National Comprehensive Cancer Network, Inc.

End User License Agreement for the NCCN Clinical Practice Guidelines in Oncology™

This End User License Agreement (the "Agreement") is an agreement between you and the National Comprehensive Cancer Network, Inc. ("NCCN") for access to and use of the electronic version of the Complete Library of NCCN Clinical Practice Guidelines in Oncology™, which, together with any updates, are referred to collectively as the "Guidelines", the NCCN Drugs and Biologics Compendium™, which together with any updates, are referred to collectively as the "Compendium", and the NCCN Chemotherapy Order Templates™, which, together with any updates, are referred to collectively as the "Templates" and provided to you on the NCCN website (the "website"), through which you have accessed this document. BY CLICKING ON THE "I AGREE" BUTTON BELOW, YOU AGREE TO BE BOUND BY THE TERMS AND CONDITIONS OF THIS LICENSE AGREEMENT. IF YOU DO NOT AGREE WITH THE TERMS OF THIS LICENSE AGREEMENT, DO NOT VIEW, ACCESS, OR USE THE TEMPLATES.

1. Grant of License. NCCN hereby grants to you a non-transferable, non-exclusive, limited license to access and use the Guidelines, the Compendium, and/or the Templates subject to the terms set forth in this License Agreement.

2. Proprietary Rights. You acknowledge that, as between you and NCCN, NCCN is the owner of all right, title and interest in and to the Guidelines, the Compendium, and/or the Templates, including, without limitation, all copyrights, trademarks, goodwill, derivative works, and other intellectual property and proprietary rights related thereto. Except for the limited rights expressly enumerated herein, you are not granted any rights relating to copyrights, trade names, trademarks (whether registered or unregistered) or any other rights, franchises or licenses with respect to the Guidelines, the Compendium, and/or the Templates or NCCN. You hereby agree that you shall not at any time dispute, challenge, or contest, directly or indirectly, NCCN's right, title and interest in and to the Templates, or assist or aid others to do so.

3. Restrictions on Use. A) Complete Library of NCCN Clinical Practice Guidelines in Oncology™ and NCCN Drugs and Biologics Compendium™. You may not copy, transfer, reproduce, or create derivative works from, any part of the Guidelines or the Compendium for any reason. You may make and retain file copies of "Insubstantial Portions" of the Guidelines or the Compendium solely for your internal purposes. "Insubstantial Portions" means a quantity of data from the Guidelines or the Compendium that would not reasonably substitute for a comprehensive copy of the Guidelines or the Compendium and would not prejudice or diminish NCCN's advantage in licensing the Guidelines or the Compendium for commercial gain. Notwithstanding the foregoing, you may include Insubstantial Portions of the Guidelines or the Compendium in materials prepared in the ordinary course of your business for re-distribution in connection with the delivery of your principal services. Any such materials shall cite NCCN as the source of the Guidelines or the Compendium and provide notice of NCCN's copyrights and other proprietary rights, as follows: © National Comprehensive Cancer Network, Inc. 2009. NCCN and NATIONAL COMPREHENSIVE CANCER NETWORK are registered trademarks of National Comprehensive Cancer Network, Inc. You shall provide NCCN with examples of re-distributed materials including any portion of the Guidelines or the Compendium upon NCCN's reasonable request, but shall not be required to provide confidential information to NCCN. You agree to immediately cease any such re-distribution on receipt of notice from NCCN that, in NCCN's reasonable judgment, such re-distribution involves more than an Insubstantial Portion of the Compendium or Guidelines or is otherwise in violation of this Agreement.

B) NCCN Chemotherapy Order Templates™ You may use the Templates to guide your treatment decisions if you are a clinician. You may reproduce the Templates in paper media only, to use verbatim in your institution to facilitate others in making treatment decisions. At all times and for all purposes, the Templates may only be used in the context of clinicians exercising independent medical or professional judgment and may not be relied upon as an order. You are expected to use the Templates in making treatment choices and decisions within the scope of your professional license. Except as explicitly provided for in this provision, you may not copy, transfer, reproduce, edit or create derivative works from the Templates. You may not at any time claim, assert, represent, state or imply that any Template which you have altered in any way, without limitation, is derived from, based on, related to or arises out of the NCCN Templates. You shall provide NCCN with examples of re-distributed materials of any kind including any portion of the Templates upon NCCN's reasonable request. You agree to immediately cease any such re-distribution on receipt of notice from NCCN that, in NCCN's reasonable judgment, such re-distribution is otherwise in violation of this Agreement.

4. Limited Warranty; Disclaimers; Limitation of Damages.

A) The Guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

The recommendations regarding the uses and indications in the Compendium have been derived directly from the Guidelines. The Compendium neither represents an all-inclusive listing of every drug and biologic nor every appropriate use and indication for drugs and biologics. The listing of drugs and biologics in the Compendium is limited in consideration to a discussion of the uses of drugs and biologics in cancer care. NCCN considers clinical trials participation to be appropriate care. Any clinician seeking to apply or consult the Compendium is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment.

B) The Templates are peer reviewed statements of consensus of their authors derived from the Guidelines for the conditions the Templates address. A template does not constitute an order. Any clinician seeking to treat a patient using any template is expected to use independent medical judgment in the context of individual clinical circumstances of a specific patient's care or treatment. NCCN makes no representations or warranties and explicitly disclaims the appropriateness or applicability of the Template to any specific patient's care or treatment. The Templates are an adjunct to the Guidelines and the Compendium. The Templates should be used in conjunction with the Guidelines and the Compendium. This collection of Templates is not exhaustive and does not necessarily represent the full spectrum of care or treatment options described in the Guidelines or the Compendium. The Templates do not necessarily include all appropriate combinations of drugs or biologics for the treatment of cancer. The Templates are updated at NCCN's discretion to reflect updates and changes in the Guidelines and the Compendium. The most updated versions of the Templates are available through the NCCN website. NCCN has no obligation to advise you of any updates nor does NCCN have any obligation to update the Templates at any time for any reason.
C) NCCN MAKES NO WARRANTIES CONCERNING THE GUIDELINES, THE COMПENDIUM, AND/OR THE TEMPLATES OR ANY ELECTRONIC DELIVERY MEDIA SUPPLIED BY NCCN, WHICH ARE PROVIDED "AS IS." NCCN DISCLAIMS ALL WARRANTIES, EXPRESS OR IMPLIED INCLUDING, WITHOUT LIMITATION, THE IMPLIED WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE. NCCN DOES NOT WARRANT THE ACCURACY, CURRENCY APPROPRIATENESS, APPLICABILITY OR COMPLETENESS OF THE TEMPLATES OR OF ANY PARTICULAR TEMPLATE OR MAKE ANY REPRESENTATION REGARDING THE USE OR THE RESULTS OF THE USE OF ANY TEMPLATE IN TREATMENT. NCCN DOES NOT WARRANT THE ACCURACY, CURRENCY APPROPRIATENESS, APPLICABILITY OR COMPLETENESS OF THE GUIDELINES, THE COMПENDIUM, AND/OR THE TEMPLATES, NOR OF ANY PARTICULAR GUIDELINE OR TEMPLATE, NOR DOES NCCN MAKE ANY REPRESENTATION REGARDING THE USE OR THE RESULTS OF THE USE OF THE GUIDELINE OR THE COMПENDIUM, OR ANY TEMPLATE IN TREATMENT.

IN NO EVENT SHALL NCCN OR ITS MEMBERS BE LIABLE FOR ANY DAMAGES OF ANY KIND INCLUDING INCIDENTAL, INDIRECT, SPECIAL, PUNITIVE OR CONSEQUENTIAL DAMAGES ARISING OUT OF OR IN CONNECTION WITH THE LICENSE GRANTED UNDER THIS AGREEMENT OR USE OF THE GUIDELINES, THE COMПENDIUM, AND/OR THE TEMPLATES INCLUDING, WITHOUT LIMITATION, LOSS OF LIFE, LOSS OF DATA, LOSS OF INCOME OR PROFIT, OR OTHER LOSSES SUSTAINED AS A RESULT OF INJURY TO ANY PERSON, OR LOSS OR DAMAGE TO PROPERTY, OR CLAIMS OF THIRD PARTIES, EVEN IF NCCN HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES.

SOME JURISDICTIONS DO NOT ALLOW THE LIMITATION OF IMPLIED WARRANTIES OR LIABILITY FOR INCIDENTAL, INDIRECT, SPECIAL, PUNITIVE OR CONSEQUENTIAL DAMAGES, SO THE ABOVE LIMITATIONS MAY NOT APPLY.

FOR ANY CLAIM YOU MAY HAVE AGAINST NCCN UNDER THIS AGREEMENT, YOUR EXCLUSIVE REMEDY AND NCCN'S ENTIRE LIABILITY SHALL BE TO PROVIDE REPLACEMENT TEMPLATES TO YOU.

5. Trademarks. NCCN and the NATIONAL COMPREHENSIVE CANCER NETWORK are trademarks (the "Marks") of the National Comprehensive Cancer Network, Inc. and nothing in this Agreement shall constitute a license with respect to such trademarks. You shall not use the Marks or any confusingly similar Marks for any purpose, including, without limitation, for purposes of marketing or promoting your services, without the prior written approval of NCCN, which approval may be withheld in NCCN's sole discretion. Each approved use of the Marks shall require the independent written approval of NCCN.

6. Registration. To access the website version of the Guidelines, the Compendium, and/or the Templates, you are required to register. If registration is requested, you agree to provide NCCN with accurate, complete registration information. It is your responsibility to inform NCCN of any changes to that information. Each registration is for a single person only, unless specifically designated otherwise on the registration page. You agree not to permit (a) any other person to use the registered sections under your name; or (b) multiple users of a network access through a single name. You are responsible for preventing such unauthorized use.

7. Updates and Corrections. NCCN has no obligation to notify you of updates to the Guidelines, the Compendium, and/or the Templates, amendments or corrections to them, nor does NCCN represent or warrant that the website, the Guidelines, the Compendium, or the Templates are or will be error-free, free of viruses or other harmful components, or that errors or defects will be corrected. NCCN hereby reserves the right make improvements and/or changes to the website, its content, features, functionality and/or to the Guidelines, the Compendium, and/or the Templates at any time without notice.

8. Modification of License Agreement. NCCN reserves the right to change the terms of this Agreement at any time. Updated versions of this Agreement will appear on this website or that portion of the website containing the web version of the Guidelines, the Compendium, and/or the Templates, and are effective immediately. You are responsible for regularly reviewing this Agreement. Continued use of any updated version of the Guidelines, the Compendium, and/or the Templates after any such changes constitutes your agreement to be bound by such changes.

9. Remedies for Violation. NCCN reserves the right to seek all remedies available at law and in equity for violations of this License Agreement, including but not limited to the right to block access from updated electronic versions of the Guidelines, the Compendium, and/or the Templates.

10. General. This Agreement contains the entire agreement between NCCN and you relating to its subject matter. Except as otherwise explicitly provided for in section 8, no amendment, change, or modification of this Agreement shall be binding on either party unless mutually agreed to by the parties in writing. If any provision of this Agreement is held to be invalid or unenforceable by a court of competent jurisdiction, the validity and enforceability of the remaining provisions shall not be affected thereby. This Agreement will be governed by and construed in accordance with the laws of the Commonwealth of Pennsylvania without giving any effect to the conflict of law provisions thereof, and each party agrees to submit to personal jurisdiction in the federal and state courts of Pennsylvania and waives any objection to venues in said courts. This Agreement will not be governed by the United Nations Conventions of Contracts for the International Sale of goods, the application of which is expressly excluded. You agree that the Guidelines, the Compendium, and/or the Templates will not be shipped, transferred or exported into any country or used in any manner prohibited by the United States Export Administration Act, or any other export laws, restrictions. This Agreement will terminate automatically upon failure by you to comply with its terms.

BY ACCESSING THE DATA CONTAINED IN THIS PDF, YOU ACKNOWLEDGE THAT YOU HAVE READ THIS AGREEMENT, UNDERSTAND IT, AND AGREE TO BE BOUND BY ITS TERMS AND CONDITIONS.
NCCN Breast Cancer Panel Members

Robert W. Carlson, MD/Chair †
Stanford Comprehensive Cancer Center

D. Craig Allred, MD≠
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Benjamin O. Anderson, MD ¶
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Harold J. Burstein, MD, PhD †
Dana-Farber/Brigham and Women's Cancer Center

W. Bradford Carter, MD ¶
H. Lee Moffitt Cancer Center & Research Institute

Stephen B. Edge, MD ¶
Roswell Park Cancer Institute

John K. Erban, MD †
Massachusetts General Hospital Cancer Center

William B. Farrar, MD ¶
Arthur G. James Cancer Hospital & Richard J. Solove Research Institute at The Ohio State University

Sharon Hermes Giordano, MD MPH †
The University of Texas M.D. Anderson Cancer Center

Lori J. Goldstein, MD †
Fox Chase Cancer Center

William J. Gradishar, MD ‡
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Daniel F. Hayes, MD †
University of Michigan Comprehensive Cancer Center

Clifford A. Hudis, MD †
Memorial Sloan-Kettering Cancer Center

Mohammad Jahanzeb, MD ‡
St. Jude Children's Research Hospital/University of Tennessee Cancer Institute

Britt-Marie Ljung, MD ≠
UCSF Helen Diller Family Comprehensive Cancer Center

P. Kelly Marcom, MD †
Duke Comprehensive Cancer Center

Ingrid A. Mayer, MD †
Vanderbilt-Ingram Cancer Center

Beryl McCormick, MD §
Memorial Sloan-Kettering Cancer Center

Lisle M. Nabell, MD ‡
University of Alabama at Birmingham Comprehensive Cancer Center

Lori J. Pierce, MD §
University of Michigan Comprehensive Cancer Center

Elizabeth C. Reed, MD † ¶
UNMC Eppley Cancer Center at The Nebraska Medical Center

Mary Lou Smith, JD, MBA ¥
Consultant

George Somlo, MD ‡ ¶
City of Hope

Neal S. Topham, MD ¶
Fox Chase Cancer Center

John H. Ward, MD ‡
Huntsman Cancer Institute at the University of Utah

Eric P. Winer, MD †
Dana-Farber/Brigham and Women's Cancer Center | Massachusetts General Hospital Cancer Center

Antonio C. Wolff, MD †
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University

NCCN Guidelines Panel Disclosures

† Medical Oncology
‡ Hematology/Oncology
¶ Surgical Oncology
≠ Pathology
¥ Patient Advocacy
* Writing Committee Member
£ Bone Marrow Transplantation
Й Reconstructive Surgery

Version 1.2010 10/23/2009 © 2009 National Comprehensive Cancer Network, Inc. All rights reserved. These guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN.
Invasive Breast Cancer (continued)

- **Surgical Axillary Staging - Stage I, IIA, and IIB (BINV-C)**
- **Axillary Lymph Node Staging (BINV-D)**
- **Margin Status in Infiltrating Carcinoma (BINV-E)**
- **Special Considerations to Breast-Conserving Therapy Requiring Radiation Therapy (BINV-F)**
- **Principles of Breast Reconstruction Following Mastectomy (BINV-G)**
- **Principles of Radiation Therapy (BINV-H)**
- **Adjuvant Endocrine Therapy (BINV-I)**
- **Definition of Menopause (BINV-K)**
- **Subsequent Endocrine Therapy (BINV-L)**
- **Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-M)**

**Special Considerations**
- **Phyllodes Tumor (PHYLL-1)**
- **Paget’s Disease (PAGET-1)**
- **Breast Cancer During Pregnancy (PREG-1)**
- **Inflammatory Breast Cancer (IBC-1)**

These guidelines are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2009.
### Lobular Carcinoma in Situ

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>WORKUP</th>
<th>PRIMARY TREATMENT</th>
<th>RISK REDUCTION</th>
<th>SURVEILLANCE/FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobular carcinoma in situ (LCIS) Stage 0 Tis, N0, M0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>• History and physical • Diagnostic bilateral mammogram • Pathology review&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Observation&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Counseling regarding risk reduction with tamoxifen for premenopausal women,&lt;sup&gt;d&lt;/sup&gt; or with tamoxifen or raloxifene for postmenopausal women (category 1, see also NCCN Breast Cancer Risk Reduction Guidelines) or In special circumstances, bilateral mastectomy (see also NCCN Breast Cancer Risk Reduction Guidelines) ± reconstruction&lt;sup&gt;e&lt;/sup&gt; may be considered for risk reduction</td>
<td>• Interval history and physical exam every 6-12 mo • Mammogram every 12 mo, unless postbilateral mastectomy • If treated with tamoxifen, monitor per NCCN Breast Cancer Risk Reduction Guidelines</td>
</tr>
</tbody>
</table>

<sup>a</sup>See NCCN Breast Cancer Screening and Diagnosis Guidelines.

<sup>b</sup>The panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and non-invasive carcinomas of the breast. [http://www.cap.org](http://www.cap.org)

<sup>c</sup>Some variants of LCIS ("pleomorphic LCIS") may have a similar biological behavior to that of DCIS. Clinicians may consider complete excision for pleomorphic LCIS but outcome data regarding the efficacy of surgical excision to negative margins and/or radiotherapy are lacking.

<sup>d</sup>Some serotonin reuptake inhibitors decrease the formation of endoxifen, an active metabolite of tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. The clinical impact of these observations is not known.

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

---

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
# Ductal Carcinoma in Situ (DCIS)

## Stage 0

### Tis, N0, M0

<table>
<thead>
<tr>
<th>Workup</th>
<th>Primary Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical exam</td>
<td>Lumpectomy&lt;sup&gt;d,e&lt;/sup&gt; without lymph node surgery&lt;sup&gt;f&lt;/sup&gt; + whole breast radiation therapy (category 1)&lt;sup&gt;g,h,i,j,k&lt;/sup&gt; or Total mastectomy with or without sentinel node biopsy&lt;sup&gt;f,i&lt;/sup&gt; ± reconstruction&lt;sup&gt;l&lt;/sup&gt; or Lumpectomy&lt;sup&gt;d,e&lt;/sup&gt; without lymph node surgery&lt;sup&gt;f&lt;/sup&gt; without radiation therapy (category 2B)&lt;sup&gt;h,j,k&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diagnostic bilateral mammogram</td>
<td></td>
</tr>
<tr>
<td>Pathology review&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Determination of tumor estrogen receptor (ER) status</td>
<td></td>
</tr>
<tr>
<td>Genetic counseling if patient is high risk for hereditary breast cancer&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

---

<sup>a</sup>See NCCN Breast Cancer Screening and Diagnosis Guidelines.<br>
<sup>b</sup>The panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and non-invasive carcinomas of the breast. [http://www.cap.org](http://www.cap.org)<br>
<sup>c</sup>See NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Guidelines.<br>
<sup>d</sup>Re-resection(s) may be performed in an effort to obtain negative margins in patients desiring breast conserving therapy. Patients not amenable to margin-free lumpectomy should have total mastectomy.<br>
<sup>e</sup>See Margin Status in DCIS (DCIS-A).<br>
<sup>f</sup>Complete axillary lymph node dissection should not be performed in the absence of evidence of invasive cancer or proven metastatic disease in women with apparent pure DCIS. However, a small proportion of patients with apparent pure DCIS will be found to have invasive cancer at the time of their definitive surgical procedure. Therefore, the performance of a sentinel lymph node procedure may be considered if the patient with apparent pure DCIS is to be treated with mastectomy or with excision in an anatomic location compromising the performance of a future sentinel lymph node procedure.<br>
<sup>g</sup>See Principles of Radiation Therapy (BINV-H).<br>
<sup>h</sup>Complete resection should be documented by analysis of margins and specimen radiography. Post-excision mammography should also be performed whenever uncertainty about adequacy of excision remains.<br>
<sup>i</sup>Patients found to have invasive disease at total mastectomy or re-excision should be managed as stage I or stage II disease, including lymph node staging.<br>
<sup>j</sup>See Special Considerations Breast-Conserving Therapy (BINV-F).<br>
<sup>k</sup>Whole breast radiation therapy following lumpectomy reduces recurrence rates in DCIS by about 50%. Approximately half of the recurrences are invasive and half DCIS. A number of factors determine that local recurrence risk, include size, tumor grade, margin status and patient age. Some patients may be treated by excision alone, if the patient and physician view the individual risks as "low". All data evaluating the three local treatments show no differences in patient survival.<br>
<sup>l</sup>See Principles of Breast Reconstruction Following Surgery (BINV-G).
### Risk reduction therapy for ipsilateral breast following breast conserving surgery:
Consider tamoxifen\(^m\) for 5 years for:
- Patients treated with breast-conserving therapy (lumpectomy) and radiation therapy (category 1),\(^n\) especially for those with ER-positive DCIS. The benefit of tamoxifen for ER-negative DCIS is uncertain
- Patients treated with excision alone\(^n\)

### Risk reduction therapy for contralateral breast:
- Counseling regarding consideration of tamoxifen for risk reduction (category 2B).\(^m\) See also NCCN Breast Cancer Risk Reduction Guidelines

### Surveillance/Follow-up
- Interval history and physical exam every 6-12 mo for 5 y, then annually
- Mammogram every 12 mo (and 6-12 mo postradiation therapy if breast conserved [category 2B])
- If treated with tamoxifen, monitor per NCCN Breast Cancer Risk Reduction Guidelines

---

\(^m\) Some serotonin reuptake inhibitors decrease the formation of endoxifen, an active metabolite of tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. The clinical impact of these observations is not known.

\(^n\) Available data suggest tamoxifen provides risk reduction in the ipsilateral breast treated with breast conservation and in the contralateral breast in patients with mastectomy or breast conservation with ER-positive primary tumors. Since a survival advantage has not been demonstrated, individual consideration of risks and benefits is important (See also NCCN Breast Cancer Risk Reduction Guidelines).

---

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
MARGIN STATUS IN DCIS

Substantial controversy exists regarding the definition of a negative pathologic margin in DCIS. Controversy arises out of the heterogeneity of the disease, difficulties in distinguishing the spectrum of hyperplastic conditions, anatomic considerations of the location of the margin, and inadequate prospective data on prognostic factors in DCIS. Margins greater than 10 mm are widely accepted as negative (but may be excessive and may lead to a less optimal cosmetic outcome). Margins less than 1 mm are considered inadequate. With pathologic margins between 1-10 mm, wider margins are generally associated with lower local recurrence rates. However, close surgical margins (< 1 mm) at the fibroglandular boundary of the breast (chest wall or skin) do not mandate surgical re-excision but can be an indication for higher boost dose radiation to the involved lumpectomy site. (category 2B)
CLINICAL STAGE WORKUP

**Stage I**
- T1, N0, M0
- or
- Stage IIA
- T0, N1, M0
- T1, N1, M0
- T2, N0, M0
- or
- Stage IIB
- T2, N1, M0
- T3, N0, M0
- or
- T3, N1, M0

General workup including:
- History and physical exam
- CBC, platelets
- Liver function tests and alkaline phosphatase
- Diagnostic bilateral mammogram, ultrasound as necessary
- Pathology review\(^a\)
- Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status\(^b\)
- Genetic counseling if patient is high risk for hereditary breast cancer\(^c\)

Optional studies for breast imaging:
- Breast MRI\(^d\)

If clinical stage IIIA (T3, N1, M0) consider:
- Bone scan (category 2B)
- Abdominal ± pelvis CT or US or MRI
- Chest imaging

Additional studies as directed by symptoms:\(^e\)
- Bone scan indicated if localized bone pain or elevated alkaline phosphatase
- Abdominal ± pelvis CT or US or MRI if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, abnormal physical examination of the abdomen or pelvis
- Chest imaging (if pulmonary symptoms are present)

---


\(^b\) See Principles of HER2 Testing (BINV-A).

\(^c\) See NCCN Genetics/Familial High-Risk Assessment: Breast and Ovarian Guidelines.

\(^d\) See Principles of Dedicated Breast MRI Testing (BINV-B).

\(^e\) The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer.
LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0

Radiation therapy to whole breast with or without boost\(^1\) (by photons, brachytherapy, or electron beam) to tumor bed (category 1), infracavicular region and supraclavicular area. Consider radiation therapy to internal mammary nodes\(^m\) (category 3). Radiation therapy should follow chemotherapy when chemotherapy indicated.

Radiation therapy to whole breast with or without boost\(^1\) (by photons, brachytherapy, or electron beam) to tumor bed (category 1) following chemotherapy when chemotherapy indicated. Strongly consider radiation therapy to infracavicular region and supraclavicular area (category 2B). Consider radiation therapy to internal mammary nodes\(^m\) (category 3). Radiation therapy should follow chemotherapy when chemotherapy indicated.

Radiation therapy to whole breast with or without boost\(^1\) (by photons, brachytherapy, or electron beam) to tumor bed. Radiation therapy should follow chemotherapy when chemotherapy indicated.\(^n\)

### Lumpectomy with Surgical Axillary Staging (category 1)\(^{f,g,h}\)

- \(\geq 4\) positive axillary nodes
- 1-3 positive axillary nodes
- Negative axillary nodes

### Total Mastectomy with Surgical Axillary Staging\(^{f,g,i}\) (category 1) ± Reconstruction\(^j\)

If T2 or T3 and fulfills criteria for breast conserving therapy except for size\(^h\)

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

\(^1\) See Principles of Reconstruction Following Surgery (BINV-G).
\(^2\) Consideration may be given to additional staging including bone scan and abdominal CT/US/MRI; chest CT (category 2B).
\(^3\) See Principles of Radiation Therapy (BINV-H).
\(^4\) Radiation therapy should be given to the internal mammary lymph nodes if they are clinically or pathologically positive, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where radiation therapy is delivered to the internal mammary lymph nodes.
\(^5\) Breast irradiation may be omitted in those 70 y of age or older with estrogen-receptor positive, clinically node negative, T1 tumors who receive adjuvant endocrine therapy (category 1).

See Surgical Axillary Staging (BINV-C).
See Axillary Lymph Node Staging (BINV-D) and Margin Status in Infiltrating Carcinoma (BINV-E).
See Special Considerations to Breast-Conserving Therapy (BINV-F).
Except as outlined in the NCCN Genetics/Familial High-Risk Assessment: Breast and Ovarian Guidelines and the NCCN Breast Cancer Risk Reduction Guidelines, 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.
LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0

≥ 4 positive axillary nodes\(^k\) → Postchemotherapy radiation therapy to chest wall (category 1) + supraclavicular area.\(^l\) Consider radiation therapy to internal mammary nodes (category 3).\(^l,m\)

1-3 positive axillary nodes → Strongly consider postchemotherapy radiation therapy to chest wall + supraclavicular area; if radiation therapy is given, consider internal mammary node radiation therapy.\(^l,m\) (category 3).

Total mastectomy with surgical axillary staging\(^f,g\) (category 1) ± reconstruction\(^l\)

- Negative axillary nodes and tumor > 5 cm or margins positive → Postchemotherapy radiation therapy to chest wall.\(^l\)
- Negative axillary nodes and tumor ≤ 5 cm and close margins (< 1 mm) → Consider radiation therapy to chest wall ± supraclavicular nodes. Consider radiation therapy to internal mammary nodes (category 3).\(^l\)
- Negative axillary nodes and tumor ≤ 5 cm and margins ≥ 1 mm → No radiation therapy

\(^f\) See Surgical Axillary Staging (BINV-C).
\(^g\) See Axillary Lymph Node Staging (BINV-D) and Margin Status in Infiltrating Carcinoma (BINV-E).
\(^l\) See Principles of Reconstruction Following Surgery (BINV-G).
\(^k\) Consideration may be given to additional staging including bone scan; abdominal CT/US/MRI; chest CT (category 2B).
\(^m\) Radiation therapy should be given to the internal mammary lymph nodes that are clinically or pathologically positive, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where radiation therapy is delivered to the internal mammary lymph nodes.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
# Invasive Breast Cancer

## HISTOLOGY

- Ductal
- Lobular
- Mixed
- Metaplastic

## HORMONE RECEPTOR STATUS

- ER-positive and/or PR positive
- ER-negative and PR-negative

## HER2 STATUS

- HER2 positive
- HER2 negative

## SYSTEMIC ADJUVANT TREATMENT

- **HER2 positive**
  - [See Systemic Adjuvant Treatment - Hormone Receptor Positive - HER2 Positive Disease (BINV-5)]

- **HER2 negative**
  - [See Systemic Adjuvant Treatment - Hormone Receptor Positive - HER2 Negative Disease (BINV-6)]
  - [See Systemic Adjuvant Treatment - Hormone Receptor Negative - HER2 Positive Disease (BINV-7)]
  - [See Systemic Adjuvant Treatment - Hormone Receptor Negative - HER2 Negative Disease (BINV-8)]
  - [See Systemic Adjuvant Treatment - Favorable Histologies (BINV-9)]

---

*b See Principles of HER2 Testing (BINV-A).*

°This includes medullary and micropapillary subtypes.

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR POSITIVE - HER2 POSITIVE DISEASE

- Tumor ≤ 0.5 cm or
- Microinvasive or
- Tumor 0.6-1.0 cm, grade 1

- pT1, pT2, or pT3; and pN0 or pN1mi

- Tumor 0.6-1.0 cm, grade 2 or 3, unfavorable features

- Tumor > 1 cm

- Node positive (one or more metastases > 2 mm to one or more ipsilateral axillary lymph nodes)

pN0 → No adjuvant therapy
pN1mi → Consider adjuvant endocrine therapy

Adjuvant endocrine therapy ± adjuvant chemotherapy (category 1)
± trastuzumab (category 3)

Adjuvant endocrine therapy + adjuvant chemotherapy + trastuzumab (category 1)

Adjuvant endocrine therapy + adjuvant chemotherapy + trastuzumab (category 1)

See Principles of HER2 Testing (BINV-A)

Mixed lobular and ductal carcinoma as well as metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.

Unfavorable features: angiolymphatic invasion, high nuclear grade, or high histologic grade.

If ER-positive consider endocrine therapy for risk reduction and to diminish the small risk of disease recurrence.

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. Early evidence suggests similar benefits from ovarian suppression (ie, LHRH agonist) as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.

Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. The benefits of chemotherapy and of endocrine therapy are additive. However, the absolute benefit from chemotherapy may be small. The decision to add chemotherapy to endocrine therapy should be individualized, especially in those with a favorable prognosis and in women age ≥ 60 y where the incremental benefit of chemotherapy may be smaller. Available data suggest sequential or concurrent endocrine therapy with radiation therapy is acceptable.

There are insufficient data to make chemotherapy recommendations for those over 70 y old. Treatment should be individualized with consideration of comorbid conditions.

The prognosis of patients with T1a and T1b tumors that are node negative is generally favorable even when HER2 is amplified or over-expressed. 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.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR POSITIVE - HER2 NEGATIVE DISEASE**

<table>
<thead>
<tr>
<th>Histology:</th>
<th>( \leq 0.5 \text{ cm or Microinvasive or Tumor 0.6-1.0 cm, grade 1, no unfavorable features} )</th>
<th>( \text{Tumor 0.6-1.0 cm, grade 2 or 3 or unfavorable features} )</th>
<th>( \text{Tumor &gt; 1 cm} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Ductal</td>
<td>( \text{pT1, pT2, or pT3; and pN0 or pN1mi (} \leq 2 \text{ mm axillary node metastasis)} )</td>
<td>Consider 21-gene RT-PCR assay (category 2B)</td>
<td>Adjuvant endocrine therapy + adjuvant chemotherapy (category 1)</td>
</tr>
<tr>
<td>- Lobular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mixed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Metaplastic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node positive (one or more metastases &gt; 2 mm to one or more ipsilateral axillary lymph nodes)</td>
<td>Adjuvant endocrine therapy + adjuvant chemotherapy (category 1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **pN0** → No adjuvant therapy
- **pN1mi** → Consider adjuvant endocrine therapy
- **pN1mi** → Adjuvant endocrine therapy ± adjuvant chemotherapy (category 1)
- **pN1mi** → Adjuvant endocrine therapy + adjuvant chemotherapy (category 2B)
- **pN1mi** → Adjuvant endocrine therapy + adjuvant chemotherapy (category 2B)
- **pN1mi** → Adjuvant endocrine therapy + adjuvant chemotherapy (category 2B)
- **pN1mi** → Adjuvant endocrine therapy + adjuvant chemotherapy (category 2B)

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR NEGATIVE - HER2 POSITIVE DISEASE\(^b\)

- **Histology:**
  - Ductal
  - Lobular
  - Mixed
  - Metaplastic

- **Node positive (one or more metastases > 2 mm to one or more ipsilateral axillary lymph nodes)**

\[\text{Tumor} > 1\text{ cm} \rightarrow \text{Adjuvant chemotherapy}^{u \dagger} + \text{trastuzumab (category 1)}\]

\[\text{pN0} \rightarrow \text{No adjuvant therapy}\]

\[\text{pN1mi} \rightarrow \text{Consider chemotherapy} \pm \text{trastuzumab (category 3)}^{u, v}\]

\[\text{Tumor} 0.6-1.0\text{ cm} \rightarrow \text{Consider chemotherapy (category 1)} \pm \text{trastuzumab (category 3)}^{u, v}\]

\[\text{Tumor} 0.5 \text{ cm or Microinvasive} \rightarrow \text{Consider chemotherapy (category 1)}\]

- **pT1, pT2, or pT3; and pN0 or pN1mi (≤ 2 mm axillary node metastasis)**

\[\text{Tumor} \leq 0.5\text{ cm or Microinvasive} \rightarrow \text{No adjuvant therapy}\]

\[\text{pN1mi} \rightarrow \text{Consider chemotherapy} \pm \text{trastuzumab (category 3)}^{u, v}\]

\[\text{Tumor} 0.6-1.0\text{ cm} \rightarrow \text{Consider chemotherapy (category 1)} \pm \text{trastuzumab (category 3)}^{u, v}\]

- **Node positive (one or more metastases > 2 mm to one or more ipsilateral axillary lymph nodes)**

\[\text{Adjuvant chemotherapy}^{u \dagger} + \text{trastuzumab (category 1)}\]

\(^b\) See Principles of HER2 Testing (BINV-A).

\(^u\) Mixed lobular and ductal carcinoma as well as metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.

\(^u \dagger\) There are insufficient data to make chemotherapy recommendations for those over 70 y old. Treatment should be individualized with consideration of comorbid conditions.

\(^v\) The prognosis of patients with T1a and T1b tumors that are node negative is generally favorable even when HER2 is amplified or over-expressed. 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 of trastuzumab therapy.

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR NEGATIVE - HER2 NEGATIVE DISEASE

pT1, pT2, or pT3; and pN0 or pN1mi (≤ 2 mm axillary node metastasis)

Histology:
- Ductal
- Lobular
- Mixed
- Metaplastic

Node positive (one or more metastases > 2 mm to one or more ipsilateral axillary lymph nodes)

• Tumor ≤ 0.5 cm or Microinvasive
   - pN0
   - pN1mi

• Tumor 0.6-1.0 cm

• Tumor > 1 cm

- Adjuvant chemotherapy (category 1)u

- Consider chemotherapy (category 1)u

- Consider chemotherapyu

- No adjuvant therapy

See Follow-Up (BINV-15)

See Adjuvant Chemotherapy (BINV-J)

b See Principles of HER2 Testing (BINV-A).

p Mixed lobular and ductal carcinoma as well as metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.

u There are insufficient data to make chemotherapy recommendations for those over 70 y old. Treatment should be individualized with consideration of comorbid conditions.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SYSTEMIC ADJUVANT TREATMENT - FAVORABLE HISTOLOGIES

**Histology:**
- Tubular
- Colloid

**ER-positive and/or PR-positive**

- **Node positive (one or more metastasis > 2 mm to one or more ipsilateral axillary lymph nodes)**
  - **pT1, pT2, or pT3; and pN0 or pN1mi (≤ 2 mm axillary node metastasis)**
    - **< 1 cm**
      - No adjuvant therapy
    - **1-2.9 cm**
      - Consider adjuvant endocrine therapy
    - **≥ 3 cm**
      - Adjuvant endocrine therapy

**ER-negative and PR-negative**

- Repeat determination of tumor estrogen/progesterone receptor (ER/PR) status
  - **ER-positive and/or PR-positive**
    - **Follow appropriate pathway above**
  - **ER-negative and PR-negative**
    - **Treat as usual breast cancer histology**
      - (See BINV-7 and BINV-8)

---

*If ER-positive consider endocrine therapy for risk reduction and to diminish the small risk of disease recurrence.*

*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. Early evidence suggests similar benefits from ovarian suppression (ie, LHRH agonist or antagonist) as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.*

*There are insufficient data to make chemotherapy recommendations for those over 70 y old. Treatment should be individualized with consideration of comorbid conditions.*

---

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
# Preoperative Chemotherapy Guideline

## CLINICAL STAGE

### Tumor Size

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>T2, N0, M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2, N1, M0, T3, N0, M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3, N1, M0, and fulfills criteria for breast conserving surgery except for tumor size</td>
</tr>
</tbody>
</table>

## WORKUP

- General workup including:
  - History and physical
  - CBC, platelets
  - Liver function tests and alkaline phosphatase
  - Diagnostic bilateral mammogram, ultrasound as necessary
  - Pathology review
  - Determination of tumor ER/PR status and HER2 status
  - Genetic counseling if patient is high risk for hereditary breast cancer

- Optional additional studies for breast imaging:
  - Breast MRI

- If clinical stage IIIA (T3, N1, M0) consider:
  - Bone scan (category 2B)
  - Abdominal ± pelvis CT or US or MRI
  - Chest imaging

- Additional studies as directed by symptoms:
  - Bone scan indicated if localized bone pain or elevated alkaline phosphatase
  - Abdominal ± pelvis CT or US or MRI if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, abnormal physical examination of the abdomen or pelvis
  - Chest imaging (if pulmonary symptoms are present)

---

\( ^a \) The panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and non-invasive carcinomas of the breast. [http://www.cap.org](http://www.cap.org)

\( ^b \) See Principles of HER2 Testing (BINV-A).

\( ^c \) See Principles of Dedicated Breast MRI Testing (BINV-B).

\( ^d \) The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III breast cancer.

\( ^e \) See NCCN Genetics/Familial High-Risk Assessment: Breast and Ovarian Guidelines.
Preoperative Chemotherapy Guideline

**Desires breast preservation**

- Core biopsy of breast tumor, localization of tumor bed for future surgical management
- Consider sentinel lymph node procedure

**Does not desire breast preservation**

- Consider alternative chemotherapy

**PRIMARY TREATMENT**

- No response after 3-4 cycles or Progressive disease
- Partial response, lumpectomy possible or Complete response

**Preoperative chemotherapy**

- (endocrine therapy alone may be considered for receptor positive disease in postmenopausal patients)

**Partial response, lumpectomy possible or Complete response**

- Consider alternative chemotherapy

**No response after 3-4 cycles or Progressive disease**

- Partial response, lumpectomy possible

**Complete response or partial response, lumpectomy possible**

- **See Lumpectomy Pathway (BINV-12)**

**No response after 3-4 cycles or Progressive disease**

- **See Mastectomy Pathway (BINV-12)**

---

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

- Anumber of combination and single agent chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting (See BINV-J) may be considered in the preoperative setting. If treated with endocrine therapy, an aromatase inhibitor is preferred for postmenopausal women.

- Patients with HER2-positive tumors should be treated with preoperative chemotherapy incorporating trastuzumab for at least 9 weeks of preoperative therapy (See BINV-J).

- See Surgical Axillary Staging (BINV-C).

- See Definition of Menopause (See BINV-K).
## Preoperative Chemotherapy Guideline

### LOCAL TREATMENT

- **Mastectomy and surgical axillary staging**
  - If sentinel lymph node biopsy performed prechemotherapy and negative findings, may omit axillary lymph node staging.
  - Consider additional chemotherapy in the context of a clinical trial.

- **Lumpectomy with surgical axillary staging.**
  - If sentinel lymph node biopsy performed prechemotherapy and negative findings, may omit axillary lymph node staging.
  - Consider additional chemotherapy in the context of a clinical trial.

### ADJUVANT TREATMENT

- Adjuvant radiation therapy post-mastectomy is based on prechemotherapy tumor characteristics as per [BINV-3](#).
- Endocrine therapy if ER-positive and/or PR-positive (category 1).
- Complete up to one year of trastuzumab therapy if HER2-positive (category 1).
  - May be administered concurrent with radiation therapy and with endocrine therapy if indicated. If capecitabine administered as a radiation sensitizer, trastuzumab may be given concurrent with the capecitabine.

### References

1. [See Principles of Radiation Therapy (BINV-H)].
2. Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. The benefits of chemotherapy and of endocrine therapy are additive. However, the absolute benefit from chemotherapy may be small. The decision to add chemotherapy to endocrine therapy should be individualized, especially in those with a favorable prognosis and in women age ≥ 60 y where the incremental benefit of chemotherapy may be smaller. Available data suggest sequential or concurrent endocrine therapy with radiation therapy is acceptable.
3. Axillary staging may include sentinel node biopsy (category 3) or level I/II dissection.

---

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

---

**BINV-12**
### Locally Advanced Invasive Breast Cancer (Non-Inflammatory)

#### Clinical Stage

<table>
<thead>
<tr>
<th>Stage IIIA</th>
<th>Workup</th>
</tr>
</thead>
</table>
| T0, N2, M0 | History and physical exam  
 CBC, platelets  
 Liver function tests and alkaline phosphatase  
 Chest imaging  
 Diagnostic bilateral mammogram, ultrasound as necessary  
 Pathology review  
 Prechemotherapy determination of tumor ER/PR status and HER2 status  
 Genetic counseling if patient is high risk for hereditary breast cancer  
 Optional additional studies or as directed by symptoms or other abnormal staging studies:  
 Breast MRI  
 Bone scan (category 2B)  
 Abdominal ± pelvic CT or US or MRI (category 2B)  
 PET/CT scan (category 2B) |

<table>
<thead>
<tr>
<th>Stage IIIB</th>
<th>Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4, N0, M0</td>
<td>See Preoperative Chemotherapy and Locoregional Treatment (BINV-14)</td>
</tr>
<tr>
<td>T4, N1, M0</td>
<td></td>
</tr>
<tr>
<td>T4, N2, M0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage IIIC</th>
<th>Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any T, N3, M0</td>
<td>See Initial Workup for Stage IV Disease (BINV-15)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage IV</th>
<th>Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any T, any N, M1</td>
<td></td>
</tr>
</tbody>
</table>

---

*Note: All recommendations are category 2A unless otherwise indicated.*

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Invasive Breast Cancer

**PREOPERATIVE CHEMOTHERAPY FOR LOCALLY ADVANCED INVASIVE BREAST CANCER (NON-INFLAMMATORY)**

- **Preoperative chemotherapy, anthracycline ± taxane preferred**
  - Response
  - Consider additional systemic chemotherapy and/or preoperative radiation
  - No response

**LOCOREGIONAL TREATMENT**

- Total mastectomy + level I/II axillary dissection + radiation therapy to chest wall and supraclavicular nodes (plus internal mammary nodes if involved, consider internal mammary nodes if not clinically involved [category 3]) ± delayed breast reconstruction
  - or
  - Consider lumpectomy + level I/II axillary dissection + radiation therapy to breast and supraclavicular nodes (plus internal mammary nodes if involved)

**ADJUVANT TREATMENT**

- Complete planned chemotherapy regimen course if not completed preoperatively plus endocrine treatment if ER-positive and/or PR-positive (sequential chemotherapy followed by endocrine therapy).
- Complete up to one year of trastuzumab therapy if HER2-positive (category 1). May be administered concurrent with radiation therapy and with endocrine therapy if indicated. If capecitabine administered as a radiation sensitizer, trastuzumab may be given concurrent with the capecitabine.

- Response - See above pathway
- No response
- Individualized treatment

---

1. See Principles of Radiation Therapy (BINV-H).
2. See Principles of Reconstruction Following Surgery (BINV-G).
3. A number of combination and single agent chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting (See BINV-J) may be considered in the preoperative setting. If treated with endocrine therapy, an aromatase inhibitor is preferred for postmenopausal women.
4. Patients with HER2-positive tumors should be treated with preoperative chemotherapy incorporating trastuzumab for at least 9 weeks of preoperative therapy (See BINV-J).

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SURVEILLANCE/FOLLOW-UP

• Interval history and physical exam every 4-6 mo for 5 y, then every 12 mo
• Mammogram every 12 mo (and 6-12 mo post-radiation therapy if breast conserved [category 2B])
• Women on tamoxifen: annual gynecologic assessment every 12 mo if uterus present
• Women on an aromatase inhibitor or who experience ovarian failure secondary to treatment should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter
• Assess and encourage adherence to adjuvant endocrine therapy.

RECURRENT WORKUP

or

INITIAL WORKUP FOR STAGE IV DISEASE

• History and physical exam
• CBC, platelets
• Liver function tests
• Chest imaging
• Bone scan
• X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan
• Consider abdominal CT or MRI
• Biopsy documentation of first recurrence, if possible
• Consider determination of tumor ER/PR and HER2 status if unknown, originally negative or not over-expressed
• Genetic counseling if patient is high risk for hereditary breast cancer

Local disease only

Systemic disease

• Assess and encourage adherence to adjuvant endocrine therapy.
Invasive Breast Cancer

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE

**Local recurrence**
- Initial treatment with lumpectomy + radiation therapy
- Initial treatment with mastectomy + level I / II axillary dissection and prior radiation therapy
- Initial treatment with mastectomy no prior radiation therapy

**Bone disease present**
- Add bisphosphonate

**Bone disease not present**

**Systemic disease**
- Bone disease present
- Bone disease not present

**Total mastectomy + axillary lymph node staging if level I/II axillary dissection not previously done**
- Consider systemic therapy

**Initial treatment with mastectomy + level I / II axillary dissection and prior radiation therapy**

**Initial treatment with mastectomy**
- Surgical resection if possible

**Initial treatment with lumpectomy + radiation therapy**

**Surgical resection if possible**

**Consider systemic therapy**

**Add bisphosphonate**

**ER and/or PR positive; HER2 negative**

**ER and or PR positive; HER2 positive**

**ER and PR negative, or ER and/or PR positive and endocrine refractory; HER2 negative**

**ER/PR negative; HER2 positive**

**See BINV-16**

**See BINV-17**

**See BINV-18**

**See BINV-19**

---

**Surgery, radiation ± hyperthermia (category 3 for hyperthermia), or regional chemotherapy (e.g., intrathecal methotrexate) indicated for localized clinical scenarios:**
1. Brain metastases
2. Leptomeningeal disease
3. Choroid metastases
4. Pleural effusion
5. Pericardial effusion
6. Biliary obstruction
7. Ureteral obstruction
8. Impending pathologic fracture
9. Pathologic fracture
10. Cord compression
11. Localized painful bone or soft-tissue disease
12. Chest wall disease

**Pamidronate or zoledronic acid (with calcium 1200-1500 mg and vitamin D 400-800 IU daily supplement) should be given (category 1) in addition to chemotherapy or endocrine therapy if bone metastasis present, expected survival ≥ 3 months, and creatinine < 3.0 mg/dL. Patients should undergo a dental examination with preventive dentistry prior to initiation of bisphosphonate therapy.**

**In women with a local breast recurrence after breast conserving surgery who had a prior sentinel lymph node biopsy, a repeat SNB may be technically possible. The accuracy of repeat SNB is unproven, and the prognostic significance of repeat SNB after mastectomy is unknown and its use discouraged.**

**If not technically resectable, consider systemic therapy to best response, then resect if possible.**
SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE

ER and/or PR POSITIVE; HER2 NEGATIVE OR POSITIVE

Prior endocrine therapy within 1y

ER and/or PR positive; HER2 negative

ER and/or PR positive; HER2 positive

No prior endocrine therapy within 1y

Visceral crisis

Consider initial chemotherapy (See BINV-18 and BINV-19)

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

Aromatase inhibitor or Antiestrogen

Aromatase inhibitor or Antiestrogen

Visceral crisis

Postmenopausal

Consider initial chemotherapy (See BINV-18 and BINV-19)

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

Antiestrogen

Antiestrogen

Visceral crisis

Postmenopausal

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

Premenopausal

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

Premenopausal

No prior endocrine therapy within 1y

Visceral crisis

Consider initial chemotherapy (See BINV-18 and BINV-19)

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

Antiestrogen

Antiestrogen

Women presenting at time of initial diagnosis with metastatic disease may benefit from the performance of local breast surgery and/or radiation therapy. Generally this palliative local therapy should be considered only after response to initial systemic therapy.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Invasive Breast Cancer

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE

ER and PR NEGATIVE; or ER and/or PR POSITIVE and ENDOCRINE REFRACTORY; HER2 NEGATIVE

**b** See Principles of HER2 Testing (BINV-A).

**e** See NCCN Palliative Care Guidelines.

**hh** See Subsequent Endocrine Therapy (BINV-L).

**jj** See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-M).

**kk** False negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor positive tumor (eg, long disease free interval, limited sites of recurrence, indolent disease, or older age).

---

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE

ER and PR NEGATIVE; or ER and/or PR POSITIVE and ENDOCRINE REFRACTORY; and HER2 POSITIVE

<table>
<thead>
<tr>
<th>ER and PR negative; or ER and/or PR positive and endocrine refractory; and HER2 positive b</th>
<th>Bone or soft tissue only or Asymptomatic visceral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Trastuzumab ± chemotherapy ii, ll, mm</td>
</tr>
<tr>
<td>No</td>
<td>When prior therapy with anthracycline, taxane, and trastuzumab: capcitabine + lapatinib (preferred)</td>
</tr>
<tr>
<td></td>
<td>No response to 3 sequential regimens or ECOG performance status ≥ 3</td>
</tr>
<tr>
<td></td>
<td>Consider no further cytotoxic therapy; transition to palliative care ee</td>
</tr>
</tbody>
</table>

Consider trial of endocrine therapy, if not endocrine refractory hh, kk

See Endocrine Therapy (BINV-17)

b See Principles of HER2 Testing (BINV-A).

e See NCCN Palliative Care Guidelines.
hh See Subsequent Endocrine Therapy (BINV-L).

ii See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-M).

kk False negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor positive tumor (eg, long disease free interval, limited sites of recurrence, indolent disease, or older age).

ll Continued trastuzumab following progression on first line-trastuzumab containing chemotherapy for metastatic breast cancer is an option. The optimal duration of trastuzumab in patients with long-term control of disease is unknown.

mm Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
FOLLOW-UP THERAPY FOR ENDOCRINE TREATMENT OF RECURRENT OR STAGE IV DISEASE

Continue endocrine therapy until progression or unacceptable toxicity → Progression → No clinical benefit after 3 consecutive endocrine therapy regimens or Symptomatic visceral disease

- Yes → Chemotherapy (As in BINV-16)
- No → Trial of new endocrine therapy

See Subsequent Endocrine Therapy (BINV-L)
See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-M)

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**PRINCIPLES OF HER2 TESTING**

1. **Initial testing by IHC**
   - Laboratory meets quality assurance standards for IHC HER2 testing methodology
   - No → Send sample to reference laboratory
   - Yes → IHC testing
     - IHC 0, 1+ → HER2 (-)
     - IHC 2+ → Borderline result
     - IHC 3+ → HER2 (+)

2. **Initial testing by FISH**
   - Laboratory meets quality assurance standards for FISH HER2 testing methodology
   - No → Send sample to reference laboratory
   - Yes → FISH testing
     - FISH (-) → HER2 (-)
     - Borderline result → FISH retest
     - Count additional cells → HER2 (+)
     - FISH+ → HER2 (+)

---

Note: All recommendations are category 2A unless otherwise indicated.

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

---

2 HER2 testing should be done only in laboratories accredited to perform such testing. Ongoing proficiency testing and full reporting of HER2 assay methods and results are required. A laboratory may perform only those tests which have been demonstrated to conform to these quality assurance standards. All other HER2 testing should be sent to a qualified reference laboratory.
3 Either an immunohistochemistry (IHC) assay or a fluorescence in situ hybridization (FISH) assay can be used to make an initial assessment of HER2 tumor status. All HER2 assays, whether FDA-approved or not, must be validated. Validation of a HER2 test is defined as at least 95% concordance when the testing method performed in a laboratory is compared with one of the following: a validated HER2 testing method performed in the same laboratory; a validated HER2 testing method performed in another laboratory; or validated reference lab results. Borderline samples should not be included in the validation study. These algorithms are based on the assumption that all validated HER2 tests have been shown to be at least 95% concordant with the complementary form of the HER2 test, either by direct testing or association with the levels of concordance between complementary testing achieved by the validating laboratory.
4 Borderline IHC samples (eg, IHC 2+) are subjected to reflex testing by a validated complementary (eg, FISH) method that has shown at least 95% concordance between IHC 0, 1+ results and FISH non-amplified results, and IHC 3+ results and FISH amplified results.
5 Borderline FISH samples (eg, an average HER2 gene/chromosome 17 ratio of 1.8-2.2 or an average HER2 gene copy number of > 4 - < 6) should undergo: counting of additional cells; retesting by FISH; or reflex testing by a validated IHC method which is at least 95% concordant with FISH as described above.
PRINCIPLES OF DEDICATED BREAST MRI TESTING

See NCCN Breast Screening and Diagnosis Guidelines for indications for screening MRI in women at increased breast cancer risk.

Personnel, facility and equipment

- Breast MRI examinations should be performed and interpreted by an expert breast imaging team working in concert with the multidisciplinary treatment team.

- Breast MRI examinations require a dedicated breast coil and breast imaging radiologists familiar with the optimal timing sequences and other technical details for image interpretation. The imaging center should have the ability to perform MRI guided needle sampling and/or wire localization of MRI detected findings.

Clinical indications and applications

- May be used for staging evaluation to define extent of cancer or presence of multifocal or multicentric cancer in the ipsilateral breast, or as screening of the contralateral breast cancer at time of initial diagnosis (category 2B). There are no data that demonstrate that use of MRI to affect choice of local therapy improves outcome (local recurrence or survival).

- May be helpful for breast cancer evaluation before and after neoadjuvant therapy to define extent of disease, response to treatment, and potential for breast conserving therapy.

- May be useful to detect additional disease in women with mammographically dense breast, but available data do not show differential detection rates by any subset by breast pattern (breast density) or disease type (eg. DCIS, invasive ductal cancer, invasive lobular cancer)

- May be useful for identifying primary cancer in women with axillary nodal adenocarcinoma or with Paget’s disease of the nipple with breast primary not identified on mammography, ultrasound, or physical examination

- Falsely positive findings on breast MRI are common. Surgical decisions should not be based solely on the MRI findings. Additional tissue sampling of areas of concern identified by breast MRI is recommended.

- Utility in follow-up screening of ipsilateral and contralateral breast of women with prior breast cancer is not defined.


Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**SURGICAL AXILLARY STAGING - STAGE I, IIA, AND IIB**

**Clinical Stage I/II**

**Sentinel lymph node candidate AND Experienced sentinel node team**

**No**

**Clinically node positive at time of diagnosis**

- **FNA or core biopsy negative**
  - **Sentinel node mapping and excision**
  - **Sentinel node positive**
    - **Axillary dissection level I/II**
  - **Sentinel node negative**
    - **No further surgery**

**Yes**

**Clinically node negative at time of diagnosis**

- **Sentinel node not identified**
  - **Axillary dissection level I/II**

**Refer to experienced sentinel node team**

---

1 Sentinel node team must have documented experience with sentinel node biopsy in breast cancer. Team includes surgeon, radiologists, nuclear medicine physician, pathologist, and prior discussion with medical and radiation oncologists on use of sentinel node for treatment decisions.

2 Consider pathologic confirmation of malignancy in clinically positive nodes using ultrasound guided FNA or core biopsy in determining if patient needs axillary lymph node dissection.

3 Axillary sentinel node biopsy in all cases; internal mammary sentinel node biopsy optional if drainage maps to internal mammary nodes (category 3).

4 Sentinel lymph node mapping injections may be peritumoral, subareolar or subdermal. However, only peritumoral injections map to the internal mammary lymph node(s).

5 Results of randomized clinical trials indicate that there is a lower risk of morbidity associated with sentinel node mapping and excision than with level I/II axillary dissection.

6 Sentinel node involvement is defined by multilevel node sectioning with hematoxylin and eosin staining. Cytokeratin Immunohistochemistry (IHC) may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is controversial (category 3).

---

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
AXILLARY LYMPH NODE STAGING

In the absence of definitive data demonstrating superior survival from the performance of axillary lymph node dissection, patients who have particularly favorable tumors, patients for whom the selection of adjuvant systemic therapy is unlikely to be affected, for the elderly, or those with serious comorbid conditions, the performance of axillary lymph node dissection may be considered optional. The axillary dissection should be extended to include level III nodes only if there is gross disease apparent in the level II nodes.

Sentinel lymph node biopsy is the preferred method of axillary lymph node staging if there is an experienced sentinel node team and the patient is an appropriate sentinel lymph node biopsy candidate (See BINV-C).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
The use of breast conserving therapy is predicated on achieving a pathologically negative margin of resection. Cases where there is a positive margin should generally undergo further surgery, either a re-excision to achieve a negative margin or a mastectomy. If re-excision is technically feasible to allow for breast conserving therapy, this can be done with resection of the involved margin guided by the orientation of the initial resection specimen or re-excision of the entire original excision cavity. If multiple margins remain positive, mastectomy may be required for optimal local control.

It may be reasonable to treat selected cases with breast conserving therapy with a microscopically focally positive margin in the absence of an extensive intraductal component.\(^1\) For these patients, the use of a higher radiation boost dose to the tumor bed should be considered.

Margins should be evaluated on all surgical specimens from breast conserving surgery. Requirements for optimal margin evaluation include:

- Orientation of the surgical specimens
- Description of the gross and microscopic margin status
- Reporting of the distance, orientation, and type of tumor (invasive or DCIS) in relation to the closest margin.

\(^1\)An extensive intraductal component is defined as an infiltrating ductal cancer where greater than 25% of the tumor volume is DCIS and DCIS extends beyond the invasive cancer into surrounding normal breast parenchyma.
SPECIAL CONSIDERATIONS TO BREAST-CONSERVING THERAPY REQUIRING RADIATION THERAPY

Contraindications for breast-conserving therapy requiring radiation therapy include:

Absolute:
- Prior radiation therapy to the breast or chest wall
- Radiation therapy during pregnancy
- Diffuse suspicious or malignant appearing microcalcifications
- Widespread disease that cannot be incorporated by local excision through a single incision that achieves negative margins with a satisfactory cosmetic result.
- Positive pathologic margin

Relative:
- Active connective tissue disease involving the skin (especially scleroderma and lupus)
- Tumors > 5 cm (category 2B)
- Focally positive margin
- Women ≤ 35 y or premenopausal women with a known BRCA 1/2 mutation:
  - May have an increased risk of ipsilateral breast recurrence or contralateral breast cancer with breast conserving therapy
  - Prophylactic bilateral mastectomy for risk reduction may be considered.

See NCCN Breast Cancer Risk Reduction Guidelines.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

1See Margin Status in Infiltrating Carcinoma (BINV-E).
Invasive Breast Cancer

PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

- The breast can be reconstructed in conjunction with mastectomy using breast implants, autologous tissue ("flaps") or a combination of the two (e.g., latissimus / implant composite reconstructions).

- Breast reconstruction for mastectomy can be performed at the same time as mastectomy ("immediate") or at some time following the completion of cancer treatment ("delayed").

- As with any mastectomy, there is a risk of local and regional cancer recurrence, and evidence suggests skin sparing mastectomy is probably equivalent to standard mastectomy in this regard. Skin sparing mastectomy should be performed by an experienced breast surgery team that works in a coordinated, multidisciplinary fashion to guide proper patient selection for skin sparing mastectomy, determine optimal sequencing of the reconstructive procedure(s) in relation to adjuvant therapies, and to perform a resection that achieves appropriate surgical margins. Post-mastectomy radiation as outlined in these guidelines should be applied in cases treated by skin sparing mastectomy. The nipple-areolar complex is sacrificed with skin sparing mastectomy for cancer therapy. Current data are inadequate to support the use of nipple-areolar complex sparing procedures for breast cancer therapy outside the confines of a prospective clinical trial.

- When post-mastectomy radiation is required, delayed reconstruction is generally preferred after completion of radiation therapy in autologous tissue reconstruction, because of reported loss in reconstruction cosmesis (category 2B). When implant reconstruction is used, immediate rather than delayed reconstruction is preferred to avoid tissue expansion of radiated skin flaps. Immediate implant reconstruction in patients requiring post-operative radiation has an increased rate of capsular contracture. Surgery to exchange the tissue expanders with permanent implants can be performed prior to radiation or after completion of radiation therapy. Some experienced breast cancer teams have employed protocols in which immediate reconstructions are followed by radiation therapy (category 2B). Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis and implant exposure. In the previously radiated patient the use of tissue expanders/implants is relatively contraindicated.

- Reconstruction selection is based on an assessment of cancer treatment, patient body habitus, smoking history, co-morbidities and patient concerns. Smoking increases the risk of complications for all types of breast reconstruction whether with implant or flap. Smoking is therefore considered a relative contra-indication to breast reconstruction and patients should be made aware of increased rates of wound healing complications and partial or complete flap failure among smokers.

- An evaluation of the likely cosmetic outcome of lumpectomy should be performed prior to surgery.

- Women who are not satisfied with the cosmetic outcome following completion of breast cancer treatment should be offered a plastic surgery consultation.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Invasive Breast Cancer

PRINCIPLES OF RADIATION THERAPY

Whole Breast Radiation:
Target delineation includes the majority of the breast tissue, and is best done by both clinical assessment and CT-based treatment planning. A uniform dose distribution is the objective, using compensators such as wedges, forward planning using segments, or intensity modulated radiation therapy (IMRT). The breast should receive a dose of 45-50 Gy in 1.8 - 2 Gy per fraction, or 42.5 Gy at 2.66 Gy per fraction. A boost to the tumor bed is recommended in patients at higher risk for local failure, (age < 50, positive axillary nodes, lymphovascular invasion, or close margins). This can be achieved with brachytherapy or electron beam or photon fields. Typical doses are 10-16 Gy at 2 Gy/fx. All dose schedules are given 5 days per week.

Chest Wall Radiation (including breast reconstruction):
The target includes the ipsilateral chest wall, mastectomy scar, and drain sites where possible. Depending on whether the patient has been reconstructed or not, several techniques using photons and/or electrons are appropriate. CT-based treatment planning is encouraged, in order to identify lung and heart volumes, and minimize exposure of these organs. Special consideration should be given to the use of bolus material when photon fields are used, to ensure the skin dose is adequate.

Regional Nodal Radiation:
Target delineation is best achieved by the use of CT-based treatment planning. For the paraclavicular and axillary nodes, prescription depth varies based on the size of the patient. For internal mammary node identification, the internal mammary artery and vein location can be used as a surrogate for the nodal locations, which usually are not visible on imaging.

Dose is 50 Gy, given as 1.8 - 2.0 Gy fraction size (± scar boost at 2 Gy per fraction to a total dose of approximately 60 Gy); all dose schedules given 5 days per week.
If internal mammary lymph nodes are clinically or pathologically positive, radiation therapy should be given to the internal mammary nodes, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where radiation therapy is delivered to the internal mammary lymph node field.

Partial breast radiation (PBI)
PBI should be performed only as part of a prospective trial. PBI can be delivered with brachytherapy or external beam radiation using 3-D conformal radiation or IMRT. If not trial eligible, PBI should be reserved for patients with a low risk of recurrence. The target includes the tumor bed and a 1 cm margin. A 1-1.5 cm margin should be added when using photon radiation, to account for respiration. 34 Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day with photon radiation is prescribed the edge of the target. Intraoperative radiation with photons or electrons with a single fraction (targeted intra-operative radiotherapy) can be used in institutions with that expertise and experience.

Neoadjuvant chemotherapy:
Indications for radiation therapy and fields of treatment should be based upon the pretreatment tumor characteristics in patients treated with neoadjuvant chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Some serotonin reuptake inhibitors decrease the formation of endoxifen, an active metabolite of tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. The clinical impact of these observations is not known. At this time, based on current data the Panel discourages CYP 2D6 testing.

The panel believes the three selective aromatase inhibitors (anastrozole, letrozole, exemestane) have similar antitumor efficacy and similar toxicity profiles. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.

This specific patient subset was not included in the trials of aromatase inhibitors given sequentially with adjuvant tamoxifen. Some women who appear to become postmenopausal on tamoxifen therapy have resumption of ovarian function after discontinuation of tamoxifen and initiation of an aromatase inhibitor. Therefore, serial monitoring of plasma estradiol and FSH levels is encouraged in this clinical setting. Should ovarian function resume, the aromatase inhibitor should be discontinued and tamoxifen resumed. **See Definition of Menopause (BINV-K).**
ADJUVANT CHEMOTHERAPY 1,2,3,4,5

NON-TRASTUZUMAB CONTAINING REGIMENS (all category 1)

Preferred Adjuvant Regimens:
- TAC (docetaxel/doxorubicin/cyclophosphamide)
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
- AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel and cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)

Other Adjuvant Regimens:
- FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide)
- FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by docetaxel every 3 weeks
- EC (epirubicin/cyclophosphamide)
- A followed by T followed by C (doxorubicin followed by paclitaxel followed by cyclophosphamide) every 2 weekly regimen with filgrastim support
- FEC followed by T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel)
- FEC (fluorouracil/epirubicin/cyclophosphamide) followed by weekly paclitaxel

TRASTUZUMAB CONTAINING REGIMENS (all category 1)

Preferred Adjuvant Regimen:
- AC followed by T + concurrent trastuzumab
  (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)
- TCH (docetaxel, carboplatin, trastuzumab)

Other Adjuvant Regimens:
- Docetaxel + trastuzumab followed by FEC
  (fluorouracil/epirubicin/cyclophosphamide)
- Chemotherapy followed by trastuzumab sequentially
- AC followed by docetaxel + trastuzumab

Neoadjuvant:
- T + trastuzumab followed by CEF + trastuzumab
  (paclitaxel plus trastuzumab followed by cyclophosphamide/epirubicin/fluorouracil plus trastuzumab)

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

1 Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2 positive tumors.
2 In patients with HER2 positive and axillary lymph node positive breast cancer, trastuzumab should be incorporated into the adjuvant therapy. (category 1) Trastuzumab should also be considered for patients with HER2 positive lymph node negative tumors greater than or equal to 1 cm. (category 1) Trastuzumab may be given beginning either concurrent with paclitaxel as part of the AC followed by paclitaxel regimen, or alternatively after the completion of chemotherapy. Trastuzumab should not be given concurrent with an anthracycline because of cardiac toxicity, except as part of the neoadjuvant trastuzumab with paclitaxel followed by CEF regimen. Trastuzumab should be given for one year, (with the exception of the docetaxel + trastuzumab followed by FEC regimen in which trastuzumab is given for 9 weeks), with cardiac monitoring, and by either the weekly or every three weekly schedule.
3 CMF and radiation therapy may be given concurrently, or the CMF may be given first. All other chemotherapy regimens should be given prior to radiotherapy.
4 Chemotherapy and tamoxifen used as adjuvant therapy should be given sequentially with tamoxifen following chemotherapy.
5 Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## Invasive Breast Cancer

### NON-TRASTUZUMAB CONTAINING COMBINATIONS

#### PREFERRED ADJUVANT REGIMENS

**TAC chemotherapy**
- Docetaxel 75 mg/m^2^ IV day 1
- Doxorubicin 50 mg/m^2^ IV day 1
- Cyclophosphamide 500 mg/m^2^ IV day 1
  - Cycled every 21 days for 6 cycles.
  - (All cycles are with filgrastim support).

**Dose-dense AC followed by paclitaxel chemotherapy**
- Doxorubicin 60 mg/m^2^ IV day 1
- Cyclophosphamide 600 mg/m^2^ IV day 1
  - Cycled every 14 days for 4 cycles.
  - Followed by:
    - Paclitaxel 175 mg/m^2^ by 3 h IV infusion day 1
      - Cycled every 14 days for 4 cycles.
      - (All cycles are with filgrastim support).

**AC chemotherapy**
- Doxorubicin 60 mg/m^2^ IV day 1
- Cyclophosphamide 600 mg/m^2^ IV day 1
  - Cycled every 21 days for 4 cycles.

**AC followed by paclitaxel chemotherapy**
- Doxorubicin 60 mg/m^2^ IV day 1
- Cyclophosphamide 600 mg/m^2^ IV day 1
  - Cycled every 21 days for 6 cycles.

**TC chemotherapy**
- Docetaxel 75 mg/m^2^ IV day 1
- Cyclophosphamide 600 mg/m^2^ IV day 1
  - Cycled every 21 days for 4 cycles.

**AC chemotherapy**
- Doxorubicin 60 mg/m^2^ IV day 1
- Cyclophosphamide 600 mg/m^2^ IV day 1
  - Cycled every 21 days for 4 cycles.

### OTHER ADJUVANT REGIMENS

**FAC chemotherapy**
- 5-Fluorouracil 500 mg/m^2^ IV days 1 & 8 or days 1 & 4
- Doxorubicin 50 mg/m^2^ IV day 1
  - (or by 72 h continuous infusion)
- Cyclophosphamide 500 mg/m^2^ IV day 1
  - Cycled every 21 days for 6 cycles.

**CAF chemotherapy**
- Cyclophosphamide 100 mg/m^2^ IV day 1
- Doxorubicin 30 mg/m^2^ IV day 1 & 8
- 5-Fluorouracil 500 mg/m^2^ IV days 1 & 8
  - Cycled every 28 days for 6 cycles.

**CEF chemotherapy**
- Cyclophosphamide 75 mg/m^2^ PO days 1-14
- Epirubicin 60 mg/m^2^ IV days 1 & 8
- 5-Fluorouracil 600 mg/m^2^ IV days 1 & 8
  - With cotrimoxazole support.
  - Cycled every 28 days for 6 cycles.

**CMF chemotherapy**
- Cyclophosphamide 100 mg/m^2^ PO days 1-14
- Methotrexate 40 mg/m^2^ IV days 1 & 8
- 5-Fluorouracil 600 mg/m^2^ IV days 1 & 8
  - Cycled every 28 days for 6 cycles.

**AC followed by docetaxel chemotherapy**
- Doxorubicin 60 mg/m^2^ on day 1
- Cyclophosphamide 600 mg/m^2^ IV day 1
  - Cycled every 21 days for 4 cycles.

**CMF followed by docetaxel chemotherapy**
- Doxorubicin 100 mg/m^2^ day 1
  - Cycled every 21 days for 4 cycles.

**EC chemotherapy**
- Epirubicin 100 mg/m^2^ IV day 1
- Cyclophosphamide 830 mg/m^2^ IV day 1
  - Cycled every 21 days for 8 cycles.

**Dose-dense A-T-C chemotherapy**
- Doxorubicin 60 mg/m^2^ IV day 1
  - Cycled every 14 days for 4 cycles.
  - Followed by:
    - Paclitaxel 175 mg/m^2^ by 3 h IV day 1
      - Cycled every 14 days for 4 cycles.
      - Followed by:
        - Cyclophosphamide 600 mg/m^2^ IV day 1
          - Cycled every 14 days for 4 cycles.
          - (All cycles are with filgrastim support).

**FEC followed by docetaxel chemotherapy**
- 5-Fluorouracil 500 mg/m^2^ IV day 1
- Epirubicin 100 mg/m^2^ IV day 1
- Cyclophosphamide 500 mg/m^2^ IV day 1
  - Cycled every 21 days for 3 cycles.
  - Followed by:
    - Docetaxel 100 mg/m^2^ day 1
      - Cycled every 21 days for 3 cycles.

**FEC followed by weekly paclitaxel**
- 5-fluorouracil 600 mg/m^2^ IV day 1
- Epirubicin 90 mg/m^2^ IV day 1
- Cyclophosphamide 600 mg/m^2^ IV day 1
  - 3 weeks of no treatment
  - Paclitaxel 100 mg/m^2^ IV
    - Cycled every week for 8 cycles

---

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
AC followed by T chemotherapy with Trastuzumab

Doxorubicin 60 mg/m² IV day 1
Cyclophosphamide 600 mg/m² IV day 1
Cycled every 21 days for 4 cycles.
Followed by
Paclitaxel 80 mg/m² by 1 h IV weekly for 12 wks
Trastuzumab 4 mg/kg IV with first dose of paclitaxel
Followed by
Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment. As an alternative, trastuzumab 6 mg/kg IV every 3 wk may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment.
Cardiac monitoring at baseline, 3, 6, and 9 mo.

Dose-dense AC followed by paclitaxel chemotherapy

Doxorubicin 60 mg/m² IV day 1
Cyclophosphamide 600 mg/m² IV day 1
Cycled every 14 days for 4 cycles.
Followed by
Paclitaxel 175 mg/m² by 3 h IV infusion day 1
Cycled every 14 days for 4 cycles.
(All cycles are with filgrastim support).
Trastuzumab 4 mg/kg IV with first dose of paclitaxel
Followed by
Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment. As an alternative, trastuzumab 6 mg/kg IV every 3 wk may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment.
Cardiac monitoring at baseline, 3, 6, and 9 mo.

TCH chemotherapy

Docetaxel 75 mg/m² IV day 1
Carboplatin AUC 6 IV day 1
Cycled every 21 days for 6 cycles
Trastuzumab 4 mg/kg wk 1
Followed by
Trastuzumab 2 mg/kg for 17 wks
Followed by
Trastuzumab 6 mg/kg IV every 3 wks to complete 1 year of trastuzumab therapy
Cardiac monitoring at baseline, 3, 6, and 9 mo.

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.
Invasive Breast Cancer

OTHER ADJUVANT REGIMENS

Docetaxel + trastuzumab followed by FEC chemotherapy
- Docetaxel 100 mg/m² by 1 h IV day 1
  Cycled every 21 days for 3 cycles
  With
  - Trastuzumab 4 mg/kg IV with first dose of docetaxel day 1
    Followed by
  - Trastuzumab 2 mg/kg IV weekly to complete 9 wks of trastuzumab.
    Followed by
  - 5-Fluorouracil 600 mg/m² IV day 1
  - Epirubicin 60 mg/m² day 1
  - Cyclophosphamide 600 mg/m² day 1
  Cycled every 21 days for 3 cycles
  Cardiac monitoring at baseline, after last FEC cycle, at 12 and 36 mo after chemotherapy.

Chemotherapy followed by trastuzumab
- Approved adjuvant chemotherapy regimen for at least 4 cycles
  Followed by
  - Trastuzumab 8 mg/kg IV times 1 dose
  Followed by
  - Trastuzumab 6 mg/kg IV every 21 days for 1 y
  Cardiac monitoring at baseline, 3, 6, and 9 mo.

AC followed by docetaxel chemotherapy with trastuzumab
- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² day 1
  Cycled every 21 days for 4 cycles
  Followed by
  - Docetaxel 100 mg/m²
  Cycled every 21 days for 4 cycles
  With
  - Trastuzumab 4 mg/kg IV wk one
    Followed by
  - Trastuzumab 2 mg/kg IV weekly for 11 wks
    Followed by
  - Trastuzumab 6 mg/kg every 21 days to complete 1 y of trastuzumab therapy
  Cardiac monitoring at baseline, 3, 6, and 9 mo.

TRASTUZUMAB CONTAINING COMBINATIONS

NEOADJUVANT REGIMENS

Neoadjuvant T followed by FEC chemotherapy with trastuzumab
- Trastuzumab 4 mg/kg IV for one dose beginning just prior to first dose of paclitaxel
  Followed by
  - Trastuzumab 2 mg/kg IV weekly for 23 wks
  - Paclitaxel 225 mg/m² by 24 h IV infusion every 21 days for 4 cycles
    (alternatively paclitaxel may be administered as paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 wks)
  Followed by
  - 5-Fluorouracil 500 mg/m² on days 1 and 4
  - Epirubicin 75 mg/m² IV on day 1
  - Cyclophosphamide 500 mg/m² on day 1
  Cycled every 21 days for 4 cycles.

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Note: All recommendations are category 2A unless otherwise indicated.

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


DEFINITION OF MENOPAUSE

Clinical trials in breast cancer have utilized a variety of definitions of menopause. Menopause is generally the permanent cessation of menses, and as the term is utilized in breast cancer management includes a profound and permanent decrease in ovarian estrogen synthesis. Reasonable criteria for determining menopause include any of the following:

- Prior bilateral oophorectomy
- Age ≥ 60 y
- Age < 60 y and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and FSH and estradiol in the postmenopausal range
- If taking tamoxifen or toremifene, and age < 60 y, then FSH and plasma estradiol level in postmenopausal ranges

It is not possible to assign menopausal status to women who are receiving an LH-RH agonist or antagonist. In women premenopausal at the beginning of adjuvant chemotherapy, amenorrhea is not a reliable indicator of menopausal status as ovarian function may still be intact or resume despite anovulation/amenorrhea after chemotherapy. For these women with therapy-induced amenorrhea, oophorectomy or serial measurement of FSH and/or estradiol are needed to ensure postmenopausal status if the use of aromatase inhibitors is considered as a component of endocrine therapy.
SUBSEQUENT ENDOCRINE THERAPY FOR SYSTEMIC DISEASE
(For first-line endocrine therapy see BINV-16)

Premenopausal patients with ER-positive disease should have ovarian ablation/suppression and follow postmenopausal guideline

POSTMENOPAUSAL PATIENTS
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator (exemestane)
- Fulvestrant
- Tamoxifen or Toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

PREFERRED SINGLE AGENTS

**Anthracyclines**
- Doxorubicin
- Epirubicin
- Pegylated liposomal doxorubicin

**Taxanes**
- Paclitaxel
- Docetaxel
- Albumin-bound paclitaxel

**Anti-metabolites**
- Capecitabine
- Gemcitabine

**Other microtubule inhibitors**
- Vinorelbine

OTHER SINGLE AGENTS

- Cyclophosphamide
- Mitoxantrone
- Cisplatin
- Etoposide (po) (category 2B)
- Vinblastine
- Fluorouracil CI
- Ixabepilone

PREFERRED AGENTS WITH BEVACIZUMAB
- Paclitaxel

PREFERRED CHEMOTHERAPY COMBINATIONS

- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- AT (doxorubicin/docetaxel; doxorubicin/paclitaxel)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)

OTHER COMBINATIONS
- Ixabepilone + capecitabine (category 2B)

PREFERRED FIRST-LINE AGENTS FOR HER2-POSITIVE DISEASE

**Trastuzumab with:**
- Paclitaxel ± carboplatin
- Docetaxel
- Vinorelbine
- Capecitabine

PREFERRED AGENTS FOR TRASTUZUMAB-EXPOSED HER2-POSITIVE DISEASE

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

---

1There is no compelling evidence that combination regimens are superior to sequential single agents.

2A single randomized clinical trial documents superior time to progression with the combination of bevacizumab plus paclitaxel compared with paclitaxel alone for first line chemotherapy of metastatic disease.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER

PREFERRED CHEMOTHERAPY COMBINATIONS

CAF chemotherapy
- Cyclophosphamide 100 mg/m^2 PO days 1-14
- Doxorubicin 30 mg/m^2 IV days 1 & 8
- 5-Fluorouracil 500 mg/m^2 IV days 1 & 8
Cycled every 28 days.

FAC chemotherapy
- 5-Fluorouracil 500 mg/m^2 IV days 1 & 8 or days 1 & 4
- Doxorubicin 50 mg/m^2 IV day 1
- Cyclophosphamide 500 mg/m^2 IV day 1
Cycled every 21 days.

FEC chemotherapy
- Cyclophosphamide 400 mg/m^2 IV days 1 & 8
- Epirubicin 50 mg/m^2 IV days 1 & 8
- 5-Fluorouracil 500 mg/m^2 IV days 1 & 8
Cycled every 28 days.

AC chemotherapy
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1
Cycled every 21 days.

EC chemotherapy
- Epirubicin 75 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1
Cycled every 21 days.

AT chemotherapy
- Doxorubicin 50 mg/m^2 IV day 1
- Docetaxel 75 mg/m^2 IV day 1
Cycled every 21 days

CMF chemotherapy
- Cyclophosphamide 100 mg/m^2 PO days 1-14
- Methotrexate 40 mg/m^2 IV days 1 & 8
- 5-Fluorouracil 600 mg/m^2 IV days 1 & 8
Cycled every 28 days.

Docetaxel/capecitabine chemotherapy
- Docetaxel 75 mg/m^2 IV day 1
- Capecitabine 950 mg/m^2 PO twice daily days 1-14
Cycled every 21 days.

GT chemotherapy
- Paclitaxel 175 mg/m^2 IV day 1
- Gemcitabine 1250 mg/m^2 IV days 1 & 8 (following paclitaxel on day 1)
Cycled every 21 days.

OTHER COMBINATIONS

Ixabepilone/capecitabine (category 2B)
- Ixabepilone 40 mg/m^2 IV day 1
- Capecitabine 2000 mg/m^2 PO days 1-14
Cycled every 21 days.

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**INVASIVE BREAST CANCER**

**PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER**

**PREFERRED SINGLE AGENTS**

**Anthracyclines:**
- Doxorubicin 60-75 mg/m² IV day 1¹¹
  Cycled every 21 days
- OR
  - Doxorubicin 20 mg/m² IV weekly¹²
- Epirubicin 60-90 mg/m² IV day 1¹³
  Cycled every 21 days.
- Pegylated liposomal encapsulated doxorubicin 50 mg/m² IV day 1⁴
  Cycled every 28 days.

**Taxanes:**
- Paclitaxel 175 mg/m² IV day 1¹⁵
  Cycled every 21 days.
- OR
  - Paclitaxel 80 mg/m² IV weekly¹⁶
- Docetaxel 60-100 mg/m² IV day 1¹⁷,¹⁸
  Cycled every 21 days.
- OR
  - Docetaxel 40 mg/m² IV weekly for 6 wks followed by a 2 week rest, then repeat¹⁹
- Albumin-bound paclitaxel 100 mg/m² or 150 mg/m² days 1, 8, and 15 IV²⁰,²¹
  Cycled every 28 days.
- Albumin-bound paclitaxel 260 mg/m² IV²⁰
  Cycled every 21 days.

**Anti-metabolites:**
- Capecitabine 1000-1250 mg/m² PO twice daily days 1-14²²
  Cycled every 21 days.
- Gemcitabine 800-1200 mg/m² IV days 1, 8 & 15²³
  Cycled every 28 days.

**Other microtubule inhibitors:**
- Vinorelbine 25 mg/m² IV weekly²⁴

**OTHER SINGLE AGENTS**
- Cyclophosphamide
- Mitoxantrone
- Cisplatin
- Etoposide (PO) (category 2B)
- Vinblastine
- Fluorouracil CI
- Ixabepilone

**PREFERRED AGENTS WITH BEVACIZUMAB**

- Paclitaxel plus bevacizumab
  - Paclitaxel 90 mg/m² by 1 h IV days 1, 8 & 15
  - Bevacizumab 10 mg/kg IV days 1 & 15
  Cycled every 28 days.

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
# Invasive Breast Cancer

## Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer

### Preferred First-Line Agents with Trastuzumab for HER2-Positive Disease

**Combinations**
- PCH chemotherapy
  - Carboplatin AUC of 6 IV day 1
  - Paclitaxel 175 mg/m² IV day 1
  - Cycled every 21 days.

**Weekly TCH chemotherapy**
- Paclitaxel 80 mg/m² IV days 1, 8 & 15
- Carboplatin AUC of 2 IV days 1, 8 & 15
- Cycled every 28 days.

**Single Agents**
- Paclitaxel 175 mg/m² IV day 1
  - Cycled every 21 days.
  - OR
  - Paclitaxel 80-90 mg/m² IV weekly
- Docetaxel 80 to 100 mg/m² IV day 1
  - Cycled every 21 days
  - OR
  - Docetaxel 35 mg/m² IV infusion weekly
- Vinorelbine 25 mg/m² IV weekly
- Capecitabine 1000-1250 mg/m² PO twice daily days 1-14
  - Cycled every 21 days

### Trastuzumab Component

- Trastuzumab 4 mg/kg IV day 1
  - Followed by 2 mg/kg IV weekly
  - OR
  - Trastuzumab 8 mg/kg IV day 1
  - Followed by 6 mg/kg IV every 3 wks

### Preferred Agents for Trastuzumab-Exposed HER2-Positive Disease

- Capecitabine plus lapatinib
  - Capecitabine 1000 mg/m² PO twice daily Days 1 - 14
  - OR
  - Lapatinib 1250 mg PO daily Days 1-21
  - Cycled every 21 days

- Trastuzumab + other first-line agents

- Trastuzumab + capecitabine

- Trastuzumab + lapatinib
  - Lapatinib 1000 mg PO daily

### Note

All recommendations are category 2A unless otherwise indicated.

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

---

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.
Invasive Breast Cancer

PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER


The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER


Gradishar W, Krasnojon D, Cheporov S, et al. Randomized comparison of weekly or every-3-week nab-paclitaxel compared to q3w docetaxel as first-line therapy in patients with metastatic breast cancer. 25(June 20 suppl):Abstract 1032, 2007.


The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
# Phyllodes Tumor

<table>
<thead>
<tr>
<th>CLINICAL PRESENTATION</th>
<th>WORKUP</th>
<th>FINDINGS</th>
<th>TREATMENT</th>
</tr>
</thead>
</table>
| Clinical suspicion of phyllodes tumor: | - Palpable mass  
- Rapid growth  
- Large size (> 2 cm)  
- Imaging with ultrasound suggestive of fibroadenoma except for size and/or history of growth | - History and physical exam  
- Ultrasound  
- Mammogram for women ≥ 30 y | - Fibroadenoma  
- Phyllodes tumor includes benign, borderline and malignant  
- Invasive or in situ cancer  
| Excisional biopsy b  
FNA will not, and core biopsy may not distinguish fibroadenoma from phyllodes tumor in most cases.  
Excisional biopsy includes complete mass removal, but without the intent of obtaining surgical margins.  
Wide excision means excision with the intention of obtaining surgical margins ≥ 1 cm. Narrow surgical margins are associated with heightened local recurrence risk, but are not an absolute indication for mastectomy when partial mastectomy fails to achieve margin width ≥ 1 cm. | - Excisional biopsy b  
Core needle biopsy a  
Fibroadenoma or indeterminate  
Phyllodes tumor  
Invasive or in situ cancer | - See findings above  
- See findings above  
- See appropriate guidelines |

### Clinical Trials

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

---

**Note:** All recommendations are category 2A unless otherwise indicated.
### PHYLLODES TUMOR RECURRENCE

<table>
<thead>
<tr>
<th>CLINICAL PRESENTATION</th>
<th>WORKUP</th>
<th>FINDINGS</th>
<th>TREATMENT</th>
</tr>
</thead>
</table>
| Locally recurrent breast mass following excision of phyllodes tumor | • History and physical exam  
• Ultrasound  
• Mammogram  
• Tissue sampling (histology preferred)  
• Consider chest imaging | - No metastatic disease  
- Metastatic disease | - Re-excision with wide margins without axillary staging  
- Metastatic disease management following principles of soft tissue sarcoma  
- Consider post-operative radiation (category 2B)\(^d\)  
- See NCCN Soft Tissue Sarcoma Guidelines |

\(^d\)There is no prospective randomized data supporting the use of radiation treatment with phyllodes tumors. However, in the setting where additional recurrence would create significant morbidity, eg, chest wall recurrence following salvage mastectomy, radiation therapy may be considered, following the same principles that are applied to the treatment of soft tissue sarcoma.

**Note:** All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
CLINICAL PRESENTATION

Clinical suspicion of Paget's disease a

WORKUP

- Clinical breast exam
- Diagnostic bilateral mammogram, ultrasound as necessary

Examination or imaging positive for breast lesion

Examination and imaging negative for breast lesion

Note: All recommendations are category 2A unless otherwise indicated.

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

aNipple or areolar eczema, ulceration, bleeding, itching.
**Paget’s Disease**

**WORKUP**

- **Examination or imaging positive for breast lesion**
  - Core biopsy of breast lesion and full thickness skin biopsy of involved nipple-areola complex (NAC)

- **Examination and imaging negative for breast lesion**
  - Full thickness skin biopsy of involved NAC

**TREATMENT**

- **Breast and NAC biopsy negative**
  - Clinical follow-up
  - Re-biopsy if not healing

- **Breast DCIS**
  - Clinical follow-up
  - Re-biopsy if not healing

- **Breast invasive cancer and NAC Paget’s**
  - Mastectomy ± axillary staging
  - or
  - Excision of breast tumor and excision NAC with whole breast radiation, consider boost to breast and NAC sites

- **Breast negative for cancer and positive NAC Paget’s**
  - Mastectomy + axillary staging
  - or
  - Excision of breast tumor and excision NAC + axillary staging with whole breast radiation, consider boost to breast and NAC sites

- **NAC biopsy positive for Paget’s**
  - Mastectomy + axillary staging
  - or
  - Excision of NAC with whole breast radiation, consider boost to NAC sites

- **NAC biopsy negative for Paget’s**
  - Clinical follow-up
  - Re-biopsy if not healing

---

**Note:**

- All recommendations are category 2A unless otherwise indicated.
- Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

---

**b** To assess extent of disease or confirm additional disease consider MRI (See BINV-B).

**c** Mastectomy is always an option with any manifestation of Paget’s disease (see manuscript text).

**d** With Paget’s disease and no associated peripheral cancer, or with associated DCIS, consider tamoxifen 20 mg per day for 5 years.

**e** With associated invasive breast cancer, treat with appropriate systemic adjuvant therapy (See BINV-4)

---

**PAGET-2**
Breast Cancer During Pregnancy

**CLINICAL PRESENTATION**

- Pregnant patient with confirmed breast cancer diagnosis (core biopsy preferred)
  - No distant metastases on staging

**PRIMARY TREATMENT**

1. **1st trimester**
   - Discuss termination: Non-therapeutic
   - Continuing pregnancy
   - Mastectomy + axillary staging\(^{a,b,c}\)

2. **2nd trimester/Early 3rd trimester**
   - Mastectomy\(^a\) or breast-conserving surgery + axillary staging\(^{a,b,c}\)
   - or
   - Neoadjuvant chemotherapy\(^a\), mastectomy or breast-conserving surgery + axillary staging\(^{a,b,c}\) post-partum

3. **Late 3rd trimester**
   - Mastectomy\(^a\) or breast-conserving surgery + axillary staging\(^{a,b,c}\)

**ADJUVANT TREATMENT**

- Begin adjuvant chemotherapy in 2nd trimester\(^a\)
  - ± Adjuvant radiation therapy post-partum\(^a\)
  - ± Adjuvant endocrine therapy post-partum\(^a\)

- Adjuvant chemotherapy\(^a\)
  - ± Adjuvant radiation therapy post-partum\(^a\)
  - ± Adjuvant endocrine therapy post-partum\(^a\)

- ± Adjuvant radiation therapy post-partum\(^a\)
  - ± Adjuvant endocrine therapy post-partum\(^a\)

- Adjuvant chemotherapy\(^a\)
  - ± Adjuvant radiation therapy post-partum\(^a\)
  - ± Adjuvant endocrine therapy post-partum\(^a\)

\(^a\)Considerations and selection of optimal local therapy and systemic therapy are similar to that recommended in non-pregnancy associated breast cancer, see other sections of this guideline. However, the selection and timing of chemotherapy, endocrine therapy, and radiation therapy is different in the pregnant versus non-pregnant patient. Please see discussion section. Chemotherapy should not be administered during the first trimester of pregnancy and radiation therapy should not be administered during any trimester of pregnancy. Most experience with chemotherapy during pregnancy for breast cancer is from regimens that utilize various combinations of doxorubicin, cyclophosphamide, and fluorouracil. Consideration for post-partum chemotherapy are the same as for non-pregnancy associated breast cancer.

\(^b\)See Surgical Axillary Lymph Node Staging (BINV-C).

\(^c\)There are insufficient safety data to recommend general use of taxanes during pregnancy. The use of blue dye and trastuzumab are contraindicated during pregnancy.

---

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
**CLINICAL PRESENTATION**

Inflammatory breast cancer is a clinical syndrome in women with invasive breast cancer that is characterized by erythema and edema (peau d'orange) of a third or more of the skin of the breast and with a palpable border to the erythema. The differential diagnosis includes cellulitis of the breast or mastitis. Pathologically, tumor is typically present in the dermal lymphatics of the involved skin, but dermal lymphatic involvement is neither required for, nor sufficient for by itself, a diagnosis of inflammatory breast cancer.

**WORKUP**

- History and physical exam
- CBC, platelets
- Liver function tests
- Pathology review
- Determination of tumor ER/PR status and HER2 status
- Bilateral diagnostic mammogram, ultrasound as necessary
- Breast MRI (optional)
- Bone scan (category 2B)
- CT scan chest/abd/pelvis (category 2B)
- Chest imaging (if pulmonary symptoms are present)
- Genetic counseling if patient is high risk for hereditary breast cancer
- PET/CT scan (category 2B)

**TREATMENT**

- Preoperative chemotherapy, anthracycline ± taxane
  - If tumor HER2 positive, trastuzumab containing regimen but not concurrent with anthracycline
  - Consider additional systemic chemotherapy and/or preoperative radiation

- Total mastectomy + level I/II axillary dissection + radiation therapy to chest wall and supraclavicular nodes (plus internal mammary nodes if involved, consider internal mammary nodes if not clinically involved [category 3]) ± delayed breast reconstruction

- Complete planned chemotherapy regimen course if not completed preoperatively plus endocrine treatment if estrogen receptor positive (sequential chemotherapy followed by endocrine therapy).
  - Complete 1 year of trastuzumab if tumor HER2-positive

**Response**

- No response

**Individualized treatment**

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## Table 1

### Staging

#### American Joint Committee on Cancer (AJCC)

**TNM Staging System For Breast Cancer**

**Primary Tumor (T)**

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by the physical examination, the examiner will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic measurements, are used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1 cm increment.

- **TX**: Primary tumor cannot be assessed
- **T0**: No evidence of primary tumor
- **Tis**: Carcinoma in situ
- **Tis (DCIS)**: Ductal carcinoma in situ
- **Tis (LCIS)**: Lobular carcinoma in situ
- **Tis (Paget's)**: Paget's disease of the nipple with no tumor

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

- **T1**: Tumor 2 cm or less in greatest dimension
  - **T1mic**: Microinvasion 0.1 cm or less in greatest dimension
  - **T1a**: Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
  - **T1b**: Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
  - **T1c**: Tumor more than 1 cm but not more than 2 cm in greatest dimension

- **T2**: Tumor more than 2 cm but not more than 5 cm in greatest dimension

- **T3**: Tumor more than 5 cm in greatest dimension

- **T4**: Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
  - **T4a**: Extension to chest wall, not including pectoralis muscle
  - **T4b**: Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
  - **T4c**: Both T4a and T4b
  - **T4d**: Inflammatory carcinoma

**Regional Lymph Nodes (N)**

- **NX**: Regional lymph nodes cannot be assessed (e.g., previously removed)
- **N0**: No regional lymph node metastasis
- **N1**: Metastases in ipsilateral axillary lymph node(s)
- **N2**: Metastases in ipsilateral axillary lymph nodes fixed or matted, or in *clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis
  - **N2a**: Metastases in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
  - **N2b**: Metastasis only in *clinically apparent* ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
- **N3**: Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in *clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
  - **N3a**: Metastasis in ipsilateral infraclavicular lymph node(s)
  - **N3b**: Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
  - **N3c**: Metastasis in ipsilateral supraclavicular lymph node(s)

*Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.*

Staging continued on next page (ST-2)
### Table 1 (continued)

#### Pathologic (pN)*

<table>
<thead>
<tr>
<th>pNX</th>
<th>Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0</td>
<td>No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITC)</td>
</tr>
</tbody>
</table>

**Note:** Isolated tumor cells (ITC) are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but which may be verified on H&E stains. ITCs do not usually show evidence of malignant activity e.g., proliferation or stromal reaction.

<table>
<thead>
<tr>
<th>pN0(i-)</th>
<th>No regional lymph node metastasis histologically, negative IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN0(i+)</td>
<td>No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm</td>
</tr>
<tr>
<td>pN0(mol-)</td>
<td>No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)*</td>
</tr>
<tr>
<td>pN0(mol+)</td>
<td>No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)*</td>
</tr>
</tbody>
</table>

*Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary node dissection is designated (sn) for "sentinel node," e.g., pN0(i+) (sn).

*RT-PCR: reverse transcriptase/polymerase chain reaction.

<table>
<thead>
<tr>
<th>pN1</th>
<th>Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not <em>clinically apparent</em>**</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN1mi</td>
<td>Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)</td>
</tr>
<tr>
<td>pN1a</td>
<td>Metastasis in 1 to 3 axillary lymph nodes</td>
</tr>
<tr>
<td>pN1b</td>
<td>Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not <em>clinically apparent</em>**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>pN1c</th>
<th>Metastasis in 1 to 3 axillary lymph nodes and in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not <em>clinically apparent</em>** (If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN2</td>
<td>Metastasis in 4 to 9 axillary lymph nodes, or in <em>clinically apparent</em> internal mammary lymph nodes in the absence of axillary lymph node metastasis</td>
</tr>
<tr>
<td>pN2a</td>
<td>Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)</td>
</tr>
<tr>
<td>pN2b</td>
<td>Metastasis in <em>clinically apparent</em> internal mammary lymph nodes in the absence of axillary lymph node metastasis</td>
</tr>
<tr>
<td>pN3</td>
<td>Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in <em>clinically apparent</em> ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes</td>
</tr>
<tr>
<td>pN3a</td>
<td>Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes</td>
</tr>
<tr>
<td>pN3b</td>
<td>Metastasis in <em>clinically apparent</em> ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not <em>clinically apparent</em>**</td>
</tr>
<tr>
<td>pN3c</td>
<td>Metastasis in ipsilateral supraclavicular lymph nodes</td>
</tr>
</tbody>
</table>

* Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

** Not clinically apparent is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

---

*S Staging continued on next page (ST-3)*
Table 1 (continued)

Distant Metastasis (M)

<table>
<thead>
<tr>
<th>M</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

STAGE GROUPING

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 0</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stage I</strong></td>
<td>T1*</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IIA</strong></td>
<td>T0</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1*</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IIB</strong></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td><strong>Stage IIIA</strong></td>
<td>T0</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1*</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
</tr>
</tbody>
</table>

Note: Stage designation may be changed if post-surgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.

* T1 includes T1mic

HISTOPATHOLOGIC TYPE

The histopathologic types are the following:

**In situ Carcinomas**

NOS (not otherwise specified)

Intradiuctal

Paget's disease and intraductal

**Invasive Carcinomas**

NOS

Ductal

Inflammatory

Medullary, NOS

Medullary with lymphoid stroma

Mucinous

Papillary (predominantly micropapillary pattern)

Tubular

Lobular

Paget's disease and infiltrating

Undifferentiated

Squamous cell

Adenoid cystic

Secretory

Cribriform

HISTOPATHOLOGIC GRADE (G)

All invasive breast carcinomas with the exception of medullary carcinoma should be graded. The Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) is recommended. The grade for a tumor is determined by assessing morphologic features (tubule formation, nuclear pleomorphism, and mitotic count), assigning a value of 1 (favorable) to 3 (unfavorable) for each feature, and adding together the scores for all three categories. A combined score of 3-5 points is grade 1; a combined score of 6-7 points is grade 2; a combined score of 8-9 points is grade 3.


HISTOLOGIC GRADE (NOTTINGHAM COMBINED HISTOLOGIC GRADE IS RECOMMENDED)

GX | Grade cannot be assessed
G1 | Low combined histologic grade (favorable)
G2 | Intermediate combined histologic grade (moderately favorable)
G3 | High combined histologic grade (unfavorable)

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer-Verlag New York, Inc., on behalf of the AJCC.
Discussion To view the most up-to-date discussion, click here.

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.