PFS
NCT00662129	Metastatic	Gemcitabine, Bevacizumab	First line	Apr-08	PFS
NCT00675259	Locally advanced	Carboplatin and bevacizumab	Neoadjuvant	May-08	pCR
NCT00709761	Metastatic, HER2+	Lapatinib	First or second line	Jul-08	ORR
NCT00733408	Metastatic, triple negative breast cancer	Bevacizumab, erlotinib	First line	Aug-08	PFS
NCT00748553	Metastatic breast cancer and other advanced solid tumors	Azacitidine	First line	Sep-08	Safety and efficacy
NCT00777673	Locally advanced, triple negative	Carboplatin, bevacizumab, doxorubicin, cyclophosphamide	Neoadjuvant	Oct-08	pCR
NCT00821964	Chest wall or cutaneous metastasis	Imiquimod	Second line	Jan-09	Safety and efficacy
NCT00856492	Locally advanced, HER2- IBC	Carboplatin, bevacizumab, doxorubicin, cyclophosphamide	Neoadjuvant	Mar-09	pCR
NCT00934895	Locally advanced, metastatic	Everolimus (RAD001)	First line	Jul-07	Tumor response
NCT00944047	Locally advanced, low HER2 expression	Trastuzumab	Neoadjuvant	Jul-09	pCR
NCT01036087	Locally advanced, HER2- IBC	Panitumumab and carboplatin	Neoadjuvant	Dec-09	pCR
NCT01207102	Metastatic, triple negative breast cancer	Carboplatin	First line	Sep-10	PFS
NCT01204437	Locally advanced	Capectabine	Adjuvant	Sep-10	Compliance and safety

Abbreviations: pCR, pathologic complete response; PFS, progression free survival; pK, pharmacokinetics; ORR, overall response rate; IBC, inflammatory breast cancer.

(7.6 months vs. 6.2 months; p = 0.118)" to "Median TTP (7.6 months vs. 5.7 months; p = 0.03) was significantly higher in the *nab*-paclitaxel group. The most common toxicities reported were alopecia (78%), peripheral neuropathy (75%, 7% grade 3) and neutropenia (65%) and were similar between the 2 groups.

These trials corroborate the results of the preclinical and phase I/II clinical trials that the use of the *nab*-paclitaxel formulation could result in clinically relevant improvements in the toxicity and the efficacy of paclitaxel. In particular the incidence of any grade 3 and 4 neutropenia was significantly reduced in patients receiving *nab*-paclitaxel compared with those receiving paclitaxel, despite an increase in the dose of paclitaxel. Grade 3 sensory neuropathy was higher with *nab*-paclitaxel but manageable with quick improvement to lower grades. Interestingly, *nab*-paclitaxel prolonged survival in patients with metastatic breast cancer that was resistant to anthracycline after treatment in the adjuvant or metastatic setting.

Therapeutic applicability of *nab*-paclitaxel is now being tested in variety of tumor types, including non small cell lung cancer, pancreatic cancer and melanoma at different stages of disease, as a single agent and in combination with other cytotoxic chemotherapy and/or biologic agents. The currently active Phase III clinical trials in breast cancer with *nab*-paclitaxel are listed in Table 4.

Tolerability and Economic Analysis of *nab*-paclitaxel

The overall tolerability of *nab*-paclitaxel 260 mg/m^2 was reported to be similar to that of CrEL-paclitaxel 175 mg/m^2 in the phase III trial.[27] No differences in quality of life throughout the study were noted between the two treatment groups despite higher dose-intensity of paclitaxel in the *nab*-paclitaxel group (85.13 vs. 57.02 mg/m^2/week). The most commonly reported toxicities/adverse events during the study were as expected for paclitaxel and included alopecia (90% vs. 94%), sensory neuropathy (71% vs. 56%), fatigue (47% vs. 38%), neutropenia (34% vs. 49%), arthralgia (35% vs. 33%), myalgia (28% vs. 32%), nausea (30% vs. 21%), infections (24% vs. 20%), and diarrhea (26% vs. 15%) for *nab*-paclitaxel vs. CrEL-paclitaxel groups respectively. Fewer events of neutropenia and skin flushing were reported among *nab*-paclitaxel

Table 4. Phase III clinical trials in breast cancer with *nab*-paclitaxel.

Study	N	Stage	Regimen	ORR	TTP	OS
***nab*-paclitaxel in breast cancer: III trials (completed)**						
Gradishar et al[27]	454	Metastatic	*nab*-paclitaxel 260 mg/m^2 q 3 weeks (n = 229) vs. CrEl-paclitaxel 175 mg/m^2 q 3 weeks	33% vs. 19% (P = 0.001)	23.0 vs. 16.9 weeks (HR, 0.75; P = 0.006)	56.4 vs. 46.7 weeks (HR, 0.73; P = 0.24)
Guan et al[28]	210	Metastatic	*nab*-paclitaxel 260 mg/m^2 q 3 weeks (n = 104) vs. CrEl-paclitaxel 175 mg/m^2 q 3 weeks (n = 106)	52% vs. 27% (P < 0.001)	7.8 vs. 5.7 months (P = 0.03)	NR

Study	Stage and specifiers	Regimen		Setting	Start date	Primary endpoint
***nab*-paclitaxel in breast cancer: III trials (on-going)[36]**						
NCT00397761	Locally advanced	Capecitabine plus *nab*-paclitaxel		Neoadjuvant	Nov-06	pCR
NCT00785291	Locally recurrent, metastatic	Bevacizumab plus paclitaxel, *nab*-paclitaxel or ixabepilone		First line	Nov-08	PFS

Abbreviations: ORR, overall response rate; TTP, time to progression; OS, overall survival; HR, hazard ratio; NR, not reported; pCR, pathologic complete response; PFS, progression free survival.

recipients than CrEL-paclitaxel recipients, where as sensory neuropathy and gastrointestinal symptoms were higher with *nab*-paclitaxel but this resolved more rapidly after treatment withdrawal. There was no report of grade 4 sensory neuropathy. The side effects are summarized in Table 5.

Dose adjustment is recommended in patients with hepatic dysfunction, neutropenia and sensory neuropathy.[29] *nab*-paclitaxel is generally avoided in patients with aspartate transaminase (AST) level greater than 10 times upper limit of normal (ULN) or bilirubin greater than 5 times ULN. Starting dose for patients with an AST less than 10 times ULN and a

bilirubin 2.01 to 5 times the ULN is 130 mg/m^2 every 3 weeks with subsequent doses potentially increased up to 200 mg/m^2 based on individual tolerance; starting dose for patients with an AST less than 10 times ULN and a bilirubin 1.26 to 2 times ULN is 200 mg/m^2 with subsequent doses adjusted based on individual tolerance; no dose adjustment is necessary in patients with an AST less than 10 times ULN and a bilirubin greater than ULN but less than or equal to 1.25 times ULN. Patients who experience severe neutropenia (neutrophil counts $<$ 500 cells/mm^3 for a week or longer) or severe sensory neuropathy during treatment with *nab*-paclitaxel should have dosage reduced to 220 mg/m^2 for subsequent courses of *nab*-paclitaxel. For recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. Treatment should be withheld until neutrophils are greater than 1500 cells/mm^3 and platelets recover to a level greater than 100,000 cells/mm^3. For grade 3 sensory neuropathy, treatment is held until resolution to grade 1 or 2, followed by a dose reduction for all subsequent courses of *nab*-paclitaxel. Premedication to prevent hypersensitivity reactions is not required prior to administration of *nab*-paclitaxel. The use of *nab*-paclitaxel has not been studied in patients with renal dysfunction. In randomized controlled trials, patients were excluded for serum creatinine $>$ 2 mg/dL.

Although *nab*-paclitaxel is more expensive than solvent based taxanes, its better toxicity profile, faster infusion time and pack of need for premedications are significant cost savings compared to solvent based product. Dranitsaris et al[30] has recently published an economic analysis of the phase II randomized study comparing *nab*-paclitaxel weekly or every 3 weeks to standard docetaxel as first line therapy in patients with MBC. Clinical and resource use data was captured from the trial's database and an economic analysis was performed from the perspective of United Kingdom National Health Service (UK NHS). The costs of chemotherapy, drug delivery, monitoring, supportive care drugs and hospitalization due to toxicity was included. A univariate and multivariate regression analysis was performed to compare the total cost of therapy in patients randomized to each of the four arms of the study. When all cost components were combined for the entire study population (n = 300), patients in *nab*-paclitaxel 100 mg/m^2 once

Table 5. Adverse events: *nab*-paclitaxel vs. CrEL-paclitaxel.

	nab-paclitaxel 260 mg/m^2 (% patients; n = 229)	CrEL-paclitaxel 175 mg/m^2 (% patients; n = 225)
Adverse events: *nab*-paclitaxel vs. CrEL-paclitaxel[27]		
Alopecia	90	94
Sensory neuropathy*		
Any grade	71	56
Severe	10	2
Asthenia		
Any grade	47	38
Severe	8	3
Neutropenia*		
Any grade	80	82
Severe	9	22
Febrile neutropenia	2	1
Arthralgia/Myalgia		
Any grade	44	49
Severe	8	4
Liver enzymes elevation		
AST†	39	32
Alkaline phosphatase	36	31
Bilirubin	7	6
Nausea*		
Any grade	30	21
Grade $\geq$ 3	3	$<$1
Infections	24	20
Vomiting		
Any grade	18	9
Severe	4	1
Diarrhea*		
Any grade	26	15
Severe	$<$1	1
Hypersensitivity reactions	4	12

Notes: *$P < 0.05$; †aspartate transaminase.

weekly (£ 15,396) and 300 mg/m^2 every 3 weeks arms (£ 15,809) had comparable costs to the docetaxel arm (£ 12,923) while the *nab*-paclitaxel 150 mg/m^2 weekly arm had significantly higher overall costs (£ 27,222). Thus, given its safety profile and better efficacy with comparable costs, *nab*-paclitaxel could be considered as a reasonable alternative to docetaxel as first-line chemotherapy in MBC.

Future Perspectives
Biomarker studies
SPARC is known to be over expressed in several tumor types including breast cancer and may be associated with a poor prognosis. In preclinical breast cancer models[12] and recently in a retrospective analysis of a clinical study[31] of *nab*-paclitaxel in head and neck cancer, SPARC expression and its interaction with albumin has been suggested to be the reason for enhanced uptake and intratumoral accumulation indicating a possible role for SPARC as a bio-marker for *nab*-paclitaxel effectiveness. To corroborate these findings, a current phase III study (NCT00785291) in MBC by Cancer and Leukemia Group B/North Central Cancer Treatment Group (CALGB/NCCTG) is evaluating the serum and tumor biomarkers (caveolin-1 and SPARC) along with circulating tumor cells to assess their possible role as predictive markers of response in MBC.

nab-paclitaxel in lung cancer
Besides breast cancer, *nab*-paclitaxel is being investigated in a variety of other solid tumors. Results from Phase II study[32] in advanced non small cell lung cancer (NSCLC) has demonstrated that *nab*-paclitaxel at a dose of 260 mg/m^2 every 3 weeks is well tolerated; showed a response rate of 16%, and disease control rate of 49% with a median time to progression of 6 months and median survival of 11 months. In another phase II study[33] in elderly patients with NSCLC, *nab*-paclitaxel administered weekly at a dose of 100 mg/m^2 for 3 weeks once every 28 days cycle showed a response rate of 30%, and disease control rate of 50% with a PFS of 5 months and median survival of 11 months. Results of a phase III study[34] involving 1,050 patients with stage IIIB or IV NSCLC comparing *nab*-paclitaxel (100 mg/m^2 weekly) vs. CrEL-paclitaxel (200 mg/m^2 every 3 weeks) in combination with carboplatin as a first line treatment was

presented recently were in favor of *nab*-paclitaxel. The objective response rate for *nab*-paclitaxel/carboplatin was 33% vs. 25% for paclitaxel/carboplatin as determined by independent radiologic review. The *nab*-paclitaxel/carboplatin combination was particularly beneficial for patients with squamous cell carcinoma, with an objective response rate of 41% vs. 24% in the paclitaxel/carboplatin arm. Sensory neuropathy, myalgia, and neutropenia occurred in significantly more patients on paclitaxel while thrombocytopenia and anemia were significantly more likely in patients who received *nab*-paclitaxel.

nab-paclitaxel as a radiosensitizer
Preclinical studies in mice bearing syngeneic ovarian or breast cancer have shown that *nab*-paclitaxel improved radiotherapy in a supra-additive manner suggesting that combining *nab*-paclitaxel with radiotherapy would improve the outcome of taxane-based chemoradiotherapy.[35]

Other *nab*-compounds in pipeline
The *nab* technology has potential for improving drug delivery and enhancing therapeutic ratio of other water-insoluble drugs. Three such drugs with *nab*-application are currently in the clinical studies. *nab*-docetaxel (ABI-008), a solvent-free nanometer sized form of docetaxel is being studied in phase I/II trial for patients with hormone refractory prostate cancer (NCT00477529).[36] Rapamycin is an inhibitor of mammalian target of rapamycin (mTOR), a kinase member of signaling pathway that promotes tumor growth. *nab*-rapamycin (ABI-009) currently being studied in a phase I trial (NCT00635284)[36] in various non-hematological malignancies is purported to overcome the poor aqueous solubility and poor chemical stability, which had limited rapamycin's development as an anticancer agent. 17-AAG (17-N-allylamino-17-demethoxygeldanamycin; tanespimycin) is an antineoplastic antibiotic derivative of geldanamycin and is a heat shock protein 90 (hsp90) inhibitor. *nab*-17-AAG (ABI-010) in combination with *nab*-paclitaxel administered weekly will be studied in a currently pending phase I trial (NCT00820768) for various non-hematological malignancies.[36]

Concluding remarks
Contemporary cancer therapeutics, including treatment of breast cancer, is centered on the concept of

personalized medicine. The emphasis is to tailor therapy to each patient based on specific tumor phenotype and genomic analysis. Treatment decisions are based not only on predictive and prognostic factors, but also on safety profile, impact on quality of life and patient preference. In the past decade, several studies have demonstrated that taxanes are an essential component in treatment of breast cancer both in adjuvant and metastatic settings. Using *nab*-technology platform, *nab*-paclitaxel was developed to overcome the limitations of solvents used in conventional solvent-based taxanes. Clinical data show that *nab*-paclitaxel has a better safety and side effect profile with an improved efficacy compared to solvent-based taxanes. Higher doses can be administered over a shorter infusion time without the need for special infusion sets or premedications. The phase II and Phase III studies showed significant improvement in tumor response rate and progression free intervals with *nab*-paclitaxel but did not demonstrate survival benefit except when used in second-line or greater therapy where the benefit was about 9.7 weeks. These encouraging results have prompted initiation of several clinical trials, which are currently underway evaluating the role of *nab*-paclitaxel as a single agent or in combination with cytotoxic and/or biologic agents in breast cancer and other solid tumors.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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