Breast Cancer, Version 3.2020

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ABSTRACT

Several new systemic therapy options have become available for patients with metastatic breast cancer, which have led to improvements in survival. In addition to patient and clinical factors, the treatment selection primarily depends on the tumor biology (hormone-receptor status and HER2-status). The NCCN Guidelines specific to the workup and treatment of patients with recurrent/stage IV breast cancer are discussed in this article.

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-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 of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

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The complete NCCN Guidelines for Breast Cancer are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.

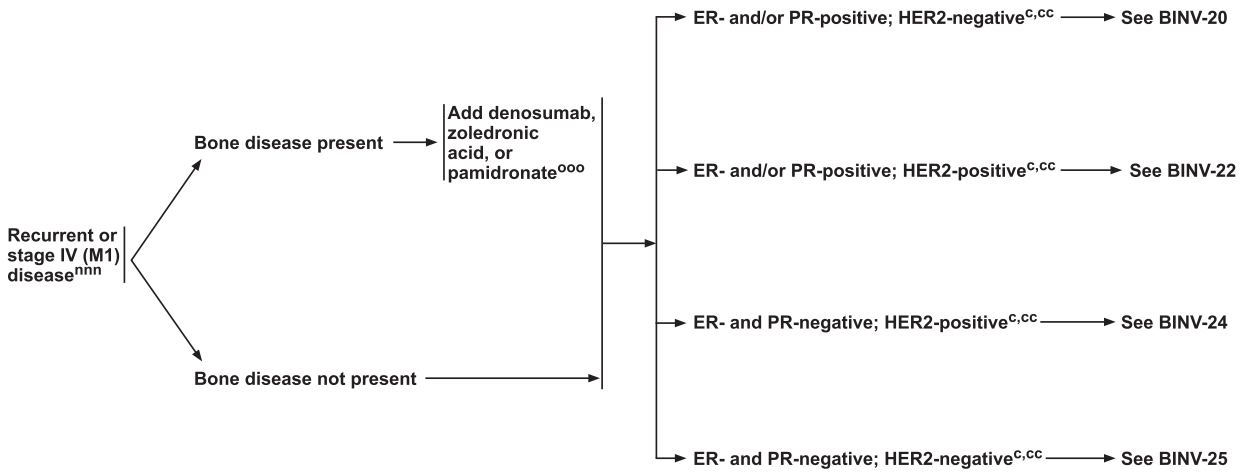
Disclosures for the NCCN Breast Cancer Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Breast Cancer Panel members can be found on page 478. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE



[c] See Principles of Biomarker Testing (BINV-A*).

[cc] 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. This should be considered in decision-making for other adjuvant therapy and overall treatment pathway. See Principles of Biomarker Testing (BINV-A*).

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[nnn] The role and timing of surgical removal of the primary tumor in patients presenting with de novo stage IV (M1) is the subject of ongoing investigations and must be individualized. Performance of local breast surgery and/or RT is reasonable in select patients responding to initial systemic therapy.

[ooo] Denosumab, zoledronic acid, or pamidronate (all with calcium and vitamin D supplementation) should be given (category 1) in addition to chemotherapy 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.

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Overview

Breast cancer is the most common malignancy in women in the United States. The NCCN Guidelines specific to the workup and treatment of patients with recurrent/stage IV breast cancer are discussed in this article. The full NCCN Guidelines for Breast Cancer are available at NCCN.org. The primary goals of systemic treatment of recurrent/stage IV breast cancer are palliating symptoms, prolonging survival, and maintaining or improving quality of life. Hormone receptor (HR) status, human epidermal growth factor receptor 2 (HER2) overexpression, tumor burden, and patient preference are important factors in selecting appropriate therapeutic strategy for patients with recurrent/stage IV disease.

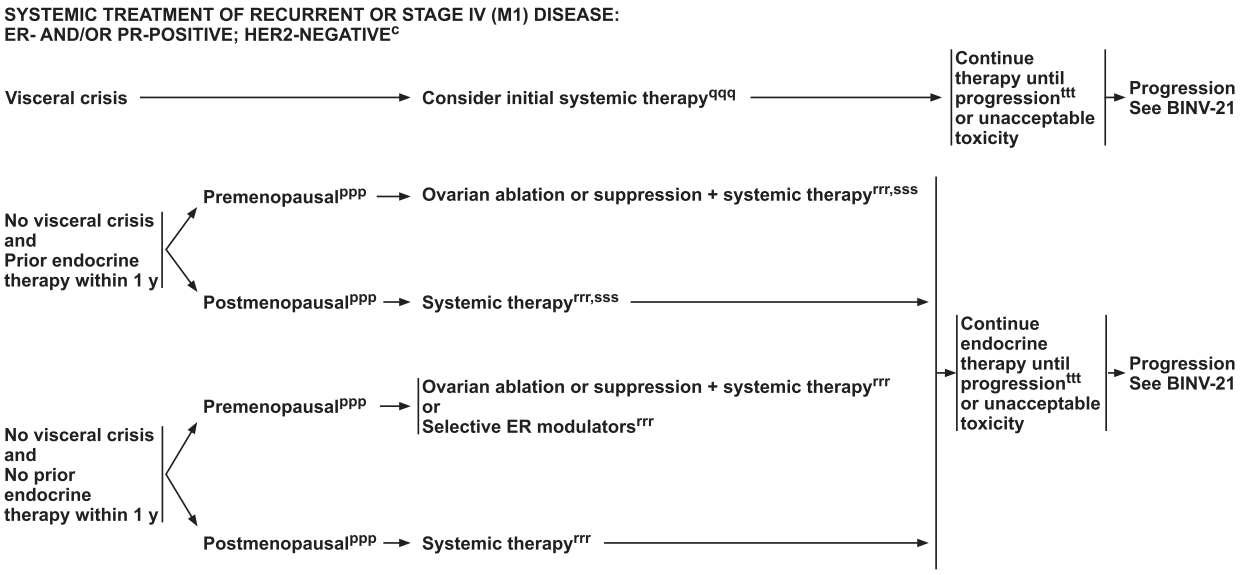
These guidelines have been developed by the NCCN Breast Cancer Panel. Expert medical clinical judgment is required to apply these guidelines in the context of an individual patient to provide optimal care. Although not stated at every decision point of the guidelines, patient participation in prospective clinical trials is the preferred option of treatment of all stages of breast cancer. For management of other clinical stages of breast cancer, please refer to the online version of the NCCN Guidelines at NCCN.org.

Management of Recurrent or Stage IV Disease

From the time of diagnosis of recurrent/stage IV metastatic disease, patients should be offered appropriate supportive care and symptom-related interventions as a routine part of their care. NCCN believes that the best management of any patient with cancer is in a clinical trial. Patients should be encouraged to participate in clinical trials whenever clinical trials are available.

Surgery for Recurrent or Stage IV Disease

The primary treatment approach recommended by the NCCN panel for women with metastatic breast cancer and an intact primary tumor is systemic therapy, with consideration of surgery after initial systemic treatment of those women requiring palliation of symptoms or with impending complications, such as skin ulceration, bleeding, fungation, and pain.[1] Generally, such surgery should be undertaken only if complete local clearance of tumor may be obtained and if other sites of disease are not immediately threatening to life. Alternatively, radiation therapy may be considered as an option to surgery. Often such surgery requires collaboration between the breast surgeon and the reconstructive surgeon to provide optimal cancer control and wound closure.



[c] See Principles of Biomarker Testing (BINV-A*).
[ppp] See Definition of Menopause (BINV-O*).
[qqq] See Systemic Therapy Regimens for Recurrent or Stage IV (M1) Disease (BINV-Q).
[rrr] See Systemic Therapy for ER- and/or PR-Positive Recurrent or Stage IV (M1) Disease (BINV-P).
[sss] If progression on initial endocrine therapy, switch to a different endocrine therapy option.
[ttt] See Principles of Monitoring Metastatic Disease (BINV-S*).

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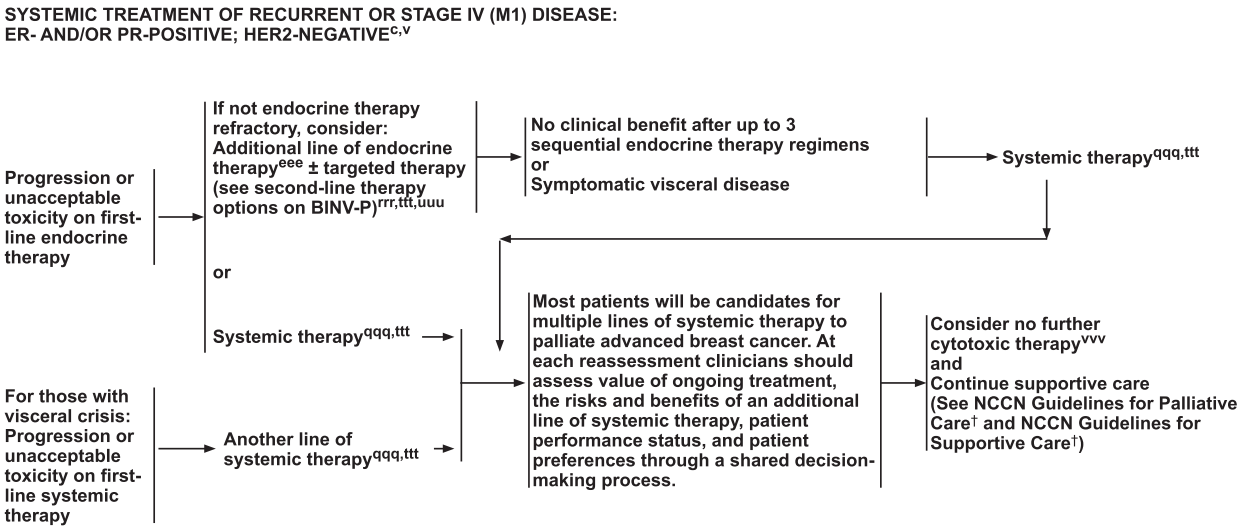
BINV-20

Retrospective studies suggest a potential survival benefit from complete excision of the in-breast tumor in select patients with metastatic breast cancer.[2–5] Substantial selection biases exist in all of these studies and are likely to confound the study results.[6,7]

Two prospective, randomized studies assessed whether surgery on the primary tumor in the breast is necessary for women who are diagnosed with metastatic/stage IV breast cancer.[8,9] In the first prospective trial, women (n=350) with de novo metastatic breast cancer who experienced a partial or complete response to anthracycline-based chemotherapy were randomly assigned to either surgery of the primary tumor plus adjuvant radiation versus no locoregional treatment.[8] There was no difference in the overall survival (OS) between the group that received surgery and the group that did not (19.2 vs 20.5 months; hazard ratio [HR] 1.04; 95% CI, 0.81–1.34).[8] In a separate multiple center prospective registry study, women who responded to first-line systemic therapy were randomized to management of the primary tumor by surgery or not.[10] Preliminary data showed no difference in OS between the 2 groups[10]

However, another trial by the Turkish Federation, MF07-01, of women (n=274) with de novo metastatic breast cancer randomized to local management (mastectomy, or BCS with radiation) followed by systemic therapy versus systemic therapy only, observed a benefit with surgery.[11] Although no difference in survival was seen at 36 months, at 40 months, patients treated with local management showed an improvement in survival with locoregional treatment (46.4% vs 26.4%; HR, 0.66; 95% CI, 0.49–0.88).[11] The design of this trial is different from the other, the first being 2 prospective studies described previously in which patients were included only if they had experienced a response to systemic therapy. Second, randomization in the Turkish trial was not balanced. Patients who received surgery had lower rates of triple-negative disease (7% vs 17%) and visceral metastases (29% vs 45%), and many had solitary bone metastases only (33% vs 20%).[11] In an unplanned subgroup analysis, patients who appeared to derive the greatest OS benefit from local management included those with HR-positive disease (HR, 0.63; 95% CI, 0.44–0.89; P=.008); HER2-negative disease (HR, 0.64; 95% CI, 0.45–0.91; P=.01); those younger than 55 years (HR, 0.57; 95% CI, 0.38–0.86; P=.007); and those with solitary bone metastases (HR, 0.47; 95% CI, 0.23–0.98; P=.04).[11]



[c] See Principles of Biomarker Testing (BINV-A*).
[v] See Special Considerations for Breast Cancer in Men (BINV-J*).
[eee] False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, 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 (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).
[qqq] See Systemic Therapy Regimens for Recurrent or Stage IV (M1) Disease (BINV-Q).
[rrr] See Systemic Therapy for ER- and/or PR-Positive Recurrent or Stage IV (M1) Disease (BINV-P).
[ttt] See Principles of Monitoring Metastatic Disease (BINV-S*).
[uuu] If there is disease progression while on CDK4/6 inhibitor therapy, there are limited data to support an additional line of therapy with another CDK4/6-containing regimen. Likewise, if there is disease progression while on a everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.
[vvv] The potential side effects of additional chemotherapy may outweigh any clinical benefit in a patient who has a compromised performance status. Patient preference must be taken into account.

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The panel recognizes the need for more data from randomized clinical trials that will address the risks and benefits of local therapy for patients with stage IV disease while eliminating selection biases. Although the available data does not support broadly considering local therapy with surgery and/or RT, this may be reasonable in select patients responding to initial systemic therapy. In such clinical scenarios, patient engagement in the decision is encouraged.

Guideline Stratification for Systemic Therapy for Stage IV/Recurrent Disease

The systemic treatment of breast cancer recurrence or stage IV disease prolongs survival and enhances quality of life (QOL) but is not curative. Therefore, treatments associated with minimal toxicity are preferred. Thus, the use of the minimally toxic endocrine therapies is preferred to the use of cytotoxic therapy whenever reasonable.[12] Guidance for treatment of patients with breast cancer and brain metastases is included the NCCN Guidelines for Central Nervous System Cancers.

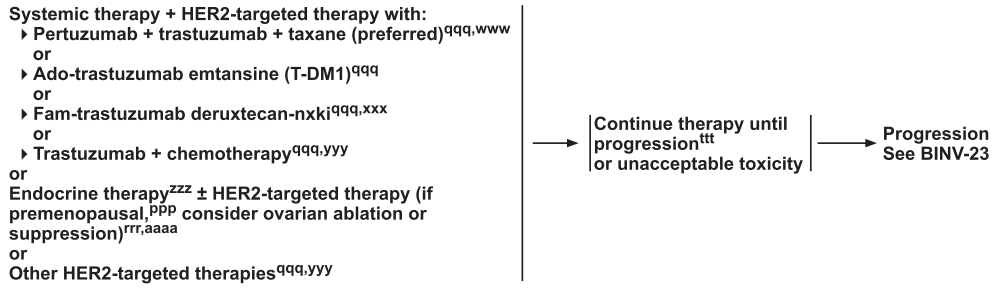
Patients with recurrent/stage IV breast cancer at diagnosis are initially stratified according to whether bone metastases are present. These 2 patient subsets (those with and without bony metastases) are then stratified further by tumor HR and HER2 status.

Therapy for Bone Metastases

Complications from bone metastases include pain, decreased performance status, and decreased 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.

The NCCN panel recommends treatment with a bone-modifying agent such as zoledronic acid, pamidronate, or denosumab (category 1) in addition to chemotherapy or endocrine therapy if bone metastasis is present; expected survival is ≥3 months. Patients should undergo a dental examination with preventive dentistry before starting this therapy. The bisphosphonates and denosumab are associated with a risk of development of osteonecrosis of the jaw (ONJ). Poor baseline dental health or dental procedures during treatment are known risk factors for ONJ. Thus, a dental examination with preventive dentistry intervention is recommended before treatment with intravenous bisphosphonate or denosumab, and dental procedures invasive of gum or

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE: ER- and/or PR-POSITIVE; HER2-POSITIVE[c]



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[rrr] See Systemic Therapy for ER- and/or PR-Positive Recurrent or Stage IV (M1) Disease (BINV-P).
[ttt] See Principles of Monitoring Metastatic Disease (BINV-S*).
[www] If treatment was initiated with chemotherapy and trastuzumab + pertuzumab, and the chemotherapy was stopped, endocrine therapy may be added to trastuzumab + pertuzumab.
*Available online, in these guidelines, at NCCN.org.
[xxx] Fam-trastuzumab deruxtecan-nxki is indicated following two or more lines of prior HER2-targeted therapy in the metastatic setting. This agent is contraindicated for patients with pneumonitis or interstitial lung disease (ILD).
[yyy] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[zzz] If prior endocrine therapy within 1 y, consider a different endocrine therapy.
[aaaa] For premenopausal women, selective ER modulators alone (without ovarian ablation/suppression) + HER2-targeted therapy is also an option.

BINV-22

bone during treatment should be avoided if at all possible. Additional risk factors for the development of ONJ include administration of chemotherapy or corticosteroids and poor oral hygiene with periodontal disease and dental abscess.[13]

Bisphosphonates

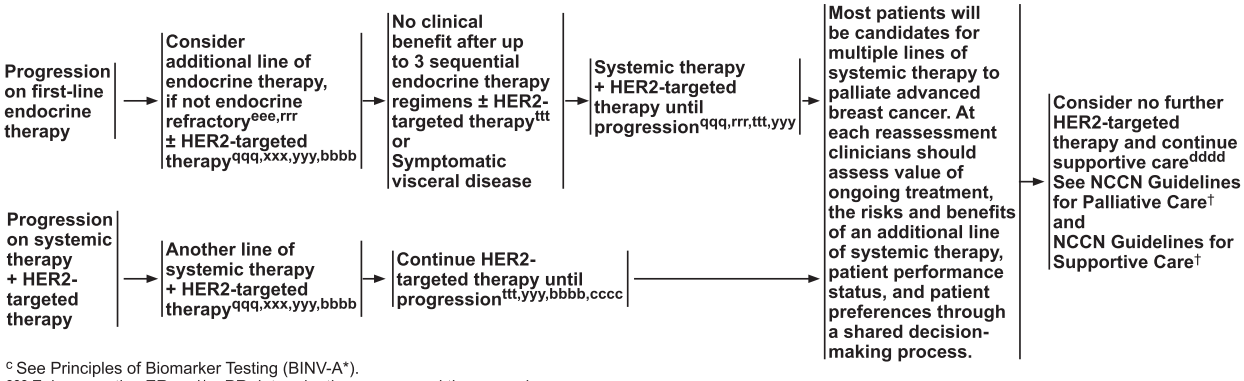
Extensive data from randomized trials exist that support the use of bisphosphonates for patients with metastatic disease to bone. The randomized clinical trial data include the use of zoledronic acid and pamidronate in the United States and ibandronate and clodronate in European countries.[14–21] In 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 OS has been observed in patients treated with bisphosphonates.

The data indicate that zoledronic acid and pamidronate may be given on a 3- to 4-week schedule in conjunction with antineoplastic therapy (ie, endocrine therapy, chemotherapy, biologic therapy) or every 12 weeks. Three randomized trials have compared zoledronic acid dosed every 4 weeks versus every 12 weeks.[22–24] Data from these trials show that among women 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.[22,23,25] In the ZOOM trial,[22] the rate of skeletal morbidities was 0.22 (95% CI, 0.14–0.29) in those receiving zoledronic acid every 4 weeks and 0.26 (95% CI, 0.15–0.37) in those receiving zoledronic acid every 12 weeks. In the CALGB 70604 trial,[23] the SRE rate in the 4-week arm was 29.5% versus 28.6% in the 12-week arm. In the OPTIMIZE-2 trial,[24] the rate of SREs was 22% in the 4-week arm and 23.2% in the 12-week arm.[24] The panel recommends an optimal dosing of every 12 weeks.

The use of bisphosphonates should be accompanied by calcium and vitamin D supplementation with daily doses of calcium of 1,200 to 1,500 mg and vitamin D_3 of 400 to 800 IU. Recommended agents for use in the United States are pamidronate 90 mg intravenously over 2 hours or zoledronic acid 4 mg intravenously over 15 minutes. The original studies continued treatment of up to 24 months; however, there are limited long-term safety data indicating treatment can continue beyond that time.[17,19,26] The risk of renal toxicity necessitates

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE: ER- and/or PR-POSITIVE; HER2-POSITIVE[c]



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[qqq] See Systemic Therapy Regimens for Recurrent or Stage IV (M1) Disease (BINV-Q).
[rrr] See Systemic Therapy for ER- and/or PR-Positive Recurrent or Stage IV (M1) Disease (BINV-P).
[ttt] See Principles of Monitoring Metastatic Disease (BINV-S*).
[xxx] Fam-trastuzumab deruxtecan-nxki is indicated following two or more lines of prior HER2-targeted therapy in the metastatic setting. This agent is contraindicated for patients with pneumonitis or interstitial lung disease (ILD).
[yyy] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[bbbb] Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.
[cccc] Continue HER2-targeted therapy following progression on first-line HER2-targeted chemotherapy for metastatic breast cancer. The optimal duration of trastuzumab in patients with long-term control of disease is unknown.
[dddd] The potential side effects of additional HER2-targeted therapy may outweigh any clinical benefit in a patient who has a compromised performance status. Patient preference must be taken into account.

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monitoring of serum creatinine before administration of each dose and dose reduction or discontinuation if renal function is reduced. Current clinical trial results support the use of bisphosphonates for up to 2 years. Longer durations of bisphosphonate therapy may provide additional benefit, but this has not yet been tested in clinical trials.

Denosumab

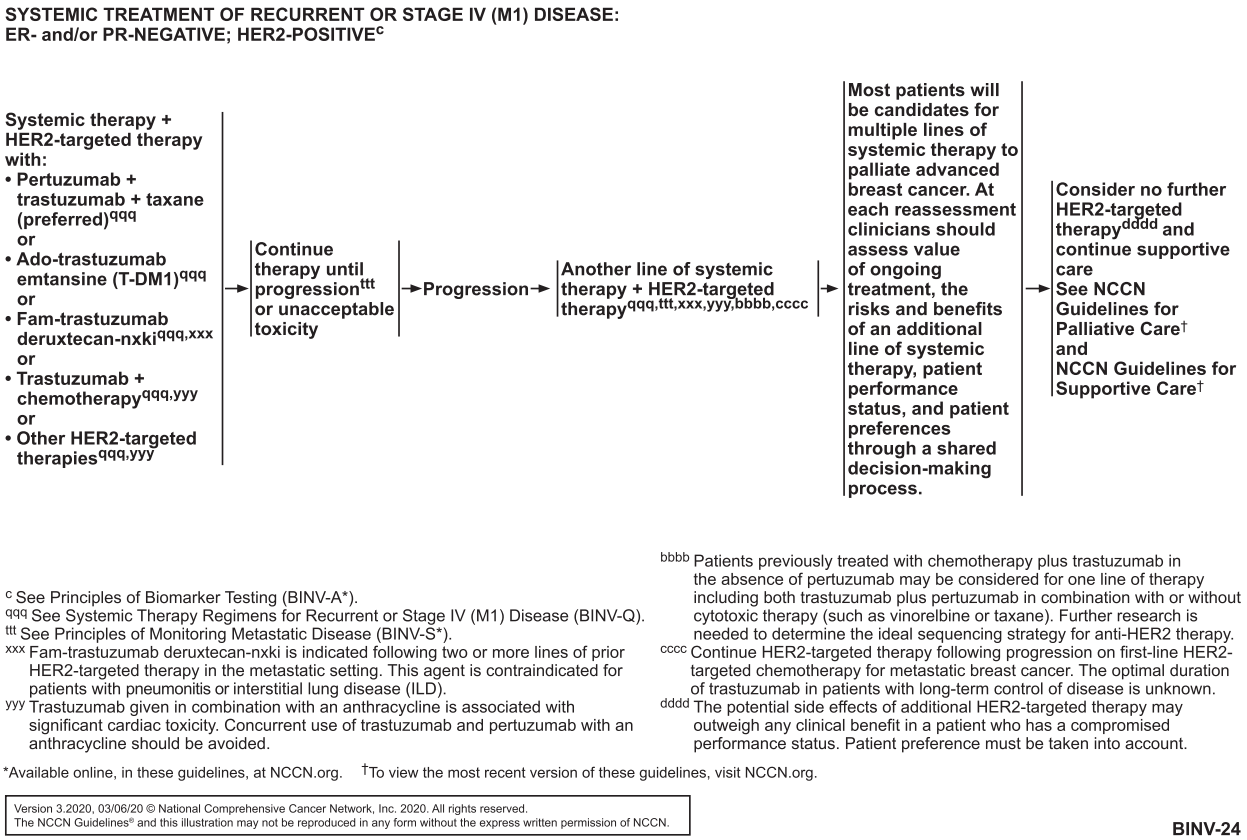
Women with metastatic breast cancer to bone who are candidates for bisphosphonate therapy may also be considered for treatment with denosumab. This recommendation is based on the results of a single randomized trial comparing denosumab to zoledronic acid.[27] All trial patients were recommended to supplement with vitamin D and calcium. Patients on the experimental arm were given 120 mg of denosumab injected subcutaneously every 4 weeks plus intravenous placebo versus the control arm where patients were given an intravenous infusion of 4 mg of zoledronic acid every 4 weeks, and a subcutaneous placebo. In this trial with noninferiority as the primary endpoint, denosumab was shown to significantly delay time to first SRE by 18% as compared with zoledronic acid (HR, 0.82; 95% CI, 0.71–0.95; $P<.001$ for noninferiority; $P=.01$ for superiority) and time to first and subsequent SREs (rate ratio, 0.77; 95% CI, 0.66–0.89; $P=.001$). No difference in time to progression or OS was observed.[27] Dosing of denosumab outside of every 3–6 weeks has not been studied.

Systemic Therapy for Stage IV or Recurrent Metastatic HR-Positive, HER2-Negative Breast Cancer

Women with stage IV or recurrent disease characterized by HR-positive, HER2-negative tumors with no visceral crisis are treated with endocrine therapy alone or endocrine therapy in combination with targeted agents.

Women whose disease progresses after a year from the end of adjuvant endocrine-based therapy and those who present with de novo stage IV/metastatic breast cancer are eligible for first-line endocrine therapies.

Many premenopausal and postmenopausal women with HR-positive breast cancer benefit from sequential use of endocrine therapies at disease progression. Therefore, women with breast cancers who respond to an endocrine-based therapy with either shrinkage of the tumor or long-term disease stabilization (clinical benefit) should receive additional endocrine therapy at disease



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[xxx] Fam-trastuzumab deruxtecan-nxki is indicated following two or more lines of prior HER2-targeted therapy in the metastatic setting. This agent is contraindicated for patients with pneumonitis or interstitial lung disease (ILD).
[yyy] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[bbbb] Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.
[cccc] Continue HER2-targeted therapy following progression on first-line HER2-targeted chemotherapy for metastatic breast cancer. The optimal duration of trastuzumab in patients with long-term control of disease is unknown.
[dddd] The potential side effects of additional HER2-targeted therapy may outweigh any clinical benefit in a patient who has a compromised performance status. Patient preference must be taken into account.

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progression. Those who progress on or within 12 months of completing adjuvant endocrine therapy or patients who progress on first-line endocrine therapy for metastatic disease are eligible for second-line endocrine therapy either as monotherapy or in combination with a targeted agent. The optimal sequence for endocrine therapy is not well defined. The choice would depend on previous therapy, tolerance of treatment, and patient preference.

Many trials in patients with HR-positive cancer have not included premenopausal women. The NCCN panel recommends that women with HR-positive disease should have adequate ovarian suppression/ablation and then be treated in the same way as postmenopausal women. The NCCN panel has outlined endocrine-based therapies that would be used in the first-line versus second- and subsequent-line settings.

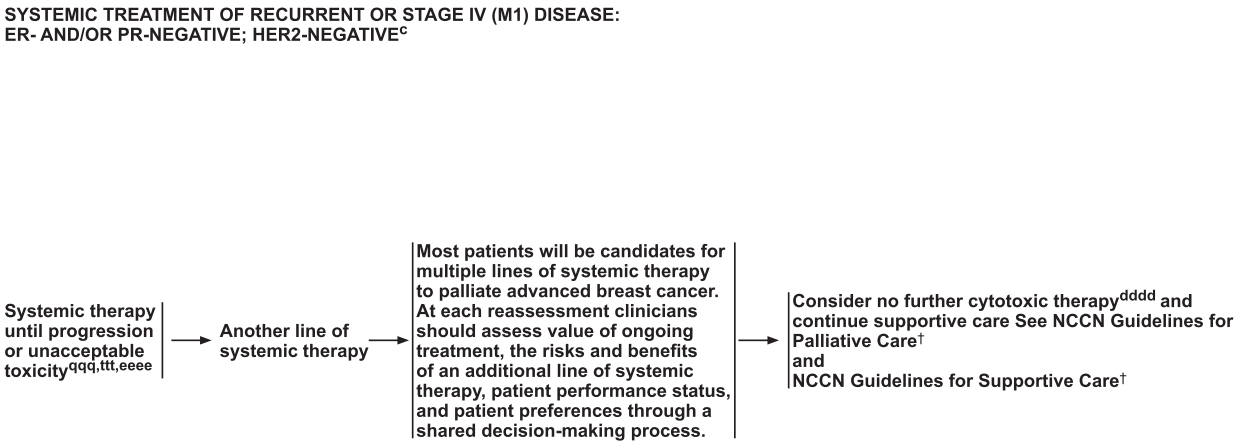
Preferred First-Line Therapy for HR-Positive, HER2-Negative Breast Cancer

Aromatase Inhibitor in Combination With Cyclin-Dependent Kinase 4/6 Inhibitor

In postmenopausal women or premenopausal women receiving ovarian ablation or ovarian function suppression with a luteinizing hormone-releasing hormone agonist, combinations of aromatase inhibitors (AIs) with cyclin-dependent kinase (CDK) 4/6 inhibitors (palbociclib, ribociclib, or abemaciclib) have demonstrated improved progression-free survival (PFS) relative to an AI alone.

Palbociclib in combination with letrozole was studied in a phase III study that included postmenopausal patients (n=666) with metastatic, HR-positive, HER2-negative breast cancer who had not received prior treatment of advanced disease.[28] An improvement in PFS (24.8 vs 14.5 months; HR, 0.58; 95% CI, 0.46–0.72) and objective response rate (ORR; 42% vs 35%) was seen with the combination of palbociclib and letrozole compared with letrozole alone.[28] Grade 3 and 4 adverse effects seen with the combination of palbociclib and letrozole included neutropenia (66.5% vs 1.4%), leukopenia (24.8% vs 0%), anemia (5.4% vs 1.8%), and fatigue (1.8% vs 0.5%).[28]

Ribociclib in combination with letrozole was also studied as first-line therapy in a phase III study of postmenopausal women (n=668) with HR-positive, HER2-negative recurrent/stage IV breast cancer. At a median follow-up of 26.4 months, an improvement in PFS (25.3 vs 16.0 months; HR for progression or death was 0.56; 95% CI, 0.45–0.70) and improved ORR of 43% vs 29% was seen with ribociclib plus letrozole compared with



[c] See Principles of Biomarker Testing (BINV-A*).
[qqq] See Systemic Therapy Regimens for Recurrent or Stage IV (M1) Disease (BINV-Q).
[ttt] See Principles of Monitoring Metastatic Disease (BINV-S*).
[dddd] The potential side effects of additional chemotherapy may outweigh any clinical benefit in a patient who has a compromised performance status. Patient preference must be taken into account.
[eeee] See Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease (BINV-R).

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letrozole alone.[29] Grade 3 or 4 adverse events were more common with the combination, including neutropenia (62% vs 1.2%), leukopenia (21.3% vs 0.9%), and abnormal liver function tests (10.2% vs 2.4%).[29]

The phase III MONARCH trial studied the combination of abemaciclib either with an AI (letrozole or anastrozole) versus AI monotherapy as first-line treatment of women with advanced HR-positive, HER2-negative breast cancer. The combination of abemaciclib with the AI improved PFS compared with AI alone (median not reached vs 14.7 months, respectively; HR, 0.54; 95% CI, 0.41–0.72).[30] The ORR was higher with the combination compared with AI monotherapy (59% vs 44%).[30] The most frequent grade 3 or higher adverse events for abemaciclib versus placebo included diarrhea (9.5% vs 1.2%), neutropenia (21.1% vs 1.2%), leukopenia (8% vs 0.6%), and fatigue (2% vs 0%).[30]

Most trials studying CDK 4/6 inhibitor with an AI have mainly included postmenopausal women and only a small subset of premenopausal women on ovarian suppression. However, in the phase III MONALEESA-7 trial, 672 pre- or perimenopausal women with HR-positive, HER2-negative, advanced breast cancer were randomly assigned to first-line treatment with ribociclib or placebo with goserelin plus either a nonsteroidal AI or tamoxifen.[31] An improvement in PFS was seen with the addition of ribociclib (median PFS, 24 vs 13 months; HR, 0.55; 95% CI, 0.4–0.69).[31]

At 3.5 years, an improvement in OS was reported with ribociclib (70% vs 46%; HR, 0.71; 95% CI, 0.54–0.95).[32] Grade 3 and 4 adverse events reported in greater than 10% of patients in either group included neutropenia (61% vs 4%), hot flashes (34% in each arm), and leukopenia (14% vs 1%).[31]

Based on the previously cited data, the NCCN panel has included AI in combination with CDK 4/6 inhibitors as a category 1 first-line option for postmenopausal women and premenopausal women with ovarian ablation/suppression with HR-positive, HER2-negative recurrent/stage IV breast cancer.

Single Agent Fulvestrant

Fulvestrant is an estrogen receptor (ER) antagonist and was originally approved as a monthly intramuscular injection (250 mg per month); higher dose has been proven to be more effective in subsequent randomized trials. In the first-line setting, fulvestrant was found to be as effective as anastrozole in terms of ORR (36.0%

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT OR STAGE IV (M1) DISEASE

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

Preferred Regimens
First-Line Therapy
- Aromatase inhibitor + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)
- Selective ER down-regulator (fulvestrant, category 1)[b] ± non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[b]
- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Selective estrogen receptors modulator (tamoxifen or toremifene)
- Steroidal aromatase inactivator (exemestane)

Preferred Regimens
Second- and Subsequent-Line Therapy
- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[a]
- For *PIK3CA*-mutated tumors, see additional targeted therapy options (see BINV-R)[c]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[a,e]
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator (exemestane)
- Selective ER down-regulator (fulvestrant)
- Selective estrogen receptors modulator (tamoxifen or toremifene)

Useful in Certain Circumstances[c]
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol
- Abemaciclib[a,d]

HER2-Positive and Postmenopausal[f,g,h] **or Premenopausal Receiving Ovarian Ablation or Suppression**
- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

[a] If there is disease progression while on CDK4/6 inhibitor therapy, there are limited data to support an additional line of therapy with another CDK4/6-containing regimen. If there is disease progression while on a everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.
[b] 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 and overall survival. Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. Two studies with similar design (FACT and SOFEA) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole.
[c] See Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease (BINV-R).
[d] Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting.
[e] A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal aromatase inhibitor).
[f] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[g] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine or fam-trastuzumab deruxtecan-nxki.
[h] If treatment was initiated with chemotherapy and trastuzumab + pertuzumab, and the chemotherapy was stopped, endocrine therapy may be added to the trastuzumab + pertuzumab.

BINV-P

vs 35.5%; odds ratio, 1.02; 95% CI, 0.56–1.87).[33] An improved time to progression was seen with fulvestrant compared with anastrazole (median time to progression was 23.4 months for fulvestrant vs 13.1 months for anastrozole; HR, 0.63; 95% CI, 0.39–1.00; *P*=.0496).[34] This study also used a higher loading dose of 500 mg every 2 weeks for 3 doses and then maintenance dose of 500 mg monthly.[33] The median OS was observed to be longer in the fulvestrant group than in the anastrozole group (54.1 vs 48.4 months; HR, 0.70; *P*=.041).[35]

A separate phase III randomized study in postmenopausal women with metastatic HR-positive breast cancer compared fulvestrant 500 mg every 2 weeks for 3 doses followed by 500 mg monthly versus fulvestrant 250 mg monthly. The PFS was superior with the fulvestrant 500 mg regimen (HR, 0.80; 95% CI, 0.68–0.94; *P*=.006),[36] indicating an increased duration of response with the higher dose of fulvestrant. The final analyses demonstrated an increase in median OS (4.1 months) and reduced risk of death (19%) with a dose of 500 mg compared with 250 mg. Median OS was 26.4 versus 22.3 months (HR, 0.81; 95% CI, 0.69–0.96; *P*=.02).[37]

Results from another phase III trial (FALCON) of first-line treatment with fulvestrant compared with anastrozole in endocrine therapy–naïve patients with metastatic ER-positive breast cancer, showed improved PFS with fulvestrant (at the higher dose, 500 mg) over anastrozole at a median follow-up of 25.0 months (16.6 vs 13.8 months, HR for progression or death, 0.797; 95% CI, 0.637–0.999).[38] The QOL outcomes were similar between the 2 groups, with the most common adverse effects being arthralgia (17% vs 10%) and hot flashes (11% vs 10%) for fulvestrant and anastrozole, respectively.[38]

Fulvestrant + CDK 4/6 Inhibitor

In the phase III trial MONALEESA-3, patients (n=726) with advanced HR-positive breast cancer who had no prior endocrine therapy or had progressed on prior therapy, the combination of ribociclib with fulvestrant showed improved PFS versus fulvestrant alone (21 vs 13 months; HR, 0.59; 95% CI, 0.48–0.73).[39] The PFS benefits were consistent across patients with and without prior endocrine treatment. In a subsequent analysis, a significant improvement in OS was observed.[40] At 42 months, the estimated OS was 57.8% (95% CI, 52.0–63.2) in the ribociclib group and 45.9% (95% CI, 36.9–54.5) in the placebo group.[40]

SYSTEMIC THERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE[a,b,c]

HER2-Negative

Preferred Regimens

- Anthracyclines
  - Doxorubicin
  - Liposomal doxorubicin
- Taxanes
  - Paclitaxel
- Anti-metabolites
  - Capecitabine
  - Gemcitabine
- Microtubule inhibitors
  - Vinorelbine
  - Eribulin

- For germline BRCA1/2 mutations[d] see additional targeted therapy options (BINV-R)[e]
- Platinum (option for patients with triple-negative tumors and germline BRCA1/2 mutation)[d]
  - Carboplatin
  - Cisplatin
- For PD-L1–positive TNBC see additional targeted therapy options (BINV-R)[e]

Other Recommended Regimens[f]

- Cyclophosphamide
- Docetaxel
- Albumin-bound paclitaxel
- Epirubicin
- Ixabepilone

Useful in Certain Circumstances[f]

- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[g]
- Carboplatin + paclitaxel or albumin-bound paclitaxel

HER2-Positive[h,i]

Preferred regimens

- Pertuzumab + trastuzumab + docetaxel (category 1)[j]
- Pertuzumab + trastuzumab + paclitaxel[i]

Other recommended regimens

- Ado-trastuzumab emtansine (T-DM1)
- Fam-trastuzumab deruxtecan-nxki[k]
- Trastuzumab + paclitaxel[j] ± carboplatin
- Trastuzumab + docetaxel[j]
- Trastuzumab + vinorelbine[j]
- Trastuzumab + capecitabine
- Lapatinib + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[j,l,m]
- Neratinib + capecitabine
- See additional targeted therapy options (BINV-R)[e]

[a] Albumin-bound paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m².
[b] Consider scalp cooling to reduce incidence of chemotherapy-induced alopecia for patients receiving chemotherapy. Results may be less effective with anthracycline-containing regimens.
[c] For treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.†
[d] Assess for germline BRCA1/2 mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy.
[e] See Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease (BINV-R).
[f] Sequential single agents are preferred, but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis.
[g] Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.
[h] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[i] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine or fam-trastuzumab deruxtecan-nxki.
[j] Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.
[k] Fam-trastuzumab deruxtecan-nxki is indicated following two or more lines of prior HER2-targeted therapy in the metastatic setting. This agent is contraindicated for patients with pneumonitis or interstitial lung disease (ILD).
[l] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[m] Trastuzumab may be safely combined with all non-anthracycline containing preferred and other single agents listed above for recurrent or metastatic breast cancer.

†To view the most recent version of these guidelines, visit NCCN.org.

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Comparison across multiple trials, including those in the second-line settings, studying the combination of fulvestrant with palbociclib or abemaciclib have shown statistically significant improvement in PFS. Based on the results of the Monaleesa-3 trial and extrapolation results from the second-line setting, the NCCN panel has included fulvestrant in combination with CDK 4/6 inhibitors as a category 1 first-line option for postmenopausal women and premenopausal women with ovarian ablation/suppression with HR-positive, HER2-negative recurrent/stage IV breast cancer.

Fulvestrant + Nonsteroidal AI

Combination of 2 endocrine agents as first-line treatment in postmenopausal women with HR-positive metastatic breast cancer has been reported from studies comparing single-agent anastrozole versus anastrozole plus fulvestrant.

In one study (FACT), combination of fulvestrant with anastrozole was not superior to single-agent anastrozole (time to progression HR, 0.99; 95% CI, 0.81–1.20; P=.91).[41] In a second phase III trial (SoFEA), the effect of fulvestrant alone or in combination with anastrozole or exemestane was studied in patients with advanced breast cancer with acquired resistance to an nonsteroidal AI.[42] An AI had been given as adjuvant treatment to 18% of patients for a median of 27.9 months, and to 82% of patients for locally advanced/metastatic disease for a median of 19.3 months. Median PFS was 4.8 months, 4.4 months, and 3.4 months for patients treated with fulvestrant alone, anastrazole plus fulvestrant, and fulvestrant plus exemestane, respectively. No differences were observed for ORR, clinical benefit rate, and OS.

In the trial by the Southwest Oncology Group (SWOG), S0226, PFS (HR, 0.80; 95% CI, 0.68–0.94; stratified log-rank P=.007) and OS (HR, 0.81; 95% CI, 0.65–1.00; stratified P=.049) were superior with the combination of anastrozole plus fulvestrant.[43] A subgroup analysis in this trial suggested that patients without prior adjuvant tamoxifen experienced the greatest OS benefit with combination therapy compared with monotherapy (median, 52.2 vs 40.3 months, respectively; HR, 0.73; 95% CI, 0.58–0.92).[44]

The reasons for the divergent outcomes in these trials are not very clear. The 3 trials discussed previously had slightly different patient populations. For example, there were more cases of patients with no prior endocrine exposure (with de novo stage IV metastatic disease) in the SWOG S0226 trial compared with the FACT trial.

ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies					
Breast Cancer Subtype	**Biomarker**	**Detection**	**FDA-Approved Agents**	**NCCN Category of Evidence**	**NCCN Category of Preference**
Any[a]	*BRCA1* mutation *BRCA2* mutation	Germline sequencing	Olaparib	Category 1	Preferred
			Talazoparib	Category 1	Preferred
HR-positive/ HER2-negative[b]	*PIK3CA* mutation	PCR (blood or tissue block if blood negative), molecular panel testing	Alpelisib + fulvestrant[d]	Category 1	Preferred second-line therapy
HR-negative/ HER2-negative[c]	PD-L1 expression • Threshold for positivity: ≥1% on tumor-infiltrating immune cells	IHC	Atezolizumab + albumin-bound paclitaxel	Category 2A	Preferred
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[e]	Category 2A	Useful in certain circumstances[e]
			Entrectinib[e]	Category 2A	Useful in certain circumstances[e]
Any	MSI-H/dMMR	IHC, PCR (tissue block)	Pembrolizumab[f]	Category 2A	Useful in certain circumstances[f]

[a] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. While olaparib and talazoparib are FDA indicated in HER2-negative disease, the panel supports use in any breast cancer subtype associated with a germline *BRCA1* or *BRCA2* mutation.

[b] For HR-positive/HER2-negative breast cancer, assess for *PIK3CA* mutations with tumor or liquid biopsy if HR-positive/HER2-negative and if considering therapy with to identify candidates for alpelisib plus fulvestrant. *PIK3CA* mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended.

[c] For TNBC, assess PD-L1 expression biomarker status on tumor-infiltrating immune cells to identify candidates for atezolizumab plus albumin-bound paclitaxel.

[d] The safety of alpelisib in patients with Type 1 or uncontrolled Type 2 diabetes has not been established.

[e] Larotrectinib and entrectinib are indicated for the treatment of solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation and have no satisfactory alternative treatments or that have progressed following treatment.

[f] Pembrolizumab is indicated for the treatment of patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.

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The FACT trial included a more heterogeneous population of both premenopausal and postmenopausal women with locally advanced and metastatic disease. The SoFEA trial only enrolled patients with acquired endocrine resistance (who had disease progression while they were receiving an AI). Further studies are needed to confirm the results of the SWOG S0226 trial.

The NCCN panel has included an AI and fulvestrant as first-line therapy (category 1) for postmenopausal patients based on the previously noted data.

Monotherapy With Endocrine Agents

In postmenopausal women, there is evidence supporting the use of an AI as first-line therapy for recurrent disease.[45,46] Prospective randomized trials comparing AIs head-to-head have shown that all AIs are the same.[47] Tamoxifen is the commonly used selective estrogen- receptor modulator (SERM) for premenopausal women.[48] In postmenopausal women, AI monotherapy has been shown to have superior outcome compared with tamoxifen, although the differences are modest.[49–53] A randomized phase III trial comparing tamoxifen with exemestane as first-line endocrine therapy for postmenopausal women with metastatic breast cancer showed no significant differences in PFS or OS between the 2 arms.[51]

NCCN Recommendations for First-Line Therapy

For postmenopausal women with HR-positive, HER2-positive recurrent/stage IV breast cancer, NCCN category 1 preferred regimens include a CDK 4/6 inhibitor with an AI; fulvestrant with or without a CDK 4/6 inhibitor; fulvestrant with a nonsteroidal AI. The NCCN category 2A preferred regimen includes nonsteroidal AIs (anastrozole, letrozole); steroidal AI (exemestane), and SERM (tamoxifen or toremifene). For premenopausal women, first-line endocrine treatment includes ovarian suppression/ablation and endocrine therapy listed previously for postmenopausal women or alternately with a SERM alone.

Preferred Regimens for Second and Subsequent Lines of Therapy for HR-Positive, HER2-Negative Breast Cancer

Fulvestrant-Containing Regimens

Fulvestrant + CDK 4/6 Inhibitors

Fulvestrant in combination with a CDK 4/6 inhibitor may be offered to patients who experienced progression

during prior treatment with AIs with or without 1 line of prior chemotherapy (category 1), because PFS was improved compared with fulvestrant alone in a phase III trial (PALOMA-3).[54] The NCCN panel notes that treatment should be limited to those *without* prior exposure to CDK 4/6 inhibitors.

The phase III trial (PALOMA-3) compared the combination of palbociclib and fulvestrant to fulvestrant in pre- or postmenopausal patients with HR-positive, HER2-negative advanced breast cancer whose disease progressed on prior endocrine therapy. Pre- or perimenopausal patients also received goserelin. The median PFS was 9.5 months for the combination compared with 4.6 months for fulvestrant (HR, 0.46; $P<.000001$)[55] Grade 3/4 adverse events of palbociclib and fulvestrant were mainly confined to neutropenia (in 65% of patients).

In the MONARCH 2 phase III trial, patients who had progressed while receiving endocrine therapy were randomly assigned to fulvestrant with or without abemaciclib.[56] Those receiving combination therapy experienced an improved PFS relative to those receiving fulvestrant alone (16.4 vs 9.3 months; HR, 0.55; 95% CI, 0.45–0.68). The ORR was higher in those receiving abemaciclib and fulvestrant (48% vs 21%).[56] In addition, an improvement was seen in OS with abemaciclib plus fulvestrant compared with fulvestrant alone (46.7 vs 37.3 months; HR, 0.757; 95% CI, 0.606–0.945).[57]

Based on the previously cited data that shows that the addition of a CDK 4/6 inhibitor to fulvestrant in patients previously exposed to endocrine therapy provides a significant improvement in median PFS, the NCCN panel has included fulvestrant in combination with a CDK 4/6 inhibitor as a category 1 first-line option for postmenopausal women and premenopausal women with ovarian ablation/suppression with HR-positive, HER2- negative recurrent/stage IV breast cancer. The panel notes that if the disease progresses while on CDK4/6 inhibitor therapy, there are limited data to support an additional line of therapy with another CDK4/6-containing regimen.

Fulvestrant Monotherapy

Fulvestrant monotherapy appears to be at least as effective as anastrozole in patients whose disease progressed on previous tamoxifen.[58,59] A randomized phase II study compared anastrozole versus fulvestrant in more than 200 patients with advanced breast cancer.[33,34] In the initial analysis, fulvestrant was as effective as anastrozole in terms of ORR (36.0% vs 35.5%; odds ratio, 1.02; 95% CI, 0.56–1.87; $P=.947$) in evaluable patients (n=89 for fulvestrant and n=93 for anastrozole).[33] An improved time to progression was seen with fulvestrant compared with anastrazole (median time to progression was 23.4 months for fulvestrant vs 13.1 months for anastrozole; HR, 0.63; 95% CI, 0.39–1.00; $P=.0496$).[34] This study used a higher, 500 mg, loading dose every 2 weeks for 3 doses and then 500 mg monthly.[33] The median OS was observed to be longer in the fulvestrant group than in the anastrozole group (54.1 vs 48.4 months; HR, 0.70; $P=.041$).[35]

A phase II study of fulvestrant in postmenopausal women with advanced breast cancer and disease progression after AI therapy documented a partial response rate of 14.3% with an additional 20.8% of patients experiencing stable disease for at least 6 months.[60] The clinical benefit rates of exemestane versus fulvestrant observed in a phase III trial of postmenopausal women with HR-positive advanced breast cancer who experienced disease progression on prior nonsteroidal AI therapy were comparable (32.2% vs 31.5%; $P=.853$).[61] In that study, fulvestrant was administered as a 500 mg loading dose followed by doses of 250 mg on day 14 and day 28 and then monthly.[61]

Fulvestrant Plus Alpelisib

In a randomized phase III trial of patients (n=572) with advanced HR-positive breast cancer and confirmed phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) mutated tumors, all of whom had received a prior AI either for local or advanced disease, patients were randomized to receive fulvestrant plus the phosphoinositide 3-kinase (PI3K) inhibitor, alpelisib versus fulvestrant plus placebo. Patients receiving alpelisib showed improved PFS compared with fulvestrant alone. At a median follow-up of 20 months, PFS was 11.0 months (95% CI, 7.5–14.5) in the alpelisib group compared with 5.7 months (95% CI, 3.7–7.4) in the group that received fulvestrant alone (HR for progression or death, 0.65; 95% CI, 0.50–0.85; $P<.001$); in the cohort without PIK3CA-mutated tumors, the HR was 0.85 (95% CI, 0.58–1.25). In the overall population, the most frequently reported grade 3 or 4 adverse events seen with alpelisib and fulvestrant versus fulvestrant alone were hyperglycemia (36.6% vs 0.7%); rash (9.9% vs 0.3%) and diarrhea (grade 3; 6.7% vs 0.3%; no diarrhea of grade 4 was reported).[62]

Everolimus Plus Endocrine Therapy

Resistance to endocrine therapy in women with HR-positive disease is frequent. One mechanism of resistance to endocrine therapy is activation of the mammalian target of rapamycin (mTOR) signal transduction pathway.

A randomized phase II study estimated the efficacy of tamoxifen alone versus tamoxifen combined with everolimus, an oral inhibitor of mTOR, in women with HR-positive, HER2-negative metastatic breast cancer previously treated with an AI.[63] After a median follow-up

of 13 months, an intent-to-treat analysis showed that the clinical benefit was 42.1% (95% CI, 29.1–55.9) with tamoxifen alone and 61.1% (95% CI, 46.9–74.1) with tamoxifen plus everolimus. An improvement in median time to progression was seen when everolimus was combined with tamoxifen compared with tamoxifen alone. Median time to progression was 4.5 months (95% CI, 3.7–8.7) with tamoxifen alone versus 8.5 months (95% CI, 6.01–13.9) with everolimus and tamoxifen.[63]

A phase III trial in postmenopausal women with advanced, HR-positive breast cancer with no prior endocrine therapy for advanced disease that randomized subjects to letrozole with or without the mTOR inhibitor temsirolimus has been reported.[64] In this study, PFS was not different between the treatment arms (HR, 0.89; 95% CI, 0.75–1.05; long-rank P=.18).

The results of this trial differ from that of the BOLERO-2 trial (described subsequently). The reasons for the differences in the outcomes of these 2 randomized phase III studies[64,65] is uncertain, but may be related to the issues of patient selection and extent of prior endocrine therapy.

A phase III study (BOLERO-2) randomized postmenopausal women with HR-positive advanced breast cancer that had progressed or recurred during treatment with a nonsteroidal AI to exemestane with or without the mTOR inhibitor everolimus.[66] Final results reported after median 18-month follow-up show that median PFS (by central review) remained significantly longer with everolimus plus exemestane versus placebo plus exemestane at 11.0 versus 4.1 months, respectively; (HR, 0.38; 95% CI, 0.31–0.48; P<.0001).[65] The adverse events (all grades) that occurred more frequently in those receiving everolimus included stomatitis, infections, rash, pneumonitis, and hyperglycemia.[65,66] Analysis of safety and efficacy in the elderly patients enrolled in this trial showed that elderly patients treated with an everolimus-containing regimen had similar incidences of these adverse events, but the younger patients had more on-treatment deaths.[67] Based on the evidence from the BOLERO-2 trial, the NCCN panel has included everolimus plus exemestane as an option for women who fulfill the entry criteria for BOLERO-2. Tamoxifen or fulvestrant in combination with everolimus have also been included as options. The NCCN panel also notes that if there is disease progression while on an everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.

Aromatase Inhibitors

AIs as monotherapy are options as subsequent-line therapy. The 3 AIs (anastrozole, letrozole, and exemestane) have shown similar efficacy in the second-line setting.[47,68,69] AI monotherapy maybe be useful in patients desiring single-agent treatment, if they have not received an AI as first-line treatment or in patients who may not be suitable for combination therapy. Patients who have received a prior nonsteroidal AI may benefit from a steroidal AI as subsequent-line therapy or vice-versa.

Selective Estrogen Receptor Modulator

An analysis of 2 randomized studies of first-line treatment with anastrozole followed by second-line tamoxifen and vice versa showed that tamoxifen is effective as a second-line option.[70]

NCCN Recommendations for Second-Line Treatment

For postmenopausal women with HR-positive, HER2-positive recurrent/stage IV breast cancer, the preferred options available include fulvestrant with a CDK 4/6 inhibitor (palbociclib, ribociclib, abemaciclib) (category 1), or for those with tumor *PIK3CA* mutations, fulvestrant with alpelisib, everolimus with either an AI, tamoxifen, or fulvestrant; monotherapy with fulvestrant, nonsteroidal or steroidal AI, or SERM. Estrogen receptor 1–activating mutations are frequently detected in patients with prior exposure to AIs. Tumors with these mutations are generally resistant to both AIs and tamoxifen. Certain tumors with these mutations retain sensitivity to fulvestrant. All may benefit from the addition of a CDK 4/6 inhibitor, mTOR inhibitor, or alpelisib in combination with fulvestrant if the tumor has a *PIK3CA* mutation.

Regimens Useful in Certain Circumstances for Therapy for HR-Positive, HER2-Negative Breast Cancer

Megestrol acetate,[45,71–73] estradiol[74] androgens such as fluoxymesterone, and single agent abemaciclib have been listed as options useful in certain circumstances. The phase II MONARCH 1 trial evaluated the activity of abemaciclib as a single agent in patients (n=132) with refractory HR-positive, HER2-negative metastatic breast cancer who had progressed on endocrine therapy and already received multiple systemic therapies (average of 3 prior systemic regimens).[75] Ninety percent of patients had visceral disease, and 50.8% had more than 3 sites of metastases.[75] Single-agent abemaciclib induced partial response in 26 (19.7%) and demonstrated an ORR of 19.7% (95% CI: 13.3–27.5).[75] Median PFS was 6 months (95% CI: 4.2–7.5). At the final analysis, at 18 months, median OS was 22.3 months (95% CI: 17.7–not reached).[75] Diarrhea was the most frequent adverse event, reported in 90.2% of patients. Other common adverse events were fatigue (65.2%), nausea (64.4%), and decreased appetite (45.5%). Grade 3 and 4 neutropenia occurred in 26.9% of patients.[75] The NCCN panel has included single-agent

abemaciclib as an option for those with disease progression on prior endocrine therapy and prior chemotherapy in the metastatic setting.

Systemic Therapy for Stage IV or Recurrent HR-Negative, HER2-Positive Breast Cancer

For patients with HER2-positive, HR-negative recurrent/stage IV breast cancer, the treatment approach is HER2-targeted therapy in combination with systemic chemotherapy. The NCCN panel notes that an FDA-approved biosimilar is an appropriate substitute for trastuzumab. Also, trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. This subcutaneous option has different dosage and administration instructions compared with intravenous trastuzumab. Doses and schedules of representative regimens for use in HER2-positive metastatic breast cancer are also included in NCCN Guidelines.

Patients progressing on a HER2-targeted therapy should be offered additional subsequent treatment with a HER2-targeted therapy since it is beneficial to continue suppression of the HER2 pathway. The choice of the HER2-targeted therapy will depend on previously administered therapy, relapse-free interval, and patients' preference and access.

The optimal sequence of available HER2-targeted therapies and the optimal duration of HER2-targeted therapy for recurrent/stage IV is currently unknown. The NCCN panel recommends continuing HER2-targted therapy until progression or unacceptable toxicity.

Preferred Regimens for Stage IV/Recurrent HER2-Positive Breast Cancer

A randomized, double-blind, phase III study (CLEOPATRA) compared the efficacy and safety of pertuzumab in combination with trastuzumab and docetaxel versus trastuzumab and docetaxel as first-line treatment of 808 women (n=808) with HER2-positive metastatic breast cancer.[76] This trial included patients (about 10%) who had previously received trastuzumab in the adjuvant or neoadjuvant setting. At a median follow-up of 19 months, the addition of pertuzumab to docetaxel plus trastuzumab resulted in improvement in PFS compared with placebo (median, 18.5 vs 12.4 months; HR, 0.62; 95% CI, 0.51-0.75; $P<.001$).[76] At a median follow-up of 30 months, the results showed a statistically significant improvement in OS in favor of the pertuzumab-containing regimen, with a 34% reduction in the risk of death (HR, 0.66; 95% CI, 0.52–0.84; $P=.0008$).[77] The most common adverse reactions reported in the pertuzumab group compared with the control group were diarrhea (67% vs 46%), rash (34% vs 24%), mucosal inflammation (27% vs 20%), febrile neutropenia (14% vs 8%), and dry skin (10% vs 4%). Peripheral edema and constipation were greater in the control group.[76] Cardiac adverse events or left ventricular systolic dysfunction were reported slightly more frequently in the control group.[78] Health-related QOL was not different in the 2 treatment groups.[79] In the PERUSE study, patients (n=1,436) with advanced HER2-positive breast cancer and no prior systemic therapy (except endocrine therapy) received docetaxel, paclitaxel or nab-paclitaxel with trastuzumab, and pertuzumab until disease progression or unacceptable toxicity. The preliminary results after 52 months median follow-up show that median PFS was comparable between docetaxel, paclitaxel, and nab-paclitaxel (median PFS reported was 19.6, 23.0, and 18.1 months with docetaxel, paclitaxel, and nab-paclitaxel, respectively).[80] Compared with docetaxel-containing therapy, paclitaxel-containing therapy was associated with more neuropathy (31% vs 16%) but less febrile neutropenia (1% vs 11%) and mucositis (14% vs 25%).

Phase II trials have also found activity and tolerability for pertuzumab, pertuzumab with trastuzumab, and for other regimens combining pertuzumab and trastuzumab together with other active cytotoxic agents (ie, paclitaxel, vinorelbine).[81–83] Phase III trials of pertuzumab plus chemotherapy without trastuzumab have not been reported.

The NCCN panel recommends pertuzumab plus trastuzumab in combination with a taxane as a preferred option for first-line treatment of patients with HER2-positive metastatic breast cancer. Pertuzumab plus trastuzumab in combination with docetaxel is an NCCN category 1 and in combination with paclitaxel is an NCCN category 2A recommendation.

Other Regimens for Stage IV/Recurrent HER2-Positive Breast Cancer

Ado-trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that stably links the HER2-targeting property of trastuzumab to the cytotoxic activity of the microtubule-inhibitory agent DM1 (derivative of maytansine).

In a phase III trial (MARIANNE), 1,095 patients with locally advanced or metastatic breast cancer were randomized to first-line treatment with T-DM1 with or without pertuzumab or trastuzumab plus a taxane. The primary endpoints were safety and PFS assessed by independent review. The PFS for T-DM1 with pertuzumab was found noninferior to trastuzumab and a taxane (15.2 and 13.7 months respectively; HR, 0.87; 97.5% CI, 0.69–1.08; $P=.14$).[84] The PFS for T-DM1 alone was noninferior to trastuzumab plus a taxane (14.1 and 13.7, respectively; HR, 0.91; 97.5% CI, 0.73–1.13; $P=.31$).[84] The incidence of grade 3–5 adverse events was 54.1%, 45.4%, and 46.2% in the trastuzumab plus a taxane arm, T-DM1 arm, and T-DM1 plus pertuzumab arm, respectively.

Health-related QOL was maintained for a longer duration with a median of 7.7 months for T-DM1 (HR, 0.70; 95% CI, 0.57–0.86) and a median of 9 months for T-DM1 plus pertuzumab (HR, 0.68; 95% CI, 0.55–0.84) compared with a median of 3.9 months for trastuzumab and a taxane.[84]

Based on the MARIANNE trial data demonstrating T-DM1 and T-DM1 with pertuzumab being noninferior, with better QOL compared with trastuzumab plus taxane and possibly better-tolerated for some patients,[84] the NCCN panel included T-DM1 as an option for treatment of patients with HER2-positive metastatic breast cancer. Pertuzumab, trastuzumab, and a taxane, however, remains the preferred first-line regimen for HER2-positive metastatic disease based on data demonstrating improved OS compared with trastuzumab and a taxane. TDM-1 as first-line therapy should be considered only in those not suitable for the preferred treatment.

First-line trastuzumab in combination with selected chemotherapy[85] is an additional option for patients with HER2-positive metastatic breast cancer. Randomized trials demonstrate benefit from adding trastuzumab to other agents including paclitaxel with or without carboplatin,[85–88] docetaxel,[86] and vinorelbine,[86] for patients with HER2-positive metastatic disease. In addition, the combination of trastuzumab and capecitabine has also shown efficacy as a first-line trastuzumab-containing regimen in this setting.[89,90] The NCCN panel believes the 27% frequency of significant cardiac dysfunction in patients treated with the combination of trastuzumab and doxorubicin/cyclophosphamide chemotherapy in the metastatic setting is too high for use of this combination outside the confines of a prospective clinical trial.[85,90,91]

In those with disease progression on first-line trastuzumab-containing regimens, the NCCN panel recommends continuation of HER2 blockade. This recommendation also applies to patients who are diagnosed with HER2-positive metastatic disease after prior exposure to trastuzumab in the adjuvant setting. Several trials have demonstrated benefit of continuation of trastuzumab therapy after disease progression on a trastuzumab-containing regimen.[92–94] However, the optimal duration of trastuzumab in patients with long-term control of disease is unknown.

Pertuzumab is active in patients beyond the first-line setting. The results of a multicenter, open-label, single-arm, phase II study (n=66) show that the combination of pertuzumab and trastuzumab is active and well tolerated in patients with HER2-positive metastatic breast cancer that has progressed on prior trastuzumab therapy.[95] The trial reported an objective response rate of 24.2% (16 patients out of 66). The median PFS time observed with pertuzumab and trastuzumab combination was 15.5 months (range, 0.9–17.0 months; 80% CI, 18-31 months.[95] The reported median duration of response with the combination was 5.8 months (range, 2.9–15.3 months).[95]

To determine whether the clinical benefit seen in the study was from pertuzumab alone or was a result of the combined effect of pertuzumab and trastuzumab, a cohort of patients (n=29) whose disease progressed during prior trastuzumab-based therapy received pertuzumab monotherapy until progressive disease or unacceptable toxicity. Of these, patients with disease progression (n=17) continued to receive pertuzumab with the addition of trastuzumab. In the 29 patients who received pertuzumab monotherapy, the objective response rate and clinical benefit rate reported were 3.4% and 10.3%, respectively, whereas in the patients who received dual blockade after progression on pertuzumab, the objective response rate and clinical benefit rate were 17.6% and 41.2%, respectively.[96]

According to the NCCN panel, for patients with disease progression after treatment with trastuzumab-based therapy without pertuzumab, a line of therapy containing both trastuzumab plus pertuzumab with or without a cytotoxic agent (such as vinorelbine or taxane) may be considered. Further research is needed to determine the ideal sequencing strategy for HER2-targeted therapy.

T-DM1 also has also shown activity in the second-line setting. A randomized, international, multicenter, open-label, phase III study (EMILIA) evaluated the safety and efficacy of T-DM1 compared with lapatinib plus capecitabine for patients with HER2-positive locally advanced breast cancer or metastatic breast cancer previously treated with trastuzumab and a taxane.[97] The primary endpoints of this study were PFS, OS, and safety. T-DM1 demonstrated a statistically significant improvement in both primary endpoints of PFS and OS. PFS (assessed by independent review) was significantly improved with T-DM1, with a median PFS of 9.6 months vs 6.4 months with lapatinib plus capecitabine; HR for progression or death from any cause was 0.65 (95% CI, 0.55–0.77; $P<.001$). At the first interim analysis, T-DM1 also demonstrated significant improvement in OS. The stratified HR for death from any cause with T-DM1 versus lapatinib plus capecitabine was 0.62 (95% CI, 0.48–0.81; $P=.0005$).[97] Rates of grade 3 or 4 adverse events were higher with lapatinib plus capecitabine than with T-DM1 (57% vs 41%). The incidences of thrombocytopenia and increased serum aminotransferase levels were higher with T-DM1 (frequency >25%), whereas the incidences of diarrhea, nausea, vomiting, and palmar-plantar erythrodysesthesia were higher with lapatinib plus capecitabine.[97]

A phase II single-arm study evaluated fam-trastuzumab deruxtecan-nxki, a HER2 antibody conjugated with a

topoisomerase I inhibitor, in adults (n=184) with pathologically documented HER2-positive metastatic breast cancer who had received multiple previous treatments including treatment with T-DM1.[98] After a median duration of follow-up of 11.1 months (range 0.7– 19.9), the median response duration with fam-trastuzumab deruxtecan-nxki was 14.8 months (95% CI, 13.8–16.9), and the median PFS was 16.4 months (95% CI, 12.7–not reached).[98] Most commonly reported adverse events (grade 3 or higher) were a decreased neutrophil count (20.7%), anemia (in 8.7%), nausea (in 7.6%), and fatigue (6%).[98] Interstitial lung disease was reported in 13.6% of the patients (grade 1 or 2, 10.9%; grade 3 or 4, 0.5%; and grade 5, 2.2%). Based on this study and the approval from the US FDA, the NCCN panel has included this as an option for HER-2 positive metastatic disease noting that it is indicated in patients after 2 or more lines of prior HER2-targeted therapy regimens in the metastatic setting and contraindicated for those with a history of or active interstitial lung disease.

Lapatinib in combination with capecitabine or trastuzumab are options for patients with HER2-positive disease after progression on a trastuzumab-containing regimen.

A phase III study compared lapatinib plus capecitabine with capecitabine alone in women with advanced or metastatic breast cancer refractory to trastuzumab in the metastatic setting and with prior treatment with an anthracycline and a taxane in either the metastatic or adjuvant setting.[99] Time to progression was increased in the group receiving combination therapy when compared with the group receiving capecitabine monotherapy (8.4 vs 4.4 months; HR, 0.49; 95% CI, 0.34–0.71; $P<.001$). The patients who progressed on monotherapy were allowed to cross over to the combination arm. This resulted in insufficient power to detect significant differences in OS; an exploratory analysis showed a trend toward a survival advantage with lapatinib plus capecitabine.[100] The analysis reported a median OS of 75.0 weeks for the combination arm and 64.7 weeks for the monotherapy arm (HR, 0.87; 95% CI, 0.71–1.08; $P=.210$).[100]

Results from a phase III trial in which patients with heavily pretreated metastatic breast cancer and disease progression on trastuzumab therapy randomly assigned to trastuzumab plus lapatinib or lapatinib monotherapy showed that PFS was increased from 8.1 weeks to 12 weeks ($P=.008$) with the combination.[101] The OS analysis data showed that lapatinib plus trastuzumab improved median survival by 4.5 months, with median OS of 14 months for the combination therapy and 9.5 months for lapatinib alone (HR, 0.74; 95% CI, 0.57–0.97; $P=.026$).[102] This improvement in OS analysis included patients who were initially assigned to monotherapy and crossed over to receive combination therapy at the time of progression.[102] Based on the absence of data, the panel does not recommend the addition of chemotherapy to the trastuzumab and lapatinib combination.

In a phase II trial, patients (n=49) with progressive, HER2-positive disease and brain metastases (92% received central nervous system surgery and/or radiotherapy),[103] were treated with capecitabine plus neratinib, a second-generation (irreversible) pan-HER TKI inhibitor of the tyrosine kinase domains of EGFR, HER2 and HER4. The patients were separated based on prior lapatinib treatment. The combination therapy resulted in a central nervous system objective response rate of 49% (95% CI, 32%–66%), among lapatinib-naïve patients, and 33% (95% CI, 10%–65%) among those with prior lapatinib treatment.[103] Median PFS and OS among lapatinib-naïve patients was 5.5 and 13.3 months, and 3.1 and 15.1 months among those with prior lapatinib treatment. Grade 3 diarrhea occurred in 29% of patients.[103]

A prospective randomized phase III trial (NALA) randomized patients (n=621) with HER2-positive disease to neratinib in combination with capecitabine or lapatinib plus capecitabine until disease progression.[104] All enrolled patients received ≥2 lines of prior HER2-targeted treatment in the metastatic setting. Approximately 30% had received ≥3 prior treatment lines. About a third of all patients had received prior treatment with trastuzumab, pertuzumab, and T-DM1.

The ORR (32.8% vs 26.7%; $P=.1201$), the clinical benefit rate (44.5% vs 35.6%; $P=.0328$), and median duration of response (8.5 vs 5.6 months) all favored the neratinib arm. Fewer patients required intervention for central nervous system metastases with neratinib. The risk of progression was reduced by 24% in the neratinib group (HR, 0.76; 95% CI, 0.63–0.93; $P=.0059$). There was a nonsignificant trend toward improved survival. The OS rates at 6 and 12 months were 90.2% vs 87.5% with neratinib plus capecitabine compared with 72.5% vs 66.7% for lapatinib in combination with capecitabine (HR, 0.88; 95% CI, 0.72–1.07; $P=.2086$). Diarrhea was the most frequent side effect in the NALA trial in both arms, but a higher rate was observed in patients in the neratinib group (any grade diarrhea, 83% vs 66%; grade 3/4 diarrhea, 24% vs 13%). Based on the results of the NALA trial and the recent FDA approval, NCCN has included neratinib plus capecitabine as a category 2A option in this setting.

Systemic Therapy for Recurrent or Stage IV HR-Positive, HER2-Positive Breast Cancer

Women with stage IV or recurrent disease characterized by HR-positive, HER2-positive tumors have the option of receiving HER2-directed therapy as a component of their treatment plan. Options include treatment with a

HER2-targeted therapy plus chemotherapy or endocrine therapy alone or in combination with HER2-targeted therapy. Endocrine therapy alone or in combination with HER2-targeted therapy is a less toxic approach compared with HER2-targeted therapy combined with chemotherapy. Premenopausal women treated with HER2-targeted therapy and endocrine therapy should receive ovarian suppression or ablation.

Adding trastuzumab or lapatinib to an AI has demonstrated a PFS advantage compared with AI alone in postmenopausal women with stage IV or recurrent HR-positive, HER2-positive tumors.

In the TAnDEM study, postmenopausal women (n=207) with metastatic HR-positive and HER2-positive tumors were randomized to receive anastrozole alone or anastrozole plus trastuzumab.[105] Compared with single-agent anastrozole, an improvement in PFS was seen with combination therapy (4.8 vs 2.4 months; HR, 0.63; 95% CI, 0.47–0.84; *P*=.0016). The combination was associated with a higher incidence of toxicities (all grades), fatigue (21% vs 9%), diarrhea (20% vs 8%), vomiting (21% vs 4%), and pyrexia (18% vs 7%); serious (grade 3/4) toxicities were rare in both treatment arms.

The phase III eLEcTRA trial studied the efficacy and safety of trastuzumab plus letrozole in patients (n=93) with HER2-positive and HR-positive metastatic breast cancer. Median time to progression was 3.3 months with letrozole and 14.1 months with trastuzumab plus letrozole. The results are consistent with the TAnDEM trial; however, due to smaller numbers of patients enrolled in this trial, this was not statistically significant (HR, 0.67; 95% CI, 0.35 to 1.29; *P*=.23).[106]

In a phase III study of postmenopausal patients (n=219) with HER2-positive and HR-positive disease, first-line treatment with lapatinib plus letrozole reduced the risk of disease progression compared with treatment with letrozole alone (median PFS, 8.2 vs 3.0 months; HR, 0.71, 95% CI, 0.53–0.96; *P*=.019).[107] The combination of letrozole plus trastuzumab was associated with a higher rate of grade 3 or 4 toxicities, including diarrhea (10% vs 1%) and rash (1% vs 0%).[107]

In a randomized phase II study (PERTAIN), postmenopausal women (n=258) were randomly assigned to either first-line pertuzumab plus trastuzumab and an AI (anastrozole or letrozole) or trastuzumab plus an AI. Results showed an improvement in PFS with the 3-drug combination (18.9 vs 15.8 months; HR, 0.65; 95% CI, 0.48–0.89).[108] Grade 3 or higher adverse events observed were higher with trastuzumab and pertuzumab versus pertuzumab alone (50% vs 39%). Of note, about half of women received induction therapy with a taxane for 18 to 24 weeks before the start of endocrine therapy. Based on the results of the PERTAIN trial,[108] the NCCN panel notes that if treatment was initiated with chemotherapy and trastuzumab plus pertuzumab and the chemotherapy was stopped, endocrine therapy may be added to the trastuzumab plus pertuzumab.

In the ALTERNATIVE trial, postmenopausal women (n=355) with HER2-positive, HR-positive metastatic breast cancer were randomized to receive lapatinib plus trastuzumab plus an AI, lapatinib plus an AI, or trastuzumab plus AI without chemotherapy.[109] All patients in the trial received prior trastuzumab and prior endocrine therapy, either in the adjuvant or metastatic disease setting. AI in combination with lapatinib plus trastuzumab demonstrated significant increase in PFS compared with trastuzumab without lapatinib (11 vs 5.7 months; HR, 0.62; 95% CI, 0.45–0.88; *P*=.0064).[109] Most common adverse events with the combination compared with trastuzumab or lapatinib monotherapy were diarrhea (69%, 9%, 51%), rash (36%, 2%, 28%), nausea (22%, 9%, 22%), and paronychia (30%, 0%, 15%).

The NCCN panel has also included other combinations of available endocrine therapies such as fulvestrant or tamoxifen with trastuzumab as options for HR-positive and HER2-positive metastatic disease. These options would be mostly considered after completion of chemotherapy plus HER2-therapy or in a few patients with indolent or asymptomatic disease based on the need for continuing HER2-targeted therapy for disease control. The selection of appropriate endocrine therapy would depend on agents the patient has already received and/or progressed on.

Systemic Therapy for Recurrent or Stage IV Disease With Germline BRCA1/2 Mutations

About 5% of all patients with breast cancer carry the germline breast cancer susceptibility gene (*BRCA)* mutations and rates of these mutations are higher among those with HER2-negative disease.[110,111]

Poly (ADP-Ribose) Polymerase Inhibitors

The phase III OlympiAD trial randomized patients (n=302) with metastatic breast cancer harboring the germline *BRCA* mutations to the poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib (n=205), or physicians choice (n=97) of nonplatinum chemotherapy (capecitabine, eribulin, or vinorelbine).[112] An improvement in PFS was seen in those receiving olaparib relative to those receiving chemotherapy (7.0 vs 4.2 months; HR, 0.58; 95% CI, 0.43–0.80; *P*<.001).[112] The study included all subtypes: those with HR-positive, HER2-negative and -positive, and triple-negative disease. The PFS improvements noted with olaparib were noted in all subtypes and greatest in the triple-negative population. Subsequent follow-up did not show a statistically significant difference in OS between treatment arms, and the study was also not powered to evaluate OS. The median OS with olaparib compared with treatment of physician's choice

was 19.3 months versus 17.1 months, respectively (HR, 0.90; 95% CI, 0.66–1.23; *P*=.513).[113] QOL was significantly better in the olaparib arm. It is interesting to note that patients who had not received prior chemotherapy in the metastatic setting achieved a 7.9-month longer median OS compared with treatment of physician's choice.[113]

In the phase III EMBRACA trial, patients with advanced breast cancer harboring the germline *BRCA* mutations to a PARP inhibitor were randomized to talazoparib (n=287) or to physicians choice of single-agent chemotherapy (n=144).[114] The median PFS among patients in the talazoparib group was longer than the control group (8.6 months [95% CI, 7.2–9.3] vs 5.6 months [95% CI, 4.2–6.7]; HR for disease progression or death, 0.54; 95% CI, 0.41 to 0.71; *P*<.001).[114] The comparator arms of OlympiAD and EMBRACA did not include patients previously treated with either taxanes or platinum agents.

Based on the results of the previously discussed phase II trials, the 2 FDA approved PARP inhibitors, olaparib and talazoparib, are included as category 1 preferred options for those with germline *BRCA1/2* mutations. The NCCN panel recommends assessing for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. Although olaparib and talazoparib are FDA indicated in HER2-negative disease, the NCCN panel supports use in any breast cancer subtype associated with germline *BRCA1/2* mutations.

Platinums

The phase III TNT trial compared docetaxel with carboplatin in the first-line setting in women (n=376) with triple-negative breast cancer. In the unselected population, carboplatin was not more active than docetaxel (ORR, 31.4% vs 34.0%; *P*=.66).[115] Patients with a germline *BRCA1/2* mutation had a significantly better response to carboplatin than docetaxel (ORR, 68.0% vs 33.3%, absolute difference, 34.7%; *P*=.03).[115] PFS was also improved with carboplatin treatment in patients with a germline *BRCA1/2* mutation (median PFS, 6.8 vs 4.4 months), no difference was found in OS. However, patients with somatic *BRCA1/2* mutation in the tumor DNA did not appear to have the same advantage.

For those with triple-negative recurrent or stage IV breast cancer and germline *BRCA1/2* mutations, the NCCN panel has included platinum agents (cisplatin and carboplatin) as preferred treatment options. It is unknown how PARP inhibitors compare with platinum agents in this setting.

Systemic Therapy for PD-L1–Positive, Triple-negative, Recurrent or Stage IV Disease

In a randomized trial (IMpassion 130), patients (n=902) with triple-negative breast cancer who had not received treatment in the metastatic setting were randomized to the programmed cell death ligand 1 (PD-L1) inhibitor atezolizumab plus albumin-bound paclitaxel or placebo plus albumin-bound paclitaxel.[116]

All patients enrolled in the trial had to have completed previous chemotherapy (preoperative or adjuvant) at least 12 months before randomization and not received any chemotherapy in the metastatic setting. At a median follow-up of 12.9 months, there was statistically significant difference in PFS in those receiving atezolizumab plus albumin-bound paclitaxel than in the placebo plus albumin-bound paclitaxel (7.2 vs 5.5 months; HR for progression or death, 0.80; 95% CI, 0.69–0.92), and a nonsignificant trend toward improved OS (21.3 vs 17.6 months; HR for death, 0.84; 95% CI, 0.69–1.02).[116] However, in a planned subset analysis of patients with PD-L1-expressing tumors, treatment with atezolizumab plus albumin-bound paclitaxel showed statistically significant improvement in PFS (7.5 vs 5 months; HR, 0.62; 95% CI, 0.49–0.78), and OS (25 vs 15.5 months; HR, 0.62; 95% CI, 0.45–0.86).[116] Grade 3 or higher adverse events occurred in 48.7% receiving atezolizumab plus albumin-bound paclitaxel versus 42.2% receiving placebo plus albumin-bound paclitaxel. Grade 3 or 4 neuropathy was more frequently seen among those receiving atezolizumab (5.5% vs 2.7%). There were 3 treatment-related deaths among the patients who received atezolizumab, consistent with other studies of checkpoint inhibitors. Adverse events led to treatment discontinuation in 16% in the atezolizumab arm versus 8% in the control arm.[116] PD-L1-positive expression in tumor-infiltrating immune cells of 1% or more has been associated with a better outcome with PD-L1 inhibitor treatment.[117] A subsequent 18-month follow-up analysis confirmed PFS and OS benefits among those with PD-L1-expressing tumors.[118] Atezolizumab plus albumin-bound paclitaxel is included as a preferred option for those with advanced triple-negative breast cancer with PD-L1 expression in ≥1% tumor-infiltrating immune cells.

Systemic Chemotherapy for Recurrent or Stage IV Disease

Women with HR-negative tumors not localized to the bone or soft tissue only or that are associated with symptomatic visceral metastasis irrespective of HR- or HER-status, or that have HR-positive tumors that are refractory to endocrine therapy should receive systemic chemotherapy.

A variety of chemotherapy regimens are felt to be appropriate, as outlined in the treatment algorithm. Combination chemotherapy generally provides higher rates of objective response and longer time to progression, in comparison with single-agent chemotherapy. Combination chemotherapy is, however, associated with an increase in toxicity and is of little survival

benefit.[119–123] Furthermore, administering single agents sequentially decreases the likelihood that dose reductions will be needed. Thus, the NCCN panel finds no compelling evidence that combination chemotherapy is superior to sequential single agents. Therefore, sequential monotherapy is preferred and combination therapy is useful in patients with rapid clinical progression or need for rapid symptom and/or disease control.

Usually the first-line regimens are given until progression or unacceptable toxicity. What is unacceptable toxicity and considering no further cytotoxic therapy should be decided together with the patient. Adverse effects may require dose reduction and cessation of chemotherapy prior to disease progression.

The NCCN panel recommends considering scalp cooling to reduce incidence of chemotherapy-induced alopecia for patients receiving chemotherapy. The data on efficacy of scalp cooling is mainly from the adjuvant setting and also show that results may be less effective with anthracycline-containing regimens.[124–128]

A meta-analysis showed favorable impact on OS by prolonging treatment until disease progression.[129] In this analysis, data from 4 studies involving 666 patients indicated that median OS was increased by 23% (95% CI, 9%–38%; P=.01) in women receiving longer durations of chemotherapy versus a limited number of cycles.[129] In a systematic review, longer durations of chemotherapy demonstrated a marginal increase in OS (HR, 0.91; 95% CI, 0.84–0.99) and a significant improvement in PFS (HR, 0.66; 95% CI, 0.6–0.72), compared with shorter durations.[123]

A more recent study of patients (n=420) with HER2-negative, advanced breast cancer showed that intermittent first-line treatment with paclitaxel plus bevacizumab was not inferior to continuous treatment. The median overall PFS for intermittent versus continuous was 7.4 months and 9.7 months, respectively (HR, 1.17; 95% CI, 0.88–1.57). Median OS was 17.5 months versus 20.9 months for intermittent versus continuous treatment, with a HR of 1.38 (95% CI, 1.00–1.91).[130]

Determining the duration of chemotherapy in an individual patient typically depends on the efficacy and tolerability and shared decision-making between the treating physician and patient. Most patients will be candidates for multiple lines of systemic therapies for palliation. At each reassessment, clinicians should assess value of ongoing treatment, the risks and benefits of an additional line of systemic therapy, patient performance status, and patient preferences through a shared decision-making process.

Preferred Chemotherapy Regimens for Stage IV or Recurrent Metastatic Disease

The NCCN panel has classified the chemotherapy agents into 3 categories: "preferred," "other recommended," and "useful in certain circumstances." The treatment decision should be individualized and consider previous therapies, pre-existing comorbidities, nature of the disease, toxicity profiles, patient preferences, and in some cases access to agents.

Among preferred single agents, the NCCN panel has included taxanes (paclitaxel), anthracyclines (doxorubicin and liposomal doxorubicin), antimetabolites (capecitabine and gemcitabine), microtubule inhibitors (eribulin and vinorelbine), and platinum agents for patients with triple-negative tumors and germline *BRCA1/2* mutations.

Paclitaxel can be administered weekly (80 mg/m^2)[131] or every 3 weeks (175 mg/m^2).[88] A meta-analysis of randomized controlled trials that compared weekly and every-3-week taxanes regimens in advanced breast cancer showed that compared with every-3-week treatment, weekly administration of paclitaxel resulted in an improvement in OS (HR, 0.78; 95% CI, 0.67–0.89).[132]

Doxorubicin 60–75 mg/m^2 every 3 weeks or 20 mg/m^2 weekly has shown an ORR between 30% and 47%.[133–136] Liposomal doxorubicin (50 mg/m^2 every 4 weeks) has been shown to have efficacy similar to doxorubicin (60 mg/m^2 every 3 weeks).[137] It has also been shown to have efficacy in the second-line setting for patients with metastatic breast cancer.[137] Compared with doxorubicin, liposomal doxorubicin has a less-frequent dosing schedule and decreased risk of cardiotoxicity (7% vs 26%; HR, 3.16; 95% CI, 1.58–6.31), decreased rate of nausea (37% vs 53%) and vomiting (19% vs 31%), lower rates of alopecia (20% vs 66%), and neutropenia (4% vs 10%).[137] However, compared with doxorubicin, it was associated with a higher rate of palmar-plantar erythrodysesthesia (48% vs 2%), stomatitis (22% vs 15%), and mucositis (23% vs 13%).[137]

The benefit of capecitabine as a treatment option for patients with metastatic breast cancer has been demonstrated in multiple phase II trials. Results of one study of patients (n=126) treated with capecitabine showed ORR of 28%, median time to progression of 4.9 months and median OS of 15.2 months (95% CI, 13.5–19.6 months).[138] In another study, women (n=95) were randomized to receive capecitabine or cyclophosphamide, methotrexate, and fluorouracil (CMF).[139] Treatment with single agent capecitabine resulted in a higher ORR compared with CMF (30% vs 16%). The median time to progression and OS were similar in both groups.[139]

Eribulin is a nontaxane microtubule inhibitor used for the treatment of patients with metastatic breast cancer who have previously received at least 2 chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting. In a phase III trial, patients (n=762) with

metastatic breast cancer were randomized 2:1 to eribulin or treatment of physicians' choice. The OS was improved in women assigned to eribulin (median 13.1 months; 95% CI, 11.8–14.3) compared with those receiving other treatments (10.6 months; 9.3–12.5), a 19% statistically significant risk reduction (HR, 0·81, 95% CI, 0.66–0.99; P=.041).[140]

A phase III trial compared eribulin with capecitabine in patients with metastatic breast cancer and showed that both treatments were similar with respect to OS and PFS.[141] The median PFS times for eribulin and capecitabine were 4.1 and 4.2 months, respectively (HR, 1.08; 95% CI, 0.93–1.25; P=.30) and the OS with eribulin versus capecitabine was 15.9 versus 14.5 months (HR, 0.88; 95% CI, 0.77–1.00).[141]

In addition to the previously noted, gemcitabine[142] and vinorelbine are both active as single agents even in heavily pretreated patients with metastatic breast cancer.[143–145] Among other recommended single agents, the NCCN panel has included taxanes (docetaxel,[146] albumin-bound paclitaxel[147–149]), anthracyclines (epirubicin)[150]), and ixabepilone.[151–153] as other recommended regimens.

Ixabepilone as monotherapy has been evaluated in several phase II trials of women with metastatic breast cancer: in a first-line setting in patients previously treated with anthracycline chemotherapy[151]; in patients with taxane-resistant metastatic breast cancer[152]; and in patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine.[153] In the phase II trials, ORR, median duration of response, and median OS duration were 41.5% (95% CI, 29.4%–54.4%), 8.2 months (95% CI, 5.7–10.2 months), and 22.0 months (95% CI, 15.6–27.0 months) in the first-line setting[151]; 12% (95% CI, 4.7%–26.5%), 10.4 months, and 7.9 months for the taxane-resistant patients[152]; and 11.5% (95% CI, 6.3%–18.9%), 5.7 months, and 8.6 months for the patients previously treated with an anthracycline, a taxane, and capecitabine.[153] In the study by Perez et al,[153] grade 3/4 treatment-related toxicities included peripheral sensory neuropathy (14%) and neutropenia (54%).

The NCCN panel had included combination chemotherapy regimens as useful in certain circumstances. The combination regimen options include doxorubicin/cyclophosphamide (AC)[154,155]; epirubicin/cyclophosphamide (EC)[156]; docetaxel and capecitabine[121]; gemcitabine and paclitaxel (GT)[157]; cyclophosphamide/methotrexate/fluorouracil (CMF)[158]; gemcitabine/carboplatin[159–161]; carboplatin with paclitaxel or albumin-bound paclitaxel[162–164]; and paclitaxel/bevacizumab.[165–167]

For the doublet regimens that are included, randomized phase III trials have shown that the ORR with first-line AC treatment ranges from 47% to 54% and OS is around 20 months.[154,155] For first-line EC, the ORR reported from a phase III trial is 7.1 months and OS was 14 months.[156] For first-line capecitabine/docetaxel, a phase III trial reported an ORR of 53% and time to progression of 11 months.[168] In the second-line setting, another phase III trial compared the efficacy and tolerability of capecitabine/docetaxel therapy in anthracycline-pretreated patients and showed significantly superior efficacy in time to disease progression (HR, 0.652; 95% CI, 0.545–0.780; P=.0001; median, 6.1 vs 4.2 months), OS (HR, 0.775; 95% CI, 0.634–0.947; P=.0126; median, 14.5 vs 11.5 months), and ORR (42% v 30%, P=.006) compared with single-agent docetaxel.[121]

Combination chemotherapy regimens containing a platinum agent or a taxane have been shown to be efficacious in patients with metastatic triple-negative breast cancer. A randomized phase II study compared the addition of iniparib to gemcitabine/carboplatin versus gemcitabine/carboplatin in patients with triple-negative breast cancer who had received no more than 2 prior chemotherapies. ORR was similar in both groups: 30.2% (95% CI, 24.6–35.8) with gemcitabine/carboplatin,[159] and the median OS was 11.1 months with gemcitabine/carboplatin (HR, 0.88; 95% CI, 0.69–1.12).[159]

Several phase II studies have evaluated the efficacy of paclitaxel/carboplatin as first-line treatment for patients with metastatic breast cancer and found the combination to be an effective therapeutic option in this setting.[163,164] The randomized trial, tnAcity, evaluated the efficacy and safety of first-line albumin-bound paclitaxel plus carboplatin, albumin-bound paclitaxel plus gemcitabine, and gemcitabine plus carboplatin in patients with metastatic triple-negative breast cancer.[162] The results of this trial reported that median PFS was significantly longer with albumin-bound paclitaxel plus carboplatin versus albumin-bound paclitaxel/gemcitabine (8.3 vs 5.5 months; HR, 0.59; 95% CI, 0.38–0.92; P=.02) or gemcitabine/carboplatin (8.3 vs 6.0 months; HR, 0.58; 95% CI, 0.37–0.90; P=.02). The median OS was also longer with albumin-bound paclitaxel plus carboplatin versus albumin-bound paclitaxel/gemcitabine (16.8 vs 12.1 months; HR, 0.73; 95% CI, 0.47–1.13; P=.16) or gemcitabine/carboplatin (16.8 vs 12.6 months; HR, 0.80; 95% CI, 0.52–1.22; P=.29). The ORRs were 73%, 39%, and 44%, respectively.[162]

A series of trials have sought to define the role for bevacizumab in the treatment of metastatic breast cancer. The E2100 trial randomized 722 women with recurrent or metastatic breast cancer to first-line chemotherapy with paclitaxel with or without bevacizumab.[165] This trial documented superior PFS (11.8 vs 5.9 months; HR, 0.60; P<.001) favoring bevacizumab plus paclitaxel compared with paclitaxel alone. A similar trial enrolled 736 patients who were randomized to treatment with docetaxel and

bevacizumab or docetaxel and placebo.[169] This trial also documented increased PFS in the arm containing bevacizumab (10.1 vs 8.2 months with docetaxel alone; HR 0.77; P=.006). An additional trial, RIBBON-1, combined bevacizumab with capecitabine, with a taxane (docetaxel, nab-paclitaxel), with anthracyclines (FEC, CAF, AC, or EC), or with the same chemotherapy alone. Results of this trial show a statistically significant increase in PFS with bevacizumab and capecitabine (8.6 vs 5.7 months; HR, 0.69; P<.001) and taxane- or anthracycline- (9.2 months vs 8.0 months; HR, 0.64; P<.001) containing arms.[166,167] In a subset analysis of the phase III CALGB 40502 trial, for patients (n=201) with metastatic triple-negative breast cancer, first-line albumin-bound paclitaxel in combination with bevacizumab resulted in a median PFS of 7.4 months.[170]

The NCCN panel notes that albumin-bound paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m^2.

The data from the previously mentioned randomized trials document that the addition of bevacizumab to first- or second-line chemotherapy agents modestly improves time to progression and response rates. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel. None of these studies demonstrates an increase in OS or QOL when analyzed alone or in a meta-analysis of the trials.[171] Therefore, the NCCN panel has included bevacizumab in combination with paclitaxel as an option useful in only select circumstances.

The only triplet regimen listed as an option in the metastatic setting is CMF. This regimen was compared in the first-line setting with capecitabine monotherapy, and results show similar ORR and PFS.[158] However, CMF resulted in a shorter OS (median, 22 vs 18 months; HR, 0.72; 95% CI, 0.55–0.94) compared with capecitabine.

Additional Targeted Therapies for Stage IV Disease Useful in Certain Circumstances

Neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusions are seen in a few rare types of cancer, such as secretory carcinoma of the breast or salivary gland and infantile fibrosarcoma and also infrequently in some common cancers, such as melanoma, glioma, and carcinomas of the thyroid, lung, and colon.[172] *NTRK* fusions are identified by fluorescence in situ hybridization, next generation sequencing, or polymerase chain reaction. Larotrectinib[173–175] and entrectinib[175,176] are 2 NTRK-inhibitors that are FDA approved for the treatment of solid tumors that have an NTRK gene fusion without a known acquired resistance mutation and have no satisfactory alternative treatments or that have progressed following treatment. If a patient with recurrent or stage IV breast cancer presents with a tumor with an *NTRK* fusion, treatment with an NTRK inhibitor is an option if no satisfactory alternative treatment exists or that have progressed following treatment.

Pembrolizumab is FDA approved for the treatment of patients with unresectable or metastatic, microsatellite instability-high or mismatch repair deficient solid tumors that have progressed after prior treatment and who have no satisfactory alternative treatment options.[177–179] Pembrolizumab has demonstrated antitumor activity in heavily pretreated patients with metastatic breast cancer and high tumor mutation burden (≥9 mutations/megabase) determined by commercially available tests.[180] If patient with recurrent or stage IV breast cancer has a tumor with microsatellite instability-high/mismatch repair deficient mutation, whose disease has progressed after prior treatments and no satisfactory alternative treatment options, treatment with pembrolizumab is an option.

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The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:
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