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REVIEW

Taxanes for the Treatment of Metastatic Breast Cancer

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Abstract: Taxanes have remained a cornerstone of breast cancer treatment over the past three decades, improving the lives of patients with both early- and late-stage disease. The purpose of this review is to summarize the current role of taxanes, including an albumin-bound formulation that enhances delivery of paclitaxel to tumors, in the management of metastatic breast cancer (MBC). Since the introduction of Cremophor EL-paclitaxel to the clinic in the mid-1990s, a substantial amount of investigation has gone into subjects such as formulation, dose, schedule, and taxane resistance, allowing physicians greater flexibility in treating patients with MBC. This review will also examine how the shrinking pool of taxane-naive patients, a result of the expansion of taxanes into the neoadjuvant and adjuvant settings, will respond to taxane retreatment for metastatic disease. Taxane treatment seems likely to continue to play an important role in the treatment of MBC.

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

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Introduction

Apart from cancers of the skin, breast cancer is the most common cancer among women.[1] Since 1990, mortality rates for breast cancer have steadily declined.[1] However, despite significant improvements in survival, breast cancer remains second to lung cancer as one of the leading causes of cancer-related deaths among women in the United States.[1] It is estimated that 226,870 women will be diagnosed with invasive breast cancer in 2012 and that breast cancer will claim the lives of almost 40,000 women over the year.[1] Most new diagnoses of breast cancer are made at an early stage of disease; however, of those diagnosed with early breast cancer, an estimated 1 in 3 will eventually develop recurrent or metastatic disease.[2] For these women, prognosis remains poor, with median 5-year survival of <25%.[1,3] Moreover, treatment-related toxicities in conjunction with common complications associated with metastatic disease, including bone fractures, liver failure, pneumonia, and respiratory failure, negatively impact the health and quality of life (QOL) of women with metastatic breast cancer (MBC).

MBC remains an incurable disease for the majority of patients. Only a select few with highly chemosensitive tumors will achieve complete response with combination chemotherapy regimens. For the remaining patients, treatment for metastatic disease is strictly palliative and is initiated with the hope of delaying disease progression, alleviating disease symptoms, improving or maintaining QOL, and potentially prolonging survival.[2] Thus, systemic chemotherapies with minimal toxicity are preferred. No single standard of care for MBC exists and treatment plans are largely individualized according to patient- (eg, age, patient preference, and QOL considerations) and tumor-specific factors. Treatment selection for MBC is highly influenced by hormone receptor (HR; composed of estrogen receptor and progesterone receptor) status and human epidermal growth factor receptor 2 (HER2) status of the tumor.[4] Current guidelines recommend systemic chemotherapy for women with HR-negative disease that is not localized to bone or soft tissue and is associated with symptomatic visceral disease or for women with HR-positive disease that has demonstrated resistance to endocrine therapy.[4] Single agents including taxanes, anthracyclines, antimetabolites, and vinca alkaloids or combinations of these agents have demonstrated clinically meaningful benefit in such women with HR-negative MBC. For women with HER2-positive disease, trastuzumab in combination with a taxane, vinorelbine, or capecitabine are the preferred treatment regimens.[4]

Taxane-based regimens are among the most effective and commonly used systemic therapies for breast cancer, particularly in the adjuvant setting. Accordingly, the role of taxanes in the metastatic setting continues to evolve as clinicians seek new strategies to optimize outcomes of their patients. This review describes the evolution of taxane therapy for MBC including the development of the novel delivery platform of nanoparticle albumin-bound (*nab*-) paclitaxel (Abraxane) and the challenges regarding treatment selection in the metastatic setting.

Historical Overview of Taxanes for the Treatment of Breast Cancer

The introduction of taxanes in the mid-1990s marked a significant advance in the treatment of MBC. In clinical trials, these potent antitumor agents provided improved outcomes for patients with both early and advanced disease.[5,6] The antitumor activity of paclitaxel, isolated from extracts from Pacific yew trees (*Taxus brevifolia*), was initially described in the 1960s and subsequently in animal models for melanoma and breast, lung, and colon cancers.[7–9]

Docetaxel, a more potent semisynthetic derivative of paclitaxel, derived from extracts from the needles of the European yew tree (*Taxus baccata*), was subsequently discovered in the 1980s.[10–12] The mechanism of action of both paclitaxel and docetaxel is the inhibition of microtubule dynamics that promote microtubule polymerization and inhibit depolymerization, which results in cell cycle arrest in G_2 and M phase, leading to cell death.[7,10,12,13]

Cremophor EL (CrEL-) paclitaxel (Taxol), initially approved for the treatment of relapsed ovarian cancer, received US Food and Drug Administration (FDA) approval in 1994 for the treatment of patients with MBC who did not respond to anthracycline-based combination chemotherapy or with breast cancer that recurred within 6 months of adjuvant chemotherapy.[7,13–15] Approval was based on a phase III trial of 2 different doses (175 or 135 mg/m^2) of CrEL-paclitaxel given every 3 weeks (q3w) in patients

with MBC who had failed to respond to previous chemotherapy. The higher dose (175 mg/m^2) vs. the lower dose (135 mg/m^2) of CrEL-paclitaxel was associated with a longer median time to disease progression (4.2 vs. 3.0 months, respectively; $P = 0.027$) and a longer median survival time (11.7 vs. 10.5 months, respectively; $P = 0.321$).[16] The approval of CrEL-paclitaxel marked a significant milestone in the management of MBC. In a retrospective analysis of patients with MBC treated over a 20-year period, the introduction of CrEL-paclitaxel in 1994 was associated with a significant improvement in survival. From 1983 to 1994, median overall survival (OS) ranged between 17.2 and 19.2 months. After the introduction of CrEL-paclitaxel into first-line treatment regimens for MBC, median OS increased, ranging between 23.6 and 26.1 months.[17]

Docetaxel (Taxotere) received FDA approval in 1996 for locally advanced or metastatic breast cancer after failure of prior chemotherapy, marking a second important milestone in the treatment of MBC.[10,18] In a phase III trial in patients with MBC whose disease had progressed despite previous anthracycline-containing therapy, single-agent docetaxel 100 mg/m^2 q3w was superior to mitomycin 12 mg/m^2 dose every 6 weeks plus vinblastine 6 mg/m^2 q3w in terms of overall response rate (ORR; 30.0% vs. 11.6%; $P < 0.0001$), time to tumor progression (TTP; 19 vs. 11 weeks; $P = 0.001$), and OS (11.4 vs. 8.7 months; $P = 0.01$).[19] However, grade 3/4 neutropenia occurred in 93% of patients receiving docetaxel.

The promising activity of docetaxel as a single-agent therapy spurred direct comparison of docetaxel and CrEL-paclitaxel in the treatment of MBC. In a phase III randomized trial comparing CrEL-paclitaxel 175 mg/m^2 given by 3-hour infusion q3w and docetaxel 100 mg/m^2 given by 1-hour infusion q3w in patients with MBC whose disease had progressed during or within 12 months of receiving anthracycline-containing chemotherapy, docetaxel was superior to CrEL-paclitaxel in terms of OS (15.4 vs. 12.7 months, respectively; $P = 0.03$) and median TTP (5.7 vs. 3.6 months; $P < 0.0001$).[11] ORR was also higher for docetaxel (32% vs. 25%), but the difference was not statistically significant ($P = 0.10$). Although docetaxel proved to be superior to CrEL-paclitaxel in terms of efficacy, it was associated with more treatment-related toxicities (Tables 1 and 2), including higher rates of grade 3/4 neutropenia (93% vs. 55%), febrile neutropenia (15% vs. 2%), and grade 3/4 peripheral edema (7% vs. 0.5%).

Role of *nab*-Paclitaxel in the Management of MBC

Both CrEL-paclitaxel and docetaxel have demonstrated significant clinical efficacy in MBC; however, both agents are associated with characteristic toxicities, mainly hypersensitivity reactions and peripheral neuropathy at least partially due to their respective solvents—CrEL and polysorbate 80.[10,13,20] Efforts to improve on the tolerability of the solvent-based taxanes using a novel method for drug delivery

Table 1. Efficacy in head-to-head trials of taxanes.

Trial	CrEL-Paclitaxel		Docetaxel		*nab*-Paclitaxel					
	175 mg/m^2 q3w		100 mg/m^2 q3w		260–300 mg/m^2 q3w		100 mg/m^2 qw 3/4		150 mg/m^2 qw 3/4	
	n	%	n	%	n	%	n	%	n	%
ORR										
Jones et al[11]	224	25	225	32	–	–	–	–	–	–
Gradishar et al[22]	225	19	–	–	229	33	–	–	–	–
Gradishar et al[47]	–	–	74	39	76	46	76	63	74	74
	n	**OS**	**n**	**OS**	**n**	**OS**	**n**	**OS**	**n**	**OS**
Median OS, months										
Jones et al[11]	224	15.4	225	12.7	–	–	–	–	–	–
Gradishar et al[22]	225	13.9	–	–	229	16.3	–	–	–	–
Gradishar et al[48]	–	–	74	26.6	76	27.7	76	22.2	74	33.8

Abbreviations: CrEL, Cremophor EL; ORR, overall response rate; OS, overall survival.

Table 2. Safety in head-to-head trials of taxanes (grade 3/4 adverse events).

Trial	CrEL-Paclitaxel		Docetaxel		*nab*-Paclitaxel					
	175 mg/m² q3w		100 mg/m² q3w		260–300 mg/m² q3w		100 mg/m² qw 3/4		150 mg/m² qw 3/4	
	n	%	n	%	n	%	n	%	n	%
Sensory neuropathy										
Jones et al[11]	222	4.1	222	7.2	–	–	–	–	–	–
Gradishar et al[22]	222	2	–	–	226	10	–	–	–	–
Gradishar et al[48]	–	–	74	12	76	21	76	9	74	22
Neutropenia										
Jones et al[11]	222	54.5	222	93.3	–	–	–	–	–	–
Gradishar et al[22]	222	46	–	–	226	31	–	–	–	–
Gradishar et al[47]	–	–	74	92	76	43	76	25	74	45

led to the development of *nab*-paclitaxel (Abraxane), a combination of albumin and paclitaxel that forms particles of a mean 130 nm in diameter.[21] Unlike previous taxanes, the *nab*-paclitaxel formulation is solvent free and employs a novel delivery mechanism for paclitaxel to tumors.[21] *nab*-paclitaxel, the only solvent-free taxane indicated for the treatment of MBC, does not require premedication to prevent solvent-related hypersensitivity reactions.[21] Although *nab*-paclitaxel was initially designed to minimize the toxic effects of taxane treatment and improve tolerability, it became evident that this formulation of paclitaxel was also more effective compared with standard CrEL-paclitaxel for the treatment of MBC.[22]

nab-paclitaxel received FDA approval in 2005 for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy (prior therapy should have included an anthracycline unless clinically contraindicated).[21] This approval was based on the findings of a randomized phase III pivotal trial involving women with MBC randomly assigned to receive *nab*-paclitaxel 260 mg/m² over a 30-minute infusion q3w (n = 229) or CrEL-paclitaxel 175 mg/m² over a 3-hour infusion q3w (n = 225) with corticosteroid or antihistamine premedication.[22] Treatment with *nab*-paclitaxel led to a significantly higher ORR compared with CrEL-paclitaxel based on the intent-to-treat (ITT) population (33% vs. 19%, respectively; $P = 0.001$).

The ORR was also significantly higher in patients who received *nab*-paclitaxel as first-line therapy (42% vs. 27%; $P = 0.029$) or second-line or greater therapy (27% vs. 13%; $P = 0.006$). Patients who received *nab*-paclitaxel had a 25% lower risk of progression compared with those receiving CrEL-paclitaxel (hazard ratio, 0.75; $P = 0.006$). The incidence of grade 4 neutropenia was significantly lower with *nab*-paclitaxel treatment: 9% vs. 22% with CrEL ($P < 0.001$). A higher incidence of grade 3 sensory neuropathy was associated with *nab*-paclitaxel treatment (10% vs. 2% with CrEL-paclitaxel; $P < 0.001$); however, it improved to grade ≤ 2 in a median of 22 days. Although treatment with *nab*-paclitaxel only demonstrated a modest, nonsignificant trend toward improved OS in the ITT population (65 vs. 56 weeks with CrEL-paclitaxel; $P = 0.374$), the difference in OS was statistically significant in patients who received *nab*-paclitaxel as second-line or greater therapy (56.4 vs. 46.7 weeks with CrEL-paclitaxel; $P = 0.024$). This was the first trial to demonstrate improved efficacy and a promising safety profile with a paclitaxel formulation that uses the inherent properties of albumin to deliver a drug to tumors and that overcomes the limitations of CrEL-paclitaxel, which requires premedication, longer infusion, and dose modifications.

The proposed mechanism of drug delivery of *nab*-paclitaxel to tumors involves the binding of albumin to receptors on endothelial cells and active transcytosis of the albumin-bound drug through endothelial cells and into the subendothelial space.[23,24] Desai et al[24] showed that the *nab*-paclitaxel formulation allows for higher transport across endothelial cells compared with CrEL-paclitaxel. Another proposed mechanism of drug delivery of *nab*-paclitaxel to tumors centers on around increased vascularization

and tumor-specific leakiness of blood vessels.[25–28] It is believed that once localized in the tumor microenvironment, extracellular matrix albumin-binding proteins, such as secreted protein acidic and rich in cysteine (SPARC), draw albumin-bound paclitaxel to tumor cells, thus enriching tumor uptake of the drug.[25] Indeed, tumors are known to take up large quantities of albumin for energy.[28,29] In fact, when paclitaxel was administered as *nab*-paclitaxel to mice bearing human breast tumor xenografts, paclitaxel accumulated 33% more efficiently than paclitaxel given as CrEL-paclitaxel at equal doses (20 mg/kg).[24]

SPARC is overexpressed in many tumors, especially in cells associated with the tumor stroma and vasculature, and may play a role in cancer progression and metastasis.[30] SPARC appears to be more highly expressed in breast tumors relative to normal tissue,[31] and Jones et al[32] found that high levels of SPARC transcription in tumor samples were significantly associated with a shorter OS of patients with breast cancer. More recently, it has been shown that SPARC expression positively correlates with treatment response to *nab*-paclitaxel in some tumor types, including breast, head and neck, and pancreas.[25,33–35] Future studies are looking to further investigate and validate SPARC as a biomarker for response to *nab*-paclitaxel. In addition, a number of molecular signaling pathways will also be explored for their potential contribution to the activity of *nab*-paclitaxel.

Optimizing Taxane Therapy

Combination therapies with taxanes

A number of combination therapies have been studied for the treatment of MBC, and several taxane combinations are highlighted by the National Comprehensive Cancer Network (NCCN) as preferred regimens, including doxorubicin with docetaxel or CrEL-paclitaxel, capecitabine with docetaxel, and gemcitabine with CrEL-paclitaxel.[4] The NCCN guidelines go on to state that although combination chemotherapy often produces higher response rates and longer disease-free intervals in comparison with single agents, these regimens are associated with increased toxicity and do not lead to significant improvements in OS. Administering single agents sequentially reduces the likelihood for dose reductions. Thus, the NCCN panel states that there is "little compelling evidence that combination chemotherapy is superior to sequential single agents."[4]

Schedule: CrEL-paclitaxel and docetaxel

Single-agent CrEL-paclitaxel administered q3w[36,37] or weekly[38] is active as initial or subsequent therapy for MBC. Similarly, docetaxel is active in anthracycline-resistant and/or pretreated patients with MBC when administered q3w or weekly.[39–41] A phase III study showed efficacy benefits of a weekly (n = 346) vs. q3w (n = 383) schedule of CrEL-paclitaxel in terms of ORR (42% vs. 29%, respectively; $P = 0.0004$), TTP (9 vs. 5 months; $P < .0001$), and OS (24 vs. 12 months; $P = 0.009$) (Table 1).[42] However, grade 3 sensory neuropathy was more common with the weekly schedule (24% vs. 12%; $P = 0.0003$).

Docetaxel, on the other hand, may exhibit greater clinical efficacy on a q3w schedule for patients with MBC (Table 3). A phase III study comparing a q3w schedule vs. a first-3-of-4-weeks (qw 3/4) schedule (n = 59 for each) for docetaxel demonstrated a higher ORR (35.6% vs. 20.3%, respectively) and similar progression-free survival (PFS; 5.7 vs. 5.5 months; $P = 0.46$) and OS (18.3 vs. 18.6 months; $P = 0.34$) but higher rates of grade 3/4 toxicities (88.1% vs. 55.9%; $P = 0.0001$) for the q3w schedule.[43] A recent meta-analysis of 11 randomized controlled trials comparing q3w vs. weekly taxane regimens in advanced breast cancer found that ORR was better on a q3w schedule for CrEL-paclitaxel, whereas OS was longer in patients on weekly schedules.[44] No difference was found for PFS. For docetaxel, no differences were found between schedules in terms of ORR, PFS, and OS. Weekly taxane schedules were associated with a lower incidence of serious adverse events, neutropenia, febrile neutropenia, and peripheral neuropathy. Based on this meta-analysis, the authors recommended a weekly schedule for taxane treatment of advanced breast cancer.

Schedule: *nab*-paclitaxel

Early dosing regimens of *nab*-paclitaxel for MBC began at 260 mg/m^2 q3w based on positive findings from a phase I study, pharmacokinetic study, and the registration phase III trial vs. CrEL-paclitaxel.[22,45] However, other investigations provided the rationale

Table 3. Dose optimization for the taxanes: efficacy.

Trial	CrEL-Paclitaxel				Docetaxel				*nab*-Paclitaxel					
	175 mg/m² q3w		80 mg/m² weekly		75 mg/m² q3w		35 mg/m² qw 3/4		300 mg/m² q3w		100 mg/m² qw 3/4		150 mg/m² qw 3/4	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
ORR														
Seidman et al[42]	383	29	346	42	–	–	–	–	–	–	–	–	–	–
Rivera et al[43]	–	–	–	–	59	35.6	59	20.3	–	–	–	–	–	–
Gradishar et al[47]	–	–	–	–	–	–	–	–	76	46	76	63	74	74
	n	OS	n	OS	n	OS	n	OS	n	OS	n	OS	n	OS
Overall survival in months, median														
Seidman et al[42]	383	12	346	24	–	–	–	–	–	–	–	–	–	–
Rivera et al[43]	–	–	–	–	59	18.3	59	18.6	–	–	–	–	–	–
Gradishar et al[48]	–	–	–	–	–	–	–	–	76	27.7	76	22.2	74	33.8

to test dosing on a weekly schedule. Nyman et al[46] reported promising results from a phase I and pharmacokinetic study on a qw 3/4 schedule. Indeed, that trial demonstrated a linear increase in maximal systemic drug concentration and systemic drug exposure (area under the curve) over a dosing range of 80 to 200 mg/m^2 of *nab*-paclitaxel in patients with solid tumors. Furthermore, 5 patients in that study who previously had been treated with CrEL-paclitaxel achieved clinical responses.

The influence of schedule on clinical outcomes in patients receiving taxanes and the feasibility of dosing *nab*-paclitaxel on both q3w and qw 3/4 schedules suggested a need to examine prospectively the effect of different dosing schedules of *nab*-paclitaxel in patients with MBC. Therefore, a randomized phase II trial was designed to test clinical outcomes in patients receiving *nab*-paclitaxel at 2 different qw 3/4 schedules (100 and 150 mg/m^2) against a q3w schedule (at 300 mg/m^2). A fourth arm consisting of docetaxel 100 mg/m^2 q3w allowed for direct comparisons of the different *nab*-paclitaxel regimens against each other and against docetaxel (Tables 1–3).[47] In this trial of first-line treatment for patients, the *nab*-paclitaxel 150 mg/m^2 arm demonstrated the highest investigator-assessed ORR (74% vs. 46% in the *nab*-paclitaxel 300 mg/m^2 q3w arm, 63% in the *nab*-paclitaxel 100 mg/m^2 qw 3/4, and 39% in the docetaxel 100 mg/m^2 q3w arm; overall P for all 4 arms < 0.001) and the longest median PFS (14.6 vs. 10.9, 7.5, and 7.8 months; overall $P = 0.008$) and OS (33.8 vs. 27.7, 22.2, and 26.6 months; overall $P = 0.047$).[47,48] Patients receiving *nab*-paclitaxel 150 mg/m^2 qw 3/4 also experienced the highest rate of sensory neuropathy (22% vs. 21% in the *nab*-paclitaxel 300 mg/m^2 q3w arm, 9% in the *nab*-paclitaxel 100 mg/m^2 qw 3/4, and 12% in the docetaxel 100 mg/m^2 q3w arm) and of dose reductions due to adverse events (47% vs. 20%, 18%, and 30%, respectively; overall $P < 0.001$); however, dose reductions effectively managed toxicities as evidenced by the patients in this arm receiving the longest median duration of treatment (38 vs. 22, 30, and 21 weeks, respectively; overall P for all 4 arms < 0.001).[48] Taken together, the results of this trial suggested that qw 3/4 dosing of *nab*-paclitaxel may be superior to q3w dosing in terms of clinical efficacy.

Breast Cancer Subtypes

Histologic subtypes

In the era of personalized medicine, it is prudent to consider how taxanes are used to treat different subtypes of breast cancer. Histological subtypes of breast cancer are defined by tumor expression of estrogen receptor (ER), progesterone receptor (PR), and HER2.[4] Physicians now have the ability to tailor treatment based on the expression of these molecules. Guidelines defined by the NCCN recommend that patients with ER/PR+ metastatic disease receive first-line endocrine therapy.[4] On the other hand, patients whose tumors are negative for hormone receptor expression should consider chemotherapy. Among the options for ER/PR– disease are single-agent therapy or combination therapy. CrEL-paclitaxel, docetaxel, and *nab*-paclitaxel are all among the preferred single-agent regimens for MBC. For patients with ER/PR–, HER2+ disease, the guidelines recommend a trastuzumab-containing regimen. As for taxanes, current guidelines suggest trastuzumab plus docetaxel or trastuzumab plus CrEL-paclitaxel with or without carboplatin as combination regimens for ER/PR–, HER2+ disease. Preliminary investigation into the combination of *nab*-paclitaxel plus trastuzumab for HER2+ disease in the first-line setting has revealed promising activity, with an ORR of 52% in 21 patients in a phase II trial.[49]

BRCA1 and BRCA2

The breast cancer genes 1 and 2 (BRCA1 and BRCA2) are known to play important roles in DNA repair,[50,51] and mutation of these genes is known to associate with breast cancer.[52] The utility of taxane treatment for patients with mutations in BRCA1 and BRCA2 vs. patients with "sporadic" breast cancer has been examined in the metastatic setting.[53] In this trial, the majority of patients received docetaxel (83%), and the most treatment took place in either the second- or third-line setting (84%). Interestingly, it appeared that patients with BRCA1 mutations demonstrated lower response rates (23% vs. 38%, $P < 0.001$) and a shorter median PFS (2.2 vs. 4.9 months, $P = 0.004$) vs. patients without BRCA1 mutations. However, patients with BRCA1 mutations and HER2+ disease (n = 11) had similar ORR (36% and 38%, respectively, $P = 0.83$) and median PFS (5.7 months for both, $P = 0.26$) vs. patients with sporadic HER2+ disease. Unfortunately, the study only included 13 patients with BRCA2 mutation, making such comparisons somewhat less robust. However, among BRCA2 mutation carriers, 10 of 13 demonstrated an objective response (ORR = 84%), suggesting that the decrement in sensitivity of BRCA1 mutation carriers to taxane therapy may not apply to BRCA2 mutation carriers. In vitro experiments suggest that BRCA1 may actually be required for sensitivity to CrEL-paclitaxel, supporting the idea that patients with defective BRCA1 may suffer limited benefit from CrEL-paclitaxel therapy.[54,55]

Genetic Markers for Taxane Treatment

Genetic markers that predict response, resistance, or toxicity are a promising avenue by which to identify patients most appropriate for treatment with taxanes. Several studies have focused on identifying mechanisms that underlie resistance to taxane treatment. Mutations in or differential expression of β-tubulin and the multidrug resistance 1 (*MDR1*) gene have been identified as molecular events that may correlate with response to taxanes.[56–58] Because taxanes act through their interactions with microtubules,[10,13] changes in tubulin subunits or microtubule-binding proteins may influence taxane activity. Overexpression of MDR1, a membrane-bound drug efflux pump, may lower the intracellular concentration of anticancer drugs, such as the taxanes.[58,59] In addition to markers of response, a number of genetic markers have been identified as predictors of sensory neuropathy in response to taxane treatment, including alterations of *MDR1* and single nucleotide polymorphisms in the genes RWD domain containing 3 (*RWDD3*) and tectorin alpha (*TECTA*).[60,61] As more markers of response and toxicity become available, oncologists will have greater ability to personalize care for MBC.

CrEL-Paclitaxel and Docetaxel in Early Breast Cancer

The management of breast cancer continues to evolve with the introduction of new, more effective agents and the expanding role of taxanes in early breast cancer treatment.[6] In 1999, CrEL-paclitaxel administered sequentially with standard doxorubicin-containing combination therapy was approved as adjuvant treatment for patients with node-positive breast cancer.[13,14] Subsequently in 2004, a similar

indication was added for docetaxel in the adjuvant setting with an approval in combination with doxorubicin and cyclophosphamide for patients with node-positive resectable breast cancer.[10,18] A Cochrane meta-analysis reported a positive benefit in a combined analysis of both taxanes in the adjuvant treatment of breast cancer in terms of OS (hazard ratio, 0.81; 95% CI, 0.75–0.88; $P < 0.00001$) and disease-free survival (hazard ratio, 0.81; 95% CI, 0.77–0.86; $P < 0.00001$).[62] More recently, the Early Breast Cancer Trials' Collaborative Group reported similar findings in a large meta-analysis. Analysis of data from 44,000 women treated in 33 trials of taxanes given either in combination or sequentially with anthracycline-based regimens vs. anthracycline-based regimens alone revealed a significant reduction in breast cancer mortality with adjuvant taxane- or anthracycline-based regimens (mortality rate ratio, 0.87; $P < 0.00001$).[63]

One of the first trials to demonstrate the benefit of a taxane in the neoadjuvant setting was a trial of 162 women with locally advanced breast cancer who were treated with doxorubicin/cyclophosphamide plus vincristine and prednisolone as induction chemotherapy.[64] Patients who responded to induction therapy were then randomized to continue the induction chemotherapy regimen or switch to docetaxel. Responding patients who switched to docetaxel achieved a significantly higher pathologic complete response compared with those who did not (34% vs. 16%; $P = 0.04$). Furthermore, 55% of nonresponders to induction therapy who were sequentially administered docetaxel went on to achieve a clinical response (partial or complete).[64] Clearly, taxanes have made a significant impact on the treatment of early breast cancer and are now among the preferred agents in adjuvant and neoadjuvant treatment regimens.[4]

Impact of Early Taxane Use on Decision Making by Physicians for Treating MBC

Treatments for taxane- or anthracycline-treated MBC

Resistance to chemotherapy accounts for >90% of treatment failures in patients with metastatic cancer.[65,66] As a result, treatment options have become limited for these patients with MBC and prior exposure to chemotherapy. Until recently, capecitabine was the only approved agent for the treatment of patients with anthracycline- or taxane-resistant MBC.[67,68] Numerous trials have shown response rates of 15% to 40% in patients receiving capecitabine after exhibiting resistance to anthracycline- or taxane-based therapy. In these trials, the median TTPs were 3 to 6 months.[69–72] Recently, two additional agents were approved by the FDA for the treatment of anthracycline- or taxane-resistant MBC: ixabepilone with or without capecitabine and eribulin mesylate.[68,73,74] Other drugs used in this setting include *nab*-paclitaxel, vinorelbine, gemcitabine, pemetrexed, carboplatin, cisplatin, pegylated liposomal doxorubicin, etoposide, and irinotecan.[68]

Retreatment with taxanes

More patients with breast cancer are receiving anthracycline- or taxane-containing regimens in the adjuvant setting, which has resulted in a higher number of patients with resistant or refractory disease in the metastatic setting.[49,64,66] Several studies have looked at retreatment with a taxane for metastatic disease after failure of prior taxane therapy. In two small retrospective studies, patients had received CrEL-patients had received prior CrEL-paclitaxel or docetaxel, respectively.[75,76] In both studies, partial cross-resistance between CrEL-paclitaxel and docetaxel was observed. Retreatment of 24 patients with docetaxel 75 mg/m^2 q3w after failure of CrEL-paclitaxel treatment led to an ORR of 25%.[75] A similar ORR of 32% was observed in 44 patients retreated with CrEL-paclitaxel 80 mg/m^2 weekly after prior exposure to docetaxel (42 patients had also received prior anthracycline therapy).[76] Response lasted a median of 6 months, and median TTP was 5 months. Among the 14 responders to taxane retreatment with CrEL-paclitaxel, half had documented primary resistance to docetaxel therapy, which was defined as disease progression during docetaxel treatment or within 12 months of completing docetaxel treatment. In this trial, the most common grade 3/4 adverse events were neutropenia (27%), leukopenia (25%), and sensory neuropathy (14%).

Prospective studies of taxane retreatment documented similar findings. In a phase II trial of CrEL-paclitaxel 80 mg/m^2 given weekly to previously treated patients with MBC (n = 212), 25% (54 patients) had received prior taxane therapy (38 CrEL-pacli-

taxel, 15 docetaxel, and 1 patient had received both).[38] Prior taxane therapy was primarily given in the metastatic setting (49 patients), whereas 5 patients had received adjuvant CrEL-paclitaxel. The median duration from prior taxane therapy to retreatment with CrEL-paclitaxel was 83 days, and 28 patients had previously been exposed to a taxane within 3 months of retreatment. Among the 45 evaluable patients who had received prior taxane therapy, 7 patients (15.6%) had a response to CrEL-paclitaxel retreatment. In a separate phase II trial, retreatment of CrEL-paclitaxel–resistant patients with MBC (n = 44 evaluable patients) with docetaxel 100 mg/m^2 q3w led to an ORR of 18.1% (1 complete and 7 partial).[77] Duration of response lasted 29 weeks, and median TTP was 10 weeks. An interesting finding from this study was that it appeared that the length of CrEL-paclitaxel infusion correlated with the response to retreatment with docetaxel. None of the 12 patients who received CrEL-paclitaxel over a 24-hour infusion responded to retreatment with docetaxel, whereas 25% of the 32 patients receiving short infusions of CrEL-paclitaxel (1- or 3-hour infusion) achieved an objective response. The most common severe adverse events were febrile neutropenia (24%), asthenia (22%), and infection (13%). Grade 3 sensory neuropathy occurred in 7% of patients. Taken together, the results from these trials demonstrate that 20% to 30% of patients who failed a prior taxane-containing regimen may still be able to achieve a response with taxane retreatment.

Many of the studies described above defined patients with prior exposure to a taxane in the metastatic setting and not exclusively the neoadjuvant or adjuvant setting. A recent study out of Germany called the Taxane Re-Challenge Cohort Study retrospectively identified 381 patients with recurrent disease who were treated in the neoadjuvant or adjuvant setting with a taxane-based regimen.[78] Data were collected on their subsequent treatment. A total of 106 patients (27.8%) were retreated with a taxane-containing regimen as first-line or later-line therapy for recurrent disease. A response rate of 48.6% was observed for 74 patients who received first-line taxane-based therapy for recurrent disease; 27% had complete response. The ORR for later-line therapy was 28.2%. Response to taxane retreatment was dependent on the disease-free interval. If patients had disease recurrence within 1 year, response rates were 34.8%; 1 to 2 years, 42.9%; and >2 years, 63.3% ($P = 0.04$).

Physicians must base the decision to treat patients with taxane-refractory disease by rechallenge with a taxane vs. a switch to a different agent on a number of factors. If taxane rechallenge is desirable, the oncologist must consider the dosing schedule of previous taxane regimens. Another important consideration is the length of time that has passed from the completion of previous taxane therapy (adjuvant or metastatic). Patients with disease recurrence several years after taxane therapy can receive taxane therapy again. For treatment very soon after the failure of a taxane, a different regimen, such as single-agent capecitabine, eribulin mesylate, or ixabepilone, may be considered.[4,66] Additionally, the combination of ixabepilone plus capecitabine demonstrated a longer PFS vs. capecitabine alone in women with MBC that had progressed during anthracycline and taxane treatment (5.8 vs. 4.2 months; hazard ratio = 0.75; $P < 0.001$).[79] Drug rechallenge with a taxane is also limited by the possibility of cumulative toxicities or exacerbation of chronic toxicities including neuropathy (common to CrEL-paclitaxel), edema (common to docetaxel), and neutropenia (common to both taxanes).[10,13,20] Patients with known sensitivities to these conditions in response to taxane treatment should consider other agents with non-overlapping toxicity profiles. Sensory neuropathy is of particular concern because some cases are irreversible.[80]

nab-Paclitaxel for taxane-exposed patients

Taxane formulation may also play a key role in determining whether previously taxane-exposed patients will respond to taxane rechallenge. Specifically, there is evidence that patients who have previously received solvent-based taxanes may benefit from treatment with *nab*-paclitaxel. As discussed earlier, a phase I trial of qw 3/4 *nab*-paclitaxel over a range of doses in such patients revealed antitumor activity in the form of clinical responses in 5 of 12 patients who previously had received CrEL-paclitaxel.[46] Blum et al[81] reported findings of a phase II trial in which *nab*-paclitaxel was administered qw 3/4 at 100 or 125 mg/m^2 to patients (N = 181) with MBC that had progressed during taxane therapy or had relapsed within 12 months of adjuvant taxane therapy. Most

of the patients had been treated with a taxane in the metastatic setting (88%–89%), and the median number of previous chemotherapy regimens for metastatic disease among these patients was out of instances <10. Clinical responses were observed in 14% and 16% of the patients in the 100 and 125 mg/m^2 arms, respectively. Median OS values were 9.2 and 9.1 months in these heavily pretreated patients. Grade 4 adverse events were rare in this trial, and the most common grade 3 adverse events observed were leukopenia, neutropenia, and sensory neuropathy. The results of this study suggested that *nab*-paclitaxel may provide a clinical benefit in patients with MBC who are refractory to treatment with other taxanes.

The response rates in taxane-exposed patients in the Blum et al study described above agree with those of a study presented at the annual meeting of the American Society of Clinical Oncology in 2011 on the repeat use of taxanes for MBC.[82] That study reported a response rate of 14.7% in patients (n = 34) receiving *nab*-paclitaxel after having received a different taxane for the treatment of metastatic disease. Additionally, responses were observed in 2 of 6 patients (33%) who were rechallenged with *nab*-paclitaxel after having received it earlier for MBC. By contrast, among the 14 patients rechallenged with docetaxel, no patients achieved a clinical response. Although it must be noted that the number of patients analyzed in this study was small, these data are consistent with the idea that *nab*-paclitaxel is a reasonable option for patients with MBC whose disease has progressed during treatment with taxanes.

Although the studies above describe clinical outcomes in patients who had received taxanes as a previous course of therapy for MBC, it is also important to establish the role of *nab*-paclitaxel among patients whose metastatic disease had progressed during treatment with other chemotherapeutic regimens. The registration phase III trial upon which approval of *nab*-paclitaxel was based included patients who had received previous chemotherapy in the metastatic setting (n = 132 of 229 [58%] for *nab*-paclitaxel and n = 136 of 225 [60%] for CrEL-paclitaxel).[22] Among these patients, ORR (27% vs. 13%; $P = 0.006$), TTP (20.9 vs. 16.1 weeks; $P = 0.02$), and OS (56.4 vs. 46.7 weeks; $P = 0.024$) all favored *nab*-paclitaxel over CrEL-paclitaxel. More specifically, 50% and 58% of patients had received anthracycline-based chemotherapy for metastatic disease in the *nab*-paclitaxel and CrEL-paclitaxel arms, respectively. ORRs in this patient population (27% for *nab*-paclitaxel vs. 14% for CrEL-paclitaxel; $P = 0.01$) were similar to those of the more general population described above. These results demonstrated greater clinical activity for *nab*-paclitaxel vs. CrEL-paclitaxel among patients who had previously received chemotherapy, particularly anthracycline-based regimens, for the treatment of MBC.

Conclusions

As discussed throughout this review, the taxanes remain a key component of MBC treatment. Data presented here demonstrate the gains in efficacy that have been seen with the evolution of taxane treatment from the development of CrEL-paclitaxel beginning in the 1960s through the ongoing investigation of *nab*-paclitaxel, which has demonstrated median OS values as high as 33.8 months in a phase II trial.[48] Although optimization of the schedule and formulation of taxanes have led to such promising OS values in the first-line setting, therapy for MBC must also evolve to account for the growing number of patients who have been exposed to taxanes in earlier lines of therapy. Indeed, taxanes are among the agents recommended for both the adjuvant and neoadjuvant treatment of early-stage breast cancer.[4,10,13] *nab*-Paclitaxel is also being investigated in various regimens in these settings.[83–86] Therefore, an understanding of how past exposure to taxanes influences the decision to rechallenge with a taxane or switch to a different agent are of growing importance.

Resistance to taxane treatment has spurred investigation of numerous combination therapies. Although many taxane-containing combination therapies are recognized as possessing benefits in terms of response rates and PFS, NCCN guidelines point to the lack of OS benefit and increased toxicities that combination therapies have demonstrated as disadvantages to combination therapy.[4] However, sequential systemic therapies do not appear to suffer from these same drawbacks.

The development of *nab*-paclitaxel has provided oncologists with a novel taxane formulation that has shown efficacy benefits relative to CrEL-paclitaxel and docetaxel in ORR, OS, and PFS in patients with MBC. In addition to enhanced efficacy in some patients, the use of albumin in place of chemical

solvents to deliver paclitaxel to the tumor allows patients to avoid pretreatment with corticosteroids and antihistamines and to benefit from a shorter infusion time of 30 minutes. Furthermore, despite a higher dose of paclitaxel, the safety profile of *nab*-paclitaxel compares favorably with that of CrEL-paclitaxel.[22] Although grade 3 sensory neuropathy has occurred more frequently among patients receiving *nab*-paclitaxel vs. those receiving docetaxel or CrEL-paclitaxel in head-to-head trials, the time to improvement to a lesser grade is substantially shorter for *nab*-paclitaxel, perhaps reflecting the absence of the chemical solvents used to suspend docetaxel and paclitaxel.[22,47,48] Finally, a phase II study in patients with MBC who previously had been treated heavily with CrEL-paclitaxel and docetaxel showed promising efficacy in response to *nab*-paclitaxel.[81] Thus, *nab*-paclitaxel may prove to be a valuable treatment option for patients with MBC both in the first-line setting and among patients who have already shown resistance to treatment with previous taxanes.

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Author Contributions

Conceived and designed the experiments: WJG. Analysed the data: WJG. Wrote the first draft of the manuscript: WJG. Contributed to the writing of the manuscript: WJG. Agree with manuscript results and conclusions: WJG. Jointly developed the structure and arguments for the paper: WJG. Made critical revisions and approved final version: WJG. The author reviewed and approved of the final manuscript.

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References

1. Cancer facts and figures 2012. American Cancer Society Web site. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf. Updated 2012. Accessed Mar 6, 2012.
2. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. *Oncologist*. 2005;10 Suppl 3:20–9.
3. Giordano SH, Buzdar AU, Smith TL, Kau SW, Yang Y, Hortobagyi GN. Is breast cancer survival improving? *Cancer*. 2004;100(1):44–52.
4. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. *Breast Cancer*. version 2.2012.
5. Ghersi D, Wilcken N, Simes RJ. A systematic review of taxane-containing regimens for metastatic breast cancer. *Br J Cancer*. 2005;93(3):293–301.
6. Nowak AK, Wilcken NR, Stockler MR, Hamilton A, Ghersi D. Systematic review of taxane-containing versus non-taxane-containing regimens for adjuvant and neoadjuvant treatment of early breast cancer. *Lancet Oncol*. 2004;5(6):372–80.
7. Rowinsky EK, Donehower RC. Paclitaxel (taxol). *N Engl J Med*. 1995;332(15):1004–14.
8. Wani MC, Taylor HL, Wall ME, Coggon P, McPhail AT. Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from taxus brevifolia. *J Am Chem Soc*. 1971;93(9):2325–7.
9. National Cancer Institute. Success story: Taxol (NCS125973). http://dtp.nci.nih.gov/timeline/flash/success_stories/S2_taxol.htm. Accessed Jan 6, 2012.
10. *Taxotere (docetaxel)* [package insert]. Bridgewater, NJ: Sanofi-Aventis US. LLC; 2010.
11. Jones SE, Erban J, Overmoyer B, et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol*. 2005;23(24):5542–51.
12. Ringel I, Horwitz SB. Studies with RP 56976 (taxotere): A semisynthetic analogue of taxol. *J Natl Cancer Inst*. 1991;83(4):288–91.
13. *Taxol (paclitaxel)* [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2010.
14. US Food and Drug Administration. Taxol.Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetail. Accessed Jan 06, 2012.
15. Cortazar P, Justice R, Johnson J, Sridhara R, Keegan P, Pazdur R. US Food and Drug Administration approval overview in metastatic breast cancer. *J Clin Oncol*. 2012;30(14):1705–11.
16. Nabholtz JM, Gelmon K, Bontenbal M, et al. Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. *J Clin Oncol*. 1996;14(6):1858–67.
17. Gennari A, Conte P, Rosso R, Orlandini C, Bruzzi P. Survival of metastatic breast carcinoma patients over a 20-year period: A retrospective analysis based on individual patient data from six consecutive studies. *Cancer*. 2005;104(8):1742–50.

18. Us Food and Drug Administration. taxotere. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Accessed Jan 6, 2012.
19. Nabholtz JM, Senn HJ, Bezwoda WR, et al. Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. 304 study group. *J Clin Oncol*. 1999;17(5):1413–24.
20. ten Tije AJ, Verweij J, Loos WJ, Sparreboom A. Pharmacological effects of formulation vehicles: Implications for cancer chemotherapy. *Clin Pharmacokinet*. 2003;42(7):665–85.
21. Abraxane for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound). Summit, NJ: Celgene Corporation. 2012.
22. Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol*. 2005;23(31):7794–803.
23. John TA, Vogel SM, Tiruppathi C, Malik AB, Minshall RD. Quantitative analysis of albumin uptake and transport in the rat microvessel endothelial monolayer. *Am J Physiol Lung Cell Mol Physiol*. 2003;284(1):L187–96.
24. Desai N, Trieu V, Yao Z, et al. Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. *Clin Cancer Res*. 2006;12(4):1317–24.
25. Desai N, Trieu V, Damascelli B, Soon-Shiong P. SPARC expression correlates with tumor response to albumin-bound paclitaxel in head and neck cancer patients. *Transl Oncol*. 2009;2(2):59–64.
26. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: A review. *J Control Release*. 2000;65(1–2):271–84.
27. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: Mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. *Cancer Res*. 1986;46(12 Pt 1):6387–92.
28. Kratz F. Albumin as a drug carrier: Design of prodrugs, drug conjugates and nanoparticles. *J Control Release*. 2008;132(3):171–83.
29. Stehle G, Sinn H, Wunder A, et al. Plasma protein (albumin) catabolism by the tumor itself—implications for tumor metabolism and the genesis of cachexia. *Crit Rev Oncol Hematol*. 1997;26(2):77–100.
30. Podhajcer OL, Benedetti LG, Girotti MR, Prada F, Salvatierra E, Llera AS. The role of the matricellular protein SPARC in the dynamic interaction between the tumor and the host. *Cancer Metastasis Rev*. 2008;27(4):691–705.
31. Watkins G, Douglas-Jones A, Bryce R, Mansel RE, Jiang WG. Increased levels of SPARC (osteonectin) in human breast cancer tissues and its association with clinical outcomes. *Prostaglandins Leukot Essent Fatty Acids*. 2005;72(4):267–72.
32. Jones C, Mackay A, Grigoriadis A, et al. Expression profiling of purified normal human luminal and myoepithelial breast cells: Identification of novel prognostic markers for breast cancer. *Cancer Res*. 2004;64(9):3037–45.
33. Hamilton EP, Kimmick GG, Desai N, et al. Use of SPARC, EGFR, and VEGFR expression to predict response to nab-paclitaxel (nabP)/carboplatin (C)/bevacizumab (B) chemotherapy in triple-negative metastatic breast cancer (TNMBC). *J Clin Oncol (Meeting Abstracts)*. 2010;28(15s):(Suppl; abstract 1109).
34. Yardley DA, Danie B, Inhorn RC, et al. SPARC microenvironment signature (SMS) analysis of a phase II trial of neoadjuvant gemcitabine (G), epirubicin (E), and nab-paclitaxel (nab-P) in locally advanced breast cancer (LABC). *J Clin Oncol (Meeting Abstracts)*. 2010;28(15s):Abstract 10574.
35. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: A phase I/II trial. *J Clin Oncol*. 2011;29(34):4548–54.
36. Holmes FA, Walters RS, Theriault RL, et al. Phase II trial of taxol, an active drug in the treatment of metastatic breast cancer. *J Natl Cancer Inst*. 1991;83(24):1797–805.
37. Seidman AD, Tiersten A, Hudis C, et al. Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. *J Clin Oncol*. 1995;13(10):2575–81.
38. Perez EA, Vogel CL, Irwin DH, Kirshner JJ, Patel R. Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. *J Clin Oncol*. 2001;19(22):4216–23.
39. Burris HA 3rd. Single-agent docetaxel (taxotere) in randomized phase III trials. *Semin Oncol*. 1999;26(3 Suppl 9):1–6.
40. Burstein HJ, Manola J, Younger J, et al. Docetaxel administered on a weekly basis for metastatic breast cancer. *J Clin Oncol*. 2000;18(6):1212–9.
41. Valero V. Docetaxel as single-agent therapy in metastatic breast cancer: Clinical efficacy. *Semin Oncol*. 1997;24(4 Suppl 13):S13-11–8.
42. Seidman AD, Berry D, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: Final results of cancer and leukemia group B protocol 9840. *J Clin Oncol*. 2008;26(10):1642–9.
43. Rivera E, Mejia JA, Arun BK, et al. Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. *Cancer*. 2008;112(7):1455–61.
44. Mauri D, Kamposioras K, Tsali L, et al. Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: A meta-analysis. *Cancer Treat Rev*. 2010;36(1):69–74.
45. Ibrahim NK, Desai N, Legha S, et al. Phase I and pharmacokinetic study of ABI-007, a cremophor-free, protein-stabilized, nanoparticle formulation of paclitaxel. *Clin Cancer Res*. 2002;8(5):1038–44.
46. Nyman DW, Campbell KJ, Hersh E, et al. Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematologic malignancies. *J Clin Oncol*. 2005;23(31):7785–93.
47. Gradishar WJ, Krasnojon D, Cheporov S, et al. Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. *J Clin Oncol*. 2009;27(22):3611–9.
48. Gradishar WJ, Krasnojon D, Cheporov S, et al. Phase II trial of nab-paclitaxel compared with docetaxel as first-line chemotherapy in patients with metastatic breast cancer: Final analysis of overall survival. *Clin Breast Cancer*. 2012. [Epub ahead of print.]
49. Mirtsching B, Cosgriff T, Harker G, Keaton M, Chidiac T, Min M. A phase II study of weekly nanoparticle albumin-bound paclitaxel with or without trastuzumab in metastatic breast cancer. *Clin Breast Cancer*. 2011;11(2):121–8.
50. Genetics Home Reference. BRCA1. BRCA1 Web site. http://ghr.nlm.nih.gov/gene/BRCA1. Updated 2012. Accessed July 30 2012.
51. Genetics Home Reference. BRCA2. BRCA2 Web site. http://ghr.nlm.nih.gov/gene/BRCA2. Updated 2012. Accessed Jul 30, 2012.
52. American Cancer Society. Breast cancer facts and figures 2011–2. Website of the American Cancer Society Web site. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-030975.pdf. Published 2012. Updated 2012. Accessed Mar 13, 2012.
53. Kriege M, Jager A, Hooning MJ, et al. The efficacy of taxane chemotherapy for metastatic breast cancer in BRCA1 and BRCA2 mutation carriers. *Cancer*. 2012;118(4):899–907.
54. Promkan M, Liu G, Patmasiriwat P, Chakrabarty S. BRCA1 suppresses the expression of survivin and promotes sensitivity to paclitaxel through the calcium sensing receptor (CaSR) in human breast cancer cells. *Cell Calcium*. 2011;49(2):79–88.
55. Chabalier C, Lamare C, Racca C, Privat M, Valette A, Larminat F. BRCA1 downregulation leads to premature inactivation of spindle checkpoint and confers paclitaxel resistance. *Cell Cycle*. 2006;5(9):1001–7.
56. Bernard-Marty C, Treilleux I, Dumontet C, et al. Microtubule-associated parameters as predictive markers of docetaxel activity in advanced breast cancer patients: Results of a pilot study. *Clin Breast Cancer*. 2002;3(5):341–5.
57. Yusuf RZ, Duan Z, Lamendola DE, Penson RT, Seiden MV. Paclitaxel resistance: Molecular mechanisms and pharmacologic manipulation. *Curr Cancer Drug Targets*. 2003;3(1):1–19.
58. Pusztai L. Markers predicting clinical benefit in breast cancer from microtubule-targeting agents. *Ann Oncol*. 2007;18 Suppl 12:xii15–20.

59. Genetics Home Reference. ABCB1. ABCB1 Web site. http://ghr.nlm.nih.gov/gene/ABCB1. Updated 2012. Accessed Jul 30, 2012.
60. Schneider BP, Li L, Miller K, et al. Genetic associations with taxane-induced neuropathy by a genome-wide association study (GWAS) in E5103. *J Clin Oncol (Meeting Abstracts)*. 2011;29:Abstract 1000.
61. Sissung TM, Mross K, Steinberg SM, et al. Association of ABCB1 genotypes with paclitaxel-mediated peripheral neuropathy and neutropenia. *Eur J Cancer*. 2006;42(17):2893–6.
62. Ferguson T, Wilcken N, Vagg R, Ghersi D, Nowak AK. Taxanes for adjuvant treatment of early breast cancer. *Cochrane Database Syst Rev*. 2007;4(4): CD004421.
63. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, et al. Comparisons between different polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet*. 2012;379(9814): 432–44.
64. Smith IC, Heys SD, Hutcheon AW, et al. Neoadjuvant chemotherapy in breast cancer: Significantly enhanced response with docetaxel. *J Clin Oncol*. 2002;20(6):1456–66.
65. Longley DB, Johnston PG. Molecular mechanisms of drug resistance. *J Pathol*. 2005;205(2):275–92.
66. Rivera E. Management of metastatic breast cancer: Monotherapy options for patients resistant to anthracyclines and taxanes. *Am J Clin Oncol*. 2010; 33(2):176–85.
67. *Xeloda (capecitabine) [package insert]*. South San Francisco, CA: Genentech; 2009.
68. Fornier MN. Approved agents for metastatic breast cancer. *Semin Oncol*. 2011;38 Suppl 2:S3–10.
69. Blum JL, Jones SE, Buzdar AU, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol*. 1999;17(2):485–93.
70. Blum JL, Dieras V, Lo Russo PM, et al. Multicenter, phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. *Cancer*. 2001;92(7):1759–68.
71. Reichardt P, Von Minckwitz G, Thuss-Patience PC, et al. Multicenter phase II study of oral capecitabine (Xeloda(")) in patients with metastatic breast cancer relapsing after treatment with a taxane-containing therapy. *Ann Oncol*. 2003;14(8):1227–33.
72. Wist EA, Sommer HH, Ostenstad B, Risberg T, Bremnes Y, Mjaaland I. Oral capecitabine in anthracycline- and taxane-pretreated advanced/metastatic breast cancer. *Acta Oncol*. 2004;43(2):186–9.
73. *Ixempra (ixabepilone)* [package insert]. Princeton, NJ: Bristol-Meyers Squibb; 2011.
74. *Halaven (eribulin mesylate)* [package insert]. Woodcliff Lake, NJ: Eisai Incorporated; 2010.
75. Lin YC, Chang HK, Wang CH, Chen JS, Liaw CC. Single-agent docetaxel in metastatic breast cancer patients pre-treated with anthracyclines and paclitaxel: Partial cross-resistance between paclitaxel and docetaxel. *Anticancer Drugs*. 2000;11(8):617–21.
76. Sawaki M, Ito Y, Hashimoto D, et al. Paclitaxel administered weekly in patients with docetaxel-resistant metastatic breast cancer: A single-center study. *Tumori*. 2004;90(1):36–9.
77. Valero V, Jones SE, Von Hoff DD, et al. A phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer. *J Clin Oncol*. 1998;16(10):3362–8.
78. Guo X, Loibl S, Untch M, et al. Re-challenging taxanes in recurrent breast cancer in patients treated with (neo-)adjuvant taxane-based therapy. *Breast Care (Basel)*. 2011;6(4):279–83.
79. Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. *J Clin Oncol*. 2007;25(33):5210–7.
80. Carlson K, Ocean AJ. Peripheral neuropathy with microtubule-targeting agents: Occurrence and management approach. *Clin Breast Cancer*. 2011; 11(2):73–81.
81. Blum JL, Savin MA, Edelman G, et al. Phase II study of weekly albumin-bound paclitaxel for patients with metastatic breast cancer heavily pretreated with taxanes. *Clin Breast Cancer*. 2007;7(11):850–6.
82. Im A, Brufsky A, Reeder JG, Rosenweig MQ, Jung SY. Repeat use of chemotherapy in metastatic breast cancer. *J Clin Oncol (Meeting Abstracts)*. 2011;29:[abstract 1088].
83. Pippen J, Paul D, Vukelja S, Clawson A, Iglesias J. Dose-dense doxorubicin and cyclophosphamide followed by dose-dense albumin-bound paclitaxel plus bevacizumab is safe as adjuvant therapy in patients with early stage breast cancer. *Breast Cancer Res Treat*. 2011. [Epub ahead of print.]
84. Robert N, Krekow L, Stokoe C, Clawson A, Iglesias J, O'Shaughnessy J. Adjuvant dose-dense doxorubicin plus cyclophosphamide followed by dose-dense nab-paclitaxel is safe in women with early-stage breast cancer: A pilot study. *Breast Cancer Res Treat*. 2011;125(1):115–20.
85. Yardley DA, Raefsky E, Castillo R, et al. Results of a multicenter pilot study of weekly nab paclitaxel, carboplatin with bevacizumab and trastuzumab as neoadjuvant therapy in HER2+ locally advanced breast cancer with SPARC correlatives. *J Clin Oncol (Meeting Abstracts)*. 2009;27(15S):[abstract 527].
86. Yardley D, Burris H 3rd, Peacock N, et al. A pilot study of adjuvant nanoparticle albumin-bound (nab) paclitaxel and cyclophosphamide, with trastuzumab in HER2-positive patients, in the treatment of early-stage breast cancer. *Breast Cancer Res Treat*. 2010;123(2):471–5.