NCCN Guidelines® Insights


Featured Updates to the NCCN Guidelines

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Abstract

These NCCN Guideline Insights highlight the important updates to the systemic therapy recommendations in the 2016 NCCN Guidelines for Breast Cancer. In the most recent version of these guidelines, the NCCN Breast Cancer Panel included a new section on the principles of preoperative systemic therapy. In addition, based on new evidence, the panel updated systemic therapy recommendations for women with hormone receptor–positive breast cancer in the adjuvant and metastatic disease settings and for patients with HER2-positive metastatic breast cancer. This report summarizes these recent updates and discusses the rationale behind them. (J Natl Compr Canc Netw 2015;13:1475–1485)

Please Note

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

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Learning Objectives:
Upon completion of this activity, participants will be able to:
• Integrate into professional practice the updates to the NCCN Guidelines for Breast Cancer
• Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Breast Cancer

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**Principles of Preoperative Systemic Therapy**

- Randomized trials demonstrate similar long-term outcomes when patients are given the same treatment preoperatively compared with postoperatively.1
- Preoperative systemic therapy can render surgically inoperable tumors operable and offers potential benefits for patients with operable breast cancer. Importantly, preoperative systemic therapy can improve rates of breast conservation therapy eligibility and provides an opportunity to observe clinical and pathologic response to systemic therapy in an individual patient.
- Pathologic complete response (pCR) to preoperative systemic therapy is associated with an extremely favorable disease-free and overall survival, particularly in situations in which all treatment is given preoperatively. The correlation between pathologic response and long-term outcome is strongest for triple-negative breast cancer (TNBC), somewhat less so for HER2+ disease, and least for ER+ disease.2,3
- A number of chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting may be considered in the preoperative setting. See Preoperative/Adjuvant Therapy Regimens (BINV-K).
- Endocrine therapy alone (aromatase inhibitor [preferred for postmenopausal women; given with ovarian suppression for premenopausal women] or tamoxifen) may be considered for patients with hormone-receptor positive disease.
- Patients with HER2-positive tumors should be treated with preoperative systemic therapy incorporating trastuzumab for at least 9 weeks of preoperative therapy. A pertuzumab-containing regimen may be administered preoperatively to patients with greater than or equal to T2 or greater than or equal to N1, HER2-positive early stage breast cancer. See Preoperative/Adjuvant Therapy Regimens (BINV-K).

**Clinical Trials**

- Some studies have reported an increased risk of locoregional recurrence in patients receiving preoperative systemic therapy compared with those receiving postoperative adjuvant systemic therapy.4 This increased risk of locoregional relapse has been attributed to suboptimal delivery of definitive local therapy in patients treated in the preoperative setting.
- Not all patients are appropriate candidates for preoperative systemic therapy. Accurate clinical staging at baseline prior to initiation of preoperative systemic therapy is critical. See Preoperative Systemic Therapy: Breast and Axillary Evaluation (BINV-11).
- When electing preoperative therapy, all treatment should be given prior to surgery. Tumor response should be routinely assessed by clinical exam during delivery of preoperative therapy. Patients with operable breast cancer experiencing progression of disease during preoperative systemic therapy should be taken promptly to surgery. Locoregional therapy principles should be applied in the same manner as in patients treated with adjuvant systemic therapy.

**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 for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

**Overview**

Breast cancer is the most common malignancy in women in the United States and is second only to lung cancer as a cause of cancer death. The American Cancer Society estimates that 234,190 Americans will be diagnosed with breast cancer and 40,730 will die of the disease in the United States in 2015.1 The therapeutic options for patients with noninvasive or invasive breast cancer are complex and varied. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer include up-to-date guidelines for the clinical management of patients with carcinoma in situ, invasive breast cancer, Paget’s disease, Phyllodes tumor, inflammatory breast cancer, and breast cancer during pregnancy. These guidelines are developed by a multidisciplinary panel of representatives from NCCN Member Institutions with breast cancer–focused expertise in the fields of medical oncology, surgical oncology, radiation oncology, pathology, reconstructive surgery, and patient advocacy.
These NCCN Guidelines Insights highlight the important updates/changes specific to the update of systemic therapies in the 2016 version of the NCCN Guidelines for Breast Cancer. These include an outline of the principles of preoperative systemic therapy; new adjuvant endocrine therapy options for premenopausal women and for women with hormone receptor–positive, recurrent, or stage IV disease; and updated recommendations for adoctrastuzumab emtansine (T-DM1) for patients with HER2-positive metastatic breast cancer.

**Principles of Preoperative Systemic Therapy**

The NCCN Breast Cancer Panel has outlined the rationale, appropriate patient selection, and response assessment for preoperative systemic therapy in a new section titled “Principles of Preoperative Systemic Chemotherapy” (see BINV-L, pages 1477–1478).

**Rationale for Preoperative Chemotherapy**

Randomized clinical trials have found no significant differences in long-term outcomes when systemic chemotherapy is given before or after surgery. Historically, a primary advantage of administering preoperative systemic therapy has been to improve surgical outcomes. Preoperative systemic therapy can render inoperable tumors resectable and also allow the downstaging of patients with operable breast cancer who desire breast conservation. Results from large clinical trials and retrospective reviews indicate that breast-conservation rates are improved with preoperative systemic therapy. Clinicians need to carefully consider the extent of disease in the breast and the likelihood of adequate tumor response before recommending preoperative systemic therapy in order to improve the likelihood of successful breast conservation.

In addition, use of preoperative systemic therapy may provide important prognostic information based on response to therapy, particularly in patients with triple-negative and HER2-positive breast cancer.

ADJUVANT ENDOCRINE THERAPY

Premenopausal1 at diagnosis
- Tamoxifen for 5 y (category 1)
- Aromatase inhibitor for 5 y + ovarian suppression or ablation (category 1)

Postmenopausal1
- Aromatase inhibitor for 5 y (category 1)
- Consider tamoxifen for an additional 5 y to complete 10 y

Premenopausal1
- Tamoxifen for 2–3 y or
- Aromatase inhibitor3 for 2–3 y (category 1)

Postmenopausal1 at diagnosis
- Tamoxifen4 for 4.5–6 y
- Women with a contraindication to aromatase inhibitors, who decline aromatase inhibitors, or who are intolerant of the aromatase inhibitors

Aromatase inhibitor3 for 2–3 y (category 1)
- Tamoxifen4 for 2–3 y or
- Aromatase inhibitor3 for 5 y (category 1)

Tamoxifen4 for 4.5–6 y
- Women with a contraindication to aromatase inhibitors, who decline aromatase inhibitors, or who are intolerant of the aromatase inhibitors

Aromatase inhibitor for 5 y3 (category 1)
- Consider tamoxifen4 for an additional 5 y to complete 10 y

Premenopausal1
- Tamoxifen4 for an additional 5 y to complete 10 y
- No further endocrine therapy

Aromatase inhibitor to complete 5 y of endocrine therapy (category 1)
- Up to 5 y of an aromatase inhibitor2 (category 2B)
- Tamoxifen4 to complete 5 y of endocrine therapy (category 1)
- Aromatase inhibitor for 5 y (category 1)
- Consider tamoxifen4 for an additional 5 y to complete 10 y

Tamoxifen4 for 5 y (category 1)
- Consider tamoxifen4 for an additional 5 y to complete 10 y

Aromatase inhibitor for 5 y3 (category 1)
- Tamoxifen4 to complete 10 y
- Aromatase inhibitor for 5 y (category 1)
- Consider tamoxifen4 for an additional 5 y to complete 10 y

Up to 5 y of an aromatase inhibitor3 (category 2B)
- Aromatase inhibitor4 for 5 y (category 1)
- Consider tamoxifen4 for an additional 5 y to complete 10 y

No further endocrine therapy
- Tamoxifen4 for an additional 5 y to complete 10 y

Women with a contraindication to aromatase inhibitors, who decline aromatase inhibitors, or who are intolerant of the aromatase inhibitors
- Consider tamoxifen4 for an additional 5 y to complete 10 y

1See Definition of Menopause (BINV-M).
2Aromatase inhibitor or tamoxifen for 5 y plus ovarian suppression should be considered, based on SOFT and TEXT clinical trial outcomes, for premenopausal women at higher risk of recurrence (ie, young age, high-grade tumor, lymph node involvement, Paganini, NEJM 2014, Prudence, NEJM 2014). Survival data still pending.

3Premenopausal women who are intolerant of the aromatase inhibitors, who decline aromatase inhibitors, or for planning breast reconstruction in patients proceeding with mastectomy.

4Tamoxifen4 for an additional 5 y to complete 10 y

5Women with a contraindication to aromatase inhibitors, who decline aromatase inhibitors, or who are intolerant of the aromatase inhibitors

6–8No further endocrine therapy

§-± ovarian suppression or ablation

Preoperative therapy has shown improved outcomes. Preoperative systemic therapy also serves as an excellent research platform to test novel therapies and predictive biomarkers by providing tumor specimens and blood samples before and during systemic treatment.

Selection of Patients for Preoperative Therapy

Not all patients are appropriate candidates for preoperative systemic therapy. According to the NCCN Breast Cancer Panel, among patients with inoperable breast tumors, preoperative systemic therapy is indicated in those with locally advanced or inoperable breast cancer, including those with inflammatory breast cancer, those with N2 and N3 regional lymph node nodal disease, and those with T4 tumors. In patients with operable breast cancer who are clear candidates for adjuvant chemotherapy, preoperative systemic therapy may be administered if a patient desires breast-conserving surgery but surgery...
is not possible due to the size of the tumor relative to that of the breast, with the hope that this will help obtain clear surgical margins at final resection. Preoperative systemic therapy may also be considered for patients with operable tumors if the patient’s breast cancer subtype is associated with a high likelihood of response. When preoperative systemic therapy is used to improve the likelihood of successful breast conservation, the surgical plan should consider the possibility that clear surgical margins may not always be obtained, and a follow-up mastectomy may be required, with or without breast reconstruction. This consideration is especially important when oncoplastic breast reduction techniques or contralateral breast symmetry procedures are added to the breast-conservation surgery to achieve optimal cosmetic outcomes.

The NCCN Breast Cancer Panel cautions that preoperative systemic therapy is not appropriate for certain patients. Preoperative systemic therapy should not be offered for patients with extensive in situ disease for whom the extent of invasive disease cannot be defined; in patients in whom the extent of the tumor is poorly delineated; or in those whose tumors are not palpable or clinically assessable. The decision to use preoperative therapy should be made in the context of a coordinated and collaborative multidisciplinary team.

Preoperative Systemic Therapy Options

Chemotherapy: A number of chemotherapy regimens have activity in the preoperative setting. According to the panel, the regimens recommended in the adjuvant setting may be considered in the preoperative setting. In both settings, the underlying goal remains the same: eradication or control of undiscovered distant metastases.

Endocrine Therapy: Neoadjuvant endocrine therapy alone may be offered to those with strongly hormone receptor-positive tumors. According to

1A 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 AI, or any time on tamoxifen).
2Palbociclib in combination with letrozole may be considered as a treatment option for first-line therapy for postmenopausal patients with hormone-receptor positive, HER2-negative metastatic breast cancer.
3For postmenopausal women or for premenopausal women receiving ovarian suppression with an LHRH agonist, with hormone-receptor positive and HER2-negative metastatic breast cancer that has progressed on endocrine therapy.
4A single study (I0226) 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. 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.
CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

Preferred single agents:

- Anthracyclines
  - Doxorubicin
  - Pegylated liposomal doxorubicin
- Taxanes
  - Paclitaxel
- Anti-metabolites
  - Capecitabine
  - Gemcitabine
- Other microtubule inhibitors
  - Vinorelbine
  - Eribulin

Other single agents:

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

Chemotherapy combinations:

- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab

Preferred first-line agents for HER2-positive disease:

- Pertuzumab + trastuzumab + docetaxel (category 1)
- Pertuzumab + trastuzumab + paclitaxel

Other first-line agents for HER2-positive disease:

- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel + carboplatin
- Trastuzumab + docetaxel
- Trastuzumab + vinorelbine
- Trastuzumab + capecitabine

Preferred agents for trastuzumab-exposed HER2-positive disease:

- Ado-trastuzumab emtansine (T-DM1)

Other agents for trastuzumab-exposed HER2-positive disease:

- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents

1There is no compelling evidence that combination regimens are superior to sequential single agents.
2Randomized 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.
3Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

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HER2-Targeted Therapy: For patients with HER2-positive breast cancer who are candidates for preoperative systemic therapy, chemotherapy and trastuzumab-based therapy is recommended. Chemotherapy and dual anti-HER2 blockade associated with trastuzumab plus pertuzumab has shown significant improvements in the pCR rate when compared with chemotherapy and one anti-HER2 agent in the preoperative setting. In the Neosphere trial, the addition of pertuzumab to trastuzumab and docetaxel preoperatively led to a statistically significant increase in pCR in the breast (16.8% increase; 95% CI, 3.5–30.1; P= .0141). In the TYPHAENA trial, preoperative therapy with pertuzumab and trastuzumab given along with anthracycline-containing or anthracycline-free standard chemotherapy regimens to patients with operable, locally advanced, or inflammatory HER2-positive breast cancer showed pCR rates in all treatment arms ranging from 57% to 66%. The mean change in left ventricular ejection fraction was similar in all treatment arms. The NCCN Breast Cancer Panel supports the FDA-approved indication that a pertuzumab-containing regimen may be administered preoperatively to patients with greater than or equal to T2 or greater than or equal to N1 HER2-positive, early-stage breast cancer.

Response Assessment During Preoperative Chemotherapy: The panel recommends that tumor response should be routinely assessed by clinical examination during the delivery of preoperative systemic therapy. Patients with operable breast cancer experiencing progression of disease while undergo-
ing preoperative systemic therapy should be taken promptly to surgery. Imaging during preoperative systemic therapy should not be performed routinely but may be considered if tumor progression is suspected. Imaging before surgery should be determined by the multidisciplinary team.

**New Adjuvant Endocrine Therapy Options for Premenopausal Women**

Recent data from the randomized TEXT and SOFT trials evaluating adjuvant endocrine therapy show that the AI exemestane plus ovarian suppression significantly reduces recurrences compared with tamoxifen plus ovarian suppression.

In the TEXT and SOFT randomized trials, premenopausal women with hormone receptor–positive early-stage breast cancer were assigned to receive exemestane plus ovarian suppression or tamoxifen plus ovarian suppression for 5 years. Suppression of ovarian estrogen production was achieved with the use of the gonadotropin-releasing hormone agonist triptorelin, oophorectomy, or ovarian irradiation. The DFS was 92.8% in the exemestane plus ovarian suppression group, compared with 88.8% in the tamoxifen plus ovarian suppression group (hazard ratio [HR] for recurrence, 0.66; 95% CI, 0.55–0.80; P<.001). The OS did not differ significantly between the 2 groups (HR for death in the exemestane plus ovarian suppression group, 1.14; 95% CI, 0.86–1.51; P=.37).

In the SOFT trial, premenopausal women with hormone receptor–positive breast cancer were randomized to tamoxifen alone, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression for 5 years. In the primary analysis, tamoxifen plus ovarian suppression was not superior to tamoxifen alone for DFS. After 67 months of median follow-up,
the DFS rate at 5 years was 86.6% in the tamoxifen/ovarian suppression group and 84.7% in the tamoxifen alone group (HR, 0.83; 95% CI, 0.66–1.04; \(P = .10\)). In a subgroup analysis, women at high risk of recurrence who received prior chemotherapy had improved outcomes with ovarian suppression. Their chance of remaining disease-free at 5 years was 78% with tamoxifen alone, 82.5% with tamoxifen and ovarian suppression, and 85.7% with exemestane and ovarian suppression. In the subgroup of women with no prior chemotherapy, no meaningful benefit was seen from ovarian suppression, because women who received tamoxifen alone had a 95% chance of remaining disease-free for 5 years. The overall survival data from these trials are still pending because the overall follow-up is relatively short in the context of endocrine-sensitive disease.

**NCCN Recommendations**

Based on the results of the SOFT and TEXT trials, the NCCN Breast Cancer Panel has included ovarian suppression plus an AI for 5 years as an adjuvant endocrine therapy option for premenopausal women with hormone receptor–positive breast cancer who are at higher risk of recurrence (young age, high-grade tumor, lymph node involvement) (see BINV-J, page 1479).

### New Endocrine Therapy Options for Metastatic Breast Cancer

Palbociclib, a highly selective inhibitor of CDK 4/6 kinase activity, has a role in treating women with estrogen receptor (ER)–positive metastatic breast cancer in combination with endocrine therapy. A phase II, open-label, randomized, multicenter trial evaluated the safety and efficacy of palbociclib in combination with letrozole versus letrozole alone as first-line treatment for patients with advanced ER-positive, HER2-negative breast cancer. The reported median progression-free survival (PFS) was double with the combination regimen compared with letrozole alone (20.2 months for the palbociclib plus letrozole group and 10.2 months for the letrozole alone group; HR, 0.488; 95% CI, 0.319–0.748). Grade 3/4 adverse reactions reported at a higher incidence in the palbociclib plus letrozole versus letrozole alone group included neutropenia (54% vs 1%) and leukopenia (19% vs 0%). Based on this study, the FDA approved palbociclib in combination with letrozole for the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

The phase III trial (PALOMA-3) compared the combination of palbociclib and fulvestrant versus fulvestrant alone in premenopausal or postmenopausal patients with hormone receptor–positive, HER2-negative advanced breast cancer whose disease progressed on previous endocrine therapy. Premenopausal or perimenopausal patients also received goserelin. The median PFS was 9.2 months for the combination compared with 3.8 months for fulvestrant alone (HR, 0.42; \(P < .000001\), with similar discontinuation rates because of adverse effects (2.6% and 1.7%, respectively). Grade 3/4 adverse events of palbociclib and fulvestrant were mainly confined to neutropenia, with the same low incidence (0.6%) of febrile neutropenia in both arms. Overall survival data from this trial are immature.

**NCCN Recommendations**

The NCCN Breast Cancer Panel has included the combination of palbociclib with letrozole as a first-line endocrine therapy option for postmenopausal patients with hormone receptor–positive, HER2-negative metastatic breast cancer. In addition, the recently updated version of these guidelines includes palbociclib with fulvestrant as a category 1 option for women with hormone receptor–positive (postmenopausal or premenopausal women receiving ovarian suppression with an luteinizing hormone–releasing hormone agonist), HER2-negative metastatic breast cancer whose disease has progressed on endocrine therapy (see BINV-N, page 1480).

### New Option for First-Line HER2-Targeted Therapy in Select Patients With Metastatic Breast Cancer

HER2 is a proto-oncogene located on chromosome 17 and is amplified in 15% to 20% of breast carcinomas. Before the approval of trastuzumab, amplification of HER2 was considered a poor prognostic factor in patients with metastatic breast cancer. With the introduction of trastuzumab, the outcomes of patients with HER2-positive metastatic breast cancer dramatically improved. Newer drugs targeting the HER2 pathway, including pertuzumab and ado-trastuzumab emtansine (T-DM1), have been developed and added to the current standard of care.
In a phase III trial (MARIANNE), 1095 patients with locally advanced or metastatic breast cancer were randomized to first-line treatment with T-DM1 with or without pertuzumab or to treatment with trastuzumab plus a taxane. The primary end points were safety and PFS assessed by independent review. The PFS for T-DM1 with pertuzumab was found to be 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). 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). The incidence of grades 3 through 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 quality of life 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.

**NCCN Recommendations**

Based on the MARIANNE trial data demonstrating T-DM1 and T-DM1 with pertuzumab being noninferior, with better quality of life compared with trastuzumab plus taxane, and possibly better-tolerated for some patients, the NCCN panel included T-DM1 as one of the first-line options for the treatment of patients with HER2-positive metastatic breast cancer (see BINV-O and BINV-22, pages 1481 and 1482, respectively). Pertuzumab, trastuzumab, and a taxane, however, remains the preferred frontline 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 patients not suitable for the preferred treatment.

**Conclusions**

The NCCN Guidelines are in continuous evolution. They are updated annually, and sometimes more often when new high-quality clinical data become available in the interim. The recommendations in the NCCN Guidelines for Breast Cancer, with few exceptions, are based on the evidence from clinical trials. Expert medical clinical judgment is required to apply these guidelines in the context of an individual patient to provide optimal care. Ultimately, the physician and the patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the panel strongly encourages patient/physician participation in prospective clinical trials. The full version of the 2016 NCCN Guidelines for Breast Cancer is available online (NCCN.org).

**References**

17. Piccart-Gebhart M, Holmes AF, de Azambuja E, et al. The association between event-free survival and pathological complete response to neoadjuvant lapatinib, trastuzumab or their combination in HER2-positive breast cancer.
2. True or False: MARIANNE trial data demonstrated that T-DM1 and T-DM1 with pertuzumab are noninferior compared with trastuzumab plus taxane as first-line therapy for metastatic HER2-positive breast cancer.

3. According to the NCCN Guidelines, which of the following adjuvant therapy is listed as a category 1 recommendation for a woman who has undergone lumpectomy plus radiation therapy for stage II, hormone receptor–positive, HER2-negative breast cancer?

   a. Tamoxifen for 5 years plus ovarian ablation
   b. Tamoxifen for 5 years
   c. Aromatase inhibitor for 5 years plus ovarian ablation

   Answers:
   a. Options 1 and 2 only
   b. None of the above
   c. Options 1, 2, and 3