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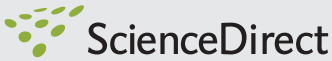

# Molecular basis for the development of novel taxanes in the treatment of metastatic breast cancer

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ABSTRACT

The identification of taxanes proved to be a significant advance in the treatment of breast cancer. First-generation taxanes achieved 35% to 55% response rates for women not previously treated with anthracyclines and exceeded 20% for anthracycline-resistant disease. Consequently, taxanes were established as a standard of care in metastatic disease. Subsequent research evaluated taxane monotherapy and combination therapy with other cytotoxic agents, as well as optimal dose and administration schedules to maximize efficacy while minimizing toxicities. Clinical trials suggested the optimal administration schedule and dose for paclitaxel was 80 mg/m$^2$ weekly, and this weekly schedule is commonly used. However, the solvents required for administration of first-generation taxanes are associated with significant toxicities and undermined clinical efficacy. These factors motivated development of taxane formulations that would enhance the therapeutic index and minimize toxicities. This article reviews the rationale for development of novel taxane formulations and emerging research regarding new formulations including oral taxanes, paclitaxel poliglumex, and vitamin E-based paclitaxel emulsion.



## 1. Introduction

Worldwide, 1.15 million women are diagnosed with breast cancer (BC) each year with approximately 500,000 deaths attributable to this disease per year despite research advances that have resulted in a wider variety of treatment options and a multidisciplinary treatment approach.[1–5] In the US, approximately 6% of new cases of breast cancer are metastatic at diagnosis with 24% to 30% of women with node-negative BC and 50% to 60% of those with node-positive tumors at risk of recurrence.[3–5] The majority of BC deaths are attributed to recurrent or metastatic disease with only 27% of women with metastatic disease surviving 5 years.[6] Treatment priorities in metastatic breast cancer emphasize palliation, prevention or delay of onset of symptoms, extension of disease-free survival (DFS) and overall survival (OS) intervals, and control of treatment-induced toxicities. Significant progress has been made with respect to identification of predictors of prognosis including performance status (PS), disease sites and number, hormone receptor status, HER-2/*neu* status, prior adjuvant therapy, and prior treatment for metastatic breast cancer (MBC).[7,8] There have also been significant advances in systemic therapeutic interventions for MBC including the following: endocrine therapy for

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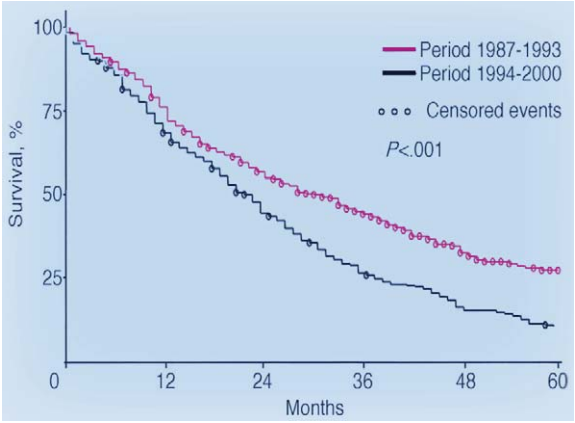


**Fig. 1 – Survival trends for metastatic breast cancer: 1987 to 2000.** [9] **From Andre F, Slimane K, Bachelot T, et al. Breast cancer with synchronous metastases: Trends in survival during a 14-year period. *J Clin Oncol* 2004;22(16):3302–8. Reprinted with permission from The American Society of Clinical Oncology.**

hormone sensitive tumors; monochemotherapy and polychemotherapy including mainly capecitabine, vinorelbine, doxorubicin, anthracyclines, and taxanes; bisphosphonates to reduce or delay skeletal-related events and bone metastases; monoclonal antibodies such as trastuzumab and bevacizumab; and tyrosine kinase inhibitors. [3,7,8,10–14] Phase II and III trials evaluating these agents demonstrate response rates (RR) ranging from 20% to 70% and increased progression-free survival (PFS). While MBC is not yet curable, significant improvements in survival have occurred from a median of 23 months during the interval of 1987 to 1993 to 29 months from 1994 to 2000. Similarly, 5-year survival rates increased from 11% for the 1987 to 1993 period to 28% during the 1994 to 2000 interval (Figure 1). [9]

## 2. Taxanes for the treatment of breast cancer

One of the most significant advances in the treatment of BC, especially MBC, was achieved in the mid-to-late 1990s with the identification of taxanes. [15–17] In fact, anthracyclines and taxanes are considered the most highly active cytotoxic agents for the treatment of BC and they have been thoroughly evaluated for efficacy and safety as monotherapy and polychemotherapy for MBC. [8,10] Taxane monotherapy was evaluated in phase II and III studies with very promising results when compared to doxorubicin, which was considered the reference agent in the late 1990s for the treatment of MBC. [18,19] A phase III trial by Chan et al. compared docetaxel with doxorubicin in 326 patients with MBC who had previously been treated with alkylating agent-containing chemotherapy. Women were randomized to receive intravenous docetaxel 100 mg/m$^2$ or doxorubicin 75 mg/m$^2$ at 3-week intervals. The overall response rate (ORR) was 47.8% for docetaxel compared to 33.3% for the doxorubicin arm ($p = 0.008$). Median time to tumor progression (TTP) was 26 weeks for the docetaxel group versus 21 weeks for the doxorubicin regimen, although this difference was not statistically significant. [20] Paclitaxel monotherapy achieved RR between 35% and 55% for women who had not previously been treated with anthracyclines and RR exceeded 20% for anthracycline-resistant MBC. [8,11,13]

Consequently, taxanes as monotherapy and in combination with other cytotoxic agents were established as standard of care for the treatment of MBC. Subsequent research efforts attempted to determine optimal dose and administration schedules for taxanes to maximize efficacy while minimizing toxicities. As an example, the Anglo-Celtic IV trial was a randomized phase III trial comparing weekly paclitaxel to the presumed standard 3-week schedule. A total of 569 patients with MBC or locally advanced BC were randomized to paclitaxel 175 mg/m$^2$ at 3-week intervals for 6 cycles (n = 291) or paclitaxel 90 mg/m$^2$ weekly for 12 weeks (n = 278). Response rates were 27% (5% complete response [CR] and 22% partial response [PR]) for patients receiving the 3-week administration regimen compared with 43% (6% CR and 37% PR) for patients treated weekly ($p = 0.002$). Median TTP was 22 weeks for the 3-week schedule (95% CI, 19.7 weeks to 24.6 weeks) compared with 23.9 weeks for weekly paclitaxel (95% CI, 20.7 weeks to 26.7 weeks; hazard ratio [HR] = 0.92, $p = 0.06$). The patterns of disease progression over time by treatment schedule are shown in Figure 2. While both treatment schedules were well-tolerated, weekly administration resulted in significantly improved RR with a trend for longer TTP and suggested that the optimal administration schedule for paclitaxel was weekly, confirming other studies. [21]

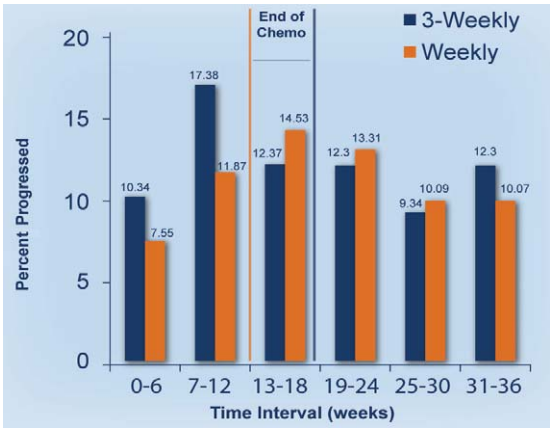


**Fig. 2 – Anglo-Celtic IV: percentage of patients progressing over time by treatment schedule.** [21] **Used with permission from Mark Verrill, MB, BChir, MA, FRCP.**

**Table 1 – Maximum response and rates of neutropenia and neuropathy for all treated patients [a]**

| Measure | Paclitaxel 175 mg/m$^2$ | Paclitaxel 210 mg/m$^2$ | Paclitaxel 260 mg/m$^2$ |
|---|---|---|---|
| Total patients, n (%) | 158 (100) | 156 (100) | 155 (100) |
| Analyzable patients, n (%) | 150 (95) | 152 (97) | 150 (97) |
| Outcome for analyzable patients, n (%) | | | |
| CR | 9 (6) | 9 (6) | 8 (5) |
| PR | 25 (17) | 30 (20) | 23 (15) |
| SD | 58 (39) | 62 (41) | 78 (52) |
| PD | 57 (38) | 45 (30) | 36 (24) |
| TTP, median months | 3.9 | 4.1 | 4.9 |
| Survival, median months | 11 | 12 | 14 |
| Neutropenia grade 4, % | 34 | 44 | 53 |
| Neuropathy grade 3, % | 7 | 19 | 32 |

[a] From Weber EP, Berry DA, Woolf S, et al. [23] Failure of higher-dose paclitaxel to improve outcome in patients with metastatic breast cancer: Cancer and Leukemia Group B Trial 9342. *J Clin Oncol* 2004;**11**(1):2061–8. Reprinted with permission from The American Society of Clinical Oncology.

Prior studies conducted to determine optimal doses of paclitaxel include a multicenter, randomized trial comparing paclitaxel 175 mg/m$^2$ to 135 mg/m$^2$ administered every 3 weeks. [22] This trial demonstrated longer TTP for the higher dose, which was subsequently established as the initial standard for paclitaxel in the USA in the mid-1990s. [23,24] Efforts to determine the optimal dose of paclitaxel for MBC continued, including a phase III, randomized trial by Winer et al. that compared outcomes of 474 patients with MBC treated with paclitaxel 175 mg/m$^2$, 210 mg/m$^2$, or 260 mg/m$^2$ administered by intravenous infusion every 3 weeks. There were no statistically significant differences in RR between the 3 dose groups and the dose response was not statistically significant (Table 1). Greater toxicity was reported for the higher doses of paclitaxel with the most common adverse events including neutropenia, neuropathy, and alopecia. There was a significant linear relationship between dose and grade of neutropenia ($p = 0.0058$). Similarly, rates of grade 3 neuropathy were significantly higher as the dose increased ($p = 0.0001$). These results confirmed that the 175 mg/m$^2$ every-3-week dose provided optimal efficacy while minimizing toxicities. [23]

## 3. Toxicity and solubility issues of first-generation taxanes

First-generation taxanes are water insoluble and require various solvents to allow parenteral administration. Such solvents include polyethylated castor oil (Cremophor® EL [CrEL]) for paclitaxel and polysorbate 80 (Tween®80) for docetaxel. [24] There is substantial evidence that both solvents are biologically and pharmacologically active and can provoke a number of life-threatening adverse events. [25,26] Most notably, CrEL is known to cause acute hypersensitivity reactions including dyspnea, flushing, rash, peripheral neuropathy, and generalized urticaria. [27] The overall frequency of minor reactions is estimated to be as high as 44% with major reactions occurring in approximately 1.5% to 3% of patients. [26] Premedication with corticosteroids and histamine receptor ($H_1$ and $H_2$) blockers do not prevent all minor hypersensitivity reactions. [24] The oleic acid in polysorbate 80 is thought to provoke hypersensitivity reactions with estimated incidence rates ranging between 5% and 40%, although the majority of these are minor reactions. [25] CrEL is also associated with an increased risk of peripheral neurotoxicity when administered with paclitaxel. Sensory neuropathy has also been reported for patients treated with docetaxel formulated with polysorbate 80, although the reaction is generally milder than that observed in studies with paclitaxel. [24–26] Other adverse events associated with polysorbate 80 and CrEL taxane formulations include vesicular degeneration, nephrotoxicity, dermatitis, axonal degeneration, demyelination, and fluid retention. [24,26] Rates of toxicities associated with first-generation taxanes and the synthetic solvents used to achieve parenteral administration are presented in Table 2. [27,28] Solvent-based (SB) taxane administration also requires intravenous administration, which is inconvenient and may require prolonged infusion times as well as special tubing. CrEL leaches plasticizers from polyvinyl chloride (PVC) bags and polyethylene-lined tubing sets, which can cause hepatotoxic reactions. [24,29–31] Thus, PVC-free equipment is recommended for administration of CrEL-paclitaxel. [26]

Importantly, there is evidence suggesting that the characteristics of SB first-generation taxanes undermine the efficacy of taxane treatment. Specifically, CrEL provokes formation of micelles, which entrap paclitaxel and carry it in the systemic circulation. This results in diminished plasma clearance, a reduction in volume of paclitaxel distribution and reduced bioavailability, which contribute to lack of a dose-dependent antitumor activity (Figure 3). [24–26]

**Table 2 – Prevalence of solvent-based taxane toxicities** [27,28]

| 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 Taxol (paclitaxel, Bristol-Myers Squibb, n = 812) and Taxotere (docetaxel, sanofi-aventis, n = 2405).

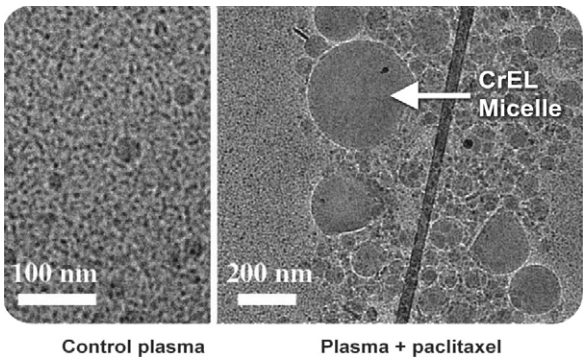


**Fig. 3 – Large micelle formation in plasma incubated with CrEL-based paclitaxel. CrEL: polyethylated castor oil. Used with permission from Alexander Sparreboom, MD.**

## 4. Improved taxane formulations

### 4.1. *Nanoparticle albumin-bound [nab]-paclitaxel*

The compromised efficacy and unfavorable toxicity profile of SB first-generation taxanes motivated research efforts to enhance the therapeutic index of taxane formulations for cancer treatment that would increase intratumoral drug uptake, promote preferential uptake of taxanes by tumor cells versus normal cells, enhance antitumor activity, and avoid the toxicities associated with SB taxanes. These included efforts to modify the formulation and vehicle of drug delivery, which resulted in development of a solvent-free formulation of paclitaxel known as nanoparticle albumin-bound [*nab*]-paclitaxel. [32] *Nab*-paclitaxel is a biologically interactive, nanometer-sized particle that uses the unique properties of albumin to safely administer higher doses of paclitaxel with shorter infusion times. [33] Albumin-bound drugs are delivered effectively to tumors via an enhanced permeability and retention (EPR) effect and gp60 receptor-mediated transcytosis, which is unique

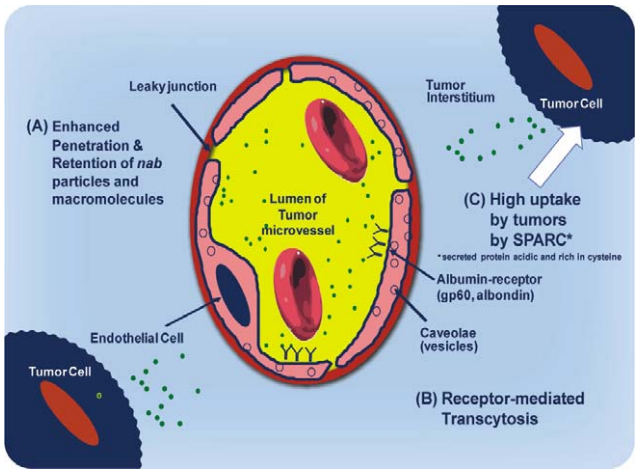


**Fig. 4 – Albumin-bound paclitaxel: transport from blood circulation through endothelial cells and penetration of tumor cells.**

to albumin. EPR refers to the preferential accumulation of albumin-bound drugs and other macromolecules in the tumor interstitium as a result of leaving the circulation via leaky vasculature surrounding the tumor and preventing release back into the vessels due to impaired lymphatic drainage in tumor tissue. Thus, there is prolonged exposure of tumor cells to the albumin-bound drugs. In addition, the albumin receptor is a 60 kDa glycoprotein (gp60 or albondin) present on the surface of endothelial cells. Binding of the albumin complex to gp60 promotes formation of vesicles in the cell membrane called caveolae. This initiates transport of the albumin complex across the cell membrane and into the surrounding tissue such as the tumor interstitium. This is the proposed primary mechanism for preferential delivery of albumin-bound drugs to tumor tissue (Figure 4). [34–36]

*Nab*-paclitaxel is an albumin-bound, 130 nm particle formulation of paclitaxel containing no solvents or ethanol. [32] A phase I pharmacokinetic study by Ibrahim et al. treated 19 patients with *nab*-paclitaxel to assess toxicities. No patients were premedicated with dexamethasone or histamine receptor blockers and the study drug was administered by intravenous infusion over 30 minutes with the exception of the first 3 patients who received infusions over 2 to 3 hours. Doses of *nab*-paclitaxel were 135 $mg/m^2$, 200 $mg/m^2$, 300 $mg/m^2$, or 375 $mg/m^2$ and all patients were monitored for toxicities. Hematologic toxicity characterized by absolute neutrophil count (ANC) and platelet nadirs was mild and dose-dependent (Table 3). Of 96 treatment cycles, 7.3% resulted in an ANC nadir <500 $mm^3$ with 6 of these 7 cases observed in patients treated with the highest dose of *nab*-paclitaxel. Nonhematologic toxicities were primarily grade 1 or 2 with no grade 4 events. Nausea, vomiting, arthralgia, myalgia, dry skin, and rash were common but mild. All patients experienced

**Table 3 – Median absolute neutrophil and platelet nadirs by dose level [33]**

| Dose | Nadir $\times 10^3$/mm (range) | |
|---|---|---|
| | ANC | Platelet |
| 135 mg/m$^2$ | 2.229 (1.85–5.04) | 204 (174–292) |
| 200 mg/m$^2$ | 1.845 (0.586–3.729) | 197 (118–270) |
| 300 mg/m$^2$ | 0.960 (0.264–3.680) | 200 (105–609) |
| 375 mg/m$^2$ | 0.966 (0.018–1.804) | 173 (25–251) |

ANC: absolute neutrophil count
From Ibrahim KN, Desai N, Legha S, et al.[33] Copyright 2002 by American Association for Cancer Research. Reproduced with permission of American Association for Cancer Research via Copyright Clearance Center.

alopecia. Peripheral neuropathy occurred in 11 of 12 patients receiving the 2 highest doses of the study drug. In addition, dose-dependent ocular side effects were reported including dry eyes, blurred vision, photosensitivity, and changes in visual acuity. Partial responses were reported for 2 patients with BC who had previously been treated with CrEL-paclitaxel.[33] Desai and colleagues subsequently compared the antitumor activity, intratumoral paclitaxel accumulation, and endothelial transport of *nab*-paclitaxel to CrEL-paclitaxel in nude mice with human tumor xenografts of lung, breast, ovarian, prostate, and colon pathology. *Nab*-paclitaxel was significantly less toxic than CrEL-paclitaxel with mortality rates of 4% for *nab*-paclitaxel and 49% for CrEL-paclitaxel at a 30 mg/kg per day dose ($p < 0.0001$). Overall intratumor concentrations of paclitaxel were 33% greater after treatment with *nab*-paclitaxel compared to identical doses of CrEL-paclitaxel. *Nab*-paclitaxel demonstrated greater antitumor activity compared with CrEL-paclitaxel for BC based on median time to tumor recurrence (103 days vs 22 days, respectively; $p = 0.004$), and tumor doubling time (>95 days vs 31.2 days respectively, $p = 0.0015$). Furthermore, intratumor paclitaxel accumulation was significantly greater for *nab*-paclitaxel than CrEL-paclitaxel following comparable doses of paclitaxel 20 mg/kg ($p < 0.0001$). Endothelial binding and transcytosis of paclitaxel was substantially greater for *nab*-paclitaxel compared with CrEL-paclitaxel; indeed, binding increased 9.9 fold for *nab*-paclitaxel and transport of paclitaxel across the endothelial cell layer was 4.2 times greater for *nab*-paclitaxel compared to CrEL-paclitaxel ($p < 0.0001$ for both comparisons). These differences were attributed to binding of albumin to the gp60 receptor and caveolar-mediated transport.[37] The uptake of albumin by heterotransplanted squamous cell carcinoma tumor cells in nude mice was also evaluated by magnetic resonance imaging in a study by Kiessling et al., which confirmed a 51% increase in signal intensity of tumor, blood, liver, kidney, and muscle tissue 24 hours following administration of the gadolinium (GD)-labeled albumin.[38]

Secreted protein acidic and rich in cysteine (SPARC; osteonectin), a 32 kDa glycoprotein that binds with a variety of proteins of the extracellular matrix, can promote growth factor efficacy, tissue remodeling, and angiogenesis, and is a potential target of *nab*-paclitaxel. Several trials have assessed the effect of SPARC on cancer cells, including human BC, and evaluated its impact on clinical outcomes. Watkins and colleagues collected 120 samples of BC tissue and 32 normal tissues and followed patients for 72 months postoperatively. Examination of the distribution of SPARC protein indicated substantial increases in staining of SPARC primarily in the BC cells and matrix with very low levels of SPARC staining in the stroma of normal tissue. Further analysis of the level of expression of SPARC mRNA in mammary tissue by quantitative polymerase chain reaction (PCR) revealed significantly higher levels of SPARC transcript in the breast tumors ($p = 0.04$). Analysis of follow-up survival data indicated that patients who died from BC had significantly higher levels of SPARC compared to those who survived with no evidence of disease ($p = 0.04$).[39] Overexpression of SPARC has also been identified as an indicator of poor prognosis for other malignancies, including head and neck cancer.[40] It has subsequently been shown that SPARC exerts an albumin-binding effect, which may establish it as an intratumoral target for *nab*-paclitaxel. Specifically, overexpression of SPARC was assessed by antibody immunostaining of primary BC, normal human breast tissue, other normal human tissue, human breast cancer MX-1 cell xenografts, and normal mouse tissues. Strong SPARC staining was evident for 46% of human BC versus 1% for normal human breast tissue ($p < 0.0001$). In addition, SPARC staining was strongly observed in MX-1 xenografts while there was no evidence of SPARC in normal mouse tissue. The investigators concluded that SPARC may be an intratumoral target for *nab*-paclitaxel due to colocalization of albumin and SPARC and enhanced albumin-binding activity. This may enhance uptake of *nab*-paclitaxel compared with CrEL-paclitaxel, and SPARC screening may identify patients who will achieve the greatest benefit from treatment with *nab*-paclitaxel.[41]

Phase II and III trials with *nab*-paclitaxel have demonstrated doubled RR, increased duration of TTP, and increased OS time compared with CrEL-paclitaxel.[42–44] A phase III trial by Gradishar et al. enrolled 460 women with MBC to compare *nab*-paclitaxel 260 mg/m$^2$ with standard paclitaxel 175 mg/m$^2$ with premedication administered at 3-week intervals. A 33% ORR was observed in the *nab*-paclitaxel group compared to 19% for standard paclitaxel ($p = 0.001$). Time to progression was significantly longer for patients who received *nab*-paclitaxel as second-line or greater therapy (20.9 weeks vs 16.1 weeks; $p = 0.020$). The toxicity profile was more favorable for women treated with *nab*-paclitaxel with respect to neutropenia and hypersensitivity reactions,

although they were more likely to experience grade 3 sensory peripheral neuropathy. [43] Subsequent trials have consistently demonstrated higher RR and longer TTP for *nab*-paclitaxel compared to CrEL-paclitaxel with a more favorable safety profile.

### 4.2. Oral taxanes

Oral administration of taxanes is a promising alternative offering greater convenience than intravenous infusion and more prolonged or continuous schedules for administration. Oral formulations also eliminate the need for SB administration, which is associated with serious toxicities and decreased efficacy of paclitaxel. However, oral bioavailability of paclitaxel is compromised by low absorption and active excretion by the P-glycoprotein efflux pump. Efforts to improve tumor uptake of oral formulations of paclitaxel have focused on concomitant treatment with P-glycoprotein inhibitors.

### 4.3. Tesetaxel (DJ-927)

Tesetaxel (DJ-927) was one of the early oral formulations of paclitaxel that demonstrated anticancer efficacy in phase II trials. However, clinical development and evaluation has been placed on hold due to complications from neutropenia, which have been fatal in some patients. [45,46]

### 4.4. Docetaxel 100 mg with OC144-093

Promising results are available for oral administration of docetaxel in combination with OC144-093, which is a potent inhibitor of P-glycoproteins. A proof of concept study that enrolled 12 patients with solid malignancies randomized patients to 1 course of oral docetaxel 100 mg with OC144-093 500 mg. This was followed by intravenous infusion of docetaxel 100 mg two weeks later. The relative apparent bioavailability of docetaxel via the oral administration route was 26% and was attributed to the effect of OC144-093. Patients experienced mostly grade 1 and 2 adverse events including gastrointestinal symptoms, neutropenia, and neurologic symptoms. Grade 3 anorexia, malaise, anemia, and neutropenia were also reported. Notably, there was a great deal of intrapatient and interpatient pharmacokinetic variability in response to both formulations of docetaxel. [47]

### 4.5. BMS-275183

Evaluation of BMS-275183, an oral formulation of C-4 methyl carbonate analogue of paclitaxel, has been performed in a phase I dose-escalating study by Bröker et al. to assess safety, tolerability, pharmacokinetic profile, and antitumor properties. A total of 48 patients with solid tumors were treated with oral doses of BMS-275183 at an initial dose of 5 mg/m$^2$ followed by either an accelerated dose escalation phase in which the dose was increased 100% at each cycle or standard dose escalation schedule according to a modified Fibonacci scheme. Patients were administered the study drug weekly with one cycle consisting of 4 weeks. The maximum tolerated dose (MTD) was 200 mg/m$^2$ with neuropathy, fatigue, diarrhea, and neutropenia reported as the most frequently occurring dose-limiting toxicities. BMS-275183 was rapidly absorbed with a half-life of 22 hours. Tumor responses were dose dependent and evident in 9 of 38 evaluable patients with non-small cell lung cancer (NSCLC), prostate cancer, and other solid tumors. [48] Of 6 clinical trials listed by the National Institutes of Health, 5 were terminated and 1 was completed. The completed trial evaluated the safety and efficacy of BMS-275183 and pemetrexed for treatment of patients with advanced or metastatic NSCLC who had received previous therapies. [49,50]

### 4.6. Paclitaxel poliglumex

Another alternative to the SB formulation of paclitaxel is paclitaxel poliglumex (PPX), which is a biodegradable, water-soluble polyglutamate polymer with antineoplastic properties. The polyglutamate residue increases water solubility of paclitaxel and enhances tumor exposure to paclitaxel via hyperpermeable vasculature. [51] There are currently 9 phase II and III ongoing clinical trials to evaluate PPX for NSCLC, prostate cancer, ovarian or peritoneal cancer, esophageal cancer, and metastatic colorectal cancer. [52] A phase II trial of PPX plus capecitabine for patients with HER2-negative MBC (NCT00265733) was undertaken to assess tumor response rate and toxicities as well as distributions of DFS times and OS times. However, the trial was discontinued due to the incidence of neurotoxicities and hypersensitivity reactions. [53,54]

### 4.7. Paclitaxel with vitamin E emulsion

A CrEL-free, P-glycoprotein-inhibiting, vitamin E-based emulsion particle formulation of paclitaxel with antineoplastic activity has also been developed. The vitamin E-based emulsion allows bolus infusion without steroid premedication and may reduce risk of hypersensitivity reactions. In addition, the vitamin E-based emulsion formulation may increase penetration of emulsion particles in tumor tissue and inhibit the P-glycoprotein drug efflux pump. [55] Currently, there is 1 ongoing phase II, open-label, nonrandomized trial (NCT00096668) to evaluate the safety and efficacy of paclitaxel with vitamin E emulsion as a first-line treatment for MBC, although this trial is not currently recruiting patients. [56]

## 5. Conclusions

One of the most significant advances in the treatment of BC was the identification of taxanes, which are

considered among the most highly active cytotoxic agents for BC. However, first-generation taxanes are hydrophobic and required synthetic solvents to allow parenteral administration. First-generation taxanes and the solvents required for administration provoked significant adverse events including hypersensitivity reactions, neuropathy, vesicular degeneration, nephrotoxicity, dermatitis, axonal degeneration, demyelination, and fluid retention. Premedication with corticosteroids and histamine receptor ($H_1$ and $H_2$) blockers and support with G-CSF did not entirely prevent these toxicities. More significantly, the solvents required for administration of first-generation taxanes were found to undermine treatment efficacy.

Subsequent research efforts resulted in the development of *nab*-paclitaxel, a biologically interactive, nanometer-sized particle that uses albumin to safely administer higher doses of paclitaxel with shorter infusion times. Albumin-bound drugs prolong exposure by tumor cells to cytotoxic agents via the EPR effect and gp60 receptor–mediated transcytosis. Preclinical studies demonstrated that overall intratumoral concentrations of paclitaxel were 33% greater following *nab*-paclitaxel compared with identical doses of CrEL-paclitaxel resulting in enhanced antitumor responses as measured by tumor doubling times and intervals to tumor recurrence. Phase II and III trials have consistently demonstrated higher RR and longer TTP for *nab*-paclitaxel compared with CrEL-paclitaxel with a more favorable safety profile. Research efforts are ongoing to evaluate other novel formulations for administration of taxanes including oral taxanes, paclitaxel poliglumex, and vitamin E-based paclitaxel emulsion to further enhance efficacy, reduce toxicities, and increase convenience of administration. Clinical evaluation of these new taxane formulations is difficult as risks and benefits may change in either a positive or negative direction. Optimal treatment of BC requires an understanding of the mechanism of action of emerging agents, particularly novel taxane formulations, and tailoring of the treatment regimen to meet the unique needs of each patient.

## Conflicts of interest

Matti S. Aapro, MD, receives grant/research support from and is a consultant and speaker for Abraxis BioScience. Additionally, he receives grant/research support from and is a consultant and speaker for sanofi-aventis. Gunter Von Minckwitz, MD, PhD, receives grant/research support from Bristol Myers-Squibb and sanofi-aventis. This supplement was funded by an educational grant from Abraxis BioScience. Abraxis BioScience performed a scientific accuracy review on this manuscript. The authors were compensated by Imedex®, LLC for their work on this manuscript.

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