

# NCCN Guidelines® Insights

## Breast Cancer, Version 1.2017

### Featured Updates to the NCCN Guidelines

William J. Gradishar, MD<sup>1,\*</sup>; Benjamin O. Anderson, MD<sup>2</sup>; Ron Balassanian, MD<sup>3</sup>; Sarah L. Blair, MD<sup>4</sup>; Harold J. Burstein, MD, PhD<sup>5</sup>; Amy Cyr, MD<sup>6,\*</sup>; Anthony D. Elias, MD<sup>7</sup>; William B. Farrar, MD<sup>8</sup>; Andres Forero, MD<sup>9</sup>; Sharon Hermes Giordano, MD, MPH<sup>10</sup>; Matthew P. Goetz, MD<sup>11</sup>; Lori J. Goldstein, MD<sup>12</sup>; Steven J. Isakoff, MD, PhD<sup>13</sup>; Janice Lyons, MD<sup>14</sup>; P. Kelly Marcom, MD<sup>15</sup>; Ingrid A. Mayer, MD<sup>16</sup>; Beryl McCormick, MD<sup>17</sup>; Meena S. Moran, MD<sup>18</sup>; Ruth M. O'Regan, MD<sup>18</sup>; Sameer A. Patel, MD<sup>12</sup>; Lori J. Pierce, MD<sup>20</sup>; Elizabeth C. Reed, MD<sup>21</sup>; Kilian E. Salerno, MD<sup>22,\*</sup>; Lee S. Schwartzberg, MD<sup>23</sup>; Amy Sitapati, MD<sup>4</sup>; Karen Lisa Smith, MD, MPH<sup>24</sup>; Mary Lou Smith, JD, MBA<sup>25</sup>; Hatem Soliman, MD<sup>26</sup>; George Somlo, MD<sup>27</sup>; Melinda Telli, MD<sup>28</sup>; John H. Ward, MD<sup>29</sup>; Dorothy A. Shead, MS<sup>30,\*</sup>; and Rashmi Kumar, PhD<sup>30,\*</sup>

#### Abstract

These NCCN Guidelines Insights highlight the important updates/changes to the surgical axillary staging, radiation therapy, and systemic therapy recommendations for hormone receptor–positive disease in the 1.2017 version of the NCCN Guidelines for Breast Cancer. This report summarizes these updates and discusses the rationale behind them. Updates on new drug approvals, not available at press time, can be found in the most recent version of these guidelines at NCCN.org.

*J Natl Compr Canc Netw 2017;15(4):433–451*

From <sup>1</sup>Robert H. Lurie Comprehensive Cancer Center of Northwestern University; <sup>2</sup>Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; <sup>3</sup>UCSF Helen Diller Family Comprehensive Cancer Center; <sup>4</sup>UC San Diego Moores Cancer Center; <sup>5</sup>Dana-Farber/Brigham and Women's Cancer Center; <sup>6</sup>Site-man Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; <sup>7</sup>University of Colorado Cancer Center; <sup>8</sup>The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; <sup>9</sup>University of Alabama at Birmingham Comprehensive Cancer Center; <sup>10</sup>The University of Texas MD Anderson Cancer Center; <sup>11</sup>Mayo Clinic Cancer Center; <sup>12</sup>Fox Chase Cancer Center; <sup>13</sup>Massachusetts General Hospital Cancer Center; <sup>14</sup>Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; <sup>15</sup>Duke Cancer Institute; <sup>16</sup>Vanderbilt-Ingram Cancer Center; <sup>17</sup>Memorial Sloan Kettering Cancer Center; <sup>18</sup>Yale Cancer Center/Smilow Cancer Hospital; <sup>19</sup>University of Wisconsin Carbone Cancer Center; <sup>20</sup>University of Michigan Comprehensive Cancer Center; <sup>21</sup>Fred & Pamela Buffett Cancer Center; <sup>22</sup>Roswell Park Cancer Institute; <sup>23</sup>St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; <sup>24</sup>The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; <sup>25</sup>Research Advocacy Network; <sup>26</sup>Moffitt Cancer Center; <sup>27</sup>City of Hope Comprehensive Cancer Center; <sup>28</sup>Stanford Cancer Institute; <sup>29</sup>Huntsman Cancer Institute at the University of Utah; and <sup>30</sup>National Comprehensive Cancer Network.

\*Provided content development and/or authorship assistance.

#### 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.**

These NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding the content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their applications or use in any way.

**The full and most current version of these NCCN Guidelines are available at NCCN.org.**

© National Comprehensive Cancer Network, Inc. 2017, All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN.

## NCCN: Continuing Education

**Target Audience:** This activity is designed to meet the educational needs of physicians, nurses, and pharmacists involved in the management of patients with cancer.

### Accreditation Statement

**Physicians:** National Comprehensive Cancer Network is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

NCCN designates this journal-based CE activity for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

**Nurses:** National Comprehensive Cancer Network is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

NCCN designates this educational activity for a maximum of 1.0 contact hour.



**Pharmacists:** National Comprehensive Cancer Network is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

NCCN designates this knowledge-based continuing education activity for 1.0 contact hour (0.1 CEUs) of continuing education credit. UAN: 0836-0000-17-004-H01-P

All clinicians completing this activity will be issued a certificate of participation. To participate in this journal CE activity: 1) review the educational content; 2) take the posttest with a 66% minimum passing score and complete the evaluation at <http://education.nccn.org/node/80546>; and 3) view/print certificate.

Release date: April 10, 2017; Expiration date: April 10, 2018

### Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for Breast Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Breast Cancer

## Disclosure of Relevant Financial Relationships

### Editor:

**Kerrin M. Green, MA**, Assistant Managing Editor, *JNCCN—Journal of the National Comprehensive Cancer Network*, has disclosed that she has no relevant financial relationships.

### JNCCN:

**Kimberly Callan, MS**, Senior Director, Professional and Patient Publications, NCCN, has disclosed that she has no relevant financial relationships.

**Genevieve Emberger Hartzman, MA**, Journal Production Specialist, NCCN, has disclosed that she has no relevant financial relationships.

### CE Authors:

**Deborah J. Moonan, RN, BSN**, Director, Continuing Education, NCCN, has disclosed that she has no relevant financial relationships. (Employed by NCCN until 2/17/17.)

**Karen Kanefield**, Manager, Continuing Education Accreditation and Program Operations, NCCN, has disclosed that she has no relevant financial relationships.

**Kathy Smith**, Manager, CE Grant Writing & Project Management, NCCN, has disclosed that she has no relevant financial relationships.

**Kristina M. Gregory, RN, MSN, OCN**, Vice President, Clinical Information Operations, NCCN, has disclosed that she has no relevant financial relationships.

**Rashmi Kumar, PhD**, Director, Clinical Information Operations, NCCN, has disclosed that she has no relevant financial relationships.

### Individuals Who Provided Content Development and/or Authorship Assistance:

**William J. Gradishar, MD**, Panel Chair, has disclosed that he has no relevant financial relationships.

**Amy Cyr, MD**, Panel Member, has disclosed that she has no relevant financial relationships.

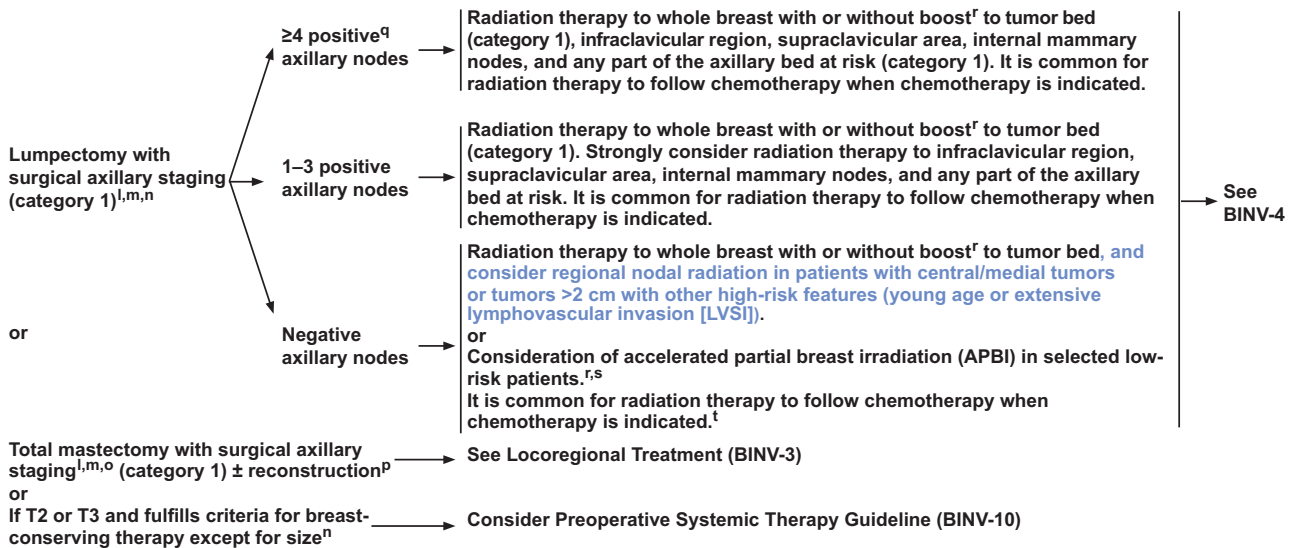
**Kilian E. Salerno, MD**, Panel Member, has disclosed that she has no relevant financial relationships.

**Dorothy A. Shead, MS**, Director, Patient & Clinical Information Operations, NCCN, has disclosed that she has no relevant financial relationships.

This activity is supported by educational grants from Astellas, AstraZeneca, Celldex Therapeutics, Clovis Oncology, Genomic Health, Inc., Kyowa Hakko Kirin, Jazz Pharmaceuticals, Novartis Pharmaceuticals Corporation, and NOVOCURE. This activity is supported by an independent educational grant from Merck Co., Inc.

# Breast Cancer, Version 1.2017

## LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0<sup>k</sup>



<sup>k</sup>See NCCN Guidelines for Older Adult Oncology for special treatment considerations.  
<sup>l</sup>See Surgical Axillary Staging (BINV-D).  
<sup>m</sup>See Axillary Lymph Node Staging (BINV-E) and Margin Status in Infiltrating Carcinoma (BINV-F).  
<sup>n</sup>See Special Considerations to Breast-Conserving Therapy Requiring Radiation Therapy (BINV-G).  
<sup>o</sup>Except as outlined in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian and the NCCN Guidelines for Breast Cancer Risk Reduction, prophylactic mastectomy of a breast contralateral to a known unilateral breast cancer is discouraged. When considered, the small benefits from contralateral prophylactic mastectomy for women with unilateral breast cancer must be balanced with the risk of recurrent disease from the known ipsilateral breast cancer,

psychological and social issues of bilateral mastectomy, and the risks of contralateral mastectomy. The use of a prophylactic mastectomy contralateral to a breast treated with breast-conserving therapy is very strongly discouraged.  
<sup>p</sup>See Principles of Breast Reconstruction Following Surgery (BINV-H).  
<sup>q</sup>Consider imaging for systemic staging, including chest/abdominal ± pelvic diagnostic CT with contrast, bone scan, and optional FDG PET/CT (See BINV-1).  
<sup>r</sup>See Principles of Radiation Therapy (BINV-I).  
<sup>s</sup>PBI may be administered prior to chemotherapy.  
<sup>t</sup>Breast irradiation may be omitted in patients ≥70 y of age with estrogen-receptor positive, clinically node-negative, T1 tumors who receive adjuvant endocrine therapy (category 1).

Version 1.2017 © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

BINV-2

### 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.

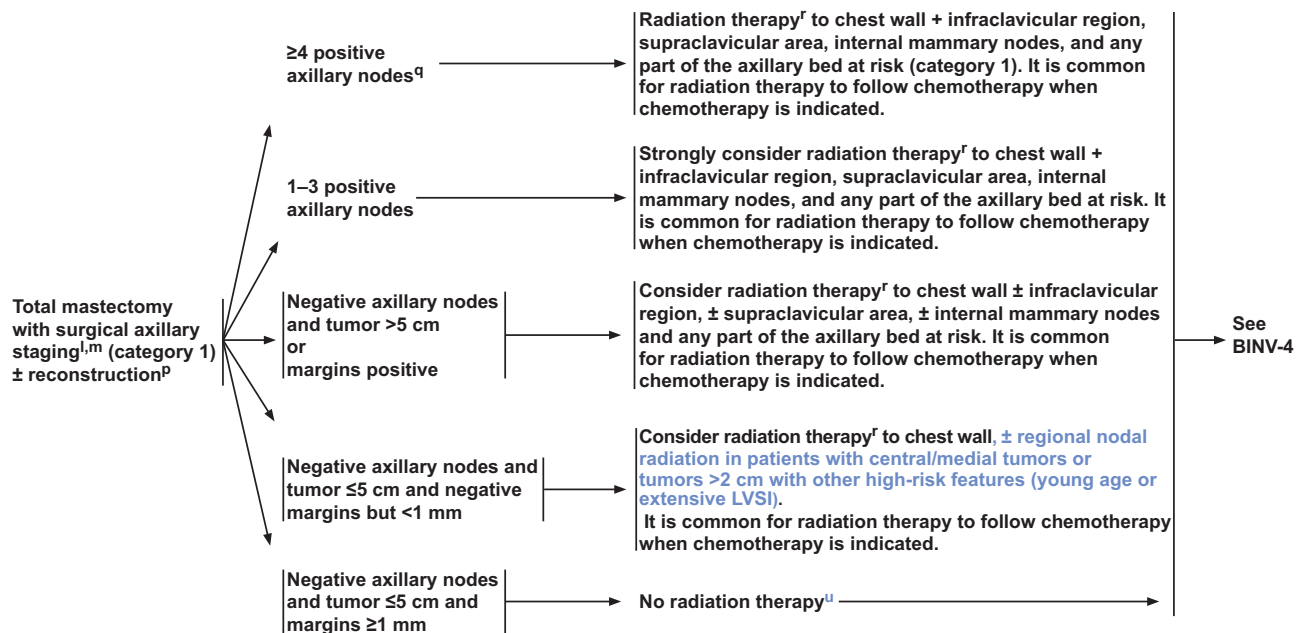
**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

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 255,180 Americans will be diagnosed with breast cancer and 41,070 will die of the disease in the United States in 2017.<sup>1</sup> 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.

LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0<sup>k</sup>

<sup>k</sup>See NCCN Guidelines for Older Adult Oncology for special treatment considerations.

<sup>l</sup>See Surgical Axillary Staging (BINV-D).

<sup>m</sup>See Axillary Lymph Node Staging (BINV-E) and Margin Status in Infiltrating Carcinoma (BINV-F).

<sup>p</sup>See Principles of Breast Reconstruction Following Surgery (BINV-H).

<sup>q</sup>Consider imaging for systemic staging, including chest/abdominal ± pelvic diagnostic CT with contrast, bone scan, and optional FDG PET/CT (See BINV-1).

<sup>r</sup>See Principles of Radiation Therapy (BINV-I).

<sup>u</sup>Postmastectomy radiation therapy may be considered for patients with multiple high-risk recurrence factors, including central/medial tumors or tumors >2 cm with other high-risk features such as young age and/or extensive LVSI.

Version 1.2017 © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. The NCCN Guidelines<sup>®</sup> and this illustration may not be reproduced in any form without the express written permission of NCCN<sup>®</sup>.

BINV-3

In the most recent version of NCCN Breast Cancer Guidelines, Version 1.2017, the NCCN panel included updated recommendations for situations where axillary lymph node dissection (ALND) can be omitted in women with stages I, II, and IIIA (T3N1M0) breast cancer; for whole-breast radiation therapy (WBRT) using hypofractionation, updates regarding accelerated partial breast irradiation (APBI) and regional nodal irradiation (RNI) in women with early-stage breast cancer; and systemic therapy for women with hormone receptor–positive breast cancer in the adjuvant and metastatic settings. The full version of these guidelines is available online (NCCN.org).

### Surgical Axillary Staging for Stages I, IIA, IIB, and IIIA (T3N1M0)

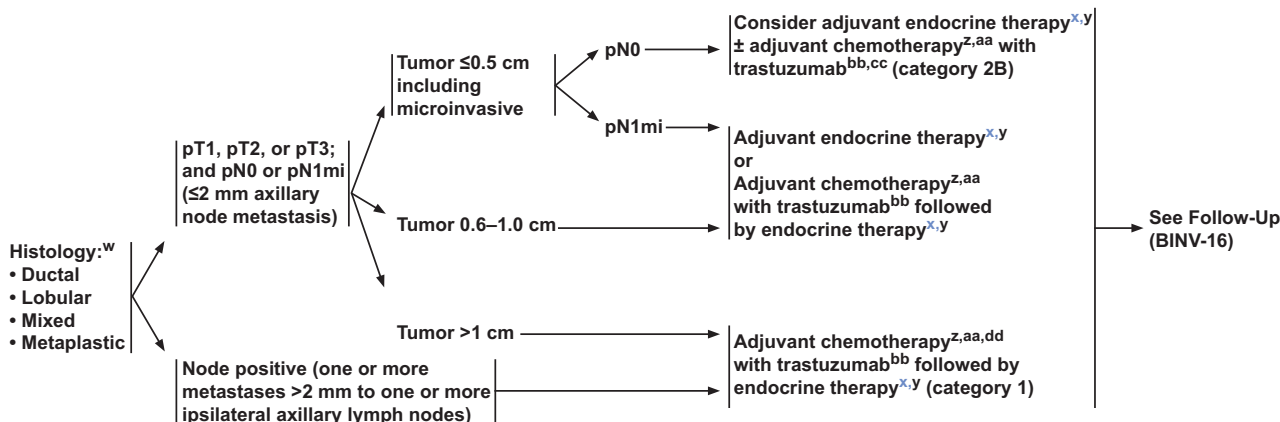
ALND is the standard of care for patients with clinically positive nodes. However, ALND is associated with lymphedema and other significant mor-

bidities,<sup>2-4</sup> and therefore sentinel lymph node biopsy (SLNB) has replaced axillary evaluation for patients with clinically node-negative disease.

Based on several randomized trials, it is now accepted that patients with a negative sentinel lymph node (SLN) do not need an ALND.<sup>5-8</sup>

The ACOSOG Z0011 trial randomized women ≥18 years of age with T1/T2 tumors, <3 positive SLNs, undergoing lumpectomy and WBRT to either SLNB alone (n=436) or ALND (n=420). In this study, no difference was seen in local recurrence, disease-free survival (DFS), or overall survival (OS) between women with positive SLNs undergoing a completion ALND versus no ALND. Only estrogen receptor (ER)–negative status, age <50 years, and lack of adjuvant systemic therapy were associated with decreased OS.<sup>9</sup> At a median follow-up of 6.3 years, locoregional recurrences were noted in 4.1% of patients in the ALND group and 2.8% of those in the SLNB group (P=.11). Median OS was approximately 92% in each group.<sup>10</sup> Long term follow-

## Breast Cancer, Version 1.2017

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-POSITIVE DISEASE<sup>b</sup>

<sup>b</sup>See Principles of HER2 Testing (BINV-A).

<sup>w</sup>Mixed lobular and ductal carcinoma should be graded based on the ductal component and treated based on this grading. For metaplastic carcinoma, the prognostic value of the histologic grading is uncertain. However, when a specific histologic subtype of metaplastic carcinoma is present and accounts for more than 10% of the tumor, the subtype is an independent prognostic variable.

<sup>x</sup>Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant endocrine therapy.

<sup>y</sup>Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-J).

<sup>z</sup>Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-J) and Preoperative/Adjuvant Therapy Regimens (BINV-K).

<sup>aa</sup>There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.

<sup>bb</sup>The prognosis of patients with T1a and T1b tumors that are node negative is uncertain even when HER2 is amplified or overexpressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.

<sup>cc</sup>Adjuvant chemotherapy with weekly paclitaxel and trastuzumab (Tolaney et al. NEJM 2015) can be considered for HER2-positive T1a N0 cancers, particularly if the primary cancer is ER negative, and the tumor size borders on T1b (>5 mm). The absolute benefit of HER2-based systemic chemotherapy is likely negligible in patients with ER-positive cancers and tumor size bordering on T1mic (<1 mm), when the estimated recurrence risk is less than 5% and endocrine therapy remains a viable option for systemic treatment.

<sup>dd</sup>A pertuzumab-containing regimen can be administered to patients with ≥T2 or ≥N1, HER2-positive, early-stage breast cancer.

Version 1.2017 © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

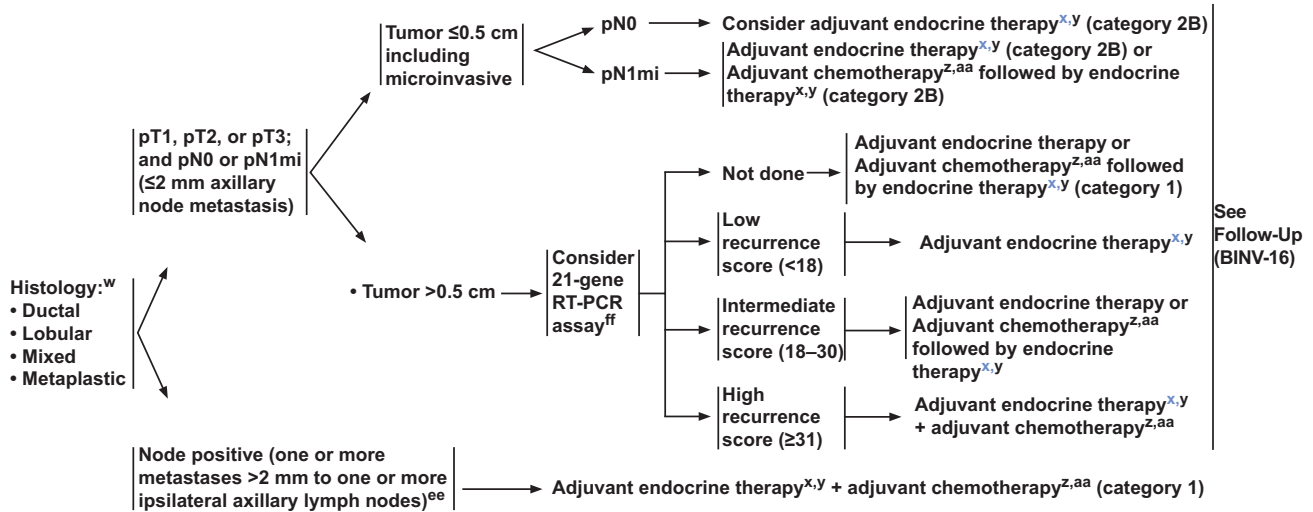
BINV-5

up (median, 9.25 years) results of the ACOSOG Z0011 study showed no statistically significant difference in local recurrence-free survival between the groups ( $P=.13$ ).<sup>11</sup> The cumulative incidence of ipsilateral axillary recurrences at 10 years was 0.5% (2 patients) in those who underwent ALND and 1.5% (5 patients) in those who underwent SLNB alone ( $P=.28$ ).<sup>11</sup> The 10-year cumulative incidence of local regional recurrences was 6.2% with ALND and 5.3% with SLNB alone ( $P=.36$ ).<sup>11</sup> Results of the ACOSOG Z0011 trial show that ALND is not needed in women with early-stage breast cancer who have only 1 or 2 SLN metastases who will receive WBRT as part of breast-conserving therapy.

Another randomized trial (IBCSG 23-01) was specifically designed to compare outcomes in patients with sentinel micrometastases (≤2 mm) treated with ALND versus no ALND.<sup>12</sup> Although the ACOSOG Z0011 trial was limited to those undergoing breast-conserving therapy, this trial included patients undergoing mastectomy (9%).<sup>12</sup> No differences were seen in

the group treated with ALND versus those not treated with ALND in 5-year DFS rate (84.4% [95% CI, 80.7%–88.1%] vs 87.8% [95% CI, 84.4%–91.2%]); cumulative incidence of breast cancer events, including local, regional, contralateral breast, and distant recurrence (10.8% [95% CI, 7.6–14.0] vs 10.6% [95% CI, 7.5–13.8]); or OS rate (97.6% [95% CI, 96.0%–99.2%] vs 97.5% [95% CI, 95.8%–99.1%]).<sup>12</sup> Regional recurrence was <1% for those who underwent ALND and 1% for those who did not.<sup>12</sup> Results of this trial show that in patients with only micrometastases in the SLNs, ALND is not needed.

The results of a trial by the European EORTC group (AMAROS) assessed whether axillary radiation therapy (RT) provides regional control with fewer side effects compared with ALND.<sup>13</sup> This trial included patients (n=4,823) with T1 or T2 breast cancer and positive SLNs (micrometastatic or macrometastatic), and included a small fraction of patients (n=248) treated with mastectomy.<sup>13</sup> The results reported no difference in 5-year OS or DFS for

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE<sup>b</sup>

<sup>b</sup>See Principles of HER2 Testing (BINV-A).

<sup>w</sup>Mixed lobular and ductal carcinoma, should be graded based on the ductal component and treated based on this grading. For metaplastic carcinoma, the prognostic value of the histologic grading is uncertain. However, when a specific histologic subtype of metaplastic carcinoma is present and accounts for more than 10% of the tumor, the subtype is an independent prognostic variable.

<sup>x</sup>Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant endocrine therapy.

<sup>y</sup>Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-J).

<sup>z</sup>Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-J) and Preoperative/Adjuvant Therapy Regimens (BINV-K).

<sup>aa</sup>There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.

<sup>ee</sup>The 21-gene RT-PCR assay recurrence score can be considered in select patients with 1–3 involved ipsilateral axillary lymph nodes to guide the addition of combination chemotherapy to standard hormone therapy. A retrospective analysis of a prospective randomized trial suggests that the test is predictive in this group similar to its performance in node-negative disease.

<sup>ff</sup>Other prognostic multigene assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy.

Version 1.2017 © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. The NCCN Guidelines<sup>®</sup> and this illustration may not be reproduced in any form without the express written permission of NCCN<sup>®</sup>.

BINV-6

patients randomized to ALND versus axillary RT.<sup>13</sup> The 5-year DFS was 86.9% (95% CI, 84.1–89.3) in the ALND group and 82.7% (95% CI, 79.3–85.5) in the axillary RT group. The 5-year OS was 93.3% (95% CI, 91.0–95.0) in the ALND group and 92.5% (95% CI, 90.0–94.4) in the axillary RT group.<sup>13</sup> At the end of 5 years, lymphedema was less frequent in the group treated with axillary RT versus ALND (11% vs 23%).<sup>13</sup> The results of this trial show that axillary RT is an acceptable alternative to ALND for axillary control in patients found to have positive SLNs, with significantly less lymphedema-related morbidity.

### NCCN Recommendations

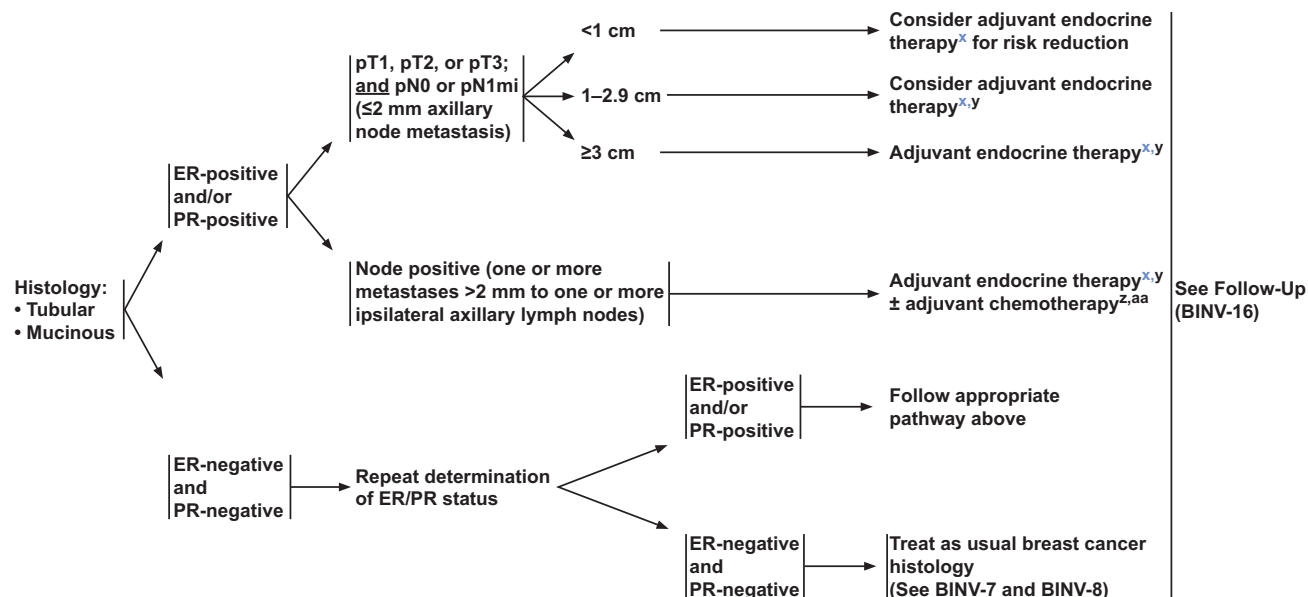
In patients with clinically positive nodes, to determine whether ALND is needed, the panel recommends pathologic confirmation of malignancy using ultrasound-guided fine-needle aspiration (FNA)<sup>14</sup> or core biopsy of suspicious nodes. According to the NCCN panel, the recommendation for axillary dissection of level I and II nodes is limited to patients

with biopsy-proven axillary metastases. Traditional level I and II ALND requires that ≥10 lymph nodes be provided for pathologic evaluation to accurately stage the axilla.<sup>15,16</sup> ALND should be extended to include level III nodes only if gross disease is apparent in the level II and III nodes. In the absence of gross disease in level II nodes, lymph node dissection should include tissue inferior to the axillary vein from the latissimus dorsi muscle laterally to the medial border of the pectoralis minor muscle (level I and II) (see BINV-D; page 440).

If axillary lymph nodes are clinically negative at diagnosis or if FNA/core biopsy results of suspicious nodes are negative, the panel recommends SLN mapping and excision. SLNs can be assessed for the presence of metastases by both hematoxylin-eosin (H&E) staining and cytokeratin immunohistochemistry (IHC). The clinical significance of a lymph node that is negative on H&E staining but positive on cytokeratin IHC is not clear. Because the historical and clinical trial data on which treatment

## Breast Cancer, Version 1.2017

## SYSTEMIC ADJUVANT TREATMENT - FAVORABLE HISTOLOGIES



<sup>x</sup>Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant endocrine therapy.

<sup>y</sup>Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-J).

<sup>z</sup>Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data

suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-J) and Preoperative/Adjuvant Therapy Regimens (BINV-K).

<sup>aa</sup>There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.

Version 1.2017 © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

BINV-9

decisions are based have relied on H&E staining, the panel does not recommend routine cytokeratin IHC to define node involvement and believes that current treatment decisions should be made based solely on H&E staining. This recommendation is further supported by a randomized clinical trial (ACOSOG Z0010) for patients with H&E-negative nodes in whom further examination by cytokeratin IHC was not associated with improved OS over a median of 6.3 years.<sup>17</sup> In the uncommon situation in which H&E staining is equivocal, reliance on the results of cytokeratin IHC is appropriate.

Based on the ACOSOG Z0011 trial results, for patients with T1 or T2 tumors and 1 to 2 positive SLNs, treated with lumpectomy but no preoperative systemic therapy, and who receive WBRT, the NCCN panel recommends no further axillary surgery. If any of these criteria are not met, the panel recommends level I and II axillary dissection. In the 2017 version of the NCCN Guidelines, based on the results of the IBCSG 23-01 trial, the NCCN

panel recommends no ALND for patients with positive SLNs when disease is only micrometastatic (see BINV-D; page 440). According to AJCC staging, micrometastatic nodal involvement is defined as a metastatic deposit >0.2 mm but ≤2.0 mm.<sup>18</sup>

When SNLs are not successfully identified, the panel recommends level I and II axillary dissection be performed for axillary staging.

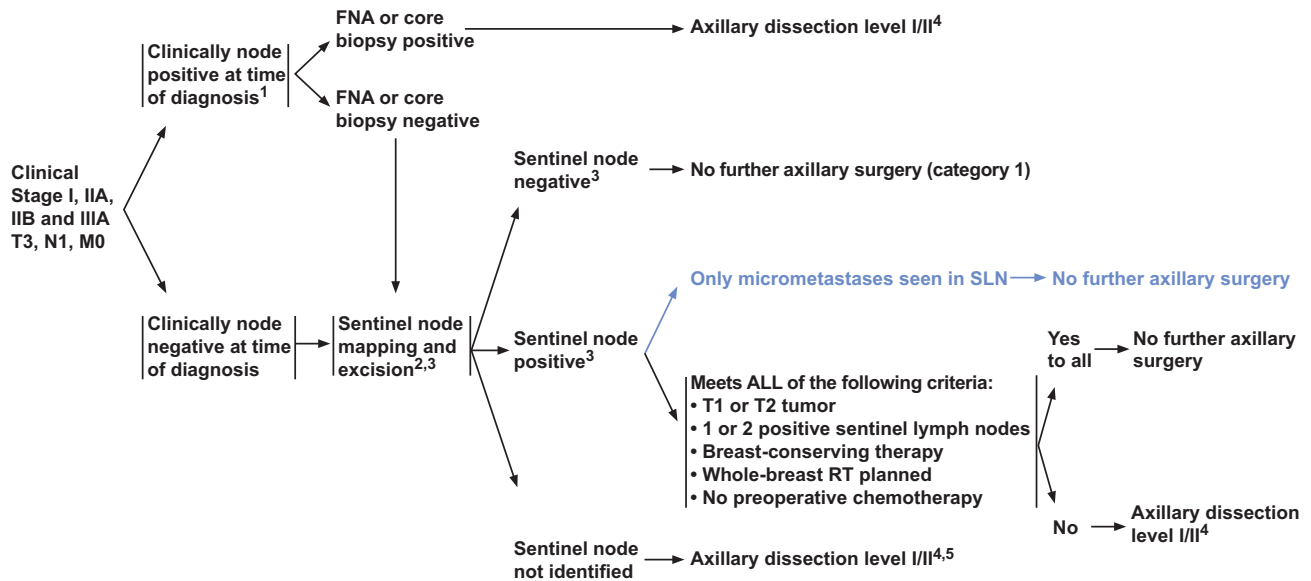
For mastectomy patients with clinically negative axillae but with positive SLNs, the panel notes that for regional control of disease, axillary RT may replace ALND (see BINV-D; page 440).

### Adjuvant RT for Stages I, IIA, IIB, and IIIA (T3N1M0)

#### Adjuvant RT After Lumpectomy

**Whole-Breast Radiation Therapy:** WBRT reduces the risk of local recurrence and has been shown to have a beneficial effect on survival. Results of a

## SURGICAL AXILLARY STAGING - STAGE I, IIA, IIB and IIIA T3, N1, M0



<sup>1</sup>Consider pathologic confirmation of malignancy in clinically positive nodes using ultrasound-guided FNA or core biopsy in determining if a patient needs axillary lymph node dissection.

<sup>2</sup>Sentinel lymph node mapping injections may be peritumoral, subareolar, or subdermal.

<sup>3</sup>Sentinel node involvement is defined by multilevel node sectioning with hematoxylin and eosin (H&E) staining. Cytokeratin immunohistochemistry (IHC) may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is not recommended in clinical decision making.

<sup>4</sup>See Axillary Lymph Node Staging (BINV-E).

<sup>5</sup>For patients with clinically negative axillae who are undergoing mastectomy and for whom radiation therapy is planned, axillary radiation may replace axillary dissection level I/II for regional control of disease.

Version 1.2017 © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

BINV-D

meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed reduction in 10-year risk of recurrence in those who received WBRT versus those who did not (19% vs 35%; relative risk [RR], 0.52; 95% CI, 0.48–0.56).<sup>19</sup> In addition, a significant reduction in 15-year risk of breast cancer death (21% vs 25%; RR, 0.82; 95% CI, 0.75–0.90) was also observed.<sup>19</sup>

**Dose and Fractionation:** The conventional dose for WBRT is 46 to 50 Gy in 23 to 25 fractions. Four randomized clinical trials including more than 7,000 patients have investigated hypofractionated WBRT schedules (39–42.9 Gy in daily fractions of 2.6–3.3 Gy) compared with standard 50 Gy doses in fractions of 2 Gy.<sup>20–23</sup> The 10-year follow-up data from the START trials<sup>24</sup> are consistent with the 10-year results of the Canadian trial,<sup>23</sup> which reported at least equivalent local tumor control and breast cosmesis between both conventional and hypofractionated regimens.<sup>23</sup> The START trials reported that

radiation-related effects to normal breast tissue, such as breast shrinkage, telangiectasia, and breast edema, were less common with the hypofractionated fraction regimen.<sup>24</sup>

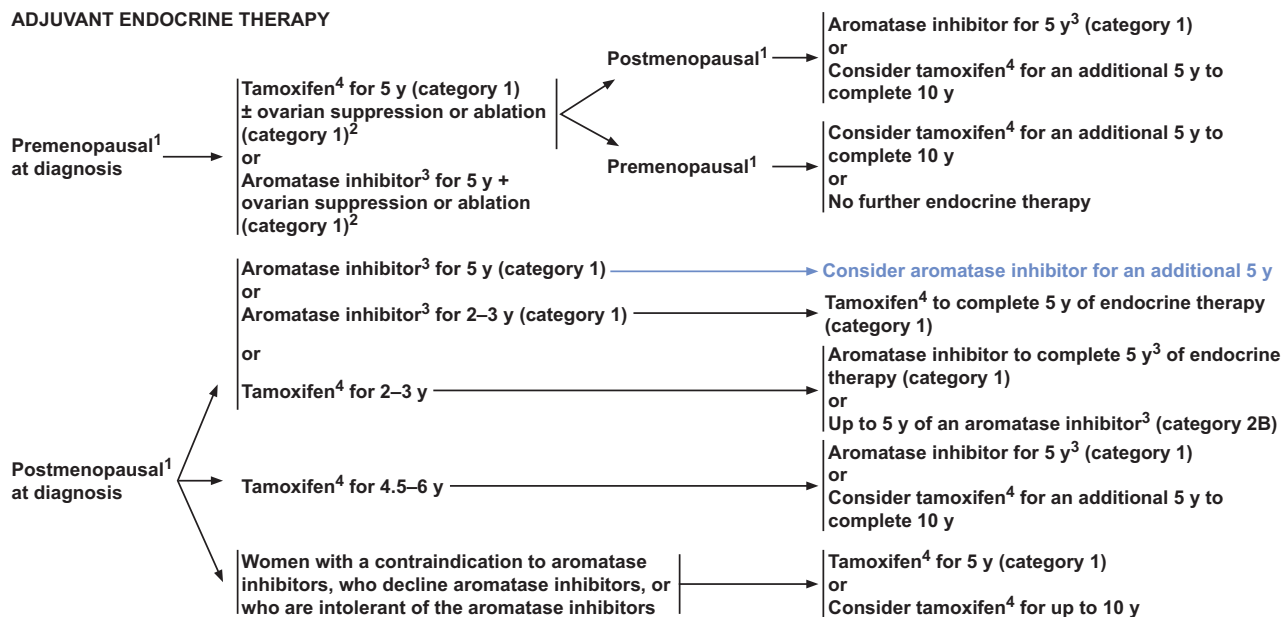
**RT Boost to the Tumor Bed:** Randomized trials have demonstrated a reduction in local recurrence with the addition of a boost to the tumor bed in patients with higher-risk characteristics (eg, age <50 years, high-grade disease, or focally positive margins).<sup>24–30</sup> Boost treatment may be delivered using photons, electrons, or brachytherapy.

**NCCN Recommendations for WBRT With or Without Boost to Tumor Bed:** After breast-conserving surgery, WBRT is recommended with or without a boost to the tumor bed (category 1). The panel recommends that WBRT include the breast tissue in its entirety. CT-based treatment planning is recommended to assure adequate target coverage of the breast tissue and lumpectomy site and limit dose to normal tissues, especially the heart and lungs.



## Breast Cancer, Version 1.2017

## ADJUVANT ENDOCRINE THERAPY



<sup>1</sup>See Definition of Menopause (BINV-M).

<sup>2</sup>A balanced discussion of the risks and benefits associated with ovarian suppression therapy is critical. Aromatase 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, Pagani, NEJM 2014, Prudence, NEJM 2014). Survival data still pending.

<sup>3</sup>The panel believes the three selective aromatase inhibitors (ie, anastrozole, letrozole, exemestane) have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and preoperative settings. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.

<sup>4</sup>Some SSRIs like fluoxetine and paroxetine decrease the formation of endoxifen, 4-OH tamoxifen, and active metabolites of tamoxifen, and may impact its efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. At this time, based on current data the panel recommends against CYP2D6 gene testing for women being considered for tamoxifen therapy. Coadministration of strong inhibitors of CYP2D6 should be used with caution.

Version 1.2017 © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

BINV-J

Compensators such as tissue wedges, forward planning using segments, and intensity-modulated RT (IMRT) may provide improved homogeneity of target dose and normal tissue sparing.<sup>31,32</sup> Treatment techniques such as respiratory control using deep inspiration breath-hold and prone positioning can further reduce dose to adjacent normal tissues, particularly the heart and lungs.<sup>33</sup>

The NCCN panel recommends a dose of 46 to 50 Gy in 23 to 25 fractions or 40 to 42.5 Gy in 15 to 16 fractions for WBRT. Based on the results from the Canadian and START trials and overall convenience, hypofractionated courses are the NCCN-preferred option for treating patients receiving WBRT. Use of hypofractionation is not recommended for RNI. A boost to the tumor bed is recommended in patients with higher-risk characteristics (eg, age <50 years, high-grade disease, or focally positive margins). Typical boost doses are 10 to 16 Gy in 4 to 8 fractions.

**RNI After Lumpectomy:** RNI includes treatment of the supraclavicular, infraclavicular nodes, axillary bed at risk, and internal mammary nodes.

Use of RNI was shown to reduce risk of locoregional and distant recurrence and improve DFS in the MA.20 and EORTC 22922/10925 trials.<sup>34,35</sup> In the MA.20 trial, women (n=1,800) who had undergone lumpectomy were randomly assigned to WBRT with or without RNI. An improvement in 10-year DFS was seen with the addition of regional RT compared with WBRT alone (82% vs 77%; hazard ratio [HR], 0.76; 95% CI, 0.61–0.94). Distant recurrences were reduced from 17.3% to 13.4% in those receiving WBRT alone versus those who also received RNI.<sup>35</sup> No improvement was seen in 10-year OS with the addition of RNI compared with WBRT alone (82.8% vs 81.8%; HR, 0.91; 95% CI, 0.72–1.13).

In the EORTC 22922/10925 trial, women (n=4,000) were treated with lumpectomy plus WBRT or mastectomy plus chest wall radiation (n=955) and were randomly assigned to radiation

**ENDOCRINE THERAPY FOR RECURRENT OR STAGE IV DISEASE****Premenopausal Patients**

- Selective ER modulators (tamoxifen or toremifene) or ovarian ablation or suppression plus endocrine therapy as for postmenopausal women

**Postmenopausal Patients**

- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator (exemestane)
- Exemestane + everolimus<sup>1,2</sup>
- Palbociclib + letrozole (category 1)<sup>2,3</sup>
- Palbociclib + fulvestrant (category 1)<sup>4</sup>
- Selective ER down-regulator (fulvestrant)<sup>5</sup>
- Tamoxifen or toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

<sup>1</sup>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 AI).

<sup>2</sup>If there is disease progression while on palbociclib + letrozole there are no data to support an additional line of therapy with another palbociclib regimen. Likewise, if there is disease progression while on exemestane + everolimus, there are no data to support an additional line of therapy with another everolimus regimen.

<sup>3</sup>Palbociclib 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.

<sup>4</sup>For 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 or after prior adjuvant or metastatic endocrine therapy.

<sup>5</sup>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. 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.

Version 1.2017 © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

BINV-N

to the internal mammary and medial supraclavicular nodes or no RNI.<sup>34</sup> At a median follow-up of 10.9 years, the addition of RNI resulted in a significant reduction in breast cancer mortality compared with no additional treatment (12.5% vs 14.4%; HR, 0.82; 95% CI, 0.70–0.97). An improved was seen in DFS as well (72.1% vs 69.1%; HR, 0.89; 95% CI, 0.80–1.00;  $P=.04$ ).

Both the MA.20 and EORTC 22922/10925 trials included patients with high-risk, node-negative disease.<sup>34,35</sup> In MA.20, patients with high-risk node-negative disease ( $n=177$ ; 10% of total enrolled) included those with a primary tumor measuring  $\geq 5$  cm, or  $\geq 2$  cm with  $<10$  axillary nodes removed, and at least one of the following: grade 3 histology, ER negativity, or lymphovascular invasion (LVSI). For those with high-risk, node-negative disease, the 10-year DFS was 83.7% with WBRT plus RNI versus 72.4% with WBRT alone (HR, 0.55; 95% CI, 0.28–1.09).<sup>35</sup> The EORTC study eligibility included patients with stage I, II, III central/medial breast

cancers irrespective of lymph node involvement, of which 44.4% ( $n=1,778$ ) were node-negative. DFS in patients who received RNI was 76% versus 72% in those who did not (HR, 0.85; 95% CI, 0.70–1.02).<sup>34</sup>

**NCCN Recommendations for RNI After Lumpectomy:** For patients with  $\geq 4$  positive lymph nodes, the NCCN panel recommends RNI to the supraclavicular and infraclavicular areas, internal mammary nodes, and any part of the axillary bed at risk (category 1). For those with 1 to 3 positive axillary nodes, the panel recommends strong consideration of RNI to these areas (category 2A).

RNI for patients with negative axillary nodes is not routinely recommended by the panel. However in patients with central/medial primary tumors or tumors  $>2$  cm with other high-risk features such as young age or extensive LVSI, according to the updated NCCN Guidelines, RNI may be considered on the basis of assessed individual risk for locoregional recurrence. The guidelines updates reflect these

## Breast Cancer, Version 1.2017

changes based on results of the MA-20 and EORTC trials (see BINV-2; page 435).

**NCCN Recommendations and Other RT Considerations for Those Undergoing Lumpectomy: Accelerated Partial Breast Irradiation:** Studies of APBI suggest that rates of local control in selected patients with early-stage breast cancer may be comparable to those treated with standard WBRT. Patients are encouraged to participate in clinical trials. The NCCN panel accepts the updated 2016 version of the ASTRO APBI consensus statement, which now defines criteria for patients “suitable” for APBI as one of the following: (1) age of  $\geq 50$  years with invasive ductal carcinoma measuring  $\leq 2$  cm (T1 disease) with negative margins by  $\geq 2$  mm, no LVSI, hormone receptor–positive, and BRCA-negative, or (2) low to intermediate grade screen-detected ductal carcinoma in situ measuring  $\leq 2.5$  cm with negative margins by  $\geq 3$  mm.<sup>36</sup>

Recent results from a randomized study of APBI using interstitial brachytherapy versus WBRT (50 Gy with 10 Gy boost) after lumpectomy in patients with low-risk disease demonstrated that APBI was not inferior to WBRT with respect to 5-year local control, DFS, and OS.<sup>37</sup> Overall recurrence rates were low in both arms. Toxicity profiles and cosmetic results were also found to be similar in both trial groups at the end of 5 years, with fewer grade 2/3 late skin side effects observed in those receiving APBI.<sup>38</sup> The applicability of these results using interstitial brachytherapy and doses of the trial to other APBI techniques is uncertain.

**Dose and Schedule:** A treatment course of 34 Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day with external-beam RT is typically prescribed to the tumor bed. Other fractionation schemes are currently under investigation.

**RT After Lumpectomy in Older Adults:** RT may be omitted after breast-conserving surgery in selected older women at overall low risk of recurrence. A study of women aged  $\geq 70$  years at diagnosis with clinical stage I, node-negative, ER-positive breast cancer with negative margins who were to receive adjuvant tamoxifen randomized patients to receive lumpectomy with WBRT or lumpectomy alone. With a median follow up of 12.6 years, the WBRT group

experienced a significantly longer time to locoregional recurrence (HR, 0.18; 95% CI, 0.07–0.42;  $P < .001$ ) compared with those who did not receive RT. At 10 years, the incidence of locoregional recurrence was 8% lower in those receiving RT. Of patients receiving RT, 98% were free from local and regional recurrences (95% CI, 96%–99%) compared with 90% of those receiving tamoxifen (95% CI, 85%–93%).<sup>39,40</sup> No differences were seen in OS, DFS, or need for mastectomy between the 2 groups.<sup>39,40</sup>

Similar results have been obtained in other studies of similar design.<sup>41,42</sup> In the Postoperative Radiotherapy in Minimum-Risk Elderly (PRIME) II study, women ( $n = 1,326$ ) aged  $\geq 65$  years with node-negative breast cancers that were  $< 3$  cm were randomly assigned to RT versus no RT.<sup>43</sup> After a median follow-up of 5 years, ipsilateral breast tumor recurrences were lower in women assigned to RT (1.3% vs 4.1%). However, no differences in OS, regional recurrence, distant metastases, or contralateral breast cancers were observed between the groups.<sup>43</sup>

In the NCCN Guidelines, breast RT may be omitted after breast-conserving surgery for women  $\geq 70$  years of age with ER-positive, clinically node-negative T1 breast cancers who will receive endocrine therapy (tamoxifen or an aromatase inhibitor [AI]; category 1).

### Adjuvant RT After Mastectomy

Multiple trials have reported decrease in locoregional recurrence and OS benefit in patients receiving postmastectomy RT (PMRT).<sup>44–46</sup> The indications for RT after mastectomy depend on the presence of risk factors for locoregional recurrence, such as large or advanced tumor ( $\geq T3$  disease or T3–4), close or positive margins, positive lymph nodes, and/or multiple other high-risk factors. After mastectomy, RT is most commonly delivered to chest wall with RNI.

#### RT to Chest Wall (Including Breast Reconstruction):

The target for chest wall irradiation includes the ipsilateral chest wall and mastectomy scar, and may include the drain sites when indicated.

#### RT for Node-Positive Disease After Mastectomy:

Randomized clinical trials of postmastectomy RT (PMRT) have shown that a DFS and OS advantage is conferred by irradiation of chest wall and regional lymph nodes.<sup>44,46–49</sup> In these trials, PMRT target volumes include the ipsilateral chest wall and

regional lymph nodes, including supraclavicular, axillary apex, and internal mammary nodes.

The results of EBCTCG meta-analyses<sup>50</sup> show that RT after mastectomy and ALND reduced both recurrence and breast cancer mortality in the women with 1 to 3 positive lymph nodes even when systemic therapy was administered.<sup>34</sup> The data from EORTC 22922/10925 trial, which included patients (n=955) who had undergone a mastectomy, further support the role of PMRT in women with positive lymph nodes.<sup>34</sup> For women with 1 to 3 involved ALNs, the most recent jointly updated guidelines by ASCO, ASTRO, and Society of Surgical Oncology recommend PMRT to reduce the risk of recurrence and improve survival taking an individualized approach based on patient preference and high-risk features.<sup>51</sup>

#### **RT for Node-Negative Disease After Mastectomy:**

Prior retrospective analyses suggest a benefit of RT after mastectomy in reducing risk of recurrence in patients with node-negative disease with high-risk factors, such as close margins, tumors  $\geq 2$  cm, premenopausal status, triple-negative intrinsic subtype, and/or LVSI.<sup>52,53</sup> Additional features of node-negative tumors that predict a higher rate of local recurrence include primary tumors  $> 5$  cm or positive pathologic margins. The Danish Breast Cancer Cooperative Group studies included patients with node-positive as well as high-risk, node-negative disease (defined as tumors that were  $> 5$  cm or invaded the skin or fascia) and demonstrated improved DFS and OS associated with RT (including the axillary, supra/infraclavicular, and ipsilateral internal mammary nodes) after mastectomy.<sup>43,45,48</sup>

#### **NCCN Recommendations for RT After Mastectomy:**

The NCCN Guidelines recommend PMRT to the chest wall and regional nodes in patients with  $\geq 4$  positive ALNs (category 1). For patients with 1 to 3 positive nodes, PMRT should be strongly considered (category 2A). RNI should include the infraclavicular and supraclavicular regions, internal mammary nodes, and the axillary bed at risk.

In patients with negative axillary nodes and tumors  $> 5$  cm, or positive surgical margins, chest wall irradiation should be considered with or without RNI.

For negative axillary nodes, tumors  $\leq 5$  cm, and negative margins but  $< 1$  mm according to the NCCN panel, RT should be considered to the chest

wall with or without regional nodal RT in patients with central/medial primary tumor or tumor  $> 2$  cm with other high-risk features, such as young age or extensive lymphovascular invasion.

In patients with negative axillary nodes, tumors  $\leq 5$  cm, and clear margins  $\geq 1$  mm, RT is generally not recommended. However, the panel has noted that in this group, RT may be considered for those with multiple risks of recurrence, including central/medial primary tumors or tumors  $> 2$  cm with other high-risk features, such as young age or extensive LVSI (see BINV-3; page 436).

CT-based treatment planning is recommended to assure adequate target coverage of the breast tissue and lumpectomy site and to limit dose to normal tissues, especially the heart and lungs.

*Treatment Planning and Dose:* CT-based treatment planning is recommended to assure adequate target coverage of the chest wall and regional lymph nodes and limit dose to normal tissues, especially the heart and lungs.

Compensators such as tissue wedges, forward planning using segments, and IMRT may provide improved homogeneity of target dose and normal tissue sparing.<sup>31,32</sup> Treatment techniques, such as respiratory control using deep inspiration breath-hold, can further reduce dose to adjacent normal tissues, particularly the heart and lungs.<sup>33</sup> The NCCN panel recommends a dose of 45 to 50 Gy in 23 to 25 fractions to the chest wall and regional lymph nodes. A scar boost of 10 Gy, at 2 Gy per fraction, to a total dose of approximately 60 Gy may be considered in patients at increased risk for recurrence.

## **Adjuvant Bisphosphonate Therapy**

The antiresorptive agents (bisphosphonates and denosumab) have an established role as preventative and therapeutic agents for the management of osteoporosis, hypercalcemia of malignancy, and bone metastases.

### **Bisphosphonates**

Oral clodronate, which is not commercially available in this country, has been studied in several randomized trials in patients with early-stage breast cancer for preventing bone metastases and improving survival. The studies have reported mixed results, with

## Breast Cancer, Version 1.2017

variable effects on DFS and OS.<sup>54–57</sup> However, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-34 trial, although DFS was similar in older and younger women, improvements in skeletal metastasis-free interval ( $P=.027$ ) and nonskeletal metastasis-free interval ( $P=.014$ ) were noted with adjuvant clodronate in women  $>50$  years of age.<sup>57</sup> Patients aged  $>60$  years appeared to derive the most benefit from adjuvant clodronate, including an almost 60% reduction in skeletal metastases and a 40% to 50% reduction in nonskeletal metastases.<sup>57</sup>

Similarly, zoledronic acid seems to have a different effect in patients with high versus low estrogen environments (postmenopausal vs premenopausal patients). In the Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12) trial, for patients  $>40$  years of age, zoledronic acid significantly reduced the risk of recurrence by 34% (HR, 0.66;  $P=.014$ ) and the risk of death by 49% (HR, 0.51;  $P=.020$ ). However, no improvement was seen in either DFS or OS in this post hoc analysis among patients  $<40$  years of age.<sup>58</sup> In a planned subgroup analysis of the AZURE trial, zoledronic acid improved DFS in women who were  $>5$  years since menopause at trial entry.<sup>59</sup> A meta-analysis of data from 7 adjuvant bisphosphonate trials (AZURE, ABCSG-12, ZO-FAST, Z-FAST, EZO-FAST, NSABP-B34, GAIN), including only those known to be aged  $\geq 50$  years, postmenopausal, or with ovarian suppression, showed a significant benefit for the use of adjuvant bisphosphonates in patients with a low-estrogen state and early-stage breast cancer.<sup>60</sup> More recently, the EBCTCG conducted a meta-analysis of all randomized adjuvant bisphosphonate studies (26 studies) and reported convincing evidence that adjuvant bisphosphonates provide benefits to postmenopausal (natural or induced) patients with breast cancer.<sup>61</sup> With bisphosphonate therapy, the greatest improvement was seen in bone recurrence (RR, 0.83;  $P=.004$ ) and bone fractures (RR, 0.85;  $P=.02$ ). No effect was seen on distant recurrence outside bone (RR, 0.98;  $P=.69$ ).<sup>61</sup> In premenopausal patients, bisphosphonate therapy did not seem to have a significant effect on bone recurrence. However, in postmenopausal patients, zoledronic acid significantly reduced bone recurrence (3.4% vs 4.5%; RR, 0.73; 99% CI, 0.53–1.00); the difference in breast cancer mortality was not statistically significant (7.1% vs 7.9%; RR, 0.88; 99% CI, 0.69–1.11).<sup>61</sup>

With respect to other bisphosphonates, one trial that studied adjuvant oral ibandronate showed no effect on DFS or OS in patients with node-positive, early-stage breast cancer treated with dose-dense chemotherapy.<sup>62</sup> Data on adjuvant oral pamidronate show no benefit on either reducing fractures or recurrence to bone in patients with breast cancer receiving adjuvant chemotherapy.<sup>63</sup>

### Denosumab

In the adjuvant setting, the ABCSG-18 trial studied the effect of denosumab in postmenopausal patients treated with adjuvant AIs and showed a reduction in clinical fractures (HR, 0.5;  $P<.0001$ ), which was the primary end point of this study.<sup>64</sup> Subsequently, in an interim analysis, an improvement in DFS—a secondary end point of the trial—was reported.<sup>65</sup> However, unlike the bisphosphonates, which have demonstrated an OS benefit when used as adjuvant therapy, no available data show an OS benefit with denosumab. Results of the ABCSG-18 and the ongoing D-CARE<sup>66</sup> trials may provide evidence for the use of denosumab in the adjuvant setting.

### NCCN Recommendations for Use of Bisphosphonates as Adjuvant Therapy

The recently updated guidelines include new indications for bisphosphonates based on the EBCTCG meta-analysis.<sup>61</sup> The panel recommends considering adjuvant bisphosphonate therapy for postmenopausal (natural or induced) women receiving adjuvant endocrine therapy (see BINV-5, BINV-6, and BINV-9; pages 437, 438, and 439, respectively).

### Adjuvant Endocrine Therapy

#### Duration of Adjuvant Endocrine Therapy for Hormone Receptor-Positive Breast Cancer

Adjuvant endocrine therapy is recommended for a minimum of 5 years. A recent retrospective analysis by the Oxford University studied risk of recurrence for years 5 through 20 after 5 years of endocrine therapy.<sup>67</sup> These data showed a considerable risk of recurrence between years 5 and 20 in these patients treated with an initial 5 years of endocrine therapy.<sup>67</sup> Data have now emerged showing benefit of extended endocrine therapy in improving DFS.

For those treated initially with adjuvant tamoxifen, evidence from several randomized trials shows

benefit from extended adjuvant endocrine therapy. In the MA-17 trial, postmenopausal women with hormone receptor–positive, early-stage breast cancer who had completed 4.5 to 6 years of adjuvant tamoxifen were randomized to extended therapy with letrozole or not.<sup>68–70</sup> With a median follow-up of 64 months, letrozole was associated with improved DFS (HR, 0.52; 95% CI, 0.45–0.61) and OS (HR, 0.61; 95% CI, 0.52–0.71) compared with placebo.<sup>70</sup>

The ATLAS trial randomly allocated premenopausal and postmenopausal women to either 5 or 10 years (extended therapy) of tamoxifen. The outcome analyses of 6,846 women with ER-positive disease showed that by extending adjuvant treatment to 10 years, the risk of relapse and breast cancer–related mortality was reduced.<sup>71</sup> The risk of recurrence during years 5 to 14 was 21.4% for women receiving tamoxifen versus 25.1% for controls (absolute recurrence reduction, 3.7%). Patients who received tamoxifen for 10 years had a greater reduction in risk of progression, possibly due to a “carryover effect.” The reduction in risk of recurrence was 0.90 (95% CI, 0.79–1.02) during 5 to 9 years of tamoxifen treatment and 0.75 (95% CI, 0.62–0.90) after 10 years of treatment. There were also decreases in the incidence of contralateral breast cancer. Furthermore, reduced mortality was also apparent after completion of 10 years of tamoxifen treatment. With regard to toxicity, the most important adverse effects noted in all women in the ATLAS trial after 10 years of tamoxifen treatment were an increased risk for endometrial cancer and pulmonary embolism.<sup>71</sup> The results of the aTTom trial confirm the reduction in recurrence and death from breast cancer seen in the ATLAS trial with 10 versus 5 years of tamoxifen therapy.<sup>72</sup>

In women initially treated with an AI, a recent randomized phase III trial (MA17.R) evaluated the effects of extending adjuvant AI therapy from 5 to 10 years.<sup>73</sup> Postmenopausal women who had completed 4.5 to 6 years of therapy with an AI (with a median duration of prior tamoxifen of 5 years), were randomized to letrozole or placebo for an additional 5 years.<sup>73</sup> Improvement was seen in 5-year DFS in those receiving letrozole compared with those who received placebo (95% [95% CI, 93%–96%] vs 91% [95% CI, 89%–93%]). The annual rate of contralateral breast cancer reported was lower with letrozole (0.49% vs 0.21%; HR, 0.42; 95% CI, 0.22%–0.81%).

However, longer duration of AI treatment resulted in more frequent bone-related adverse effects compared with placebo, and no improvement was observed with respect to OS. Bone-related adverse effects included bone pain (18% vs 14%), fractures (14% vs 9%), and new-onset osteoporosis (11% vs 6%).<sup>73</sup>

### NCCN Recommendations for Adjuvant Endocrine Therapy

**Postmenopausal Women:** The NCCN Guidelines for Breast Cancer recommend the following adjuvant endocrine therapy options for women with early-stage breast cancer who are postmenopausal at diagnosis: (1) an AI as initial adjuvant therapy for 5 years (category 1), with consideration of an additional 5 years on AI therapy based on data from the recent MA17.R trial; (2) an AI for 2 to 3 years (category 1) followed by tamoxifen to complete 5 years of endocrine therapy (category 1); (3) tamoxifen for 2 to 3 years followed by one of the following options: an AI to complete 5 years of adjuvant endocrine therapy (category 1) or 5 years of AI therapy (category 2B); or (4) tamoxifen for 4.5 to 6 years followed by 5 years of an AI (category 1), or consideration of tamoxifen for up to 10 years. In postmenopausal women, the use of tamoxifen alone for 5 years (category 1) or up to 10 years is limited to those who decline or have a contraindication to AIs (see BINV-J; page 441).

**Premenopausal Women:** For women who were premenopausal at diagnosis, the NCCN Guidelines for Breast Cancer recommend 5 years of tamoxifen (category 1) with or without ovarian suppression (category 1), or ovarian suppression plus an AI for 5 years (category 1). Women who are premenopausal at diagnosis and who become amenorrheic with chemotherapy may have continued estrogen production from the ovaries without menses. Serial assessment of circulating luteinizing hormone, follicle-stimulating hormone, and estradiol to assure a true postmenopausal status is mandatory if this subset of women is to be considered for therapy with an AI<sup>74,75</sup> (see BINV-J; page 441).

After 5 years of initial endocrine therapy, for women who are postmenopausal at that time (including those who have become postmenopausal during the 5 years of tamoxifen therapy), the NCCN panel recommends considering extended therapy with an AI for up to 5 years (category 1) or consid-

## Breast Cancer, Version 1.2017

ering tamoxifen for an additional 5 years. For those who remain premenopausal after the initial 5 years of tamoxifen, the panel recommends considering continuing up to 10 years of tamoxifen therapy (see BINV-J; page 441).

### First-Line Endocrine Therapy for Metastatic Hormone Receptor–Positive Breast Cancer

**Editor’s Note:** Updates on new drug approvals, not available at press time, can be found in the most recent version of these guidelines at NCCN.org.

Women with recurrent or metastatic disease characterized by tumors that are hormone receptor–positive are appropriate candidates for endocrine therapy. First-line endocrine treatment is for women presenting with metastatic disease >12 months after completion of adjuvant endocrine therapy or those presenting with de novo metastatic breast cancer.

In premenopausal women, first-line endocrine treatment is typically with a selective ER modulator (SERM) alone or with ovarian suppression/ablation and endocrine therapy listed for postmenopausal women.<sup>76</sup> Tamoxifen is the commonly used SERM for premenopausal women.

In postmenopausal women, AIs appear to have superior outcome compared with tamoxifen, although the differences are modest.<sup>77–80</sup> A Cochrane review has also suggested a survival benefit favoring the AIs over other endocrine therapies, although the advantage is small.<sup>81</sup> 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 progression-free survival (PFS) or OS between the 2 arms.<sup>79</sup>

Fulvestrant is an 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 overall response (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).<sup>82</sup> An improved time to progression was seen with fulvestrant compared to anastrozole (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;  $P=.0496$ ).<sup>83</sup> This study also used a higher loading dose of 500 mg every 2 weeks for 3 doses and then a maintenance dose of 500 mg monthly.<sup>82</sup> 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;  $P=.041$ ).<sup>84</sup>

Results from a recent phase III trial (FALCON) of first-line treatment with fulvestrant compared with anastrozole in women with metastatic ER–positive breast cancer demonstrated 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).<sup>85</sup> Quality-of-life outcomes were similar between the groups, with the most common adverse effects being arthralgia (17% vs 10%) and hot flashes (11% vs 10%) for fulvestrant and anastrozole, respectively.<sup>85</sup> Importantly, patients in the FALCON trial had not received any prior endocrine therapy in any setting.

Combination of 2 endocrine agents as first-line treatment in postmenopausal women with hormone receptor–positive, metastatic breast cancer has been reported from 2 studies comparing single-agent anastrozole versus anastrozole plus fulvestrant. In one study (FACT), combination endocrine therapy was not superior to single-agent anastrozole (time to progression: HR, 0.99; 95% CI, 0.81–1.20;  $P=.91$ ).<sup>86</sup> In the second study (S0226) by SWOG, 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 combination anastrozole plus fulvestrant.<sup>87</sup> An unplanned subset analysis in this trial suggested that patients without prior adjuvant tamoxifen experienced the greatest benefit. The reason for the divergent outcomes in these 2 studies is not known.

The CDK 4/6 inhibitor, palbociclib in combination with letrozole received accelerated approval by the FDA as first-line therapy for metastatic, ER–positive, HER2–negative breast cancer. This approval was based on a phase II, open-label, randomized, multicenter trial (PALOMA-1) that 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.<sup>88</sup> Median PFS reported was double

with the combination regimen compared with letrozole alone (20.2 months for the palbociclib plus letrozole group vs 10.2 months for the letrozole alone group; HR, 0.488; 95% CI, 0.319–0.748).<sup>88</sup> 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%).

In a subsequent phase III study (PALOMA-2), the combination of palbociclib and letrozole demonstrated improved PFS (24.8 vs 14.5 months; HR, 0.58, 95% CI, 0.46–0.72) and objective response rate (42% vs 35%) compared with letrozole alone.<sup>89</sup> The most commonly reported adverse events in the palbociclib and letrozole group compared with the letrozole alone group included neutropenia (79.5% vs 6.3%), fatigue (37.4% vs 27.5%) and nausea (35.1% vs 26.1%) and grade 1 and 2 alopecia (32.9% vs 15.8%).<sup>89</sup>

### NCCN Recommendations for Endocrine Therapy for Metastatic Breast Cancer

All of the endocrine therapy options recommended by the NCCN panel for premenopausal and postmenopausal women with hormone receptor–positive metastatic breast cancer are listed on BINV-N (page 442).

In the recently updated guidelines, based on the results of the PALOMA-2 study, the NCCN panel included the combination of palbociclib with letrozole as a category 1 first-line endocrine therapy option for postmenopausal patients with hormone receptor–positive, HER2-negative metastatic breast cancer.

Fulvestrant and palbociclib may be offered to patients who experienced progression during prior treatment with AIs with or without one line of prior chemotherapy (category 1), because PFS was improved compared with fulvestrant alone in a phase III trial (PALOMA-3).<sup>90</sup> The NCCN panel notes that treatment should be limited to those without prior exposure to cyclin-dependent kinase 4/6 inhibitors.

### Conclusions

This report highlights the updates to the surgical axillary staging, RT, and systemic therapy recommendations for hormone receptor–positive disease in the 2017 version of the NCCN Guidelines for Breast Cancer. The NCCN Guidelines are in continuous evolution. They are updated annually, and sometimes more often if/when new high-quality clinical data become available in the interim. The recommendations in the NCCN Guidelines, 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 patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the panel strongly encourages patient/physician participation in prospective clinical trials.

### References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017;67:7–30.
2. Deutsch M, Land S, Begovic M, Sharif S. The incidence of arm edema in women with breast cancer randomized on the National Surgical Adjuvant Breast and Bowel Project study B-04 to radical mastectomy versus total mastectomy and radiotherapy versus total mastectomy alone. *Int J Radiat Oncol Biol Phys* 2008;70:1020–1024.
3. Fleissig A, Fallowfield LJ, Langridge CI, et al. Post-operative arm morbidity and quality of life. Results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. *Breast Cancer Res Treat* 2006;95:279–293.
4. Lucci A, McCall LM, Beitsch PD, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *J Clin Oncol* 2007;25:3657–3663.
5. Ashikaga T, Krag DN, Land SR, et al. Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. *J Surg Oncol* 2010;102:111–118.
6. Land SR, Kopec JA, Julian TB, et al. Patient-reported outcomes in sentinel node-negative adjuvant breast cancer patients receiving sentinel-node biopsy or axillary dissection: National Surgical Adjuvant Breast and Bowel Project phase III protocol B-32. *J Clin Oncol* 2010;28:3929–3936.
7. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J Natl Cancer Inst* 2006;98:599–609.
8. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 2003;349:546–553.
9. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg* 2010;252:426–432; discussion 432–423.
10. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 2011;305:569–575.
11. Giuliano AE, Ballman K, McCall L, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: long-term follow-up from the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 randomized trial. *Ann Surg* 2016;264:413–420.



## Breast Cancer, Version 1.2017

12. Galimberti V, Cole BF, Zurrada S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol* 2013;14:297–305.
13. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014;15:1303–1310.
14. Rocha RD, Girardi AR, Pinto RR, de Freitas VA. Axillary ultrasound and fine-needle aspiration in preoperative staging of axillary lymph nodes in patients with invasive breast cancer. *Radiol Bras* 2015;48:345–352.
15. Axelsson CK, Mouridsen HT, Zedeler K. Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The Danish Breast Cancer Cooperative Group (DBCG). *Eur J Cancer* 1992;28A:1415–1418.
16. Kiricuta CI, Tausch J. A mathematical model of axillary lymph node involvement based on 1446 complete axillary dissections in patients with breast carcinoma. *Cancer* 1992;69:2496–2501.
17. Giuliano AE, Hawes D, Ballman KV, et al. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. *JAMA* 2011;306:385–393.
18. Edge S, Byrd D, Compton C, et al, eds. *AJCC Cancer Staging Manual*, 7th ed. New York, NY: Springer; 2010.
19. Early Breast Cancer Trialists' Collaborative Group, Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378:1707–1716.
20. Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008;371:1098–1107.
21. Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008;9:331–341.
22. Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. *Lancet Oncol* 2006;7:467–471.
23. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010;362:513–520.
24. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013;14:1086–1094.
25. Romestaing P, Lehingue Y, Carrie C, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. *J Clin Oncol* 1997;15:963–968.
26. Vrieling C, Collette L, Fourquet A, et al. The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC 'boost vs. no boost' trial. *EORTC Radiotherapy and Breast Cancer Cooperative Groups. Radiother Oncol* 2000;55:219–232.
27. Bartelink H, Horiot JC, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 2001;345:1378–1387.
28. Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol* 2007;25:3259–3265.
29. Antonini N, Jones H, Horiot JC, et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. *Radiother Oncol* 2007;82:265–271.
30. Jones HA, Antonini N, Hart AA, et al. Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC boost versus no boost trial. *J Clin Oncol* 2009;27:4939–4947.
31. Pignol JP, Olivetto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *J Clin Oncol* 2008;26:2085–2092.
32. Mukesh MB, Barnett GC, Wilkinson JS, et al. Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis. *J Clin Oncol* 2013;31:4488–4495.
33. Mulliez T, Veldeman L, van Greveling A, et al. Hypofractionated whole breast irradiation for patients with large breasts: a randomized trial comparing prone and supine positions. *Radiother Oncol* 2013;108:203–208.
34. Poortmans PM, Collette S, Kirkove C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med* 2015;373:317–327.
35. Whelan TJ, Olivetto IA, Parulekar WR, et al. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 2015;373:307–316.
36. Correa C, Harris EE, Leonardi MC, et al. Accelerated partial breast irradiation: executive summary for the update of an ASTRO evidence-based consensus statement. *Pract Radiat Oncol* 2017;7:73–79.
37. Strnad V, Ott OJ, Hildebrandt G, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet* 2016;387:229–238.
38. Polgar C, Ott OJ, Hildebrandt G, et al. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2017;18:259–268.
39. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *N Engl J Med* 2004;351:971–977.
40. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol* 2013;31:2382–2387.
41. Fyles AW, McCready DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med* 2004;351:963–970.
42. Kunkler IH, Williams LJ, Jack WJ, et al. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol* 2015;16:266–273.
43. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997;337:949–955.
44. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366:2087–2106.
45. Nielsen HM, Overgaard M, Grau C, et al. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. *J Clin Oncol* 2006;24:2268–2275.
46. Ragaz J, Olivetto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J Natl Cancer Inst* 2005;97:116–126.
47. Hellman S. Stopping metastases at their source. *N Engl J Med* 1997;337:996–997.
48. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999;353:1641–1648.
49. Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. *Radiother Oncol* 2007;82:247–253.
50. Early Breast Cancer Trialists' Collaborative Group, McGale P, Taylor C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014;383:2127–2135.
51. Recht A, Comen EA, Fine RE, et al. Postmastectomy radiotherapy: an American Society of Clinical Oncology, American Society for Radiation Oncology, and Society of Surgical Oncology focused guideline update. *Pract Radiat Oncol* 2016;6:e219–234.
52. Jagi R, Raad RA, Goldberg S, et al. Locoregional recurrence rates and prognostic factors for failure in node-negative patients treated with mastectomy: implications for postmastectomy radiation. *Int J Radiat Oncol Biol Phys* 2005;62:1035–1039.

## Breast Cancer, Version 1.2017

53. Abdulkarim BS, Cuartero J, Hanson J, et al. Increased risk of locoregional recurrence for women with T1-2N0 triple-negative breast cancer treated with modified radical mastectomy without adjuvant radiation therapy compared with breast-conserving therapy. *J Clin Oncol* 2011;29:2852–2858.
54. Powles T, Paterson A, McCloskey E, et al. Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [ISRCTN83688026]. *Breast Cancer Res* 2006;8:R13.
55. Diel IJ, Jaschke A, Solomayer EF, et al. Adjuvant oral clodronate improves the overall survival of primary breast cancer patients with micrometastases to the bone marrow: a long-term follow-up. *Ann Oncol* 2008;19:2007–2011.
56. Saarto T, Blomqvist C, Virkkunen P, Elomaa I. Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial. *J Clin Oncol* 2001;19:10–17.
57. Paterson AH, Anderson SJ, Lembersky BC, et al. Oral clodronate for adjuvant treatment of operable breast cancer (National Surgical Adjuvant Breast and Bowel Project protocol B-34): a multicentre, placebo-controlled, randomised trial. *Lancet Oncol* 2012;13:734–742.
58. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al. Long-term follow-up in ABCSG-12: significantly improved overall survival with adjuvant zoledronic acid in premenopausal patients with endocrine-receptor-positive early breast cancer [abstract]. *Cancer Res* 2011;71(24 Suppl):Abstract S1–2.
59. Coleman RE, Marshall H, Cameron D, et al. Breast-cancer adjuvant therapy with zoledronic acid. *N Engl J Med* 2011;365:1396–1405.
60. Gregory W, Marshall H, Bell R, et al. Adjuvant zoledronic acid (ZOL) in postmenopausal women with breast cancer and those rendered postmenopausal: results of a meta-analysis [abstract]. *J Clin Oncol* 2012;30(Suppl):Abstract 513.
61. Early Breast Cancer Trialists' Collaborative Group, Coleman R, Powles T, et al. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *Lancet* 2015;386:1353–1361.
62. von Minckwitz G, Mobus V, Schneeweiss A, et al. German adjuvant intergroup node-positive study: a phase III trial to compare oral ibandronate versus observation in patients with high-risk early breast cancer. *J Clin Oncol* 2013;31:3531–3539.
63. Kristensen B, Ejlersen B, Mouridsen HT, et al. Bisphosphonate treatment in primary breast cancer: results from a randomised comparison of oral pamidronate versus no pamidronate in patients with primary breast cancer. *Acta Oncol* 2008;47:740–746.
64. Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2015;386:433–443.
65. Gnant M, Pfeiler G, Dubsky PC, et al. The impact of adjuvant denosumab on disease-free survival: results from 3,425 postmenopausal patients of the ABCSG-18 trial [Abstract]. *Cancer Res* 2016;76(4 Suppl):Abstract S2-02.
66. Goss PE, Barrios CH, Chan A, et al. Denosumab versus placebo as adjuvant treatment for women with early-stage breast cancer at high risk of disease recurrence (D-CARE): a global, placebo-controlled, randomized, double-blind, phase 3 clinical trial [abstract]. *Cancer Res* 2013;73(24 Suppl):Abstract OT2-6-02.
67. Pan H, Gray R, Davies C, et al. Predictors of recurrence during years 5-14 in 46,138 women with ER+ breast cancer allocated 5 years only of endocrine therapy (ET) [abstract]. *J Clin Oncol* 2016;34(Suppl):Abstract 505.
68. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003;349:1793–1802.
69. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005;97:1262–1271.
70. Jin H, Tu D, Zhao N, et al. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. *J Clin Oncol* 2012;30:718–721.
71. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805–816.
72. Gray R, Rea D, Handley K, et al. aTTom: long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer [abstract]. *J Clin Oncol* 2013;31(Suppl):Abstract 5.
73. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. *N Engl J Med* 2016;375:209–219.
74. Smith IE, Dowsett M, Yap YS, et al. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. *J Clin Oncol* 2006;24:2444–2447.
75. Yu B, Douglas N, Ferin MJ, et al. Changes in markers of ovarian reserve and endocrine function in young women with breast cancer undergoing adjuvant chemotherapy. *Cancer* 2010;116:2099–2105.
76. Klijn JG, Blamey RW, Boccardo F, et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001;19:343–353.
77. Bonnetterre J, Thurlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol* 2000;18:3748–3757.
78. Nabholz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. *Arimidex Study Group. J Clin Oncol* 2000;18:3758–3767.
79. Paridaens RJ, Dirix LY, Beex LV, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol* 2008;26:4883–4890.
80. Vergote I, Bonnetterre J, Thurlimann B, et al. Randomised study of anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women. *Eur J Cancer* 2000;36(Suppl 4):S84–85.
81. Gibson L, Lawrence D, Dawson C, Bliss J. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. *Cochrane Database Syst Rev* 2009;CD003370.
82. Robertson JF, Llombart-Cussac A, Rolski J, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. *J Clin Oncol* 2009;27:4530–4535.
83. Robertson JF, Lindemann JP, Llombart-Cussac A, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized 'FIRST' study. *Breast Cancer Res Treat* 2012;136:503–511.
84. Ellis MJ, Llombart-Cussac A, Felt D, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: overall survival analysis from the phase II FIRST study. *J Clin Oncol* 2015;33:3781–3787.
85. Robertson JF, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. *Lancet* 2016;388:2997–3005.
86. Bergh J, Jonsson PE, Lidbrink EK, et al. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. *J Clin Oncol* 2012;30:1919–1925.
87. Mehta RS, Barlow WE, Albain KS, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. *N Engl J Med* 2012;367:435–444.
88. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol* 2015;16:25–35.
89. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* 2016;375:1925–1936.
90. Turner NC, Ro J, Andre F, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2015;373:209–219.

## Breast Cancer, Version 1.2017

### Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at <http://education.nccn.org/node/80546>; and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-

choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on "New Member? Sign up here" link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet

### Posttest Questions

1. Which of the statements regarding regional nodal RT is not true?
  - a. Regional nodal RT is a category 1 recommendation for women with  $\geq 4$  positive axillary lymph nodes.
  - b. According to the NCCN Guidelines for Breast Cancer, regional nodal RT should be strongly considered in those with 1 to 3 positive axillary lymph nodes.
  - c. Regional nodal RT is not recommended in patients with negative axillary nodes regardless of other risk factors.
2. True or False: Based on the results of the IBCSG 23-01 trial, the NCCN panel recommends no ALND for pa-

tients with positive SLNs when only micrometastatic ( $>0.2$  but  $\leq 2.0$  mm) disease is present.

3. Which of the following combination therapies is an NCCN category 1 option as first-line therapy for postmenopausal patients with hormone receptor–positive, HER2–negative metastatic breast cancer?
  - a. Palbociclib + fulvestrant
  - b. Palbociclib + letrozole
  - c. Everolimus + exemestane

