Breast cancer is the most frequently diagnosed cancer in American women with the exception of skin cancer. In 2008, an estimated 182,460 new cases of invasive breast cancer will be diagnosed in women in the United States, translating to a 1 in-8 chance (12 percent) of developing invasive breast cancer in the lifetime of an American woman. Despite decreasing rates of breast cancer incidence since the advent of the 21st century, it is estimated that 40,480 women will die of breast cancer in 2008, with breast cancer ranking second only to lung cancer in women’s cancer-related mortality. The majority of breast cancer-related deaths are the result of complications from recurrent or metastatic disease. While metastatic breast cancer (MBC) is rare as an initial presentation, occurring in only about 6 percent of newly diagnosed cases, approximately 30 percent of women initially diagnosed with earlier stages of breast cancer eventually develop recurrent advanced or metastatic disease. The prognosis for patients with metastatic disease tends to be poor, with a 5-year relative survival rate of 20 percent in women with Stage IV breast cancer, compared with 100 percent in women with Stage 0 or I breast cancer. As a result, therapy for metastatic disease is largely palliative in nature.

General Treatment Considerations
No single standard of care exists for patients with MBC, as treatment plans must be individualized based on a myriad of factors. Among the patient-specific considerations that must be factored into treatment decisions are specific tumor biology, disease growth rate, presence of visceral metastases, history of prior therapy and response, risk for toxicity, and patient preference. As mentioned previously, since MBC remains essentially incurable, the goals of therapy include minimizing symptoms and improving quality of life, delaying disease progression, and prolonging overall survival. The initial overall direction of treatment for MBC is essentially very simple: Since MBC is always a disseminated disease, systemic therapy is nearly always necessary. Local treatment is reserved for symptom control purposes only, and radiation and/or surgery are rarely employed alone. The rare exception to this rule lies in the <3 percent of cases where a single lesion is locally isolated in another part of the body, such as the lung, brain, liver, etc.
in selecting primary systemic therapy for MBC, two initial determinations must first be made: 1) whether or not the cancer is hormone-sensitive and 2) whether or not the cancer is human epidermal growth factor receptor 2 (HER2/neu) positive. If the cancer is hormone-sensitive, antientrogen therapies such as tamoxifen or aromatase-inhibitors (e.g., anastrozole [ARIMIDEX], exemestane [AROMASIN], and letrozole [FEMARA]) should be the foundation of treatment. If the cancer is HER2/neu-positive, targeted therapies such as trastuzumab (HERCEPTIN) or lapatinib (TYKERB) should form the base of treatment. In the event that a patient’s cancer is hormone-sensitive and/or HER2/neu-negative, chemotherapy is indicated as the primary course of treatment. Chemotherapy may also be indicated for a patient whose disease has progressed despite anti-estrogen therapy. When selecting the appropriate chemotherapy for MBC in a particular patient, the patient’s prior chemotherapy regimens and her response to those regimens is of utmost importance. Generally, clinicians should select therapies to which the patient is naïve and for which the patient’s disease and MBC is generally recurrent and/or treatment-resistant, potentially indicating failure on previous chemotherapy trials. Of course, the aforementioned targeted therapies may also be used in combination with conventional chemotherapy when proper testing indicates HER2/neu-positive cancer.

Another significant factor that must be taken into consideration when selecting the appropriate chemotherapy is the severity and growth rate of a patient’s disease. Ultimately, clinicians should use the treatment that offers the highest palliative value, while at the same time minimizing toxicity. For example, if the patient is experiencing a relatively low level of pain, with symptoms manageable through the self-administration of over-the-counter non-steroidal anti-inflammatory drugs, chemotherapy with a single agent will likely be an ideal option. In this scenario, a different single-agent chemotherapy agent is administered only after the first single agent fails. Conversely, aggressive treatment with combination chemotherapy regimens may be indicated if the patient’s condition is dire with rapidly progressing disease and/or extreme symptoms. In this latter scenario, the severe side effects that often accompany combination chemotherapy regimens become a justifiable risk considering the need for aggressive treatment.

Chemotherapy Options and the Role of Taxanes
In terms of monotherapy effectiveness, a number of single agents have well established activity in MBC, such as taxanes, anthracyclines, capecitabine (XELODA), gemcitabine (CEMAZAR), and vinorelbine (NABVELINE). While evidence supports the use of these drugs for treatment of MBC, taxanes and anthracyclines are still generally considered to be the most active in single-agent therapy.5 Of these two groups of agents, taxanes, in particular, deserve further consideration due to their role in combination regimens with doxorubicin [ADRIAMYCIN], epirubicin [ELLENCE], and capecitabine.6,7 Furthermore, taxanes serve as ideal agents for recurrent breast cancer when compared with other classes of chemotherapy drugs. As mentioned previously, evidence-based medicine dictates that no one agent should be used twice in patients with recurrent or metastatic breast cancer. Since many patients with recurrent disease will already have had substantial anthracycline exposure from adjuvant chemotherapy, taxane-based therapy is recommended in favor of anthracyline-based therapy for MBC.

Developed in the 1990s as cytotoxic chemotherapy for MBC, the taxanes are diterpenes produced by the plants of the genus Taxus (yews). These agents act by disrupting microtubule function, essentially inhibiting mitosis. Three taxanes are FDA-approved for the treatment of MBC: paclitaxel (TAXOL), docetaxel (TAXOTERE), and protein-bound paclitaxel (ABRAXANE). All three approved taxanes feature the same mechanism of action and offer similar efficacy and adverse-event profiles, with certain documented differences between the agents. While docetaxel has demonstrated a higher tubulin affinity in vitro compared to paclitaxel, clinical results between the two are very similar. Furthermore, both paclitaxel and docetaxel have demonstrated side effects such as myelosuppression, alopecia, and neurological events, but docetaxel has documented cases of febrile neutropenia associated with the myelosuppression, as well as nail changes and fluid retention. Protein-bound paclitaxel is bounded to albumin as the delivery agent as an alternative to the often toxic solvent delivery method of standard paclitaxel, presumably decreasing the rate of certain adverse events associated with the agent.8

Aside from their proven efficacy and tolerability, taxanes fill a significant role in the treatment of MBC with regard to their position among available therapeutic options. Beyond robust effectiveness as single-agent therapy for MBC, taxanes have demonstrated activity in combination regimens with doxorubicin [ADRIAMYCIN], epirubicin [ELLENCE], and capecitabine.9,10 Furthermore, taxanes serve as ideal agents for recurrent breast cancer when compared with other classes of chemotherapy drugs. As mentioned previously, evidence-based medicine dictates that no one agent should be used twice in patients with recurrent or metastatic breast cancer. Since many patients with recurrent disease will already have had substantial anthracycline exposure from adjuvant chemotherapy, taxane-based therapy is recommended in favor of anthracyline-based therapy for MBC.

Initially indicated for administration every 3 weeks, taxanes are now mostly used on a weekly schedule. Both solvent-based paclitaxel and albumin-bound paclitaxel have demonstrated improved efficacy and tolerability than once-every-3-weeks schedules.4 At ASCO 2007, Gradishar et al. presented a randomized phase 2 trial comparing different schedules of albumin-bound paclitaxel to once-every-3-weeks docetaxel.11 When administered at 100 mg/m2 or 150 mg/m2 every week for 3 out of 4 weeks, albumin-bound paclitaxel showed higher response rates than docetaxel 100 mg/m2 given every 3 weeks. Additionally, the albumin-bound paclitaxel 100 mg/m2 weekly for 3 out of 4 weeks demonstrated equivalent progression free survival with the 150 mg/m2 arm of albumin-bound paclitaxel and demonstrated significantly longer progression free survival than the docetaxel arm.12

Conclusion
Taxanes represent a valuable therapeutic option for the treatment of MBC due to their proven effectiveness, safety, and versatility. Taxanes serve a significant role in managed care oncology, where their widespread use and wealth of available data have achieved them widespread acceptance. Taxanes are often a first-choice therapy for MBC, both in anthracycline-naïve and -experienced patients, and these agents hold a secure position in a number of treatment guidelines and algorithms.

References