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REVIEW

Albumin-Bound Paclitaxel in the Treatment of Metastatic Breast Cancer

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Abstract: The taxanes, paclitaxel and docetaxel, are an important class of antineoplastic agents with relevant clinical activity in both early and advanced breast cancer. Nanoparticle albumin-bound paclitaxel (Abraxane®) is a 130–nm particle cremophor-free formulation of paclitaxel. Exploiting endogenous albumin pathways and avoiding solvent-based toxicities, nab-paclitaxel allows higher intratumor concentrations of paclitaxel through gp60 mediated endothelial transcytosis. Also, because it is free solvents, nab-paclitaxel offers shorter infusions and easily administration with no premedication and special infusions sets.

In a phase III randomized trial, nab-paclitaxel at 260 mg/m^2 every 3 weeks seems to have a superior therapeutic index than Cr-El paclitaxel, with a higher response rate and longer time to progression and with less toxicity, except peripheral neuropathy. Based on these results, nab-paclitaxel was approved for the treatment of metastatic breast cancer in patients who have failed first-line treatment for metastatic disease and for whom standard; anthracycline containing therapy is not indicated.

The results of the comparison of three doses of nab-paclitaxel with docetaxel in a randomized phase II trial suggest a superior efficacy and safety of weekly nab-paclitaxel compared with 3-weekly docetaxel.

All the available data suggest the superior therapeutic index of nab-paclitaxel compared with both docetaxel and Cr-EL paclitaxel. Weekly nab-paclitaxel may be an adequate alternative to classic formulations of taxanes in the treatment of patients with metastatic breast cancer.

Keywords: metastatic breast cancer, chemotherapy, nab-paclitaxel, taxane, albumin, solvent-based paclitaxel

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Breast cancer is the most common malignancy in women with 192.370 estimated new cases in USA in 2009. Approximately 30%–35% of all female cancers are breast cancer.[1] Breast cancer is a major health problem in spite that the mortality has decreased during the last 10 years, which is in part due to early diagnosis, the use of new treatment for early-stage disease and the availability of new drugs in advanced disease. Metastatic breast cancer is essentially an incurable disease[2,3] with the main objectives of the treatment are the improvement of quality of life and the prolongation of survival. Although some studies have reported a recent improvement of survival of metastatic breast cancer, the median survival time seen in more studies is of 2–3 years. New agents with improved antitumor activity are clearly required for the treatment of this disease.

The taxanes are an important class of antineoplastic agents with relevant clinical activity in both early and advanced breast cancer.[4,5] Paclitaxel and docetaxel are included in many chemotherapy schedules recommended for the treatment of early and advanced breast cancer by the main clinical practice breast cancer guidelines.[6] The development of taxanes has been limited by their relative insolubility in water and lipid-based solvents, such cremophor, are necessary excipients. Cremophor contributes to some important side effects of paclitaxel, including peripheral neuropathy and hypersensitivy reactions and, in combination with antracyclines, cardiotoxicity.[7,8] Long infusions time, special infusions sets and premedication with dexametasone and antihistamines are necessary to reduce the risk of hypersensitivity reactions. Also, cremophor limits the tumour penetration of paclitaxel and this might have negative impact on efficacy. To avoid these problems associated with cremophor, new systemic paclitaxel formulations are being developed. Nanoparticle albumin-bound paclitaxel is a nab-paclitaxel novel albumin-bound 130 nm particle formulation of paclitaxel that is free solvent and, consequently, less toxic than the cremophor-containing formulation.

Role of Taxanes in the Treatment of Breast Cancer

The taxanes have shown antitumoral activity in a variety of malignancies, including ovarian cancer, non-small- cell lung cancer, testicular cancer, bladder cancer, and are essential in the treatment of early-stage and metastatic breast cancer.[9,10]

Multiple studies have indicated a prominent role on taxanes in the treatment of breast cancer. More than 20 studies of paclitaxel monotherapy in patients (N = 3674) with metastatic breast cancer have showed response rates varied beetwen 6% and 62%, depended on the extent of disease and prior chemotherapy and others factors predictive of response to treatment.[11,12] In a three-arm randomized study in patients with metastatic breast cancer previously untreated with any chemotherapy, responses occurred in 34% of patients with paclitaxel, 36% with doxorubicin and 47% with the combination of doxorubicin and paclitaxel. The median time to treatment failure was 6, 5.8 and 8 months in paclitaxel, doxorubicin and combination respectively. Secondary response to paclitaxel after doxorubicin failure was 20% and to doxorubicin after paclitaxel failure was 22%. The authors concluded that paclitaxel and doxorubicin have equivalent activity in this study and there was not survival advantage for the combination of antracyclines and taxanes based on that sequential single agent therapy (cross-over) was as effective in prolonging survival and quality of life than combination treatment.[13]

In 2003, an adjuvant trial which included more than 3000 breast cancer patients showed that 4 cycles of paclitaxel after 4 cycles of doxorubicin and cyclophosphamide were able to improve disease-free survival and overall survival of node positive primary breast cancer compared with cyclophosphamide and doxorubicin alone. This trial, together with other similar studies, changed the adjuvant treatment of node-positive breast cancer, with taxanes and antracyclines as the new gold standard in clinical practice.[14]

About 1,500 patients with metastasic breast cancer have participated in various studies of docetaxel as a single agent and reported response from 30% to 68%. Indirect comparisons of the response rates of both taxanes when used in conventional schedules suggest that docetaxel is more active than paclitaxel. Only one phase III randomized study has compared docetaxel with paclitaxel directly in metastatic breast cancer. The median time to progression and overall survival were significantly longer for docetaxel, although the toxicity was also significantly higher.[15] As paclitaxel, docetaxel has been tested

in the adjuvant setting. Several studies have shown that a number of regimens including combinations of docetaxel and anthracyclines or alkylatings are able to increase disease-free survival (DFS) and overall survival (OS) with respect to the classical anthracyline-containing regimens.[16–20]

The current standard of care for breast cancer treatment is a taxane in combination with others drugs, both in the adjuvant and metastatic settings. The taxanes, however, have many disturbing side-effects, including severe hypersensitivity reaction, such as anaphylaxis, that limit the utility of these compounds. The investigation of new taxanes with similar efficacy and a better toxicity profile constitutes an urgent need for the treatment of breast cancer.

Characteristics of Taxanes

Paclitaxel is extracted from the bark of western yew tree (taxus brevifolia).[21,22] It is considered an antimicrotubule agent, since the promotion of assembly and stabilization of microtubules, preventing tubular depolymerisation, has been postulated as its main mechanism of antitumor effect. The stabilization of the microtubules compromises cell interphase and mitosis and lead to apoptosis and death. A similar mechanism of action has been postulated for the related compound, docetaxel.

Paclitaxel is relatively insoluble in water. To overcome this poor water solubility, lipid-based solvents are used as a vehicle. The solubility of paclitaxel is increased with cremophor (a non-ionic surfactant polyoxyethylated castor oil) and ethanol, while docetaxel is formulated in polysorbate 80 and ethanol diluent. These solvents alter the distribution of the taxanes and increase the toxicity. Cremophor and polysorbate 80 may limit the tumour penetration, thus decreasing the efficacy. The formation of large polar micelles of Cr-EL paclitaxel in the plasma compartment traps the drug and can lead to non-linear pharmacokinetics, consequently decreasing the volume of distribution and drug clearance. When Cr-El paclitaxel is administered in combination with other drugs, such antracyclines, the distribution of these drugs is altered by this phenomenon.

Cremophor is chemically, pharmacologically and biologically active and can release di-pthalate from plastic intravenous tubing; the infusion of dipthalate produces histamine release, and thus resulting in hypersensitivity reactions. These reactions are characterized by flushing, rash, urticaria, chest pain, dyspnea, tachycardia, hypotension and angioedema. In phase I trials, 20% to 40% patients without premedication were developed hypersensitivity reactions.[9,10] The incidence has been reduced using premedication with dexametasone, cimetidine and dyphenhydramine and by increasing the duration of infusion. Even after premedication, reactions occur in 1.5% to 3% of patients. Many studies indicate that cremophor contributes significantly to these reactions. Additionally, cremophor has been associated with hyperlipedemia, aggregation of blood red cells, abnormal lipoprotein patterns and sometimes irreversible sensory neuropathy, which in part due to axonal degeneration and demyelization. When high doses of cremophor are administered to rats, axonal swelling and demyelization appear in these animals. In addition, it has been recently demonstrated *in vitro* that cremophor inhibits endothelial of paclitaxel, reducing bioavailability.[23,24]

Polysorbate 80, lipid-base solvent which is formulated with docetaxel may produce hypersensitivy reactions, thought less than those produced by cremophor. Polysorbate 80 has also been associated with severe and irreversible neuropathy and can alter the fluidity of membrane causing cumulative fluid retention, which, may be reduced by prophylactic corticosteroids.

Because of these solvents-induced problems, patients who receive paclitaxel must be premedicated with steroids and antihistamines to reduce the risk of hypersensitivity reactions and administration of the drug requires special infusion sets (line filters and tubing) in order to minimize the exposure to dipthalate.

nab-paclitaxel was specifically developed to minimize the toxicities associated with cremophor and to eliminate the need for prophylactic medication aimed to avoid the hypersensitivity reactions caused by cremophor.

Nanotechnology

Because of dose-limiting toxicities and adverse impact on associated with conventional taxane formulations, new delivery vehicles are needed to improve antitumor activity and reduce toxicity of these drugs. Nanoparticle therapy offers potential solutions to many of these problems.

The biological application of nanoparticles is a rapidly developing area of nanotechnology that raises new possibilities in the treatment of human cancers. Nanotechnology was initially used to refer to small scale applicative materials (1 to 100 nm).[25]

Exploiting endogenous albumin pathways and avoiding solvent-based toxicities, protein based drug delivery can potentially result in higher intratumor concentrations of the chemotherapeutic agents.[26–28] Also, by avoiding the need for premedication, prolonged times of administration and special infusion sets, nanotechnology offers shorter infusions, easily administration and reduced toxicity.

Chemistry of nab-Paclitaxel

nab-paclitaxel is a 130–nm particle cremophor-free formulation of paclitaxel (Figure 1). It is free from solvent. A lyophilized formulation of paclitaxel is added to serum albumin diluted in 0.9% sodium chloride solution to produce a colloidal suspension with albumin concentration of 45 mg/ml and paclitaxel concentration of 5 mg/ml. The relatively small size of the drug particle prevents any risk of capillary obstruction; the absence of cremophor avoids the need of premeditation with steroids and antihistamines. The preparation can be administered as intravenous infusion systems.

Administration of nab-Paclitaxel

nab-paclitaxel is prepared by high pressure homogenization mixing paclitaxel with human serum albumin. Since a nanoparticle colloidal suspension is produced, nab-paclitaxel reaches concentrations of 2–10 mg/ml, while Cr-EL paclitaxel can only be reconstituted in concentrations of 0.3–1.2 mg/ml. Therefore, it can be administered intravenously in 100–150 ml of saline solution (0.9% NaCl) over 30 minutes without an in-line filter.

Mechanism of Action of nab-Paclitaxel

Paclitaxel in Abraxane has the same mechanism of action than in Taxol, which is the inhibition of the microtubular network needed for mitosis.

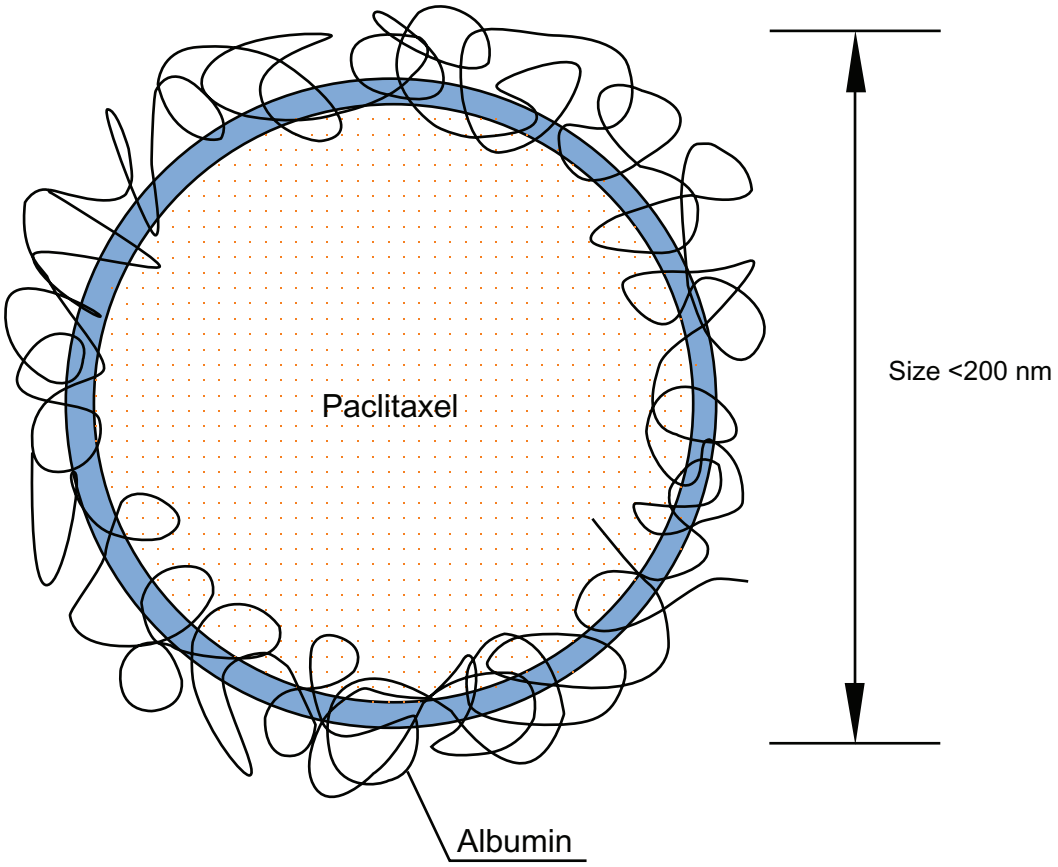

Figure 1. Representation of nab-paclitaxel nanoparticle.

Albumin possesses many properties that make it a particularly appropriate vehicle for targeted drug delivery in oncology. Albumin binds in a reversible non-covalent manner to hydrophobic molecules and various nutrients and is as a natural carrier for them. It also aids in endothelial transcytosis of plasma constituents into the extravacular space. This phenomenon is initiated by the binding of albumin to gp60 (receptor endothelial cells), which in turn results in a binding of gp60 with caveolin-1 (intracellular protein), leading to invagination of the cell membrane and the formation of transcytotic vesicles (caveolaes). These vesicles transport the drug-albumin complex across the endothelial cells and into the insterstitium.[29] Albumin may also have an important role in intratumoral accumulation of paclitaxel with nab-paclitaxel infusion. Osteonectin (SPARC) has been shown to bind albumin because of a sequence homology with gp60.

Caveolin-1 and SPARC are present in numerous malignant cells (i.e. melanoma, prostate, lung, pancreatic, and breast cancer), which, in part, explain the albumin and albumin-bound agents accumulation in tumor cells.[30–33]

Antitumor Activity of nab-Paclitaxel in Animal Models

In a preclinical study conducted by Desai et al[29] the efficacy of nab-paclitaxel 30 mg/kg/day was compared with both an equivalent and equitoxic dose of Cr-El paclitaxel. At equitoxic doses, nab-paclitaxel showed more complete regressions, longer doubling time, longer time recurrence, and prolonged survival than CrEl-paclitaxel (Table 1), with most sensitive tumours xenografts being breast MX-1, ovarian SK-OV3, and lung H522.

nab-Paclitaxel and docetaxel have been compared in rats and tumor-bearing mice. At equitoxic doses (22 and 15 mg/kg for nab-paclitaxel and docetaxel respectively) the antitumor activity of nab-paclitaxel was significantly greater than docetaxel ($P < 0.0001$).

Pharmacokinetics and Metabolism of nab-Paclitaxel

Desai et al[29] investigated the intratumoral accumulation of paclitaxel from both nab-paclitaxel and CrEL-paclitaxel and the comparative antitumor activity of both preparations in xenograft tumours models. They investigated the possible mechanisms of increased intratumoral accumulation by studying endothelial cell transport and its inhibition by cremophor. The human tumor lines used in this study were MX-1 (breast), SK-OV-3 (ovarian), PC-3 (prostate), H522 (lung), and HT29 (colon).

When the drug was administered for 5 consecutive days, mice with or without tumours tolerated significantly higher doses of nab-paclitaxel with respect to Cr-El paclitaxel. The LD50 (limiting dose 50) was

Table 1. Comparison of antitumor activity of nab-paclitaxel and CrEL-paclitaxel at equitoxic and equal doses in animal tumor models.

	H522: Lung cancer	Mx-1: Breast cancer	SK-OV-3: Ovarian cancer	PC-3: Prostate cancer	HT29: Colon cancer
nab-paclitaxel 30 mg/kg/day					
Tumor-free survivors	9/10	10/10	7/29	1/8	0/9
Recurrency day. Median range*	>78 (61 to >78)	>103	63 (26 to >77)	48 (26 to >80)	36 (26–61)
CrEL-paclitaxel 13.4 mg/kg/day					
Tumor-free survivors	7/10	1/5	0/10	1/9	0/9
Recurrency day. Median range*	>78 (26 to >78)#	22 (22 to >103)~	26 (26–63)□	26 (26 to >80)^	26 (26–29)°
CrEL-paclitaxel 30 mg/kg/day					
Tumor-free survivors	3/3	2/4	0/3	0/4	0/9
Recurrency day. Median range*	>78 (>78 to >78)	47 (22 to >103)	63 (26–63)	41 (26–48)	29 (26–33)×

Notes: Drugs were administered intravenously once daily for 5 consecutive days. The main comparasion is between the calculated maximum tolerated dose (MTD) of nab-paclitaxel 30 mg/kg/day and MTD of CrEL paclitaxel 13.4 mg/kg/day. *The day of recurrence was defined as the first observation of increased tumor size following a tumor regression. The lethal toxicity of Cr-EL paclitaxel at 30 mg/kg/d prohibited comparasions of antitumor activity for the ovarian, prostate and lung tumor; #$P = 0.2$; ~$P = 0.004$; □$P < 0.0001$; ^$P = 0.04$; °$P = 0.003$; ×$P = 0.01$.

47 mg/kg/day for nab-paclitaxel and 30 mg/kg/day for CrEl-paclitaxel. At the 30 mg/kg/ day dose, mortality for nab-paclitaxel and Cr-El. Paclitaxel were 4% and 49%, respectively. MTDs (maximum tolerated doses) were 30 and 13.4 mg/kg/day for nab-paclitaxel and Cr-El paclitaxel, respectively; these doses were considered equitoxic since both induced a mortality rate of 4% in the treated mice.

nab-Paclitaxel and docetaxel have been compared in rats and tumours-bearing mice. Single doses of each drug were administered to rats at 25, 50, 75, 100, and 125 mg/kg. Also each drug was administered to rats 3 times at 4-day intervals using 5, 10, 15, 30 and 50 mg/kg each time. The LD50 for nab-paclitaxel was 63 mg/kg and for docetaxel 12.5 mg/kg. There were no differences in nab-paclitaxel and docetaxel induced mortality. At 5 mg/kg (the only dose at which no rats died with either drug) organ and hematologic toxicity were significantly less with in nab-paclitaxel and docetaxel induced mortality). Equitoxic doses were 22 and 15 mg/kg for nab-paclitaxel and docetaxel respectively.[34]

Intratumoral paclitaxel accumulation

At equal dose of paclitaxel, the intratumor paclitaxel accumulation was significantly higher for nab-paclitaxel than for Cr-El paclitaxel. Tumour paclitaxel AUC (area under the curve) was 33% higher for nab-paclitaxel versus paclitaxel, indicating more effective intratumoral accumulation of nab-paclitaxel.

Binding and transport *in vitro* studies

Desai et al[29] also compared the endothelial binding and transport of paclitaxel when formulated as nab-paclitaxel or Cr-El paclitaxel, to investigate potential mechanisms responsible for increased intratumor concentrations of paclitaxel with nab-paclitaxel. Endothelial binding and transcytosis of paclitaxel were higher for nab-paclitaxel vs. Cr-El paclitaxel, and this difference was abrogated by an inhibitor of endothelial gp60 transport. The relatively small size of nab-paclitaxel and the process of transcytosis of albumin/paclitaxel are the 2 possible explanations for the increased delivery of paclitaxel to cell tumors with nab-paclitaxel. In normal tissues, capillaries are continuous, with small gaps between the capillary endothelial cells. Conversely, the endothelial gaps in the tumor capillaries are much large, of 100–800 nm in length. These gaps allow particles of the size of nab-paclitaxel (130 nm) to pass from the blood into tumor tissue, while these particles have more difficulty to pass through the smaller gaps of blood vessels in normal tissues. This fact could allow the differential distribution of paclitaxel from normal to tumoral tissues. In addition to paclitaxel particles passing thought leaky capillaries. The nab-paclitaxel allows a 9.9 fold increase in endothelial binding of paclitaxel; 4.2 fold increase in the transport of paclitaxel across endothelial cells, in comparison with CrEL-paclitaxel. The transendothelial cell transport of albumin is mediated by the gp60 (albodin) receptor and subsequent caveolar transport. Albumin binding to gp60 activates caveolin-1 to caveolin, which transport albumin and other plasma elements across the endothelial cell to the interstitial space. Unexpectedly, at clinically achievable concentrations, cremophor is able to inhibit the binding and transport of paclitaxel. These results suggest that tumour microvessel endothelial cells could play an active role in the transport of nab-paclitaxel from the vasculature to the tumour intersticium via an albumin-based receptor mediated pathway that is inhibited by cremophor (Figure 2).

Other protein, SPARC –osteonectin- that is frequently found on the surface of tumours may increase the binding of nab-paclitaxel to tumor cells. This protein plays a role in tissue remodelling, morphogenesis and angiogenesis, in particular activating the AKT pathway that is associated with cell survival and increased resistance to cancer therapies. The presence of SPARC has been associated with poor prognosis in different tumours, including breast cancer.[30–33,35,36]

Preclinical pharmacokinetic studies

The pharmacokinetics of nab-paclitaxel and CrEl-paclitaxel were compared in Hartlan Sprague-Dawley rats.[37] Both the volume of distribution and clearance were approximately 50% higher for nab-paclitaxel than CrEL-paclitaxel. This difference was observed in radioactivite and non-radioactivite experiments (Table 2).

Dose escalation of CrEl-paclitaxel beyond 10 mg/ kg was not possible due to toxicity. The limited data for doses of 5 and 10 mg/kg suggested nonlinearity of CrEl-paclitaxel pharmacokinetic

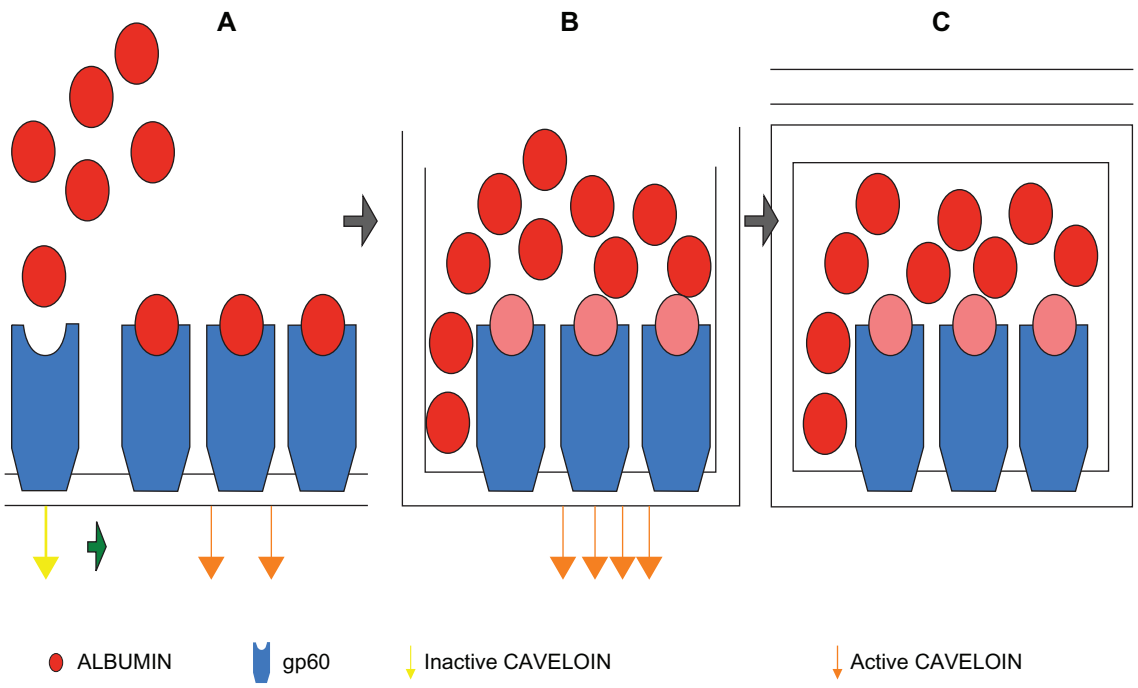

Figure 2. A) Albumin receptor (gp60) binds albumin which activates caveloin-I. **B**) Caveloin-I induces membrane invagination and internalization, trapping free and protein-bound plasma moleculs. **C**) Formation of caveolae, transcytosis and axtravascular deposition of the caveolae contents.

properties, with a twofold increase in the dose of CrEl-paclitaxel resulting in a 4.8-fold decrease in clearance. In contrast, the clearance of nab-paclitaxel was not significantly related to the dose in the range of 5–148 mg/kg.

Paclitaxel metabolism

There were no significant differences in the metabolism of both preparations. The two preparations showed a similar and gradual accumulation of paclitaxel metabolites during a 24-h period. At increasing doses of nab-paclitaxel, the paclitaxel metabolism of the nab-paclitaxel formulation was not saturable, consistently with the dose independent clearance.

Paclitaxel distribution

The distribution of the two preparations in normal tissues at 24 hours and 5 days was similar except for lung tissue; in which there was a 3.6 fold increase in CrEl-paclitaxel treated rats than in nab-paclitaxel treated rats ($P < 0.0001$).

Paclitaxel elimination

Excretion of paclitaxel was primarily (approximately 75%) trough the faecal route and volume was similar for both formulations. Faecal elimination was essentially complete by 48 hours after dosing for both formulations. Similar to the faecal route, renal elimination was complete by 2 days after dosing for both formulations.

Table 2. Comparison of the pharmacokinetics of CrEL-paclitaxel and nab-paclitaxel.

	CrEL-paclitaxel		nab-paclitaxel	
	Non-Radioactive	**Radioactive**	**Non-Radioactive**	**Radioactive**
$T_{1/2}$ (h)	7.24	20.78	11.42	19.01
Vz (l/kg)	8.75	9.36	18.33	14.18
CL (l/h·kg)	0.837	0.312	1.112	0.517
C_{max} (μg/ml)	11.8	13.5	4.0	4.2
AUC∞ (μg·h/ml)	5.85	15.69	4.59	9.86

Notes: Comparasion of the pharmacokinetics of CrEL-paclitaxel and nab-paclitaxel in Harlan Sprague-Dawley rats, administered as an intravenous dose of 5 mg/kg. Two methods were used for paclitaxel quantitation: radioactivity and high pressure liquid chromatography of non-radiactivite drug.
Abbreviations: T1/2, half-life; Vz, volume of distribution; CL, clearance; AUC, area under the curve.

Clinical pharmacokinetic studies

The half-life of nab-paclitaxel at doses 80–375 mg/m^2 is 13–22 hours. The AUC is linear up to 300 mg/m^2. The AUC increased disproportionately to the dose increase at doses of 375 mg/m^2. A 30% increase in the Cr-El paclitaxel dose (135→175 mg/m^2) resulted in a 75% increase in AUC. The AUC and C_{max} were higher for patients given a 3 hours infusion of nab-paclitaxel compared with 30 minutes.[38]

The pharmacokinetics of the two formulations of paclitaxel were compared directly in a study in which 13 patients received CrEL- paclitaxel 175 mg/m^2 over 3 hours with standard premedication, and 14 patients received nab-paclitaxel 260 mg/m^2 for 30 minutes with cycles repeated every 3 weeks (Table 3). With both formulations, paclitaxel was cleared in a biphasic manner. The C_{max} was 6.5 –fold greater for nab-paclitaxel than for CrEL-paclitaxel (22,968.6 vs. 3,543.3 ng/ml; $P < 0.001$), reflecting the higher dose of nab-paclitaxel administered. T max was significantly less for nab-paclitaxel compared with taxol (0.36 vs. 2.65 hours; $P < 0.001$), reflecting the shorter infusion duration. The AUC was not significantly different for the two formulations. This phenomenon is due the clearance and volume of distribution were both approximately 50% higher for nab-paclitaxel than for CrEL-paclitaxel (21.13 vs. 14.76 L/h/m^2 ($P = 0.048$) and 663.48 vs. 433.4 L/m^2 ($P = 0.040$) respectively), suggesting that Cremphor prevented the distribution of paclitaxel out of the circulation and into the tissues.[37]

Clinical Efficacy and Toxicity of nab-Paclitaxel

Phase I studies

In a phase I study, 19 patients with advanced solid tumours (including breast cancer) who had been previously treated with other drugs received nab-paclitaxel at 3-weekly intervals beginning with a dose of 135 mg/m^2. No premedication was administered. The objectives of the trial were to determine the toxicity, the maximum tolerated dose (MTD) and the pharmacokinetic profile.[38]

The MTD for nab-paclitaxel administered as a 30 minutes infusion every 21 days was 300 mg/m^2. The dose- limiting toxicities, which occurred in 3 of 6 patients treated a level 3 (375 mg/m^2), were sensory neuropathy, superficial kerotopathy and stomatitis. Hematologic toxicity was well tolerated and not cumulative. There were only 7 of 96 cycles administered in which absolute neutrophil count was below 500, 6 of which occurred at the highest dose evaluated, 375 mg/m^2. Almost no thrombocytopenia was observed, only one patient treated at level 3 had a platelet nadir of 25000 on cycle 1; this patient also experienced grade 3 non hematologic toxicities. No hypersensitivity reactions were reported. All patients developed alopecia.

Most non hematologic toxicity were grade 1–2, only one patient experienced grade 3 or higher toxicity among those treated with less than 375 mg/m^2. Gastrointestinal toxicity (nausea and vomiting) and arthralgias were common but mild. Cutaneous toxicity, consisting of dry skin and vesicular rash was also well tolerated. The toxicity ocular was varied and dose dependient. At the lower doses, ocular effects were described as dry eyes and transient disturbances. At highest doses, two superficial keratopathies were observed. Peripheral neuropathy appearing in 11 of 12 patients treated at levels 2 and 3. Neuropathy appeared in the form of pain and numbness with a characteristic distribution in glove and sock (Table 4).

Two patients with breast cancer showed partial response, both previously had received paclitaxel.

Table 3. Comparasion of the pharmacokinetics of CrEL-paclitaxel and nab-paclitaxel.

	CrEL-paclitaxel 175 mg/m^2 n = 12		nab-paclitaxel 260 mg/m^2 n = 14		*P*-value
	Mean	Range	Mean	Range	
$T_{1/2}$ (h)	20.5	17.5–26.3	21.6	16.5–29.6	0.48
Vz (l/kg)	433.4	308.7–809.7	663.8	296.3–1347.3	0.04
CL (l/h·kg)	14.76	10.2–28.8	21.13	8.7–43.4	0.05
C_{max} (µg/ml)	3543.3	1540–9380	22,968.6	4060–86,700	<0.001
AUC∞ (ng·h/ml)	12,607.7	6087–17,081	14,788.6	5982–28,680	0.524

Abbreviations: T1/2, half-life; Vz, volume of distribution; CL, clearance; AUC, area under the curve.

Table 4. Phase I study of 19 patients receiving nab-paclitaxel at 3-week intervals.

Dose level	**0**		**1**		**2**		**3**	
Dose (mg/m^2) every 3 weeks	135		200		300		375	
n	4		3		6		6	
Number of patients with symptoms								
Symptom	**G1/2**	**G3**	**G1/2**	**G3**	**G1/2**	**G3**	**G1/2**	**G3**
Arthalgia/myalgia	3	0	3	0	4	0	4	1
Diarrea	1	0	2	0	3	0	1	1
Fever (non-neutropenic)	0	0	0	0	2	0	3	0
Ocular toxicity	1	0	0	0	2	0	2	2
Sensor neuropathy	0	0	0	0	4	1	3	3
Skin	0	0	0	0	5	0	2	0
Stomatitis	0	0	1	0	4	0	3	2
Vomiting	1	0	1	0	0	0	2	1
Median absolute neutrhophil and platelet nadirs								
ANC nadir (range) $\times 10^3$	2.23 (1.8–5.0)		1.85 (0.6–3.7)		0.96 (0.3–3.7)		0.97 (0.2–1.8)	
Platelet nadir (range) $\times 10^3$	204 (174–292)		197 (118–270)		200 (105–609)		173 (25–251)	

Abbreviations: G, Grade; ANC, absolute neutrophil count.

Pharmacokinetics analyses revealed paclitaxel C_{max} and AUC values to increase linearly on the nab-paclitaxel dose range of 135–300 mg/m^2; on a similar dose range, CrEl-paclitaxel pharmacokinetics is nonlinear. C_{max} and AUC values for individual patients correlated well with toxicity.

In another phase I study, 39 patients with non-hematologic malignancies received nab-paclitaxel at dose levels from 80 to 200 mg/m^2 as a 30 minute intravenous infusion once a week for 3 weeks, followed by one week of rest.[39] The primary objectives of the study were to determine the toxicity of nab-paclitaxel administered weekly for three weeks every four weeks, the MTD of nab-paclitaxel and the pharmacokinetic parameters when administered on a weekly schedule. Patients were enrolled into one of two cohorts, lightly or heavily pretreated, based on the cytotoxic chemotherapy they had received previously. MTDs for heavily and lightly pretreated patients were 100 and 150 mg/m^2 respectively; and the dose limiting toxicities were grade 4 neutropenia and grade 3 peripheral neuropathy, respectively. In preclinical models and other clinical trials using 3 weekly administration, the equitoxic paclitaxel dose of nab-paclitaxel was 50% to 70% higher than that of CrEL-paclitaxel. A similar increase in the amount of paclitaxel that can be delivered with nab-paclitaxel in the weekly schedule was observed in this study.

Myelosupression from nab-paclitaxel was minimal. No grade 4 anaemia and thrombocytopenia were observed in this study. Neuropathies were primarily sensory, and three of five patients with grade 3 neuropathy continued treatment at a lower dose. Other toxicities occurring in this study were myalgias, onycholysis, vomiting, nausea and alopecia. These secondary effects were generally mild and not more frequent than in the 3-weekly schedule (Table 5).

Partial responses were observed in five patients, all of them had previously received paclitaxel. Maximum paclitaxel concentration and AUC increased linearly with dose. Dose- dependent changes in plasma clearance were not observed.

In all phase I studies described above, nab-paclitaxel was well tolerated. The preparation can be administrated without premedication and had demonstrated significant antitumor activity, even in patients previously treated with taxanes.[38–40]

Phase II studies

A phase II trial confirmed that nab-paclitaxel has important antitumor activity in patients with metastatic breast cancer. Sixty-three women were enrolled in this study, they received 300 mg/m^2 nab-paclitaxel over 30 minutes every three weeks.[41] The primary endpoint was tumour response rate and secondary objectives were to determinate survival, time to disease progression, and evaluate quality of life.

Table 5. Phase I study of 39 patients receiving nab-paclitaxel once a week for 3 weeks, followed by 1 week of rest.

Dose level	**1**		**2**		**3**		**4**		**5**		**5**	
Dose (mg/m^2)	80		100		125		150		175		200	
weekly*	3		12		9		7		6		2	
n												
Number of patients with symptoms												
Symptom	**G1/2**	**G3**	**G1/2**	**G3**	**G1/2**	**G3**	**G1/2**	**G3**	**G1/2**	**G3**	**G1/2**	**G3**
Fatigue	2	1	7	2	6	1	1	2	2	1	2	0
Myalgia	1	0	3	0	1	0	1	0	3	1	0	0
Nail changes	0	0	0	0	0	0	2	0	1	1	1	0
Neuropathy	1	0	3	0	1	2	2	0	0	3	1	0
Vomiting	0	1	5	1	5	0	2	0	2	0	1	0
Median absolute neutrhophil and platelet nadirs												
Nadir neutropenia (range) $\times 10^3$	1.65 (1.2–6.0)		1.69 (0.2–5.5)		2.03 (0.5–6.6)		1.73 (0.5–5.4)		1.28 (0.3–3.9)		1.70 (1.0–3.6)	

*Weekly for 3 weeks, followed by one week of rest (1 cycle); G, grade.

Forty-eight patients had received prior chemotherapy, thirty-nine patients received no prior treatment for metastatic disease and eleven patients had been treated previously with taxanes. The overall response rate was 48% (95% CI, 35.3% to 60%). Partial responses were observed in 28 patients and complete response in 2 patients. The response rate in chemotherapy-naïve patients in metastasic disease was 64%, compared with 21% for patients with prior treatment. Higher responses were observed in anthracycline-naïve patients, compared with those who had received antracyclines (58% and 41% respectively). Median time to disease progression was 26.6 weeks and median survival was 63.3 weeks.

No severe hypersensitivity reactions were reported. Treatment toxicities that occurred in 20% or more of the patients were anemia, neutropenia, infection, alopecia, nausea and vomiting, fatigue, sensory neuropathy, stomatitis and myalgia (Table 6).

The incidence of grade 3–4 neutropenia was higher in the phase II study than in the phase I, but the incidence of sensory neuropathy was about the same. Ocular toxicities, which were dose limiting toxicities in the phase I were observed in 24% patients. No grade 3–4 ocular side effects were detected.

Dose reductions because of toxicities, primarily hematologic were required in 25% of patients. Compared with equivalent doses of Cr-paclitaxel, nab-paclitaxel showed a less frequent and severe toxicity, especially neutropenia and sensory neuropathy. These findings suggested that nab-paclitaxel may offer important advantages over Cr-EL paclitaxel.

A weekly schedule of nab-paclitaxel was evaluated in a phase II trial in patients with metastatic breast cancer heavily pretreated with taxanes.[42,43] The main objectives were to determinate the antitumor activity, safety and tolerability of weekly nab-paclitaxel. One hundred and six patients received nab-paclitaxel 100 mg/m^2 intravenous over 30 minutes on days 1, 8, and 15, followed by one week rest. Because minimal toxicity was observed with this dose, seventy-five patients were included in an additional cohort and received nab-paclitaxel 125 mg/m^2 weekly on days 1, 8 and 15, followed by one week of rest. Response rates were 14% in the 100 mg/m^2 cohort and 16% in the 125 mg/m^2 cohort. Stable disease for $>$16 weeks was observed in 12% and 21%, respectively. Median progression free survival times were three months at 100 mg/m^2 and 3.5 months at 125 mg/m^2. Median survival times were 9.2 months and 9.1 months, respectively. In this study, no statistically significant differences were observed in, progression -free survival, disease control rate and overall response rates between the two cohorts. Although the tumour activity of weekly nab-paclitaxel in patients who had received weekly paclitaxel was limited, thirty-five percent of patients had some benefit after progressing on weekly docetaxel (Table 7).

Table 6. Phase II of nab-paclitaxel 300 mg/m^2 every 3 weeks.

Drug	**nab-paclitaxel**			
Dose (mg/m^2)	300			
Infusion duration	30 min			
n	63			
Characteristics	**No.**	**%**		
Patients with prior taxane treatment in metastatic disease	8	13		
Patients without prior chemotherapy for metastases	39	62		
Chemotherapy naive	15	24		
Chemotherapy exposed	48	76		
Antrhacycline naive	26	41		
Antrhacycline exposed	37	59		
Response	**No.**	**%**	**95% CI**	
Overall responses (CR + PR)	30 of 63	48	35.3 to 60.0	
CR	2	3		
PR	28	44		
Patients without prior chemotherapy for metastases	25 of 39	64	49.1 to 79.2	
Toxicity	**Grade 3**		**Grade 4**	
	No.	**%**	**No.**	**%**
Diarrhea	3	5	0	0
Fatigue	8	13	0	0
Sensor neuropathy	7	11	0	0
Mucositis	1	2	0	0
Myalgia	5	8	0	0
Vomiting	1	2	0	0
Nausea	1	2	0	0
Anemia	3	5	1	2
Neutropenia	17	27	15	24
Thrombocytopenia	3	5	0	0

Therefore, nab-paclitaxel does not demonstrate cross-resistance with Cr-El paclitaxel and docetaxel. No severe hypersensitivity reactions were reported. The treatment was in generally well tolerated. Grade 4 neutropenia occurred in <5% of patients in both cohorts. The incidence of grade 3 neuropathy was higher in the cohort of 125 mg/m^2 (14 patients) than at the 100 mg/m^2 dose (9 patients). Patients who developed neuropathy typically could be restarted on a reduced dose of nab-paclitaxel after a 1–2 week delay. In general, the toxicity was similar in younger patients than in patients aged >65 years. In conclusion, nab-paclitaxel 100 mg/m^2 weekly has demonstrated the same antitumor activity as nab-paclitaxel 125 mg/m^2 weekly and a more favourable safety profile in patients that had progressed with previous taxane therapy.

Phase III studies

Comparison of nab-paclitaxel with Cr-EL paclitaxel

In a large international randomized phase III study, equitoxic doses of nab-paclitaxel and Cr-EL paclitaxel were compared in patients with metastatic breast cancer.[44,45] 460 patients were randomized to receive 3-weekly cycles of either nab-paclitaxel 230 mg/m^2 intravenously without premedication (n = 229) or Cr-El paclitaxel 175 mg/m^2 intravenously with premedication (n = 225) (Figure 3). Six patients (1%) did not receive any study drug. Eligible patients had not previously received a taxane following the documentation of distant metastases or within 1 year of completion of a taxane as a part of an adjuvant chemotherapy regimen. In total, 86% of patients had

Table 7. Phase II of nab-paclitalex weekly for 3 out of 4 weeks in patients with metastatic breast cancer previously treated with taxane.

	Weekly dose					
	100 mg/m^2			125 mg/m^2		
n	106			75		
Characteristic						
Prior taxane metastastic treatment (paclitaxel, docetaxel or boths taxanes)	87%			97%		
Prior adyuvant chemotherapy	80%			79%		
Progression with previous taxane therapy	88%			89%		
Response (%)						
Overall response rate	14%			16%		
Disease control (complete + partial response + stable disease ≥16 weeks)	26%			37%		
Toxicity						
	Grade 2	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**
Diarrea	8%	<1%	0%	12%	5%	0%
Fatigue	32%	5%	0%	33%	12%	0%
Nausea	10%	4%	0%	15%	3%	0%
Neutropenia	31%	14%	4%	30%	31%	3%
Sensory neuropathy	17%	8%	0%	32%	19%	0%
Vomiting	7%	3%	0%	11%	1%	0%

previously received chemotherapy, but only 41% had received chemotherapy as treatment for metastases.

The primary endpoint of the study was response rate; secondary objectives were overall survival and time to progresion. The study had a non-inferiority design, assuming that nab-paclitaxel was at least 75% as effective as Cr-EL paclitaxel.

Efficacy analysis was based on the intent-to-treat. nab-paclitaxel showed a significantly higher response rate compared with Cr-EL paclitaxel (33% vs. 19%; $P < 0.001$). In patients who received first-line treatment the response rates were 42% and 27% ($P < 0.029$), and in those who had received prior anthracycline chemotherapy 34% and 18%, respectively ($P = 0.002$). Tumor response rate was also significantly higher for nab-paclitaxel than for Cr-EL paclitaxel in patients aged younger tan 65 years, and in patients with visceral dominant lesions.

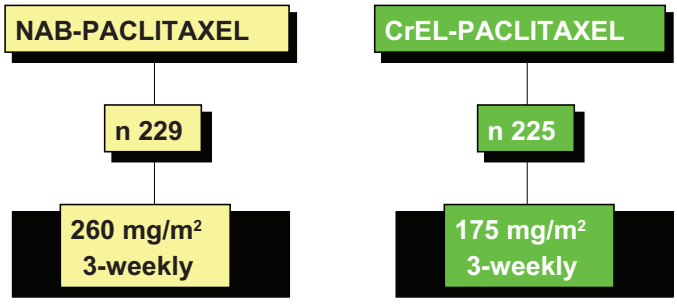

Figure 3. Schema of randomized Phase III comparing nab-paclitaxel with Cr-EL paclitaxel.

nab-paclitaxel demonstrated significantly longer time to progression than with standard paclitaxel (23.0 vs. 16.9 weeks, hazard ratio = 0.75; $P = 0.006$). In this study patients who received nab-paclitaxel as second or subsequent lines of therapy showed a statistically significant difference in survival (56,4 vs. 46,7 weeks, hazard ratio = 0.73; $P = 0.024$). Although this difference was not observed in first-line chemotherapy.

The treatment compliance was excellent on both groups of the study, 96% of the patients in the nab-paclitaxel group and 94% of standard paclitaxel groups received more than 90% of the prescribed dose.

The incidence of hypersensitivity reactions was minimal for both arms, no several hypersensitivity reactions occurred in the nab-paclitaxel arm.

In this trial the incidence of toxicities was significantly lower in the nab-paclitaxel group;

in particular, grade 4 neutropenia (9% vs. 22%, respectively, $P = 0.001$) despite the approximately 50% higher dose. Febrile neutropenia was rare (<2%) in both study arms. Grade 3 sensory neuropathy was significantly more common on the nab-paclitaxel than the Cr-EL-paclitaxel arm (10% vs. 2%, $P < 0.001$), but easyly resolution. With discontinuance of treatment, the median time to neuropathy improvement to grade 2 or 1 was 22 days. The laboratory toxicity that was notably more frequently in patients on Cr-EL paclitaxel was hyperglucemia, and this was more common for patients > 65 years (Table 8).

The authors of the study report concluded that nab-paclitaxel was more efficacious and safer to use than standard paclitaxel in patients with metastatic breast cancer.

Comparison of nab-paclitaxel with docetaxel

A randomized phase II study examined the antitumor activity and safety of weekly and every 3 week nab-paclitaxel compared with docetaxel as first line treatment in patients with metastatic breast cancer.[46] Patients were randomized to one of four arms: nab-paclitaxel 300 mg/m^2 every 3 weeks, nab-paclitaxel 100 mg/m^2 weekly for 3 out of 4 weeks, nab-paclitaxel 150 mg/m^2 weekly for 3 out of 4 weeks or docetaxel 100 mg/m^2 every 3 weeks. (Figure 4) The primary endpoint was overall response rate using RECIST criteria. Secondary end points were disease control rate (complete response, partial response and stable disease for >16 weeks), progression-free survival, duration of response and survival.

Three hundred-two patients were enrolled in the study. Patients had received no prior chemotherapy for metastases. In total, 41% patients had received prior adjuvant or neo-adjuvant chemotherapy, but none had received taxanes.

On the basis of independent radiologist review, the weekly nab-paclitaxel schedules were associated with a numerically superior response rate (100 mg/m^2: 45% and 150 mg/m^2: 49%) than docetaxel (35%), but this difference did not reach statistical significance.

Table 8. Phase III comparing CrEL-paclitaxel or nab-paclitaxel at 3- weekly intervals.

Characteristics	CrEL-paclitaxel	nab-paclitaxel	
Dose	175 mg/m^2	260 mg/m^2	
n	225	229	
Prior chemotherapy	85%	88%	
Prior chemotherapy for metastases	60%	58%	
Anthracycline therapy	78%	77%	
Response			
All patients	19%	33%	$P < 0.001$
First-line therapy	27%	42%	$P = 0.29$
Second-line or greather therapy	13%	27%	$P = 0.006$
Prior anthracycline therapy	18%	34%	$P = 0.002$
Median time to progression in weeks	16.9	23	$P = 0.006$
First line	19.7	24	NS
Second-line or greather therapy	16.1	20.9	$P = 0.020$
Median survival in weeks	55.7	65	$P = 0.374$
Second-line or greather therapy	46.7	56.4	$P = 0.024$
Toxicity			
Neutropenia grade 3/4	53%	34%	$P < 0.001$
Anemia grade 3/4	43%	21%	
Asthenia	38%	47%	
Hyperglycemia	7%	1%	$P < 0.003$
Mucositis	7%	7%	
Vomiting	9%	18%	
Nausea	21%	30%	
Neuropathy	56%	71%	

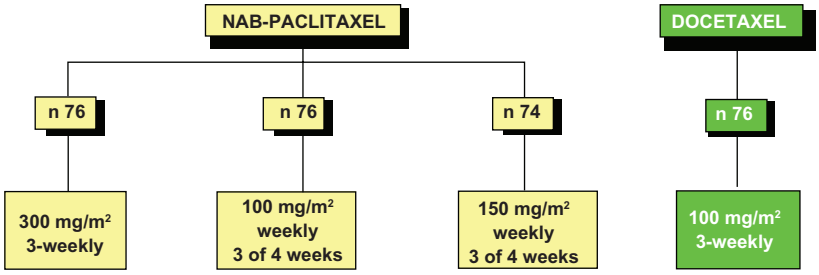

Figure 4. Schema of randomized Phase II comparing nab-paclitaxel with docetaxel.

This trend was supported by the investigators analysis, which found a significantly superior overall response rate for both weekly nab-paclitaxel doses versus docetaxel. On the basis of both analyses, the investigator review and the independent radiologist review, disease control rate was significantly higher for patients receiving weekly nab-paclitaxel compared with docetaxel. nab-paclitaxel 150 mg/m^2 weekly demonstrated significantly longer progression free survival compared with docetaxel 100 mg/m^2 in both the independent radiologist analysis (12.9 vs. 7.5 months; $P = 0.0065$) and investigator analysis (14.6 vs. 7.8 months; $P = 0.012$). A comparison of docetaxel and nab-paclitaxel 300 mg/m^2 showed no statistical difference for overall response rate or progression–free survival (Table 9).

The most common secondary effects were neutropenia, neuropathy, arthralgia and alopecia.

Table 9. Phase II trial comparing three different dose schedules of nab-paclitaxel with docetaxel.

Characteristic	**nab-paclitaxel**						**Docetaxel**	
Dose	**300 mg/m² 3-weekly**		**100 mg/m² weekly**		**150 mg/m² weekly**		**100 mg/m² 3-weeky**	
n	76		76		74		76	
Prior chemotheray	46%		39%		39%		46%	
Neoadyuvant	18%		18%		15%		19%	
Adyuvant	36%		26%		32%		39%	
Metastatic	1%		0%		0%		0%	
Response								
Investigator assesment								
Confirmes overall response rate	46%		63%		74%		39%	
Stable disease ≥16 weeks	26%		20%		16%		30%	
Disease control rate	72%		83%		91%		69%	
Median progression free survival in months	10.9		7.5		14.6		7.8	
Indepent radiologist assesment								
Confirmes overall response rate	37%		45%		49%		35%	
Stable disease ≥16 weeks	32%		30%		31%		23%	
Disease control rate	68%		75%		80%		58%	
Median progression free survival in months	11.0		12.8		12.9		7.5	
Toxicity								
	Grade 3	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Alopecia	0%	0%	0%	0%	0%	0%	0%	0%
Arthralgia	1%	0%	0%	0%	0%	0%	0%	0%
Fatigue	5%	0%	0%	0%	3%	0%	19%	0%
Neutropenia	39%	5%	20%	5%	35%	9%	14%	75%
Sensory neuropathy	17%	0%	8%	0%	14%	0%	12%	0%

Neutropenia and febrile neutropenia were less frequent in all nab-paclitaxel arms. The incidence of sensory neuropathy was similar in all arms, but this resolved faster after treatment withdrawal with nab-paclitaxel compared with patients who received docetaxel. The authors concluded that weekly nab-paclitaxel compared with docetaxel has superior efficacy and safety in first-line metastatic breast cancer, with a statistically significant prolongation of progression-free survival more than five months in patients receiving nab-paclitaxel 150 mg/m^2 weekly compared with docetaxel 100 mg/m^2 every three week.

nab-paclitaxel in Combination with Others Drugs

nab-paclitaxel in combination with bevacizumab

Danso et al[47] presented interim analysis of a phase II multicentre, open-label study with 51 patients with local recurrent HER2-negative metastasic breast cancer patients receiving first-line therapy nab-paclitaxel 125 mg/m^2 weekly (days1, 8, and 15) in combination with bevacizumab 10 mg/kg every two weeks (days 1 and 15 of a 28-day cycle) aimed to evaluate safety and tolerability. From 45 patients evaluable for response, 94% of patients had visceral disease, 59% had prior chemotherapy, 41% had anthracycline, and 12% had standard paclitaxel in the adjuvant setting. The overall response rate was 33% (14/45 patients with a partial response) and 22% (10/45) had stable disease ≥ 16 weeks. The median progression-free survival was 7.4 months (95% CI, 5.4–4.2). Grade 3/4 toxicities were neutropenia (34%, 16%) and anemia (7%, 5%).

In a randomized phase II trial[48] evaluating nab-paclitaxel in combination with bevacizumab as first-line therapy for HER2-negative metastatic breast cancer, 209 patients were randomized to 1 of 3 dosing arms: nab-paclitaxel 260 mg/m^2 and bevacizumab 15 mg/kg Q3W (arm A), nab-paclitaxel 260 mg/m^2 and bevacizumab 10 mg/kg Q2W with growth factor support (arm B), and nab-paclitaxel 130 mg/m^2 QW and bevacizumab 10 mg/kg Q2W (arm C). Endpoints evaluated in the trial included response rate, duration of response, time to progression, progression-free survival, overall survival, and toxicity. As per pre-specified stopping rule, Arm B was closed early due to significantly more grade ≥2 fatigue and bone pain. 1 patient had a confirmed complete response (CR) and 31 patients had confirmed partial response (PR). The time to progression was longer in Arm C (9 months) versus both arms B (6.3 months) and C (7.7 months) (overall $P = 0.028$). Neurotoxicity grade ≥2 was equivalent across all 3 arms (50%); febrile neutropenia occurred in <2% of patients in all arms. nab-paclitaxel QW with bevacizumab (Arm C) appears to have the highest therapeutic index, however sensory neuropathy is limiting suggesting a 3 week on/1 week off schedule may be preferable and should be studied comparatively.

nab-paclitaxel in combination with trastuzumab

In a phase II, open-label, non-randomized study of weekly nab-paclitaxel therapy with or without trastuzumab as first line treatment of advanced breast cancer.[49] Patients with locally advanced or metastatic breast cancer received nab-paclitaxel 125 mg/m^2 IV over 30 minutes on days 1, 8, and 15 of a 28-day cycle. Patients were stratified by HER2 status; 48 patients were HER2-negative, 22 patients were HER2-positive, and HER2 status was unknown in 2 patients. HER2 positive patients received trastuzumab therapy. The trial enrolled 72 patients, 47 patients were evaluable for response. A tumour response was noted in 20/47 patients (42.6%, 95% Clopper-Pearson confidence interval 56.7%–87.5%). A complete response was demonstrated in 2/47 patients and a partial response was observed in 18/42 patients. Disease stabilization was achieved in 24/47 patients. Median time to progression was 15.9 months, and the overall survival at 1 year was 79% and at 2 years 59%. The most common grade 3 toxicities were neutropenia (11.1%) and neuropathy (8.3%). The only grade 4 toxicities were supra-ventricular tachycardia (1.5%) and vascular disorder (1.5%).

Seidman et al reviewed the early results from a phase II study of nab-paclitaxel, carboplatin, and trastuzumab as first-line therapy for HER2-positive metastatic breast cancer.[50] 30 patients were included in the current analysis. The first 4 patients enrolled received nab-paclitaxel 75 mg/m^2 weekly for 3 weeks every 28 days in order to establish a safety profile. Subsequent patients received nab-paclitaxel 100 mg/m^2 as well as carboplatin at an AUC of 2 on the same schedule. Trastuzumab 4 mg/kg loading dose followed by 2 mg/kg/week without rest was

also administered. Patients were treated until disease progression or until unacceptable toxicity. Total of 47% of the patients received prior adjuvant or neo-adjuvant chemotherapy: 44% with anthracycline and 34% patients with taxane. Overall response was observed in 16 patients (7% complete response and 47% partial response). In addition 30% of patients had stable disease (SD) for ≥16 weeks (Clinical Benefit Rate: 53% + 30% = 83%). The median response duration was 28.0 months and median progression free survival was 15.9 months (95% CI, 7.3–28.0 months). Toxicities observed included grade 3 and 4 neutropenia in 41% and 13% of patients respectively, with 1 (3%) occurrence of febrile neutropenia. Also, 1 (3%) patient experienced grade 3 neuropathy was noted on 4 out of 13 receiving carboplatin monthly.

nab-paclitaxel in combinaton with gemcitabine

In a phase II trial, fifty patients with previously untreated metastatic breast cancer were enrolled to receive nab-paclitaxel 125 mg/m^2 and gemcitabine 1000 mg/m^2 on day 1 and 8 of a 21 day cycle until disease progression.[51] 80% patients had visceral disease and twenty-five were naïve.chemoterapy patients, 30% patients had received prior taxane therapy. Confirmed response rate was observed in 25 (50%) patients (95% CI, 36% to 64%) by RECIST criteria., partial response in twenty one (42%) and compete response in four (8%). Median duration of response was 6.9 months (95% CI, 5.7, not reached) and median progression free survival was 7.9 months (95% CI, 5.4–10 months).. The main toxicity was hematologic. Grade 3–4 neutropenia occurred in 54% patients, thrombocytopenia in 12% and anemia in 14% patients. Grade 3 neuropathy occurred in only four patients.

The authors concluded that weekly nab-paclitaxel and gemcitabine combination has significant activity and a favourable toxicity profile as first-line therapy of breast cancer.

nab-paclitaxel in Combination with Capecitabine

A phase II ongoing study utilized nab-paclitaxel 125 mg/m^2 on day 1, 8 and capecitabine 825 mg/m^2 po BID days 1–14 on a 3 week cycle without premeditation. The primary endpoint was objective response rate.[52] 50 patients have been enrolled, of whom 37% had received prior adjuvant anthracycline and 33% prior adjuvant taxanes. 38 patients were available for analysis of response: eight patients (21%) had compete response and 15 (39, 5%) partial response, for an overall response rate of 61.5%. Fifteen patients had stable disease.

The main hematologic toxicity was grade 3–4 neutropenia (5 patients). The incidence of Grade 1–2 neuropathy was 25%. The most common clinical adverse effects were gastrointestinal, dermatological, fatigue and hand-foot syndrome.

Conclusions

In summary, nab-paclitaxel has antitumor activity and is well tolerated as a monotherapy in patients with metastatic breast cancer. nab-paclitaxel was approved in January 2005 by the FDA and on January 2008 by the EMEA for the treatment of metastatic breast cancer in patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated.

nab-paclitaxel at 260 mg/m^2 every 3 weeks seems to have a superior therapeutic index than Cr-El paclitaxel, with a higher response rate and longer time to progression and with less toxicity, except peripheral neuropathy. The incidence of grade 3 sensory neuropathy is more frequent with nab-paclitaxel than with Cr-El paclitaxel, but only a small proportion of patients develop prolonged neurotoxicity.

The results of the comparison of three doses of nab-paclitaxel with docetaxel in a randomized phase II trial suggest a superior efficacy and safety of nab-paclitaxel compared with docetaxel, with a statically significant prolongation of progression free survival in patients who receive nab-paclitaxel at 150 mg/m^2 weekly compared with conventional doses of docetaxel.

Based on these results, a phase III study to evaluate the efficacy and safety of nab-paclitaxel 150 mg/m^2 weekly versus docetaxel 100 mg/m^2 3weekly is planned.

All the available data suggest the superior therapeutic index of nab-paclitaxel compared with both docetaxel and Cr-EL paclitaxel. Weekly nab-paclitaxel may be an adequate alternative to classic formulations of taxanes in the treatment of patients with metastatic breast cancer.

Disclosures

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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