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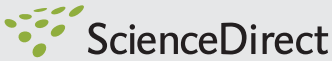

Clinical efficacy and emerging therapeutic utilization of novel taxanes

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ABSTRACT

A significant advance in cancer treatment was achieved in the mid-1990s with the introduction of solvent-based taxanes. However, first-generation taxanes required synthetic solvents to promote parenteral administration, occasionally caused serious toxicities, and compromised treatment efficacy. This led to the development of second-generation taxanes, including a solvent-free albumin-bound form of paclitaxel (*nab*-paclitaxel). Numerous studies have demonstrated the safety and efficacy of *nab*-paclitaxel monotherapy and in combination with other anticancer agents for the treatment of breast cancer. Results from several recent trials also suggest a role for *nab*-paclitaxel in the treatment of lung cancer, melanoma, ovarian cancer, prostate cancer, and pancreatic cancer. This article reviews the clinical efficacy and emerging role for novel taxanes in the treatment of breast and other solid tumors, and provides an overview of key issues for consideration in the clinical application of novel taxanes in cancer treatment regimens in order to achieve optimal antitumor efficacy while minimizing adverse events.

1. Introduction

A significant advance in the treatment of cancer occurred in the mid-1990s with the introduction of solvent-based taxanes, including paclitaxel and docetaxel. Taxanes exert cytotoxic effects against malignant cells by binding tubulin and stabilizing nonfunctional microtubule bundles. This blocks the process of normal mitotic spindle development and arrests the cell proliferation process (Figure 1).[1,2] Development of taxanes was suspended for several years because first-generation taxanes were extremely hydrophobic and required synthetic solvents

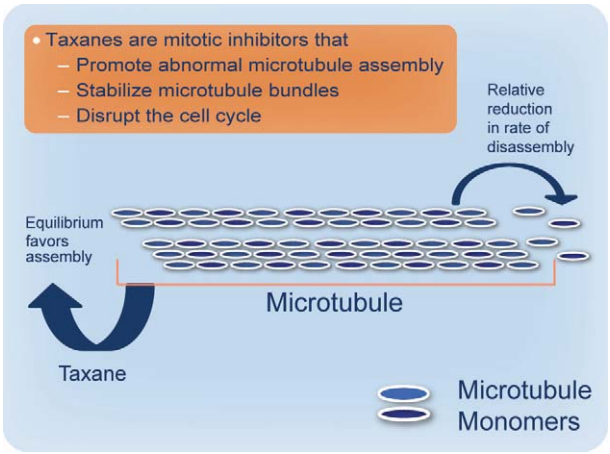

Fig. 1 – Taxane mechanism of action.

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Table 1 – Prevalence of solvent-based taxane toxicities [9,10]

Reaction	Docetaxel	Paclitaxel
Hypersensitivity reaction, grade 3 or 4	2.6% [a]	2%
Neutropenia (<500 mm^3)	85.9%	52%
Leukopenia (<1000 mm^3)	43.7%	17%
Thrombocytopenia (<100,000/mm^3)	9.2%	20%
Anemia (<11 g/dL)	93.6%	78%
Peripheral neuropathy, grade 3 or 4	5.5%	3%
Arthralgia/myalgia, grade 3 or 4	10%	8%
Mucositis	7.4%	31%
Cardiovascular events	8.1%	16%

[a] Regardless of premedication. Adapted from prescribing information for paclitaxel (Taxol, Bristol-Myers Squibb, n = 812) and docetaxel (Taxotere, sanofi-aventis, n = 2405).

to promote parenteral administration. [2,3] It was subsequently determined that a combination of 50% polyethylated castor oil (50% Cremophor® EL or CrEL) and 50% dehydrated ethanol USP for paclitaxel and polysorbate 80 (Tween® 80) for docetaxel were biologically and pharmacologically active, nonionic surfactants that effectively reversed multidrug resistance in malignant cells *in vitro* and overcame barriers to parenteral administration. [2–4]

Use of first-generation taxanes required monitoring and management of patients for solvent-based (SB) toxicities with moderate-to-high doses of corticosteroids and histamine antagonists and reduced infusion rates [5–8] (Table 1). [9,10] There was also evidence suggesting that SB first-generation taxanes undermined treatment efficacy due to entrapment of active drug micelles formed in plasma compartments. This led to increased systemic drug exposure and risk of adverse events as well as decreased drug clearance, and diminished dose-dependent antitumor activity. [5,7] The compromised efficacy and unfavorable toxicity profile of first-generation taxanes motivated innovative research efforts to enhance the therapeutic index of taxanes. These included evaluation of different administration schedules and modifications to the formulations and vehicles for drug delivery. New taxane formulations included conjugation of paclitaxel to docosahexaenoic acid, use of polymeric micelle-formulated paclitaxel, and changes in the taxoid structure. [11–16] Other efforts led to development of a solvent-free formulation of paclitaxel. This new compound was albumin-bound paclitaxel (*nab*-paclitaxel), a novel, biologically interactive, nanometer-sized particle that used albumin to safely administer higher doses of paclitaxel with shorter infusion times. *Nab* technology enhanced permeation and retention, which allowed the nanoparticles of *nab*-paclitaxel to exit cell vasculature through gaps or leaky junctions existing between endothelial cells. [17] In addition, receptor-mediated transcytosis drew *nab*-paclitaxel from the vessel lumen, through the endothelial cell layer, and into the tumor interstitium. Tumor cells absorbed nutrients bound to albumin, which enhanced delivery of *nab*-paclitaxel to malignant cells. [18]

2. Efficacy of standard and novel formulations of taxanes for breast cancer

Numerous studies have demonstrated the safety and efficacy of *nab*-paclitaxel for the treatment of breast cancer (BC), especially metastatic breast cancer (MBC). A phase III trial that enrolled 460 women with MBC compared *nab*-paclitaxel with polyethylated castor oil-based paclitaxel (CrEL-paclitaxel). Patients were randomly assigned to 3-week cycles of *nab*-paclitaxel 260 mg/m^2 with no standard premedications or CrEL-paclitaxel 175 mg/m^2 plus premedication with dexamethasone and antihistamines. Overall response rates (ORR; complete response [CR] + partial response [PR]) consistently favored *nab*-paclitaxel, 33% for *nab*-paclitacel *vs* 19% for CrEL-paclitaxel; ($p = 0.001$) (Table 2). In addition,

Table 2 – Overall response rate comparison between *nab*-paclitaxel and standard paclitaxel for metastatic breast cancer [19]

Overall response rate	*Nab*-paclitaxel (n = 229)	Standard paclitaxel (n = 225)	*p*-value
All patients	33%	19%	0.001
First-line therapy	42%	27%	0.029
Second-line therapy	27%	13%	0.006
Prior anthracycline adjuvant therapy	34%	18%	0.002
Prior anthracycline metastatic therapy	27%	14%	0.010

median time to progression (TTP) was 23 weeks in the *nab*-paclitaxel group compared to 16.9 weeks in the CrEL-paclitaxel arm (hazard ratio [HR] = 0.75; $p = 0.006$). Rates of adverse events were generally lower in the *nab*-paclitaxel arm with 9% of patients experiencing grade 4 neutropenia compared to 22% of those receiving CrEL-paclitaxel ($p < 0.001$). However, grade 3 sensory neuropathy was more common in the *nab*-paclitaxel group (10%) than the CrEL-paclitaxel arm (2%). There were no differences between the two groups with respect to rates of thrombocytopenia, anemia, and febrile neutropenia, despite the fact that treatment with *nab*-paclitaxel required no premedications.[19] These results were confirmed by a phase III trial that enrolled 210 Chinese women with MBC and randomized them to either *nab*-paclitaxel 260 mg/m^2 or SB paclitaxel 175 mg/m^2. The ORR was 52% for women in the *nab*-paclitaxel arm compared with 27% for those administered SB paclitaxel ($p < 0.001$). Median TTP was 7.8 months for the *nab*-paclitaxel group versus 5.7 months for the SB paclitaxel arm ($p < 0.030$). [20]

The efficacy and safety of *nab*-paclitaxel 100 mg/m^2 or 125 mg/m^2 was also established for women with MBC previously treated with conventional taxane regimens. A total of 181 women with progression of MBC during administration of conventional taxane regimens or a relapse within 12 months of adjuvant conventional taxane therapy were treated with *nab*-paclitaxel 100 mg/m^2 or 125 mg/m^2 on days 1, 8, and 15 of a 28-day treatment cycle. Response rates (RR) were 14% and 16% for the 100 mg/m^2 and 125 mg/m^2 regimens (95% CI, 7.52% to 20.79%), respectively, with SD confirmed for 12% of women in the lower dose group compared to 21% of those administered the higher dose. Median progression-free survival (PFS) was 3 months and median survival was 9.2 months for the *nab*-paclitaxel 100 mg/m^2 arm compared with 3.5 months PFS and median survival of 9.1 months for the higher dose. No hypersensitivity reactions were noted in either treatment group. Eight percent of patients in the 100 mg/m^2 arm compared to 19% in the 125 mg/m^2 experienced grade 3 treatment-related sensory neuropathy, most of which resolved with dose reductions. Thus, efficacy was comparable between the 2 doses with a more favorable safety profile associated with the 100 mg/m^2 dose of *nab*-paclitaxel. [21]

Subsequent trials evaluated the efficacy and safety of different doses and administration schedules of *nab*-paclitaxel for the treatment of BC including comparisons with SB docetaxel. An open-label study of women with MBC compared first-line therapy using 3 different dose and administration schedules for *nab*-paclitaxel to SB docetaxel. Patients were randomized to 300 mg/m^2 *nab*-paclitaxel every three weeks, *nab*-paclitaxel 100 mg/m^2 or 150 mg/m^2 weekly for 3 of every 4 weeks, or SB docetaxel 100 mg/m^2 every 3 weeks (Figure 2). Primary endpoints were ORR, PFS, and toxicity. While ORRs were

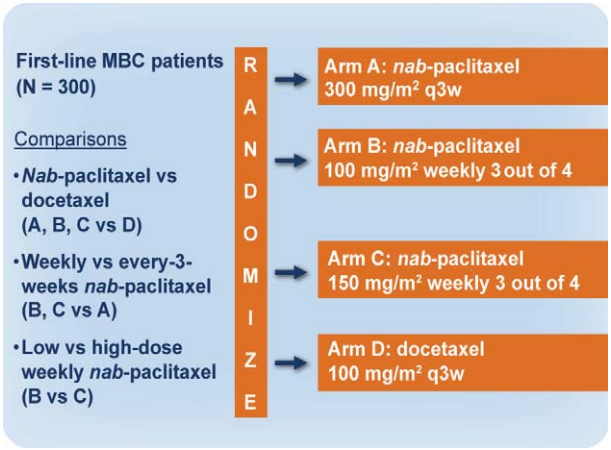

Fig. 2 – Design of a phase III trial comparison of different doses and administration schedules for *nab*-paclitaxel compared with docetaxel. [22]

comparable for the *nab*-paclitaxel 300 mg/m^2 (43%) and SB docetaxel (38%) groups, ORRs were significantly higher for both weekly doses of *nab*-paclitaxel compared with SB docetaxel at 62% for the 100 mg/m^2 dose ($p = 0.002$) and 70% for women treated with the 150 mg/m^2 dose ($p = 0.003$). Progression-free survival was significantly longer for the 150 mg/m^2 and 300 mg/m^2 *nab*-paclitaxel groups compared to SB docetaxel. Rates of neutropenia of all grades were significantly lower in each of the three *nab*-paclitaxel groups compared to SB docetaxel ($p < 0.001$ for all comparisons). However, there were no significant differences between the 3 *nab*-paclitaxel groups and the SB docetaxel group with respect to occurrence of peripheral neuropathy (all grades), although rates were significantly lower for women in the *nab*-paclitaxel 100 mg/m^2 weekly arm versus 300 mg/m^2 group. [22]

While additional research is required, these results suggest that dose and administration schedules for treatment of MBC with *nab*-paclitaxel can be modified to improve tolerability while not compromising therapeutic efficacy.

3. *Nab*-paclitaxel in combination with other anticancer agents for metastatic breast cancer

3.1. *Nab-paclitaxel plus capecitabine*

Nab-paclitaxel administered with capecitabine as first-line therapy for MBC also shows promise as a safe and effective treatment regimen. An ongoing phase II, multicenter, open-label trial has enrolled 50 women for treatment with *nab*-paclitaxel 125 mg/m^2 administered on days 1 and 8 and capecitabine 825 mg/m^2 twice daily on days 1 to 14 on a 3-week cycle. Among 38 evaluable patients, the ORR was 52.9%, with an additional 32.4% considered to have SD. Initial results indicated prolonged TTP with a favorable toxicity profile although 5 patients required capecitabine dose reductions and 3

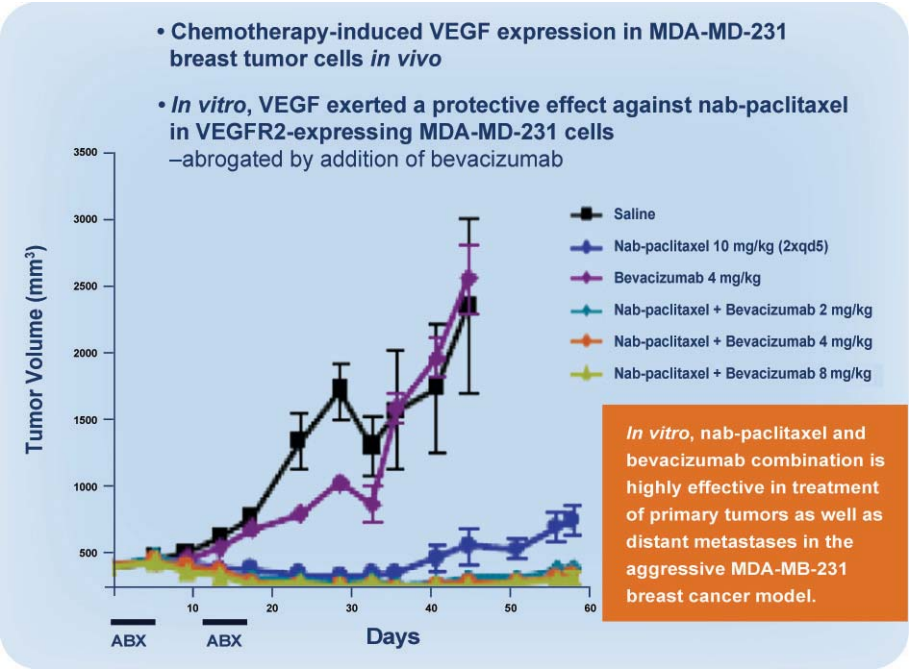

Fig. 3 – Rationale for combination of *nab*-paclitaxel and bevacizumab. [26,27] **Used with permission from Vuong Trieu, PhD.**

required dose reductions for *nab*-paclitaxel. Ten patients had grade 3 toxicities while 3 experienced grade 4 fatigue, febrile neutropenia, or neutropenia. [23]

A similar treatment regimen was evaluated in a phase II, multicenter, open-label study to assess the efficacy and safety of *nab*-paclitaxel and capecitabine as first-line therapy for MBC. Patients received *nab*-paclitaxel 125 mg/m^2 on days 1 and 8 and capecitabine 825 mg/m^2 twice daily on days 1 to 14 on a 3-week treatment cycle. An ORR of 47.5% was observed in 38 evaluable patients with PR reported for 39.5% of these and a CR noted for 8%. Stable disease was reported for 15 patients. Ten patients experienced grade 3 or 4 adverse events including neutropenia, febrile neutropenia, fatigue, hand-foot syndrome, and gastrointestinal complaints. [24]

3.2. *Nab-paclitaxel plus gemcitabine*

A recent phase II multisite trial enrolled 50 patients with MBC to assess tumor response and toxicities of first-line therapy with *nab*-paclitaxel 125 mg/m^2 followed by gemcitabine 1000 mg/m^2 on days 1 and 8 of a 3-week treatment cycle with dose modifications permitted for both agents. Confirmed RRs were reported for 50% (95% CI, 36% to 64%) of patients who completed therapy with 4 (8%) considered CR and 21 (42%) considered PR. Median response duration was 6.9 months and median PFS was 7.9 months (95% CI, 5.4 months to 9.3 months). Six-month overall survival (OS) was 92% (95% CI, 85% to 100%).The most frequent grade 3 or 4 adverse events included neutropenia (52%), fatigue (28%), anemia (14%), dyspnea (14%), and thrombocytopenia (12%). Dose delays and dose reductions were required for 33 and 29 patients, respectively, with the majority attributed to hematologic adverse events. [25]

3.3. *Nab-paclitaxel plus bevacizumab*

In vitro *nab*-paclitaxel and bevacizumab have been highly effective for the treatment of primary tumors and distant metastases in the aggressive MDA-MB-231 BC model (Figure 3). [26,27] Implanted MDA-MB-231 tumor cell lines were treated with saline, 2 cycles of *nab*-paclitaxel 10 mg/kg monotherapy or in combination with bevacizumab 2 mg/kg, 4 mg/kg, and 8 mg/kg twice weekly for 6 weeks. Significant reductions in tumor size were reported for the MDA-MB-231 tumors treated with chemotherapy compared with saline ($p < 0.006$), as well as increased vascular endothelial growth factor (VEGF) expression for the tumors treated with chemotherapy ($p < 0.0001$). Sequestration of VEGF with the addition of bevacizumab increased *in vitro* cytotoxicity of *nab*-paclitaxel. The combination regimen of *nab*-paclitaxel and bevacizumab enhanced antitumor response and significantly reduced lung and lymph node metastases in response to the highest dose of bevacizumab. [26] Similarly, Ran and colleagues implanted luciferase-tagged MDA-MB-231 cells into the mammary fatpads of female mice. The mice were treated with *nab*-paclitaxel plus bevacizumab, *nab*-paclitaxel monotherapy, bevacizumab monotherapy, or saline. Greater suppression of tumor growth and metastases was achieved with combination *nab*-paclitaxel plus bevacizumab. The combined regimen achieved a tumor growth index of 100%

Table 3 – Response rates based on tumor cell characteristics to bevacizumab/albumin-bound paclitaxel therapy in 33 heavily treated patients with metastatic breast cancer [29]

Patients	Response					
	CR (n)	PR (n)	ORR (%)	SD (n)	RR + SD (%)	PD
Total (N = 33)	3	13	48.5	5	63.6	12
ER- or PgR-positive (n = 23)	1	9	43.5	4	60.9	9
ER- or PgR-negative (n = 10)	2	4	60.0	1	70	3
HER2/*neu*-negative (n = 21)	2	8	47.6	1	52.4	10
HER2/*neu*-positive (n = 12)	1	5	50.0	4	83.3	2
Triple negative (n = 4)	1	2	75.0	0	75.0	1

CR: Complete response; ER: Estrogen receptor; ORR: Overall response rate; PD: Progressive disease; PgR: Progesterone receptor; PR: Partial response; RR: Response rate; SD: Stable disease.
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and reduced lymph and lung metastases in 100% of the mice. [27]

These results prompted clinical trials to evaluate *nab*-paclitaxel and bevacizumab in VEGF receptor-expressing BC tumors. Link and colleagues treated 27 patients with MBC with *nab*-paclitaxel 80 mg/m^2 to 125 mg/m^2 on days 1, 8, 15 or 170 mg/m^2 to 200 mg/m^2 every 2 weeks on a 28-day cycle, plus bevacizumab 10 mg/kg every 14 days with patients receiving at least 2 treatment cycles. Complete responses were reported for 11% of patients, and 48% had PR yielding an ORR of 59%. In addition, SD was reported for 7 patients while 4 patients had progressive disease (PD). [28] A retrospective analysis of outcomes among 40 women with MBC treated with at least 2 cycles of *nab*-paclitaxel and bevacizumab included 33 patients with measurable disease. The ORR was 48.5% and median TTP among responders was 128 days with median TTP of 135 days for 15% of women with SD. Response rates based on tumor cell characteristics are summarized in Table 3. Comparison of outcomes for the 2 dosing schedules suggests greater effectiveness of a weekly regimen of *nab*-paclitaxel. Specifically, RR plus SD was 73.7% for women treated weekly compared with 50% for those on a 2-week treatment cycle. Time to progression was 148 days for the weekly dose compared to 103 days for the 2-week treatment regimen. [29] A phase II trial of *nab*-paclitaxel plus bevacizumab as first-line therapy for women with HER2-negative MBC compared toxicities associated with *nab*-paclitaxel 260 mg/m^2 every 3 weeks to *nab*-paclitaxel 260 mg/m^2 every 2 weeks with filgrastim or *nab*-paclitaxel 130 mg/m^2 weekly. While results have only been reported for 66 of the planned 225 patients, no statistically or clinically significant differences in rates of grade 3 toxicities have been reported. [30]

The favorable response to combination therapy with *nab*-paclitaxel and bevacizumab prompted additional trials to determine the safety and efficacy of alternate drug combinations including *nab*-paclitaxel, bevacizumab, gemcitabine and *nab*-paclitaxel, bevacizumab, carboplatin for triple-negative BC. *Nab*-paclitaxel plus sorafenib is also under evaluation in clinical trials for treatment of MBC. There are 42 studies currently recruiting or soon to initiate recruitment for evaluation of *nab*-paclitaxel in combination with other anticancer agents for the treatment of MBC. [31]

4. *Nab*-paclitaxel as neoadjuvant therapy for breast cancer

Paclitaxel has also demonstrated efficacy as neoadjuvant treatment for early stage BC. A phase II study enrolled 66 women with locally advanced BC to determine the efficacy and safety of *nab*-paclitaxel 100 mg/m^2 administered preoperatively for 12 consecutive weeks. In addition, patients with HER2-negative BC received preoperative treatment with 4 cycles of 5-fluouracil (500 mg/m^2), epirubicin (100 mg/m^2), and cyclophosphamide (500 mg/m^2) every 3 weeks while those with HER2-positive disease were treated preoperatively with 4 cycles of 5-fluouracil (500 mg/m^2), epirubicin (75 mg/m^2), and cyclophosphamide (500 mg/m^2) plus trastuzumab every 3 weeks. *Nab*-paclitaxel 100 mg/m^2 was well tolerated and achieved a clinical CR (cCR) in 32% (95% CI, 21% to 45%) of patients. Among patients with HER2-negative, hormone receptor–negative BC, the pathologically confirmed CR (pCR) rate was 29% compared to 59% for women with HER2-positive disease who received concurrent trastuzumab. [32]

Patients with stage II–III or inflammatory BC were enrolled in a phase II randomized trial to evaluate the efficacy of neoadjuvant treatment with 6 cycles of docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2 (TAC) or doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 administered every 2 weeks for 4 cycles followed by 3 weekly doses of carboplatin (AUC 2) and *nab*-paclitaxel 100 mg/m^2 given every 4 weeks for 3 cycles (ACAC). In addition, patients with HER2-positive tumors received the ACAC regimen plus 12 weekly doses of trastuzumab (ACAC-T).

Grade 3 or 4 toxicities included neuropathy, neutropenia, febrile neutropenia, thrombocytopenia, anemia, fatigue, allergic reactions, and gastrointestinal symptoms with the highest rate of grade 4 neutropenia noted in the TAC group. Complete responses were reported for 7% of patients treated with TAC, 5% in patients receiving ACAC, and 40% of patients in the ACAC-T arm. In addition, 33% of the ACAC group achieved $\geqslant$90% PR compared to 20% and 7% of the ACAC-T and TAC arms, respectively. Stable disease was evident in 37% of women treated with TAC compared to 5% of those receiving ACAC, and there were no instances of SD in the ACAC-T group. [33]

A multicenter phase II trial enrolled 72 chemotherapy-naïve patients with 48 patients evaluable for toxicity and 35 for pathologic response to treatment with gemcitabine 2000 mg/m^2, epirubicin 50 mg/m^2, and *nab*-paclitaxel 175 mg/m^2 every 2 weeks for 6 cycles preceding surgery. Postoperative treatment included gemcitabine 2000 mg/m^2 and *nab*-paclitaxel 220 mg/m^2 supplemented by granulocyte-colony stimulating factor (G-CSF). Only 8% of patients experienced grade 3 or 4 neutropenia, 6% thrombocytopenia, 6% fatigue, 10% arthralgia, and there were no cases of febrile neutropenia or grade 3 or 4 neuropathy. Analysis of pathologic responses revealed CR in 20% of patients, PR for 74%, and SD in 6%. [34]

5. *Nab*-paclitaxel as adjuvant therapy for breast cancer

The efficacy of *nab*-paclitaxel as adjuvant therapy for BC has also been evaluated with promising results. A pilot study of dose-dense doxorubicin and cyclophosphamide (AC) followed by *nab*-paclitaxel 260 mg/m^2 every 2 weeks for 4 cycles was conducted to determine the tolerability of the regimen for early stage BC. Granulocyte-colony stimulating factor support was provided during administration of AC as well as for patients with persistent neutropenia while receiving *nab*-paclitaxel. Among 30 patients, 97% started treatment with *nab*-paclitaxel and 93% of these completed all cycles. One-third of patients required G-CSF support during administration of *nab*-paclitaxel and 31% required dose reductions in *nab*-paclitaxel due to non-hematologic toxicities with 20% experiencing grade 3 or 4 neutropenia. [35]

A total of 66 patients with stage I to III BC received a dose-dense adjuvant regimen including sequential AC administered at 2-week intervals with 4 cycles of G-CSF, followed by *nab*-paclitaxel 260 mg/m^2 every 2 weeks for 4 cycles. The primary objective was to determine incidence of treatment delay during administration of *nab*-paclitaxel. Among the first 11 patients who did not receive G-CSF in conjunction with *nab*-paclitaxel, 1 developed febrile neutropenia and 4 required treatment delays due to neutropenia grade 3 or 4. The study protocol was amended to require administration of G-CSF with *nab*-paclitaxel. Only 3 of the next 55 patients experienced febrile neutropenia during administration of AC, none while receiving *nab*-paclitaxel, with 96% of *nab*-paclitaxel cycles delivered on schedule. The investigators concluded that inclusion of *nab*-paclitaxel in a dose-dense adjuvant regimen required G-CSF support to avoid serious adverse events and treatment delays. [36] A subsequent phase II study enrolling 80 patients with early stage BC confirmed the cardiac safety of a regimen including bevacizumab 10 mg/kg every 2 weeks for 8 cycles with AC (60/600 mg/m^2) followed by *nab*-paclitaxel 260 mg/m^2 every 2 weeks for 4 cycles. The most common grade 3–4 adverse events included grade 3 fatigue (8.6%), sensory neuropathy (9.9%), and headache (4.9%) and grade 3 or 4 hypertension (9.8%). However, there was no evidence of symptomatic left ventricular dysfunction. [37] Finally, an ongoing trial will compare the safety of AC followed by either *nab*-paclitaxel 260 mg/m^2 or paclitaxel 175 mg/m^2 with bevacizumab 10 mg/kg every 2 weeks during chemotherapy administration and continued treatment with bevacizumab 15 mg/kg every 3 weeks for 1 year following completion of chemotherapy. Primary study endpoints will include treatment-related toxicities at 3 and 6 months following completion of chemotherapy and secondary endpoints will assess cardiac and laboratory abnormalities, myelosuppression, and need for G-CSF support. [38]

6. *Nab*-paclitaxel–based combinations for other cancers

Results from several recent trials suggest that *nab*-paclitaxel is effective for treatment of lung cancer, melanoma, ovarian cancer, prostate cancer, and pancreatic cancer. A total of 43 patients with histologically or cytologically confirmed non-small cell lung cancer (NSCLC) with evidence of inoperable local recurrence or metastasis were treated with *nab*-paclitaxel 260 mg/m^2 at 3-week intervals until there was evidence of disease progression or unacceptable toxicity occurred. The ORR was 16.3% (95% CI, 5.24% to 27.31%) with all classified as PR. Disease control was achieved for 48.8% of patients (95% CI, 33.90% to 63.78%) with median TTP of 6 months (95% CI, 3.9 months to 6.5 months) and medial survival of 11 months (95% CI, 9.5 months to 16.2 months). Ninety-five percent of patients completed the protocol-specified dose of *nab*-paclitaxel. The treatment was well tolerated with no grade 4 toxicities although 5% of patients experienced grade 3 neuropathy, and grade 3 neutropenia affected 9% of patients. Five percent discontinued treatment and 5% required dose reductions. [39] A phase II open-label trial evaluated *nab*-paclitaxel plus carboplatin AUC 6 on ORR, SD, TTP, and toxicities in 56 chemotherapy-naïve patients with

stage IIIB/IV NSCLC. The study protocol was amended to increase the dose of *nab*-paclitaxel from 100 mg/m^2 to 125 mg/m^2 with no change in dose of carboplatin. The ORR was 48% (95% CI, 35% to 61%) for patients receiving the lower *nab*-paclitaxel dose compared to 30% (95% CI, 17% to 46%) for patients who received the 125 mg/m^2 dose. Thirty percent of those treated with the lower dose achieved SD for at least 12 weeks compared to 46.9% of patients treated with the higher dose. However, there were no differences in median TTP of 30 weeks between the two dose groups. [40,41]

Similarly, an open-label, phase II trial of 50 patients with NSCLC evaluated the effect of *nab*-paclitaxel 300 mg/m^2, carboplatin AUC 6, and bevacizumab 15 mg/kg every 3 weeks for a maximum of 4 cycles. Partial responses were evident in 31.3% of patients and 52.1% were determined to have SD with 44% of these sustaining SD for at least 6 months. Median PFS was 9.8 months (95% CI, 6.1 months to 11.5 months) and median OS was 15.8 months (95% CI, 10.4 months to not reached). Grade 3 or 4 toxicities included neutropenia (52%), fatigue (17%), neuropathy (10%), thrombocytopenia (10%), and dyspnea (6%). [42] A phase I/II open-label, single-arm trial with chemotherapy-naïve patients with stage IV or recurrent NSCLC evaluated the maximum-tolerated dose (MTD), dose-limiting toxicities (DLT), and efficacy of *nab*-paclitaxel administered on days 1, 8, and 15 of a 4-week cycle at 4 dose levels including 100 mg/m^2, 125 mg/m^2, 150 mg/m^2, and 175 mg/m^2. The first phase of the study determined that 150 mg/m^2 exceeded the MTD and the investigators defined the recommended phase II dose to be 125 mg/m^2. As such, phase II of the study treated 40 patients with *nab*-paclitaxel 125 mg/m^2 to determine efficacy and DLT. The ORR was 30% (95% CI, 16% to 44%) and SD for $\geqslant$16 weeks was noted for 8 (20%) patients. Median TTP was 5 months (95% CI, 3 months to 8 months) and median OS was 11 months (95% CI, 7 months to not reached). A total of 20% of patients experienced grade 3 (15%) or 4 (5%) neutropenia. Other toxicities included leukopenia in 20% of patients, 15% sensory neuropathy, 18% fatigue, 13% diarrhea, and 8% anemia (all grade 3 events). [43] Two recent multicenter, open-label, phase II studies assessed the efficacy and safety of *nab*-paclitaxel in combination with carboplatin (AUC 6) as first-line treatment for patients with previously untreated stage IIIB or IV NSCLC. A total of 100 patients received *nab*-paclitaxel every 3 weeks at 4 doses (225 mg/m^2, 260 mg/m^2, 300 mg/m^2, or 340 mg/m^2) plus carboplatin [44] while 75 patients were treated with 3 doses of *nab*-paclitaxel (140 mg/m^2, 100 mg/m^2, or 125 mg/m^2) plus carboplatin at weekly intervals. [45] Objective RR for the 4 doses administered every 3 weeks ranged from 23% for the 300 mg/m^2 dose and 24% for the 260 mg/m^2 dose to 27% for the 340 mg/m^2 arm and 40% for the 225 mg/m^2 group. Stable disease $\geqslant$16 weeks was observed in 0% of patients receiving the 340 mg/m^2 dose and increased to 19% for the 300 mg/m^2 dose and 24% for the 225 mg/m^2 and 260 mg/m^2 doses. More favorable ORR were evident for patients treated weekly at 36%, 44%, and 56% for the 125 mg/m^2, 100 mg/m^2, and 140 mg/m^2 doses, respectively. Twelve percent of patients in both the 100 mg/m^2 and 125 mg/m^2 dose groups maintained SD for at least 16 weeks compared to 8% of patients in the 140 mg/m^2 dose group. [44] These results fostered interest in *nab*-paclitaxel for treatment of NSCLC and other types of lung cancer and there are 88 trials in the US alone currently recruiting or soon to initiate recruitment to evaluate the efficacy and safety of *nab*-paclitaxel for lung cancer. [46]

N*ab*-paclitaxel has also been evaluated for treatment of malignant melanoma in a phase II trial including 13 chemotherapy-naive patients administered *nab*-paclitaxel 150 mg/m^2 and 36 previously treated patients (*nab*-paclitaxel 100 mg/m^2). There were no treatment-related deaths or grade 4 toxicities although grade 3 toxicities included fatigue (13%), neutropenia (13%), leukopenia (8%), and rash (8%). Two chemotherapy-naïve patients achieved a PR. Stable disease was confirmed for 1 chemotherapy-naïve and 4 previously treated patients and they continued treatment for 24 weeks or longer. [47] A randomized phase III trial is planned that will enroll 518 patients with melanoma to compare *nab*-paclitaxel 150 mg/m^2 weekly for 3 of 4 weeks with dacarbazine 1000 mg/m^2 three times weekly. The primary study endpoint will be PFS. [48]

Results are now available from an efficacy and safety study that enrolled 47 patients with recurrent ovarian, peritoneal, or fallopian tube cancer treated with *nab*-paclitaxel 260 mg/m^2 once every 3 weeks with treatment continuing until evidence of PD or a maximum of 6 cycles. Among patients meeting RECIST criteria for measurable disease and an elevated CA-125, the ORR was 64%. The ORR was 82% for patients based solely on elevated CA-125 levels while ORR declined to 45% for patients based solely on RECIST criteria. Neutropenia was the most frequent (23.9%) grade 3 or 4 toxicity with grade 3 or 4 leukopenia (13.0%) and neuropathy (8.7%) also reported. [49] Trials are ongoing to evaluate the impact of *nab*-paclitaxel in prostate and pancreatic cancer with 6 trials in the US actively recruiting subjects to evaluate the efficacy and safety of *nab*-paclitaxel for prostate cancer and 6 trials underway in the US for patients with pancreatic cancer. [50–52] Von Hoff and colleagues reported results from a phase I trial assessing the antitumor activity of *nab*-paclitaxel plus gemcitabine for chemotherapy-naïve patients with advanced pancreatic cancer. [52] All patients received an initial dose of *nab*-paclitaxel 100 mg/m^2 and gemcitabine 1000 mg/m^2 on days 1, 8, and 15 every 4 weeks. At least 1 treatment cycle has been completed for 18 of 20 patients. Carbohydrate

antigen 19-9 (CA19-9) levels were reduced >20% from baseline for 82% of patients and >70% from baseline in 59% of patients, with decreases of at least 20% in CA19-9 levels associated with significant improvements in survival rates according to other trials.[53–55] Five patients experienced grade 3 or 4 neutropenia with 1 case each of grade 3 or 4 febrile neutropenia, fatigue, and hyperglycemia.[52]

7. Conclusions

Numerous studies have demonstrated the safety and efficacy of *nab*-paclitaxel for the treatment of metastatic breast cancer. Subsequent trials have evaluated the efficacy and safety of different doses and administration schedules of *nab*-paclitaxel for treatment of BC including comparisons with SB docetaxel. Weekly administration of *nab*-paclitaxel at a dose of 150 mg/m^2 appears to yield optimal efficacy while minimizing adverse events and *nab*-paclitaxel appears to be superior to second-generation docetaxel for treatment of BC. *Nab*-paclitaxel in combination with gemcitabine, capecitabine, or bevacizumab has shown to be very active in patients with MBC. Overall response rates to *nab*-paclitaxel plus capecitabine have ranged between 47.5% and 52.9% with longer TTP and a favorable toxicity profile. Similarly, *nab*-paclitaxel plus gemcitabine has resulted in a 50% ORR while the combination of bevacizumab and *nab*-paclitaxel has achieved a RR of 59% in patients with MBC. The favorable response to combination therapy with *nab*-paclitaxel and other anticancer agents has prompted additional trials to determine efficacy of different treatment regimens including *nab*-paclitaxel plus sorafenib for MBC, and *nab*-paclitaxel, bevacizumab, gemcitabine plus *nab*-paclitaxel, bevacizumab, carboplatin both for triple-negative BC. Preliminary data with *nab*-paclitaxel has also demonstrated promise as neoadjuvant and adjuvant treatment regimens for BC, although inclusion of G-CSF may be necessary to avoid serious adverse events and treatment delays associated with biweekly administration schedules. Favorable tumor response rates and manageable toxicities have been reported for the combination of *nab*-paclitaxel and carboplatin when administered to patients with lung cancer. *Nab*-paclitaxel is currently under evaluation in phase III trials for the treatment of lung cancer and a phase III trial is planned to evaluate *nab*-paclitaxel in melanoma. In addition, it is being studied in other tumor types including ovarian cancer, prostate cancer, and pancreatic cancer, which may yield new therapeutic options for patients with these tumor types.

Conflicts of interest

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