# Use of Cytotoxic Chemotherapy in Metastatic Breast Cancer: Putting Taxanes in Perspective

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## Abstract

Agents that target microtubule (MT) dynamics have been used extensively for the treatment of metastatic breast cancer (MBC). Among these agents are taxanes (solvent-based paclitaxel [sb-paclitaxel], docetaxel, and nab-paclitaxel) and non-taxanes, such as eribulin and ixabepilone. Although these agents have been approved for the treatment of MBC, questions regarding the ideal agent, regimen (single agent vs. combination vs. sequential), and schedule still remain. This systematic review examined pivotal trials for taxanes, eribulin, and ixabepilone as well as first-line taxane trials in MBC. Only randomized trials that enrolled $\geq$ 100 patients were included. Publications on combination regimens with targeted agents were excluded unless they also included a comparison between non-targeted regimens. The studies were grouped into taxane versus taxane, sb-paclitaxel versus non-taxane, and docetaxel versus non-taxane regimens. In taxane versus taxane comparisons, the efficacy of sb-paclitaxel and docetaxel appeared similar, nab-paclitaxel every 3 weeks (q3w) appeared superior to sb-paclitaxel q3w, and weekly nab-paclitaxel appeared superior to docetaxel. In general, taxane regimens demonstrated higher overall response rates (ORRs) versus non-taxane regimens; however, only 2 trials demonstrated longer overall survival (OS) for taxane regimens. Taxanes will likely continue to be used in earlier lines of therapy, whereas eribulin and ixabepilone may be more appropriate for later lines of treatment. Ongoing research may identify biomarkers that could help in selecting the appropriate MT-targeted agent for a given patient.

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## Introduction

Breast cancer (BC) is the most common cancer type among women, with an estimated 234,190 new diagnoses in the United States in 2015.[1-3] It is also the leading cause of cancer mortality among women in Europe and the second leading cause of cancer mortality among women in the United States (only lung cancer has a higher mortality rate).[1,2] Despite the high prevalence and often poor prognosis, survival rates for patients with BC, including those with metastatic disease, have improved, which likely reflects advances in staging and treatment.[1,4,5]

Metastatic breast cancer (MBC) is a heterogeneous disease, and a large number of available and effective recommended therapies make its management complex.[6] The development of targeted therapies has improved survival in subsets of BC (eg, trastuzumab, pertuzumab, and trastuzumab emtansine for patients with human epidermal growth factor receptor 2 [HER2]-overexpressing tumors).[7-10] However, systemic chemotherapy (CT) remains a crucial component of treatment regimens, and chemotherapeutic agents are appropriate for most patients with MBC, including those with hormone receptor–positive ($HR^+$) disease with extensive visceral involvement, $HR^+$ disease after failure of hormone-directed therapy, $HER2^+$ disease (systemic chemotherapeutic agents used in combination with HER2-directed therapy [trastuzumab ± pertuzumab]), and HR-negative ($HR^-$)/$HER2^-$ disease (triple-negative disease).[6] Currently, the National Comprehensive Cancer Network recommends > 30 CT-containing regimens for the treatment of MBC, yet no single standard exists for the treatment of MBC.[6] Selection of chemotherapeutic dose, schedule, and combination partners is often empirical but is driven in part by patient and disease characteristics.

Phase III trials have reported similar survival rates and often decreased toxicities with sequential single agents compared with combination CT.[6,11-13] Thus, sequential single agents are typically recommended over combination CT unless immediate disease

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control for symptomatic visceral disease is needed.[6] In this review, we discuss the role of taxanes and other microtubule (MT)-directed agents, with a focus on first-line MBC treatment.

A number of agents that inhibit MT dynamics have been approved for the treatment of MBC (Table 1). These include taxanes (solvent-based paclitaxel [sb-paclitaxel], docetaxel, and albumin-bound paclitaxel [nab-paclitaxel]), ixabepilone, and eribulin (vinorelbine and other vinca alkaloids have been used extensively but are not approved).[14-18] Taxanes induce cell death by aberrantly stabilizing MTs during mitosis, which disrupts cell division.[17,18] Paclitaxel was originally extracted from the bark of the Pacific yew tree (*Taxus brevifolia*) in the 1960s.[19] Today, paclitaxel and its analogue docetaxel (isolated in 1986) are synthesized from baccatin III, which is found in the needles of the English or European yew tree (*Taxus baccata*).[14,18,20] sb-Paclitaxel is formulated in a 1:1 mixture of polyoxyethylated castor oil (Cremophor EL; recently renamed Kolliphor EL, BASF Corp, Ludwigshafen, Germany) and dehydrated alcohol, whereas docetaxel is formulated in a mixture of polysorbate 80 and ethanol.[14,18] The most recently approved taxane is nab-paclitaxel—an albumin-bound nanoparticle formulation of paclitaxel that can be administered in a saline solution without the need for a solvent.[17,21] Taxanes were first evaluated in phase III MBC trials in the 1990s, and each has demonstrated efficacy for anthracycline-resistant[22-24] or previously untreated MBC.[11,25,26]

**Table 1** Approvals of MT-Directed Therapies for MBC

| Agent | Year of US Approval | Indication for MBC |
|---|---|---|
| **Taxanes** | | |
| Solvent-based paclitaxel[18] | 1994 | MBC after failure of combination chemotherapy for MBC or relapse within 6 mo of adjuvant chemotherapy; previous therapy should have included an anthracycline |
| Docetaxel[14] | 1996 | Locally advanced or metastatic BC after failure of previous chemotherapy |
| nab-Paclitaxel[17] | 2005 | MBC after failure of combination chemotherapy for metastatic disease or relapse within 6 mo of adjuvant chemotherapy; previous therapy should have included an anthracycline unless clinically contraindicated |
| **Non-taxanes** | | |
| Ixabepilone[15] | 2007 | In combination with capecitabine for the treatment of patients with metastatic or locally advanced BC resistant to treatment with an anthracycline and a taxane or patients whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated[a]<br><br>As monotherapy for the treatment of metastatic or locally advanced BC in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine |
| Eribulin[16] | 2010 | MBC previously treated with at least 2 chemotherapeutic regimens for metastatic disease; previous therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting |

Abbreviations: BC = breast cancer; MBC = metastatic breast cancer.
[a]Anthracycline resistance was defined as progression while receiving therapy or within 6 months in the adjuvant setting or 3 months in the metastatic setting. Taxane resistance was defined as progression while receiving therapy or within 12 months in the adjuvant setting or 4 months in the metastatic setting.

In addition to taxanes, ixabepilone and eribulin—which arrest cells in mitosis by inhibiting MT dynamics—have also been approved for MBC treatment.[15,16,27-30] Ixabepilone is an epothilone analogue derived from *Sorangium cellulosum*,[15,27,28] and eribulin is a synthetic analogue of halichondrin B, which is isolated from the marine sponge *Halichondria okadai*.[16] Ixabepilone and eribulin have demonstrated activity in anthracycline- and taxane-treated MBC.[31,32]

The optimal place for taxane and non-taxane MT-directed therapies in the MBC treatment paradigm continues to evolve. To assess the contributions of taxanes and other MT-directed agents (specifically ixabepilone and eribulin) to MBC treatment, a systematic literature search was performed with a focus on first-line therapy for MBC.

## Materials and Methods

We performed a PubMed search to identify first-line trials in MBC (summarized in Figure 1). The search included phase II and phase III trials published between January 1, 2000 and July 1, 2014. The searches were focused on taxanes because ixabepilone and eribulin are not indicated in the first-line setting. Search terms included "metastatic breast cancer" AND "first line" AND (taxane OR paclitaxel OR sb-paclitaxel OR "solvent-based paclitaxel" OR Taxol OR docetaxel OR Taxotere OR nab-paclitaxel OR "albumin-bound paclitaxel" OR abi-007 OR Abraxane). Inclusion of articles was limited to those in English. If the same study was published in various journals or in different years (eg, subanalyses or follow-up studies), only the most recent publication was selected. Only publications on clinical efficacy and safety data were selected (ie, no trials on biomarkers or pharmacokinetics). Trials with targeted agents were not included unless a comparison between cytotoxic regimens was possible (eg, a 3-armed trial with a targeted agent in 1 arm and no targeted agent in 2 arms). For phase II trials, only randomized studies were included. A sample size of at least 100 patients was also required. Finally, the pivotal trials that led to regulatory approval of each MT-directed agent were added to the search results to examine the historical contribution of each drug to MBC treatment.

## Results

The PubMed search produced 187 articles, 25 of which met the search criteria. Reasons for exclusion (n = 162) included the following: single-arm phase II study (83 articles), targeted therapy (50 articles), not focused on primary clinical data (12 articles), enrollment of < 100 patients (11 articles), not a study of MT-directed agents (6 articles), not first-line treatment (5 articles), and not in English (3 articles). Several excluded studies failed to meet > 1 criterion. The pivotal trials for each of the 5 approved MT-directed therapies that were included in the search are summarized in Table 2 (for docetaxel, the regular approval trial is described).

### *How Did Taxanes Compare Against Control Treatments in Pivotal Trials in MBC?*

sb-Paclitaxel has demonstrated activity in the treatment of patients with MBC who previously failed to respond to 1 or 2 chemotherapeutic regimens.[22] In a randomized multicenter phase III study, patients received sb-paclitaxel (175 mg/m$^2$ [n = 235] or 135 mg/m$^2$