Abstract
These NCCN Guidelines Insights highlight the important updates/changes specific to the management of metastatic breast cancer in the 2012 version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer. These changes/updates include the issue of retesting of biomarkers (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2) on recurrent disease, new information regarding first-line combination endocrine therapy for metastatic disease, a new section on monitoring of patients with metastatic disease, and new information on endocrine therapy combined with an mTOR inhibitor as a subsequent therapeutic option. (JNCCN 2012;10:821–829)

Please Note
The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the Panel’s discussion, including the literature reviewed.

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The full and most current version of these NCCN Guidelines is available at NCCN.org.
• Interval history and physical exam every 4-6 mo for 5 y, then every 12 mo
• Annual mammography
• Women on tamoxifen: annual gynecologic assessment every 12 mo if uterus present
• Women on an aromatase inhibitor or who experience ovarian failure secondary to treatment should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter.
• Assess and encourage adherence to adjuvant endocrine therapy.
• Evidence suggests that active lifestyle, achieving and maintaining an ideal body weight (20-25 BMI) may lead to optimal breast cancer outcomes.

**Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.**

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE
ER and/or PR POSITIVE; HER2 NEGATIVE OR POSITIVE

Prior endocrine therapy within 1y

Visceral crisis

Ovarian ablation or suppression, plus endocrine therapy as for postmenopausal women

Consider initial chemotherapy

See Follow-up Therapy For Endocrine Treatment of Recurrence / Stage IV Disease (BINV-21)

No prior endocrine therapy within 1y

ER and/or PR positive; HER2 negative

ER and/or PR positive; HER2 positive

Visceral crisis

Ovarian ablation or suppression, plus endocrine therapy as for postmenopausal women

Consider initial chemotherapy

See Follow-up Therapy For Endocrine Treatment of Recurrence / Stage IV Disease (BINV-21)

Discordance between the receptor status of primary and recurrent disease has been reported in several studies. The discordance rates are in the range of 3.4% to 60% for ER-negative to ER-positive; 7.2% to 31% for ER-positive to ER-negative; and 0.7% to 10% for HER2.

Discordance in receptor status between the primary tumor and recurrence may be a result of several factors, including a change in disease biology, differential effect of prior treatment on clonal subsets, tumor heterogeneity, and less-than-perfect accuracy and reproducibility of receptor and gene amplification assays.

The knowledge of a change in receptor status from negative in primary tumor to positive in metastatic disease can be beneficial to the therapeutic decision process in the metastatic setting, because effective, relatively nontoxic therapeutic options of endocrine therapy and/or HER2-targeted therapy become available. Retesting, however, carries with it the potential for denying a patient endocrine

Retesting of Biomarkers on Recurrent Disease

Assessment of ER/PR and HER2 status in patients with breast cancer is clinically relevant when selecting patients eligible for endocrine and/or anti-HER2–based therapy. NCCN Task Forces and ASCO along with the College of American Pathologists (CAP) have issued quality-control recommendations on ER/PR testing and HER2 testing in patients with breast cancer.
therapy/HER2-targeted therapy because of a false-negative result on a second biopsy. According to the NCCN Breast Cancer Panel, retesting the receptor status of recurrent disease is especially important in cases when it was previously unknown, originally negative, or not overexpressed. Clinical judgment remains important. For patients with clinical courses consistent with hormone receptor–positive breast cancer, or with prior positive hormone receptor results, the panel agreed that a course of endocrine therapy is reasonable regardless of whether the receptor assay is repeated or is the result of the most recent hormone receptor assay.

**NCCN Recommendations**

The NCCN Breast Cancer Panel recommends that metastatic disease at presentation or first recurrence of disease be biopsied as part of the workup for patients with recurrent or stage IV disease (see BINV-16; on page 822). This ensures accurate determination of metastatic/recurrent disease and tumor histology, and allows for biomarker determination and selection of appropriate treatment. The status of the tumor biomarkers ER/PR and HER2 should be determined if unknown, originally negative, or not overexpressed (category 2A).

Combination endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor positive tumor (e.g., long disease free interval, limited sites of recurrence, indolent disease, or older age).”
in 2 studies comparing single-agent anastrozole versus anastrozole plus fulvestrant. In the first study (FACT trial), combination endocrine therapy was not superior to single-agent anastrozole (time to progression hazard rate, 0.99; 95% CI, 0.81–1.20; \( P = .91 \)). In the second study (S0226), the progression-free survival (hazard rate, 0.80; 95% CI, 0.68–0.94, stratified log-rank \( P = .007 \)) and overall survival (hazard rate, 0.81; 95% CI, 0.65–1.00; stratified \( P = .049 \)) were superior with combination anastrozole plus fulvestrant. An unplanned subset analysis of this trial suggested that patients without prior adjuvant tamoxifen experienced the greatest benefit with the combination endocrine therapy. The reason for the divergent outcomes in the 2 studies is not known.

NCCN Recommendations

Because of the contradictory results of the FACT\(^{13}\) and S0226\(^{14}\) trials, the NCCN Breast Cancer Panel has not made specific recommendations for including combination endocrine therapy in the main algorithm of the guidelines. However, the panel included a footnote on algorithm page BINV-18 (see page 823) stating, “A single study (S0226) in women with hormone receptor–positive breast cancer and no prior chemotherapy, biological therapy, or endocrine therapy for metastatic disease demonstrated that the addition of fulvestrant to anastrozole resulted in prolongation of time to progression (hazard rate for recurrence, 0.80; 95% CI, 0.68–0.94; stratified log-rank \( P = .007 \)) and improvement in overall survival (hazard rate, 0.81; 95% CI, 0.65–1.00; stratified log-rank \( P = .049 \)). Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. A study of similar design (FACT) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole (hazard rate, 0.99; 95% CI, 0.81–1.20; \( P = .91 \)).”
### Monitoring of Metastatic Disease

Very little high-level evidence exists on monitoring patients with metastatic breast cancer during the course of disease and treatment. Monitoring patients with metastatic disease is extremely important to determine whether the therapy administered is effective. Monitoring of disease activity during treatment helps ensure that the patient does not experience toxicity from an ineffective therapy. The panel included a new section in the 2012 version of the guidelines titled “Principles of Metastatic Disease Monitoring.” This section includes a discussion and recommendations on how metastatic disease should be monitored. The monitoring recommendations primarily reflect those from the prospective clinical trials on which the current treatment decisions are based.

**NCCN Recommendations**

In the new section “Principles of Monitoring of Metastatic Disease” (see BINV-M; on pages 824–826, the panel first stressed the importance of monitoring metastatic disease, and has provided the definition of progression of disease and outlined a series of components of monitoring that includes periodic assessment of symptoms, physical examination, routine laboratory tests, imaging studies, and, where appropriate, use of blood biomarkers (see BINV-M 1 of 3; on page 824). The panel acknowledges that, although integration of all of these components is important, in practice it can be challenging because the information obtained may be contradictory. Therefore, prudent clinical judgement is important to negotiate the differences in these cases.

The panel recommends objective criteria for assessing disease response, stable disease, and disease progression (see BINV-M 2 of 3; on page 825), and specifically encourages using the Response Evaluation Criteria in Solid Tumors (RECIST)\textsuperscript{15} or WHO criteria\textsuperscript{16} as a system for assigning disease activity.

The panel acknowledges the challenges of functional imaging, such as bone or PET/CT scans.

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<th>Suggested intervals of follow-up for patients with metastatic disease(^1)</th>
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\(^1\) In patients who have long-term stable disease, the frequency of monitoring can be reduced.
specific imaging studies monitor biologic function of the tumor as opposed to size of the tumor as the end point. With bone scan, responding disease may show a “flare,” or as increased activity, which may be easily misinterpreted as disease progression. The main challenge with using PET/CT scanning to monitor metastatic disease is that there is an absence of a reproducible, validated, and widely accepted set of standards for disease activity assessment. According to RECIST criteria, only progression of disease can be assessed with PET scan when a new site of PET abnormality occurs. In no other instances do the WHO or RECIST criteria allow use of PET/CT scan to declare response, disease stability, or disease progression.

The panel has provided a table outlining general recommendations for the frequency and type of monitoring as a baseline before initiation of new therapy and for monitoring the effectiveness of cytotoxic chemotherapy, monitoring the effectiveness of endocrine therapy, and assessment in the presence of evidence of disease progression. They have indicated in a footnote that the frequency of monitoring can be reduced in patients who have long-term stable disease.

Endocrine Therapy Plus an mTOR Inhibitor: A Subsequent Therapy Option

Resistance to endocrine therapy in women with hormone receptor–positive disease is frequent. One mechanism of endocrine resistance is activation of the mTOR signal transduction pathway. Two randomized studies have investigated the use of aromatase inhibition in combination with inhibitors of the mTOR pathway.

A phase III study (BOLERO-2) in postmenopausal women with hormone receptor–positive advanced breast cancer that had progressed or recurred during treatment with a nonsteroidal aromatase inhibitor randomized patients to exemestane with or without the mTOR inhibitor everolimus. The results of...
this study showed the median progression-free survival was increased with the addition of everolimus to exemestane from 2.8 to 6.9 months (hazard ratio, 0.43; 95% CI, 0.35–0.54; log-rank \( P < .001 \)).37 The results also showed that the toxicity of combination exemestane and everolimus was substantially greater than exemestane alone. The most common all-grade adverse events in patients who received everolimus versus those who did not included stomatitis (56% vs. 11%), rash (36% vs. 6%), fatigue (33% vs. 26%), diarrhea (30% vs. 16%), decreased appetite (29% vs. 10%), noninfectious pneumonitis (12% vs. 0%), and hyperglycemia (13% vs. 2%).17 Thus, in this study, the addition of everolimus prolonged time to progression but it also added substantial toxicity. No survival data have yet been reported.

Another trial phase III trial randomized postmenopausal women with advanced, hormone receptor–positive breast cancer with no prior endocrine therapy to letrozole with or without the mTOR inhibitor temsirolimus.18 In this study, progression-free survival was not different between the treatment arms (hazard rate, 0.89; 95% CI, 0.75–1.05; long-rank \( P = .18 \)).

The reasons for the difference in the outcomes of the 2 endocrine therapy with or without an mTOR inhibitor studies are uncertain, but may be related to the issues of patient selection, or the type and extent of prior endocrine therapy. A footnote has been added to the guidelines that lists subsequent endocrine therapy for systemic disease.

**NCCN Recommendations**

The panel unanimously agreed that the evidence from the BOLERO-2 trial is compelling enough to consider the addition of everolimus to exemestane in women who fulfill the entry criteria for BOLERO-2.

On the page in the algorithm listing subsequent endocrine therapy for patients (see BINV-N; on page 827), the panel added a footnote stating “A single study (BOLERO-2) in women with hormone receptor–positive, HER2-negative metastatic breast cancer and prior therapy with a non-steroidal aromatase inhibitor demonstrated improvement in time to progression with the addition of everolimus (an mTOR inhibitor) to exemestane (hazard rate, 0.44; 95% CI, 0.36–0.53; log-rank \( P = <1 \times 10^{-16} \)) and with increase in toxicity. No survival analysis is available. A randomized study using the mTOR inhibitor temsirolimus in combination with endocrine therapy did not demonstrate any improvement in outcome. Consider the addition of everolimus to exemestane in women who fulfill the eligibility criteria of BOLERO-2.”

**Conclusions**

These NCCN Guidelines Insights highlight the important updates/changes specific to the management of metastatic breast cancer in the 2012 version of the NCCN Guidelines for Breast Cancer (to view the most recent version of these guidelines, visit NCCN.org). The NCCN Guidelines are in continuous evolution. They are updated annually, or sometimes more often if new high-quality clinical data become available in the interim. The recommendations in the NCCN Guidelines, with few exceptions, are based on evidence from clinical trials. Expert medical clinical judgment is required to apply these guidelines in the context of an individual to provide optimal care. The physician and the patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the panel strongly encourages patient/physician participation in prospective clinical trials.

**References**


NCCN Task Force Report: Evaluating the Clinical Utility of Tumor Markers in Oncology

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