

Breast Cancer, Version 4.2026

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Abstract

The NCCN Clinical Practice Guidelines for Breast Cancer include recommendations for clinical management of patients with carcinoma in situ, invasive breast cancer, Paget's disease, Phyllodes tumor, inflammatory breast cancer, and management of breast cancer during pregnancy. The panel convenes annually to update recommendations based on a review of recently published clinical trials. This selection from the NCCN Guidelines for Breast Cancer focuses on the recommendations for the management of recurrent or stage IV (M1) metastatic breast cancer. It summarizes the treatment strategies stratified by tumor biology, including hormone receptor status and HER2 expression, as well as clinical factors such as prior therapy and disease-free interval. Throughout all treatment lines, supportive care, quality of life preservation, toxicity minimization, and clinical trial participation are emphasized as integral components of patient care.

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Management of Recurrent or Stage IV (M1) Disease

Therapeutic strategy for recurrent or de novo stage IV (M1) breast cancer is guided by tumor biology and clinical factors. NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. From the time of diagnosis of recurrent/stage IV disease, patients should be offered appropriate supportive care and symptom-related interventions as a routine part of their care. Systemic therapy for metastatic disease aims to prolong survival, alleviate symptoms, and maintain or improve quality of life while minimizing treatment-related toxicities. Options include endocrine therapy and cytotoxic therapy (eg, chemotherapy, antibody-drug conjugates [ADCs], immunotherapy, or targeted therapy).

For recurrent stage IV disease, the adjuvant therapy received determines the treatment selection for recurrent disease. Key factors for therapy selection include the disease-free interval and the cumulative doses of specific drugs previously received. If a patient presents with metastatic disease more than 12 months after completing adjuvant therapy, the treatment strategy would be to “rechallenge” with the same agents (eg, reuse taxanes or certain endocrine therapies). Disease recurrence within 12 months

of completing adjuvant therapy typically signals acquired resistance. It is generally recommended to switch to a different class of drugs (eg, switch from an aromatase inhibitor [AI] to fulvestrant for hormone receptor [HR]-positive disease).

The NCCN panel has initially stratified patients with recurrent or stage IV breast cancer at diagnosis according to whether bone metastases are present and then further stratified by tumor HR and HER2 status (Figure 1).

Therapy for Bone Metastases

Complications from bone metastases include pain, decreased performance status, and decreased quality of life (QOL), as well as skeletal-related events (SREs), which are defined as the need for radiation or surgery to bone, pathologic fractures, spinal cord compression, and hypercalcemia of malignancy.

Bisphosphonates

Extensive data from randomized trials are available in support of the use of bisphosphonates for patients with metastatic disease to bone. The randomized clinical trial data include the use of zoledronic acid and pamidronate in the United States and

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To view disclosures of external relationships for the NCCN Guidelines panel, go to <https://www.nccn.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels>

The full NCCN Guidelines for Breast Cancer are not printed in this issue of JNCCN. The complete and most recent version of these guidelines is available free of charge at NCCN.org.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence (≥ 1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus ($\geq 50\%$, but $< 85\%$ support of the Panel) 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 indicated.

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

PLEASE NOTE

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

NCCN CATEGORIES OF PREFERENCE

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

Other: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.

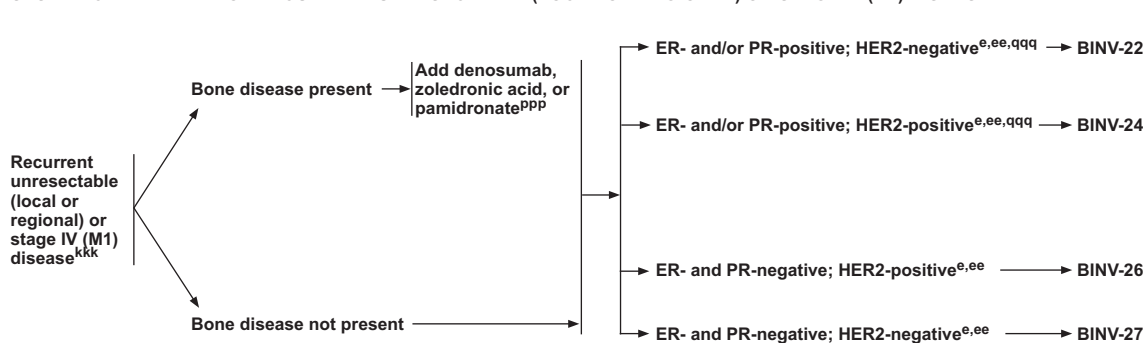
Useful in certain: Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

ibandronate and clodronate in European countries.¹⁻⁸ In metastatic bone disease, bisphosphonate treatment is associated with fewer SREs, fewer pathologic fractures, and less need for radiation therapy and surgery to treat bone pain. The use of bisphosphonates in metastatic disease is a palliative care measure. No impact on overall survival (OS) has been observed in patients treated with bisphosphonates.

Three randomized trials have compared zoledronic acid dosed every 4 weeks versus every 12 weeks.⁹⁻¹¹ Data from these trials show that among patients with breast cancer and bone metastases,

zoledronic acid administered once every 12 weeks versus once every 4 weeks does not compromise efficacy and has similar rates of SREs.^{9,10,12} In the ZOOM trial,⁹ the rate of skeletal morbidities was 0.22 (95% CI, 0.14–0.29) in those receiving zoledronic acid every 4 weeks versus 0.26 (95% CI, 0.15–0.37) in those receiving zoledronic acid every 12 weeks. In the CALGB 70604 trial,¹⁰ the rate of SREs in the 4-week arm was 29.5% versus 28.6% in the 12-week arm. In the OPTIMIZE-2 trial,¹¹ the rate of SREs was 22% in the 4-week arm and 23.2% in the 12-week arm.¹¹ The NCCN panel recommends an optimal dosing of every 12 weeks.

SYSTEMIC TREATMENT OF RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE^k

^e Principles of Biomarker Testing (BINV-A*).

^k Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J*).

^{ee} Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus, individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A*).

^{kkk} Optimal management of oligometastatic stage IV breast cancers remains uncertain. Routine utilization of locoregional treatment of the primary tumor and ablative treatment for metastatic sites have not been demonstrated to improve survival outcomes in prospective trials, however, may reduce the risk of local progression and palliate symptoms. Compared with recurrent oligometastatic disease, patients with de novo oligometastatic cancer have better outcomes and therapeutic decisions should be individualized and discussed in a multidisciplinary context. A large number of case series document long-term DFS for patients with de novo oligometastatic breast cancer who received multimodality therapy leading to NED. For de novo oligometastatic disease with favorable features (HER2+ or ER+, induced NED status after receipt of optimal multi-agent systemic regimens, limited sites of metastases, bone-only metastases, and young age/longevity), an aggressive multimodality approach involving locoregional therapy of the primary tumor, ablative treatment to all sites of metastases and "adjuvant-like" systemic therapy may offer improved long-term PFS and may be considered.

^{ppp} Denosumab, zoledronic acid, or pamidronate (all with calcium and vitamin D supplementation) should be given (category 1) in addition to systemic therapy or endocrine therapy if bone metastasis is present, expected survival is ≥ 3 months, and renal function is adequate. Patients should undergo a dental examination with preventive dentistry prior to initiation of this therapy. The optimal schedule for zoledronic acid is every 12 weeks.

^{qqq} Baseline assessment of bone density is recommended for patients receiving an aromatase inhibitor who are at risk of osteoporosis (eg, age > 65 , family history, chronic steroids).

*Available online, in these guidelines, at NCCN.org.

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BINV-21

Figure 1. BINV-21. NCCN Clinical Practice Guidelines in Oncology for Breast Cancer, Version 4.2026.