



National
Comprehensive
Cancer
Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 2.2017 — April 6, 2017

NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients

Continue



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2017 Panel Members

Breast Cancer

[NCCN Guidelines Index](#)
[Breast Cancer Table of Contents](#)
[Discussion](#)

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

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

Ron Balassanian, MD ≠
UCSF Helen Diller Family
Comprehensive Cancer Center

Sarah L. Blair, MD ¶
UC San Diego Moores Cancer Center

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

Amy Cyr, MD ¶
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Anthony D. Elias, MD †
University of Colorado Cancer Center

William B. Farrar, MD ¶
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Andres Forero, MD ‡ †
University of Alabama at Birmingham
Comprehensive Cancer Center

Sharon H. Giordano, MD, MPH †
The University of Texas
MD Anderson Cancer Center

Matthew P. Goetz, MD ‡ †
Mayo Clinic Cancer Center

Lori J. Goldstein, MD †
Fox Chase Cancer Center

Steven J. Isakoff, MD, PhD †
Massachusetts General Hospital
Cancer Center

Janice Lyons, MD §
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center and
Cleveland Clinic Taussig Cancer Institute

P. Kelly Marcom, MD †
Duke Cancer Institute

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

Beryl McCormick, MD §
Memorial Sloan Kettering Cancer Center

Meena S. Moran, MD §
Yale Cancer Center/Smilow Cancer Hospital

Ruth M. O'Regan, MD †
University of Wisconsin Carbone Cancer Center

Sameer A. Patel, MD ¶
Fox Chase Cancer Center

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

Elizabeth C. Reed, MD † §
Fred & Pamela Buffett Cancer Center

Kilian E. Salerno, MD §
Roswell Park Cancer Institute

Lee S. Schwartzberg, MD ‡ †
St. Jude Children's Research Hospital/
The University of Tennessee
Health Science Center

Amy Sitapati, MD ¶
UC San Diego Moores Cancer Center

Karen Lisa Smith, MD, MPH †
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Mary Lou Smith, JD, MBA ¶
Research Advocacy Network

Hatem Soliman, MD †
Moffitt Cancer Center

George Somlo, MD ‡ § †
City of Hope Comprehensive Cancer Center

Melinda Telli, MD †
Stanford Cancer Institute

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

† Medical oncology	§ Radiation oncology
‡ Hematology/Oncology	ξ Bone marrow transplantation
⊃ Internal medicine	¥ Patient advocacy
¶ Surgical oncology	* Discussion Section Writing Committee
≠ Pathology	
Ÿ Reconstructive surgery	

Continue

[NCCN Guidelines Panel Disclosures](#)

NCCN Staff
Rashmi Kumar, PhD
Dorothy A. Shead, MS



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2017 Table of Contents

Breast Cancer

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

[NCCN Breast Cancer Panel Members](#)
[Summary of Guidelines Updates](#)

Noninvasive Breast Cancer:

[Lobular Carcinoma In Situ \(LCIS-1\)](#)
[Ductal Carcinoma In Situ \(DCIS\) Workup and Primary Treatment \(DCIS-1\)](#)
[DCIS Postsurgical Treatment and Surveillance/Follow-up \(DCIS-2\)](#)
[Margin Status in DCIS \(DCIS-A\)](#)

Invasive Breast Cancer:

[Clinical Stage, Workup \(BINV-1\)](#)
[Locoregional Treatment of Clinical Stage I, IIA, or IIB Disease or T3,N1, M0 \(BINV-2\)](#)
[Systemic Adjuvant Treatment](#)
[Hormone Receptor-Positive HER2-Positive Disease \(BINV-5\)](#)
[Hormone Receptor-Positive HER2-Negative Disease \(BINV-6\)](#)
[Hormone Receptor-Negative HER2-Positive Disease \(BINV-7\)](#)
[Hormone Receptor-Negative HER2-Negative Disease \(BINV-8\)](#)
[Favorable Histologies \(BINV-9\)](#)
[Preoperative Systemic Therapy for Operable Breast Cancer: Workup \(BINV-10\)](#)
[Preoperative Systemic Therapy: Breast and Axillary Evaluation \(BINV-11\)](#)
[Preoperative Systemic Therapy: Surgical Treatment \(BINV-12\)](#)
[Preoperative Systemic Therapy: Adjuvant Therapy \(BINV-13\)](#)
[Preoperative Systemic Therapy for Inoperable or Locally Advanced Breast Cancer \(Non-Inflammatory\): Workup \(BINV-14\)](#)
[Preoperative Systemic Therapy for Inoperable or Locally Advanced Breast Cancer \(Non-Inflammatory\) \(BINV-15\)](#)
[Surveillance/Follow-Up \(BINV-16\)](#)
[Recurrent/Stage IV Disease \(BINV-17\)](#)
[Treatment of Recurrence \(BINV-18\)](#)
[Treatment of Stage IV Disease \(BINV-19\)](#)
[ER and/or PR Positive; HER2 Negative or Positive \(BINV-20\)](#)
[ER and PR Negative; or ER and/or PR Positive and Endocrine Refractory; HER2 Negative \(BINV-21\)](#)
[ER and PR Negative; or ER and/or PR Positive and Endocrine Refractory; HER2 Positive \(BINV-22\)](#)
[Follow-Up Therapy for Endocrine Treatment of Recurrent or Stage IV Disease \(BINV-23\)](#)
[Principles of HER2 Testing \(BINV-A\)](#)
[Principles of Dedicated Breast MRI Testing \(BINV-B\)](#)
[Fertility and Birth Control \(BINV-C\)](#)
[Surgical Axillary Staging - Stage I, IIA, IIB, and IIIA T3, N1, M0 \(BINV-D\)](#)
[Axillary Lymph Node Staging \(BINV-E\)](#)
[Margin Status in Infiltrating Carcinoma \(BINV-F\)](#)
[Special Considerations to Breast-Conserving Therapy Requiring Radiation Therapy \(BINV-G\)](#)

[Principles of Breast Reconstruction Following Surgery \(BINV-H\)](#)
[Principles of Radiation Therapy \(BINV-I\)](#)
[Adjuvant Endocrine Therapy \(BINV-J\)](#)
[Preoperative/Adjuvant Therapy Regimens \(BINV-K\)](#)
[Principles of Preoperative Systemic Therapy \(BINV-L\)](#)
[Definition of Menopause \(BINV-M\)](#)
[Endocrine Therapy for Recurrent or Stage IV Disease \(BINV-N\)](#)
[Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer \(BINV-O\)](#)
[Principles of Monitoring Metastatic Disease \(BINV-P\)](#)

Special Considerations:

[Phyllodes Tumor \(PHYLL-1\)](#)
[Paget's Disease \(PAGET-1\)](#)
[Breast Cancer During Pregnancy \(PREG-1\)](#)
[Inflammatory Breast Cancer \(IBC-1\)](#)
[Staging \(ST-1\)](#)

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

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical_trials/physician.html](#).

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See [NCCN Categories of Evidence and Consensus](#).

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2017.



NCCN Guidelines Version 2.2017 Updates

Breast Cancer

Updates in Version 2.2017 of the NCCN Guidelines for Breast Cancer from Version 1.2017 include:

[BINV-20](#)

- Added ribociclib + letrozole as a category 1 option for postmenopausal patients with no prior endocrine therapy within 1 y.
- Modified footnote ggg: "Palbociclib *or ribociclib* in combination with letrozole may be considered in HER2-negative, metastatic breast cancer."

[BINV-23](#) and [BINV-N](#)

- Modified the footnote: "If there is disease progression while on ~~palbociclib~~ *a CDK4/6 inhibitor* + letrozole, there are no data to support an additional line of therapy with another palbociclib regimen. Likewise, if there is disease progression while on exemestane + everolimus, there are no data to support an additional line of therapy with another everolimus regimen."

[BINV-N](#)

- Added footnote 2 to palbociclib + fulvestrant (category 1) option.

Updates in Version 1.2017 of the NCCN Guidelines for Breast Cancer from Version 3.2016 include:

[LCIS-1](#)

- Under diagnosis, removed ~~Stage 0 Tis, N0, M0~~
- Biopsy was core needle biopsy, divided pathway into three:
 - ▶ Classic LCIS
 - ▶ Pleomorphic LCIS
 - ▶ Non-concordant with imaging
 - ▶ Modified footnote b: "Some variants of LCIS (pleomorphic LCIS) may have a similar biological behavior to that of DCIS. Clinicians may consider complete excision with negative margins for pleomorphic LCIS, *but this may lead to high mastectomy rate without proven clinical benefit. ~~but outcomes data regarding the efficacy of surgical excision to negative margins are lacking.~~* There are no data to support using radiotherapy in this setting."

[DCIS-1](#)

- Removed link to NCCN Guidelines for Breast Screening and Diagnosis

[DCIS-A](#)

- Added the following statements:
 - ▶ The NCCN Panel accepts the definition of a negative margin as "No ink on the tumor," from the 2016 SSO/ASTRO/ASCO Consensus Guidelines on Margins.
 - ▶ For pure DCIS, margins of at least 2 mm are associated with a reduced risk of ipsilateral breast tumor recurrence (IBTR) relative to narrower negative margin widths in patients receiving WBRT. The routine practice of obtaining negative margin widths wider than 2 mm is not supported by the evidence. DCIS with micro-invasion (defined as no invasive focus >1 mm in size) should be considered as DCIS when considering the optimal margin width.
 - ▶ For patients treated with excision alone (without radiation), regardless of margin width, the risk of IBTR is substantially higher than treatment with excision and whole breast radiation therapy (even in predefined low-risk patients). The optimal margin width for treatment with excision alone is unknown, but should be at least 2 mm. Some evidence suggests lower rates of IBTR with margin widths wider than 2 mm.

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

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

NCCN Guidelines Version 2.2017 Updates

Breast Cancer

Updates in Version 1.2017 of the NCCN Guidelines for Breast Cancer from Version 3.2016 include:

[DCIS-A continued](#)

• Removed the following statements:

- ▶ ~~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).~~

[BINV-1](#), [BINV-10](#), [BINV-14](#), [BINV-17](#), [IBC-1](#)

• Workup:

- ▶ Added Comprehensive metabolic panel
- ▶ Clarified "with contrast" to imaging recommendations
- ▶ Removed "category 2B" from FDG PET/CT (optional)

[BINV-1](#)

Added links to preoperative systemic therapy pages [BINV-10](#) and [BINV-14](#).

[BINV-2](#)

• Negative axillary nodes:

- ▶ Modified - "Radiation therapy to whole breast with or without boost to tumor bed, *and consider regional nodal radiation in patients with central/medial tumors or tumors >2 cm with other high-risk features (young age or extensive lymphovascular invasion [LVSI]).*"
- ▶ Modified - "Consideration of accelerated partial breast irradiation (APBI) in selected *low-risk* patients."

- Modified footnote "q" for consistency: "Consider imaging for systemic staging, including *chest/abdominal ± pelvic* diagnostic CT with contrast, bone scan, and optional FDG PET/CT (category 2B) ([See BINV-1](#))."

[BINV-3](#)

- Negative axillary nodes and tumor ≤5 cm and negative margins but <1 mm: Modified "Consider radiation therapy" to chest wall, *± regional nodal radiation in patients with central/medial tumors or tumors >2 cm with other high-risk features (young age or extensive LVSI).*"
- Modified footnote "u": "Postmastectomy radiation therapy may be considered for patients with multiple high-risk recurrence factors, including *central/medial tumors or tumors >2 cm with other high-risk features such as young age and/or extensive LVSI.*"

[BINV-5](#)

- Tumor ≤0.5 cm including microinvasive - consider adjuvant endocrine therapy ± adjuvant chemotherapy with trastuzumab, added a footnote.
 - ▶ New footnote: "Adjuvant chemotherapy with weekly paclitaxel and trastuzumab (Tolaney et al. NEJM 2015) can be considered for HER2-positive T1a N0 cancers, if the primary cancer is ER negative, and the tumor size borders on T1b (> 5mm). The absolute benefit of HER2-based systemic chemotherapy is likely negligible in patients with ER-positive cancers and tumor size bordering on T1mic (< 1mm), when the estimated recurrence risk is less than 5% and endocrine therapy remains a viable option for systemic treatment." (footnote also included on [BINV-7](#))

[BINV-5](#), [BINV-6](#), [BINV-7](#), [BINV-8](#)

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

[BINV-13](#)

• Lumpectomy:

- ▶ Removed the endocrine therapy in the first bullet, since this is covered in detail in bullets 3 and 4, following the radiation bullet.

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

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

NCCN Guidelines Version 2.2017 Updates

Breast Cancer

Updates in Version 1.2017 of the NCCN Guidelines for Breast Cancer from Version 3.2016 include:

[BINV-13 \(continued\)](#)

- ▶ Changed: "Adjuvant radiation therapy post-lumpectomy is based on *maximal disease stage from pre-chemotherapy tumor characteristics at diagnosis and post-chemotherapy pathology results. Adjuvant radiation therapy is recommended:*

- ◊ As indicated on [BINV-2](#)
- ◊ For cT3-4, cN2-3, stage III, residual disease >2 cm any ypN+"

[BINV-16](#)

- Added: "Periodic screening for changes in family history and referral to genetic counseling as indicated, added [see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#)."
- Modified footnote "pp": The use of estrogen, progesterone, or selective estrogen receptor modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. The use of a bisphosphonate (*oral/IV*) or *denosumab* is acceptable to maintain or to improve bone mineral density and reduce risk of fractures in postmenopausal (*natural or induced*) patients receiving adjuvant endocrine therapy. Optimal duration of *either* therapy has not been established. *Duration beyond 3 y is not known*. Factors to consider for duration of anti-osteoporosis therapy include bone mineral density, response to therapy, and risk factors for continued bone loss or fracture. Women treated with a bisphosphonate or *denosumab* should undergo a dental examination with preventive dentistry prior to the initiation of therapy, and should take supplemental calcium and vitamin D."

[BINV-20](#)

- Added palbociclib + letrozole as a category 1 option for postmenopausal patients with no prior endocrine therapy within 1 y.
- Modified footnote "ddd": It is unclear that women presenting at time of initial diagnosis with *an intact primary and metastatic disease* will benefit from the performance of palliative local breast surgery and/or radiation therapy. Generally this palliative local therapy *should only* be considered ~~only~~ after response to initial systemic therapy.
- Added footnote "ddd" to each treatment option.
- Added footnote "ggg": Palbociclib in combination with letrozole may be considered in HER2-negative, metastatic breast cancer.

[BINV-23](#) and [BINV-N](#)

- Added a new footnote: "If there is disease progression while on palbociclib + letrozole there are no data to support an additional line of therapy with another palbociclib regimen. Likewise, if there is disease progression while on exemestane + everolimus, there are no data to support an additional line of therapy with another everolimus regimen."

[BINV-B](#)

- Modified: "May be useful for identifying primary cancer in women with axillary nodal adenocarcinoma *and occult (or unidentified) primary cancer, with Paget's disease, or with invasive lobular carcinoma poorly (or inadequately) defined on mammography, ultrasound, or physical examination.*"

[BINV-G](#)

- Contraindications for breast-conserving therapy requiring radiation therapy include:
 - ▶ Absolute: Homozygous for ATM mutation (category 2B)
 - ▶ Relative: Li-Fraumeni syndrome (category 2B)

[BINV-H](#)

- 2nd bullet: "In general, the nipple-areolar complex (NAC) is sacrificed with skin-sparing mastectomy for cancer therapy. However, NAC-sparing procedures may be an option in cancer patients who are carefully selected by experienced multidisciplinary teams. Retrospective data support the use of NAC-sparing procedures for breast cancer therapy with low nipple-involvement rates and low local recurrence rates for early-stage, *and select advanced* biologically favorable (~~eg, Nottingham grade 1 or 2, node-negative, HER2/neu-negative, no lymphovascular invasion~~), *invasive cancers and/or DCIS. Preoperative clinical evidence of nipple involvement including Paget's disease, nipple discharge associated with malignancy, and/or imaging findings suggesting malignant involvement of the nipple or subareolar tissues contraindicates nipple preservation. Intraoperative that is peripherally located in the breast (>2 cm from nipple)). Nipple margin assessment is mandatory, and the nipple margin should be clearly designated."*

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

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

NCCN Guidelines Version 2.2017 Updates

Breast Cancer

Updates in Version 1.2017 of the NCCN Guidelines for Breast Cancer from Version 3.2016 include:

[BINV-I](#)

- Updated the following statement in the APBI section:
 - ▶ The NCCN Panel accepts the updated 2016 version of the ASTRO APBI guideline, which now defines patients "suitable" for APBI to be one of the following: a) 50 years or older with invasive ductal carcinoma measuring ≤ 2 cm (T1 disease) with negative margin widths of ≥ 2 mm, no LVSI, ER-positive, and BRCA negative or b) Low/intermediate nuclear grade, screen-detected DCIS measuring size ≤ 2.5 cm with negative margin widths of ≥ 3 mm.
 - ▶ ~~Removed: If not trial eligible, per the consensus statement from the American Society for Radiation Oncology (ASTRO), patients who may be suitable for APBI are women 60 y and older who are not carriers of BRCA 1/2 mutation treated with primary surgery for a unifocal T1N0 ER-positive cancer. Histology should be infiltrating ductal or a favorable ductal subtype and not associated with EIC or LCIS, and margins should be negative.~~

[BINV-J](#)

- Postmenopausal at diagnosis, added "Consider aromatase inhibitor for an additional 5 y."
- Footnote 2, added: "A balanced discussion of the risks and benefits associated with ovarian suppression therapy is critical."

[BINV-K \(1 of 7\)](#)

- Regimens for HER2-negative disease:
 - ▶ Removed "FEC/CEF followed by T"
 - ▶ Removed "FAC followed by T"
- Added a new footnote: "Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m²."

[BINV-K \(7 of 7\)](#)

- Removed the following references:
 - ▶ Roche H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: The FNCLCC PACS 001 trial. *J Clin Oncol* 2006; 24:5664-5671.
 - ▶ Martin M, Rodriguez-Lescure A, Ruiz A, et al: Randomized phase 3 trial of fluorouracil, epirubicin, and cyclophosphamide alone or followed by paclitaxel for early breast cancer. *J Natl Cancer Inst* 2008;100:805-814.

[BINV-L](#)

- Removed: "Endocrine therapy alone (aromatase inhibitor [preferred for postmenopausal women; given with ovarian suppression for premenopausal women] or tamoxifen) may be considered for patients with hormone-receptor positive disease."
- Added "Preoperative endocrine therapy alone may be considered for patients with ER-positive disease based on comorbidities or low-risk luminal biology."

[BINV-N](#)

- Premenopausal Patients: Selective ER modulators, added "(*tamoxifen or toremifene*)" to "or ovarian ablation or suppression, plus endocrine therapy as for postmenopausal women."
- Postmenopausal Patients: Palbociclib + letrozole, added (*category 1*).
- Modified footnote 1: "A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal AI)," removed ~~or any time on tamoxifen.~~
- Modified footnote 4: "For postmenopausal women or for premenopausal women receiving ovarian suppression with an LHRH agonist, with hormone-receptor positive and HER2-negative metastatic breast cancer that has progressed on *or after prior adjuvant or metastatic* endocrine therapy."
- Added *selective ER down-regulator* to fulvestrant

[BINV-O](#)

- Added a new footnote: "Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m²."

[BINV-P \(3 of 3\)](#)

- Changed the suggested follow-up with PET/CT for patients with metastatic disease from "unknown" to "*optional*" following chemotherapy and endocrine therapy.

[PHYLL-2](#)

- Clarified: "Consider chest imaging (*x-ray or CT, CT contrast optional*)."

[IBC-2](#)

- Added a link to See Adjuvant Endocrine Therapy (BINV-J).

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

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



NCCN Guidelines Version 2.2017

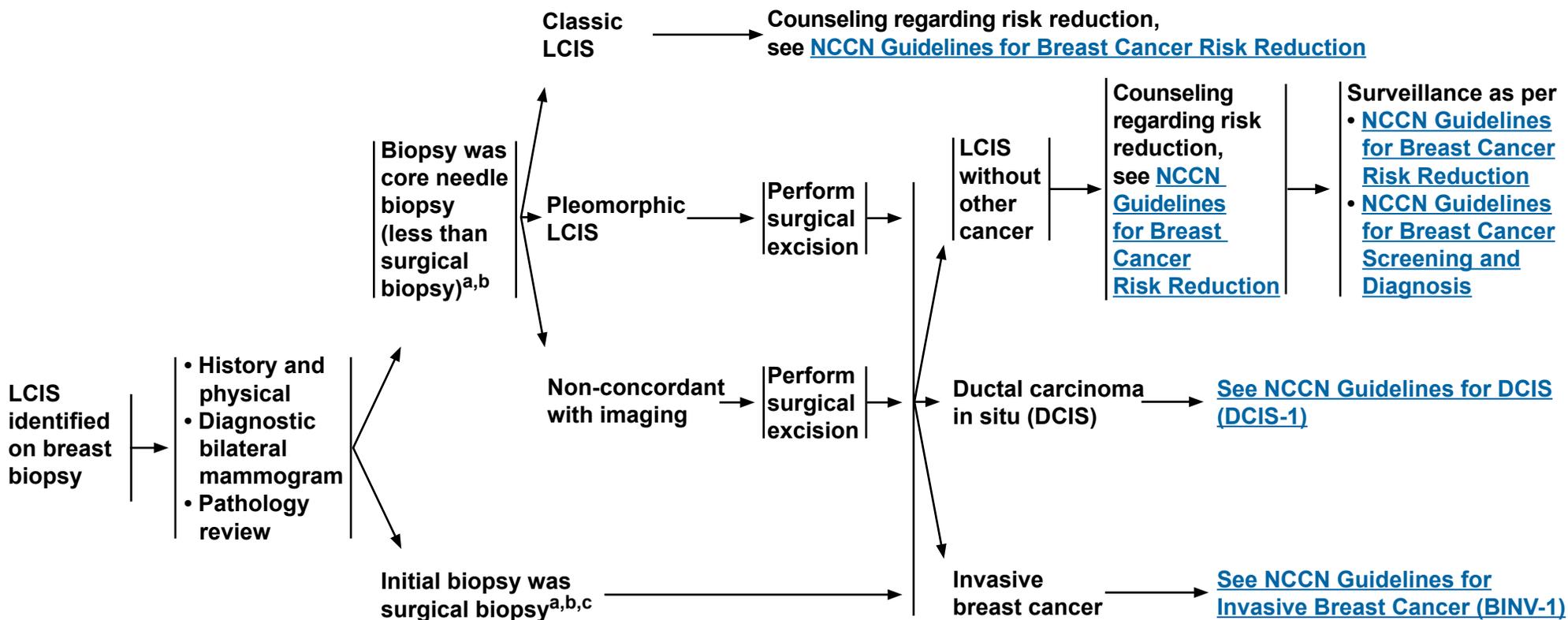
Lobular Carcinoma in Situ (LCIS)

DIAGNOSIS

WORKUP

RISK REDUCTION

SURVEILLANCE



^aLCIS is present on initial biopsy (needle or surgical) or on final excision with or without other proliferative changes (atypical ductal or lobular hyperplasia).
^bSome variants of LCIS (pleomorphic LCIS) may have a similar biological behavior to that of DCIS. Clinicians may consider complete excision with negative margins for pleomorphic LCIS, but this may lead to high mastectomy rate without proven clinical benefit. There are no data to support using radiotherapy in this setting.
^cMultifocal/extensive LCIS involving >4 terminal ductal lobular units on a core biopsy may be associated with increased risk for invasive cancer on surgical excision.

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



NCCN Guidelines Version 2.2017

Ductal Carcinoma in Situ (DCIS)

DIAGNOSIS

WORKUP

PRIMARY TREATMENT

DCIS
Stage 0
Tis, N0, M0

- History and physical exam
- Diagnostic bilateral mammogram
- Pathology review^a
- Determination of tumor estrogen receptor (ER) status
- Genetic counseling if patient is high-risk for hereditary breast cancer^b
- Breast MRI^{c,d} (optional)

- Lumpectomy^{e,f} without lymph node surgery^g + whole breast radiation therapy^{h,i,j,k,l} (category 1)
- or
- Total mastectomy with or without sentinel node biopsy^{g,j} ± reconstruction^m
- or
- Lumpectomy^{e,f} without lymph node surgery^g without radiation therapy^{h,i,j,k,l} (category 2B)

[See Postsurgical Treatment \(DCIS-2\)](#)

^aThe panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. <http://www.cap.org>.

^bSee [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#).

^cSee [Principles of Dedicated Breast MRI Testing \(BINV-B\)](#).

^dThe use of MRI has not been shown to increase likelihood of negative margins or decrease conversion to mastectomy. Data to support improved long-term outcomes are lacking.

^eRe-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.

^fSee [Margin Status in DCIS \(DCIS-A\)](#).

^gComplete axillary lymph node dissection should not be performed in the absence of evidence of invasive cancer or proven axillary metastatic disease in women with apparent pure DCIS or mammographically detected DCIS with microcalcifications. 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 should be strongly 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.

^hSee [Principles of Radiation Therapy \(BINV-I\)](#).

ⁱComplete resection should be documented by analysis of margins and specimen radiography. Post-excision mammography could also be performed whenever uncertainty about adequacy of excision remains.

^jPatients found to have invasive disease at total mastectomy or re-excision should be managed as having stage I or stage II disease, including lymph node staging.

^kSee [Special Considerations to Breast-Conserving Therapy Requiring Radiation Therapy \(BINV-G\)](#).

^lWhole-breast radiation therapy following lumpectomy reduces recurrence rates in DCIS by about 50%. Approximately half of the recurrences are invasive and half are DCIS. A number of factors determine local recurrence risk: palpable mass, larger size, higher grade, close or involved margins, and age <50 years. If the patient and physician view the individual risk as “low,” some patients may be treated by excision alone. Data evaluating the three local treatments show no differences in patient survival.

^mSee [Principles of Breast Reconstruction Following Surgery \(BINV-H\)](#).

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

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

**DCIS POSTSURGICAL TREATMENT****SURVEILLANCE/FOLLOW-UP****Risk reduction therapy for ipsilateral breast following breast-conserving surgery:**

- Consider endocrine therapy for 5 years for:
 - ▶ Patients treated with breast-conserving therapy (lumpectomy) and radiation therapyⁿ (category 1), especially for those with ER-positive DCIS.
 - ▶ The benefit of endocrine therapy for ER-negative DCIS is uncertain
 - ▶ Patients treated with excision aloneⁿ
- Endocrine therapy:
 - ▶ Tamoxifen^o for premenopausal patients
 - ▶ Tamoxifen^o or aromatase inhibitor for postmenopausal patients with some advantage for aromatase inhibitor therapy in patients <60 years old or with concerns for thromboembolism

Risk reduction therapy for contralateral breast:

- Counseling regarding risk reduction
[See NCCN Guidelines for Breast Cancer Risk Reduction](#)

- 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 endocrine therapy, monitor per [NCCN Guidelines for Breast Cancer Risk Reduction](#)

ⁿAvailable data suggest endocrine therapy 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 Guidelines for Breast Cancer Risk Reduction](#)).

^oCYP2D6 genotype testing is not recommended in women who are considering tamoxifen.

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

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



MARGIN STATUS IN DCIS

The NCCN Panel accepts the definition of a negative margin as "No ink on the tumor," from the 2016 SSO/ASTRO/ASCO Consensus Guidelines on Margins.

For pure DCIS, margins of at least 2 mm are associated with a reduced risk of ipsilateral breast tumor recurrence (IBTR) relative to narrower negative margin widths in patients receiving WBRT. The routine practice of obtaining negative margin widths wider than 2 mm is not supported by the evidence. DCIS with micro-invasion (defined as no invasive focus >1 mm in size) should be considered as DCIS when considering the optimal margin width.

For patients treated with excision alone (without radiation), regardless of margin width, the risk of IBTR is substantially higher than treatment with excision and whole breast radiation therapy (even in predefined low-risk patients). The optimal margin width for treatment with excision alone is unknown, but should be at least 2 mm. Some evidence suggests lower rates of IBTR with margin widths wider than 2 mm.

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

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



NCCN Guidelines Version 2.2017

Invasive Breast Cancer

CLINICAL STAGE	WORKUP	See Locoregional Treatment (BINV-2) ^k
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 Stage IIIA T3, N1, M0	<p>WORKUP</p> <ul style="list-style-type: none"> • History and physical exam • 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 • Breast MRI^d (optional), with special consideration for mammographically occult tumors • Counseling for fertility concerns if premenopausal^e • Assess for distress^f <p>For clinical stage I-IIB, consider additional studies only if directed by signs or symptoms:^g</p> <ul style="list-style-type: none"> • Complete blood count (CBC) • Comprehensive metabolic panel, including liver function tests and alkaline phosphatase • Bone scan indicated if localized bone pain or elevated alkaline phosphatase • Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis • Chest diagnostic CT with contrast (if pulmonary symptoms present) <p>If clinical stage IIIA (T3, N1, M0) consider:</p> <ul style="list-style-type: none"> • CBC • Comprehensive metabolic panel, including liver function tests and alkaline phosphatase • Chest diagnostic CT with contrast • Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast • Bone scan or sodium fluoride PET/CT^h (category 2B) • FDG PET/CT^{i,j} (optional) 	
If considering preoperative systemic therapy for Stage II and III	<p>See Preoperative Systemic Therapy for Operable Breast Cancer: Workup (BINV-10)</p> <p>or</p> <p>See Preoperative Systemic Therapy for Inoperable or Locally Advanced Breast Cancer (Non-Inflammatory): Workup (BINV-14)</p>	

^aThe panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. <http://www.cap.org>.

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

^c[See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#).

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

^e[See Fertility and Birth Control \(BINV-C\)](#).

^f[See NCCN Guidelines for Distress Management](#).

^gRoutine systemic staging is not indicated for early breast cancer in the absence of symptoms.

^hIf FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed.

ⁱFDG PET/CT can be performed at the same time as diagnostic CT. The use of PET or PET/CT is not indicated in the staging of clinical stage I, II, or operable stage III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.

^jFDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.

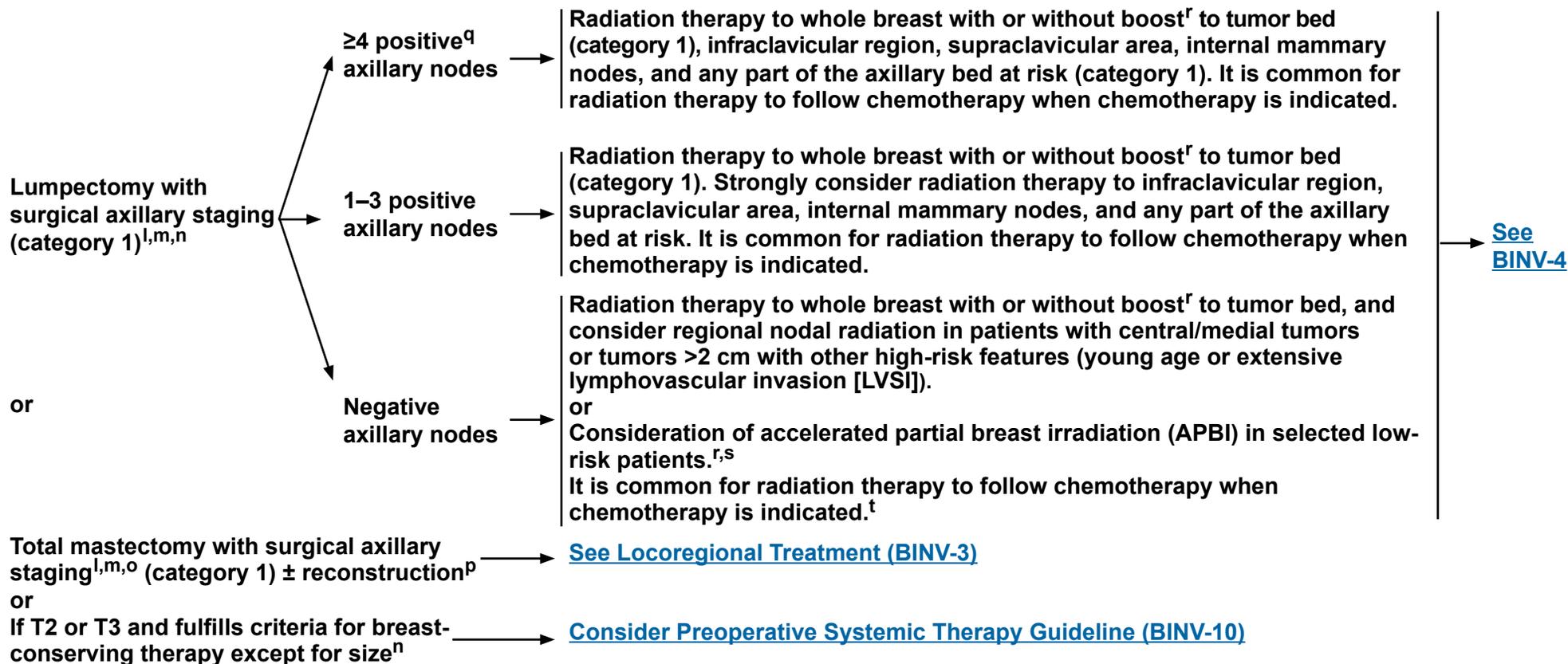
^k[See NCCN Guidelines for Older Adult Oncology](#) for special treatment considerations.

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

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



LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0^k



^kSee [NCCN Guidelines for Older Adult Oncology](#) for special treatment considerations.

^lSee [Surgical Axillary Staging \(BINV-D\)](#).

^mSee [Axillary Lymph Node Staging \(BINV-E\)](#) and [Margin Status in Infiltrating Carcinoma \(BINV-F\)](#).

ⁿSee [Special Considerations to Breast-Conserving Therapy Requiring Radiation Therapy \(BINV-G\)](#).

^oExcept as outlined in the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#) and the [NCCN Guidelines for Breast Cancer Risk Reduction](#), prophylactic mastectomy of a breast contralateral to a known unilateral breast cancer is discouraged. When considered, the small benefits from contralateral prophylactic mastectomy for women with unilateral breast cancer must be balanced with the risk of recurrent disease from the known ipsilateral breast cancer,

psychological and social issues of bilateral mastectomy, and the risks of contralateral mastectomy. The use of a prophylactic mastectomy contralateral to a breast treated with breast-conserving therapy is very strongly discouraged.

^pSee [Principles of Breast Reconstruction Following Surgery \(BINV-H\)](#).

^qConsider imaging for systemic staging, including chest/abdominal ± pelvic diagnostic CT with contrast, bone scan, and optional FDG PET/CT ([See BINV-1](#)).

^rSee [Principles of Radiation Therapy \(BINV-I\)](#).

^sPBI may be administered prior to chemotherapy.

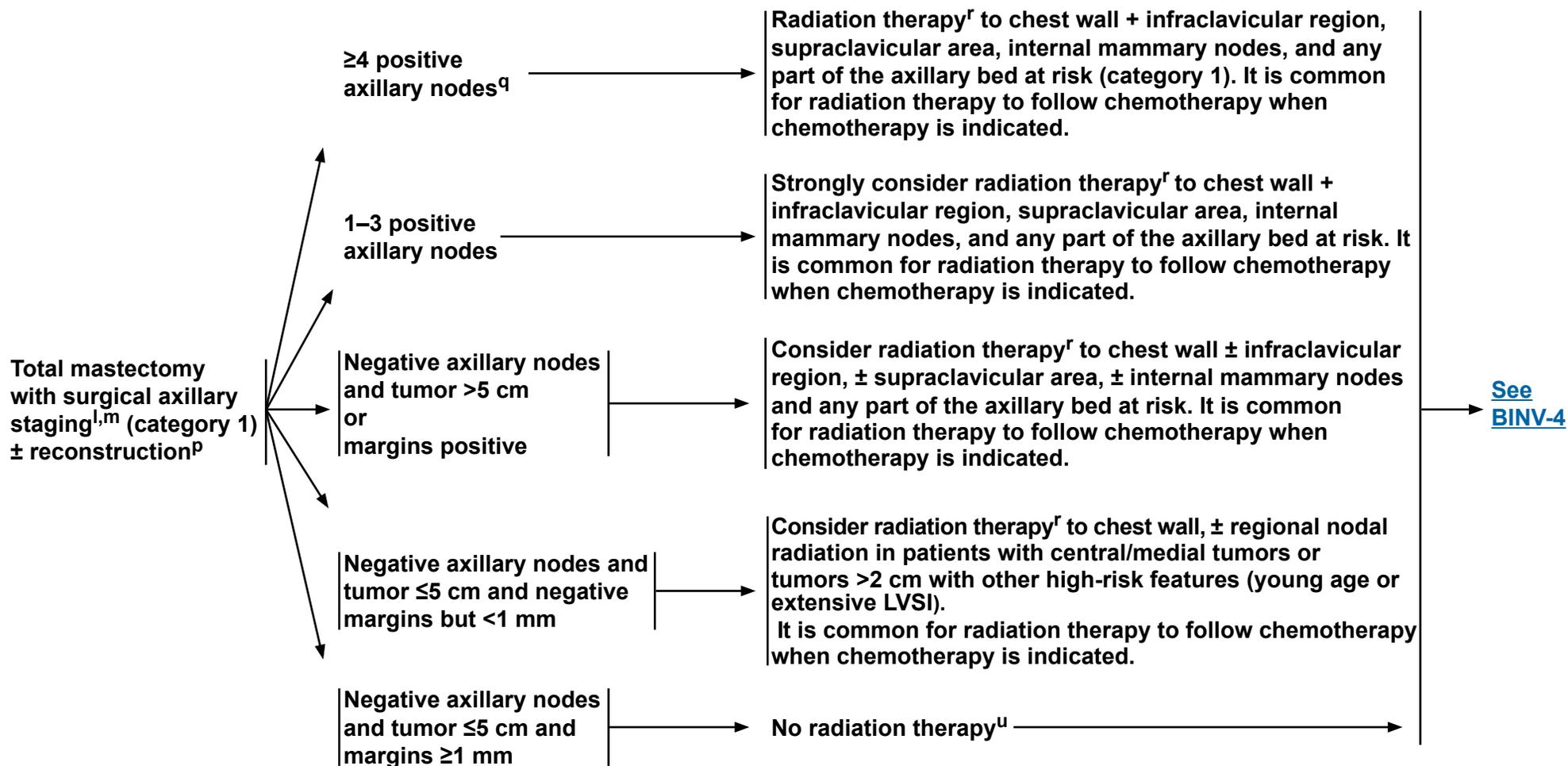
^tBreast irradiation may be omitted in patients ≥70 y of age with estrogen-receptor positive, clinically node-negative, T1 tumors who receive adjuvant endocrine therapy (category 1).

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

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



LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0^k



^kSee [NCCN Guidelines for Older Adult Oncology](#) for special treatment considerations.

^lSee [Surgical Axillary Staging \(BINV-D\)](#).

^mSee [Axillary Lymph Node Staging \(BINV-E\)](#) and [Margin Status in Infiltrating Carcinoma \(BINV-F\)](#).

^pSee [Principles of Breast Reconstruction Following Surgery \(BINV-H\)](#).

^qConsider imaging for systemic staging, including chest/abdominal ± pelvic diagnostic CT with contrast, bone scan, and optional FDG PET/CT ([See BINV-1](#)).

^rSee [Principles of Radiation Therapy \(BINV-I\)](#).

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

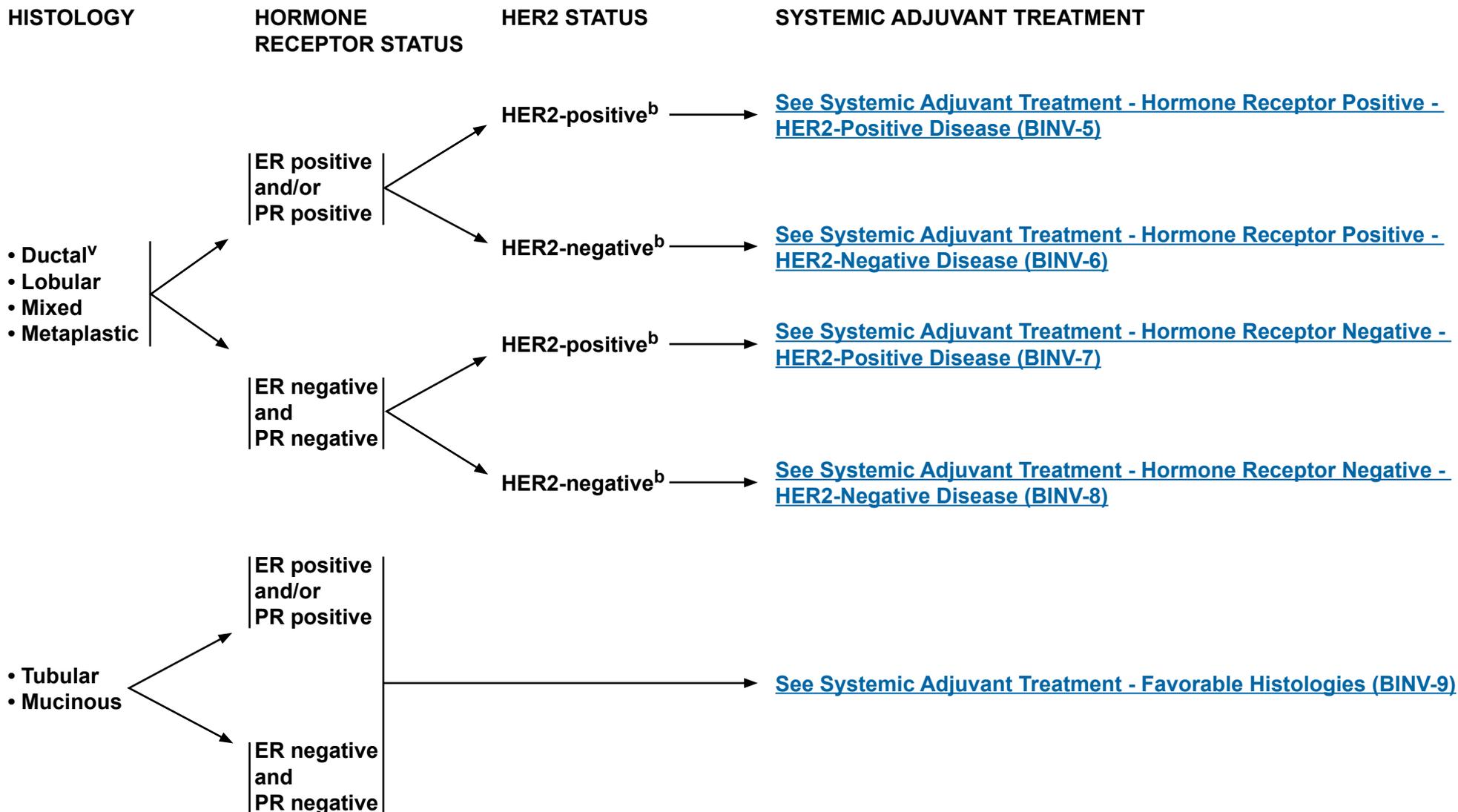
Note: All recommendations are category 2A unless otherwise indicated.

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



NCCN Guidelines Version 2.2017

Invasive Breast Cancer



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

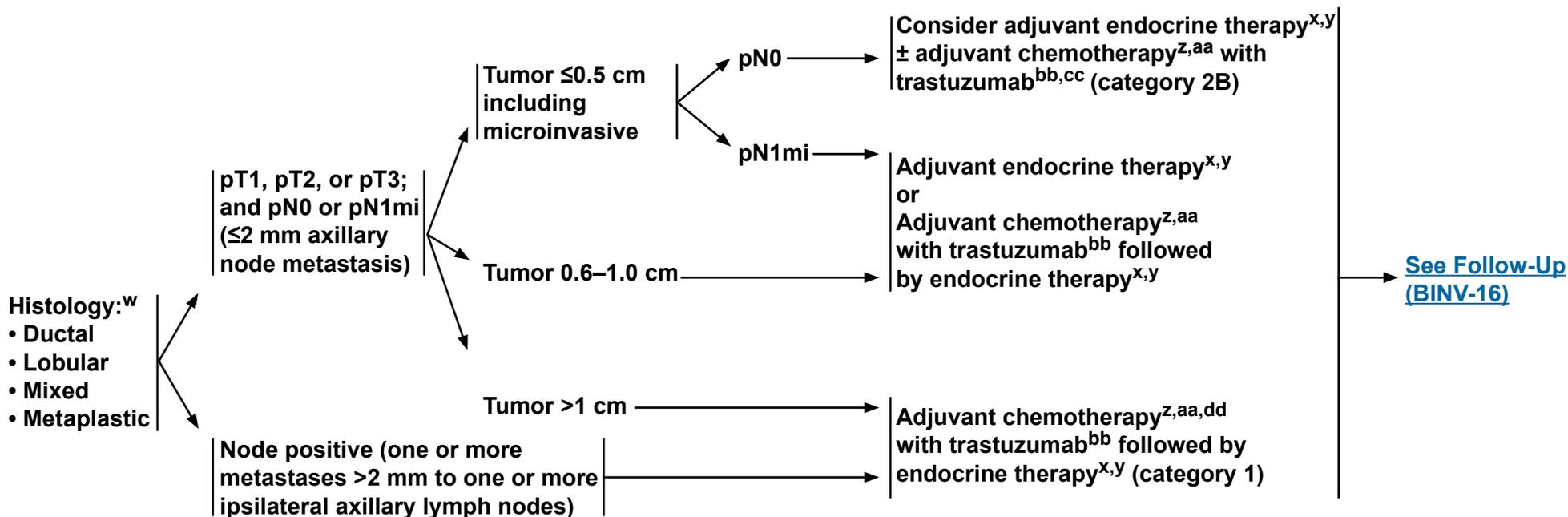
^vThis includes medullary and micropapillary subtypes.

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

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



SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-POSITIVE DISEASE^b



^bSee Principles of HER2 Testing (BINV-A).

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

^xConsider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant endocrine therapy.

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

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

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

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

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

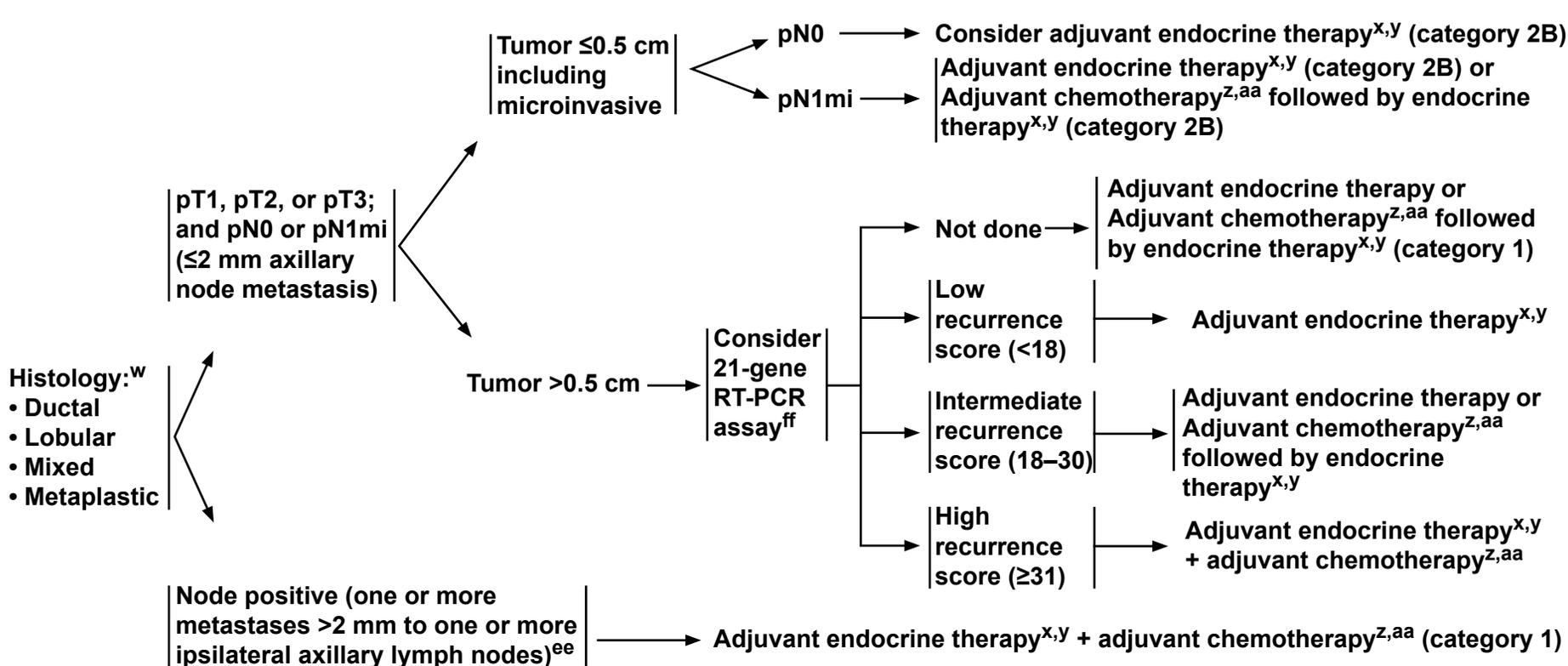
^{dd}A pertuzumab-containing regimen can be administered to patients with ≥T2 or ≥N1, HER2-positive, early-stage breast cancer.

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

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



SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-NEGATIVE DISEASE^b



See
Follow-Up
(BINV-16)

^bSee Principles of HER2 Testing (BINV-A).

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

^xConsider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant endocrine therapy.

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

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

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

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

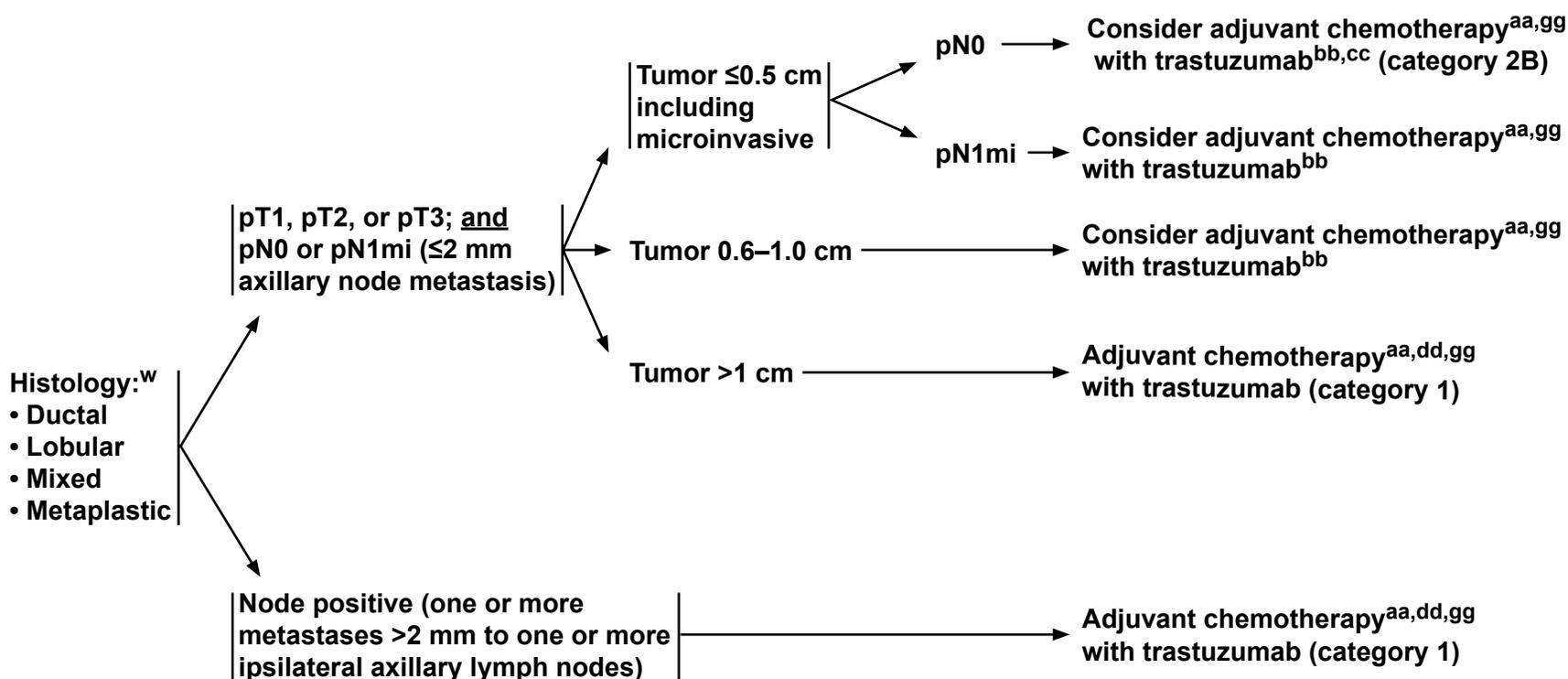
^{ff}Other prognostic multigene assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy.

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

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



SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-NEGATIVE - HER2-POSITIVE DISEASE^b



[See
Follow-Up
\(BINV-16\)](#)

^bSee Principles of HER2 Testing (BINV-A).

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

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

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

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

^{dd}A pertuzumab-containing regimen can be administered to patients with ≥T2 or ≥N1, HER2-positive, early-stage breast cancer.

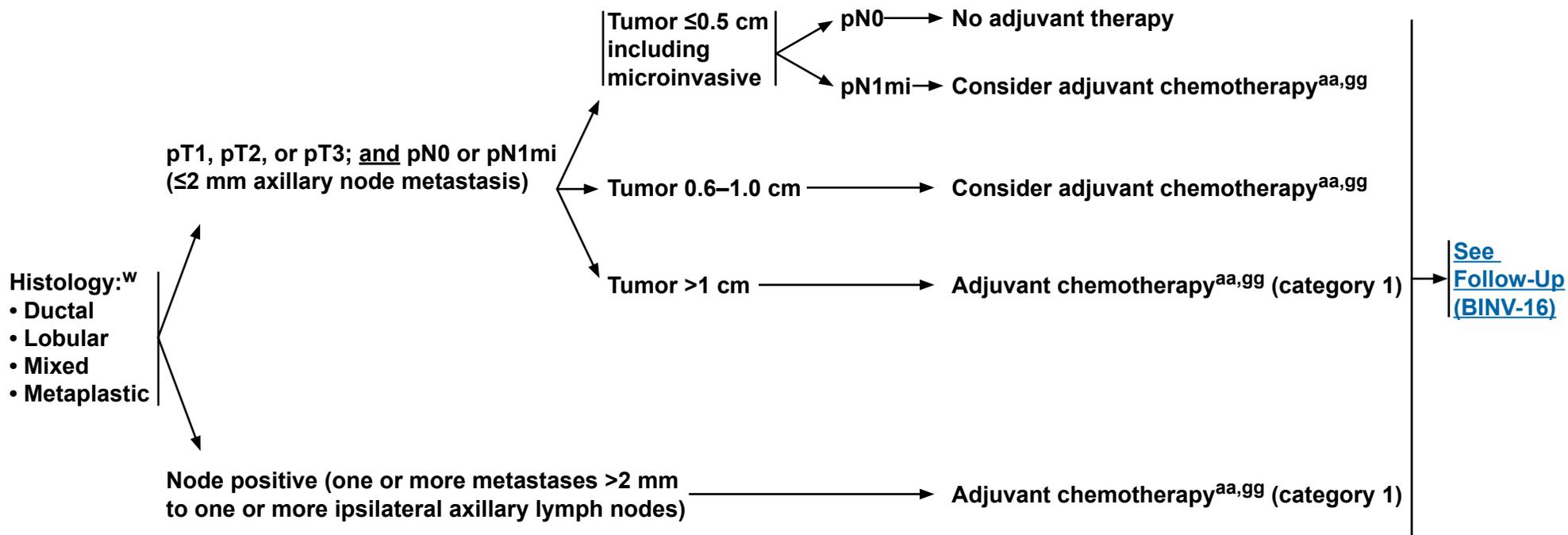
^{gg}See Preoperative/Adjuvant Therapy Regimens (BINV-K).

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

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



SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-NEGATIVE - HER2-NEGATIVE DISEASE^b



^bSee Principles of HER2 Testing (BINV-A).

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

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

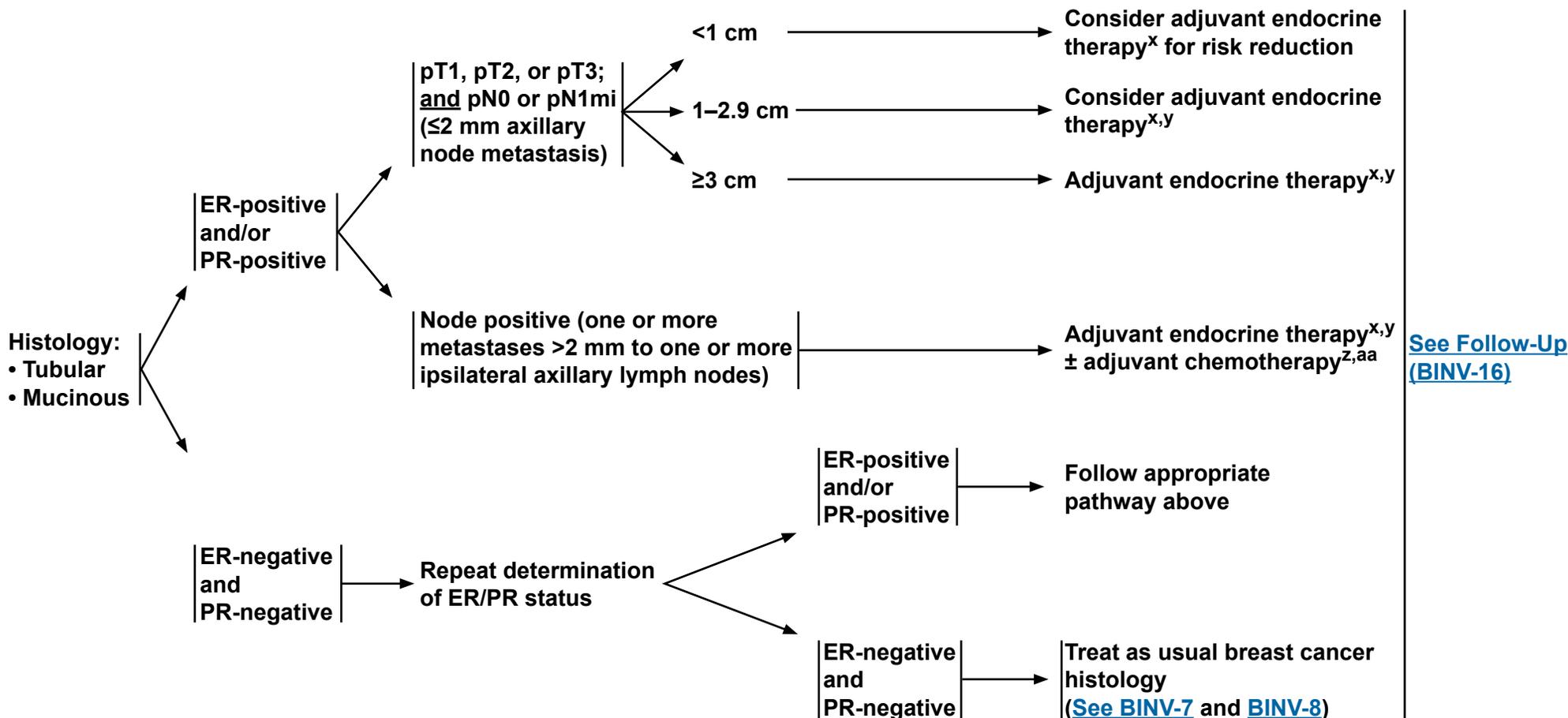
^{gg}See Preoperative/Adjuvant Therapy Regimens (BINV-K).

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

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



SYSTEMIC ADJUVANT TREATMENT - FAVORABLE HISTOLOGIES



^xConsider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant endocrine therapy.

^yEvidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. [See Adjuvant Endocrine Therapy \(BINV-J\)](#).

^zChemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data

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

^{aa}There are limited data to make chemotherapy recommendations for those >70 y of age. [See NCCN Clinical Practice Guidelines for Older Adult Oncology](#).

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

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



PREOPERATIVE SYSTEMIC THERAPY FOR OPERABLE BREAST CANCER: WORKUP

CLINICAL STAGE

WORKUP

Stage IIA
T2, N0, M0

Stage IIB
T2, N1, M0
T3, N0, M0

Stage IIIA
T3, N1, M0

and

Fulfills criteria for breast-conserving surgery except for tumor size^{hh}

- History and physical exam
 - Diagnostic bilateral mammogram; ultrasound as necessary
 - Pathology review^a
 - Determination of tumor ER/PR status and HER2 status^b
 - Genetic counseling if patient is high risk for hereditary breast cancer^c
 - Breast MRI^d (optional), with special consideration for mammographically occult tumors
 - Fertility counseling if premenopausal^e
 - Assess for distress^f
- Additional studies consider:^g
- CBC
 - Comprehensive metabolic panel, including liver function tests and alkaline phosphatase
 - Chest diagnostic CT with contrast
 - Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast
 - Bone scan or sodium fluoride PET/CT^h (category 2B)
 - FDG PET/CT^{i,j} (optional)

[See Preoperative Systemic Therapy: Breast and Axillary Evaluation \(BINV-11\)](#)

^aThe panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. <http://www.cap.org>.

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

^c[See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#).

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

^e[See Fertility and Birth Control \(BINV-C\)](#).

^f[See NCCN Guidelines for Distress Management](#).

^gRoutine systemic staging is not indicated for early breast cancer in the absence of symptoms.

^hIf FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed.

ⁱFDG PET/CT can be performed at the same time as diagnostic CT.

The use of PET or PET/CT is not indicated in the staging of clinical stage I, II, or operable III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.

^jFDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.

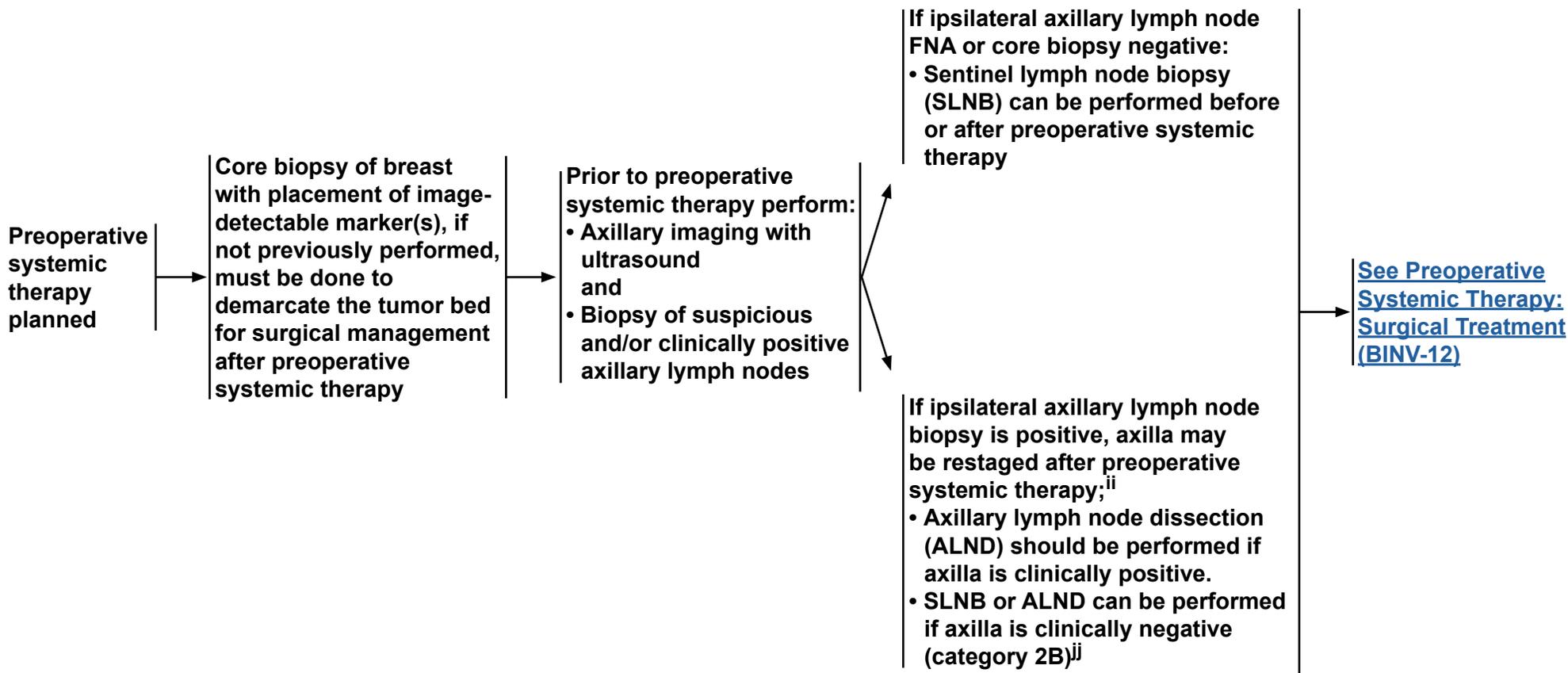
^{hh}In cases where breast-conserving surgery may not be possible but patient will need chemotherapy, preoperative systemic treatment remains an acceptable option.

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

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



PREOPERATIVE SYSTEMIC THERAPY: BREAST AND AXILLARY EVALUATION



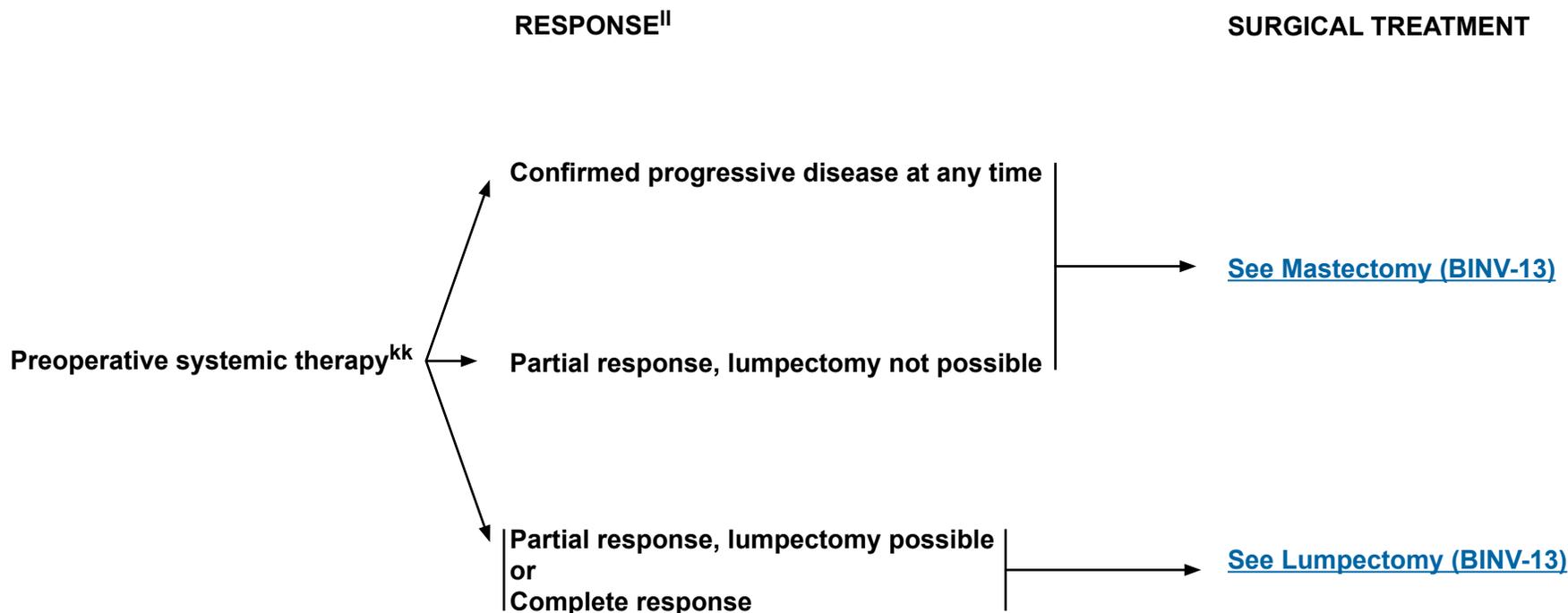
ⁱⁱMarking of sampled axillary nodes with a tattoo or clip should be considered to permit verification that the biopsy-positive lymph node has been removed at the time of definitive surgery.

^{jj}Among patients shown to be node-positive prior to preoperative systemic therapy, SLNB has a >10% false-negative rate when performed after preoperative systemic therapy. This rate can be improved by marking biopsied lymph nodes to document their removal, using dual tracer, and by removing more than 2 sentinel nodes.

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



PREOPERATIVE SYSTEMIC THERAPY: SURGICAL TREATMENT



^{ll}The accurate assessment of in-breast tumor or regional lymph node response to preoperative systemic therapy is difficult, and should include physical examination and performance of imaging studies (mammogram and/or breast MRI) that were abnormal at the time of initial tumor staging. Selection of imaging methods prior to surgery should be determined by the multidisciplinary team.

^{kk}[See Principles of Preoperative Systemic Therapy \(BINV-L\).](#)

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

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



PREOPERATIVE SYSTEMIC THERAPY: ADJUVANT THERAPY

SURGICAL TREATMENT

Mastectomy and surgical axillary staging^{l,mm} ± reconstruction.^p
If SLNB performed prechemotherapy and negative findings, omit axillary lymph node staging.
[See BINV-11](#)

Lumpectomy with surgical axillary staging.^{l,mm}
If SLNB performed prechemotherapy and negative findings, omit axillary lymph node staging.
[See BINV-11](#)

ADJUVANT TREATMENT

- Complete planned chemotherapy regimen course if not completed preoperatively.
- Adjuvant radiation therapy^r post-mastectomy is based on maximal disease stage from pre-chemotherapy tumor characteristics at diagnosis and post-chemotherapy pathology results. Adjuvant radiation therapy is recommended:
 - ▶ As indicated on [BINV-3](#)
 - ▶ For cT3-4, cN2-3, stage III, residual disease >2 cm any ypN+ and
- Endocrine therapy if ER-positive and/or PR-positive^z (category 1)
- Complete up to one year of trastuzumab therapy if HER2-positive (category 1). May be administered concurrently with radiation therapy^r and with endocrine therapy if indicated.

- Complete planned chemotherapy regimen course if not completed preoperatively.
- Adjuvant radiation therapy^r post-lumpectomy is based on maximal disease stage from pre-chemotherapy tumor characteristics at diagnosis and post-chemotherapy pathology results. Adjuvant radiation therapy is recommended:
 - ▶ As indicated on [BINV-2](#)
 - ▶ For cT3-4, cN2-3, stage III, residual disease >2 cm any ypN+ and
- Endocrine therapy if ER-positive and/or PR-positive^z (category 1)
- Complete up to one year of trastuzumab therapy if HER2-positive (category 1). May be administered concurrently with radiation therapy^r and with endocrine therapy if indicated.

[See Surveillance/ Follow-up \(BINV-16\)](#)

^lSee [Surgical Axillary Staging \(BINV-D\)](#).

^pSee [Principles of Breast Reconstruction Following Surgery \(BINV-H\)](#).

^rSee [Principles of Radiation Therapy \(BINV-I\)](#).

^zChemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See [Adjuvant Endocrine Therapy \(BINV-J\)](#) and [Preoperative/Adjuvant Therapy Regimens \(BINV-K\)](#).

^{mm}Axilla may be restaged after preoperative systemic therapy; ALND should be performed if axilla is clinically positive; SLNB or ALND can be performed if axilla is clinically negative (category 2B). Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol* 2013;14(7):609-18. Epub 2013/05/21. Boughhey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA* 2013;310(14):1455-61. Epub 2013/10/09.

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

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



PREOPERATIVE SYSTEMIC THERAPY FOR INOPERABLE OR LOCALLY ADVANCED BREAST CANCER (NON-INFLAMMATORY): WORKUP

CLINICAL STAGE	WORKUP
Stage IIIA T0, N2, M0 T1, N2, M0 T2, N2, M0 T3, N2, M0 Stage IIIA patients with T3, N1, M0 disease, see BINV-1	<ul style="list-style-type: none"> • History and physical exam • Diagnostic bilateral mammogram; ultrasound as necessary • Pathology review^a • Determination of tumor ER/PR status and HER2 status^b • Genetic counseling if patient is high risk for hereditary breast cancer^c • Breast MRI^d (optional), with special consideration for mammographically occult tumors • Fertility counseling if premenopausal^e • Assess for distress^f <p>Additional studies consider:</p> <ul style="list-style-type: none"> • CBC • Comprehensive metabolic panel, including liver function tests and alkaline phosphatase • Chest diagnostic CT with contrast • Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast • Bone scan or sodium fluoride PET/CT^h (category 2B) • FDG PET/CT^{i,j} (optional)
Stage IIIB T4, N0, M0 T4, N1, M0 T4, N2, M0	
Stage IIIC Any T, N3, M0	

[See Preoperative Systemic Therapy For Inoperable or Locally Advanced Breast Cancer \(Non-Inflammatory\) \(BINV-15\)](#)

^aThe panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. <http://www.cap.org>.

^bSee [Principles of HER2 Testing \(BINV-A\)](#).

^cSee [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#).

^dSee [Principles of Dedicated Breast MRI Testing \(BINV-B\)](#).

^eSee [Fertility and Birth Control \(BINV-C\)](#).

^fSee [NCCN Guidelines for Distress Management](#).

^hIf FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed.

ⁱFDG PET/CT can be performed at the same time as diagnostic CT. The use of PET or PET/CT is not indicated in the staging of clinical stage I, II, or operable III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.

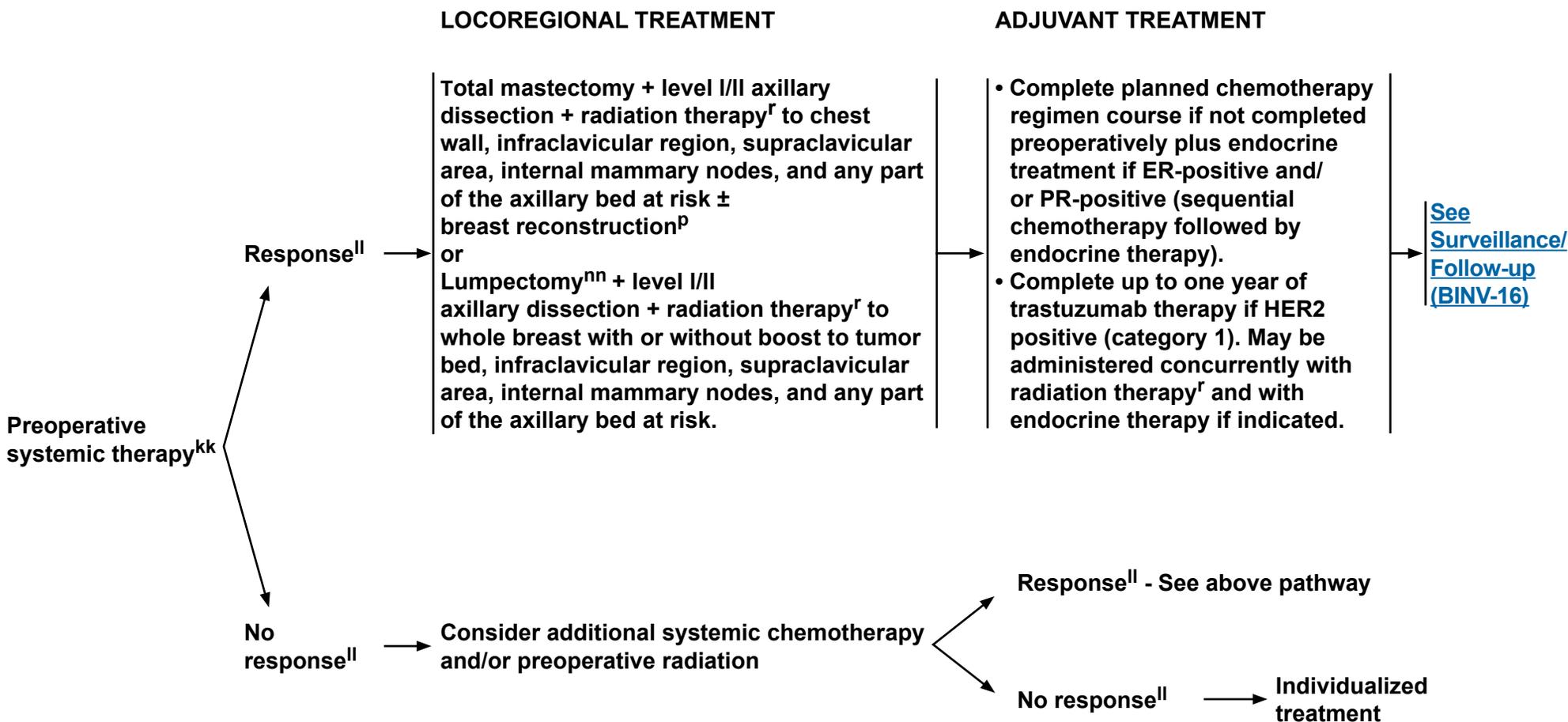
^jFDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.

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

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



PREOPERATIVE SYSTEMIC THERAPY FOR INOPERABLE OR LOCALLY ADVANCED BREAST CANCER (NON-INFLAMMATORY)



^pSee Principles of Breast Reconstruction Following Surgery (BINV-H).

^rSee Principles of Radiation Therapy (BINV-I).

^{kk}See Principles of Preoperative Systemic Therapy (BINV-L).

^{ll}The accurate assessment of in-breast tumor or regional lymph node response to preoperative systemic therapy is difficult, and should include physical examination and performance of imaging studies (mammogram and/or breast MRI) that were abnormal at the time of initial tumor staging. Selection of imaging methods prior to surgery should be determined by the multidisciplinary team.

ⁿⁿFor patients with skin and/or chest wall involvement (T4 non-inflammatory) prior to preoperative systemic therapy, breast conservation may be performed in carefully selected patients based on a multidisciplinary assessment of local recurrence risk. In addition to standard contraindications to breast conservation (see BINV-G), exclusion criteria for breast conservation include: inflammatory (T4d) disease before preoperative systemic therapy and incomplete resolution of skin involvement after preoperative systemic therapy.

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

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

**SURVEILLANCE/FOLLOW-UP**

- History and physical exam 1–4 times per year as clinically appropriate for 5 y, then annually
- Periodic screening for changes in family history and referral to genetic counseling as indicated, [see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#)
- Educate, monitor, and refer for lymphedema management
- Mammography every 12 mo^{oo}
- Routine imaging of reconstructed breast is not indicated
- In the absence of clinical signs and symptoms suggestive of recurrent disease, there is no indication for laboratory or imaging studies for metastases screening
- 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^{pp}
- Assess and encourage adherence to adjuvant endocrine therapy
- Evidence suggests that active lifestyle, healthy diet, limited alcohol intake, and achieving and maintaining an ideal body weight (20–25 BMI) may lead to optimal breast cancer outcomes
- [See NCCN Guidelines for Survivorship](#)

[See Recurrent Disease \(BINV-17\)](#)

^{oo}Studies indicate that annual mammograms are the appropriate frequency for surveillance of breast cancer patients who have had breast-conserving surgery and radiation therapy with no clear advantage to shorter interval imaging. Patients should wait 6 to 12 months after the completion of radiation therapy to begin their annual mammogram surveillance. Suspicious findings on physical examination or surveillance imaging might warrant a shorter interval between mammograms.

^{pp}The use of estrogen, progesterone, or selective estrogen receptor modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. The use of a bisphosphonate (oral/IV) or denosumab is acceptable to maintain or to improve bone mineral density and reduce risk of fractures in postmenopausal (natural or induced) patients receiving adjuvant endocrine therapy. Optimal duration of either therapy has not been established. Duration beyond 3 y is not known. Factors to consider for duration of anti-osteoporosis therapy include bone mineral density, response to therapy, and risk factors for continued bone loss or fracture. Women treated with a bisphosphonate or denosumab should undergo a dental examination with preventive dentistry prior to the initiation of therapy, and should take supplemental calcium and vitamin D.

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

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



RECURRENT/STAGE IV DISEASE

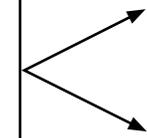
CLINICAL STAGE

WORKUP

Recurrent or
Stage IV disease



- History and physical exam
- CBC
- Comprehensive metabolic panel, including liver function tests and alkaline phosphatase
- Chest diagnostic CT with contrast
- Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast
- Brain MRI with contrast if suspicious CNS symptoms
- Spine MRI with contrast if back pain or symptoms of cord compression
- Bone scan or sodium fluoride PET/CT^h (category 2B)
- FDG PET/CT^{j,qq} (optional)
- X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan
- First recurrence of disease should be biopsied
- Determination of tumor ER/PR and HER2 status on metastatic site^{b,rr,ss}
- Genetic counseling if patient is high risk for hereditary breast cancer^c



[See Treatment of Recurrence \(BINV-18\)](#)

[See Treatment of Stage IV Disease \(BINV-19\)](#)

^bSee Principles of HER2 Testing (BINV-A).

^cSee NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

^hIf FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed. ^jFDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.

^{qq}FDG PET/CT can be performed at the same time as diagnostic CT. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.

^{rr}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 may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).

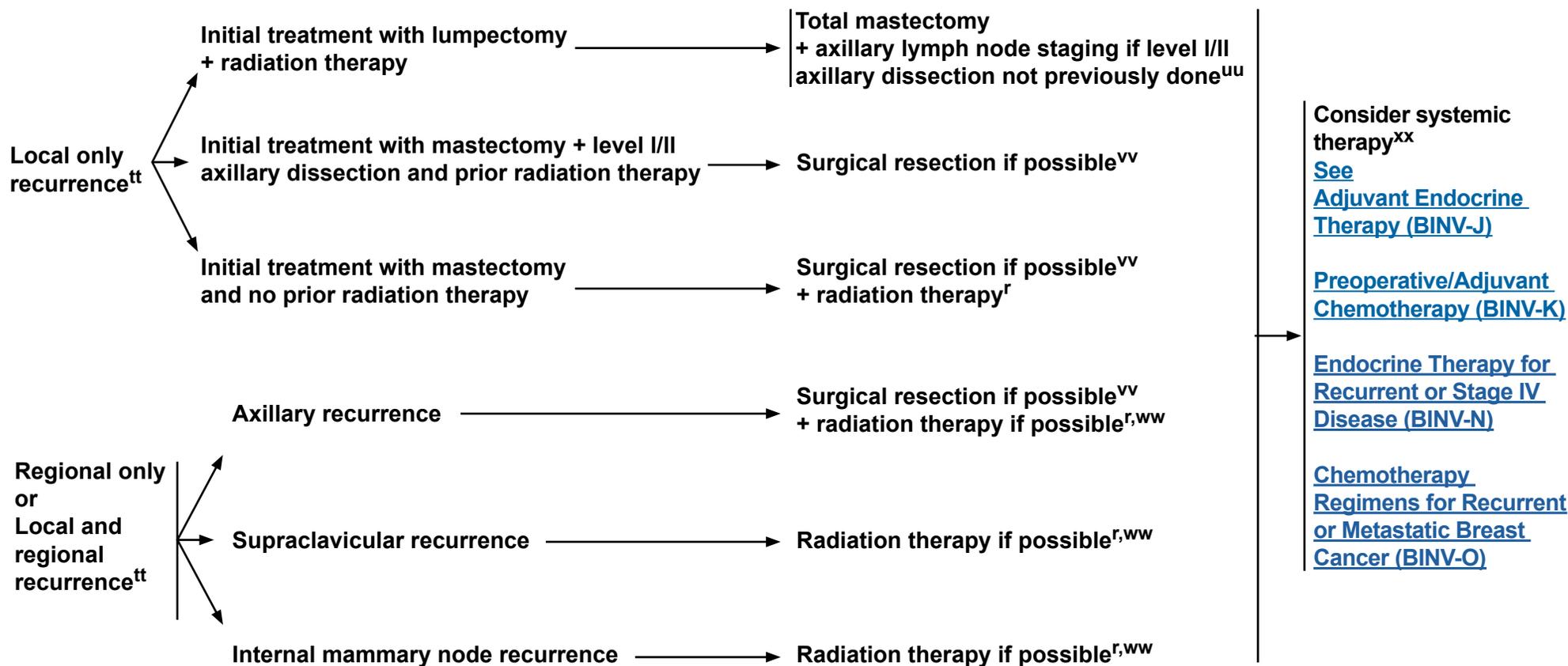
^{ss}In clinical situations where a biopsy cannot safely be obtained but the clinical evidence is strongly supportive of recurrence, treatment may commence based on the ER/PR/HER2 status of the primary tumor.

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

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



TREATMENT OF RECURRENCE



^r[See Principles of Radiation Therapy \(BINV-I\).](#)

^{tt}Multidisciplinary approach is especially important in the management of breast cancer recurrence to consider all potential treatment options for optimal outcomes.
^{uu}In women with a local breast recurrence after breast-conserving surgery who had a prior sentinel node biopsy (SNB), 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 is discouraged.

^{vv}If not technically resectable, consider systemic therapy to best response, then resect if possible.

^{ww}The decision to use radiation therapy to treat locoregional recurrence must factor in any prior radiation to the area and the risk of late normal tissue toxicity from the sum of the prior and planned radiation courses.

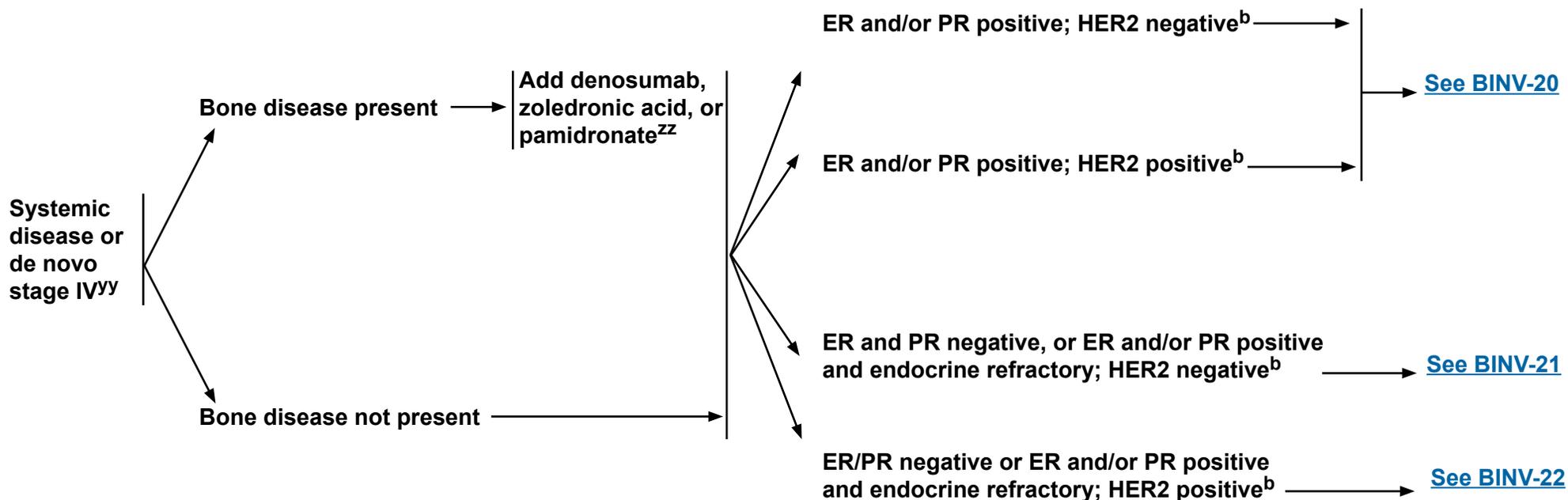
^{xx}For additional information see the [Discussion section](#).

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

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



TREATMENT OF STAGE IV DISEASE



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

^{yy}The role and timing of surgical removal of the primary in patients presenting with de novo stage IV disease is the subject of ongoing investigations.

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

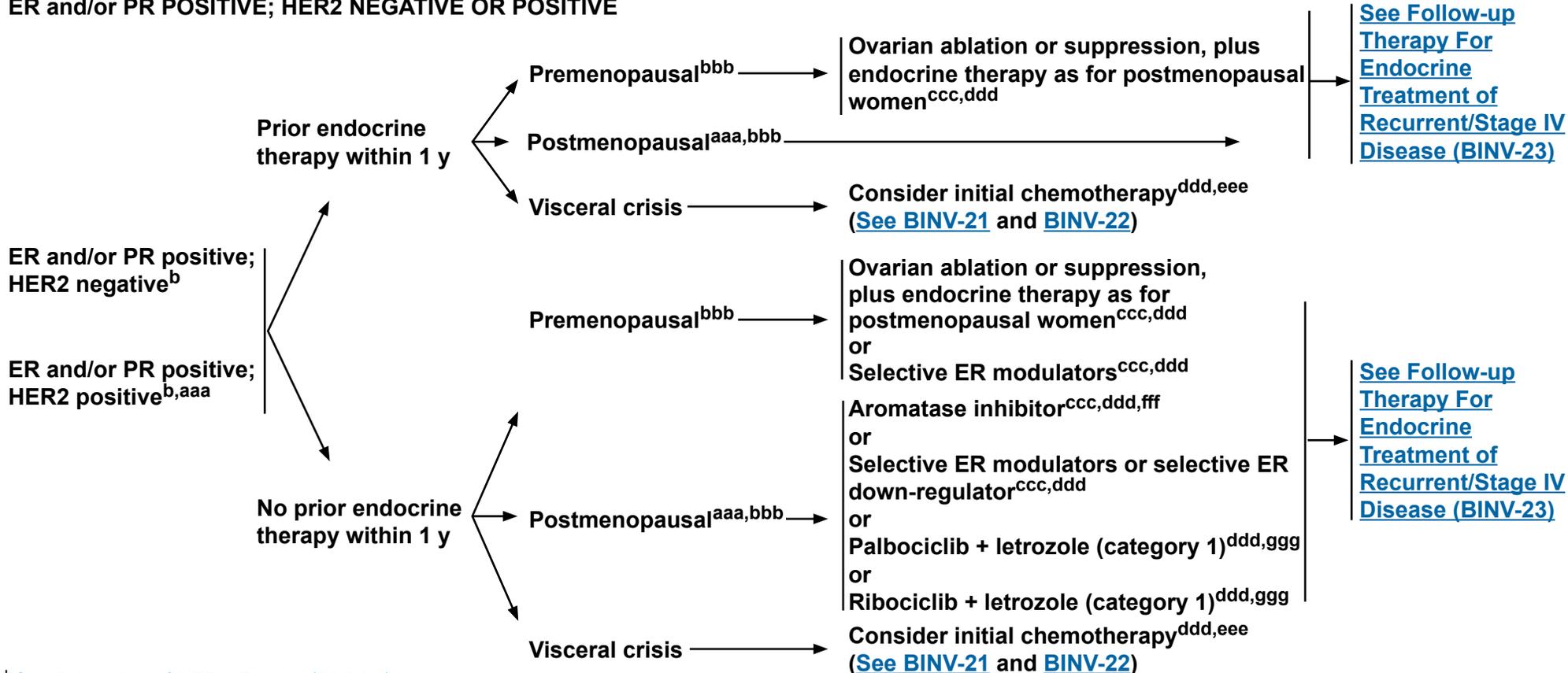
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2017

Invasive Breast Cancer

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE ER and/or PR POSITIVE; HER2 NEGATIVE OR POSITIVE



^bSee Principles of HER2 Testing (BINV-A).

^{aaa}Limited studies document a progression-free survival advantage of adding trastuzumab or lapatinib to aromatase inhibition in postmenopausal patients with ER-positive, HER2-positive disease. However, no overall survival advantage has been demonstrated.

^{bbb}See Definition of Menopause (BINV-M).

^{ccc}See Endocrine Therapy for Recurrent or Stage IV Disease (BINV-N).

^{ddd}It is unclear that women presenting at time of initial diagnosis with an intact primary and metastatic disease will benefit from the performance of palliative local breast surgery and/or radiation therapy. Generally this palliative local therapy should only be considered after response to initial systemic therapy.

^{eee}See Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-O).

^{fff}A single study (S0226) in women with hormone receptor-positive breast cancer and no prior chemotherapy, biological therapy, or endocrine therapy for metastatic disease demonstrated that the addition of fulvestrant to anastrozole resulted in prolongation of time to progression. Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. Two studies with similar design (FACT and SOFEA) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole.

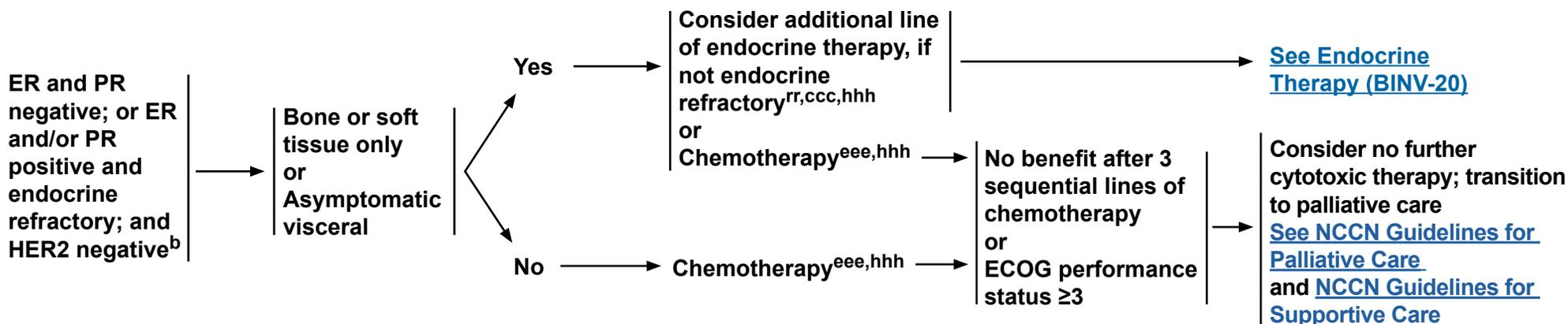
^{ggg}Palbociclib or ribociclib in combination with letrozole may be considered in HER2-negative, metastatic breast cancer.

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

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



SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE
ER and PR NEGATIVE; or ER and/or PR POSITIVE and ENDOCRINE REFRACTORY; HER2 NEGATIVE



^bSee [Principles of HER2 Testing \(BINV-A\)](#).

^{rr}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 may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).

^{ccc}See [Endocrine Therapy for Recurrent or Stage IV Disease \(BINV-N\)](#).

^{eee}See [Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer \(BINV-O\)](#).

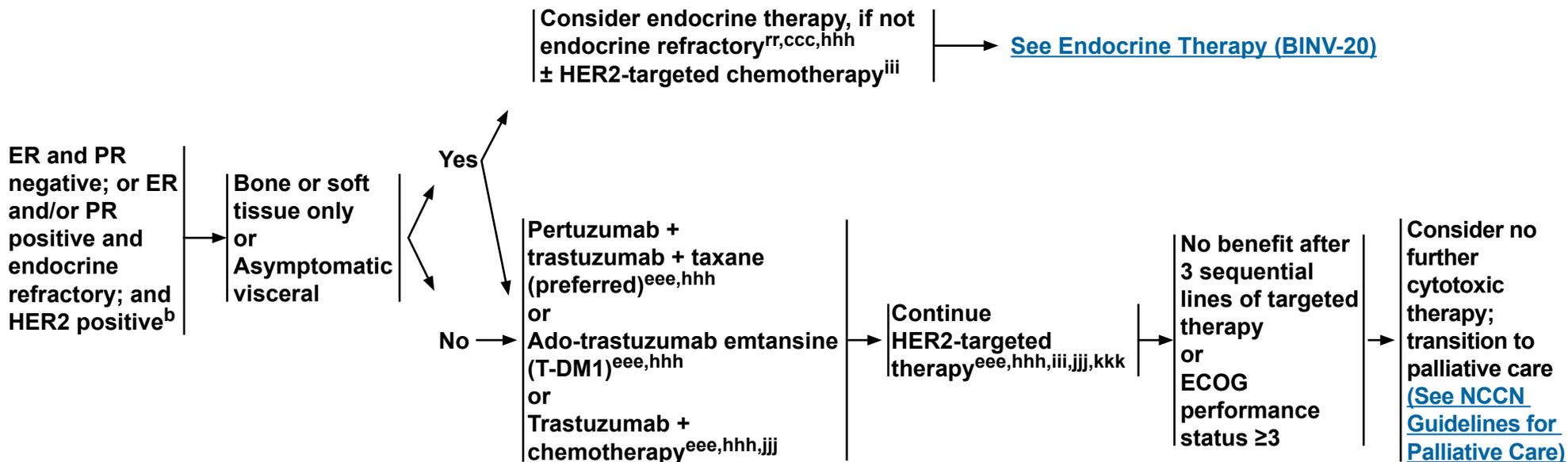
^{hhh}See [Principles of Monitoring Metastatic Disease \(BINV-P\)](#).

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

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



SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV DISEASE ER and PR NEGATIVE; or ER and/or PR POSITIVE and ENDOCRINE REFRACTORY; and HER2 POSITIVE



^bSee Principles of HER2 Testing (BINV-A).

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

^{ccc}See Endocrine Therapy for Recurrent or Stage IV Disease (BINV-N).

^{eee}See Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-O).

^{hhh}See Principles of Monitoring Metastatic Disease (BINV-P).

ⁱⁱⁱContinue HER2-targeted therapy following progression on first-line HER2-targeted chemotherapy for metastatic breast cancer. The optimal duration of trastuzumab in patients with long-term control of disease is unknown.

^{jjj}Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

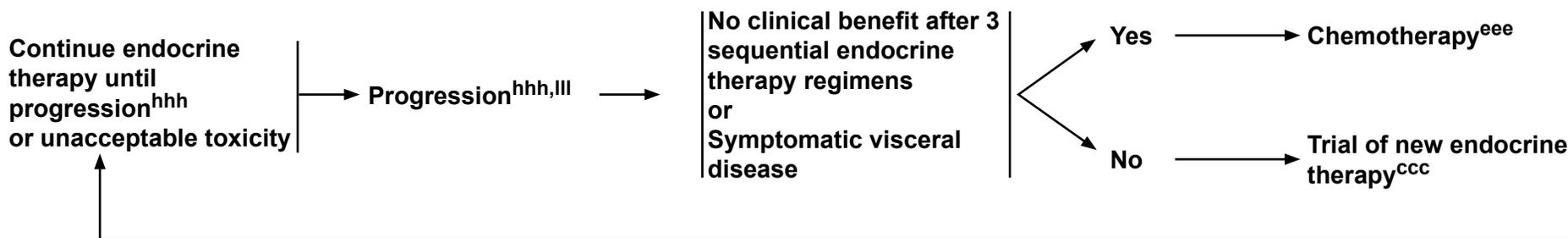
^{kkk}Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.

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

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



FOLLOW-UP THERAPY FOR ENDOCRINE TREATMENT OF RECURRENT OR STAGE IV DISEASE



^{ccc}See [Endocrine Therapy for Recurrent or Stage IV Disease \(BINV-N\)](#).

^{eee}See [Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer \(BINV-O\)](#).

^{hhh}See [Principles of Monitoring Metastatic Disease \(BINV-P\)](#).

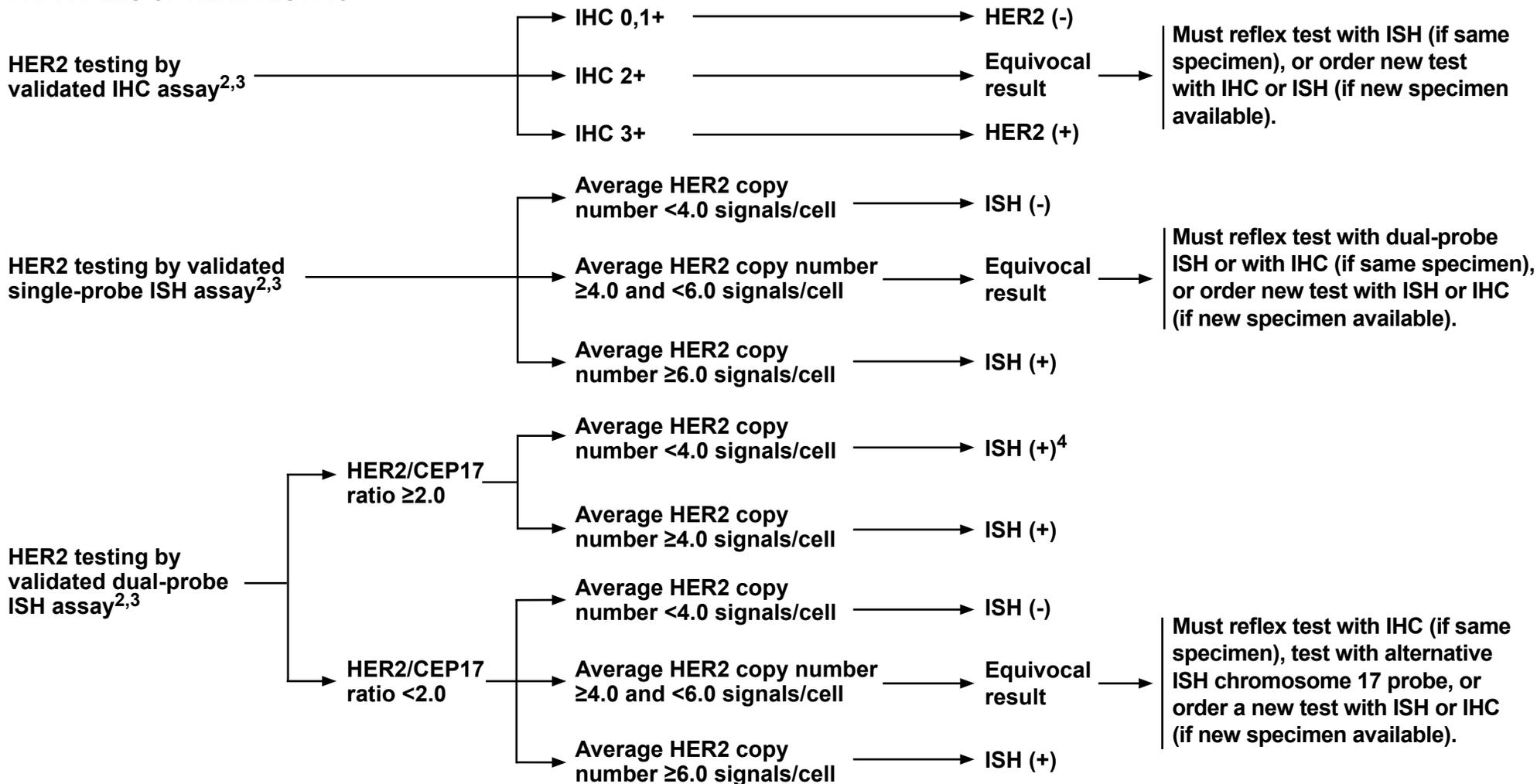
^{III}If there is disease progression while on a CDK4/6 inhibitor + letrozole, there are no data to support an additional line of therapy with another palbociclib regimen. Likewise, if there is disease progression while on exemestane + everolimus, there are no data to support an additional line of therapy with another everolimus regimen.

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

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



PRINCIPLES OF HER2 TESTING^{1,2}



¹NCCN Endorses the ASCO/CAP HER2 testing guideline. "Principles of HER2 Testing" modified with permission from Wolff AC, Hammond EH, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update. J Clin Oncol 2013;31:3997-4013.

²Laboratory must participate in a quality assurance accreditation program for HER2 testing. Otherwise, tissue specimen should be sent to an accredited laboratory for testing. Health care systems and providers must cooperate to ensure the highest quality testing.

³Evidence from trastuzumab adjuvant trials show that HER2 testing by ISH or IHC have similar utility to predict clinical benefit from HER2-targeted therapy.

⁴See ASCO/CAP HER2 Guideline Data Supplement 2E (available at http://www.asco.org/sites/www.asco.org/files/final_her2_testing_ds_10-3-13.pdf) for more information on these rare scenarios.

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

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



PRINCIPLES OF DEDICATED BREAST MRI TESTING

[See NCCN Guidelines for Breast Cancer Screening and Diagnosis](#) for indications for screening MRI in women at increased breast cancer risk.

Personnel, Facility, and Equipment

- Breast MRI examinations are performed with IV contrast and 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 image-guided 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 high-level data to demonstrate that the use of MRI to facilitate local therapy decision-making improves local recurrence or survival.¹
- May be helpful for breast cancer evaluation before and after preoperative systemic therapy to define extent of disease, response to treatment, and potential for breast-conserving therapy.
- May be useful for identifying primary cancer in women with axillary nodal adenocarcinoma and occult (or unidentified) primary cancer, with Paget's disease, or with invasive lobular carcinoma poorly (or inadequately) defined on mammography, ultrasound, or physical examination.
- False-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.
- The utility of MRI in follow-up screening of women with prior breast cancer is undefined. It should generally be considered only in those whose lifetime risk of a second primary breast cancer is greater than 20% based on models largely dependent on family history, such as in those with the risk associated with inherited susceptibility to breast cancer.

¹Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. *J Clin Oncol* 2008;26:3248-3258.

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

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



FERTILITY AND BIRTH CONTROL

[See NCCN Guidelines for Adolescent and Young Adult Oncology](#)

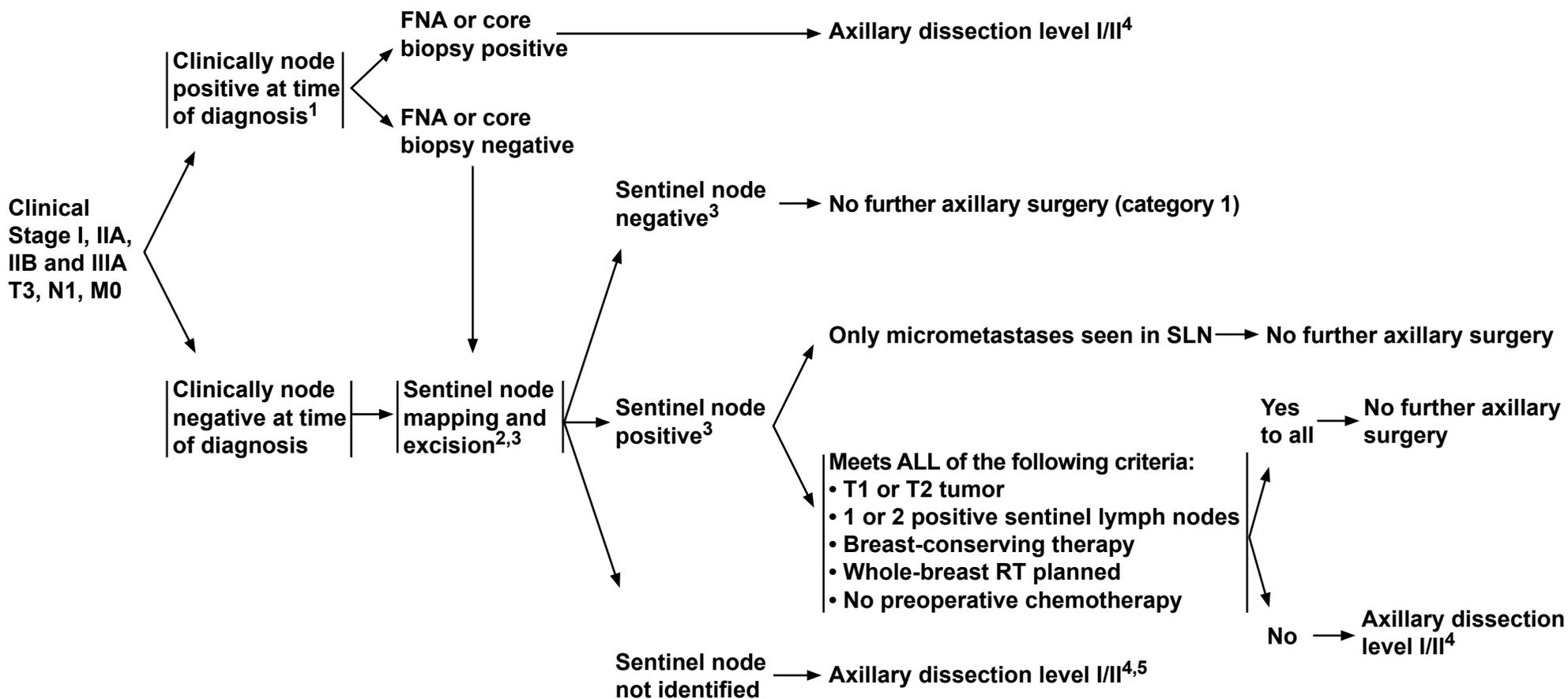
- **All premenopausal patients should be informed about the potential impact of chemotherapy on fertility and asked about their desire for potential future pregnancies. Patients who may desire future pregnancies should be referred to fertility specialists before chemotherapy and/or endocrine therapy to discuss the options based on patient specifics, disease stage, and biology (which determine the urgency and type and sequence of treatment). Timing and duration allowed for fertility preservation, options inclusive of oocyte and embryo cryopreservation as well as evolving technologies, and the probability of successful pregnancies subsequent to completion of breast cancer therapy are also to be discussed.**
- **Although amenorrhea frequently occurs during or after chemotherapy, it appears that the majority of women younger than 35 y resume menses within 2 y of finishing adjuvant chemotherapy.**
- **Menses and fertility are not necessarily linked. Absence of regular menses, particularly if the patient is taking tamoxifen, does not necessarily imply lack of fertility. Conversely, the presence of menses does not guarantee fertility. There are limited data regarding continued fertility after chemotherapy.**
- **Patients should not become pregnant during treatment with radiation therapy, chemotherapy, or endocrine therapy.**
- **Although data are limited, hormone-based birth control is discouraged regardless of the hormone receptor status of the patient's cancer.**
- **Alternative methods of birth control include intrauterine devices (IUDs), barrier methods, or, for patients with no intent of future pregnancies, tubal ligation or vasectomy for the partner.**
- **Randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with ER-negative tumors may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea.**
- **Breast feeding following breast-conserving cancer treatment is not contraindicated. However, the quantity and quality of breast milk produced by the breast conserved may not be sufficient or may be lacking some of the nutrients needed. Breast feeding during active treatment with chemotherapy and endocrine therapy is not recommended.**
- **Smaller historical experiences in patients with ER-positive disease have reported conflicting results with regard to the protective effect of GnRH agonist therapy on fertility.**

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

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



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



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

²Sentinel lymph node mapping injections may be peritumoral, subareolar, or subdermal.

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

⁴[See Axillary Lymph Node Staging \(BINV-E\).](#)

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

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

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



AXILLARY LYMPH NODE STAGING

SLNB should be performed and is the preferred method of axillary lymph node staging if the patient is an appropriate SLNB candidate ([See BINV-D](#)).

In the absence of definitive data demonstrating superior survival, the performance of axillary staging may be considered optional in patients who have particularly favorable tumors, patients for whom the selection of adjuvant systemic and/or radiation therapy is unlikely to be affected, the elderly, or those with serious comorbid conditions.

Level III dissection to the thoracic inlet should be performed only in cases with gross disease in level II and/or III.

In the absence of gross disease in level II nodes, lymph node dissection should include tissue inferior to the axillary vein from the latissimus dorsi muscle laterally to the medial border of the pectoralis minor muscle (level I/II).

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

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



MARGIN STATUS IN INFILTRATING CARCINOMA

The use of breast-conserving therapy is predicated on achieving a pathologically negative margin of resection. The NCCN Panel accepts the definition of a negative margin as "No ink on the tumor," from the 2014 Society of Surgical Oncology-American Society for Radiation Oncology Consensus Guidelines on Margins.¹ 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.

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 (EIC).² For these patients, the use of a higher radiation boost dose to the tumor bed should be considered. A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical doses are 10–16 Gy at 2 Gy/fx.

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

¹Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol 2014 May 10;32(14):1507-15.

²An 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.

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

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



SPECIAL CONSIDERATIONS TO BREAST-CONSERVING THERAPY REQUIRING RADIATION THERAPY

Contraindications for breast-conserving therapy requiring radiation therapy include:

Absolute:

- Radiation therapy during pregnancy
- Diffuse suspicious or malignant-appearing microcalcifications
- Widespread disease that cannot be incorporated by local excision of a single region or segment of breast tissue that achieves negative margins with a satisfactory cosmetic result
- Diffusely positive pathologic margins¹
- Homozygous for ATM mutation (category 2B)

Relative:

- Prior radiation therapy to the chest wall or breast; knowledge of doses and volumes prescribed is essential.
- Active connective tissue disease involving the skin (especially scleroderma and lupus)
- Tumors >5 cm (category 2B)
- Positive pathologic margin¹
- Women with a known or suspected genetic predisposition to breast cancer:
 - ▶ 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.
[\(See NCCN Guidelines for Genetic/Familial High-Risk Assessment Breast and Ovarian\).](#)
 - ▶ Li-Fraumeni syndrome (category 2B)

¹[See Margin Status in Infiltrating Carcinoma \(BINV-F\).](#)

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

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



PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

- Breast reconstruction may be an option for any woman receiving surgical treatment for breast cancer. All women undergoing breast cancer treatment should be educated about breast reconstructive options as adapted to their individual clinical situation. However, breast reconstruction should not interfere with the appropriate surgical management of the cancer or the scope of appropriate surgical treatment for this disease. Coordinating consultation and surgical treatment with a reconstructive surgeon should be executed within a reasonable time frame. The process of breast reconstruction should not govern the timing or the scope of appropriate surgical treatment for this disease. The availability of or the practicality of breast reconstruction should not result in the delay or refusal of appropriate surgical intervention.
- An evaluation of the likely cosmetic outcome of lumpectomy should be performed prior to surgery. Oncoplastic techniques for breast conservation can extend breast-conserving surgical options in situations where the resection by itself would likely yield an unacceptable cosmetic outcome. Application of these procedures may reduce the need for mastectomy and reduce the chances of secondary surgery for re-excision while minimizing breast deformity. Patients should be informed of the possibility of positive margins and potential need for secondary surgery, which could include re-excision segmental resection, or could require mastectomy with or without loss of the nipple. Oncoplastic procedures can be combined with surgery on the contralateral unaffected breast to minimize long-term asymmetry.
- For mastectomy, the possibility of reconstruction should be discussed and a preoperative evaluation of reconstructive options should be considered. Surgical options for breast reconstruction following mastectomy include:
 - ▶ Procedures that incorporate breast implants (ie, tissue expander placement followed by implant placement, immediate implant placement)
 - ▶ Procedures that incorporate autologous tissue transplantation (ie, pedicled TRAM flap, fat grafting, various microsurgical flaps from the abdomen, back, buttocks, and thigh)
 - ▶ Procedures that incorporate both breast implants and autologous tissue transplantation (eg, latissimus dorsi flaps)
- Breast reconstruction following mastectomy can commence at the same time as mastectomy (“immediate”) or at some time following the completion of cancer treatment (“delayed”). In many cases, breast reconstruction involves a staged approach requiring more than one procedure such as:
 - ▶ Surgery on the contralateral breast to improve symmetry
 - ▶ Revision surgery involving the breast and/or donor site
 - ▶ Nipple and areola reconstruction and tattoo pigmentation
- 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 perform a resection that achieves appropriate surgical margins. Post-mastectomy radiation should still be applied in cases treated by skin-sparing mastectomy following the same selection criteria as for standard mastectomy.

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

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

**PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY**

- **Immediate reconstruction is contraindicated in the setting of mastectomy for inflammatory breast cancer (IBC) due to the high risk of recurrence, aggressive nature of the disease, and consequent need to proceed expeditiously to postoperative radiotherapy for local control without any potential delay. As skin-sparing mastectomy has not yet been demonstrated to be safe for IBC there is also a need to resect currently or previously involved skin at the time of mastectomy. Thus, there is no advantage to immediate reconstruction in this setting.**
- **In general, the nipple-areolar complex (NAC) is sacrificed with skin-sparing mastectomy for cancer therapy. However, NAC-sparing procedures may be an option in cancer patients who are carefully selected by experienced multidisciplinary teams. Retrospective data support the use of NAC-sparing procedures for breast cancer therapy with low nipple-involvement rates and low local recurrence rates for early-stage, and select advanced biologically favorable, invasive cancers and/or DCIS. Preoperative clinical evidence of nipple involvement including Paget's disease, nipple discharge associated with malignancy, and/or imaging findings suggesting malignant involvement of the nipple or subareolar tissues contraindicates nipple preservation. Nipple margin assessment is mandatory, and the nipple margin should be clearly designated.**
- **In the previously radiated patients, the use of tissue expanders/implants is relatively contraindicated. Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis, implant exposure, and failed reconstruction. In the setting of previous radiation, autologous tissue reconstruction is the preferred method of breast reconstruction.**
- **While noninflammatory, locally advanced breast cancer is not an absolute contraindication to immediate reconstruction, post-mastectomy radiation should still be applied regardless of the reconstruction approach:**
 - ▶ **When post-mastectomy radiation is required and autologous tissue reconstruction is planned, reconstruction is either delayed until after the completion of radiation therapy, or it can be initiated at the time of mastectomy with tissue expander placement followed by autologous tissue reconstruction. While some experienced breast cancer teams have employed protocols in which immediate tissue reconstructions are followed by radiation therapy, it is generally preferred that the radiation therapy precede the placement of the autologous tissue, because of reported loss in reconstruction cosmesis (category 2B).**
 - ▶ **When implant reconstruction is planned in a patient requiring radiation therapy, a staged approach with immediate tissue expander placement followed by implant placement is preferred. Surgery to exchange the tissue expanders with permanent implants can be performed prior to radiation or after completion of radiation therapy. Immediate placement of an implant in patients requiring postoperative radiation has an increased rate of capsular contracture, malposition, poor cosmesis, and implant exposure.**
- **Reconstruction selection is based on an assessment of cancer treatment, patient body habitus, obesity, smoking history, comorbidities, and patient concerns. Smoking and obesity increase the risk of complications for all types of breast reconstruction whether with implant or flap. Smoking and obesity are therefore considered a relative contraindication to breast reconstruction and patients should be made aware of increased rates of wound healing complications and partial or complete flap failure among smokers and obese patients.**
- **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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



PRINCIPLES OF RADIATION THERAPY

Optimizing Delivery of Individual Therapy:

It is important to individualize radiation therapy planning and delivery. CT-based treatment planning is encouraged to delineate target volumes and adjacent organs at risk. Greater target dose homogeneity and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments, and intensity-modulated radiation therapy (IMRT).

Respiratory control techniques including deep inspiration breath-hold and prone positioning may be used to try to further reduce dose to adjacent normal tissues, in particular heart and lung. Boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy. Chest wall scar boost when indicated is typically treated with electrons or photons.

Verification of daily setup consistency is done with weekly imaging. In certain circumstances, more frequent imaging may be appropriate. Routine use of daily imaging is not recommended.

Whole Breast Radiation:

Target definition is the breast tissue in entirety. The whole breast should receive a dose of 46–50 Gy in 23–25 fractions or 40–42.5 Gy in 15–16 fractions (hypofractionation is preferred). All dose schedules are given 5 days per week. A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical boost doses are 10–16 Gy in 4–8 fractions.

Chest Wall Radiation (including breast reconstruction):

The target includes the ipsilateral chest wall, mastectomy scar, and drain sites when indicated. Depending on whether the patient has had breast reconstruction 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. Dose is 46–50 Gy in 23–25 fractions to the chest wall +/- scar boost at 2 Gy per fraction to a total dose of approximately 60 Gy. All dose schedules are given 5 days per week. Special consideration should be given to the use of bolus material to ensure that 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 patient anatomy. For internal mammary node identification, the internal mammary artery and vein can be used as a surrogate for the nodal location (as the nodes themselves are not usually visible on planning imaging). Based on the post-mastectomy radiation randomized studies and recent trials, radiation therapy of the internal mammary lymph nodes should be strongly considered when delivering regional nodal irradiation. CT treatment planning should be utilized when treating the internal mammary lymph nodal volume to evaluate dose to normal tissues, especially the heart and lung, and dose constraints respected. Dose is 46–50 Gy in 23–25 fractions to the regional nodal fields. All dose schedules are given 5 days per week.

Accelerated Partial Breast Irradiation (APBI):

Preliminary studies of APBI suggest that rates of local control in selected patients with early-stage breast cancer may be comparable to those treated with standard whole breast RT. However, compared to standard whole breast radiation, several recent studies document an inferior cosmetic outcome with APBI. Follow-up is limited and studies are ongoing. Patients are encouraged to participate in clinical trials. The NCCN Panel accepts the updated 2016 version of the ASTRO APBI guideline, which now defines patients "suitable" for APBI to be one of the following: a) 50 years or older with invasive ductal carcinoma measuring ≤ 2 cm (T1 disease) with negative margin widths of ≥ 2 mm, no LVSI, ER-positive, and BRCA negative or b) Low/intermediate nuclear grade, screen-detected DCIS measuring size ≤ 2.5 cm with negative margin widths of ≥ 3 mm. A course of 34 Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day with external beam photon therapy is typically prescribed to the tumor bed. Other fractionation schemes are currently under investigation.

Preoperative Systemic Therapy:

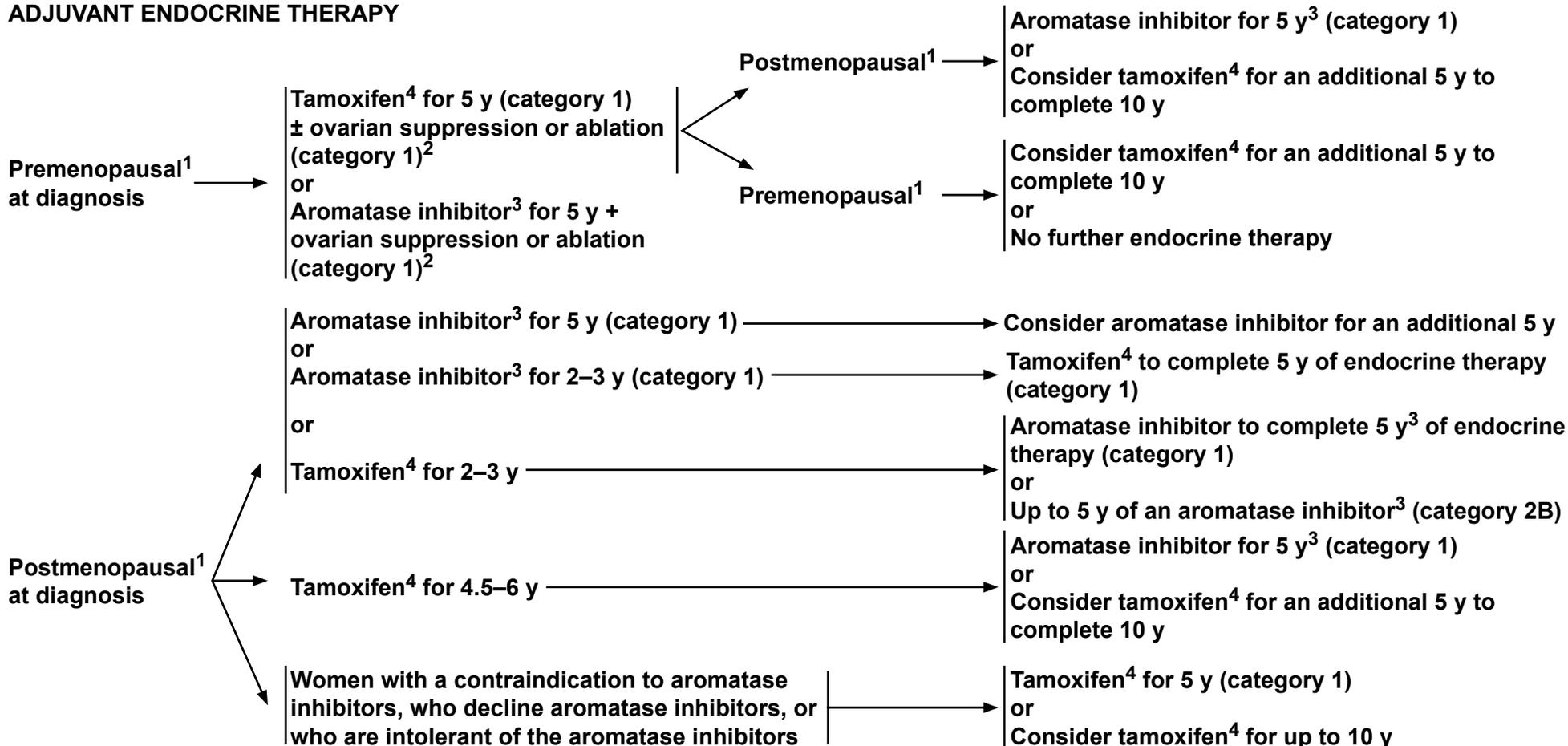
In patients treated with preoperative systemic therapy, indications for radiation therapy and treatment fields should be based on the maximum stage from the pre-therapy clinical stage, pathologic stage, and tumor characteristics.

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

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



ADJUVANT ENDOCRINE THERAPY



¹See Definition of Menopause (BINV-M).

²A balanced discussion of the risks and benefits associated with ovarian suppression therapy is critical. Aromatase inhibitor or tamoxifen for 5 y plus ovarian suppression should be considered, based on SOFT and TEXT clinical trial outcomes, for premenopausal women at higher risk of recurrence (ie, young age, high-grade tumor, lymph node involvement, Pagani, NEJM 2014, Prudence, NEJM 2014). Survival data still pending.

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

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

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

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

**PREOPERATIVE/ADJUVANT THERAPY REGIMENS** ^{1,2,3,4}**Regimens for HER2-negative disease**^{5,6}**Preferred regimens:**

- Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks
- Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel
- TC (docetaxel and cyclophosphamide)

Other regimens:

- Dose-dense AC (doxorubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC followed by docetaxel every 3 weeks
- AC followed by weekly paclitaxel
- EC (epirubicin/cyclophosphamide)
- TAC (docetaxel/doxorubicin/cyclophosphamide)

Regimens for HER2-positive disease^{6,7,8,9}**Preferred regimens:**

- AC followed by T + trastuzumab ± pertuzumab¹⁰ (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)
- TCH (docetaxel/carboplatin/trastuzumab) ± pertuzumab

Other regimens:

- AC followed by docetaxel + trastuzumab ± pertuzumab¹⁰
- Docetaxel + cyclophosphamide + trastuzumab
- FEC (fluorouracil/epirubicin/cyclophosphamide) followed by docetaxel + trastuzumab + pertuzumab¹⁰
- FEC followed by paclitaxel + trastuzumab + pertuzumab¹⁰
- Paclitaxel + trastuzumab¹¹
- Pertuzumab + trastuzumab + docetaxel followed by FEC¹⁰
- Pertuzumab + trastuzumab + paclitaxel followed by FEC¹⁰

¹Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2-positive tumors.

²Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.

³CMF and radiation therapy may be given concurrently, or the CMF may be given first. All other chemotherapy regimens should be given prior to radiotherapy.

⁴Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy.

⁵The regimens listed for HER2-negative disease are all category 1 (except where indicated) when used in the adjuvant setting.

⁶Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m².

⁷In patients with HER2-positive and axillary node-positive breast cancer, trastuzumab should be incorporated into the adjuvant therapy (category 1). Trastuzumab should also be considered for patients with HER2-positive node-negative tumors ≥1 cm (category 1).

⁸Trastuzumab should optimally be given concurrently with paclitaxel as part of the AC followed by paclitaxel regimen, and should be given for one year total duration.

⁹A pertuzumab-containing regimen can be administered to patients with ≥T2 or ≥N1, HER2-positive, early-stage breast cancer preoperatively. Patients who have not received a pertuzumab-containing regimen can receive adjuvant pertuzumab.

¹⁰Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

¹¹Paclitaxel + trastuzumab may be considered for patients with low-risk stage I, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.

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

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



DOSING SCHEDULES FOR COMBINATIONS FOR HER2-NEGATIVE DISEASE: PREFERRED REGIMENS

Dose-dense AC followed by paclitaxel chemotherapy¹

- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 14 days for 4 cycles.

(All cycles are with myeloid growth factor support,
[See NCCN Guidelines for Myeloid Growth Factors](#))

Followed by:

- Paclitaxel 175 mg/m² by 3 h IV infusion day 1

Cycled every 14 days for 4 cycles.

(All cycles are with myeloid growth factor support,
[See NCCN Guidelines for Myeloid Growth Factors](#))

[OTHER REGIMENS LISTED ON NEXT PAGE](#)

Dose-dense AC followed by weekly paclitaxel chemotherapy¹

- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 14 days for 4 cycles.

(All cycles are with myeloid growth factor support)

Followed by:

- Paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 wks.

TC chemotherapy²

- Docetaxel 75 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 4 cycles.

(All cycles are with myeloid growth factor support,
[See NCCN Guidelines for Myeloid Growth Factors](#))

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 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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



DOSING SCHEDULES FOR COMBINATIONS FOR HER2-NEGATIVE DISEASE: OTHER REGIMENS

Dose-dense AC chemotherapy¹

- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 14 days for 4 cycles.

(All cycles are with myeloid growth factor support,

[See NCCN Guidelines for Myeloid Growth Factors](#))

AC chemotherapy³

- Doxorubicin 60 mg/m² IV on day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 4 cycles.

TAC chemotherapy⁴

- Docetaxel 75 mg/m² IV day 1
- Doxorubicin 50 mg/m² IV day 1
- Cyclophosphamide 500 mg/m² IV day 1

Cycled every 21 days for 6 cycles.

(All cycles are with myeloid growth factor support,

[See NCCN Guidelines for Myeloid Growth Factors](#))

CMF chemotherapy⁵

- Cyclophosphamide 100 mg/m² PO days 1–14
- Methotrexate 40 mg/m² IV days 1 & 8
- 5-fluorouracil 600 mg/m² IV days 1 & 8

Cycled every 28 days for 6 cycles.

AC followed by docetaxel chemotherapy⁶

- Doxorubicin 60 mg/m² IV on day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 4 cycles.

Followed by:

- Docetaxel 100 mg/m² IV on day 1
- Cycled every 21 days for 4 cycles.

AC followed by weekly paclitaxel⁷

- 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 infusion weekly for 12 wks.

EC chemotherapy⁸

- Epirubicin 100 mg/m² IV day 1
- Cyclophosphamide 830 mg/m² IV day 1

Cycled every 21 days for 8 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 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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



DOSING SCHEDULE FOR COMBINATIONS FOR HER2-POSITIVE DISEASE: PREFERRED REGIMENS

AC followed by T chemotherapy with trastuzumab⁹

- 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

With:

- 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 21 days may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment.

Evaluate left ventricular ejection fraction (LVEF) prior to and during treatment.*

AC followed by T chemotherapy with trastuzumab + pertuzumab

- Doxorubicin 60 mg/m² IV day 1
 - Cyclophosphamide 600 mg/m² IV day 1
- Cycled every 21 days for 4 cycles.

Followed by:

- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Paclitaxel 80 mg/m² IV days 1, 8, and 15

Cycled every 21 days for 4 cycles

- Trastuzumab 6 mg/kg IV day 1

Cycled every 21 days to complete 1 y of trastuzumab therapy

Evaluate LVEF prior to and during treatment.*

*The optimal frequency of LVEF assessment during adjuvant trastuzumab therapy is not known. The FDA label recommends LVEF measurements prior to initiation of trastuzumab and every 3 mo during therapy.

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 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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Dose-dense AC followed by paclitaxel chemotherapy with trastuzumab¹⁰

- 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.

With:

- 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 21 days may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment.

Evaluate LVEF prior to and during treatment.*

(All cycles are with myeloid growth factor support, [See NCCN Guidelines for MGF](#))

TCH chemotherapy¹¹

- Docetaxel 75 mg/m² IV day 1
 - Carboplatin AUC 6 IV day 1
- Cycled every 21 days for 6 cycles

With:

- Trastuzumab 4 mg/kg IV wk 1

Followed by:

- Trastuzumab 2 mg/kg IV for 17 wks

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

OR

- Trastuzumab 8 mg/kg IV wk 1

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Evaluate LVEF prior to and during treatment.*

TCH chemotherapy + pertuzumab¹²

- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
 - Pertuzumab 840 mg IV day 1 followed by 420 mg IV
 - Docetaxel 75 mg/m² IV day 1
 - Carboplatin AUC 6 IV day 1
- Cycled every 21 days for 6 cycles

Cycled every 21 days for 6 cycles

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Evaluate LVEF prior to and during treatment.*

**DOSING SCHEDULE FOR COMBINATIONS FOR HER2-POSITIVE DISEASE: OTHER REGIMENS****AC followed by docetaxel chemotherapy with trastuzumab¹¹**

- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 4 cycles

Followed by:

- Docetaxel 100 mg/m² IV day 1

Cycled every 21 days for 4 cycles

With:

- Trastuzumab 4 mg/kg IV wk 1

Followed by:

- Trastuzumab 2 mg/kg IV weekly for 11 wks

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Evaluate LVEF prior to and during treatment.*

AC followed by docetaxel chemotherapy with trastuzumab and pertuzumab

- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 4 cycles

Followed by:

- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Docetaxel 75–100 mg/m² IV day 1

Cycled every 21 days for 4 cycles

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Evaluate LVEF prior to and during treatment.*

*The optimal frequency of LVEF assessment during adjuvant trastuzumab therapy is not known. The FDA label recommends LVEF measurements prior to initiation of trastuzumab and every 3 mo during therapy.

Docetaxel/cyclophosphamide chemotherapy with trastuzumab¹³

- Docetaxel 75 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 4 cycles

With:

Trastuzumab 4 mg/kg IV wk 1

Followed by

Trastuzumab 2 mg/kg IV weekly for 11 wks

Followed by

Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

OR

- Trastuzumab 8 mg/kg IV wk 1

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Evaluate LVEF prior to and during treatment.*

FEC chemotherapy followed by pertuzumab + trastuzumab + docetaxel¹⁴

- Fluorouracil 500 mg/m² IV day 1
- Epirubicin 100 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 3 cycles

Followed by:

- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Docetaxel 75–100 mg/m² IV day 1

Cycled every 21 days for 3 cycles

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Evaluate LVEF prior to and during treatment.*

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 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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**DOSING SCHEDULE FOR COMBINATIONS FOR HER2-POSITIVE DISEASE: OTHER REGIMENS (continued)****FEC chemotherapy followed by pertuzumab + trastuzumab + paclitaxel**

- Fluorouracil 500 mg/m² IV day 1
- Epirubicin 100 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 3 cycles

Followed by:

- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Paclitaxel 80 mg/m² IV days 1, 8, and 15

Cycled every 21 days for 3 cycles

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Evaluate LVEF prior to and during treatment.*

Paclitaxel + trastuzumab¹⁴

- Paclitaxel 80 mg/m² IV weekly for 12 weeks

With:

- 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 21 days may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment.

Evaluate LVEF prior to and during treatment.*

*The optimal frequency of LVEF assessment during adjuvant trastuzumab therapy is not known. The FDA label recommends LVEF measurements prior to initiation of trastuzumab and every 3 mo during therapy.

Pertuzumab + trastuzumab + docetaxel followed by FEC chemotherapy¹⁵

Neoadjuvant therapy:

- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Docetaxel 75–100 mg/m² IV day 1

Cycled every 21 days for 4 cycles

Followed by adjuvant therapy

- Fluorouracil 600 mg/m² IV day 1
- Epirubicin 90 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 3 cycles

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Evaluate LVEF prior to and during treatment.*

Pertuzumab + trastuzumab + paclitaxel followed by FEC chemotherapy

Neoadjuvant therapy:

- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Paclitaxel 80 mg/m² IV days 1, 8, and 15

Cycled every 21 days for 4 cycles

Followed by adjuvant therapy

- Fluorouracil 600 mg/m² IV day 1
- Epirubicin 90 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 3 cycles

Followed by:

- Trastuzumab 6 mg/kg IV every 21 days to complete 1 y of trastuzumab therapy

Evaluate LVEF prior to and during treatment.*

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 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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**REFERENCES FOR PREOPERATIVE/ADJUVANT THERAPY REGIMENS**

- ¹Citron ML, Berry DA, Cirincione C, et al: Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of intergroup trial C9741/cancer and leukemia group B trial 9741. *J Clin Oncol* 2003;21:1431-1439.
- ²Jones S, Holmes F, O'Shaughnessey J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research trial 9735. *J Clin Oncol* 2009;27:1177-1183.
- ³Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. *J Clin Oncol* 1990;8:1483-1496.
- ⁴Martin, Pienkowski T, Mackey J, et al: Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med* 2005;352:22.
- ⁵Goldhirsch A, Colleoni M, Coates AS, et al: Adding adjuvant CMF chemotherapy to either radiotherapy or tamoxifen: are all CMFs alike? The International Breast Cancer Study Group (IBCSG). *Ann Oncol* 1998;9:489-93.
- ⁶von Minckwitz G1, Raab G, Caputo A, et al. Doxorubicin with cyclophosphamide followed by docetaxel every 21 days compared with doxorubicin and docetaxel every 14 days as preoperative treatment in operable breast cancer: the GEPAR DUO study of the German Breast Group. *J Clin Oncol* 2005;23(12):2676-85.
- ⁷Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in adjuvant treatment of breast cancer. *N Engl J Med* 2008;258:1663-1671.
- ⁸Piccart MJ, Di Leo A, Beauduin M, et al: Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. *J Clin Oncol* 2001;19:3103-3110.
- ⁹Romond EH, Perez EZ, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2 positive breast cancer. *N Engl J Med* 2005;353:1673-1684.
- ¹⁰Dang C, Fornier M, Sugarman S, et al: The safety of dose-dense doxorubicin and cyclophosphamide followed by paclitaxel with trastuzumab in HER-2/neu over-expressed/amplified breast cancer. *J Clin Oncol* 2008;26(8):1216-22.
- ¹¹Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011;365:1273-1283.
- ¹²Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol* 2013;24:2278-2284.
- ¹³Jones SE, Collea R, Paul D, et al. Adjuvant docetaxel and cyclophosphamide plus trastuzumab in patients with HER2-amplified early stage breast cancer: a single-group, open-label, phase 2 study. *Lancet Oncol* 2013;14:1121-8.
- ¹⁴Tolaney S, Barry W, Dang C, et al. Adjuvant paclitaxel and trastuzumab for node-negative HER2-positive breast cancer. *N Engl J Med* 2016;372:134-141.
- ¹⁵Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012;13:25-32.

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

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

**PRINCIPLES OF PREOPERATIVE SYSTEMIC THERAPY**

- Randomized trials demonstrate similar long-term outcomes when patients are given the same treatment preoperatively compared with postoperatively.¹
- Preoperative systemic therapy can render surgically inoperable tumors operable and offers potential benefits for patients with operable breast cancer. Importantly, preoperative systemic therapy can improve rates of breast conservation therapy eligibility and provides an opportunity to observe clinical and pathologic response to systemic therapy in an individual patient.
- Pathologic complete response (pCR) to preoperative systemic therapy is associated with an extremely favorable disease-free and overall survival, particularly in situations in which all treatment is given preoperatively. The correlation between pathologic response and long-term outcome is strongest for triple-negative breast cancer (TNBC), somewhat less so for HER2+ disease, and least for ER+ disease.^{2,3}
- A number of chemotherapy regimens have activity in the preoperative setting. In general, those chemotherapy regimens recommended in the adjuvant setting may be considered in the preoperative setting. [See Preoperative/Adjuvant Therapy Regimens \(BINV-K\)](#).
- Preoperative endocrine therapy alone may be considered for patients with ER-positive disease based on comorbidities or low-risk luminal biology.
- Patients with HER2-positive tumors should be treated with preoperative systemic therapy incorporating trastuzumab for at least 9 weeks of preoperative therapy. A pertuzumab-containing regimen may be administered preoperatively to patients with greater than or equal to T2 or greater than or equal to N1, HER2-positive early stage breast cancer. [See Preoperative/Adjuvant Therapy Regimens \(BINV-K\)](#)
- Some studies have reported an increased risk of locoregional recurrence in patients receiving preoperative systemic therapy compared with those receiving postoperative adjuvant systemic therapy.⁴ This increased risk of locoregional relapse has been attributed to suboptimal delivery of definitive local therapy in patients treated in the preoperative setting.
- Not all patients are appropriate candidates for preoperative systemic therapy. Accurate clinical staging at baseline prior to initiation of preoperative systemic therapy is critical. [See Preoperative Systemic Therapy: Breast and Axillary Evaluation \(BINV-11\)](#)
- When electing preoperative chemotherapy, all treatment should be given prior to surgery. Tumor response should be routinely assessed by clinical exam during delivery of preoperative therapy. Patients with operable breast cancer experiencing progression of disease during preoperative systemic therapy may be given an alternate systemic therapy or taken to surgery. Locoregional therapy principles should be applied in the same manner as in patients treated with adjuvant systemic therapy.

¹Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol* 2008 Feb 10;26(5):778-85.

²von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012 May 20;30(15):1796-804.

³Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014 Jul 12;384(9938):164-72.

⁴Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst*. 2005 Feb 2;97(3):188-94.

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

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



PRINCIPLES OF PREOPERATIVE SYSTEMIC THERAPY

Known benefits of preoperative systemic therapy:

- Facilitates breast conservation
- Can render inoperable tumors operable
- Provides important prognostic information at an individual patient level based on response to therapy, particularly in patients with triple-negative and HER2-positive breast cancer
- Allows time for genetic testing
- Allows time to plan breast reconstruction in patients electing mastectomy

Opportunities:

- May allow SLNB alone if a positive axilla is cleared with therapy
- May provide an opportunity to modify systemic treatment if no preoperative therapy response or progression of disease
- Might allow for the addition of adjuvant treatments in patients with poor response
- May allow for smaller radiotherapy ports or less radiotherapy if axillary nodal disease cleared
- Excellent research platform to test novel therapies and predictive biomarkers

Cautions:

- Possible overtreatment with systemic therapy if clinical stage is overestimated
- Possible undertreatment locoregionally with radiotherapy if clinical stage is underestimated
- Possibility of disease progression during preoperative systemic therapy

Candidates for preoperative systemic therapy

- Patients with inoperable breast cancer:
 - ▶ Inflammatory breast cancer
 - ▶ Bulky or matted N2 axillary nodes
 - ▶ N3 nodal disease
 - ▶ T4 tumors
- Patients with operable breast cancer:
 - ▶ Large primary tumor relative to breast size in a patient who desires breast conservation

Non-candidates for preoperative systemic therapy

- Patients with extensive in situ disease when extent of invasive carcinoma is not well defined
- Patients with a poorly delineated extent of tumor preoperatively
- Patients whose tumors are not palpable or clinically assessable

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

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



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 follicle-stimulating hormone (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 LHRH 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.

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

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



ENDOCRINE THERAPY FOR RECURRENT OR STAGE IV DISEASE

Premenopausal Patients

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

Postmenopausal Patients

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

¹A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal AI).

²If there is disease progression while on a CDK4/6 inhibitor + letrozole, there are no data to support an additional line of therapy with another palbociclib regimen. Likewise, if there is disease progression while on exemestane + everolimus, there are no data to support an additional line of therapy with another everolimus regimen.

³Palbociclib or ribociclib in combination with letrozole may be considered as a treatment option for first-line therapy for postmenopausal patients with hormone-receptor positive, HER2-negative metastatic breast cancer.

⁴For postmenopausal women or for premenopausal women receiving ovarian suppression with an LHRH agonist, with hormone-receptor positive and HER2-negative metastatic breast cancer that has progressed on or after prior adjuvant or metastatic endocrine therapy.

⁵A single study (S0226) in women with hormone receptor-positive breast cancer and no prior chemotherapy, biological therapy, or endocrine therapy for metastatic disease demonstrated that the addition of fulvestrant to anastrozole resulted in prolongation of time to progression. Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. Two studies with similar design (FACT and SOFEA) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole.

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

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

**CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER^{1,2}****Preferred single agents:*****Anthracyclines***

- Doxorubicin
- Pegylated liposomal doxorubicin

Taxanes

- Paclitaxel

Anti-metabolites

- Capecitabine
- Gemcitabine

Other microtubule inhibitors

- Vinorelbine
- Eribulin

Other single agents:

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

Chemotherapy combinations:

- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab³

Preferred first-line agents for HER2-positive disease:

- Pertuzumab + trastuzumab + docetaxel (category 1)⁴
- Pertuzumab + trastuzumab + paclitaxel⁴

Other agents for HER2-positive disease:

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

Agents for trastuzumab-exposed HER2-positive disease:

- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents^{4,5,6}

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

²Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m².

³Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

⁴Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.

⁵Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

⁶Trastuzumab may be safely combined with all non-anthracycline containing preferred and other single agents listed above for recurrent or metastatic breast cancer.

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

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

**DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER****Preferred single agents:*****Anthracyclines:*****Doxorubicin**

- 60–75 mg/m² IV day 1, cycled every 21 days¹

or

- 20 mg/m² IV day 1 weekly²

Pegylated liposomal encapsulated doxorubicin³

- 50 mg/m² IV day 1

Cycled every 28 days.

Taxanes:**Paclitaxel**

- 175 mg/m² IV day 1

Cycled every 21 days.⁴

or

- 80 mg/m² IV day 1 weekly⁵

Antimetabolites:**Capecitabine⁶**

- 1000–1250 mg/m² PO twice daily days 1–14

Cycled every 21 days.

Gemcitabine⁷

- 800–1200 mg/m² IV days 1, 8, and 15

Cycled every 28 days.

Other microtubule inhibitors:**Vinorelbine⁸**

- 25 mg/m² IV day 1 weekly

Eribulin⁹

- 1.4 mg/m² IV days 1 and 8

Cycled every 21 days.

Other single agents:**Cyclophosphamide¹⁰**

- 50 mg PO daily on days 1–21

Cycled every 28 days.

Carboplatin¹¹

- AUC 6 IV on day 1

Cycled every 21–28 days.

Docetaxel^{12,13}

- 60–100 mg/m² IV day 1

Cycled every 21 days.

or

- 35 mg/m² IV weekly for 6 wks followed by a 2-week rest, then repeat¹⁴

Albumin-bound paclitaxel

- 100 mg/m² or 125 mg/m² IV days 1, 8, and 15

Cycled every 28 days.^{15,16}

or

- 260 mg/m² IV

Cycled every 21 days.¹⁵**Cisplatin¹⁷**

- 75 mg/m² IV on day 1

Cycled every 21 days.

Epirubicin¹⁸

- 60–90 mg/m² IV day 1

Cycled every 21 days.

Ixabepilone¹⁹

- 40 mg/m² IV day 1

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 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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER****Chemotherapy combinations:****CAF chemotherapy²⁰**

- Cyclophosphamide 100 mg/m² PO days 1–14
 - Doxorubicin 30 mg/m² IV days 1 & 8
 - 5-fluorouracil 500 mg/m² IV days 1 & 8
- Cycled every 28 days.

FAC chemotherapy²¹

- 5-fluorouracil 500 mg/m² IV days 1 & 8 or days 1 & 4
 - Doxorubicin 50 mg/m² IV day 1
(or by 72-h continuous infusion)
 - Cyclophosphamide 500 mg/m² IV day 1
- Cycled every 21 days.

FEC chemotherapy²²

- Cyclophosphamide 400 mg/m² IV days 1 & 8
 - Epirubicin 50 mg/m² IV days 1 & 8
 - 5-fluorouracil 500 mg/m² IV days 1 & 8
- Cycled every 28 days.

AC chemotherapy²³

- Doxorubicin 60 mg/m² IV day 1
 - Cyclophosphamide 600 mg/m² IV day 1
- Cycled every 21 days.

EC chemotherapy²⁴

- Epirubicin 75 mg/m² IV day 1
 - Cyclophosphamide 600 mg/m² IV day 1
- Cycled every 21 days.

CMF chemotherapy²⁵

- Cyclophosphamide 100 mg/m² PO days 1–14
 - Methotrexate 40 mg/m² IV days 1 & 8
 - 5-fluorouracil 600 mg/m² IV days 1 & 8
- Cycled every 28 days.

Docetaxel/capecitabine chemotherapy²⁶

- Docetaxel 75 mg/m² IV day 1
 - Capecitabine 950 mg/m² PO twice daily days 1–14
- Cycled every 21 days.

GT chemotherapy²⁷

- Paclitaxel 175 mg/m² IV day 1
 - Gemcitabine 1250 mg/m² IV days 1 & 8 (following paclitaxel on day 1)
- Cycled every 21 days.

Gemcitabine/carboplatin²⁸

- Gemcitabine 1000 mg/m² on days 1 & 8
 - Carboplatin AUC 2 IV on days 1 & 8
- Cycled every 21 days.

Paclitaxel plus bevacizumab²⁹

- 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 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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR HER2-POSITIVE RECURRENT OR METASTATIC BREAST CANCER

Preferred first-line agents for HER2-positive disease:

Pertuzumab + trastuzumab + docetaxel³⁰

- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
 - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
 - Docetaxel 75–100 mg/m² IV day 1
- Cycled every 21 days.

Pertuzumab + trastuzumab + paclitaxel³¹

- Pertuzumab 840 mg IV day 1 followed by 420 mg IV cycled every 21 days
- Trastuzumab
 - ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
 - or
 - ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV cycled every 21 days³²
- Paclitaxel 80 mg/m² IV day 1 weekly³¹
- or
- Paclitaxel 175 mg/m² day 1 cycled every 21 days

Other agents for HER2-positive disease:

Ado-trastuzumab emtansine (T-DM1)³³

- 3.6 mg/kg IV day 1
- Cycled every 21 days.

Paclitaxel/carboplatin + trastuzumab³⁴

- Carboplatin AUC 6 IV day 1
 - Paclitaxel 175 mg/m² IV day 1
- Cycled every 21 days.
- Trastuzumab
 - ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
 - or
 - ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Weekly paclitaxel/carboplatin + trastuzumab³⁵

- Paclitaxel 80 mg/m² IV days 1, 8, & 15
 - Carboplatin AUC 2 IV days 1, 8, & 15
- Cycled every 28 days.
- Trastuzumab
 - ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
 - or
 - ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Trastuzumab + paclitaxel

- Paclitaxel
 - ▶ 175 mg/m² IV day 1 cycled every 21 days³⁶
 - or
 - ▶ 80–90 mg/m² IV day 1 weekly³⁷
- Trastuzumab
 - ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
 - or
 - ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Trastuzumab + docetaxel

- Docetaxel
 - ▶ 80–100 mg/m² IV day 1 cycled every 21 days³⁸
 - or
 - ▶ 35 mg/m² IV days 1, 8, and 15 weekly³⁹
- Trastuzumab
 - ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
 - or
 - ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

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

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



DOSING SCHEDULES FOR CHEMOTHERAPY REGIMENS FOR HER-2 POSITIVE RECURRENT OR METASTATIC BREAST CANCER

Trastuzumab + vinorelbine^{40,41}

- Vinorelbine

- ▶ 25 mg/m² IV day 1 weekly
or
- ▶ 30–35 mg/m² IV days 1 and 8

Cycled every 21 days.

- Trastuzumab

- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
or
- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Trastuzumab + capecitabine⁴²

- Capecitabine 1000–1250 mg/m² PO twice daily days 1–14
cycled every 21 days

- Trastuzumab

- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly^{36,43}
or
- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Agents for trastuzumab-exposed HER2-positive disease:

Lapatinib + capecitabine⁴⁴

- Lapatinib 1250 mg PO daily days 1–21
 - Capecitabine 1000 mg/m² PO twice daily days 1–14
- Cycled every 21 days.

Trastuzumab + capecitabine⁴⁵

- Capecitabine 1000–1250 mg/m² PO twice daily days 1–14
- Cycled every 21 days.
- Trastuzumab
 - ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly^{36,43}
or
 - ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

Trastuzumab + lapatinib⁴⁶

- Lapatinib 1000 mg PO daily
- Trastuzumab
- ▶ 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
or
- ▶ 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days³²

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

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

**REFERENCES**

- ¹Chan S, Friedrichs K, Noel D, et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol* 1999;17:2341-2354.
- ²Gasparini G, Dal Fior S, Panizzoni GA, et al. Weekly epirubicin versus doxorubicin as second line therapy in advanced breast cancer. A randomized clinical trial. *Am J Clin Oncol* 1991;14:38-44.
- ³O'Brien ME, Wigler N, Inbar M, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Ann Oncol* 2004;15:440-449.
- ⁴Seidman AD, Tiersten A, Hudis C, et al. Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. *J Clin Oncol* 1995;13:2575-2581.
- ⁵Perez EA, Vogel CL, Irwin DH, et al. Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. *J Clin Oncol* 2001;19:4216-4223.
- ⁶Bajetta E, Procopio G, Celio L, et al. Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. *J Clin Oncol* 2005;23:2155-2161.
- ⁷Seidman AD. Gemcitabine as single-agent therapy in the management of advanced breast cancer. *Oncology (Williston Park)* 2001;15:11-14.
- ⁸Zelev L, Barthier S, Riofrio M, et al. Weekly vinorelbine is an effective palliative regimen after failure with anthracyclines and taxanes in metastatic breast carcinoma. *Cancer* 2001;92:2267-2272.
- ⁹Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet* 2011;377:914-923.
- ¹⁰Licchetta A, Correale P, Migali C, et al. Oral metronomic chemo-hormonal-therapy of metastatic breast cancer with cyclophosphamide and megestrol acetate. *J Chemother* 2010;22(3):201-4.
- ¹¹Isakoff SJ, Mayer EL, He L, et al. TBCRC009: A multicenter phase II clinical trial of platinum monotherapy with biomarker assessment in metastatic triple-negative breast cancer. *J Clin Oncol* 2016 June 10;33(17):1902-9 doi:10.1200/JCO.2014.57.6660.Epub 2016 Apr 6.
- ¹²Burris HA, 3rd. Single-agent docetaxel (Taxotere) in randomized phase III trials. *Semin Oncol* 1999;26:1-6.
- ¹³Harvey V, Mouridsen H, Semiglazov V, et al: Phase III trial comparing three doses of docetaxel for second-line treatment of advanced breast cancer. *J Clin Oncol* 2006;24(31):4963-70.
- ¹⁴Rivera E, Mejia JA, Arun BJ, et al. Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. *Cancer* 2008 Apr 1;112(7):1455-61.
- ¹⁵Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol* 2005;23:7794-7803.
- ¹⁶Gradishar W, Dimitry K, Sergey C, et al: Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer. *J Clin Oncol* 2009;27(22):3611-9.
- ¹⁷Silver DP, Richardson AL, Eklund AC, et al. Efficacy of neoadjuvant cisplatin in triple-negative breast cancer. *J Clin Oncol* 2010;28(7):1145-53.
- ¹⁸Bastholt L, Dalmark M, Gjedde SB, et al. Dose-response relationship of epirubicin in the treatment of postmenopausal patients with metastatic breast cancer: a randomized study of epirubicin at four different dose levels performed by the Danish Breast Cancer Cooperative Group. *J Clin Oncol* 1996;14:1146-1155.
- ¹⁹Perez E, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. *J Clin Oncol* 2007;25(23):3407-14.
- ²⁰Bull JM, Tormey DC, Li SH, et al. A randomized comparative trial of adriamycin versus methotrexate in combination drug therapy. *Cancer* 1978;41:1649-1657.
- ²¹Hortobagyi GN, Gutterman JU, Blumenschein GR, et al: Combination chemoimmunotherapy of metastatic breast cancer with 5-fluorouracil, adriamycin, cyclophosphamide, and BCG. *Cancer* 1979;43:1225-33.
- ²²Ackland SP, Anton A, Breitbach GP, et al. Dose-intensive epirubicin-based chemotherapy is superior to an intensive intravenous cyclophosphamide, methotrexate, and fluorouracil regimen in metastatic breast cancer: a randomized multinational study. *J Clin Oncol* 2001;19:943-953.
- ²³Nabholtz JM, Falkson C, Campos D, et al: Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. *J Clin Oncol* 2003; 21(6): 968-75.

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

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

**REFERENCES**

- ²⁴Langlely RE, Carmichel J, Jones AL, et al. Phase III trial of epirubicin plus paclitaxel compared with epirubicin plus cyclophosphamide as first-line chemotherapy for metastatic breast cancer: United Kingdom Cancer Research Institute. *J Clin Oncol* 2005;23:8322-8330.
- ²⁵Bonadonna G, Brusamolino E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med* 1976;294:405-410.
- ²⁶Mavroudis D, Papakotoulas P, Ardavanis A, et al. Randomized phase III trial comparing docetaxel plus epirubicin versus docetaxel plus capecitabine as first-line treatment in women with advanced breast cancer. *Ann Oncol* 21:48(2010).
- ²⁷Albain KS, Nag S, Calderillo-Ruiz G, et al. Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *J Clin Oncol* 2008;26(24):3950-7.
- ²⁸O'Shaughnessy J, Schwartzberg LS, Danso MA, et al. A randomized phase III study of iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC). [abstract]. *J Clin Oncol* 2011;29 (Suppl. 15):Abstract 1007.
- ²⁹Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007;357:2666-2676.
- ³⁰Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012;366:109-119.
- ³¹Datko F, D'Andrea G, Dickler M, et al. Phase II study of pertuzumab, trastuzumab, and weekly paclitaxel in patients with metastatic HER2-overexpressing metastatic breast cancer [abstract]. *Cancer Research* 2012;72:Abstract P5-18-20.
- ³²Leyland-Jones B, Gelmon K, Ayoub JP, et al. Pharmacokinetics, safety, and efficacy of trastuzumab administered every three weeks in combination with paclitaxel. *J Clin Oncol* 2003;21:3965-3971.
- ³³Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer [supplementary appendix available online]. *N Engl J Med* 2012;367:1783-1791.
- ³⁴Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. *J Clin Oncol* 2006;24:2786-2792.
- ³⁵Perez EA, Suman VJ, Rowland KM, et al. Two concurrent phase II trials of paclitaxel/carboplatin/trastuzumab (weekly or every-3-week schedule) as first-line therapy in women with HER2-overexpressing metastatic breast cancer: NCCTG study 983252. *Clin Breast Cancer* 2005;6:425-432.
- ³⁶Siamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783-792.
- ³⁷Seidman A, Berry DA, Cirincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *J Clin Oncol* 2008;26:1642-1649.
- ³⁸Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005;23:4265-4274.
- ³⁹Esteva FJ, Valero V, Booser D, et al. Phase II study of weekly docetaxel and trastuzumab for patients with HER-2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002;20:1800-1808.
- ⁴⁰Burstein HJ, Keshaviah A, Baron AD, et al. Trastuzumab plus vinorelbine or taxane chemotherapy for HER2-overexpressing metastatic breast cancer: the trastuzumab and vinorelbine or taxane study. *Cancer* 2007;110:965-972.
- ⁴¹Andersson M, Lidbrink E, Bjerre K, et al. Phase III randomized study comparing docetaxel plus trastuzumab with vinorelbine plus trastuzumab as first-line therapy of metastatic or locally advanced human epidermal growth factor receptor 2-positive breast cancer: the HERNATA study. *J Clin Oncol* 2011;29:264-271.
- ⁴²von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. *J Clin Oncol* 2009;27:1999-2006.
- ⁴³Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol* 1999;17:2639-2648.
- ⁴⁴Geyer C, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;355:2733-2743.
- ⁴⁵Bartsch R, Wenzel C, Altorjai G, et al. Capecitabine and trastuzumab in heavily pretreated metastatic breast cancer. *J Clin Oncol* 2007;25:3853-3858.
- ⁴⁶Blackwell KL, Burstein H, et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol* 2010;28(7):1124-30.

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

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



PRINCIPLES OF MONITORING METASTATIC DISEASE

Monitoring of patient symptoms and cancer burden during treatment of metastatic breast cancer is important to determine whether the treatment is providing benefit and that the patient does not have toxicity from an ineffective therapy.

Components of Monitoring:

Monitoring includes periodic assessment of varied combinations of symptoms, physical examination, routine laboratory tests, imaging studies, and blood biomarkers where appropriate. Results of monitoring are classified as response/continued response to treatment, stable disease, uncertainty regarding disease status, or progression of disease. The clinician typically must assess and balance multiple different forms of information to make a determination regarding whether disease is being controlled and the toxicity of treatment is acceptable. Sometimes, this information may be contradictory.

Definition of Disease Progression:

Unequivocal evidence of progression of disease by one or more of these factors is required to establish progression of disease, either because of ineffective therapy or acquired resistance of disease to an applied therapy. Progression of disease may be identified through evidence of growth or worsening of disease at previously known sites of disease and/or of the occurrence of new sites of metastatic disease.

• Findings concerning for progression of disease include:

- ▶ Worsening symptoms such as pain or dyspnea
- ▶ Evidence of worsening or new disease on physical examination
- ▶ Declining performance status
- ▶ Unexplained weight loss
- ▶ Increasing alkaline phosphatase, ALT, AST, or bilirubin
- ▶ Hypercalcemia
- ▶ New radiographic abnormality or increase in the size of pre-existing radiographic abnormality
- ▶ New areas of abnormality on functional imaging (eg, bone scan, PET/CT)
- ▶ Increasing tumor markers (eg, CEA, CA15-3, CA27.29)¹

¹Rising tumor markers (eg, CEA, CA15-3, CA27.29) are concerning for tumor progression, but may also be seen in the setting of responding disease. An isolated increase in tumor markers should rarely be used to declare progression of disease. Changes in bone lesions are often difficult to assess on plain or cross-sectional radiology or on bone scan. For these reasons, patient symptoms and serum tumor markers may be more helpful in patients with bone-dominant metastatic disease.

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

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



PRINCIPLES OF MONITORING METASTATIC DISEASE

Use of Objective Criteria for Response/Stability/Progression:

- **The most accurate assessments of disease activity typically occur when previously abnormal studies are repeated on a serial and regular basis. Generally, the same method of assessment should be used over time (eg, an abnormality found on chest CT should generally be monitored with repeat chest CT).**
- **Some non-clinically important variation in measurement of abnormalities by all serial studies is common and expected. Therefore, the use of objective and widely accepted criteria for response, stability, and progression of disease are encouraged. Such systems include the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines (Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-247) and the WHO criteria (Miller AB, Hoogstraten B, Staquet M, and Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207-214).**
- **Studies of functional imaging, such as radionuclide bone scans and PET imaging, are particularly challenging when used to assess response. In the case of bone scans, responding disease may result in a flare or increased activity on the scan that may be misinterpreted as disease progression, especially on the first follow-up bone scan after initiating a new therapy. PET imaging is challenging because of the absence of a reproducible, validated, and widely accepted set of standards for disease activity assessment.**

[Continued on next page](#)

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

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

**PRINCIPLES OF MONITORING METASTATIC DISEASE****Frequency of Monitoring:**

The optimal frequency of repeat testing is uncertain, and is primarily based on the monitoring strategies utilized in breast cancer clinical trials. The frequency of monitoring must balance the need to detect progressive disease, avoid unnecessary toxicity of any ineffective therapy, resource utilization, and determine cost. The following table is to provide guidance, and should be modified for the individual patient based on sites of disease, biology of disease, and treatment regimen. Reassessment of disease activity should be performed in patients with new or worsening signs or symptoms of disease, regardless of the time interval from previous studies.

Suggested intervals of follow-up for patients with metastatic disease¹

	Baseline prior to new therapy	Chemotherapy	Endocrine therapy	Restaging if concern for progression of disease
Symptom assessment	Yes	Prior to each cycle	Every 1–3 months	Yes
Physical examination	Yes	Prior to each cycle	Every 1–3 months	Yes
Performance status	Yes	Prior to each cycle	Every 1–3 months	Yes
Weight	Yes	Prior to each cycle	Every 1–3 months	Yes
LFTs, CBC	Yes	Prior to each cycle	Every 1–3 months	Yes
CT chest/abd/pelvis with contrast	Yes	Every 2–4 cycles	Every 2–6 months	Yes
Bone scan	Yes	Every 4 cycles	Every 4–6 months	Yes
PET/CT	Optional	Optional	Optional	Optional
Tumor markers	Optional	Optional	Optional	Optional

¹In patients who have long-term stable disease, the frequency of monitoring can be reduced.

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

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



NCCN Guidelines Version 2.2017

Phyllodes Tumor

CLINICAL PRESENTATION

Clinical suspicion of phyllodes tumor:

- Palpable mass
- Rapid growth
- Large size (>3 cm)
- Imaging with ultrasound suggestive of fibroadenoma except for size and/or history of growth

WORKUP

- History and physical exam
- Ultrasound
- Mammogram for women ≥30 y

FINDINGS

TREATMENT

Excisional biopsy^a

Fibroadenoma

→ **Observe**

Phyllodes tumor includes benign, borderline, and malignant

→ **Wide excision^c without axillary staging^d**

Invasive or in situ cancer

→ **See appropriate guidelines**

Core needle biopsy^b

Fibroadenoma or indeterminate

→ **Excisional biopsy^a** → **See findings above**

Phyllodes tumor includes benign, borderline, and malignant

→ **Wide excision^c without axillary staging^d**

Invasive or in situ cancer

→ **See appropriate guidelines**

^aExcisional biopsy includes complete mass removal, but without the intent of obtaining surgical margins.

^bFNA or core biopsy may not distinguish a fibroadenoma from a phyllodes tumor in some cases. The sensitivity of core biopsy for the diagnosis of phyllodes tumor is greater than that of FNA biopsy, but neither core biopsy nor FNA biopsy can always differentiate phyllodes tumors from fibroadenomas. In cases with clinical suspicion for phyllodes tumor, excision of the lesion may be needed for definitive pathologic classification.

^cWide 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.

^dThere are 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 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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



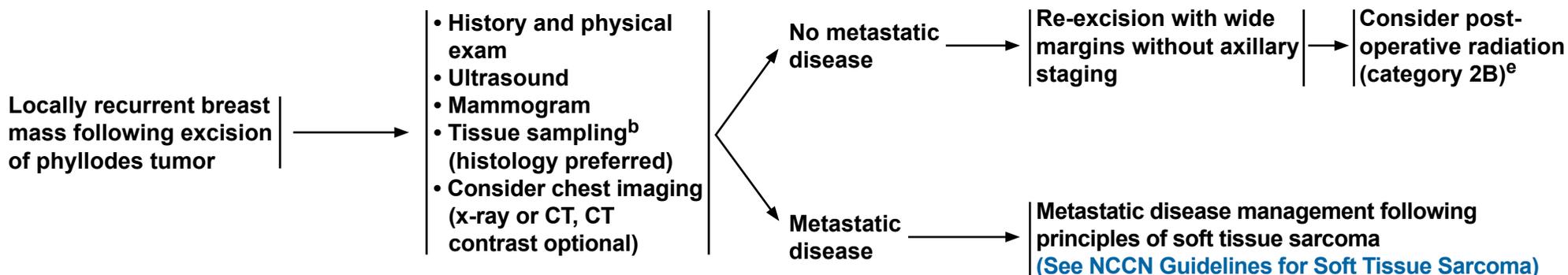
PHYLLODES TUMOR RECURRENCE

CLINICAL PRESENTATION

WORKUP

FINDINGS

TREATMENT



^bFNA or core biopsy may not distinguish a fibroadenoma from a phyllodes tumor in some cases. The sensitivity of core biopsy for the diagnosis of phyllodes tumor is greater than that of FNA biopsy, but neither core biopsy nor FNA biopsy can always differentiate phyllodes tumors from fibroadenomas. In cases with clinical suspicion for phyllodes tumor, excision of the lesion may be needed for definitive pathologic classification.

^eThere are 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 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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

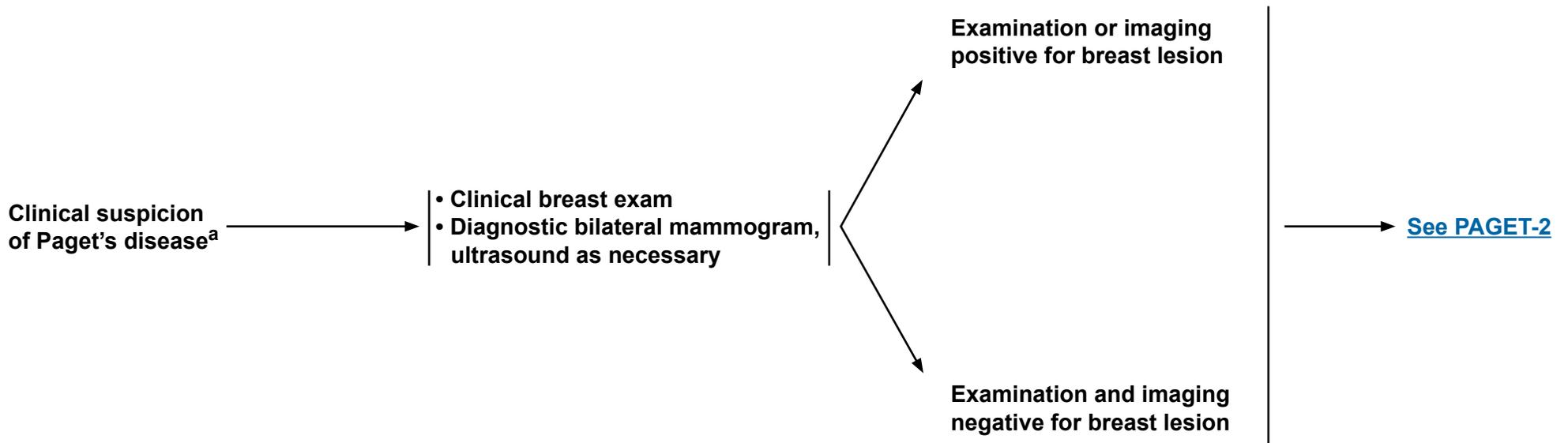


NCCN Guidelines Version 2.2017

Paget's Disease

CLINICAL PRESENTATION

WORKUP



^aNipple or areolar eczema, ulceration, bleeding, or itching.

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

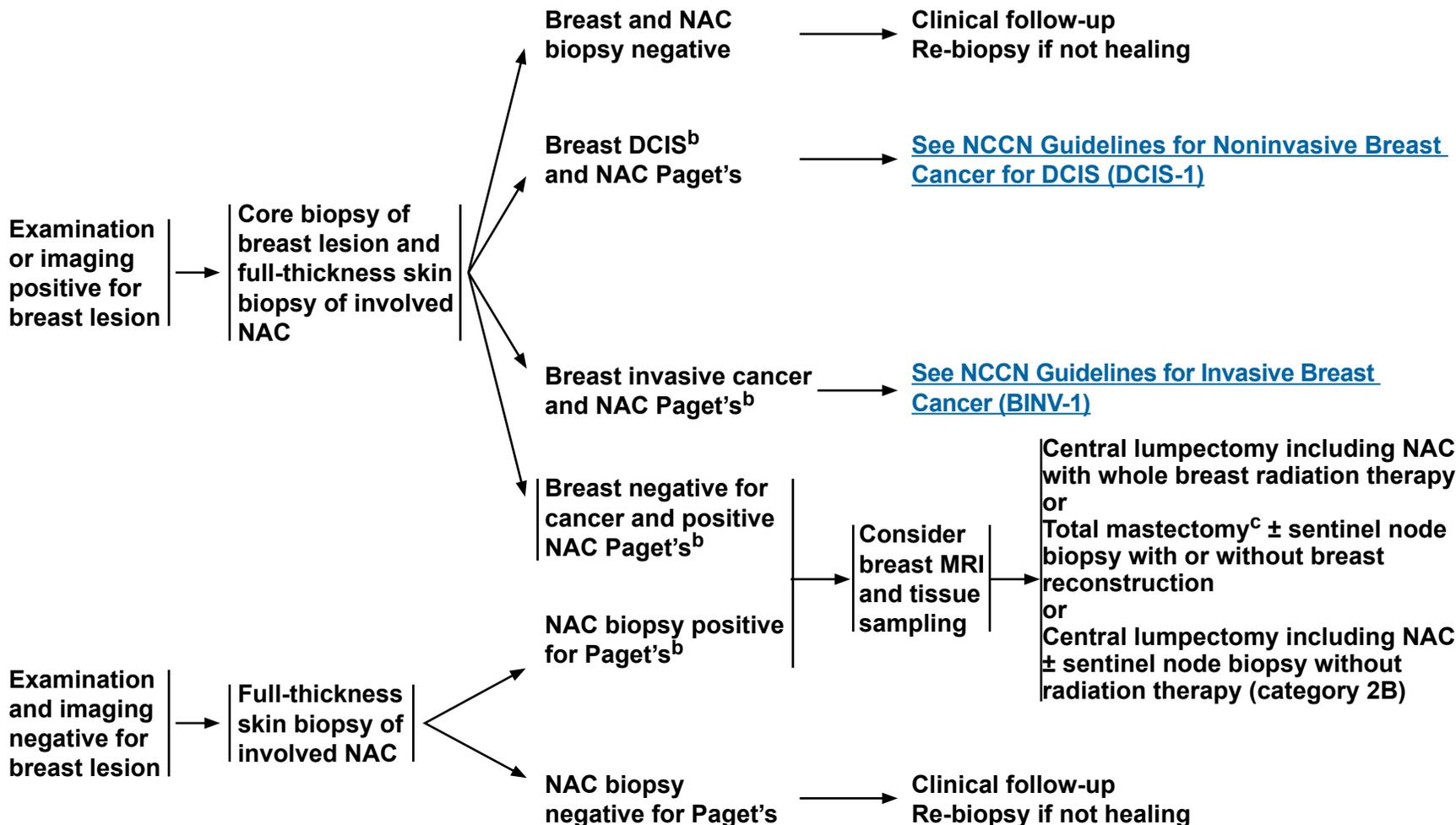
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 2.2017

Paget's Disease

WORKUP



Appropriate systemic adjuvant therapy as clinically indicated

[See NCCN Guidelines for DCIS or Invasive Breast Cancer](#)

^bTo assess the extent of disease or to confirm additional disease, consider MRI. [See Principles of Dedicated Breast MRI Testing \(BINV-B\)](#).

^cMastectomy is always an option with any manifestation of Paget's disease ([See Discussion section](#)).

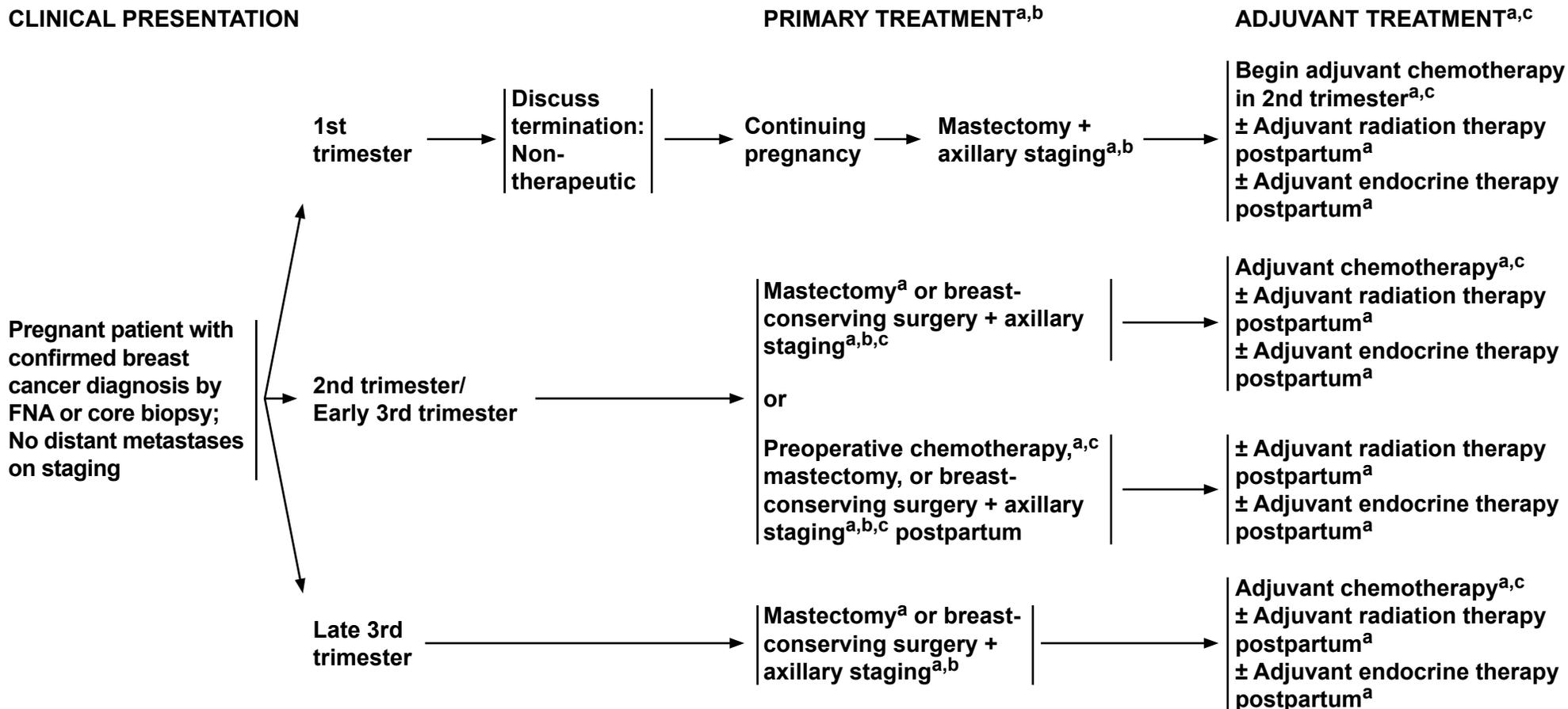
Note: All recommendations are category 2A unless otherwise indicated.

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



NCCN Guidelines Version 2.2017

Breast Cancer During Pregnancy



^aConsiderations 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 ([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. Considerations for postpartum chemotherapy are the same as for non-pregnancy-associated breast cancer.

^bUse of blue dye is contraindicated in pregnancy; radiolabeled sulfur colloid appears to be safe for sentinel node biopsy in pregnancy. [See Surgical Axillary Staging \(BINV-D\)](#).

^cThere are insufficient safety data to recommend general use of taxanes during pregnancy. However, the use of paclitaxel weekly administration after the first trimester is acceptable if clinically indicated by disease status. The use of anti-HER2 therapy is contraindicated during pregnancy.

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

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



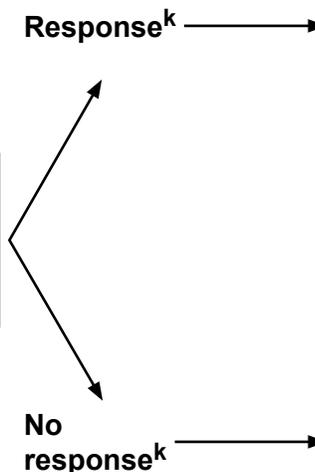
NCCN Guidelines Version 2.2017 Inflammatory Breast Cancer

CLINICAL PRESENTATION^a WORKUP

Clinical pathologic diagnosis of inflammatory breast cancer (IBC) Stage T4d, N0-N3, M0

- History and physical exam by multidisciplinary team
- CBC
- Comprehensive metabolic panel, including liver function tests and alkaline phosphatase
- Pathology review^b
- Determination of tumor ER/PR status and HER2 status^c
- Bilateral diagnostic mammogram, ultrasound as necessary
- Breast MRI (optional)
- Fertility counseling if premenopausal^d
- Bone scan or sodium fluoride PET/CT (category 2B)^e
- Chest/abdominal/pelvic diagnostic CT with contrast (category 2B)
- Chest diagnostic CT with contrast (if pulmonary symptoms are present)
- Genetic counseling if patient is high risk for hereditary breast cancer^f
- FDG PET/CT^{g,h} (optional)

Preoperative systemic therapy,ⁱ anthracycline + taxane (preferred).ⁱ If tumor HER2 positive, HER2-targeted therapy^j



^aInflammatory 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. The differential diagnosis includes cellulitis of the breast or mastitis. Pathologically, a tumor is typically present in the dermal lymphatics of the involved skin, but dermal lymphatic involvement is neither required, nor sufficient by itself for a diagnosis of inflammatory breast cancer.

^bThe panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. <http://www.cap.org>.

^cSee Principles of HER2 Testing (BINV-A).

^dSee Fertility and Birth Control (BINV-C).

^eIf FDG PET/CT is performed and clearly indicates bone metastasis on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed.

^fSee NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

^gFDG PET/CT can be performed at the same time as diagnostic CT. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.

^hFDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to standard staging studies.

ⁱSee Preoperative Systemic Therapy/Adjuvant Chemotherapy (BINV-K).

^jA pertuzumab-containing regimen may be administered preoperatively to patients with HER2-positive IBC.

^kThe accurate assessment of in-breast tumor or regional lymph node response to preoperative systemic therapy is difficult, and should include physical examination and performance of imaging studies (mammogram and/or breast MRI) that were abnormal at the time of initial tumor staging. Selection of imaging methods prior to surgery should be determined by the multidisciplinary team.

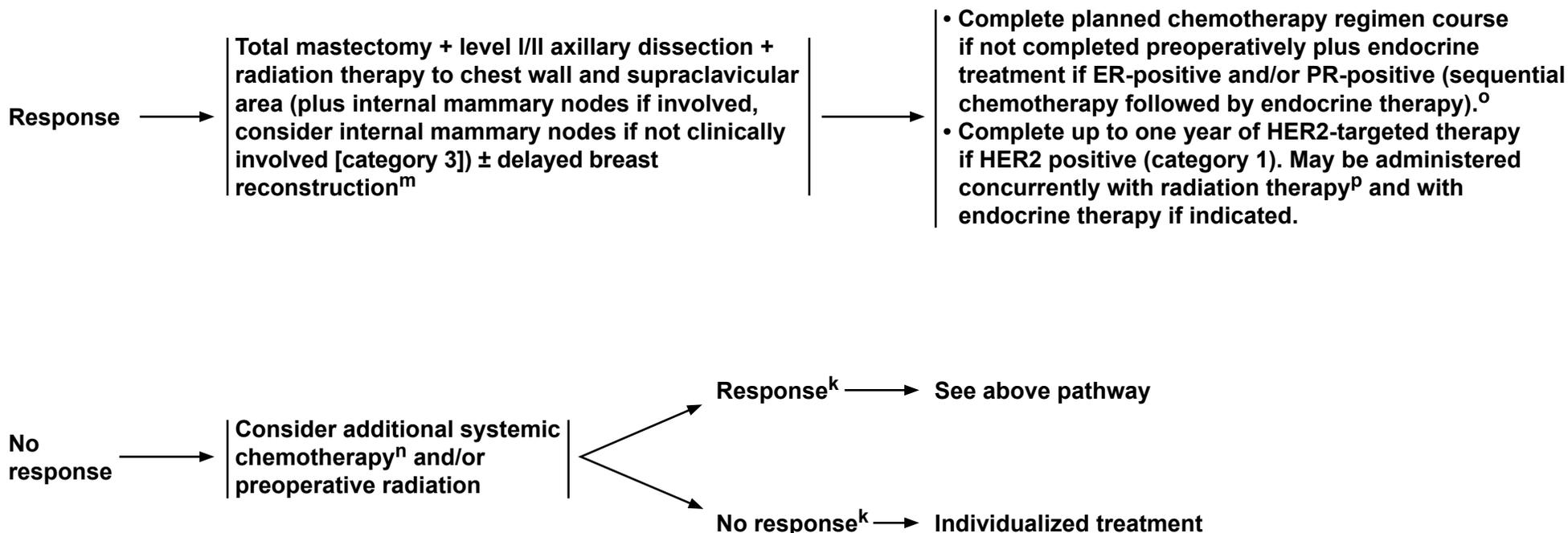
Note: All recommendations are category 2A unless otherwise indicated.

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



NCCN Guidelines Version 2.2017 Inflammatory Breast Cancer

TREATMENT^l



^kThe accurate assessment of in-breast tumor or regional lymph node response to preoperative systemic therapy is difficult, and should include physical examination and performance of imaging studies (mammogram and/or breast MRI) that were abnormal at the time of initial tumor staging. Selection of imaging methods prior to surgery should be determined by the multidisciplinary team.

^lPatients with stage IV or recurrent IBC should be treated according to the guideline for recurrence/stage IV disease ([BINV-17](#) to [BINV-22](#)).

^m[See Principles of Breast Reconstruction Following Surgery \(BINV-H\)](#).

ⁿ[See Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer \(BINV-O\)](#).

^o[See Adjuvant Endocrine Therapy \(BINV-J\)](#).

^p[See Principles of Radiation Therapy \(BINV-I\)](#).

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

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



NCCN Guidelines Version 2.2017

Breast Cancer Staging

Table 1

**American Joint Committee on Cancer (AJCC)
TNM Staging System For Breast Cancer**

Primary Tumor (T) The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cutoff for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2.0 cm. Designation should be made with the subscript “c” or “p” modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

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 NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted
T1	Tumor ≤20 mm or less in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension

T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules).

Note: Invasion of the dermis alone does not qualify as T4

T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

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

**Table 1 (continued)****Regional Lymph Nodes (N)****Clinical**

NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastasis
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the <i>absence</i> of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected* ipsilateral internal mammary nodes and in the <i>absence</i> of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases 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)

**Note: Clinically detected* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration.

Pathologic (pN)*

pNX Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)

pN0 No regional lymph node metastasis histologically

Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.

pN0(i-)	No regional lymph node metastasis histologically, negative IHC
pN0(I+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
pN0(mol-)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR),** but no regional lymph node metastases detected by histology or IHC

* Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for “sentinel node,” for example, pN0(sn).

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

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

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

**Table 1 (continued)****Pathologic (pN) (continued)**

pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the <i>absence</i> of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected**** internal mammary lymph nodes in the <i>absence</i> of axillary lymph node metastases
pN3	Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the <i>presence</i> of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected*** ; or in ipsilateral supraclavicular lymph nodes

pN3a	Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the <i>presence</i> of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes

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

**** “Clinically detected” is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

Distant Metastasis (M)

M0	No clinical or radiographic evidence of distant metastases
cM0(I+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

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

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



NCCN Guidelines Version 2.2017

Breast Cancer Staging

Table 1 (continued)

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage 0	Tis	N0	M0	Stage IIIA	T0	N2	M0
Stage IA	T1*	N0	M0		T1*	N2	M0
Stage IB	T0	N1mi	M0		T2	N2	M0
	T1*	N1mi	M0		T3	N1	M0
Stage IIA	T0	N1**	M0		T3	N2	M0
	T1*	N1**	M0	Stage IIIB	T4	N0	M0
	T2	N0	M0		T4	N1	M0
Stage IIB	T2	N1	M0		T4	N2	M0
	T3	N0	M0	Stage IIIC	Any T	N3	M0
				Stage IV	Any T	Any N	M1

* T1 includes T1mi

** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

- M0 includes M0(i+).
- The designation pM0 is not valid; any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
- Stage designation may be changed if postsurgical 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.
- Postneoadjuvant therapy is designated with “yc” or “yp” prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

HISTOLOGIC GRADE (G)

All invasive breast carcinomas should be graded. The Nottingham combined histologic grade (Elston-Ellis modification of Scarff–Bloom–Richardson grading system) is recommended.^{1,2} 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 designated as 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)

HISTOPATHOLOGIC TYPE

The histopathologic types are the following:

In situ Carcinomas

- | | |
|---------------------------------|--|
| NOS (not otherwise specified) | Papillary (predominantly micropapillary pattern) |
| Intraductal | Tubular |
| Paget's disease and intraductal | Lobular |

Invasive Carcinomas

- | | |
|--------------------------------|----------------------------------|
| NOS | Paget's disease and infiltrating |
| Ductal | Undifferentiated |
| Inflammatory | Squamous cell |
| Medullary, NOS | Adenoid cystic |
| Medullary with lymphoid stroma | Secretory |
| Mucinous | Cribriform |

¹Harris L, Fritsche H, Mennel R, et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. *J Clin Oncol* 2007;25:5287–312.

²Singley SE, Allred C, Ashley P, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. *J Clin Oncol* 2002;20:3628–36.

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, Seventh Edition (2010) published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, 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 SBM, on behalf of the AJCC.

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

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



NCCN Guidelines Version 2.2017 Breast Cancer

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 05/06/16

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

Table of Contents

Overview	2
Literature Search Criteria and Guidelines Update Methodology	2
Staging	3
Pathology Assessment	3
Treatment Approach	5
Pure Noninvasive Carcinomas (Stage 0)	6
Lobular Carcinoma in Situ	6
Ductal Carcinoma in Situ	7
Invasive Breast Cancer	13

Stage I, IIA, IIB, or III A (T3, N1, M0)	13
Workup	13
Locoregional Treatment	15
Breast Reconstruction	22
Systemic Therapies (Preoperative and Adjuvant)	26
Post-Therapy Surveillance and Follow-up	45
Stage III Invasive Breast Cancer	45
Staging and Workup	45
Operable Locally Advanced Breast Cancer	47
Inoperable Locally Advanced Breast Cancer	47
Post-Therapy Surveillance and Follow-up for Stage I-III	48
Stage IV Metastatic or Recurrent Breast Cancer	50
Staging and Workup	50
Management of Local Disease Only	51
Management of Stage IV or Recurrent Metastatic Disease	52
Surgery for Stage IV or Recurrent Metastatic Disease	63
Monitoring Metastatic Disease	64
Special Situations	65
Paget's Disease	65
Phyllodes Tumors of the Breast	66
Breast Cancer During Pregnancy	67
Inflammatory Breast Cancer	69
Axillary Breast Cancer	72
Summary	73
References	74

Overview

Breast cancer is the most frequently diagnosed cancer globally and is the leading cause of cancer-related death in women.¹ The American Cancer Society estimates that 249,260 Americans will be diagnosed with invasive breast cancer and 40,890 will die of the disease in the United States in 2016.²

Historically, white women have had the highest breast cancer incidence rates among women aged 40 years and older; however, incidence rates are converging among white and African American women, particularly among women aged 50 to 59 years.³ Since 1991, breast cancer mortality has been declining,^{4,5} suggesting a benefit from the combination of early detection and more effective treatment.⁶

The etiology of the vast majority of breast cancer cases is unknown. However, numerous risk factors for the disease have been established. These risk factors include: female gender; increasing patient age; family history of breast cancer at a young age; early menarche; late menopause; older age at first live childbirth; prolonged hormone replacement therapy; previous exposure to therapeutic chest wall irradiation; benign proliferative breast disease; increased mammographic breast density; and genetic mutations such as of the *BRCA1/2* genes. However, except for female gender and increasing patient age, these risk factors are associated with only a minority of breast cancers. Women with a strong family history of breast cancer should be evaluated according to the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#). Women at increased risk for breast cancer (generally those with $\geq 1.7\%$ 5-year risk for breast cancer using the Gail model of risk assessment⁷) may

consider risk reduction strategies (see [NCCN Guidelines for Breast Cancer Risk Reduction](#)).

Proliferative abnormalities of the breast are limited to the lobular and ductal epithelium. In both the lobular and ductal epithelium, a spectrum of proliferative abnormalities may be seen, including hyperplasia, atypical hyperplasia, in situ carcinoma, and invasive carcinoma.⁸ Approximately 85% to 90% of invasive carcinomas are ductal in origin.⁹ The invasive ductal carcinomas include unusual variants of breast cancer, such as mucinous, adenoid cystic, and tubular carcinomas, which have especially favorable natural histories.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Breast Cancer, an electronic search of the PubMed database was performed to obtain key literature in Breast Cancer, published between 06/19/14 and 06/29/15, using the following search terms: Breast Cancer OR DCIS OR Inflammatory Breast Cancer OR Phyllodes. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.¹⁰

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The potential relevance of the PubMed search was examined. The data from key PubMed articles selected by the panel for review during the

Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section.

Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN [webpage](#).

Staging

All patients with breast cancer should be assigned a clinical stage of disease, and, if appropriate evaluation is available, a pathologic stage of disease. The routine use of staging allows for efficient identification of local treatment options, assists in identifying systemic treatment options, allows for the comparison of outcome results across institutions and clinical trials, and provides baseline prognostic information.

Effective January 2010, the AJCC implemented a revision of the 7th edition of the AJCC Cancer Staging Manual containing important changes and additions to the TNM staging system for breast cancer.¹¹ This revision differs from the 2003 edition of the AJCC staging manual by providing more direction relating to the specific methods of clinical and pathologic tumor measurement; recommending that all invasive cancers should be assigned a combined histologic tumor grade using the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system; providing clarification of the classification of isolated tumor cells in axillary lymph node (ALN) staging; subdividing stage I into stage IA and IB based upon the presence or absence of nodal micrometastases (N0 versus N0mi+); and defining a new category of M0(i+) disease referring to tumor cells microscopically detectable in bone marrow or circulating blood or found incidentally in other tissues not exceeding 0.2 mm in patients who have no signs or symptoms of metastasis. This

version of the AJCC staging manual also recommends the collection of biomarkers such as hormone receptor status (estrogen receptor [ER] and progesterone receptor [PR]) and human epidermal growth factor receptor 2 [HER2] status, although these characteristics do not specifically influence assigned stage of disease.

Pathology Assessment

A central component of the treatment of breast cancer is full knowledge of extent of disease and biologic features. These factors contribute to the determination of the stage of disease, assist in the estimation of the risk that the cancer will recur, and provide information that predicts response to therapy (eg, ER, PR, HER2). These factors are determined by examination of excised tissue and are provided in a written pathology report. Accurate pathology reporting requires communication between the clinician and the pathologist relating to relevant patient history, prior breast biopsies, prior irradiation to the chest, pregnancy status, characteristics of the abnormality biopsied (eg, palpable, mammographically detected microcalcifications), clinical state of lymph nodes, presence of inflammatory change or other skin abnormality, and any prior treatment administered (eg, chemotherapy, radiation therapy). The specimens should be oriented for the pathologist, and specific requests for determination of biomarkers should be stated (eg, ER, PR, and HER2 status). The use of consistent, unambiguous standards for reporting is strongly encouraged. Data from both national and local surveys show that as many as 50% of pathology reports for breast cancer are missing some elements critical to patient management.^{12,13} Significant omissions include failure to orient and report surgical margins and failure to report tumor grade consistently.

The College of American Pathologists (CAP) has developed pathology reporting protocols to promote complete and standardized reporting of

malignant specimens. CAP provides a protocol for each disease site that includes cancer case summaries (checklists) along with background documentation. These checklists form the basis for a synoptic, standardized reporting of pathologic findings. The checklists are available without charge through the CAP website at www.cap.org. Consistent, unambiguous, and complete pathology reporting is a cornerstone of quality breast cancer care, and the NCCN Breast Cancer Panel endorses the use of the CAP protocols for reporting the pathologic analysis of all breast cancer specimens.

ER status should be determined for all samples of ductal carcinoma in situ (DCIS), and ER and PR tumor status should be determined for all samples of invasive breast cancer. ER and PR tumor status is normally determined by immunohistochemistry (IHC) testing. Although this method is considered reliable when performed by experienced pathology personnel, there have been several reports indicating that the reliability of ER and PR determinations can vary widely from one laboratory to another.¹⁴⁻¹⁶ These inter-laboratory differences may be attributable to the diverse methodologies and diverse interpretation schema used to evaluate tumor hormonal status. An NCCN Task Force and a panel of ASCO and CAP members have reviewed this topic and issued recommendations on ER and PR testing in breast cancer.^{17,18} Breast cancers that have at least 1% of cells staining positive for ER should be considered ER-positive.¹⁷⁻¹⁹

Principles of HER2 Testing

Along with ER and PR, the determination of HER2 tumor status is recommended for all newly diagnosed invasive breast cancers and for first recurrences of breast cancer whenever possible. The NCCN Breast Cancer Panel endorses CAP accreditation for anatomic pathology laboratories performing HER2 testing.

HER2 status can be assessed by measuring the number of *HER2* gene copies using in situ hybridization (ISH) techniques, or by a complementary method in which the quantity of HER2 cell surface receptors is assessed by IHC.²⁰ Assignment of HER2 status based on mRNA assays or multigene arrays is not recommended. The accuracy of HER2 assays used in clinical practice is a major concern, and results from several studies have shown that false-positive²¹⁻²⁴ as well as false-negative^{21,25} HER2 test results are common. A joint panel from ASCO and CAP has issued updated HER2 testing guidelines to avoid such false-positive or false-negative results. These updated guidelines have been published in the *Archives of Pathology & Laboratory Medicine* and ASCO's *Journal of Clinical Oncology*.^{26,27} The NCCN Panel endorses these updated ASCO/CAP recommendations for quality HER2 testing and has outlined these recommendations in *Principles of HER2 Testing* in the NCCN Guidelines for Breast Cancer.

HER2 testing should be performed in laboratories accredited by CAP or another equivalent authority to carry out such testing. Further, these laboratories should have standardized HER2 testing procedures in place, as well as programs to periodically evaluate the proficiency of personnel performing HER2 testing. HER2 test reports should also include information on site of tumor, specimen type, histologic type, fixation method and time, block examined, and details on the HER2 testing method(s) used. Clinicians should be familiar with the significance of these criteria when making clinical recommendations for an individual patient.

HER2-Positive Result

Consistent with the ASCO/CAP guidelines, the NCCN Panel considers either IHC or ISH with either a single or dual probe as an acceptable method for making an initial determination of HER2 tumor status. Breast cancer tumors are classified as HER2-positive if they are scored as 3+

by an IHC method defined as uniform membrane staining for HER2 in 10% or more of tumor cells or demonstrate *HER2* gene amplification by an ISH method (single probe, average *HER2* copy number ≥ 6.0 signals/cell; dual probe *HER2/CEP17* ratio ≥ 2.0 with an average *HER2* copy number ≥ 4.0 signals/cell; dual probe *HER2*/chromosome enumeration probe (*CEP*)17 ratio ≥ 2.0 with an average *HER2* copy number < 4.0 signals/cell; and *HER2/CEP17* ratio < 2.0 with an average *HER2* copy number ≥ 6.0 signals/cell).

High average copy number of HER2 (≥ 6.0 signals/cell) is considered positive regardless of the *HER2/CEP17* ratio. The rationale cited by the joint committee for including rare scenarios such as HER2 positivity when dual probe *HER2/CEP17* ratio is greater than or equal to 2.0 and average HER2 copy number is less than 4.0 signals/cell is that the first-generation trials of adjuvant trastuzumab included a small number of patients with a *HER2/CEP17* ratio greater than or equal to 2.0 and an average *HER2* copy number less than 4.0 signals/cell. There is no trend in these data, suggesting that these patients were not responsive to trastuzumab and the trastuzumab has a favorable safety profile.

Equivocal Result

The NCCN Panel agrees with the ASCO/CAP HER2 committee that results of IHC are equivocal if scored as IHC 2+ “based on circumferential membrane staining that is incomplete and/or weak/moderate and within greater than 10% of the invasive tumor cells or complete and circumferential membrane staining that is intense and within less than or equal to 10% of the invasive tumor cells.” In such cases, the panel recommends reflex testing using the ISH method on the same specimen *or* repeating tests if a new specimen is available.

Similarly, samples with equivocal results by an ISH assay (for example, single probe ISH average *HER2* copy number ≥ 4.0 and < 6.0 signals/cell; and dual probe *HER/CEP17* ratio < 2.0 with an average *HER2* copy number ≥ 4.0 signals/cell) must be confirmed by reflex testing using the IHC method on the same specimen *or* repeating tests if a new specimen is available.

Treatment Approach

The treatment of breast cancer includes the treatment of local disease with surgery, radiation therapy, or both, and systemic treatment with chemotherapy, endocrine therapy, biologic therapy, or combinations of these. The need for and selection of various local or systemic therapies are based on several prognostic and predictive factors. These factors include tumor histology, clinical and pathologic characteristics of the primary tumor, ALN status, tumor hormone receptor (ER/PR) content, tumor HER2 status, multi-gene testing, presence or absence of detectable metastatic disease, patient comorbid conditions, patient age, and menopausal status. One percent of breast cancers occur in men,⁵ and men with breast cancer should be treated similarly to postmenopausal women, except that the use of aromatase inhibitors is ineffective without concomitant suppression of testicular steroidogenesis.^{28,29} Patient preference is a major component of the decision-making process, especially in situations in which survival rates are equivalent among the available treatment options.

In terms of treatment, breast cancer may be divided into: 1) the pure noninvasive carcinomas, which include lobular carcinoma in situ (LCIS) and DCIS (stage 0); 2) operable, locoregional invasive carcinoma with or without associated noninvasive carcinoma (clinical stage I, stage II, and some stage IIIA tumors); 3) inoperable locoregional invasive carcinoma with or without associated noninvasive carcinoma (clinical

stage IIIB, stage IIIC, and some stage IIIA tumors); and 4) metastatic (stage IV) or recurrent carcinoma.

Pure Noninvasive Carcinomas (Stage 0)

Both LCIS and DCIS may be difficult to distinguish from atypical hyperplasia or from invasive carcinomas with early invasion.^{30,31} Therefore, pathology review of all cases is recommended.

Bilateral diagnostic mammography should be performed to identify the presence of multiple primary tumors and to estimate the extent of the noninvasive lesion. Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer as defined by the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#). Testing for genetic mutations without formal genetic counseling is discouraged.

The goal of treatment of pure in situ carcinoma is either preventing the occurrence of invasive disease or diagnosing the development of an invasive component when still localized to the breast. Patients with invasive disease, even if microinvasive, on pathology review or during re-excision, mastectomy, or ALN staging should be treated according to the stage-appropriate guideline for invasive carcinoma.

Lobular Carcinoma in Situ (Stage 0, Tis, N0, M0)

Workup

Recommended workup includes history and physical examination, diagnostic bilateral mammography, and pathology review.

Controversy exists regarding whether an open surgical excision should be performed of the region of LCIS diagnosed by core biopsy and that is not associated with a mammographic structural abnormality or residual

mammographic calcifications. Small retrospective studies have concluded that excision following the diagnosis of LCIS on core needle biopsy is not necessary.³²⁻³⁴ Other studies have shown that 17% to 27% of patients with LCIS diagnosed by core needle biopsy are upgraded to having invasive cancer or DCIS after larger excisional biopsy.³⁵⁻³⁹ Based on core needle biopsies, it may be possible to identify subsets of patients with LCIS who can be safely spared a surgical excision.³⁴ There are some data of small groups of patients suggesting that LCIS subtypes, including pleomorphic LCIS and LCIS associated with necrosis, carry a risk for associated invasive carcinoma similar to DCIS. Therefore, according to the NCCN Panel, it is reasonable to perform surgical excision of LCIS found in a core biopsy to exclude an associated invasive cancer or DCIS. More than 4 foci of LCIS may also increase the risk for upstaging on surgical biopsy.⁴⁰ The NCCN Panel recommends that LCIS of the usual type (involving <4 terminal ductal lobular units in a single core) found on core biopsy, as a result of routine screening for calcifications and without imaging discordance, may be managed by imaging follow-up.

Primary Treatment

Classic LCIS does not require surgical treatment. There is evidence to support the existence of histologically aggressive variants of LCIS (eg, “pleomorphic” LCIS), which may have a greater potential than classic LCIS to develop into invasive lobular carcinoma.⁴¹ Clinicians may consider complete excision with negative margins for pleomorphic LCIS. However, outcomes data regarding treatment of patients with pleomorphic LCIS are lacking, due in part to a paucity of histologic categorization of variants of LCIS. Therefore, recommendations on the treatment of pleomorphic LCIS as a distinct entity of LCIS have not been made by the panel (see [NCCN Guidelines for Breast Screening and Diagnosis](#)).

Patients with a confirmed diagnosis of LCIS should be counseled regarding reducing the risk of developing invasive cancer (see [NCCN Guidelines for Breast Cancer Risk Reduction](#)).

Surveillance

Follow-up of patients with LCIS includes interval history and physical examinations every 6 to 12 months. Annual diagnostic mammography is recommended in patients being followed with clinical observation; see also the [NCCN Guidelines for Breast Cancer Screening and Diagnosis](#). Patients receiving a risk reduction agent should be monitored as described in the [NCCN Guidelines for Breast Cancer Risk Reduction](#).

Ductal Carcinoma in Situ

(Stage 0, Tis, N0, M0)

Workup

The recommended workup and staging of DCIS includes: history and physical examination; bilateral diagnostic mammography; pathology review; and tumor ER determination. Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer as defined by the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#).

Although HER2 status is of prognostic significance in invasive cancer, its importance in DCIS has not been elucidated. To date, studies have either found unclear or weak evidence of HER2 status as a prognostic indicator in DCIS.⁴²⁻⁴⁵ The NCCN Panel concluded that knowing the HER2 status of DCIS does not alter the management strategy and routinely should not be determined.

MRI has been prospectively shown to have a sensitivity of up to 98% for high-grade DCIS.⁴⁶ In a prospective, observational study, 193 women with pure DCIS underwent both mammography and MRI imaging

preoperatively; 93 (56%) women were diagnosed by mammography and 153 (92%) were diagnosed by MRI ($P < .0001$). Of the 89 women with high-grade DCIS, 43 (48%) who were not diagnosed by mammography were diagnosed by MRI alone. Another study evaluated the role of MRI in determining appropriate candidacy for partial breast irradiation for women with DCIS. Twenty percent of women with DCIS were identified as ineligible for partial breast irradiation after a bilateral breast MRI.⁴⁷ However, large prospective clinical trials will be necessary to further investigate the clinical role of MRI for diagnosing DCIS and to investigate its effect on recurrence rates or mortality. The NCCN Panel has included breast MRI as optional during the initial workup of DCIS, noting that the use of MRI has not been shown to increase likelihood of negative margins or decrease conversion to mastectomy with DCIS.

Primary Treatment

Seemingly pure DCIS on core needle biopsy will be found to be associated with an invasive cancer on surgical excision in about 25% of patients.⁴⁸

For the vast majority of patients with limited disease where negative margins are achieved with the initial excision or with re-excision, lumpectomy or total mastectomy are appropriate treatment options.

Patients with DCIS and evidence of widespread disease (ie, disease in two or more quadrants) on mammography or other imaging, physical examination, or biopsy require a total mastectomy without lymph node dissection.

Complete ALN dissection is not recommended in the absence of evidence of invasive cancer or proven axillary metastatic disease in patients with apparent pure DCIS, or mammographically detected DCIS with microcalcifications. However, a small proportion of women with

seemingly pure DCIS on initial biopsy will have invasive breast cancer at the time of the definitive surgical procedure and thus will ultimately require ALN staging. In patients with seemingly pure DCIS to be treated with mastectomy or with excision in an anatomic location (eg, tail of the breast), which could compromise the performance of a future sentinel lymph node biopsy (SLNB), an SLNB procedure may be considered.⁴⁹⁻⁵²

Reducing Risk of Recurrence:

Many factors impact recurrence risk, including patient age, tumor size, tumor grade, and margin width. The definition of a negative margin has not been firmly established in DCIS. There appears to be a consensus that margins greater than 10 mm are accepted as negative (but may be excessive and may compromise cosmetic outcome) and margins less than 1 mm are inadequate, but no uniform consensus exists for margin status between these values. With pathologic margins between 1 and 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.

The choice of local treatment does not impact overall disease-related survival; therefore, the individual patient's acceptance of the potential for an increased risk of local recurrence must be considered.

An analysis of specimen margins and specimen radiographs should be performed to ensure that all mammographically detectable DCIS has been excised. In addition, a post-excision mammogram should be considered where appropriate (eg, the mass and/or microcalcifications are not clearly within the specimen).⁵³

Prospective randomized trials have shown that the addition of whole breast radiation to a margin-free excision of pure DCIS decreases the rate of in-breast disease recurrence, but does not affect survival⁵⁴⁻⁶⁰ or distant metastasis-free survival.⁶¹ Whole breast irradiation after breast-conserving surgery reduces the relative risk of a local failure by approximately one half.

There is retrospective evidence suggesting that selected patients have a low risk of in-breast recurrence with excision alone without radiation therapy to the breast.⁶²⁻⁶⁵ For example, in a retrospective review, 10-year disease-free survival (DFS) rates of 186 patients with DCIS treated with lumpectomy alone were 94% for patients with low-risk DCIS and 83% for patients with both intermediate- and high-risk DCIS.⁶²

In another retrospective study of 215 patients with DCIS treated with lumpectomy without radiation therapy, endocrine therapy, or chemotherapy, the recurrence rate over 8 years was 0%, 21.5%, and 32.1% in patients with low-, intermediate- or high-risk DCIS, respectively.⁶³

A multi-institutional, nonrandomized, prospective study of selected patients with low-risk DCIS treated without radiation has also provided some support for the use of excision without radiation in the treatment of DCIS.⁶⁶ At a median follow-up of 6.2 years, the 5-year risk of ipsilateral breast recurrence was 6.1% (95% confidence interval [CI], 4.1%–8.2%) in the subset of patients with low-/intermediate-grade DCIS and median tumor size of 6 mm. Margin widths were greater than or equal to 5 mm in 69.2% and 82.9% of patients in the low-/intermediate-risk and high-risk arms, respectively, with margin widths of greater than or equal to 10 mm or no tumor on re-excision observed in 48.5% and 53.3% of patients in the respective groups.⁶⁶ Although an acceptably low ipsilateral recurrence rate was observed in

the low-/intermediate-grade arm of the study at 5 years, the 7-year ipsilateral recurrence rate in this group of patients was considerably higher (10.5%; 95% CI, 7.5%–13.6%), suggesting that these events may be delayed but not prevented in this population. Ipsilateral breast recurrences were approximately equally divided between invasive breast cancer and DCIS in the low-/intermediate-risk group but only about one-third of patients with an in-breast recurrence in the high-risk group had invasive disease.

Another retrospective study reviewed 220 patients with DCIS treated with breast conservation surgery and radiation. Thirty-six percent received a radiation boost. At 46 months, none of the 79 patients who received a radiation boost experienced a local recurrence, whereas 8 of 141 patients who did not receive a boost experienced a local recurrence.⁶⁷

More recently, a prospective phase II study followed women with low-risk DCIS who underwent wide excision alone (without adjuvant treatment with radiation or tamoxifen). Low-risk criteria for this study included mammographically detected DCIS, measuring ≤ 2.5 cm, with a predominant nuclear grade of 1 or 2, and a margin of ≥ 1 cm or a negative re-excision. The cumulative incidence of local recurrence at 10 years was estimated at 15.5%.⁶⁸

Prospective randomized trials have not been carried out to analyze whether wider margins can replace the need for radiation therapy for DCIS. A retrospective series demonstrated that for margin width of 10 mm, radiation had no additional benefit in reducing the already low local recurrence rate of 4% at the end of 8 years.⁶⁵ Also, if margin width was between 1 mm and less than 10 mm, the addition of radiation therapy led to a non-statistically significant reduction in local recurrence.

However, when margins were less than 1 mm a significant benefit was seen.⁶⁵

A meta-analysis of four large multicenter randomized trials confirmed the results of the individual trials that adding radiation therapy to breast-conserving surgery for DCIS provides a statistically and clinically significant reduction in ipsilateral breast events (HR [hazard ratio], 0.49; 95% CI; 0.41–0.58, $P < .0000$).⁶⁹

Results from a retrospective study of 445 patients with pure DCIS treated by excision alone indicated that margin width was the most important independent predictor of local recurrence, although the trend for decreasing local recurrence risk with increasing margin width was most apparent with margins less than 1 mm and greater than or equal to 10 mm.⁷⁰

In a meta-analysis of 4660 patients with DCIS treated with breast-conserving surgery and radiation, a surgical margin of less than 2 mm was associated with increased rates of ipsilateral breast tumor recurrence compared with margins of 2 mm, although no significant differences were observed when margins of greater than 2 mm to 5 mm or greater than 5 mm were compared with 2-mm margins.⁷¹ The results of this study suggest that wide margins (≥ 2 mm), which can compromise cosmetic outcome, do not provide additional benefit in the population of patients with DCIS receiving radiation therapy following breast-conserving therapy.

A study retrospectively reviewed a database of 2996 patients with DCIS who underwent breast-conserving surgery to investigate the association between margin width and recurrence, controlling all other characteristics.⁷² Wider margins were significantly associated with a

lower rate of recurrence only in women who did not receive radiation therapy ($P < .0001$), but not in those treated with radiation ($P = .95$).⁷²

After 20 years of follow-up, the SweDCIS trial reported 12% (95% CI, 6.5–17.7) reduction in absolute risk of local recurrence and 37.5% reduction in relative risk in women who received radiation therapy.⁷³

A recent prospective randomized trial (RTOG 9804) compared radiation therapy with observation after breast-conserving surgery in a subset of women with defined, mammographically detected low- or intermediate-grade DCIS, measuring less than 2.5 cm with margins ≥ 3 mm.⁷⁴ At 7 years, the local recurrence rate was 0.9% (95% CI, 0.0%–2.2%) in the radiation therapy arm versus 6.7% (95% CI, 3.2%–9.6%) in the observation arm (HR, 0.11; 95% CI, 0.03–0.47; $P < .001$). In the subset of patients with good-risk disease features, the local recurrence rate was low with observation but was decreased significantly with the addition of radiation therapy.⁷⁴

The long-term follow-up of the NSABP B-17 showed that at 15 years, radiation therapy resulted in a 52% reduction of ipsilateral invasive recurrence compared with excision alone (HR, 0.48; 95% CI, 0.33–0.69, $P < .001$).⁶⁰ However, overall survival (OS) and cumulative all-cause mortality rate through 15 years was similar between the two groups (HR for death, 1.08; 95% CI, 0.79–1.48).⁶⁰

Similar findings were reported by a large observational study of the SEER database that included 108,196 patients with DCIS.⁷⁵ In a subgroup analysis at 10 years, of 60,000 women treated with breast-conserving therapy, with or without radiation therapy, although radiation therapy was associated with a 50% reduction in the risk of ipsilateral recurrence (adjusted HR, 0.47 [95% CI, 0.42–0.53]; $P < .001$), breast

cancer-specific mortality was found to be similar (HR, 0.86 [95% CI, 0.67–1.10]; $P = .22$).⁷⁵

NCCN Recommendations for Primary Treatment of DCIS

According to the NCCN Panel, primary treatment options for women with DCIS along with their respective categories of consensus are: lumpectomy plus whole breast radiation therapy (category 1) as decreased rates of local recurrence following lumpectomy have been observed in randomized trials with the addition of whole breast radiation; total mastectomy, with or without SLNB with or without reconstruction (category 2A); or lumpectomy alone followed by clinical observation (category 2B). The option of lumpectomy alone should be considered only in cases where the patient and the physician view the individual as having a low risk of disease recurrence. There is no evidence that OS differs between the three treatment options.

According to the NCCN Panel, 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. Clips are used to demarcate the biopsy area because DCIS may be clinically occult and further surgery may be required pending the margin status review by pathology.

Women treated with mastectomy are appropriate candidates for breast reconstruction (see *Principles of Breast Reconstruction Following Surgery* in the NCCN Guidelines for Breast Cancer). Contraindications to breast-conserving therapy with radiation therapy are listed in the algorithm (see *Special Considerations to Breast-Conserving Therapy Requiring Radiation Therapy* in the NCCN Guidelines for Breast Cancer).

Management of DCIS after Primary Treatment

DCIS falls between atypical ductal hyperplasia and invasive ductal carcinoma within the spectrum of breast proliferative abnormalities. The Breast Cancer Prevention Trial performed by National Surgical Adjuvant Breast and Bowel Project (NSABP) showed a 75% reduction in the occurrence of invasive breast cancer in patients with atypical ductal hyperplasia treated with tamoxifen.^{76,77} These data also showed that tamoxifen led to a substantial reduction in the risk of developing benign breast disease.⁷⁸ The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview analysis showed that, with 5 years of tamoxifen therapy, women with ER-positive or receptor-unknown invasive tumors had a 39% reduction in the annual odds of recurrence of invasive breast cancer.⁴

Similarly, the NSABP B-24 trial found a benefit from tamoxifen for women with DCIS after treatment with breast conservation surgery and radiation therapy. In that study, women with DCIS who were treated with breast-conserving therapy were randomized to receive placebo or tamoxifen. With 13.6 years median follow-up, the women treated with tamoxifen had a 3.4% absolute reduction in ipsilateral in-breast tumor recurrence risk (HR, 0.30; 95% CI, 0.21–0.42; $P < .001$) and a 3.2% absolute reduction in contralateral breast cancers (HR, 0.68; 95% CI, 0.48–0.95; $P = .023$).⁶⁰ The women receiving tamoxifen had a 10-year cumulative rate of 4.6% for invasive and 5.6% for noninvasive breast cancers in the ipsilateral breast compared with 7.3% for invasive and 7.2% for noninvasive breast cancers in placebo-treated women. The cumulative 10-year frequency of invasive and noninvasive breast cancer in the contralateral breast was 6.9% and 4.7% in the placebo and tamoxifen groups, respectively. No differences in OS were noted. A retrospective analysis of ER expression in NSABP B-24 suggests that increased levels of ER expression predict for tamoxifen benefit in terms

of risk reduction for ipsilateral and contralateral breast cancer development following breast-conserving therapy.⁷⁹

A phase III trial for women with excised DCIS randomized subjects in a 2 x 2 fashion to tamoxifen or not and whole breast radiation therapy or not.⁵⁹ With 12.7 years of median follow-up, the use of tamoxifen decreased all new breast events (HR, 0.71; 95% CI, 0.58–0.88; $P = .002$). The use of tamoxifen decreased ipsilateral and contralateral breast events in the subjects not given whole breast radiotherapy (ipsilateral HR, 0.77; 95% CI, 0.59–0.98; contralateral HR, 0.27; 95% CI, 0.12–0.59), but not in those receiving whole breast radiotherapy (ipsilateral HR, 0.93; 95% CI, 0.50–1.75; $P = .80$; contralateral HR, 0.99; 95% CI, 0.39–2.49; $P = 1.0$).

In women with ER- and/or PR-positive DCIS treated by wide local excision with or without breast radiotherapy, a large, randomized, double-blind, placebo-controlled trial (IBIS-II) compared anastrozole ($n = 1471$) with tamoxifen ($n = 1509$). The results demonstrated non-inferiority of anastrozole to tamoxifen.⁸⁰ After a median follow-up of 7.2 years, 67 recurrences were reported with anastrozole versus 77 for tamoxifen; HR 0.89 [95% CI, 0.64–1.23]. A total 33 deaths were recorded for anastrozole and 36 for tamoxifen; HR 0.9393 [95% CI, 0.58–1.50, $P = .78$].⁸⁰ Although the number of women reporting any adverse event was similar between anastrozole (1323 women, 91%) and tamoxifen (1379 women, 93%); the side-effect profiles of the two drugs were different. There were more fractures, musculoskeletal events, hypercholesterolemia, and strokes reported with anastrozole and more muscle spasms, gynecological cancers and symptoms, vasomotor symptoms, and deep vein thromboses reported with tamoxifen.

The NSABP B-35 study randomly assigned 3,104 postmenopausal patients to tamoxifen or anastrozole for 5 years. All patients received breast radiotherapy. Prior to being randomly assigned, patients were stratified by age—younger or older than age 60. The primary endpoint was breast cancer–free interval.⁸¹ Anastrozole treatment resulted in an overall statistically significant decrease in breast cancer-free interval events compared with tamoxifen (HR, 0.73 [95% CI, 0.56–0.96], $P = .0234$). The significant difference in breast cancer-free interval between the two treatments was apparent in the study only after 5 years of follow-up. The estimated percentage of patients with a 10-year breast cancer-free interval was 89.1% in the tamoxifen group and 93.1% in the anastrozole group.⁸¹ In addition, anastrozole resulted in further improvement in breast cancer-free interval, in younger postmenopausal patients (less than 60 years old). With respect to adverse effects, the overall incidence of thrombosis or embolism was higher in the tamoxifen group and the anastrozole group had slightly more cases of arthralgia and myalgia.⁸¹

The results of the IBIS-II and the NSAP-B-35 studies indicate that anastrozole provides benefit as adjuvant treatment for postmenopausal women with hormone-receptor-positive DCIS.

NCCN Recommendations for Management of DCIS after Primary Treatment

According to the NCCN Panel, endocrine therapy, with tamoxifen (for premenopausal and postmenopausal women) or an aromatase inhibitor (for postmenopausal women especially those under 60 years of age or in those with concerns of embolism), may be considered as a strategy to reduce the risk of ipsilateral breast cancer recurrence in women with ER-positive DCIS treated with breast-conserving therapy (category 1 for those undergoing breast-conserving surgery followed by radiation

therapy; category 2A for those undergoing excision alone). The benefit of endocrine therapy for ER-negative DCIS is not known.

Strategies for reducing the risk of recurrence to the contralateral breast are described in the [NCCN Guidelines for Breast Cancer Risk Reduction](#).

Surveillance

According to the NCCN Panel, follow-up of women with DCIS includes interval history and physical examination every 6 to 12 months for 5 years and then annually, as well as yearly diagnostic mammography. In patients treated with breast-conserving therapy, the first follow-up mammogram should be performed 6 to 12 months after the completion of breast-conserving radiation therapy (category 2B). Patients receiving risk reduction agents should be monitored as described in the [NCCN Guidelines for Breast Cancer Risk Reduction](#).

The majority of recurrences of DCIS are in-breast recurrences after breast-conserving therapy, and recurrences mostly occur close to the site of prior disease. In those women for whom the initial DCIS was treated with excision alone, the treatment for a recurrence of DCIS is similar to that followed previously. In women whom the initial DCIS was treated with breast-conserving surgery plus radiation therapy, mastectomy is usually necessary to treat DCIS recurrence. Local recurrences after mastectomy for DCIS should be treated with wide local excision with consideration for chest wall irradiation.

Overall, approximately half of the local recurrences after initial treatment for a pure DCIS are again DCIS, and the others are invasive cancer. Those with local recurrences that are invasive should receive systemic treatment as appropriate for a newly diagnosed invasive breast cancer.

Invasive Breast Cancer

Stage I, IIA, IIB, or III A (T3, N1, M0)

Workup

The recommended workup of localized invasive breast cancer includes: history and physical exam; bilateral diagnostic mammography; breast ultrasonography, if necessary; determination of tumor hormone receptor status (ER and PR determinations); determination of HER2–receptor status; and pathology review. Complete blood count (CBC) and liver function tests (LFTs) have no added benefit in the detection of underlying metastatic disease in asymptomatic early-stage breast cancer patients.⁸² In addition, monitoring of disease relapse with any tumor markers is *not* recommended.

Use of MRI is optional and is not universally recommended by experts in the field. Breast MRI advocates note its high sensitivity for evaluation of extent of disease, particularly for invasive cancer and in dense breasts where mammographically occult disease is more likely to elude preoperative detection. MRI detractors note that MRI has a high percentage of false-positive findings resulting in further diagnostic workup in many circumstances including MRI-guided biopsy.⁸³⁻⁸⁵ MRI findings tend to overestimate extent of disease⁸⁶ resulting in increase in frequency of mastectomies.⁸⁷⁻⁹⁰

MRI findings alone are insufficient to determine whether breast conservation therapy is optimal as additional tissue sampling is needed to verify true malignant disease warranting excision. MRI use may increase mastectomy rates by identifying mammographically occult disease satellites that would have been adequately treated with post-lumpectomy radiation had the disease remained undiscovered without MRI.⁹⁰

Two prospective randomized studies have examined the utility of pre-operative MRI in determining disease extent, and neither demonstrated improvement in rates of post-lumpectomy re-excision.^{91,92} Retrospective review of utility MRI showed conflicting outcome results, one with benefit⁹³ and another without.⁹⁴ One systematic review⁸⁵ documented that breast MRI staging altered surgical treatment in 7.8% to 33.3% of women,⁸⁵ however no differences in local recurrence or survival have yet been demonstrated. In addition, there is no evidence that use of breast MRI increases rates of margin-negative resection.^{95,96}

If breast MRI imaging is performed, a dedicated breast coil, an imaging team experienced with breast MRI guided biopsy, and multidisciplinary treatment team are the standard of care. Clinically positive axillary nodes and occult primary breast cancer or Paget's disease of the nipple with breast primary not identified on mammography, ultrasound, or physical examination are specific indications for breast MRI imaging. MRI may also be useful for the evaluation of breast cancer response to preoperative systemic therapy and to assess the potential for breast-conserving therapy.

Pathology Assessment: Full knowledge of extent of disease and biologic features is central to the treatment of breast cancer. Several factors contribute to the determination of the disease staging, recurrence risk assessment, and predictive response (ie, ER, PR, HER2). The excised tissue detailing the written pathology report details these key factors. The accuracy of pathology reporting requires communication between the clinician and the pathologist relating pertinent patient history, prior breast biopsies, prior chest irradiation, pregnancy status, biopsy characteristics (ie, palpable, mammographically detected microcalcifications), clinical state of lymph nodes, presence of inflammatory change or other skin abnormality, and any prior treatment administered (ie, chemotherapy, radiation therapy).

The specimens should be oriented for the pathologist, and specific requests for determination of biomarkers should be stated (eg, ER, PR, and HER2 status). Data from both national and local surveys show that as many as 50% of pathology reports for breast cancer are missing some elements critical to patient management.^{12,13} Significant omissions include failure to orient and report surgical margins and failure to report tumor grade consistently. CAP has developed pathology reporting protocols to promote complete and standardized reporting of malignant specimens (www.cap.org). The NCCN Breast Cancer Panel endorses the use of the CAP protocols for reporting the pathologic analysis of all breast cancer specimens.

Genetic counseling: For patients considered to be at high risk for hereditary breast cancer as defined by the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#), genetic counseling is recommended

Distress Assessment: Levels of distress may vary in patients and should be addressed individually. Psychological distress can be impacted by body image and other factors. Younger women have higher rates of psychosocial distress than women diagnosed at older ages.⁹⁷⁻¹⁰¹ The NCCN Breast Cancer Panel recommends assessing for distress in patients newly diagnosed with breast cancer.

Fertility Counseling: Numerous epidemiologic studies have demonstrated that child-bearing after treatment for invasive breast cancer does not increase rates of recurrence or death from breast cancer.¹⁰² The offspring of pregnancies after treatment for breast cancer do not have an increased rate of birth defects or other serious childhood illness. However, treatment for breast cancer, especially with cytotoxic agents, may impair fertility.

Many women, especially those younger than age 35, regain menstrual function within 2 years of completing chemotherapy.¹⁰³ Resumption of menses does not necessarily correlate with fertility, and fertility may be preserved without menses. All premenopausal patients should be informed about the potential impact of chemotherapy on fertility and asked about their desire for potential future pregnancies.

A decision for fertility preservation should include multiple factors such as patient preference, tumor stage and biology, age of the patient, risk of premature ovarian failure based on anticipated type and duration of chemotherapy and/or endocrine therapy, as well as the timing and duration allowed for fertility preservation.

Several studies report lower rates of fertility discussion among female patients with cancer¹⁰⁴⁻¹⁰⁶ despite the updated ASCO guidelines stating that patients should not be excluded from consideration for discussion of fertility preservation for any reason, including parity, prognosis, age, and socioeconomic status.¹⁰⁷ The NCCN Panel recommends that all women of childbearing potential should have a discussion with their treating physicians. Patients who desire to bear children after systemic therapy should be referred to a fertility specialist prior to initiating systemic (chemotherapy or endocrine) therapy.¹⁰⁷⁻¹¹³

Randomized trials have demonstrated that GnRH agonists (such as goserelin) administered prior to initiating chemotherapy and then administered concurrently with adjuvant chemotherapy protect against ovarian failure and reduce the risk of early menopause.¹¹⁴⁻¹¹⁷ In one trial goserelin improved the probability of pregnancy from 11% to 21% in patients with hormone receptor-negative early-stage breast cancer.¹¹⁷ Smaller historical experiences in patients with hormone receptor-positive disease have conflicting results with respect to the protective effects of GnRH agonists in fertility preservation.

Patients should be informed of all the various modalities available to minimize gonadal damage and preserve ovarian function and future fertility. The fertility specialist should discuss specifics of fertility preservation options inclusive of types of hormonal interventions and risks involved with ovarian stimulation, embryo or oocyte cryopreservation, and other investigational options, as well as the probability of successful gestation and childbirth.^{118,119}

Combining the various modalities for a specific patient may increase the odds of preservation of future fertility. It is important for fetal safety that women actively avoid becoming pregnant during breast cancer treatment. Also see [NCCN Guidelines for Adolescent and Young Adult Oncology](#).

Additional Workup

The panel has re-iterated that routine systemic imaging is *not* indicated for patients with early breast cancer *in the absence* of signs/symptoms of metastatic disease.¹²⁰ These recommendations are based on studies showing no additional value of these tests in patients with early-stage disease.¹²¹⁻¹²³ In one study, metastases were identified by bone scan in 5.1%, 5.6%, and 14% of patients with stage I, II, and III disease, respectively, and no evidence of metastasis was detected by liver ultrasonography or chest radiography in patients with stage I or II disease.¹²¹ For patients with stage III breast cancer, the prevalence of a positive liver ultrasound and positive chest x-ray was 6% and 7%, respectively.¹²¹

For patients presenting with disease confined to the breast (stage I to II) the NCCN Panel does not recommend routine systemic imaging in the absence of signs or symptoms suspicious for metastatic disease. According to the panel, additional tests may be considered in patients

who present with locally advanced (T3 N1-3 M0) disease and in those with signs or symptoms suspicious for metastatic disease.

CBCs and LFTs may be considered if the patient is a candidate for preoperative systemic therapy, or if otherwise clinically indicated. Additional tests may be considered only based on the signs and symptoms.

A chest diagnostic CT is indicated only if pulmonary symptoms (ie, cough or hemoptysis) are present. Likewise, abdominal imaging using diagnostic CT or MRI is indicated if the patient has elevated alkaline phosphatase, abnormal results on LFTs, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis.

A bone scan is indicated in patients presenting with localized bone pain or elevated alkaline phosphatase. The use of PET or PET/CT scanning is not indicated in the staging of clinical stage I, II, or operable III (T3 N1) breast cancer. The recommendation against the use of PET scanning is supported by the high false-negative rate in the detection of lesions that are small (<1 cm) and/or low grade, the low sensitivity for detection of axillary nodal metastases, the low prior probability of these patients having detectable metastatic disease, and the high rate of false-positive scans.¹²⁴⁻¹²⁷

FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.

Locoregional Treatment

Surgery

In general, patients with early-stage breast cancer undergo primary surgery (lumpectomy or mastectomy) with or without radiation therapy.

Following local treatment, adjuvant systemic therapy may be offered based on primary tumor characteristics, such as tumor size, grade, lymph node involvement, ER/PR status, and expression of HER2-receptor.

Several randomized trials document that mastectomy is equivalent to breast-conserving therapy (lumpectomy with whole breast irradiation) with respect to survival as primary breast local treatment for the majority of women with stage I and stage II breast cancers (category 1).¹²⁸⁻¹³²

After surgical resection, a careful histologic assessment of resection margins is essential. The NCCN Panel notes that benefit of lumpectomy is predicated on achieving pathologically negative margins after resection. The NCCN Panel accepts the most recent definition outlined in the guidelines established by the Society of Surgical Oncology (SSO)/American Society for Radiation Oncology (ASTRO) of no ink on a tumor as the standard for negative surgical margins for invasive cancer (with or without a component of DCIS).¹³³

If margins remain positive after further surgical re-excision(s), then mastectomy may be required for optimal local disease control.

In order to adequately assess margins following surgery, the panel recommends that the surgical specimens be directionally oriented and that the pathologist provide descriptions of the gross and microscopic margin status and the distance, orientation, and type of tumor (invasive cancer or pure DCIS) in relation to the closest margin. Marking the tumor bed with clips facilitates accurate planning of the radiation boost field, where appropriate. It may be reasonable to treat selected patients with invasive cancer (without extensive intraductal component) despite a microscopically focally positive margin with breast conservation therapy.

Breast-Conserving Therapy (Lumpectomy)

Lumpectomy allows patients to preserve their breast without sacrificing oncologic outcome. Lumpectomy is contraindicated for patients who are pregnant and would require radiation during pregnancy; have diffuse suspicious or malignant-appearing microcalcifications on mammography; have widespread disease that cannot be incorporated by local excision through a single incision with a satisfactory cosmetic result; or have diffusely positive pathologic margins. Relative contraindications to lumpectomy include previous radiation therapy to the breast or chest wall; active connective tissue disease involving the skin (especially scleroderma and lupus), tumors greater than 5 cm (category 2B), and positive pathologic margins.

Several studies of women with early-stage breast cancer treated with lumpectomy have identified young age as a significant predictor of an increased likelihood of ipsilateral breast tumor recurrences after lumpectomy.¹³⁴⁻¹³⁶ Risk factors, such as a family history of breast cancer or a genetic predisposition to breast cancer (ie, BRCA1/2 or other cancer-predisposing mutation), are more likely to exist in the population of young women with breast cancer, thereby confounding the independent contributions of age and treatment to clinical outcome.¹³⁷ Studies have shown that survival outcomes for young women with breast cancer receiving either lumpectomy or mastectomy are similar.^{130,131,138-140} Some recent studies show improved survival¹⁴¹⁻¹⁴³ and fewer post-surgical complications¹⁴⁴ with lumpectomy.

Mastectomy

Mastectomy is indicated for patients who are not candidates for lumpectomy and those who choose to undergo this procedure over lumpectomy.

Only limited data are available on the survival impact of risk-reducing contralateral mastectomy in women with a unilateral breast cancer.¹⁴⁵ Analysis of women included in the SEER database treated with mastectomy for a unilateral breast cancer from 1998 to 2003 showed that contralateral mastectomy performed at the time of treatment of a unilateral cancer was associated with a reduction in breast cancer-specific mortality only in the population of young women (18–49 years of age) with stage I/II, ER-negative breast cancer (HR, 0.68; 95% CI, 0.53–0.88; $P = .004$).¹⁴⁶ The 5-year breast cancer survival for this group was *slightly* improved with contralateral mastectomy versus without (88.5% vs. 83.7%, difference = 4.8%).¹⁴⁶ These differences observed in retrospective analysis could be due to selection bias among patients who chose risk-reducing contralateral mastectomy.¹⁴⁷ A statistical simulation of survival outcomes after risk-reducing contralateral mastectomy among women with stage I or II breast cancer with no *BRCA* mutation found that the absolute 20-year survival benefit from risk-reducing contralateral mastectomy was less than 1% among all age, ER status, and cancer stage groups.¹⁴⁸ Data from a recent meta-analysis found no absolute reduction in risk of distant metastases with risk-reduction mastectomy.¹⁴⁹ Furthermore, among patients with unilateral breast cancer who have an increased familial/genetic risk, although a decrease in metastatic contralateral breast cancer incidence was observed in those who received risk-reducing contralateral mastectomy, no improvement was seen in OS of these patients.¹⁴⁹

The panel recommends that women with breast cancer who are less than or equal to 35 years or premenopausal and carriers of a known *BRCA1/2* mutation consider additional risk reduction strategies following appropriate risk assessment and counseling (see [NCCN Guidelines for Breast Risk Reduction and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#)). This process should

involve multidisciplinary consultations prior to surgery, and should include a discussion of the risks associated with development of a contralateral breast cancer as compared with the risks associated with recurrent disease from the primary cancer. Except as specifically outlined in these guidelines, risk-reduction mastectomy of a breast contralateral to a known unilateral breast cancer treated with mastectomy is discouraged by the panel. The use of a prophylactic mastectomy contralateral to a breast treated with lumpectomy is very strongly discouraged in all patients.

The NCCN Panel recommends referring to the [NCCN Guidelines for Older Adult Oncology](#) for special considerations for this population.

Surgical Axillary Staging

The NCCN Guidelines for Breast Cancer include a section for surgical staging of the axilla for stages I, IIA, IIB, and IIIA (T3 N1 M0) breast cancer. Pathologic confirmation of malignancy using ultrasound-guided fine-needle aspiration (FNA)¹⁵⁰ or core biopsy must be considered in patients with clinically positive nodes to determine whether ALN dissection is needed.

Performance of SLN mapping and resection in the surgical staging of the clinically negative axilla is recommended and preferred by the panel for assessment of the pathologic status of the ALNs in patients with clinical stage I, stage II, and stage IIIA (T3 N1 M0) breast cancer.^{51,151-159} This recommendation is supported by results of randomized clinical trials showing decreased arm and shoulder morbidity (ie, pain, lymphedema, sensory loss) in patients with breast cancer undergoing SLN biopsy compared with patients undergoing standard ALN dissection.^{159,160} No significant differences in the effectiveness of the SLN procedure or level I and II dissection in determining the presence or absence of metastases in axillary nodes were seen in these studies.

However, not all women are candidates for SLN resection. An experienced SLN team is mandatory for the use of SLN mapping and excision.^{161,162} Women who have clinical stage I or II disease and do not have immediate access to an experienced SLN team should be referred to an experienced SLN team for the definitive surgical treatment of the breast and surgical ALN staging. In addition, potential candidates for SLN mapping and excision should have clinically negative ALNs at the time of diagnosis, or a negative core or FNA biopsy of any clinically suspicious ALN(s). SLNs can be assessed for the presence of metastases by both hematoxylin and eosin (H&E) staining and cytokeratin IHC. The clinical significance of a lymph node that is negative by H&E staining but positive by cytokeratin IHC is not clear. Because the historical and clinical trial data on which treatment decisions are based have relied on H&E staining, the panel does not recommend routine cytokeratin IHC to define node involvement and believes that current treatment decisions should be made based solely on H&E staining. This recommendation is further supported by a randomized clinical trial (ACOSOG Z0010) for patients with H&E negative nodes where further examination by cytokeratin IHC was not associated with improved OS over a median of 6.3 years.¹⁶³ In the uncommon situation in which H&E staining is equivocal, reliance on the results of cytokeratin IHC is appropriate. Multiple attempts have been made to identify cohorts of women with involved SLNs who have a low enough risk for non-SLN involvement that complete axillary dissection might be avoided if the SLN is positive. None of the early studies identified a low-risk group of patients with positive SLN biopsies but consistently negative non-sentinel nodes.¹⁶⁴⁻¹⁷⁰ A randomized trial (ACOSOG Z0011) compared SLN resection alone with ALN dissection in women greater than or equal to 18 years of age with T1/T2 tumors, fewer than 3 positive SLNs, and undergoing breast-conserving surgery and whole breast irradiation. In this study, there was no difference in

local recurrence, DFS, or OS between the two treatment groups. Only ER-negative status, age less than 50, and lack of adjuvant systemic therapy were associated with decreased OS.¹⁷¹ At a median follow-up of 6.3 years, locoregional recurrences were noted in 4.1% of the ALN dissection group (n = 420) and 2.8% of the SLN dissection patients (n = 436) ($P = .11$). Median OS was approximately 92% in each group.¹⁷² Therefore, based on these results after SLN mapping and excision, if a patient has a T1 or T2 tumor with 1 to 2 positive SLNs, did not receive preoperative systemic therapy, was treated with lumpectomy, and will receive whole breast radiation, the panel recommends no further axillary surgery.

The panel recommends level I and II axillary dissection when 1) patients have clinically positive nodes at the time of diagnosis that is confirmed by FNA or core biopsy; or 2) sentinel nodes are not identified. For patients with clinically negative axillae who are undergoing mastectomy and for whom radiation therapy is planned, the panel notes that axillary radiation may replace axillary dissection level I/II for regional control of disease.

Traditional level I and level II evaluation of ALN requires that at least 10 lymph nodes should be provided for pathologic evaluation to accurately stage the axilla.^{173,174} ALN should be extended to include level III nodes only if gross disease is apparent in the level II or III nodes. In the absence of gross disease in level II nodes, lymph node dissection should include tissue inferior to the axillary vein from the latissimus dorsi muscle laterally to the medial border of the pectoralis minor muscle (level I and II).

Furthermore, according to the panel, without definitive data demonstrating superior survival with ALN dissection or SLN resection, these procedures may be considered optional in patients who have

particularly favorable tumors, patients for whom the selection of adjuvant systemic therapy will not be affected by the results of the procedure, elderly patients, and patients with serious comorbid conditions. Women who do not undergo ALN dissection or ALN irradiation are at increased risk for ipsilateral lymph node recurrence.¹⁷⁵

Radiation Therapy

Planning Techniques, Targets, and Doses

It is important to individualize radiation therapy planning and delivery. CT-based treatment planning is encouraged to delineate target volumes and adjacent organs at risk. Greater target dose homogeneity and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments, and intensity-modulated radiation therapy (IMRT). Respiratory control techniques including deep inspiration breath-hold and prone positioning may be used to try to further reduce dose to adjacent normal tissues, particularly heart and lung. Boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy. Chest wall scar boost when indicated is typically treated with electrons or photons. Verification of daily setup consistency is done with weekly imaging. In certain circumstances, more frequent imaging may be appropriate. Routine use of daily imaging is not recommended.

Whole Breast Radiation

Whole breast radiation reduces the risk of local recurrence and has shown to have a beneficial effect on survival.^{129,132} Randomized trials have demonstrated decreased in-breast recurrences with an additional boost dose of radiation (by photons, brachytherapy, or electron beam) to the tumor bed.^{176,177} The panel recommends whole breast irradiation to include breast tissue in its entirety. CT-based treatment planning is recommended to limit irradiation exposure of the heart and lungs, and to assure adequate coverage of the breast and lumpectomy site.

For greater homogeneity of target dose and to spare normal tissues using compensators such as tissue wedges, forward planning using segments, and IMRT may be used.^{178,179} Respiratory control techniques including deep inspiration breath-hold and prone positioning may be used to try to further reduce dose to adjacent normal tissues, particularly heart and lung.¹⁸⁰ Radiation boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy.

Dose and Fractionation

Four randomized clinical trials have investigated hypofractionated whole breast radiation schedules (39–42.9 Gy in single fractions of 2.6–3.3 Gy) compared to standard 50 Gy in single fractions of 2 Gy.^{181–184} The 10-year follow-up data from the START trials¹⁸⁵ are consistent with the 10-year results of the Canadian trial,¹⁸⁴ which reported that local tumor control and breast cosmesis were similar with a regimen of 42.5 Gy in 16 fractions over 3.2 weeks compared with 50 Gy in 25 fractions over 5 weeks.¹⁸⁴ The START trials reported radiation-related effects to normal breast tissue such as breast shrinkage, telangiectasia, and breast edema as less common with the hypofractionated fraction regimen.¹⁸⁵ The NCCN Panel recommends whole breast irradiation, a dose of 46 to 50 Gy in 23 to 25 fractions, or a dose of 40 to 42.5 Gy in 15 to 16 fractions. Based on convenience and the data from the START trials,¹⁸⁵ the short course of radiation therapy (40–42.5 Gy in 15–16 fractions) is the NCCN-preferred option for treatment of patients receiving radiation therapy to the whole breast only. A boost to the tumor bed is recommended in patients with higher risk characteristics (such as age <50, high-grade disease, or patients with focally positive margins) in order to reduce local relapse.^{177,185–189} Typical boost doses are 10 to 16 Gy in 4 to 8 fractions.

Chest Wall Radiation (Including Breast Reconstruction)

The target includes the ipsilateral chest wall, mastectomy scar, and drain sites when indicated. Depending on whether the patient has had breast reconstruction, several techniques using photons and/or electrons are appropriate. The NCCN Panel recommends a dose of 46 to 50 Gy in 23 to 25 fractions to the chest wall. A boost at the scar with a dose of 2 Gy per fraction to a total dose of approximately 60 Gy may be considered in some cases based on risk.

Regional Nodal Irradiation

The NCCN Guidelines include updated recommendations for regional lymph node irradiation in patients treated with lumpectomy and mastectomy depending on lymph node involvement (see *Principles of Radiation Therapy* in the [NCCN Guidelines for Breast Cancer](#)).

Two studies, MA.20 and EORTC 22922/10925, evaluated the addition of regional nodal irradiation to the internal mammary nodes and the upper axillary nodes including the supraclavicular region, in addition to whole breast irradiation or chest wall irradiation after lumpectomy or mastectomy, respectively. In MA.20, regional recurrences were reduced from 2.7% with breast irradiation only to 0.7% with the addition of nodal irradiation.¹⁹⁰ The distant recurrences were reduced from 17.3% to 13.4%.¹⁹⁰ An improvement in DFS was seen from 77% to 82% at 10 years in those who received regional nodal irradiation compared to those who did not.¹⁹⁰ In EORTC 22922/10925, regional radiation therapy reduced the incidence of regional recurrences from 4.2% to 2.7% and decreased the rate of distant metastases from 19.6% to 15.9% at a median follow-up of 10.9 years.¹⁹¹

Accelerated Partial Breast Irradiation

Several studies have been reported using accelerated partial breast irradiation (APBI) rather than whole breast irradiation following complete surgical excision of in-breast disease. The panel generally views the

use of APBI as investigational, and encourages its use within the confines of a high-quality, prospective clinical trial.¹⁹² For patients who are not trial eligible, recommendations from ASTRO indicate that APBI may be suitable in selected patients with early-stage breast cancer and may be comparable to treatment with standard whole-breast RT.¹⁹³

Patients who may be suitable for APBI are women 60 years of age and older who are not carriers of a known *BRCA1/2* mutation and who have been treated with primary surgery for a unifocal stage I, ER-positive cancer. Tumors should be infiltrating ductal or have a favorable histology, should not be associated with an extensive intraductal component or LCIS, and should have negative margins. Thirty-four Gy in 10 fractions delivered twice per day with brachytherapy or 38.5 Gy in 10 fractions delivered twice per day with external beam photon therapy to the tumor bed is recommended. Other fractionation schemes are under investigation. Studies have suggested that the ASTRO stratification guidelines may not adequately predict ipsilateral breast tumor recurrences following APBI.^{194,195} Follow-up is limited and studies are ongoing.

Radiation Therapy in Patients Receiving Preoperative Systemic Therapy

The panel recommends that decisions related to administration of radiation therapy for patients receiving preoperative systemic chemotherapy should be made based on maximal stage from pre-chemotherapy tumor characteristics and/or pathological stage, irrespective of tumor response to preoperative systemic therapy.

Radiation Therapy After Lumpectomy

After lumpectomy, whole breast irradiation is strongly recommended with or without boost to tumor bed for node-positive disease (category 1 for those with positive nodes; category 2A for those with negative axillary nodes). This recommendation is supported by the results of a

meta-analysis by the EBCTCG showing reduction in 10-year risk of recurrence in those who received whole breast irradiation versus those who did not (19% vs. 35%; RR 0.52; 95% CI, 0.48–0.56).¹³² In addition, a significant reduction in 15-year risk of breast cancer death (21% vs. 25%; RR 0.82; 95% CI, 0.75–0.90) was also observed.¹³²

Regional Nodal Irradiation

The reduction in the risk of locoregional and distant recurrence and improvement in DFS seen in the MA.20 and EORTC 22922/10925 trials support the importance of regional nodal irradiation after lumpectomy.^{190,191} The NCCN Panel strongly recommends irradiation of infraclavicular and supraclavicular areas, internal mammary nodes, and any part of the axillary bed that may be suspicious (category 1 for ≥ 4 positive nodes). Irradiation of the regional nodal area is generally not recommended by the panel for those with negative axillary nodes.

If adjuvant chemotherapy is indicated after lumpectomy, radiation should be given after chemotherapy is completed.^{196,197} This recommendation is based on results of the “Upfront-Outback” trial in which patients who had undergone breast-conserving surgery and axillary dissection were randomly assigned to receive chemotherapy following radiation therapy or radiation therapy following chemotherapy. The initial results showed an increased rate of local recurrence in the group with delayed radiotherapy at a median follow-up of 58 months;¹⁹⁷ however, differences in rates of distant or local recurrence were not statistically significant when the two arms were compared at 135-month follow-up.¹⁹⁶

Radiation Therapy After Lumpectomy in Older Adults

Whole breast irradiation as a component of breast-conserving therapy is not always necessary in selected women 70 years of age or older. In a study of women with clinical stage I, ER-positive breast cancer who

were greater than or equal to 70 years of age at diagnosis, patients were randomized to receive lumpectomy with whole breast radiation or lumpectomy alone, both with tamoxifen for five years. Locoregional recurrence rates were 1% in the lumpectomy, radiation, and tamoxifen arm and 4% in the lumpectomy plus tamoxifen arm. There were no differences in OS, DFS, or need for mastectomy.¹⁹⁸ These results were confirmed in an updated analysis of this study with a median follow-up of 12.6 years.¹⁹⁹ At 10 years, a statistically significant reduction in ipsilateral breast recurrences was seen with radiation therapy with 90% of patients in the lumpectomy and tamoxifen arm compared with 98% in the lumpectomy plus radiation and tamoxifen arm who were free from locoregional recurrence.¹⁹⁹ Similar results were obtained in other studies of similar design.^{200,201} Whether the difference in tumor control is clinically significant and the patient receives breast radiotherapy should be individualized based upon discussion between the patient and her care team.

The NCCN Guidelines allow for the use of lumpectomy (pathologically negative margin required) plus tamoxifen or an aromatase inhibitor without breast irradiation in women greater than or equal to 70 years of age with clinically negative lymph nodes and ER-positive, T1 breast cancer (category 1).

Radiation Therapy After Mastectomy

Node-Positive Disease: Randomized clinical trials have shown that a DFS and OS advantage is conferred by the irradiation of chest wall and regional lymph nodes in women with positive ALNs after mastectomy and ALN dissection.²⁰²⁻²⁰⁶ In these trials, the ipsilateral chest wall and the ipsilateral locoregional lymph nodes were irradiated. The results of EBCTCG meta-analyses²⁰⁷ show that radiotherapy after mastectomy and axillary node dissection reduced both recurrence and breast cancer mortality in the women with 1 to 3 positive lymph nodes even when

systemic therapy was administered.¹⁹¹ Based on these studies, the current guidelines recommend postmastectomy chest wall irradiation in women with positive ALNs (category 1). Two retrospective analyses have provided evidence for benefit of radiation therapy for only selected patients (patients presenting with clinical stage III disease and patients with four or more positive nodes) receiving preoperative systemic therapy prior to mastectomy.^{208,209}

Regional Nodal Irradiation

The use of regional nodal irradiation for patients undergoing mastectomy is supported by a subgroup analysis of studies from the Danish Breast Cancer Cooperative Group.²¹⁰ In this analysis, a substantial survival benefit was associated with postmastectomy radiation therapy for women with 1 to 3 positive ALNs. In addition, data from the EORTC 22922/10925 trial supports the role of regional RT in this population based on the inclusion of patients who had undergone mastectomy in this study. Based on the above data, the NCCN Panel recommends irradiation of infraclavicular and supraclavicular areas, internal mammary nodes, and any part of the axillary bed that may be suspicious (category 1 for ≥ 4 positive nodes; 2A for 1–3 positive nodes).

Node-Negative Disease: Features in node-negative tumors that predict a high rate of local recurrence include primary tumors greater than 5 cm or positive pathologic margins. Chest wall irradiation is recommended for these patients.²¹¹ Consideration should be given to radiation to the ipsilateral supraclavicular area and to the ipsilateral internal mammary lymph nodes, especially in patients with tumors greater than 5 cm, or positive surgical margins. In patients with tumors less than or equal to 5 cm and negative margins but less than or equal to 1 mm, chest wall irradiation should be considered.

In patients with negative nodes, tumor less than or equal to 5 cm, and clear margins (≥ 1 mm), post-mastectomy radiation therapy is usually not recommended. However, the panel has noted that it may be considered only for patients with high risk of recurrence. A retrospective analysis suggests benefit of post-mastectomy radiation therapy in reducing risk of recurrence in patients with node-negative disease with high-risk factors such as close margins, tumors greater than or equal to 2 cm, premenopausal status, and lymphovascular invasion.²¹² Another study showed increased risk of locoregional recurrence in women with node-negative triple-negative breast cancer with tumors less than or equal to 5 cm.²¹³

Breast Reconstruction

Breast reconstruction may be an option for any woman receiving surgical treatment for breast cancer. Therefore, all women undergoing breast cancer treatment should be educated about breast reconstructive options as adapted to their individual clinical situation and be offered an opportunity to consult with a reconstructive plastic surgeon. Breast reconstruction should not interfere with the appropriate surgical management. This may increase the risk of overall and cancer-related death, especially in those with late-stage disease.²¹⁴ Coordinating consultation and surgical treatment with a reconstructive surgeon should be executed within a reasonable timeframe.

Several reconstructive approaches are summarized for these patients in the [NCCN Guidelines for Breast Cancer](#) under *Principles of Breast Reconstruction Following Surgery*.

The decision regarding type of reconstruction includes patient preference, body habitus, smoking history, comorbidities, plans for irradiation, and expertise and experience of the reconstruction team. Smoking and obesity increase the risk of complications for all types of

breast reconstruction whether with implant or flap.²¹⁵⁻²¹⁹ Smoking and obesity are therefore considered a relative contraindication to breast reconstruction by the NCCN Panel. Patients should be informed of increased rates of wound healing complications and partial or complete flap failure among smokers and obese patients.

Reconstruction is an optional procedure that does not impact the probability of recurrence or death, but it is associated with an improved quality of life for many patients. It is sometimes necessary to perform surgery on the contralateral breast (ie, breast reduction, implantation) to achieve optimal symmetry between the ipsilateral reconstructed breast and the contralateral breast.

Breast Reconstruction After Mastectomy

Mastectomy results in loss of the breast for breastfeeding, loss of sensation in the skin of the breast and nipple-areolar complex (NAC), and loss of the breast for cosmetic, body image, and psychosocial purposes. The loss of the breast for cosmetic, body image, and psychosocial issues may be partially overcome through the performance of breast reconstruction with or without reconstruction of the NAC.

Women undergoing mastectomy should be offered consultation regarding options and timing of breast reconstruction.

Many factors must be considered in the decision-making about breast reconstruction. There are several different types of breast reconstruction that include the use of implants, autogenous tissues, or both.²²⁰⁻²²² Reconstruction with implants can be performed either by immediate placement of a permanent subpectoral implant or initial placement of a subpectoral expander implant followed by gradual expansion of the implant envelope with stretching of the pectoralis

major muscle and overlying skin followed by replacement of the expander with a permanent implant. A wide variety of implants are available that contain saline, silicone gel, or a combination of saline and silicone gel inside a solid silicone envelope.

Autogenous tissue methods of reconstruction use various combinations of fat, muscle, skin, and vasculature from donor sites (ie, abdomen, buttock, back) that may be brought to the chest wall with their original blood supply (pedicle flap) or as free flaps with microvascular anastomoses to supply blood from the chest wall/thorax.²²³ Several procedures using autogenous tissue are available including transverse rectus abdominis myocutaneous flap, latissimus dorsi flap, and gluteus maximus myocutaneous flap reconstruction.

Composite reconstruction techniques use implants in combination with autogenous tissue reconstruction to provide volume and symmetry. Patients with underlying diabetes or who smoke tobacco have increased rates of complications following autogenous tissue breast cancer reconstruction, presumably because of underlying microvascular disease.

Reconstruction can be performed either at the time of the mastectomy known as “immediate breast reconstruction” and under the same anesthetic or in a delayed fashion any time, known as “delayed breast reconstruction.” In many cases, breast reconstruction involves a staged approach requiring more than one procedure such as surgery on the contralateral breast to improve symmetry, revision surgery involving the breast and/or donor site, and/or nipple and areola reconstruction and tattoo pigmentation.

Plans for post-mastectomy radiation therapy can impact decisions related to breast reconstruction since there is a significantly increased

risk of implant capsular contracture following irradiation of an implant. Furthermore, postmastectomy irradiation may have a negative impact on breast cosmesis when autologous tissue is used in immediate breast reconstruction, and may interfere with the targeted delivery of radiation when immediate reconstruction is performed using either autologous tissue or breast implants.^{224,225} Some studies, however, have not found a significant compromise in reconstruction cosmesis after radiation therapy.²²⁶ The preferred approach to breast reconstruction for irradiated patients was a subject of controversy among the panel. While some experienced breast cancer teams have employed protocols in which immediate tissue reconstructions are followed by radiation therapy, generally radiation therapy is preferred to precede autologous reconstruction due to the reported loss in reconstruction cosmesis (category 2B). When implant reconstruction is planned in a post mastectomy patient requiring radiation therapy, the NCCN Panel prefers a staged approach with immediate tissue expander placement followed by implant placement. Immediate placement of an implant in patients requiring postoperative radiation has an increased rate of capsular contracture, malposition, poor cosmesis, and implant exposure. Surgery to exchange the tissue expanders with permanent implants can be performed prior to radiation or after completion of radiation therapy.

In a previously radiated patient, the use of tissue expanders/implants is relatively contraindicated.²²⁷ Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis, implant exposure, and failed reconstruction.^{228,229} If a patient has previously received radiation therapy to the breast, autologous tissue reconstruction is the preferred method of breast reconstruction.

Skin-sparing Mastectomy

Skin-sparing mastectomy procedures are appropriate for some patients and involve removal of the breast parenchyma including the NAC while preserving the majority of the original skin envelope, and are followed by immediate reconstruction with autogenous tissue, a prosthetic implant, or a composite of autogenous tissue and an implant.

Skin-sparing mastectomy involving preservation of the skin of the NAC has become the subject of increased attention. Possible advantages of this procedure include improvements in breast cosmesis, body image, and nipple sensation following mastectomy, although the impact of this procedure on these quality-of-life issues has not been well-studied.²³⁰⁻²³²

There are limited data from surgical series, with short follow-up, that suggest that performance of NAC-sparing mastectomy in selected patients is associated with low rates of occult involvement of the NAC with breast cancer and local disease recurrence.^{231,233,234} NAC-sparing procedures may be an option in patients who are carefully selected by experienced multidisciplinary teams. According to the NCCN Panel, when considering a NAC-sparing procedure, assessment of nipple margins is mandatory. Retrospective data support the use of NAC-sparing procedures for patients with breast cancer with low rates of nipple involvement and low rates of local recurrence due to early-stage, biologically favorable (ie, Nottingham grade I or 2, node-negative, HER2-negative, no lymphovascular invasion) invasive cancers and/or DCIS that are peripherally located in the breast (>2 cm from nipple).^{235,236} Contraindications for nipple preservation include evidence of nipple involvement such as Paget's disease or other nipple discharge associated with malignancy and/or imaging findings suggesting malignant involvement of nipple and subareolar tissues. Several prospective trials are underway to evaluate NAC-sparing mastectomy in the setting of cancer and enrollment in such trials is encouraged.

Advantages of a skin-sparing mastectomy procedure include an improved cosmetic outcome resulting in a reduction in the size of the mastectomy scar and a more natural breast shape, especially when autologous tissue is used in reconstruction,²³⁷ and the ability to perform immediate reconstruction. Although no randomized studies have been performed, results of several mostly retrospective studies have indicated that the risk of local recurrence is not increased when patients receiving skin-sparing mastectomies are compared with those undergoing non-skin-sparing procedures. However, strong selection biases almost certainly exist in the identification of patients appropriate for skin-sparing procedures.²³⁸⁻²⁴² Reconstruction of the NAC may also be performed in a delayed fashion if desired by the patient.

Reconstructed nipples are devoid of sensation. According to the NCCN Panel, 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 perform a resection that achieves appropriate surgical margins. Post-mastectomy radiation should still be applied for patients treated by skin-sparing mastectomy following the same selection criteria as for standard mastectomy.

Breast Reconstruction After Lumpectomy

Issues related to breast reconstruction also pertain to women who undergo or have undergone a lumpectomy, particularly in situations where the surgical defect is large and/or expected to be cosmetically unsatisfactory. An evaluation of the likely cosmetic outcome of lumpectomy should be performed prior to surgery. Oncoplastic techniques for breast conservation can extend breast-conserving surgical options in situations where the resection by itself would likely yield an unacceptable cosmetic outcome.²⁴³ The evolving field of

oncoplastic surgery includes the use of “volume displacement” techniques performed in conjunction with a large partial mastectomy.²⁴⁴ Oncoplastic volume displacement procedures combine the removal of generous regions of breast tissue (typically designed to conform to the segmentally distributed cancer in the breast) with “mastopexy” techniques in which remaining breast tissues are shifted together within the breast envelope to fill the resulting surgical defect and thereby avoid the creation of significant breast deformity. Volume displacement techniques are generally performed during the same operative setting as the breast-conserving lumpectomy by the same surgeon who is performing the cancer resection.^{244,245}

Advantages of oncoplastic volume displacement techniques are that they permit the removal of larger regions of breast tissue, thereby achieving wider surgical margins around the cancer, and at the same time better preserve the natural shape and appearance of the breast than do standard breast resections.²⁴⁶

Limitations of oncoplastic volume displacement techniques include lack of standardization among centers, performance at only a limited number of sites in the United States, and the possible necessity for subsequent mastectomy if pathologic margins are positive when further breast-conserving attempts are deemed impractical or unrealistic. Nevertheless, the consensus of the panel is that these issues should be considered prior to surgery for women who are likely to have a surgical defect that is cosmetically unsatisfactory, and that women who undergo lumpectomy and are dissatisfied with the cosmetic outcome after treatment should be offered a consultation with a plastic surgeon to address the repair of resulting breast defects. Patients should be informed of the possibility of positive margins and potential need for secondary surgery, which could include re-excision segmental resection, or could require mastectomy with or without loss of the

nipple. Oncoplastic procedures can be combined with surgery on the contralateral unaffected breast to minimize long-term asymmetry.

Finally, decisions regarding breast reconstruction should primarily focus on treatment of the tumor, and such treatment should not be compromised.

Systemic Therapies (Preoperative and Adjuvant)

Principles of Preoperative Systemic Therapy

The NCCN Panel has outlined the rationale, appropriate patient selection, and response assessment for preoperative systemic therapy in a new section titled, *Principles of Preoperative Chemotherapy*.

Rationale for Preoperative Chemotherapy

Randomized clinical trials have found no significant differences in long-term outcomes when systemic chemotherapy is given before or after surgery.^{297,298} Historically, a primary advantage of administering preoperative systemic therapy has been to improve surgical outcomes. Preoperative systemic therapy can render inoperable tumors resectable and also downstage patients with operable breast cancer desiring breast conservation.²⁹⁹ Results from large clinical trials and retrospective reviews indicate that breast conservation rates are improved with preoperative systemic therapy.^{298,300} Clinicians need to carefully consider the extent of disease in the breast and likelihood of adequate tumor response before recommending preoperative systemic therapy to improve the likelihood of successful breast conservation.

In addition, use of preoperative systemic therapy may provide important prognostic information based on response to therapy. Achieving a pathologic complete response (pCR) to neoadjuvant therapy is associated with favorable disease-free and OS in early-stage breast cancer. The correlation between pathologic response and long-term

outcomes in patients with early-stage breast cancer is strongest for patients with triple-negative breast cancer, less so for HER2-positive disease, and least for hormone-positive disease.³⁰¹⁻³⁰³

Other benefits of preoperative systemic therapy include allowing time for appropriate genetic testing and for planning breast reconstruction in patients proceeding with mastectomy. For those with significant residual disease after standard preoperative systemic therapy, it may provide an opportunity to identify patients who are candidates for clinical trials of novel agents in the adjuvant setting. To date, the tailoring of therapy based on poor response to standard preoperative chemotherapy has not yet demonstrated improved outcomes. In addition, preoperative systemic therapy also serves as an excellent research platform to test novel therapies and predictive biomarkers by providing tumor specimens and blood samples prior to and during systemic treatment.

Selection of Patients for Preoperative Therapy

Not all patients are appropriate candidates for preoperative systemic therapy. According to the NCCN Panel, among those with inoperable breast tumors, preoperative systemic therapy is indicated in women with locally advanced or inoperable breast cancer including those with inflammatory breast cancer; those with N2 and N3 regional lymph node nodal disease; and T4 tumors. In patients with operable breast cancer who are clear candidates for adjuvant chemotherapy, preoperative systemic therapy may be considered if a patient desires breast-conserving surgery but the surgery is not possible due to the size of the tumor relative to that of the breast, with the hope that this will help obtain clear surgical margins at final resection. Preoperative systemic therapy may also be administered in patients with operable tumors if the patient's breast cancer subtype is one associated with a high likelihood of response. When preoperative systemic therapy is used to improve

the likelihood of successful breast conservation, the surgical plan should consider the possibility that clear surgical margins may not always be obtained, and a follow-up mastectomy may be required, with or without breast reconstruction. This consideration is especially important when oncoplastic breast reduction techniques or contralateral breast symmetry procedures are added to the breast-conserving surgery to achieve optimal cosmetic outcomes.

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

Preoperative Systemic Therapy Options

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

Endocrine Therapy. Neoadjuvant endocrine therapy alone may be offered to those with strongly hormone receptor-positive tumors.³⁰⁴⁻³¹¹ According to the NCCN Panel, the endocrine therapy options include an aromatase inhibitor (with ovarian suppression for premenopausal women) or tamoxifen. The preferred endocrine therapy option for postmenopausal women is an aromatase inhibitor.

HER2 Targeted Therapy: For patients with HER2-positive breast cancer, that are candidates for preoperative systemic therapy, chemotherapy and trastuzumab-based therapy is recommended.³¹² Chemotherapy and dual anti-HER2 blockade associated with trastuzumab plus pertuzumab has shown significant improvements in the pCR rate when compared with chemotherapy and one anti-HER2 agent in the preoperative setting.³¹³⁻³¹⁵ In the Neosphere trial, the addition of pertuzumab to trastuzumab and docetaxel preoperatively led to a statistically significant increase in pCR in the breast (16.8% increase; 95% CI, 3.5–30.1; $P = .0141$).³¹⁵ In the TRYPHAENA trial, preoperative therapy with pertuzumab and trastuzumab given along with anthracycline-containing or anthracycline-free standard chemotherapy regimens to patients with operable, locally advanced, or inflammatory HER2-positive breast cancer showed pCR rates in all treatment arms ranging from 57% to 66%.³¹⁶ The mean change in left ventricular ejection fraction was similar in all treatment arms.³¹⁶ The NCCN Panel supports the FDA-approved indication that a pertuzumab-containing regimen may be administered preoperatively to patients with greater than or equal to T2, or greater than or equal to N1, HER2-positive, early-stage breast cancer.

Response Assessment During Preoperative Chemotherapy. The NCCN panel recommends that tumor response should be routinely assessed by clinical exam during the delivery of preoperative systemic therapy. Patients with operable breast cancer experiencing progression of disease while undergoing preoperative systemic therapy should be taken promptly to surgery. Imaging during preoperative systemic therapy should not be done routinely, but may be considered if tumor progression is suspected. Imaging prior to surgery should be determined by a multi-disciplinary team

Systemic Adjuvant Therapy

After surgical treatment, adjuvant systemic therapy should be considered. The decision is often based on individual risk of relapse and predicted sensitivity to a particular treatment (eg, ER/PR and HER2 status).

The published results of the EBCTCG overview analyses of adjuvant chemotherapy and tamoxifen show convincing reductions in the odds of recurrence and death in all age groups for chemotherapy and endocrine therapy.^{4,247} Thus, the current guidelines recommend adjuvant therapy without regard to patient age (category 1). The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of the therapy, and comorbidity.^{248,249} The decision-making process requires collaboration between the health care team and patient.

Estimating Risk of Relapse or Death and Benefits of Systemic Treatment

Several prognostic factors predict for future recurrence or death from breast cancer. The strongest prognostic factors are patient age, comorbidity, tumor size, tumor grade, number of involved ALNs, and possibly HER2 tumor status. Algorithms have been published estimating rates of recurrence,²⁴⁸ and a validated, computer-based model (Adjuvant! Online; www.adjuvantonline.com) is available to estimate 10-year DFS and OS that incorporates all of the above prognostic factors except for HER2 tumor status.^{249,250} These tools aid the clinician in objectively estimating outcome with local treatment only, and also assist in estimating the absolute benefits expected from systemic adjuvant endocrine therapy and chemotherapy. These estimates may be utilized by the clinician and patient in their shared

decision-making regarding the toxicities and benefits of systemic adjuvant therapy.²⁵¹

A determination of the HER2 status of the tumor is recommended for prognostic purposes for patients with node-negative breast cancer.²⁵² More importantly, HER2 tumor status also provides predictive information used in selecting optimal adjuvant/neoadjuvant therapy and in the selection of therapy for recurrent or metastatic disease (category 1). For example, retrospective analyses have demonstrated that anthracycline-based adjuvant therapy is superior to non-anthracycline-based adjuvant chemotherapy in patients with HER2-positive tumors,²⁵³⁻²⁵⁷ and that the dose of doxorubicin may be important in the treatment of tumors that are HER2-positive.²⁵⁸ Prospective evidence of the predictive utility of HER2 status in early-stage²⁵⁹⁻²⁶⁴ and metastatic breast cancer²⁶⁵⁻²⁶⁷ is available for trastuzumab-containing therapies.

Use of DNA microarray technologies to characterize breast cancer has allowed for development of classification systems of breast cancer by gene expression profile.²⁶⁸ Five major subtypes of breast cancer have been identified by DNA microarray gene expression profiling: ER-positive/HER2-negative (luminal A and luminal B subtypes); ER-negative/HER2-negative (basal subtype); HER2-positive; and tumors that have characteristics similar to normal breast tissue.²⁶⁹⁻²⁷¹ In retrospective analyses, these gene expression subtypes are associated with differing relapse-free survival and OS.

There are many gene-based assays to predict prognosis such as distant recurrence, local recurrence, or survival.

The 21-gene assay using reverse transcription polymerase chain reaction (RT-PCR) on RNA isolated from paraffin-embedded breast cancer tissue is among the best-validated prognostic assays, and there

are data showing that it can predict who is most likely to respond to systemic chemotherapy.

Studies have shown that the 21-gene assay recurrence score obtained is predictive of locoregional and distant recurrence for postmenopausal women treated with tamoxifen or those treated with an aromatase inhibitor.²⁷²⁻²⁷⁴ Studies have also demonstrated the ability of the recurrence score to independently predict response to adjuvant chemotherapy.²⁷⁵⁻²⁷⁷ Unplanned, retrospective subset analysis from a single randomized clinical trial in post-menopausal, ALN-positive, ER-positive breast cancer found that the 21-gene RT-PCR assay may provide predictive information for chemotherapy benefit in addition to tamoxifen.²⁷⁵ Patients with a high score in the study benefited from chemotherapy, whereas patients with a low score did not appear to benefit from the addition of chemotherapy regardless of the number of positive lymph nodes.²⁷⁵ Many other multi-gene or multi-gene expression assay systems have been developed.

The 70-gene signature assay uses microarray technology to analyze gene expression profile from breast tumor tissue (formalin-fixed, paraffin-embedded fresh or frozen breast tumor tissue) to help identify patients with early-stage breast cancer likely to develop distant metastases.²⁷⁸⁻²⁸⁴ This assay is approved by the FDA to assist in assignment of women with ER-positive or ER-negative breast cancer into a high versus low risk for recurrence, but not for predicting benefit from adjuvant systemic therapy. The prospective RASTER study reported that breast cancer patients classified by the 70-gene signature as low risk (of whom 85% did not receive adjuvant chemotherapy) had an overall 97% distant recurrence-free interval at five years.²⁸⁵

Another assay with 50 genes identifies intrinsic breast cancer subtypes (luminal A, luminal B, HER2 enriched and basal-like) in addition to

generating a risk of recurrence (ROR) score that can be used to predict prognosis among postmenopausal women with hormone-positive breast cancer. In a retrospective analysis of the ATAC trial,²⁸⁶ the ROR score obtained using the 50-gene assay in postmenopausal patients treated with adjuvant tamoxifen or anastrozole was seen to have a continuous relationship with the risk of distant recurrence at 10 years in node-negative *and* node-positive disease. The retrospective analysis also compared the ROR score obtained using the 50-gene assay with the recurrence score obtained using the 21-gene assay. Both assays identified similar percentage of low-risk patients (hormone receptor-positive, node-negative) with similar risk of recurrence. The ABCSG-8 trial showed that the ROR score provides prognostic information and predicts the risk of distant recurrence in postmenopausal women with ER-positive early-stage breast cancer.²⁸⁷ A recent combined analysis of the ATAC and the ABCSG-8 trials reported ROR score as a strong predictor of late distant recurrence (greater than 5 years) for patients with hormone receptor-positive, node-negative disease.²⁸⁸ The NCCN Panel members acknowledge that many assays have been clinically validated for prediction of prognosis. However, based on the currently available data, the panel believes that the 21-gene assay has been best validated for its use as a prognostic test as well as in predicting who is most likely to respond to systemic chemotherapy.

Patients with a high recurrence score obtained using the 21-gene assay clearly benefit from chemotherapy, whereas patients with a low score do not appear to benefit from the addition of chemotherapy regardless of the number of positive lymph nodes.²⁷⁵ The results from the prospective TAILORx study support the use of the 21-gene assay to spare the use of chemotherapy in patients with a low-risk score.²⁸⁹ In patients with a low-risk score (≤ 10) at 5 years, the risk of the recurrence



of breast cancer at a distant site was less than 1% and the risk of any recurrence was less than 2%.²⁸⁹

The additional benefit from adjuvant chemotherapy in addition to endocrine therapy is currently unclear for patients with intermediate recurrence score. The long-term follow-up results from the TAILORx trial clarify the use of chemotherapy in women with hormone-receptor–positive, HER2-negative, axillary node–negative invasive breast cancer with mid-range 21-gene assay recurrence score (between 11–25).²⁹⁰ The ongoing RxPONDER trial is evaluating whether adjuvant chemotherapy is beneficial in patients with hormone receptor-positive, HER2-negative breast cancer with positive ALNs and a recurrence score of 25 or less.²⁹¹

The MINDACT trial is phase III trial comparing the 70-gene signature with the commonly used clinicopathologic criteria in selecting patients for adjuvant chemotherapy in breast cancer with 0 to 3 positive nodes.²⁹² The early results from the MINDACT trial suggest that the 70-gene signature can help avoid chemotherapy in certain patients regardless of larger tumor size and nodal status, without compromising the outcome.²⁹³ Among the MINDACT trial patients, if decision on administering adjuvant chemotherapy was based on clinical characteristics alone (tumor size and nodal status), 50% would receive adjuvant chemotherapy; however, only 36% received chemotherapy using the risk status based on the 70-gene signature—an absolute reduction of 14% in chemotherapy administration rate.²⁹³

Axillary Lymph Node-Negative Tumors

Small tumors (up to 0.5 cm in greatest diameter) that do not involve the lymph nodes are so favorable that adjuvant systemic therapy is of minimal incremental benefit and is not recommended as treatment of the invasive breast cancer. According to the NCCN Panel, endocrine

therapy may be considered to reduce the risk for a second contralateral breast cancer, especially in those with ER-positive disease. The NSABP database demonstrated a correlation between the ER status of a new contralateral breast tumor and the original primary tumor, which reinforced the notion that endocrine therapy is not an effective strategy to reduce the risk for contralateral breast cancer in patients diagnosed with ER-negative tumors.²⁹⁴

Patients with invasive ductal or lobular tumors greater than 0.5 cm in diameter and no lymph node involvement may be divided into patients with a low risk of recurrence and those with unfavorable prognostic features that warrant consideration of adjuvant therapy. Unfavorable prognostic features include intramammary angiolymphatic invasion, high nuclear grade, high histologic grade, HER2-positive status, or hormone receptor-negative status. The use of endocrine therapy and chemotherapy in these relatively lower risk subsets of women must be based on balancing the expected absolute risk reduction and the individual patient's willingness to experience toxicity to achieve that incremental risk reduction.

For women with lymph node-negative, hormone receptor-*negative* tumors less than or equal to 0.5 cm with micrometastasis (pN1mi) or tumors 0.6 to 1.0 cm, the NCCN Guidelines suggest considering adjuvant chemotherapy (category 2A). For tumors greater than 1 cm in diameter chemotherapy is a category 1 recommendation.

For those with lymph node-negative, hormone receptor-positive breast cancer tumors greater than 0.5 cm, the panel recommends endocrine therapy (category 1) with the consideration of chemotherapy. Incremental benefit of combination chemotherapy in patients with lymph node-negative, hormone receptor-positive breast cancer may be

relatively small.²⁹⁵ However, chemotherapy should not be withheld from these patients solely based on ER-positive tumor status.^{4,295,296} The panel considers the 21-gene RT-PCR assay an option for these patients to help estimate likelihood of recurrence *and* benefit from chemotherapy. The panel emphasizes that the recurrence score should be used for decision-making only in the context of other elements of risk stratification for an individual patient.

Axillary Lymph Node-Positive Tumors

Patients with lymph node-positive disease are most often candidates for chemotherapy and, if the tumor is hormone receptor-positive, for the addition of endocrine therapy (category 1). When HER2 is amplified or over-expressed, HER2-targeted therapy should be incorporated into the adjuvant chemotherapy. The NCCN Panel has noted in a footnote that the 21-gene RT-PCR assay recurrence score can be considered in select patients with 1 to 3 involved ipsilateral ALNs to guide the addition of combination chemotherapy to standard hormone therapy based on the retrospective study by Albain et al.²⁷⁵

Stratification for Systemic Adjuvant Therapy

The NCCN Guidelines stratify patients with breast cancer based on their hormone receptor status and HER2 expression. Patients are then further stratified based on risk of disease recurrence based on anatomic and pathologic characteristics (ie, tumor grade, tumor size, ALN status, angiolymphatic invasion).

Adjuvant Endocrine Therapy

The NCCN Guidelines call for the determination of ER and PR content in all primary invasive breast cancers.¹⁷ Patients with invasive breast cancers that are ER or PR positive should be considered for adjuvant endocrine therapy regardless of patient age, lymph node status, or whether adjuvant chemotherapy is to be administered.³¹⁷ Selected

studies suggest that HER2-positive breast cancers may be less sensitive to some endocrine therapies, although other studies have failed to confirm this finding.^{255,318-325} A retrospective analysis of tumor blocks collected in the ATAC trial indicated that HER2 amplification is a marker of relative endocrine resistance independent of type of endocrine therapy.³²⁶ However, given the favorable toxicity profile of the available endocrine therapies, the panel recommends the use of adjuvant endocrine therapy in the majority of women with hormone receptor-positive breast cancer regardless of menopausal status, age, or HER2 status of the tumor.

Tamoxifen

The most firmly established adjuvant endocrine therapy is tamoxifen for both premenopausal and postmenopausal women.⁴ In women with ER-positive breast cancer, adjuvant tamoxifen decreases the annual odds of recurrence by 39% and the annual odds of death by 31% irrespective of the use of chemotherapy, patient age, menopausal status, or ALN status.⁴ In patients receiving both tamoxifen and chemotherapy, chemotherapy should be given first, followed by sequential tamoxifen.²⁹⁶ Prospective randomized trials have demonstrated that 5 years of tamoxifen is more effective than 1 to 2 years of tamoxifen.^{327,328}

The ATLAS trial randomly allocated 12,894 women to continue tamoxifen up to 10 years or to discontinue tamoxifen (control). The outcome analyses of 6846 women with ER-positive disease showed that by extending adjuvant treatment to 10 years, the risk of relapse and breast cancer-related mortality was reduced.³²⁹ The risk of recurrence during years 5 to 14 was 21.4% for women receiving tamoxifen versus 25.1% for controls (absolute recurrence reduction 3.7%). Patients receiving tamoxifen beyond 10 years of treatment had a greater reduction in risk of progression, possibly due to a “carryover effect.” The

reduction in risk of recurrence was 0.90 (95% CI, 0.79–1.02) during 5 to 9 years of tamoxifen treatment and 0.75 (0.62–0.90) after 10 years of treatment. Furthermore, reduced mortality was apparent after completion of 10 years of treatment with tamoxifen. With regards to toxicity, the most important adverse effects noted in all women in the ATLAS trial after treatment with 10 years of tamoxifen were an increased risk for endometrial cancer and pulmonary embolism. The recurrence rate ratio reported for pulmonary embolus was 1.87 (95% CI, 1.13–3.07; $P = .01$ [including 0.2% mortality in both groups]) and for endometrial cancer was 1.74 (1.30–2.34, $P = .0002$). The cumulative risk for endometrial cancers during 5 to 14 years was 3.1%, with a mortality of 0.4% associated with endometrial cancer, higher than what was noted in the control group of patients receiving only 5 years of therapy (cumulative risk: 1.6%; mortality: 0.2%).³²⁹ The results of the aTTom trial confirm the ATLAS reduction in recurrence and death from breast cancer.³³⁰

In women who are premenopausal at diagnosis, the NCCN Panel recommends tamoxifen treatment with or without ovarian suppression/ablation. Ovarian ablation may be accomplished by surgical oophorectomy or by ovarian irradiation. Ovarian suppression utilizes luteinizing hormone-releasing hormone (LHRH) agonists that result in suppression of luteinizing hormone (LH) and release of follicle-stimulating hormone (FSH) from the pituitary and reduction in ovarian estrogen production. Available LHRH agonists in the United States include goserelin and leuprolide and, when used for ovarian suppression, both agents should be given as monthly injections as the 3-month depots do not reliably suppress estrogen levels in all patients.

The EBCTCG performed a meta-analysis of randomized studies of ovarian ablation or suppression alone versus no additional systemic adjuvant therapy for early-stage breast cancer. Analysis of ovarian

suppression versus no adjuvant therapy did not demonstrate significant reduction in recurrence (HR 0.72; 95% CI, 0.49–1.04) or death (HR 0.82; 95% CI, 0.47–1.43).³³¹ In addition, data on ovarian suppression with tamoxifen, chemotherapy, or both showed no significant reduction in reduced recurrence or death.

Studies in premenopausal women of ovarian ablation or suppression alone versus CMF (cyclophosphamide/methotrexate/fluorouracil) chemotherapy alone generally demonstrate similar antitumor efficacy in patients with hormone receptor-positive tumors and superior outcomes with CMF in patients with hormone receptor-negative tumors.³³¹⁻³³⁹ There is also the suggestion that the benefits of ovarian suppression/ablation may be greater in the younger premenopausal group. Studies in premenopausal women of ovarian ablation/suppression plus tamoxifen versus chemotherapy alone generally demonstrate no difference in rates of recurrence or survival.³⁴⁰⁻³⁴²

A large intergroup study in premenopausal women with hormone receptor-positive, node-positive breast cancer studied adjuvant CAF (cyclophosphamide/doxorubicin/5-fluorouracil) chemotherapy versus CAF plus ovarian suppression with goserelin (CAF-Z) versus CAF-Z plus tamoxifen (CAF-ZT).³³² The results demonstrated no improvement in time to recurrence or OS comparing CAF with CAF-Z. There was improvement in time to recurrence (HR, 0.73; 95% CI, 0.59–0.90; $P < .01$) but not OS with CAF-Z compared with CAF-ZT (HR, 0.91; 95% CI, 0.71–1.15; $P = .21$). This study did not include a CAF plus tamoxifen arm, so the contribution of the goserelin to the improved time to recurrence in the CAF-ZT arm cannot be assessed. The addition of ovarian suppression/ablation has also been subjected to meta-analysis by the EBCTCG.³⁴⁰ They identified no statistically significant reduction in annual rates of recurrence or death with the addition of ovarian

suppression or ablation to chemotherapy in women less than 40 years or 40 to 49 years of age.

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

In two randomized trials (TEXT and SOFT), premenopausal women with hormone receptor-positive early-stage breast cancer were assigned to receive exemestane plus ovarian suppression or tamoxifen plus ovarian suppression for a period of 5 years.³⁴³ Suppression of ovarian estrogen production was achieved with the use of the gonadotropin-releasing hormone agonist triptorelin, oophorectomy, or ovarian irradiation. The DFS was 92.8% in the exemestane plus ovarian suppression group, as compared with 88.8% in the tamoxifen plus ovarian suppression group (HR for recurrence, 0.66; 95% CI, 0.55–0.80; $P < .001$).³⁴³ The OS did not differ significantly between the two groups (HR for death in the exemestane plus ovarian suppression group, 1.14; 95% CI, 0.86–1.51; $P = .37$).³⁴³ In the SOFT trial,³⁴⁴ premenopausal women with hormone-receptor breast cancer were randomized to tamoxifen alone, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression for 5 years. In the primary analysis, tamoxifen plus ovarian suppression was not superior to tamoxifen alone for DFS. After 67 months of median follow-up, the DFS rate at 5 years was 86.6% in the tamoxifen–ovarian suppression group and 84.7% in the tamoxifen alone group (HR 0.83; 95% CI, 0.66–1.04; $P = .10$).³⁴⁴ In a subgroup analysis, women at high risk of recurrence, who received prior chemotherapy, had improved outcomes with ovarian suppression. Their chance of remaining disease-free at 5 years was 78% with tamoxifen alone, 82.5% with tamoxifen and ovarian suppression, and 85.7% with exemestane and ovarian suppression.³⁴⁴

In the subgroup of women with no prior chemotherapy, no meaningful benefit was seen from ovarian suppression, as women who received tamoxifen alone demonstrated a 95% chance of remaining disease-free for 5 years.³⁴⁴ The OS data from these trials is still pending because the overall follow-up is relatively short in the context of endocrine-sensitive disease.

Based on the results of the SOFT and TEXT trials, the NCCN Panel has included ovarian suppression plus an aromatase inhibitor for 5 years as an adjuvant endocrine therapy option for premenopausal women with hormone-receptor–positive breast cancer at higher risk of recurrence (eg, young age, high-grade tumor, lymph-node involvement).

Several studies have evaluated aromatase inhibitors in the treatment of postmenopausal women with early-stage breast cancer. These studies have utilized the aromatase inhibitors as initial adjuvant therapy, as sequential therapy following 2 to 3 years of tamoxifen, or as extended therapy following 4.5 to 6 years of tamoxifen. The aromatase inhibitors are not active in the treatment of women with functioning ovaries and should not be used in women whose ovarian function cannot reliably be assessed owing to treatment-induced amenorrhea. The results from two prospective, randomized, clinical trials have provided evidence of an OS benefit for patients with early-stage breast cancer receiving initial endocrine therapy with tamoxifen followed sequentially by anastrozole (HR, 0.53; 95% CI, 0.28–0.99; $P = .045$) or exemestane (HR, 0.83; 95% CI, 0.69–1.00; $P = .05$ [excluding patients with ER-negative disease]) when compared with tamoxifen as the only endocrine therapy.^{345,346} In addition, the NCIC-CTG MA-17 trial demonstrated a survival advantage with extended therapy with letrozole compared with placebo in women with ALN-positive (but not lymph node-negative), ER-positive breast cancer.³⁴⁷ However, no survival differences have been reported for patients receiving initial adjuvant therapy with an aromatase inhibitor

versus first-line tamoxifen.^{348,349} Tamoxifen and aromatase inhibitors have different side effect profiles. Both contribute to hot flashes and night sweats and may cause vaginal dryness. Aromatase inhibitors are more commonly associated with musculoskeletal symptoms, osteoporosis, and increased rate of bone fracture, while tamoxifen is associated with an increased risk for uterine cancer and deep venous thrombosis.

Two studies have examined initial adjuvant endocrine treatment with either tamoxifen or an aromatase inhibitor. The ATAC trial demonstrated that anastrozole is superior to tamoxifen or the combination of tamoxifen and anastrozole in the adjuvant endocrine therapy of postmenopausal women with hormone receptor-positive breast cancer.^{350,351} With a median of 100 months follow-up, results in 5216 postmenopausal women with hormone receptor-positive, early-stage breast cancer enrolled in the ATAC trial demonstrated fewer recurrences (HR for DFS, 0.85; 95% CI, 0.76–0.94; $P = .003$) with anastrozole compared with tamoxifen.³⁴⁸ No difference in survival has been observed (HR, 0.90; 95% CI, 0.75–1.07; $P = .2$). Patients in the combined tamoxifen and anastrozole group gained no benefit over those in the tamoxifen group, suggesting a possible deleterious effect from the weak estrogenic effect of tamoxifen in patients with near complete elimination of endogenous estrogen levels.³⁵¹ ATAC trial sub-protocols show a lesser effect of anastrozole compared with tamoxifen on endometrial tissue;³⁵² similar effects of anastrozole and tamoxifen on quality of life, with most patients reporting that overall quality of life was not significantly impaired;³⁵³ a greater loss of bone mineral density with anastrozole;³⁵⁴ a small pharmacokinetic interference of anastrozole in the presence of tamoxifen of unclear significance;³⁵⁵ and no evidence for an interaction between prior chemotherapy and anastrozole.³⁵⁶

BIG 1-98 is a randomized trial testing the use of tamoxifen alone for 5 years, letrozole alone for 5 years, or tamoxifen for 2 years followed sequentially by letrozole for 3 years, or letrozole for 2 years followed sequentially by tamoxifen for 3 years. An early analysis compared tamoxifen alone versus letrozole alone, including those patients in the sequential arms during their first 2 years of treatment only.³⁴⁹ With 8010 women included in the analysis, DFS was superior in the letrozole-treated women (HR, 0.81; 95% CI, 0.70–0.93; log rank $P = .003$). No interaction between PR expression and benefit was observed. No difference in OS was observed. A comparison of the cardiovascular side effects in the tamoxifen and letrozole arms of the BIG 1-98 trial showed that the overall incidence of cardiac adverse events was similar (letrozole, 4.8%; tamoxifen, 4.7%). However, the incidence of grade 3 to 5 cardiac adverse events was significantly higher in the letrozole arm, and both the overall incidence and incidence of grade 3 to 5 thromboembolic events was significantly higher in the tamoxifen arm.³⁵⁷ In addition, a higher incidence of bone fracture was observed for women in the letrozole arm compared with those in the tamoxifen arm (9.5% vs. 6.5%).³⁵⁸ After a longer follow-up (median 71 months) no significant improvement in DFS was noted with either tamoxifen followed by letrozole or the reverse sequence as compared with letrozole alone (HR for tamoxifen followed by letrozole, 1.05; 99% CI, 0.84–1.32; HR for letrozole followed by tamoxifen, 0.96; 99% CI, 0.76–1.21).³⁵⁹

Five trials have studied the use of tamoxifen for 2 to 3 years followed sequentially by a third-generation aromatase inhibitor versus continued tamoxifen in postmenopausal women. The Italian Tamoxifen Anastrozole (ITA) trial randomized 426 postmenopausal women with breast cancer who had completed 2 to 3 years of tamoxifen to either continue tamoxifen or to switch to anastrozole to complete a total of 5

years of endocrine therapy.³⁶⁰ The HR for relapse strongly favored sequential treatment with anastrozole (HR, 0.35; 95% CI, 0.18–0.68; $P = .001$) with a trend towards fewer deaths ($P = .10$).³⁶⁰ Updated results from this study show the HR for relapse-free survival as 0.56 (95% CI, 0.35–0.89; $P = .01$); P value for OS analysis remained at 0.1.³⁶¹ The IES trial randomized 4742 postmenopausal women with breast cancer who had completed a total of 2 to 3 years of tamoxifen to either continue tamoxifen or to switch to exemestane to complete a total of 5 years of endocrine therapy.³⁶² The results at a median of 55.7 months of follow-up demonstrated the superiority of sequential exemestane in DFS (HR, 0.76; 95% CI, 0.66–0.88; $P = .0001$) with a significant difference in OS in only patients with ER-positive tumors (HR, 0.83; 95% CI, 0.69–1.00; log rank $P = .05$). A prospectively planned, combined analysis of 3224 patients enrolled in the ABCSG 8 trial and the Arimidex Nolvadex (ARNO 95) trial has also been reported.³⁶³ Patients in this combined analysis had been randomized following 2 years of tamoxifen to complete 5 years of adjuvant tamoxifen or 3 years of anastrozole. With 28 months of median follow-up available, event-free survival was superior with crossover to anastrozole (HR, 0.60; 95% CI, 0.44–0.81; $P = .0009$). No statistically significant difference in survival has been observed. An analysis of the ARNO 95 trial alone after 58 months of median follow-up demonstrated that switching from tamoxifen to anastrozole was associated with significant increases in both DFS (HR, 0.66; 95% CI, 0.44–1.00; $P = .049$) and OS (HR, 0.53; 95% CI, 0.28–0.99; $P = .045$).³⁴⁶ A meta-analysis of ABCSG 8, ARNO 95, and ITA studies showed significant improvement in OS (HR, 0.71; 95% CI, 0.52–0.98; $P = .04$) with a switch to anastrozole.³⁶⁴

The TEAM trial compared treatment of exemestane alone versus sequential therapy of tamoxifen for 2.5 to 3.0 years followed by exemestane to complete 5 years of hormone therapy.³⁶⁵ At the end of 5

years, 85% of patients in the sequential group versus 86% in the exemestane group were disease free (HR, 0.97; 95% CI, 0.88–1.08; $P = .60$). This is consistent with the data from the BIG 1-98 trial,³⁵⁹ in which tamoxifen followed by letrozole or the reverse sequence of letrozole followed by tamoxifen was not associated with significant differences in efficacy versus letrozole monotherapy after a median follow-up of 71 months.

Results of the MA-17 trial in 5187 women who had completed 4.5 to 6 years of adjuvant tamoxifen demonstrated that extended therapy with letrozole provides benefit in postmenopausal women with hormone receptor-positive, early-stage breast cancer.^{347,366} At a median follow-up of 2.5 years, the results showed fewer recurrences or new contralateral breast cancers with extended letrozole (HR, 0.58; 95% CI, 0.45–0.76; $P < .001$). No difference in OS was demonstrated (HR, 0.82; 95% CI, 0.57–1.19; $P = .3$), although there was a survival advantage in the subset of patients with ALN-positive disease (HR 0.61; 95% CI, 0.38–0.98; $P = .04$). In a separate cohort analysis of the MA-17 trial, the efficacy of letrozole versus placebo was evaluated after un-blinding of the study in the 1579 women who had been randomly assigned to placebo after 4.5 to 6 years of tamoxifen.^{367,368} The median time since completion of tamoxifen was 2.8 years. Both DFS and distant DFS were significantly improved in the group receiving letrozole, thereby providing some evidence for the efficacy of letrozole in patients who had received 4.5 to 6 years of tamoxifen therapy followed by no endocrine therapy for an extended period. A formal quality-of-life analysis demonstrated reasonable preservation of quality of life during extended endocrine therapy, although women may experience ongoing menopausal symptoms and loss of bone mineral density.^{369,370} No data are available regarding use of aromatase inhibitors for more than 5 years or long-term toxic effects from extended treatment. In addition, the ATLAS

trial data do not provide clear direction for treatment of postmenopausal women.³⁷¹ There are no data available to suggest that an aromatase inhibitor for 5 years is better for long-term benefit than 10 years of tamoxifen.

In the extension study of ABCSG trial 6, hormone receptor-positive postmenopausal patients received 5 years of adjuvant tamoxifen and were randomized to 3 years of anastrozole or no further therapy.³⁷² At a median follow-up of 62.3 months, women who received anastrozole (n = 387) were reported to have a statistically significantly reduced risk of recurrence compared with women who received no further treatment (n = 469; HR, 0.62; 95% CI, 0.40–0.96; *P* = .031).³⁷²

The differences in design and patient populations among the studies of the aromatase inhibitors do not allow for the direct comparison of the results of these studies. A meta-analysis of adjuvant trials of aromatase inhibitors versus tamoxifen alone versus after 2 or 3 years of tamoxifen documented lower recurrence rates with the aromatase inhibitor-containing regimen, with no clear impact on OS.³⁷³ It is not known whether initial, sequential, or extended use of adjuvant aromatase inhibitors is the optimal strategy.

The optimal duration of aromatase inhibitor treatment is also not known, nor is the optimal use vis-à-vis chemotherapy established. Further, the long-term (greater than 5-year) safety and efficacy of these agents are still under investigation. The various studies are consistent in demonstrating that the use of a third-generation aromatase inhibitor in postmenopausal women with hormone receptor-positive breast cancer lowers the risk of recurrence, including ipsilateral breast tumor recurrences, contralateral breast cancer, and distant metastatic disease when used as initial adjuvant therapy, sequential therapy, or extended therapy. The panel finds no compelling evidence that there is

meaningful efficacy or toxicity differences between the aromatase inhibitors, anastrozole, letrozole, and exemestane. All three have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant settings.

NCCN Recommendations for Adjuvant Endocrine Therapy for Postmenopausal Women: The NCCN Guidelines for Breast Cancer recommend the following adjuvant endocrine therapy options for women with early-stage breast cancer who are postmenopausal at diagnosis: an aromatase inhibitor as initial adjuvant therapy for 5 years (category 1); and tamoxifen for 2 to 3 years followed by one of the following options: an aromatase inhibitor to complete 5 years of adjuvant endocrine therapy (category 1) or 5 years of aromatase inhibitor therapy (category 2B); or tamoxifen for 4.5 to 6 years followed by 5 years of an aromatase inhibitor (category 1) or consideration of tamoxifen for up to 10 years. In postmenopausal women, the use of tamoxifen alone for 5 years (category 1) or up to 10 years is limited to those who decline or who have a contraindication to aromatase inhibitors.

NCCN Recommendations for Adjuvant Endocrine Therapy for Premenopausal Women: For women premenopausal at diagnosis, the NCCN Guidelines for Breast Cancer recommend 5 years of tamoxifen (category 1) with or without ovarian suppression (category 1) or ovarian suppression plus an aromatase inhibitor for 5 years (category 1). Women who are premenopausal at diagnosis and who become amenorrheic with chemotherapy may have continued estrogen production from the ovaries without menses. Serial assessment of circulating LH, FSH, and estradiol to assure a true postmenopausal status is mandatory if this subset of women is to be considered for therapy with an aromatase inhibitor.^{374,375}

After 5 years of initial endocrine therapy, for women who are postmenopausal at that time (including those who have become postmenopausal during the 5 years of tamoxifen therapy), the NCCN Panel recommends considering extended therapy with an aromatase inhibitor for up to 5 years (category 1) or based on the data from the ATLAS trial considering tamoxifen for an additional 5 years. For those who remain premenopausal after the initial 5 years of tamoxifen, the panel recommends considering continuing up to 10 years of tamoxifen therapy.

Response to Adjuvant Endocrine Therapy: The measurement of the nuclear antigen, Ki-67 by IHC, gives an estimate of the tumor cells in the proliferative phase (G1, G2, and M phases) of the cell cycle. Studies have demonstrated the prognostic value of Ki-67 as a biomarker and its usefulness in predicting response and clinical outcome.³⁷⁶ One small study suggests that measurement of Ki-67 after short-term exposure to endocrine treatment may be useful to select patients with tumors resistant to endocrine therapy and those who may benefit from additional interventions.³⁷⁷ However, these data require larger analytic and clinical validation. In addition, standardization of tissue handling and processing is required to improve the reliability and value of Ki-67 testing. At this time, there is no conclusive evidence that Ki-67 alone, especially baseline Ki-67 as an individual biomarker, helps to select the type of endocrine therapy for an individual patient. Therefore, the NCCN Breast Cancer Panel does not currently recommend assessment of Ki-67.

The cytochrome P-450 (CYP450) enzyme, CYP2D6, is involved in the conversion of tamoxifen to endoxifen. Over 100 allelic variants of *CYP2D6* have been reported in the literature.³⁷⁸ Individuals with wild-type *CYP2D6* alleles are classified as extensive metabolizers of tamoxifen. Those with one or two variant alleles with either reduced

or no activity are designated as intermediate metabolizers and poor metabolizers, respectively. A large retrospective study of 1325 patients found that time to disease recurrence was significantly shortened in poor metabolizers of tamoxifen.³⁷⁹ However, the BIG 1-98 trial reported on the outcome based on CYP2D6 genotype in a subset of postmenopausal patients with endocrine-responsive, early invasive breast cancer.³⁸⁰ The study found no correlation between CYP2D6 allelic status and disease outcome or between CYP2D6 allelic status and tamoxifen-related adverse effects.³⁸⁰ A genetic analysis of the ATAC trial found no association between CYP2D6 genotype and clinical outcomes.³⁸¹ Given the limited and conflicting evidence at this time,³⁸² the NCCN Breast Cancer Panel does not recommend CYP2D6 testing as a tool to determine the optimal adjuvant endocrine strategy. This recommendation is consistent with the ASCO Guidelines.³⁸³ When prescribing a selective serotonin reuptake inhibitor (SSRI), it is reasonable to avoid potent and intermediate CYP2D6 inhibiting agents, particularly paroxetine and fluoxetine, if an appropriate alternative exists.

Adjuvant Cytotoxic Chemotherapy

Several combination chemotherapy regimens are appropriate to consider when adjuvant cytotoxic chemotherapy is utilized. All adjuvant chemotherapy regimens listed in the NCCN Guidelines have been evaluated in phase III clinical trials, and the current version of the adjuvant chemotherapy guidelines does not distinguish between options for chemotherapy regimens by ALN status.

The adjuvant chemotherapy guidelines also include specific representative doses and schedules for the recommended adjuvant chemotherapy regimens. The regimens have been categorized as “preferred” or “other.”

The purpose of distinguishing the adjuvant chemotherapy regimens as preferred and other adjuvant chemotherapy regimens is to convey the sense of the panel regarding the relative efficacy and toxicity of the regimens.³⁸⁴ Factors considered by the panel include the efficacy, toxicity, and treatment schedules of the regimens. Summarized below are clinical trial results focusing on treatment efficacy.

Preferred Regimens

Regimens listed as preferred include: dose-dense doxorubicin and cyclophosphamide (AC) with dose-dense sequential paclitaxel; dose-dense AC followed by sequential weekly paclitaxel; and docetaxel plus cyclophosphamide (TC).

The results of two randomized trials comparing AC chemotherapy with or without sequential paclitaxel chemotherapy in women with axillary node-positive breast cancer suggest improved disease-free rates, and results from one of the trials showed an improvement in OS, with the addition of paclitaxel.^{385,386} On retrospective analysis, the apparent advantage of the paclitaxel-containing regimen appears greater in women with ER-negative breast cancers.

A randomized trial evaluated the use of concurrent versus sequential chemotherapy (doxorubicin followed by paclitaxel followed by cyclophosphamide vs. doxorubicin plus cyclophosphamide followed by paclitaxel) given either every 2 weeks with filgrastim support or every 3 weeks. The results show no significant difference between the two chemotherapy regimens, but demonstrate a 26% reduction in hazard of recurrence ($P = .01$) and a 31% reduction in the hazard of death ($P = .013$) for the dose-dense regimens.³⁸⁷

The ECOG E1199 study was a four-arm trial that randomized 4950 women to receive AC chemotherapy followed by either paclitaxel or

docetaxel given by either an every-3-week schedule or a weekly schedule.³⁸⁸⁻³⁹⁰ At a median 63.8 months of follow-up, no statistically significant differences in DFS or OS were observed when comparing paclitaxel to docetaxel or weekly versus every-3-week administration. In a secondary series of comparisons, weekly paclitaxel was superior to every-3-week paclitaxel in DFS (HR, 1.27; 95% CI, 1.03–1.57; $P = .006$) and OS (HR, 1.32; 95% CI, 1.02–1.72; $P = .01$), and every-3-week docetaxel was superior to every-3-week paclitaxel in DFS (HR, 1.23; 95% CI, 1.00–1.52; $P = .02$) but not in OS.³⁹⁰ Based on these results, as well as the findings from the CALGB trial 9741 that showed dose-dense AC followed by paclitaxel every 2 weeks to have a survival benefit when compared with the regimen of AC followed by every-3-week paclitaxel,³⁸⁷ the every-3-week paclitaxel regimen has been removed from the guidelines.

Combination TC was compared with AC chemotherapy in a trial that randomized 1016 women with stage I to III breast cancer.³⁹¹ At a median follow-up of 7 years, overall DFS (81% vs. 75%; HR, 0.74; 95% CI, 0.56–0.98; $P = .033$) and OS (87% vs. 82%; HR, 0.69; 95% CI, 0.50–0.97; $P = .032$) were significantly improved with TC compared with AC.

Other Regimens

Other regimens included in the guidelines are: AC; epirubicin and cyclophosphamide (EC); CMF; AC with sequential docetaxel administered every 3 weeks; AC with sequential weekly paclitaxel; FEC/CEF followed by docetaxel or weekly paclitaxel; FAC followed by weekly paclitaxel; and docetaxel, doxorubicin, and cyclophosphamide (TAC).

The AC regimen for four cycles has been studied in randomized trials, resulting in relapse-free survival and OS equivalent to CMF

chemotherapy.^{392,393} No benefit from dose escalation of either doxorubicin or cyclophosphamide was shown.^{385,394}

Studies of CMF chemotherapy versus no chemotherapy have shown DFS and OS advantages with CMF chemotherapy.^{4,395} Studies using FAC/CAF chemotherapy have shown that the use of full-dose chemotherapy regimens is important.³⁹⁶ In the EBCTCG overview of polychemotherapy, comparison of anthracycline-containing regimens with CMF showed a 12% further reduction in the annual odds of recurrence ($P = .006$) and an 11% further reduction in the annual odds of death ($P = .02$) with anthracycline-containing regimens.³⁹⁵ Based on these data, the panel qualified the appropriate chemotherapy regimens by the statement that anthracycline-containing regimens are preferred for node-positive patients.

The EBCTCG analysis, however, did not consider the potential interaction between HER2 tumor status and efficacy of anthracycline-containing versus CMF chemotherapy regimens. Retrospective analysis has suggested that the superiority of anthracycline-containing chemotherapy may be limited to the treatment of those breast cancers that are HER2-positive.^{252,254,257,323,397-399} The retrospective finding across several clinical trials that anthracycline-based chemotherapy may be more efficacious in patients whose tumors are HER2-positive has led to a footnote stating that anthracycline-based chemotherapy may be superior to non-anthracycline-containing regimens in the adjuvant treatment of such patients.

A trial compared 2 dose levels of EC chemotherapy with CMF chemotherapy in women with node-positive breast cancer.⁴⁰⁰ This study showed that higher-dose EC chemotherapy was equivalent to CMF

chemotherapy and superior to moderate-dose EC in event-free survival and OS.

The NSABP B-36 phase III trial data compared six cycles of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) with four cycles of AC, both given every 3 weeks as adjuvant therapy in patients with node-negative breast cancer. The rationale for the trial was to determine whether DFS improved with extra cycles of treatments.⁴⁰¹ Patient and tumor characteristics were equally distributed between both arms (<50 years of age: 40%, lumpectomy: 68%, and hormone positivity: 65%).⁴⁰¹ The results reported that DFS after eight years was not greater for those women who had been on the longer FEC chemotherapy treatment and that the women on the FEC experienced greater side effects. Combined grade 3 and 4 toxicities with a significant difference of 3% or more between AC and FEC arms included fatigue 3.55% versus 8.45%, febrile neutropenia 3.70% versus 9.42%, and thrombocytopenia 0.74% versus 4.41%, respectively.⁴⁰¹ Five deaths resulted from the toxicity of FEC treatment, compared to the death of two women on the AC treatment.⁴⁰¹

The quality-of-life impact and menstrual history of women on the NSABP (NRG) B-36 was also investigated in a phase III trial.⁴⁰² Women on FEC treatment experienced a worse quality of life at six months and higher rate of post-chemotherapy amenorrhea.⁴⁰²

Based on the results of the NSABP B-36 trial, the NCCN Panel has now *excluded* the FEC/CEF and FAC/CAF regimens as options for adjuvant therapy.

Two randomized prospective trials of FEC chemotherapy in ALN-positive breast cancer are available. In one trial, premenopausal women with node-positive breast cancer were randomized to receive

classic CMF therapy versus FEC chemotherapy using high-dose epirubicin. Both 10-year relapse-free survival (52% vs. 45%; $P = .007$) and OS (62% vs. 58%; $P = .085$) favored the FEC arm of the trial.⁴⁰³

The second trial compared FEC given intravenously every 3 weeks at 2 dose levels of epirubicin (50 mg/m² vs. 100 mg/m²) in premenopausal and postmenopausal women with node-positive breast cancer.

Five-year DFS (55% vs. 66%; $P = .03$) and OS (65% vs. 76%; $P = .007$) both favored the epirubicin 100 mg/m² arm.⁴⁰⁴ Another randomized trial

in women with ALN-positive breast cancer compared 6 cycles of FEC with 3 cycles of FEC followed by 3 cycles of docetaxel.³⁴¹ Five-year DFS (78.4% vs. 73.2%; adjusted $P = .012$) and OS (90.7% vs. 86.7%; $P = .017$) were superior with sequential FEC followed by docetaxel.

However, no significant DFS differences were seen in a large randomized study comparing adjuvant chemotherapy with 4 cycles of every-3-week FEC followed by 4 cycles of every-3-week docetaxel with standard anthracycline chemotherapy regimens (eg, FEC or epirubicin followed by CMF) in women with node-positive or high-risk, node-negative, operable breast cancer.⁴⁰⁵

The addition of weekly paclitaxel after FEC was shown to be superior to FEC alone in a randomized study of 1246 women with early-stage breast cancer.⁴⁰⁶ The former regimen was associated with a 23% reduction in the risk of relapse compared with FEC (HR, 0.77; 95% CI, 0.62–0.95; $P = .022$), although no significant difference in OS was seen when the two arms were compared at a median follow-up of 66 months.

The phase III E1199 trial compared patients with node-positive or high-risk node-negative breast cancer who received 4 cycles of AC every 3 weeks, followed by either paclitaxel or docetaxel, either weekly or every 3 weeks. The 10-year updated results of this trial showed that incorporation of weekly paclitaxel and docetaxel every 3 weeks was associated with significant improvements in DFS, and marginal

improvements in OS, compared with paclitaxel given every 3 weeks. Among patients with triple-negative disease, the 10-year DFS rate with weekly paclitaxel was 69% and the 10-year OS rate was 75%.⁴⁰⁷

Final results from a randomized trial of TAC versus FAC chemotherapy in ALN-positive breast cancer demonstrated that TAC is superior to FAC.⁴⁰⁸ Estimated 5-year DFS was 75% with TAC and 68% with FAC (HR, 0.72; 95% CI, 0.59–0.88; $P = .001$); survival was 87% with TAC and 81% with FAC (HR, 0.70; 95% CI, 0.53–0.91; $P = .008$). DFS favored TAC in both ER-positive and ER-negative tumors. At a median follow-up of 73 months, results from the 3-arm randomized NSABP B-30 trial comparing TAC versus AT versus AC followed by docetaxel (AC followed by T) demonstrated that AC followed by T had a significant advantage in DFS (HR, 0.83; $P = .006$) but not in OS (HR, 0.86; $P = .086$) when compared with TAC. In addition, both DFS (HR, 0.080; $P = .001$) and OS (HR, 0.83; $P = .034$) were significantly increased when AC followed by T was compared with AT, with AT demonstrating non-inferiority compared with TAC.⁴⁰⁹

Several retrospective studies have evaluated the potential interaction of chemotherapy benefit and ER status.^{4,295} These studies assessed the effect of chemotherapy on the risk of breast cancer recurrence in patients with ER-positive tumors receiving adjuvant endocrine therapy when compared with patients with ER-negative tumor status not undergoing adjuvant endocrine therapy. These analyses suggest that the benefits of chemotherapy are significantly greater in patients with ER-negative disease. For example, the results of Berry et al demonstrated that 22.8% more patients with ER-negative tumors survived without disease for 5 years if they received chemotherapy; this benefit was only 7% for patients with ER-positive tumors receiving chemotherapy.²⁹⁵

For women greater than 70 years of age, the consensus of the panel is that there are insufficient data to make definitive chemotherapy recommendations. Although AC or CMF has been shown to be superior to capecitabine in a randomized trial of women aged greater than or equal to 65 years with early-stage breast cancer,⁴¹⁰ the enrollment in that study was discontinued early.⁴¹⁰ Therefore, there is also a possibility that AC/CMF is not superior to any chemotherapy in this cohort. The panel recommends that treatment should be individualized for women in this age group, with consideration given to comorbid conditions.

Adjuvant HER2-Targeted Therapy

The panel recommends HER2-targeted therapy in patients with HER2-positive tumors (see *Principles of HER2 Testing* in the NCCN Guidelines for Breast Cancer). Trastuzumab is a humanized monoclonal antibody with specificity for the extracellular domain of HER2.⁴¹¹ Results of several randomized trials testing trastuzumab as adjuvant therapy have been reported.^{259-264,412-414}

NSABP B-31 patients with HER2-positive, node-positive breast cancer were randomly assigned to 4 cycles of AC every 3 weeks followed by paclitaxel for 4 cycles every 3 weeks or the same regimen with 52 weeks of trastuzumab commencing with paclitaxel. In the NCCTG N9831 trial, patients with HER2-positive breast cancer that was node-positive, or node-negative, with primary tumors greater than 1 cm in size if ER- and PR-negative or greater than 2 cm in size if ER- or PR-positive, were similarly randomized except that paclitaxel was given by a low-dose weekly schedule for 12 weeks and a third arm delayed trastuzumab until the completion of paclitaxel.

The B-31 and NCCTG N9831 trials have been jointly analyzed with the merged control arms for both trials compared with the merged arms

using trastuzumab begun concurrently with paclitaxel. There were 4045 patients included in the joint analysis performed at 3.9 years median follow-up. A 48% reduction in the risk of recurrence (HR, 0.52; 95% CI, 0.45–0.60; $P < .001$) and a 39% reduction in the risk of death (HR, 0.61; 95% CI, 0.50–0.75; log-rank $P = .001$) were documented.⁴¹³ Similar significant effects on DFS were observed when results of the NSABP B-31 and NCCTG N9831 trials were analyzed separately. Cardiac toxicity was increased in patients treated with trastuzumab.^{262,415,416} In the adjuvant trastuzumab trials, the rates of grade III/IV congestive heart failure (CHF) or cardiac-related death in patients receiving treatment regimens containing trastuzumab ranged from 0% (FinHer trial) to 4.1% (NSABP B-31 trial).^{259,260,262,264,415,416} The frequency of cardiac dysfunction appears to be related to both age and baseline left ventricular ejection fraction. An analysis of data from N9831 showed the 3-year cumulative incidence of CHF or cardiac death to be 0.3%, 2.8%, and 3.3% in the arms of the trial without trastuzumab, with trastuzumab following chemotherapy, and with trastuzumab initially combined with paclitaxel, respectively.⁴¹⁵ The acceptable rate of significant cardiac toxicity observed in the trastuzumab adjuvant trials in part reflects rigorous monitoring for cardiac dysfunction. Furthermore, concerns have been raised regarding the long-term cardiac risks associated with trastuzumab therapy based on results of follow-up evaluations of cardiac function in patients enrolled in some of these trials.^{417,418}

A third trial (HERA) (N = 5081) tested trastuzumab for 1 or 2 years compared to none following all local therapy and a variety of standard chemotherapy regimens in patients with node-positive disease or node-negative disease with tumor greater than or equal to 1 cm.²⁶⁰ At a median follow-up of one year, a 46% reduction in the risk of recurrence was reported in those who received trastuzumab compared with those who did not (HR, 0.54; 95% CI, 0.43–0.67; $P < .0001$), there was no

difference in OS, and acceptable cardiac toxicity was reported. The 2-year data indicate that 1 year of trastuzumab therapy is associated with an OS benefit when compared with observation (HR for risk of death = 0.66; 95% CI, 0.47–0.91; $P = .0115$).⁴¹⁹ After this initial analysis, patients randomized to chemotherapy alone were allowed to cross over to receive trastuzumab. Intent-to-treat analysis including a crossover patient was reported at 4-year median follow-up.⁴¹⁴ The primary endpoint of DFS continued to be significantly higher in the trastuzumab-treated group (78.6%) versus the observation group (72.2; HR, 0.76; 95% CI, 0.66–0.87; $P < .0001$). At a median follow-up of 8 years, the study reported no significant difference in DFS, a secondary endpoint, in patients treated with trastuzumab for 2 years compared with 1 year.²⁶¹ Therefore, 1 year of adjuvant trastuzumab remains the current standard of treatment.

The BCIRG 006 study randomized 3222 women with HER2-positive, node-positive, or high-risk node-negative breast cancer to AC followed by docetaxel; AC followed by docetaxel plus trastuzumab for one year; or carboplatin, docetaxel, and trastuzumab for one year.²⁶⁴ At 65-month follow-up, patients receiving AC followed by docetaxel with trastuzumab (AC-TH) had an HR for DFS of 0.64 ($P < .001$) when compared with the group of patients in the control arm receiving the same chemotherapy regimen without trastuzumab (AC-T). The HR for DFS was 0.75 ($P = .04$) when patients in the carboplatin/docetaxel/ trastuzumab (TCH)-containing arm were compared to patients in the control arm. No statistically significant difference in the HR for DFS was observed between the two trastuzumab-containing arms. An OS advantage was reported for patients in both trastuzumab-containing arms relative to the control arm (HR for AC-TH vs. AC-T = 0.63; $P = .001$; HR for TCH vs. AC-T = 0.77; $P = .04$). Cardiac toxicity was significantly lower in the TCH arm (9.4% patients with >10% relative decline in left ventricular

ejection fraction) compared with the AC-TH arm (18.6%; $P < .0001$). CHF was also more frequent with AC-TH than TCH (2% vs. 0.4%; $P < .001$). Analysis of this trial by critical clinical event revealed more distant breast cancer recurrences with TCH (144 vs. 124) but fewer cardiac events with TCH compared with AC-TH (4 vs. 21).²⁶⁴ In the FinHer trial, 1010 women were randomized to 9 weeks of vinorelbine followed by 3 cycles of FEC chemotherapy versus docetaxel for 3 cycles followed by 3 cycles of FEC chemotherapy.²⁵⁹ Patients ($n = 232$) with HER2-positive cancers that were either node-positive or node-negative and greater than or equal to 2 cm and PR-negative were further randomized to receive or not receive trastuzumab for 9 weeks during the vinorelbine or docetaxel portions of the chemotherapy only. With a median follow-up of 3 years, the addition of trastuzumab was associated with a reduction in risk of recurrence (HR, 0.42; 95% CI, 0.21–0.83; $P = .01$). No statistically significant differences in OS (HR, 0.41; 95% CI, 0.16–1.08; $P = .07$) or cardiac toxicity were observed with the addition of trastuzumab.²⁵⁹ At 5-year follow-up, a comparison of the two arms (ie, chemotherapy with and without trastuzumab) demonstrated that the HRs for distant DFS (HR, 0.65; 95% CI, 0.38–1.12; $P = .12$) and OS (HR, 0.55; 95% CI, 0.27–1.11; $P = .094$) were higher relative to those reported at 3 years.⁴¹²

All of the adjuvant trials of trastuzumab have demonstrated clinically significant improvements in DFS, and the combined analysis from the NSABP B31 and NCCTG N9831 trials, and the HERA trial, showed significant improvement in OS with the use of trastuzumab in patients with high-risk, HER2-positive breast cancer. Therefore, regimens from each of these trials are included as trastuzumab-containing adjuvant regimen choices in the guideline. The benefits of trastuzumab are independent of ER status.^{262,263} In the FNCLCC-PACS-04 trial, 528 women with HER2-positive, node-positive breast cancer were randomly

assigned to receive trastuzumab or observation *after* completion of adjuvant anthracycline-based chemotherapy with or without docetaxel.⁴²⁰ No statistically significant DFS or OS benefit was observed with the addition of trastuzumab. These results suggest that the sequential administration of trastuzumab following chemotherapy is not as efficacious as a schedule involving concomitant chemotherapy and trastuzumab. The NCCN Guidelines recommend a total of 12 months of adjuvant trastuzumab as the standard of care. Shorter than 12-month duration has not been found to be as effective⁴²¹ and longer than 12 months duration does not have any added benefit; it has been found to be as effective as the 12 months of trastuzumab therapy.⁴²²

Retrospective analyses of low-risk patients with small tumors demonstrate that in T1a-bN0 breast cancers, HER2 overexpression added a 15% to 30% risk for recurrence.⁴²³⁻⁴²⁶ These risks rates are substantially higher than seen among similarly sized HER2-negative tumors.

A recent single-arm, multicenter trial studied the benefit of trastuzumab-based chemotherapy in patients with HER2-positive, node-negative tumors less than or equal to 3 cm. All patients received trastuzumab and weekly paclitaxel for 12 weeks, followed by completion of a year of trastuzumab monotherapy.⁴²⁷ Fifty percent of patients enrolled had tumors less than or equal to 1.0 cm and 9% of patients had tumors that were between 2 and 3 cm. The endpoint of the study was DFS. The results presented at the 2013 Annual San Antonio Breast Cancer Symposium demonstrated that the 3-year DFS rate in the overall population was 98.7% (95% CI, 97.6–99.8; $P < .0001$).

Dual anti-HER2 blockade associated with trastuzumab plus lapatinib and trastuzumab plus pertuzumab has shown significant improvements

in the pCR rate when compared with chemotherapy associated with one anti-HER2 agent in the neoadjuvant setting.^{313,314,316}

However, in the adjuvant setting, the results of the ALTTO trial failed to demonstrate a significant improvement in DFS with dual anti-HER2 therapy compared with trastuzumab alone.⁴²⁸ After a median follow-up of 4.5 years, the DFS rates were 86% for patients who received trastuzumab alone; 88% for participants treated with trastuzumab and lapatinib concurrently; and 87% for patients who received trastuzumab followed by lapatinib.⁴²⁸

NCCN Recommendation for Adjuvant HER2-Targeted Therapy

Based on these studies, the panel has designated use of trastuzumab with chemotherapy as a category 1 recommendation in patients with HER2-positive tumors greater than 1 cm.

The NCCN Panel suggests trastuzumab and chemotherapy be used for women with HER2-positive, node-negative tumors measuring 0.6 to 1.0 cm (ie, T1b) and for smaller tumors that have less than or equal to 2 mm axillary node metastases (pN1mi). Some support for this recommendation comes from studies showing a higher risk of recurrence for patients with HER2-positive, node-negative tumors less than or equal to 1 cm compared to those with HER2-negative tumors of the same size.⁴²³ Ten-year breast cancer-specific survival and 10-year recurrence-free survival were 85% and 75%, respectively, in women with tumors characterized as HER2-positive, ER-positive tumors, and 70% and 61%, respectively, in women with HER2-positive, ER-negative tumors. Two more retrospective studies have also investigated recurrence-free survival in this patient population. None of the patients in these two retrospective studies received trastuzumab. In the first study, 5-year recurrence-free survival rates of 77.1% and 93.7% ($P < .001$) were observed for patients with HER2-positive and

HER2-negative T1a-bN0M0 breast tumors, respectively, with no recurrence-free survival differences seen in the HER2-positive group when hormonal receptor status was considered.⁴²⁴ In the other retrospective study of women with small HER2-positive tumors, the risk of recurrence at 5 years was low (99% [95% CI; 96%–100%] for HER2-negative disease and 92% [95% CI; 86%–99%] for HER2-positive disease).⁴²⁹ Subgroup analyses from several of the randomized trials have shown consistent benefit of trastuzumab irrespective of tumor size or nodal status.^{264,430,431}

NCCN-Recommended HER-Targeted Regimens

The panel recommends AC followed by paclitaxel with trastuzumab for 1 year commencing with the first dose of paclitaxel as a preferred HER2-targeting adjuvant regimen. The TCH regimen is also a preferred regimen, especially for those with risk factors for cardiac toxicity, given the results of the BCIRG 006 study that demonstrated superior DFS in patients receiving TCH or AC followed by docetaxel plus trastuzumab compared with AC followed by docetaxel alone.

Other trastuzumab-containing regimens included in the NCCN Guidelines are: AC followed by docetaxel and trastuzumab,²⁶⁴ and docetaxel plus trastuzumab followed by FEC²⁵⁹ (see *Preoperative /Adjuvant Systemic Therapy* in NCCN Guidelines for Breast Cancer for a complete list of regimens).

Considering the unprecedented improvement in OS in the metastatic setting⁴³² and the significant improvement in pCR seen in the neoadjuvant setting,^{314,316} the NCCN Panel considers it reasonable to incorporate pertuzumab into the above adjuvant regimens, if the patient did *not* receive pertuzumab as a part of neoadjuvant therapy. An ongoing study is evaluating pertuzumab and trastuzumab with standard chemotherapy regimens in the adjuvant setting.^{433,434}

The NCCN Panel has included paclitaxel and trastuzumab as an option for patients with low-risk, HER2-positive, stage 1 tumors. This is based on a trial that studied this combination in 406 patients with small, node-negative, HER2-positive tumors. The results showed that the 3-year rate of DFS was 98.7% (95% CI, 97.6–99.8) and the risk of serious toxic effects with this regimen was low (incidence of heart failure reported was 0.5%).⁴³⁵

Adjuvant Therapy for Tumors of Favorable Histologies

The guidelines provide systemic treatment recommendations for the favorable histology of invasive breast cancers, such as tubular and mucinous cancers, based on tumor size and ALN status. If used, the treatment options for endocrine therapy, chemotherapy, and sequencing of treatment with other modalities are similar to those of the usual histology of breast cancers. The vast majority of tubular breast cancers are both ER-positive and HER2-negative. Thus, the pathology evaluation and accuracy of the ER and/or HER2 determination should be reviewed if a tubular breast cancer is ER-negative and/or HER2-positive, or if a tumor with an ER- and PR-negative status is grade 1.¹⁷ Should a breast cancer be histologically identified as a tubular or mucinous breast cancer and be confirmed as ER-negative, then the tumor should be treated according to the guideline for the usual histology, ER-negative breast cancers. The panel acknowledges that prospective data regarding systemic adjuvant therapy of tubular and mucinous histologies are lacking.

Systemic Therapy for Triple-Negative Breast Cancer

For women with triple-negative breast cancer, several clinical trials sought to determine whether the addition of carboplatin (alone or in combination) as neoadjuvant chemotherapy can improve outcomes for women with triple-negative breast cancer. In the German GeparSixto

trial, 315 patients with triple-negative breast cancer were administered neoadjuvant therapy consisting of weekly paclitaxel plus non-pegylated liposomal doxorubicin with bevacizumab and then randomly assigned to additional treatment with weekly carboplatin.⁴³⁶ The addition of carboplatin achieved a pCR rate of 59% compared with pCR of 38% in patients who did not receive carboplatin.⁴³⁶

In the CALGB 40603 randomized phase II trial, 443 patients with stage II to III triple-negative breast cancer received standard anthracycline- and taxane-based chemotherapy with or without carboplatin and with or without bevacizumab. Compared with standard chemotherapy, the addition of carboplatin resulted in significantly higher pCR rate (54% vs. 41%, OR 1.71).⁴³⁷ The addition of bevacizumab increased the numeric rate of pCR but was not statistically significant (with bevacizumab, pCR was 52% [95% CI; 45%–58%] and without bevacizumab pCR was 44% [95% CI; 38%–51%]; $P = .057$). In this study,⁴³⁷ as well as in the GeparSixto study,⁴³⁶ the addition of carboplatin and/or bevacizumab led to increased rates of adverse events. Neutropenia and thrombocytopenia were more common with carboplatin. Hypertension and postsurgical complications were more common with bevacizumab.

Even though the results of randomized trials show improvement in pCR rates when carboplatin is added to anthracycline- and taxane-based chemotherapy, the long-term outcomes such as OS or DFS associated with the incorporation of carboplatin are not yet known. Therefore, at this time, the NCCN Panel does not recommend addition of carboplatin to neoadjuvant standard chemotherapy for patients with triple-negative breast cancer outside a clinical trial setting.

Medullary Carcinoma

Medullary carcinoma is an uncommon variant of infiltrating ductal carcinoma characterized by high nuclear grade, lymphocytic infiltration,

a pushing tumor border, and the presence of a syncytial growth pattern. It was previously thought that medullary carcinoma has a lower potential for metastases and a better prognosis than typical infiltrating ductal carcinoma. However, the best available evidence suggests that the risk of metastases equals that of other high-grade carcinomas, even for cases that meet all the pathologic criteria for typical medullary carcinoma. Furthermore, typical medullary carcinoma is uncommon, and there is marked interobserver variation in diagnosing this entity. Many cases classified as medullary carcinoma do not have all the pathologic features on subsequent pathologic review. Given these facts, there is concern that patients may be harmed if a high-grade infiltrating ductal carcinoma is misclassified as typical medullary carcinoma and this classification is used as the basis for withholding otherwise indicated adjuvant systemic therapy. Therefore, the NCCN Panel believes that including medullary carcinoma with other special histology cancers that carry a favorable prognosis and often do not require systemic therapy is not appropriate. The panel recommends that cases classified as medullary carcinoma be treated as other infiltrating ductal carcinomas based on tumor size, grade, and lymph node status.

Post-Therapy Surveillance and Follow-up

See page [MS-48](#).

Stage III Invasive Breast Cancer

Staging and Workup

The staging evaluation for most patients with stage III invasive breast cancer is similar to the one for patients with T3, N1, M0 disease. The workup includes history and physical exam, a CBC, liver function and alkaline phosphatase tests, chest imaging, pathology review, and pre-chemotherapy determination of tumor ER/PR receptor status and HER2 status. Diagnostic bilateral mammogram and breast ultrasound

should be performed as clinically warranted. Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer as defined by the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#).

The performance of other studies, such as a breast MRI, a bone scan (category 2B), and abdominal imaging with diagnostic CT (with or without pelvic CT) or MRI (all category 2A) are optional unless directed by symptoms or other abnormal study results. PET/CT scan is also included as an optional additional study (category 2B). Ultrasound is an alternative when diagnostic CT or MRI is unavailable.

The consensus of the panel is that FDG PET/CT is most helpful in situations where standard imaging results are equivocal or suspicious. However, limited studies^{125,126,438-442} support a potential role for FDG PET/CT to detect regional node involvement as well as distant metastases in locally advanced breast cancer, including T3, N1, M0 disease.

A retrospective study comparing bone scan with integrated FDG PET/CT, in women with stages I–III breast cancer with suspected metastasis, observed a high concordance (81%) between the two studies for reporting osseous metastases.⁴⁴³ The NCCN Panel suggests that bone scan may be omitted if FDG PET/CT results are positive for bone metastases.

Equivocal or suspicious sites identified by PET/CT scanning should be biopsied for confirmation whenever possible and if the site of disease would impact the course of treatment. In the past decade, the advent of PET/CT scanners has significantly changed the approach to PET imaging.⁴⁴⁴ However, the terminology has also created confusion regarding the nature of the scans obtained from a PET/CT device.

PET/CT scanners have both a PET and CT scanner in the same gantry that allows precise coregistration of molecular (PET) and anatomic (CT) imaging. Almost all current clinical PET imaging is performed using combined PET/CT devices.

In PET/CT tomographs, the CT scanner has a second important role beyond diagnostic CT scanning.⁴⁴⁴ For PET applications, the CT scan is also used for photon attenuation correction and for anatomic localization of the PET imaging findings. For these tasks, the CT scan is usually taken without breathholding, to match PET image acquisition, and typically uses low-dose (non-diagnostic) CT. Radiation exposure for these non-diagnostic CT scans is lower than for diagnostic CT. Intravenous contrast is not needed for this task.

PET/CT scanners typically include a high-quality CT device that can also be used for stand-alone, optimized, and fully diagnostic CT. Diagnostic CT scans are acquired using breathholding for optimal chest imaging, and are often performed with intravenous contrast. For fully diagnostic CT, the CT beam current, and therefore patient radiation exposure, is considerably higher than for the low-dose CT needed for PET requirements. Radiation exposures for fully diagnostic CT are often greater than for the emission (PET) component of the study.

Currently, the approach to clinical PET/CT imaging varies widely across centers.⁴⁴⁵ Many centers perform low-dose CT as part of a PET/CT scan, and perform optimized, fully diagnostic CT only when diagnostic CT has also been requested in addition to PET/CT. Other centers combine diagnostic CT scans with PET on all of their PET/CT images. The CT scans described in the workup section of the guidelines refer to fully optimized diagnostic CT scans, while the PET or PET/CT scans refer to scans primarily directed towards the PET component, not necessarily using diagnostic-quality CT. It is important for referring

physicians to understand the differences between PET/CT performed primarily for PET imaging and fully optimized CT performed as a stand-alone diagnostic CT examination.⁴⁴⁵ It may be convenient to perform PET/CT and diagnostic CT at the same time.

Operable Locally Advanced Breast Cancer

(Clinical stage T3, N1, M0)

Locally advanced breast cancer describes a subset of invasive breast cancer where the initial clinical and radiographic evaluation documents advanced disease confined to the breast and regional lymph nodes. The AJCC clinical staging system used in these guidelines and for the determination of operability is recommended, and locally advanced disease is represented by the stage III category. Patients with stage III disease may be further divided into: 1) those where an initial surgical approach is unlikely to successfully remove all disease or to provide long-term local control; and 2) those with disease where a reasonable initial surgical approach is likely to achieve pathologically negative margins and provide long-term local control. Thus, stage IIIA patients are divided into those who have clinical T3, N1, M0 disease versus those who have clinical T any, N2, M0 disease, based on evaluation by a multidisciplinary team.

Postsurgical systemic adjuvant therapy for patients with stage IIIA breast cancer who do not receive neoadjuvant chemotherapy is similar to that for patients with stage II disease.

Inoperable Locally Advanced Breast Cancer

(Clinical stage IIIA [except for T3, N1, M0], clinical stage IIIB, or clinical stage IIIC)

For patients with inoperable, non-inflammatory, locally advanced disease at presentation, the initial use of anthracycline-based preoperative systemic therapy with or without a taxane is standard

therapy.⁴⁴⁶ Patients with locally advanced breast cancer that is HER2-positive should receive an initial chemotherapy program that incorporates preoperative trastuzumab and possibly pertuzumab. Local therapy following a clinical response to preoperative systemic therapy usually consists of: 1) total mastectomy with level I/II ALN dissection, with or without delayed breast reconstruction; or 2) lumpectomy and level I/II axillary dissection.

Both local treatment groups are considered to have sufficient risk of local recurrence to warrant the use of chest wall (or breast) and supraclavicular node irradiation. If internal mammary lymph nodes are involved, they should also be irradiated. Without detected internal mammary node involvement, consideration may be given to include the internal mammary lymph nodes in the radiation field (category 2B). Adjuvant therapy may involve completion of planned chemotherapy regimen course if not completed preoperatively, followed by endocrine therapy in patients with hormone receptor-positive disease. Up to one year of total trastuzumab therapy should be completed if the tumor is HER2-positive (category 1). Endocrine therapy and trastuzumab can be administered concurrently with radiation therapy if indicated.

Patients with an inoperable stage III tumor with disease progression during preoperative systemic therapy should be considered for palliative breast irradiation in an attempt to enhance local control. In all subsets of patients, further systemic adjuvant chemotherapy after local therapy is felt to be standard. Tamoxifen (or an aromatase inhibitor if postmenopausal) should be added for those with hormone receptor-positive tumors, and trastuzumab should be given to those with HER2-positive tumors. Post-treatment follow-up for women with stage III disease is the same as for women with early-stage invasive breast cancer.

Post-Therapy Surveillance and Follow-up for Stage I-III

Post-therapy follow-up is optimally performed by members of the treatment team and includes the performance of regular history/physical examinations every 4 to 6 months for the first 5 years after primary therapy and annually thereafter. Mammography should be performed annually.

Regarding frequency of mammograms after breast-conserving surgery followed by radiation, the NCCN Panel agrees with ASTRO's "Choosing Wisely" list of recommendations released in 2014.⁴⁴⁷ The recommendations state that "annual mammograms are the appropriate frequency for surveillance of breast cancer patients who have had breast-conserving surgery and radiation therapy with no clear advantage to shorter interval imaging. Patients should wait 6 to 12 months after the completion of radiation therapy to begin their annual mammogram surveillance. Suspicious findings on physical examination or surveillance imaging might warrant a shorter interval between mammograms."

The NCCN panel notes that any imaging of reconstructed breast is not indicated.

According to the NCCN Panel, in the absence of clinical signs and symptoms suggestive of recurrent disease, laboratory or imaging studies to screen for metastasis are not necessary. The routine performance of alkaline phosphatase tests and LFTs are not included in the guidelines.⁴⁴⁸⁻⁴⁵⁰ In addition, the panel notes no evidence to support the use of "tumor markers" for breast cancer, and routine bone scans, CT scans, MRI scans, PET scans, or ultrasound examinations in the asymptomatic patient provide no advantage in survival or ability to palliate recurrent disease and are, therefore, not recommended.^{125,451}

The use of breast MRI in follow-up of women with prior breast cancer is undefined. It may be considered as an option in women with high lifetime risk (greater than 20% based on models largely dependent on family history) of developing a second primary breast cancer. Rates of contralateral breast cancer after either breast-conserving therapy or mastectomy have been reported to be increased in women with *BRCA1/2* mutations when compared with patients with sporadic breast cancer.⁴⁵²⁻⁴⁵⁴

The panel recommends that women with intact uteri who are taking adjuvant tamoxifen should have yearly gynecologic assessments and rapid evaluation of any vaginal spotting that might occur because of the risk of tamoxifen-associated endometrial carcinoma in postmenopausal women.⁴⁵⁵ The performance of routine endometrial biopsy or ultrasonography in the asymptomatic woman is not recommended. Neither test has demonstrated utility as a screening test in any population of women. The vast majority of women with tamoxifen-associated uterine carcinoma have early vaginal spotting.

If an adjuvant aromatase inhibitor is considered in women with amenorrhea following treatment, baseline levels of estradiol and gonadotropin followed by serial monitoring of these hormones should be performed if endocrine therapy with an aromatase inhibitor is initiated.³⁷⁴ Bilateral oophorectomy assures postmenopausal status in young women with therapy-induced amenorrhea and may be considered prior to initiating therapy with an aromatase inhibitor in a young woman.

Symptom management for women on adjuvant endocrine therapies often requires treatment of hot flashes and the treatment of concurrent depression. Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI) has been studied and is an effective intervention in decreasing hot flashes.⁴⁵⁶⁻⁴⁵⁹ There is evidence suggesting that concomitant use of

tamoxifen with certain SSRIs (eg, paroxetine, fluoxetine) may decrease plasma levels of endoxifen, an active metabolite of tamoxifen.^{460,461} These SSRIs/SNRIs may interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting a particular isoform of CYP2D6. However, the mild CYP2D6 inhibitors such as citalopram, escitalopram, sertraline, and venlafaxine appear to have no or only minimal effect on tamoxifen metabolism.^{374,462,463}

Follow-up also includes assessment of patient adherence to ongoing medication regimens such as endocrine therapies. Predictors of poor adherence to medication include the presence of side effects associated with the medication, and incomplete understanding by the patient of the benefits associated with regular administration of the medication.⁴⁶⁴ The panel recommends the implementation of simple strategies to enhance patient adherence to endocrine therapy, such as direct questioning of the patient during office visits, as well as brief, clear explanations on the value of taking the medication regularly and the therapeutic importance of longer durations of endocrine therapy.

Lymphedema is a common complication after treatment for breast cancer. Factors associated with increased risk of lymphedema include extent of axillary surgery, axillary radiation, infection, and patient obesity.^{465,466} The panel recommends educating the patients on lymphedema, monitoring for lymphedema, and referring for lymphedema management as needed.

Many young women treated for breast cancer maintain or regain premenopausal status following treatment for breast cancer. For these women, the NCCN Panel discourages the use of hormonal birth control methods, regardless of the hormone receptor status of the tumor.⁴⁶⁷

Alternative birth control methods are recommended, including intrauterine devices, barrier methods, and, for those with no intent of

future pregnancy, tubal ligation or vasectomy for the partner. Breastfeeding during endocrine or chemotherapy treatment is not recommended by the NCCN Panel because of risks to the infant. Breastfeeding after breast-conserving treatment for breast cancer is not contraindicated. However, lactation from an irradiated breast may not be possible, or may occur only with a diminished capacity.^{467,468}

The panel recommends that women on an adjuvant 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. The use of estrogen, progesterone, or selective ER modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. The use of a bisphosphonate is generally the preferred intervention to improve bone mineral density. A single phase 3 study, ABCSG12, demonstrated improved outcomes with the addition of zoledronic acid in premenopausal women receiving endocrine therapy with ovarian suppression.⁴⁶⁹ Use of bisphosphonates in such patients and in other subgroups remains controversial. Denosumab has shown to significantly reduce fractures in postmenopausal women receiving adjuvant therapy aromatase inhibitors, and improves bone mineral density.⁴⁷⁰

Optimal duration of bisphosphonate therapy has not been established. Factors to consider for duration of anti-osteoporosis therapy include bone mineral density, response to therapy, and risk factors for continued bone loss or fracture. Women treated with a bisphosphonate should undergo a dental examination with preventive dentistry prior to the initiation of therapy, and should take supplemental calcium and vitamin D.

Evidence suggests that a healthy lifestyle may lead to better breast cancer outcomes. A nested case control study of 369 women with

ER-positive tumors who developed a second primary breast cancer compared with 734 matched control patients who did not develop a second primary tumor showed an association between obesity (body mass index [BMI] ≥ 30), smoking, and alcohol consumption and contralateral breast cancer.⁴⁷¹ A prospective study of 1490 women diagnosed with stage I–III breast cancer showed an association between high fruit and vegetable consumption, physical activity, and improved survivorship, regardless of obesity.⁴⁷² There is emerging evidence that obesity is associated with poorer outcomes for certain subtypes of breast cancers. The study by the Women’s Intervention Nutrition group randomized early-stage breast cancer patients to an intervention group and a control group. The intervention consisted of eight one-on-one visits with a registered dietitian who had been trained on a low-fat eating plan. OS analysis showed no significant difference between the two study arms (17% for the intervention vs. 13.6% without); however, subgroup analysis showed that those with ER- and PR-negative disease who were part of the intervention group saw a 54% improvement in OS.⁴⁷³

The NCCN Panel recommends an active lifestyle and ideal body weight (BMI 20–25) for optimal overall health and breast cancer outcomes as there are reports of proven benefits of exercise and active lifestyle during and after treatment.⁴⁷⁴⁻⁴⁷⁶

For management of issues related to survivorship including late/long-term effects of cancer and its treatment, see the [NCCN Guidelines for Survivorship](#).

Stage IV Metastatic or Recurrent Breast Cancer

Staging and Workup

The staging evaluation of women who present with metastatic or recurrent breast cancer includes history and physical exam; the performance of a CBC, LFTs, chest diagnostic CT, bone scan, and radiographs of any long or weight-bearing bones that are painful or appear abnormal on bone scan; consideration of diagnostic CT of the abdomen (with or without diagnostic CT of the pelvis) or MRI scan of the abdomen; and biopsy documentation of first recurrence if possible. The panel generally discourages the use of sodium fluoride PET or PET/CT scans for the evaluation of patients with recurrent disease, except in those situations where other staging studies are equivocal or suspicious. There is limited evidence (mostly from retrospective studies) to support the use of PET/CT scanning to guide treatment planning through determination of the extent of disease in select patients with recurrent or metastatic disease.^{125,126,477,478} The panel considers biopsy of equivocal or suspicious sites to be more likely than PET/CT scanning to provide accurate staging information in this population of patients.

The consensus of the panel is that FDG PET/CT is optional (category 2B) and most helpful in situations where standard imaging results are equivocal or suspicious. The NCCN Panel recommends bone scan or sodium fluoride PET/CT to detect bone metastases (category 2B). However, if the FDG PET results clearly indicate bone metastasis, these scans can be omitted.

The NCCN Panel recommends that metastatic disease at presentation or first recurrence of disease should be biopsied as a part of the workup for patients with recurrent or stage IV disease. This ensures accurate determination of metastatic/recurrent disease and tumor histology, and

allows for biomarker determination and selection of appropriate treatment.

Determination of hormone receptor status (ER and PR) and HER2 status should be repeated in all cases when diagnostic tissue is obtained. ER and PR assays may be falsely negative or falsely positive, and there may be discordance between the primary and metastatic tumors.^{479,480} The reasons for the discordance may relate to change in biology of disease, differential effect of prior treatment on clonal subsets, tumor heterogeneity, or imperfect accuracy and reproducibility of assays.⁴⁸⁰ Discordance between the receptor status of primary and recurrent disease has been reported in a number of studies. The discordance rates are in the range of 3.4% to 60% for ER-negative to ER-positive; 7.2% to 31% for ER-positive to ER-negative; and 0.7% to 11% for HER2.⁴⁸¹⁻⁴⁹⁰

The NCCN Panel recommends that re-testing the receptor status of recurrent disease be performed, *especially* in cases when it was previously unknown, originally negative, or not overexpressed. For patients with clinical courses consistent with hormone receptor–positive breast cancer, or with prior positive hormone receptor results, the panel has noted that a course of endocrine therapy is reasonable, regardless of whether the receptor assay is repeated or the result of the most recent hormone receptor assay.

Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer, as defined by the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#).

Management of Local Disease Only

Patients with local recurrence only are divided into 3 groups: those who had been treated initially by mastectomy alone, those who had been treated initially by mastectomy plus radiation therapy, and those who had received breast-conserving therapy.

In one retrospective study of local recurrence patterns in women with breast cancer who had undergone mastectomy and adjuvant chemotherapy without radiation therapy, the most common sites of local recurrence were at the chest wall and the supraclavicular lymph nodes.⁴⁹¹ The recommendations for treatment of the population of patients experiencing a local recurrence only are supported by analyses of a combined database of patients from the EORTC 10801 and Danish Breast Cancer Cooperative Group 82TM trials. The analyses compared breast-conserving therapy with mastectomy in patients with stage I and stage II disease. The 133 (approximately 8%) patients experiencing a local recurrence as an initial event were approximately equally divided between those who had undergone mastectomy and those who had received breast-conserving therapy as initial treatment for breast cancer. Of those in the former group, 51 (76%) were able to undergo radiation therapy with or without surgery as treatment for local disease recurrence. No difference in survival emerged between patients receiving treatment after initial treatment with mastectomy or breast-conserving therapy; approximately 50% of both groups were alive at 10-year follow-up.⁴⁹²

According to the NCCN Panel, mastectomy-treated patients should undergo surgical resection of the local recurrence (if it can be accomplished without heroic surgery) and involved-field radiation therapy to the chest wall and supraclavicular area (if the chest wall was not previously treated or if additional radiation therapy may be safely

administered). The use of surgical resection in this setting implies the use of limited excision of disease with the goal of obtaining clear margins of resection. Unresectable chest wall recurrent disease should be treated with radiation therapy if no prior radiation has been given. Women with a local recurrence of disease after initial breast-conserving therapy should undergo a total mastectomy and axillary staging if a level I/II axillary dissection was not previously performed. Limited data suggest that a repeat SLN biopsy following local recurrence of disease may be successfully performed in 80% of women who have previously undergone breast-conserving therapy and sentinel node biopsy.⁴⁹³ The consensus of the panel is that the preferred surgical approach for most women with a local recurrence following breast-conserving therapy and sentinel node biopsy is mastectomy and a level I/II axillary dissection, although sentinel node biopsy in lieu of a level I/II axillary dissection can be considered if prior axillary staging was done by sentinel node biopsy only.

The results of the CALOR trial found that after complete resection in patients with isolated locoregional recurrence, adjuvant chemotherapy improves both DFS and OS.⁴⁹⁴ After median follow-up of 4.9 years, the overall DFS was 69% in the chemotherapy group versus 57% in the group that did not receive chemotherapy (HR = 0.59, $P = .046$).⁴⁹⁴ Five-year OS in all patients in the study was also significantly improved with chemotherapy (88% vs. 76%, $P = .024$).⁴⁹⁴ The benefit of adjuvant chemotherapy was mostly seen in women with ER-negative disease. Among women with ER-negative disease, 5-year DFS was 67% versus 35% (HR, 0.32; 95% CI, 0.14–0.73) and in those ER-positive disease, the 5-year DFS was 70% versus 69% (HR, 0.94; 95% CI, 0.47–1.89).⁴⁹⁴

According to the NCCN Panel, after local treatment, women with local recurrences only should be considered for limited duration systemic chemotherapy or endocrine therapy similar to that outlined in the

adjuvant chemotherapy section. The panel emphasized the importance of individualizing treatment strategies in patients with a recurrence of disease limited to a local site.

Management of Stage IV or Recurrent Metastatic Disease

The systemic treatment of breast cancer recurrence or stage IV disease prolongs survival and enhances quality of life but is not curative. Therefore, treatments associated with minimal toxicity are preferred. Thus, the use of the minimally toxic endocrine therapies is preferred to the use of cytotoxic therapy whenever reasonable.⁴⁹⁵

Guideline Stratification for Therapy in Systemic Disease

Patients with recurrence of breast cancer or metastatic breast cancer at diagnosis are initially stratified according to whether bone metastasis is present. These two patient subsets are then stratified further by tumor hormone receptor and HER2 status.

Supportive Therapy for Bone Metastases

Treatment targeting osteoclast activity is of value in patients with metastatic breast cancer in bone to prevent bone fractures, bone pain requiring radiation therapy, spinal cord compression, and hypercalcemia (skeletal-related events; SREs).⁴⁹⁶⁻⁴⁹⁸ The bisphosphonates zoledronic acid or pamidronate have been used for this purpose, and there is extensive clinical trial support for their efficacy in prevention of SREs (see section below on *Bisphosphonates*). Denosumab is a fully human monoclonal antibody directed against RANK ligand, a mediator of osteoclast function.⁴⁹⁹ A single, randomized, active, controlled trial in metastatic breast cancer showed equivalency and superiority of time to the occurrence of SRE with denosumab, as compared with zoledronic acid.⁴⁹⁸ No study of bisphosphonate or denosumab has demonstrated an impact on OS in patients with metastatic disease.

The bisphosphonates and denosumab are associated with a risk of development of osteonecrosis of the jaw (ONJ). Poor baseline dental health or dental procedures during treatment are known risk factors for ONJ. Thus, a dental examination with preventive dentistry intervention is recommended prior to treatment with intravenous bisphosphonate or denosumab, and dental procedures during treatment should be avoided if at all possible. Additional risk factors for the development of ONJ include administration of chemotherapy or corticosteroids and poor oral hygiene with periodontal disease and dental abscess.⁵⁰⁰

Confirmation of metastatic disease by imaging, including x-ray, diagnostic CT, or MRI, and initial evaluation of serum calcium, creatinine, phosphorous, and magnesium levels should be undertaken prior to the initiation of intravenous bisphosphonate treatment or subcutaneous denosumab treatment in patients with metastatic disease. Frequent measurement of calcium, phosphorous, and magnesium may be prudent since hypophosphatemia and hypocalcemia have been reported.

Bisphosphonates

An intravenous bisphosphonate (eg, pamidronate, zoledronic acid) in combination with oral calcium citrate and vitamin D supplementation should be used in women with bone metastasis, especially if lytic and/or in weight-bearing bone, if expected survival is 3 months or longer, and if creatinine levels are below 3.0 mg/dL (category 1).^{497,501-506}

Bisphosphonates are given in addition to chemotherapy or endocrine therapy. Zoledronic acid may be superior to pamidronate in lytic breast metastasis.^{507,508}

There are extensive data from randomized trials in support of the use of bisphosphonates for patients with metastatic disease to bone. The randomized clinical trial data include the use of zoledronic acid and

pamidronate in the United States and ibandronate and clodronate in European countries.^{504,506,508-513} In metastatic bone disease, bisphosphonate treatment is associated with fewer SREs, fewer pathologic fractures, and less need for radiation therapy and surgery to treat bone pain.

The use of bisphosphonates in metastatic disease is a palliative care measure. No impact on OS has been observed in patients treated with bisphosphonates. The data indicate that zoledronic acid and pamidronate may be given on a 3- to 5-week schedule in conjunction with antineoplastic therapy (ie, endocrine therapy, chemotherapy, biologic therapy). Recent data from a phase III study showed zoledronic acid administered once every 12 weeks versus the current standard of once every four weeks does not compromise efficacy among women with breast cancer and bone metastases. The SRE rate was 22% when zoledronic acid was administered every 4 weeks versus 23.2% when administered once every 12 weeks.⁵¹⁴

The use of bisphosphonates should be accompanied by calcium and vitamin D supplementation with daily doses of calcium of 1200 to 1500 mg and vitamin D₃ of 400 to 800 IU. Recommended agents for use in the United States are pamidronate 90 mg intravenously over 2 hours or zoledronic acid 4 mg intravenously over 15 minutes. The original studies continued treatment for up to 24 months; however, there are limited long-term safety data indicating treatment can continue beyond that time.^{511,513,515} The risk of renal toxicity necessitates monitoring of serum creatinine prior to administration of each dose and dose reduction or discontinuation if renal function is reduced. Current clinical trial results support the use of bisphosphonates for up to 2 years. Longer durations of bisphosphonate therapy may provide additional benefit, but this has not yet been tested in clinical trials.

ONJ, a complication of bisphosphonate treatment, has been described. In a review of more than 16,000 cancer patients, an increased risk for jaw or facial bone surgery along with an increased risk of being diagnosed with inflammatory conditions or osteomyelitis of the jaw with the use of intravenous bisphosphonates was documented. An absolute risk of 5.48 events per 100 patients treated was seen, with an increase in risk associated with an increase in cumulative dose of drug.⁵¹⁶ It is recommended that patients should undergo a dental examination with preventive dentistry prior to initiation of bisphosphonate therapy.

Denosumab

Women with metastatic breast cancer to bone who are candidates for bisphosphonate therapy may also be considered for treatment with denosumab (category 1). This recommendation is based on the results of a single randomized trial comparing denosumab to zoledronic acid.⁴⁹⁸ All trial patients were recommended to supplement with vitamin D and calcium. Patients on the experimental arm were given 120 mg of denosumab injected subcutaneously every 4 weeks plus intravenous placebo versus the control arm where patients were given an intravenous infusion of 4 mg of zoledronic acid every 4 weeks, and a subcutaneous placebo. In this trial with non-inferiority as the primary endpoint, denosumab was shown to significantly delay time to first SRE by 18% as compared with zoledronic acid (HR, 0.82; 95% CI, 0.71–0.95; $P < .001$ for non-inferiority; $P = .01$ for superiority) and time to first and subsequent SREs (rate ratio, 0.77; 95% CI, 0.66–0.89; $P = .001$). No difference in time to progression or OS was observed. Adverse event profiles were similar for the two groups, including incidence of ONJ, with a reduced risk of renal-related and acute phase adverse events in the denosumab treatment group. Long-term risks of denosumab treatment are unknown. The optimal duration of treatment with denosumab is not known.

Endocrine Therapy for Stage IV or Recurrent Metastatic Disease

Women with recurrent or metastatic disease characterized by tumors that are ER- and/or PR-positive are appropriate candidates for initial endocrine therapy.

In premenopausal women without previous exposure to an antiestrogen, initial treatment is with selective ER modulator alone or ovarian suppression/ablation plus endocrine therapy as for postmenopausal women.⁵¹⁷ In premenopausal women who received a prior endocrine therapy within 12 months, the preferred second-line therapy is ovarian ablation or suppression followed by endocrine therapy as for postmenopausal women.

Endocrine therapies for recurrent/stage IV disease in postmenopausal women include nonsteroidal aromatase inhibitors (anastrozole and letrozole); steroidal aromatase inhibitors (exemestane); serum ER modulators (tamoxifen or toremifene); ER down-regulators (fulvestrant); progestin (megestrol acetate); androgens (fluoymesterone); and high-dose estrogen (ethinyl estradiol) and recently several new combination therapies with novel agents have become available such as exemestane with everolimus, palbociclib in combination with fulvestrant, and palbociclib with letrozole.

According to some studies, in postmenopausal women, aromatase inhibitors appear to have superior outcome compared with tamoxifen, although the differences are modest.⁵¹⁸⁻⁵²¹ A Cochrane review has also suggested a survival benefit favoring the aromatase inhibitors over other endocrine therapies, although the advantage is small.⁵²² A randomized phase III trial comparing tamoxifen with exemestane as first-line endocrine therapy for postmenopausal women with metastatic breast cancer showed no significant differences in progression-free survival (PFS) or OS between the two arms.⁵²⁰

Fulvestrant appears to be at least as effective as anastrozole in patients whose disease progressed on previous tamoxifen.^{523,524} A randomized phase II study compared anastrozole versus fulvestrant in over 200 patients with advanced breast cancer.^{525,526} In the initial analysis, fulvestrant was as effective as anastrozole in terms of overall response (36.0% vs. 35.5%; odds ratio, 1.02; 95% CI, 0.56–1.87; $P = .947$) in evaluable patients ($n = 89$ for fulvestrant and $n = 93$ for anastrozole).⁵²⁵ An improved time to progression was seen with fulvestrant compared to anastrozole (median time to progression was 23.4 months for fulvestrant vs. 13.1 months for anastrozole; HR, 0.63; 95% CI, 0.39–1.00; $P = .0496$).⁵²⁶ This study used a higher 500 mg loading dose every 2 weeks for 3 doses and then 500 mg monthly.⁵²⁵ The median OS was observed to be longer in the fulvestrant group than in the anastrozole group (54.1 months vs. 48.4 months; HR, 0.70; $P = .041$).⁵²⁷ These findings are currently being studied in a prospective phase III trial (ClinicalTrials.gov identifier: NCT01602380).

A phase II study of fulvestrant in postmenopausal women with advanced breast cancer and disease progression following aromatase inhibitor therapy documented a partial response rate of 14.3% with an additional 20.8% of patients achieving stable disease for at least 6 months.⁵²⁸ The clinical benefit rates of exemestane and fulvestrant observed in a phase III trial of postmenopausal women with hormone receptor-positive advanced breast cancer who experienced disease progression on prior nonsteroidal aromatase inhibitor therapy were comparable (32.2% vs. 31.5%; $P = .853$).⁵²⁹ In that study, fulvestrant was administered as a 500 mg loading dose followed by doses of 250 mg on day 14, day 28, and then monthly.

A separate phase III randomized study in postmenopausal women with metastatic ER-positive breast cancer compared fulvestrant 500 mg every 2 weeks for 3 doses followed by 500 mg monthly versus

fulvestrant 250 mg monthly. The PFS was superior with the fulvestrant 500 mg regimen (HR, 0.80; 95% CI, 0.68–0.94; $P = .006$),⁵³⁰ indicating an increased duration of response with the higher dose of fulvestrant. The final analyses demonstrated an increase in median OS (4.1 months) and reduced risk of death (19%) with a dose of 500 mg compared with 250 mg. Median OS was 26.4 versus 22.3 months (HR, 0.81; 95% CI, 0.69–0.96; $P = .02$).⁵³¹

Combination endocrine therapy in postmenopausal women with hormone receptor-positive, previously *untreated* metastatic breast cancer has been reported from two studies comparing single-agent anastrozole versus anastrozole plus fulvestrant.

In one study (FACT), combination endocrine therapy was not superior to single-agent anastrozole (time to progression HR, 0.99; 95% CI, 0.81–1.20; $P = .91$).⁵³² In the second study (S0226), PFS (HR, 0.80; 95% CI, 0.68–0.94; stratified log-rank $P = .007$) and OS (HR, 0.81; 95% CI, 0.65–1.00; stratified $P = .049$) were superior with combination anastrozole plus fulvestrant.⁵³³ An unplanned subset analysis in this trial suggested that patients without prior adjuvant tamoxifen experienced the greatest benefit. The reason for the divergent outcomes in these two studies is not known.

A phase III trial studied the effect of fulvestrant alone or in combination with anastrozole or exemestane in patients with advanced breast cancer and an acquired non-steroidal aromatase inhibitor-resistant disease.⁵³⁴ An aromatase inhibitor had been given as adjuvant treatment to 18% of patients for a median of 27.9 months, and to 82% of patients for locally advanced/metastatic disease for a median of 19.3 months. Median PFS was 4.8 months, 4.4 months, and 3.4 months for patients treated with fulvestrant alone, anastrozole plus fulvestrant, and fulvestrant plus exemestane, respectively. No differences were

observed for overall response rate, clinical benefit rate, and OS. This trial provides no evidence that adding an aromatase inhibitor to fulvestrant in patients with non-steroidal aromatase inhibitor-resistant disease improves the results achieved with fulvestrant alone. In postmenopausal women who have received previous antiestrogen therapy and are within one year of antiestrogen exposure, there is evidence supporting the use of a selective aromatase inhibitor as the preferred first-line therapy for their recurrent disease.^{535,536}

Palbociclib, a highly selective inhibitor of CDK 4/6 kinase activity, has a role in treating women with ER-positive metastatic breast cancer in combination with endocrine therapy. A phase II, open-label, randomized, multicenter trial evaluated the safety and efficacy of palbociclib in combination with letrozole versus letrozole alone as first-line treatment for patients with advanced ER-positive, HER2-negative breast cancer.⁵³⁷ Median PFS reported was double with the combination regimen compared to letrozole alone (20.2 months for the palbociclib plus letrozole group and 10.2 months for the letrozole alone group; HR, 0.488; 95% CI, 0.319–0.748).⁵³⁷ Grade 3/4 adverse reactions reported at a higher incidence in the palbociclib plus letrozole versus letrozole alone group included neutropenia (54% vs. 1%) and leukopenia (19% vs. 0%). Based on this study, the FDA approved palbociclib in combination with letrozole for the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

The phase III trial (PALOMA-3) compared the combination of palbociclib and fulvestrant to fulvestrant in pre- or post-menopausal hormone receptor-positive, HER2-negative advanced breast cancer patients, whose disease progressed on prior endocrine therapy. Pre- or peri-menopausal patients also received goserelin. The median PFS was 9.2

months for the combination compared to 3.8 months for fulvestrant (HR 0.42, $P < .000001$) with similar discontinuation rates because of adverse effects (2.6% and 1.7%, respectively).⁵³⁸ Grade 3/4 adverse events of palbociclib and fulvestrant were mainly confined to neutropenia with the same low incidence (0.6%) of febrile neutropenia in both arms. OS data from this trial are immature.⁵³⁸

The NCCN Panel has included the combination of palbociclib with letrozole as a first-line endocrine therapy option for postmenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer. In addition, the recently updated version includes palbociclib with fulvestrant as a category 1 option for women with hormone receptor-positive (post-menopausal or premenopausal women receiving ovarian suppression with an LHRH agonist), HER2-negative metastatic breast cancer who have progressed on endocrine therapy.

Limited studies document a PFS advantage of adding trastuzumab or lapatinib to aromatase inhibition in postmenopausal women with hormone receptor-positive metastatic breast cancer that is HER2-positive.^{539,540}

Resistance to endocrine therapy in women with hormone receptor-positive disease is frequent. One mechanism of resistance to endocrine therapy is activation of the mammalian target of rapamycin (mTOR) signal transduction pathway. Several randomized studies have investigated the use of aromatase inhibition in combination with inhibitors of the mTOR pathway.

A randomized phase II study estimated the efficacy of tamoxifen alone versus tamoxifen combined with everolimus, an oral inhibitor of mTOR, in women with hormone receptor-positive, HER2-negative metastatic breast cancer previously treated with an aromatase inhibitor.⁵⁴¹ After a

median follow-up of 13 months, an intent-to-treat analysis showed that the clinical benefit was 42.1% (95% CI, 29.1–55.9) with tamoxifen alone and 61.1% (95% CI, 46.9–74.1) with tamoxifen plus everolimus. An improvement in median time to progression was seen when everolimus was combined with tamoxifen compared with tamoxifen alone. Median time to progression was 4.5 months (95% CI, 3.7–8.7) with tamoxifen alone versus 8.5 months (95% CI, 6.01–13.9) with everolimus and tamoxifen.⁵⁴¹

A phase III trial in postmenopausal women with advanced, hormone receptor-positive breast cancer with no prior endocrine therapy for advanced disease, randomized subjects to letrozole with or without the mTOR inhibitor temsirolimus has been reported.⁵⁴² In this study, PFS was not different between the treatment arms (HR, 0.89; 95% CI, 0.75–1.05; long-rank $P = .18$).

The results of this trial differ from that of the BOLERO-2 trial (described below). The reasons for the differences in the outcomes of these two randomized phase III studies^{542,543} is uncertain, but may be related to the issues of patient selection and extent of prior endocrine therapy.

A phase III study (BOLERO-2) randomized postmenopausal women with hormone receptor-positive advanced breast cancer that had progressed or recurred during treatment with a nonsteroidal aromatase inhibitor to exemestane with or without the mTOR inhibitor everolimus.⁵⁴⁴ Final results reported after median 18-month follow-up show that median PFS (by central review) remained significantly longer with everolimus plus exemestane versus placebo plus exemestane at 11.0 versus 4.1 months, respectively; (HR, 0.38; 95% CI, 0.31–0.48; $P < .0001$).⁵⁴³ The adverse events (all grades) that occurred more frequently in those receiving everolimus included stomatitis, infections, rash, pneumonitis, and hyperglycemia.^{543,544} Analysis of safety and

efficacy in the elderly patients enrolled in this trial showed that elderly patients treated with an everolimus-containing regimen had similar incidences of these adverse events, but the younger patients had more on-treatment deaths.⁵⁴⁵ Based on the evidence from the BOLERO-2 trial, the NCCN Panel has included everolimus plus exemestane as an option for women who fulfill the entry criteria for BOLERO-2.

Many premenopausal and postmenopausal women with hormone-responsive breast cancer benefit from sequential use of endocrine therapies at disease progression. Therefore, women with breast cancers who respond to an endocrine maneuver with either shrinkage of the tumor or long-term disease stabilization (clinical benefit) should receive additional endocrine therapy at disease progression. After second-line endocrine therapy, little high-level evidence exists to assist in selecting the optimal sequence of endocrine therapy. Additional endocrine therapies for second-line and subsequent therapy are listed in the NCCN Guidelines for Breast Cancer.

Endocrine therapy may be active in patients with negative ER and PR determinations, especially on the primary tumor and in soft tissue disease and/or bone-dominant disease.⁵⁴⁶⁻⁵⁴⁸ Endocrine therapy is associated with relatively low toxicity. Further false-negative determinations of ER and PR tumor status are not unusual and the hormone receptor status of primary and metastatic sites of disease may differ. Therefore, the NCCN Breast Cancer Panel recommends consideration of a trial of endocrine therapy for patients with disease characterized as hormone receptor-negative with disease localized to the bone or soft tissue only or with asymptomatic visceral disease, irrespective of HER2 tumor status.

Cytotoxic Chemotherapy for Stage IV or Recurrent Metastatic Disease

Women with hormone receptor-negative tumors not localized to the bone or soft tissue only, that are associated with symptomatic visceral metastasis, or that have hormone receptor-positive tumors that are refractory to endocrine therapy should receive chemotherapy. A variety of chemotherapy regimens are felt to be appropriate, as outlined in the treatment algorithm. Combination chemotherapy generally provides higher rates of objective response and longer time to progression, in comparison to single-agent chemotherapy. Combination chemotherapy is, however, associated with an increase in toxicity and is of little survival benefit.⁵⁴⁹⁻⁵⁵³ Furthermore, administering single agents sequentially decreases the likelihood that dose reductions will be needed. Thus, the panel finds little compelling evidence that combination chemotherapy is superior to sequential single agents. Standard clinical practice is to continue first-line chemotherapy until progression. Adverse effects may require dose reduction and cessation of chemotherapy prior to disease progression. Limited information suggests that PFS can be prolonged with the use of continuous chemotherapy versus shorter-course chemotherapy.^{554,555} Due to the lack of consistent OS differences, the use of prolonged versus shorter chemotherapy needs to be weighed against the detrimental effects of continuous chemotherapy on overall quality of life.

Single cytotoxic agents and combination chemotherapy regimens recommended by the panel for the treatment of patients with metastatic disease are listed in the NCCN Guidelines.

Single Agents

Single agents are categorized as either preferred or other single agents based on a balance of the efficacy, toxicity, and treatment schedules of the drugs. Among preferred single agents, the panel includes: the anthracyclines, doxorubicin, epirubicin, and pegylated liposomal

doxorubicin; the taxanes, paclitaxel, docetaxel, and albumin-bound paclitaxel; anti-metabolites, capecitabine and gemcitabine; and non-taxane microtubule inhibitors, eribulin and vinorelbine.

Eribulin is a non-taxane microtubule inhibitor used for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting. In a phase III trial, 762 patients with metastatic breast cancer were randomized 2:1 to eribulin or treatment of physicians' choice. One-year OS was 53.9% for patients receiving eribulin versus 43.7% for the control arm, and median OS was 13.12 versus 10.65 months, representing a 19% statistically significant risk reduction ($P = .041$). Time to progression was greater with eribulin 3.7 versus 2.2 months for patients in the control arm ($P = .14$).⁵⁵⁶

Several studies have demonstrated that eribulin is active in metastatic breast cancer. A large randomized trial of heavily pre-treated patients with metastatic breast cancer compared treatment with eribulin versus therapy of physician's choice. Eribulin demonstrated significant improvement in OS with 2.5-month prolongation of median OS (median OS for patients treated with eribulin was 13.1 months compared with 10.6 months for those receiving other treatments. HR, 0.81; 95% CI, 0.66–0.99; $P = .041$).⁵⁵⁶

A phase III trial compared eribulin with capecitabine in patients with metastatic breast cancer. While a survival advantage was observed with eribulin treatment in all sub-groups of patients, there was a significant survival advantage observed with eribulin over capecitabine among patients with HER2-negative (15.9 vs. 13.5 months; HR 0.84; 95% CI

0.72, 0.98; $P = .03$) and triple-negative (14.4 vs. 9.4 months; HR 0.70; 95% CI 0.55, 0.91; $P = .01$) breast cancer.⁵⁵⁷

Among other single agents, the panel includes: cyclophosphamide, carboplatin, docetaxel, albumin-bound paclitaxel, cisplatin, ixabepilone, and epirubicin.

Ixabepilone, an epothilone B analogue, is also used for treatment of recurrent or metastatic breast cancer as a single agent. Use of ixabepilone as monotherapy has been evaluated in several phase II trials of women with metastatic breast cancer: in a first-line setting in patients previously treated with anthracycline chemotherapy⁵⁵⁸; in patients with taxane-resistant metastatic breast cancer⁵⁵⁹; and in patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine.⁵⁶⁰ In the phase II trials, objective response rate, median duration of response, and median OS duration were 41.5% (95% CI, 29.4%–54.4%), 8.2 months (95% CI, 5.7–10.2 months), and 22.0 months (95% CI, 15.6–27.0 months) in the first-line setting;⁵⁵⁸ 12% (95% CI, 4.7%–26.5%), 10.4 months, and 7.9 months for the taxane-resistant patients;⁵⁵⁹ and 11.5% (95% CI, 6.3%–18.9%), 5.7 months, and 8.6 months for the patients previously treated with an anthracycline, a taxane, and capecitabine.⁵⁶⁰ In the study by Perez et al,⁵⁶⁰ grade 3/4 treatment-related toxicities included peripheral sensory neuropathy (14%) and neutropenia (54%).

Combination Regimens

Among combination regimens, the panel includes FAC/CAF; FEC; AC; EC; CMF; docetaxel, capecitabine; gemcitabine, paclitaxel; gemcitabine, carboplatin; and paclitaxel, bevacizumab.

A series of trials have sought to define the role for bevacizumab, a humanized monoclonal antibody against the vascular endothelial

growth factor in the treatment of metastatic breast cancer. The E2100 trial randomized 722 women with recurrent or metastatic breast cancer to first-line chemotherapy with paclitaxel with or without bevacizumab.⁵⁶¹ This trial documented superior PFS (11.8 months vs. 5.9 months; HR 0.60; $P < .001$) favoring bevacizumab plus paclitaxel compared with paclitaxel alone. A similar trial enrolled 736 patients who were randomized to treatment with docetaxel and bevacizumab or docetaxel and placebo.⁵⁶² This trial also documented increased PFS in the arm containing bevacizumab (10.1 months vs. 8.2 months with docetaxel alone; HR 0.77; $P = .006$). An additional trial, RIBBON-1, combined bevacizumab with capecitabine, with a taxane (docetaxel, nab-paclitaxel), with anthracyclines (FEC, CAF, AC, or EC), or with the same chemotherapy alone. Results of this trial show a statistically significant increase in PFS with bevacizumab and capecitabine (8.6 months vs. 5.7 months; HR, 0.69; $P < .001$) and taxane- or anthracycline- (9.2 months vs. 8.0 months; HR, 0.64; $P < .001$) containing arms.^{563,564} None of these studies demonstrates an increase in OS or quality of life when analyzed alone or in a meta-analysis combining the trials.⁵⁶⁵ The increase in PFS with bevacizumab is modest, and appears the greatest in combination with paclitaxel, especially as reported in an unpublished analysis provided to the FDA.⁵⁶⁶

As with endocrine therapy, sequential responses are often observed with chemotherapy, supporting the use of sequential single agents and combination chemotherapy regimens. The current guidelines include doses and schedules of these single agents and combination regimens for metastatic breast cancer. Failure to achieve a tumor response to 3 sequential chemotherapy regimens or ECOG performance status of 3 or greater is an indication for supportive therapy only. In this context, failure to respond to a chemotherapy regimen means the absence of

even a marginal response to the use of a given chemotherapy regimen. Response to a chemotherapy regimen followed by progression of disease is not considered a failure to experience response.

Patients with metastatic breast cancer frequently develop many anatomically localized problems that may benefit from local irradiation, surgery, or regional chemotherapy (eg, intrathecal methotrexate for leptomeningeal carcinomatosis).

HER2-Targeted Therapy for Stage IV or Recurrent Metastatic Disease

Patients with tumors that are HER2-positive may derive benefit from treatment with HER2-targeted therapy. The panel recommends selecting patients for HER2-targeted therapy if their tumors are either positive for HER2 by ISH or 3+ by IHC. HER2 testing recommendations are described in the guideline. Patients with tumors IHC 0 or 1+ for HER2 or ISH not amplified have very low rates of HER2-targeted response and HER2-targeted therapy.⁵⁶⁷ Adequate standardization and validation of HER2 assays by ISH and IHC used in clinical practice is a concern, and data suggest that false-positive determinations are common.^{22,23,568-570} Recommendations regarding HER2 testing have been published.^{568,570}

First-Line Regimens for HER2-Positive Tumors

The NCCN Panel has categorized HER2-targeting regimens as either preferred or other.

Preferred First-Line Regimens

A randomized, double-blind, phase III study compared the efficacy and safety of pertuzumab in combination with trastuzumab and docetaxel versus trastuzumab and docetaxel as first-line treatment for HER2-positive metastatic breast cancer.⁵⁷¹ The primary endpoint of the study was independent assessment of PFS. The secondary endpoints were PFS assessed by investigator, objective response rate, OS, and

safety. A total of 808 patients were enrolled in this trial.⁵⁷¹ The addition of pertuzumab provided a statistically significant improvement in PFS compared to trastuzumab plus docetaxel alone. The median independently assessed PFS was increased by 6.1 months, from 12.4 months in the control group to 18.5 months in the pertuzumab group (HR for progression or death, 0.62; 95% CI, 0.51–0.75; $P < .001$).⁵⁷¹ At a median follow-up of 30 months the results showed a statistically significant improvement in OS in favor of the pertuzumab-containing regimen, with a 34% reduction in the risk of death (HR, 0.66; 95% CI, 0.52–0.84; $P = .0008$). The median OS was 37.6 months in the non-pertuzumab group and had not yet been reached in the pertuzumab-containing regimen.⁴³² The most common adverse reactions reported in the pertuzumab group compared to the control group were diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin. Peripheral edema and constipation were greater in the control group.⁵⁷¹ Cardiac adverse events or left ventricular systolic dysfunction were reported slightly more frequently in the control group.⁵⁷² Health-related quality of life was not different in the two treatment groups.⁵⁷³

Phase II trials have also found activity and tolerability for pertuzumab, pertuzumab with trastuzumab, and for other regimens combining pertuzumab and trastuzumab together with other active cytotoxics (ie, paclitaxel, vinorelbine).^{574,575,576} Phase III trials of pertuzumab plus chemotherapy without trastuzumab have not been reported.

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

Other First-Line Regimens for HER2-Positive Tumors

First-line trastuzumab in combination with selected chemotherapeutics²⁶⁶ or as a single agent^{265,267} is another option for HER2-positive metastatic breast cancer patients. Randomized trials demonstrate benefit from adding trastuzumab to other agents including paclitaxel with or without carboplatin,^{266,567,577,578} docetaxel,⁵⁷⁷ and vinorelbine,⁵⁷⁷ or as a single agent²⁶⁷ for patients with HER2-positive disease. In addition, the combination of trastuzumab and capecitabine has also shown efficacy as a first-line trastuzumab-containing regimen in this population of patients.^{579,580} For those patients with hormone receptor-positive, HER2-positive disease, the panel recommends initial treatment with endocrine therapy, an approach consistent with most of these studies. The panel believes the 27% frequency of significant cardiac dysfunction in patients treated with the combination of trastuzumab and doxorubicin/cyclophosphamide chemotherapy in the metastatic setting is too high for use of this combination outside the confines of a prospective clinical trial.^{266,580,581}

T-DM1 is an antibody-drug conjugate. Through a stable linker, the HER2-targeting antitumor property of trastuzumab is conjugated with the cytotoxic activity of the microtubule-inhibitory agent DM1 (derivative of maytansine).

A randomized, international, multicenter, open-label, phase III study (EMILIA) evaluated the safety and efficacy of T-DM1 compared with lapatinib plus capecitabine for HER2-positive patients with locally advanced breast cancer or metastatic breast cancer previously treated with trastuzumab and a taxane.⁵⁸² The primary endpoints of this study were PFS, OS, and safety. T-DM1 demonstrated a statistically significant improvement in both primary endpoints of PFS and OS. PFS (assessed by independent review) was significantly improved with T-DM1 with median PFS of 9.6 months vs. 6.4 months with lapatinib

plus capecitabine; HR for progression or death from any cause was 0.65 (95% CI, 0.55–0.77; $P < .001$). At the first interim analysis, T-DM1 also demonstrated significant improvement in OS. The stratified HR for death from any cause with T-DM1 versus lapatinib plus capecitabine was 0.62 (95% CI, 0.48–0.81; $P = .0005$).⁵⁸² Rates of grade 3 or 4 adverse events were higher with lapatinib plus capecitabine than with T-DM1 (57% vs. 41%). The incidences of thrombocytopenia and increased serum aminotransferase levels were higher with T-DM1 (frequency >25%), whereas the incidences of diarrhea, nausea, vomiting, and palmar-plantar erythrodysesthesia were higher with lapatinib plus capecitabine.⁵⁸²

In a phase III trial (MARIANNE), 1,095 patients with locally advanced or metastatic breast cancer were randomized to first-line treatment with T-DM1 with or without pertuzumab or to treatment with trastuzumab plus a taxane. The primary endpoints were safety and PFS assessed by independent review. The PFS for T-DM1 with pertuzumab was found non-inferior to trastuzumab and a taxane (15.2 and 13.7 months respectively; HR, 0.87; 97.5% CI, 0.69–1.08; $P = .14$).⁵⁸³ The PFS for T-DM1 alone was non-inferior to trastuzumab plus a taxane (14.1 and 13.7, respectively; HR, 0.91; 97.5% CI, 0.73–1.13; $P = .31$).⁵⁸³ The incidence of Grade 3–5 adverse events was 54.1%, 45.4%, and 46.2% in the trastuzumab plus a taxane arm, T-DM1 arm, and T-DM1 plus pertuzumab arm, respectively. Health-related quality of life was maintained for a longer duration with a median of 7.7 months for T-DM1 (HR, 0.70; 95% CI, 0.57–0.86) and a median of 9 months for T-DM1 plus pertuzumab (HR, 0.68; 95% CI, 0.55–0.84) compared with a median of 3.9 months for trastuzumab and a taxane.⁵⁸³

Based on the MARIANNE trial data demonstrating T-DM1 and T-DM1 with pertuzumab being non-inferior, with better QOL compared with trastuzumab plus taxane and possibly better-tolerated for some

patients,⁵⁸³ the NCCN Panel included T-DM1 as one of the first-line options for treatment of patients with HER2-positive metastatic breast cancer. Pertuzumab, trastuzumab, and a taxane, however, remains the preferred frontline regimen for HER2-positive metastatic disease based on data demonstrating improved OS compared to trastuzumab and a taxane. TDM-1 as first-line therapy should be considered only in those not suitable for the preferred treatment.

Regimens for Trastuzumab-Exposed HER2-Positive Disease

The NCCN Panel recommends continuation of HER2 blockade for patients with HER2-positive metastatic breast cancer that progresses on first-line trastuzumab-containing regimens. This recommendation also applies to patients who are diagnosed with HER2-positive metastatic disease after prior exposure to trastuzumab in the adjuvant setting. Several trials have demonstrated benefit of continuation of trastuzumab therapy following disease progression on a trastuzumab-containing regimen.⁵⁸⁴⁻⁵⁸⁶ However, the optimal duration of trastuzumab in patients with long-term control of disease is unknown.

The NCCN Guidelines include doses and schedules of representative regimens for use in HER2-positive metastatic breast cancer.

Pertuzumab is active in patients beyond the first-line setting. The results of a multicenter, open-label, single-arm, phase II study (n = 66) show that the combination of pertuzumab and trastuzumab is active and well tolerated in patients with HER2-positive metastatic breast cancer that has progressed on prior trastuzumab therapy.⁵⁸⁷ The trial reported an objective response rate of 24.2% (16 patients out of 66). The overall median PFS time observed with pertuzumab and trastuzumab combination was 15.5 months (range, 0.9–17.0 months; 80% CI, 18–31 months).⁵⁸⁷ The reported median duration of response with the combination was 5.8 months (range, 2.9–15.3 months).⁵⁸⁷

To determine whether the clinical benefit seen in the study was from pertuzumab alone or was a result of the combined effect of pertuzumab and trastuzumab, a cohort of patients (n = 29) whose disease progressed during prior trastuzumab-based therapy received pertuzumab monotherapy until progressive disease or unacceptable toxicity. Of these, patients with disease progression (n = 17) continued to receive pertuzumab with the addition of trastuzumab. In the 29 patients who received pertuzumab monotherapy, the objective response rate and clinical benefit rate reported were 3.4% and 10.3%, respectively, whereas in the patients who received dual blockade after progression on pertuzumab, the objective response rate and clinical benefit rate were 17.6% and 41.2%, respectively.⁵⁸⁸

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

The regimen of capecitabine plus lapatinib is also an option for patients with HER2-positive disease following progression on a trastuzumab-containing regimen. A phase III study compared lapatinib plus capecitabine with capecitabine alone in women with advanced or metastatic breast cancer refractory to trastuzumab in the metastatic setting and with prior treatment with an anthracycline and a taxane in either the metastatic or adjuvant setting.⁵⁸⁹ Time to progression was increased in the group receiving combination therapy when compared with the group receiving capecitabine monotherapy (8.4 months vs. 4.4 months; HR, 0.49; 95% CI, 0.34–0.71; *P* < .001). The patients who progressed on monotherapy were allowed to cross over to the combination arm. This resulted in insufficient power to detect significant

differences in OS; an exploratory analysis demonstrated a trend toward a survival advantage with lapatinib plus capecitabine.⁵⁹⁰ The analysis reported a median OS of 75.0 weeks for the combination arm and 64.7 weeks for the monotherapy arm (HR, 0.87; 95% CI, 0.71–1.08; $P = .210$).⁵⁹⁰

Another study of women with metastatic breast cancer showed that lapatinib in combination with letrozole increased PFS over letrozole alone in the subset of women with HER2-positive cancer (3.0 months for letrozole and placebo vs. 8.2 months for letrozole and lapatinib; HR, 0.71; 95% CI, 0.53–0.96; $P = .019$).⁵³⁹ In addition, results from a phase III trial in which patients with heavily pretreated metastatic breast cancer and disease progression on trastuzumab therapy were randomly assigned to monotherapy with lapatinib or trastuzumab plus lapatinib showed that PFS was increased from 8.1 weeks to 12 weeks ($P = .008$) with the combination.⁵⁹¹ The OS analysis data showed that lapatinib plus trastuzumab improved median survival by 4.5 months, with median OS of 14 months for the combination therapy and 9.5 months for lapatinib alone (HR, 0.74; 95% CI, 0.57–0.97; $P = .026$).⁵⁹² This improvement in OS analysis included patients who were initially assigned to monotherapy and crossed over to receive combination therapy at the time of progression.⁵⁹²

Based on the absence of data, the panel does not recommend the addition of chemotherapy to the trastuzumab and lapatinib combination.

Surgery for Stage IV or Recurrent Metastatic Disease

The primary treatment approach recommended by the NCCN Panel for women with metastatic breast cancer and an intact primary tumor is systemic therapy, with consideration of surgery after initial systemic treatment for those women requiring palliation of symptoms or with impending complications, such as skin ulceration, bleeding, fungation,

and pain.⁵⁹³ Generally such surgery should be undertaken only if complete local clearance of tumor may be obtained and if other sites of disease are not immediately threatening to life. Alternatively, radiation therapy may be considered as an option to surgery. Often such surgery requires collaboration between the breast surgeon and the reconstructive surgeon to provide optimal cancer control and wound closure.

Retrospective studies suggest a potential survival benefit from complete excision of the in-breast tumor in select patients with metastatic breast cancer.⁵⁹⁴⁻⁵⁹⁷ Substantial selection biases exist in all of these studies and are likely to confound the study results.^{598,599} Two recent prospective, randomized studies assessed whether or not surgery on the primary tumor in the breast is necessary for women who are diagnosed with metastatic/stage IV breast cancer. The results from both studies presented at the 2013 Annual San Antonio Breast Cancer Symposium were similar showing that surgical treatment of primary tumors in women presenting with stage IV disease does not produce an increase in OS.^{600,601}

Nevertheless, the panel recognizes the need for randomized clinical trials that will address the risks and benefits of local therapy for patients with stage IV disease while eliminating selection biases. Patient enrollment in such trials is encouraged.

Distant Sites of Recurrence Requiring Consideration of Therapies Local to the Metastatic Site

Surgery, radiation, or regional chemotherapy (eg, intrathecal methotrexate) may be indicated as needed for localized clinical scenarios such as brain metastases, leptomeningeal disease, choroid metastases, pleural effusion, pericardial effusion, biliary obstruction,

ureteral obstruction, impending pathologic fracture, cord compression, localized painful bone, or soft-tissue disease.

The guidelines include consideration of the addition of hyperthermia to irradiation for localized recurrences/metastasis (category 3). There have been several prospective randomized trials comparing radiation to radiation plus hyperthermia in the treatment of locally advanced/recurrent cancers, primarily breast cancer chest wall recurrences.^{602,603} While there is heterogeneity among the study results, a series with strict quality assurance demonstrated a statistically significant increase in local tumor response and greater duration of local control with the addition of hyperthermia to radiation compared to radiation alone.⁶⁰² No differences in OS have been demonstrated. Delivery of local hyperthermia is technically demanding and requires specialized expertise and equipment (eg, the monitoring of temperatures and management of possible tissue burns). The panel thus recommends that the use of hyperthermia be limited to treatment centers with appropriate training, expertise, and equipment. The addition of hyperthermia generated substantial discussion and controversy among the panel and is a category 3 recommendation.

Monitoring Metastatic Disease

Monitoring the treatment of metastatic breast cancer involves a wide array of assessments and the need for the clinician to integrate several different forms of information to make a determination of the effectiveness of treatment and the acceptability of toxicity. The information includes those from direct observations of the patient, including patient-reported symptoms, performance status, change in weight, and physical examination; laboratory tests such as alkaline phosphatase, liver function, blood counts, and calcium; radiographic imaging; functional imaging; and, where appropriate, tumor biomarkers.

The results of these evaluations generally are classified as response, continued response to treatment, stable disease, uncertainty regarding disease status, or progression of disease. The clinician typically must assess and balance multiple different forms of information to make a determination regarding whether disease is being controlled and the toxicity of treatment is acceptable. Sometimes this information may be contradictory.

The panel recommends using widely accepted criteria for reporting response, stability, and progression of disease such as the RECIST criteria⁶⁰⁴ and the WHO criteria.⁶⁰⁵ The NCCN Panel also recommends using the same method of assessment over time. For example, an abnormality initially found on diagnostic CT scan of the chest should be monitored with repeat diagnostic CT scans of the chest.

The optimal frequency of testing is uncertain, and is primarily based on the monitoring strategies utilized in breast cancer clinical trials. The page titled *Principles of Monitoring Metastatic Disease* in the algorithm provides a table outlining general recommendations for the frequency and type of monitoring as a baseline before initiation of new therapy, for monitoring the effectiveness of cytotoxic chemotherapy and endocrine therapy, and as an assessment when there is evidence of disease progression. The panel has indicated in a footnote that the frequency of monitoring can be reduced in patients who have long-term stable disease. These are guidelines and should be modified for the individual patient using clinical judgment, especially for those with stable or responding disease for long periods of time.

The clinical use of Circulating Tumor Cells (CTC) in metastatic breast cancer is not yet included in the NCCN Guidelines for Breast Cancer for disease assessment and monitoring. Patients with persistently increased CTC after 3 weeks of first-line chemotherapy have a poor

PFS and OS.⁶⁰⁶ In spite of its prognostic ability, CTC count has failed to show a predictive value. A prospective, randomized, phase 3 trial (SWOG S0500) evaluated the clinical utility of serial enumeration of CTC in patients with metastatic breast cancer.⁶⁰⁶ According to the study results, switching to an alternative cytotoxic therapy after 3 weeks of first-line chemotherapy in patients with persistently increased CTC did not affect either PFS or OS.⁶⁰⁶

Special Situations

Paget's Disease

Paget's disease of the breast is a rare manifestation of breast cancer characterized by neoplastic cells in the epidermis of the NAC.⁶⁰⁷ It most commonly presents with eczema of the areola, bleeding, ulceration, and itching of the nipple. The diagnosis is often delayed because of the rare nature of the condition and confusion with other dermatologic conditions. There is an associated cancer elsewhere in the breast in up to about 80% to 90% of cases.⁶⁰⁸⁻⁶¹⁰ The associated cancers are not necessarily located adjacent to the NAC and may be either DCIS or invasive cancer.

Women with clinical signs that raise suspicion for Paget's disease require a complete history and physical examination and diagnostic breast imaging. Any breast lesion identified by imaging or examination should be evaluated according to the [NCCN Guidelines for Breast Screening and Diagnosis](#). The skin of the NAC should undergo surgical biopsy, including the full thickness of the epidermis including at least a portion of any clinically involved NAC. When biopsy of the NAC is positive for Paget's disease, breast MRI is recommended to define the extent of disease and identify additional disease.^{610,611}

There are no category 1 data that specifically address local management of Paget's disease. Systemic therapy is based on the stage and biological characteristics of any underlying cancer, and is supported by the evidence cited in the relevant stage-specific breast cancer treatment guidelines.

Management of Paget's disease has traditionally been total mastectomy with axillary dissection. Total mastectomy remains a reasonable option for patients regardless of the absence or presence of an associated breast cancer.⁶⁰⁹ Data demonstrate that satisfactory local control may be achieved with breast-conserving surgery including the excision with negative margins of any underlying breast cancer along with resection of the NAC followed by whole breast radiation therapy.⁶¹²⁻⁶¹⁶ The risk of ipsilateral breast recurrence after breast-conserving NAC resection and radiation therapy with or without an associated cancer is similar to that with breast-conserving surgery and radiation therapy with the typical invasive or in situ cancer.

For Paget's disease without an associated cancer (ie, no palpable mass or imaging abnormality), it is recommended that breast-conserving surgery consist of removal of the entire NAC with a negative margin of underlying breast tissue. In cases with an associated cancer elsewhere in the breast, the surgery includes removal of the NAC with a negative margin and removal of the peripheral cancer using standard breast-conserving technique to achieve a negative margin. It is not necessary to remove the NAC and the peripheral cancer in continuity in a single surgical specimen or through a single incision. Mastectomy also remains an appropriate treatment option.

ALN staging is not necessary when breast-conserving therapy is used to treat Paget's disease with underlying DCIS without evidence of invasive cancer following clinical examination, imaging evaluation, and

full-thickness skin biopsy of the involved NAC. In the presence of an underlying invasive breast cancer treated with breast-conserving surgery, axillary surgery should be performed according to the *Surgical Axillary Staging* outlined in the NCCN Guidelines. In cases treated by total mastectomy, axillary staging is recommended for patients with invasive disease and should also be considered for patients with underlying DCIS without evidence of invasive disease. This is because the final pathology may reveal an invasive cancer in the mastectomy specimen and the mastectomy precludes subsequent sentinel node biopsy. Two retrospective studies have provided evidence for a high degree of accuracy in the identification of the sentinel node(s) in patients with Paget's disease.^{617,618} Patients treated with breast conservation should receive whole breast radiation. Extended-field radiation to regional lymph nodes should be used in cases of an associated invasive breast cancer with involved lymph nodes as for any breast cancer as described in the initial sections of the NCCN Guidelines. A radiation boost should be considered for the site of the resected NAC and any associated resected cancer site, if applicable.

Women with an associated invasive cancer have substantial risk of developing metastases. Adjuvant systemic therapy should be administered according to the stage of the cancer. Women with Paget's disease treated with breast conservation and without an associated cancer or those with associated ER-positive DCIS should consider tamoxifen for risk reduction. Those with an associated invasive cancer should receive adjuvant systemic therapy based on the stage and hormone receptor status.

Phyllodes Tumors of the Breast (also known as *phyllodes tumors*, *cystosarcoma phyllodes*)

Phyllodes tumors of the breast are rare tumors comprised of both stromal and epithelial elements.⁶¹⁹ Phyllodes tumors exist in benign,

borderline, and malignant subtypes, although there is not uniform agreement on the criteria for assigning subtype or for predicting biological behavior.⁶²⁰ The subtype of phyllodes tumor appears less important for risk of recurrence than does the margin of tumor-free resection achieved by surgical treatment. Diagnosis of phyllodes tumors prior to excisional biopsy/lumpectomy is uncommon. Phyllodes tumors occur in an older age distribution than fibroadenoma, a younger age distribution than the invasive ductal and lobular cancers, and with a mean age of 40.⁶²¹ Phyllodes tumors often enlarge rapidly and are usually painless. Phyllodes tumors often appear on ultrasound and mammography as fibroadenomas, and FNA cytology and even core needle biopsy are inadequate to reliably distinguish phyllodes tumors from fibroadenoma.⁶²¹ Thus, in the setting of a large or rapidly enlarging clinical fibroadenoma, excisional biopsy should be considered to pathologically exclude a phyllodes tumor. Patients with Li-Fraumeni syndrome (germline *TP53* mutation, see [NCCN Guidelines for Genetic/Familial High Risk Assessment](#)) have an increased risk for phyllodes tumors.⁶²² Local recurrences of phyllodes tumors are the most common site of recurrence. Most distant recurrences occur in the lung, and may be solid nodules or thin-walled cavities.

Treatment of phyllodes tumors (which includes benign, borderline, and malignant subtypes) is with local surgical excision with tumor-free margins of 1 cm or greater. Lumpectomy or partial mastectomy is the preferred surgical therapy. Total mastectomy is necessary only if negative margins cannot be obtained by lumpectomy or partial mastectomy.⁶²³ Since phyllodes tumors rarely metastasize to the ALNs, surgical axillary staging or ALN dissection is not necessary unless the lymph nodes are pathologic on clinical examination.⁶²⁴ In those patients who experience a local recurrence, resection of the recurrence with wide, tumor-free surgical margins should be performed. Some panel members recommend local radiation therapy of the remaining breast or

chest wall following resection of a local recurrence, but this recommendation is controversial (category 2B).⁶²⁵

While the epithelial component of most phyllodes tumors contains ER (58%) and/or PR (75%),⁶²⁶ endocrine therapy has no proven role in the treatment of phyllodes tumors. Similarly, there is no evidence that adjuvant cytotoxic chemotherapy provides benefit in reduction of recurrences or death. In the rare patient who experiences a systemic recurrence (usually in the lung), treatment should be as recommended in the [NCCN Guidelines for Soft Tissue Sarcoma](#).

Breast Cancer During Pregnancy

Breast cancer occurring concurrently with pregnancy is an infrequent clinical event. In a California registry study, there were 1.3 breast cancers diagnosed per 10,000 live births.⁶²⁷ Unfortunately, breast cancer during pregnancy is most often ALN-positive and with larger primary tumor size. Histologically the tumors are poorly differentiated, are more frequently ER/PR-negative, and approximately 30% are HER2-positive.^{628,629} The diagnosis is often delayed because neither the patient nor the physician suspects malignancy.

Evaluation of the pregnant patient with suspected breast cancer should include a physical examination with particular attention to the breast and regional lymph nodes. Mammogram of the breast with shielding can be done safely and the accuracy is reported to be greater than 80%.⁶³⁰ Ultrasound of the breast and regional lymph nodes can be used to assess the extent of disease and also to guide biopsy. Ultrasound has been reported to be abnormal in up to 100% of breast cancers occurring during pregnancy.⁶³⁰ Biopsies for cytologic evaluation of a suspicious breast mass may be done with FNA of the breast and suspicious lymph nodes. However, the preferred technique is core needle biopsy. This

provides tissue for histologic confirmation of invasive disease as well as adequate tissue for hormone receptor and HER2 analyses.

Staging assessment of the pregnant patient with breast cancer may be guided by clinical disease stage. The staging studies should be tailored to minimize fetal exposure to radiation. For clinically node-negative T1-T2 tumors, a chest x-ray (with shielding), liver function and renal function assessment, and a CBC with differential are appropriate. In patients who have clinically node-positive or T3 breast lesions, in addition to the aforementioned, an ultrasound of the liver and consideration of a screening MRI of the thoracic and lumbar spine without contrast may be employed. The documentation of the presence of metastases may alter the treatment plan and influence the patient's decision regarding maintenance of the pregnancy. Assessment of the pregnancy should include a maternal fetal medicine consultation and review of antecedent maternal risks such as hypertension, diabetes, and complications with prior pregnancies. Documentation of fetal growth and development and fetal age by means of ultrasonographic assessment is appropriate. Estimation of the date of the delivery will help with systemic chemotherapy planning. In addition, maternal fetal medicine consultation should include counseling regarding maintaining or terminating pregnancy. Counseling of the pregnant patient with breast cancer should include a review of the treatment options, which include mastectomy or breast-conserving surgery as well as the use of systemic therapy. The most common surgical procedure has been modified radical mastectomy. However, breast-conserving surgery is possible if radiation therapy can be delayed to the postpartum period,⁶³¹ and breast-conserving therapy during pregnancy does not appear to have a negative impact on survival.^{631,632} When surgery is performed at 25 weeks of gestation or later, obstetrical and prenatal specialists must

be onsite and immediately available in the event of precipitous delivery of a viable fetus.

Although there are a limited number of isolated case reports and small retrospective studies evaluating use of SLN biopsy in pregnant patients,^{633,634} the sensitivity and specificity of the procedure has not been established in this setting. Thus, there are insufficient data on which to base recommendations for its use in pregnant women. Decisions related to use of SLN biopsy in pregnancy should be individualized. A review of the relative and absolute contraindications to sentinel node biopsy concluded that sentinel node biopsy should not be offered to pregnant women under 30 weeks gestation.⁶³⁵ There are limited data with only case reports and estimations of fetal radiation dose regarding use of radioactive tracer (eg, technetium 99m sulfur colloid).⁶³⁶⁻⁶³⁸ Isosulfan blue or methylene blue dye for sentinel node biopsy procedures is discouraged during pregnancy.

The indications for systemic chemotherapy are the same in the pregnant patient as in the non-pregnant breast cancer patient, although chemotherapy should not be administered at any point during the first trimester of pregnancy. The largest experience in pregnancy has been with anthracycline and alkylating agent chemotherapy.^{639,640} Collected data of chemotherapy exposure in utero indicate that the first trimester has the greatest risk of fetal malformation.^{641,642} Fetal malformation risks in the second and third trimester are approximately 1.3%, not different than that of fetuses not exposed to chemotherapy during pregnancy. If systemic therapy is initiated, fetal monitoring prior to each chemotherapy cycle is appropriate. Chemotherapy during pregnancy should not be given after week 35 of pregnancy or within 3 weeks of planned delivery in order to avoid the potential for hematologic complications during delivery. Data from a single-institution prospective study indicate that FAC chemotherapy (5-FU 500 mg/m² IV days 1 and

4, doxorubicin 50 mg/m² by IV infusion over 72 hours, and cyclophosphamide 500 mg/m² IV day 1) may be given with relative safety during the second and third trimesters of pregnancy.⁶⁴⁰ As reported by Gwyn et al, the median gestational age at delivery was 38 weeks, more than 50% of the patients had a vaginal delivery, and there were no fetal deaths.⁶²⁸ An update of this experience reported on 57 women treated with FAC in the adjuvant or neoadjuvant setting. There were 57 live births. A survey of parents/guardians reported on the health of 40 children. There was one child with Down syndrome and two with congenital abnormalities (club foot, congenital bilateral ureteral reflux). The children are reported to be healthy and progressing well in school.^{640,643} Ondansetron, lorazepam, and dexamethasone can be used as part of the pre-chemotherapy antiemetic regimen.

There are limited data on the use of taxanes during pregnancy.⁶⁴⁴⁻⁶⁴⁷ If used, the NCCN Panel recommends weekly administration of paclitaxel after the first trimester if clinically indicated by disease status. There are only case reports of trastuzumab use during pregnancy.⁶⁴⁸⁻⁶⁵⁵ The majority of these case reports indicated oligo- or anhydramnios with administration of trastuzumab; fetal renal failure occurred in one case. If trastuzumab is otherwise indicated, it should be administered in the postpartum period; the panel recommends against its use during pregnancy.

A single case report of first trimester exposure to lapatinib during treatment for breast cancer reported an uncomplicated delivery of a healthy female neonate.⁶⁵⁶

Endocrine therapy and radiation therapy are contraindicated during pregnancy. Endocrine therapy and radiation therapy, if indicated, should thus not be initiated until the postpartum period.

Communication between the oncologist and maternal fetal medicine specialist is essential at every visit and for every treatment decision point for the patient.

Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) is a rare, aggressive form of breast cancer estimated to account for 1% to 6% of breast cancer cases in the United States.^{657,658} IBC is a clinical diagnosis that requires erythema and dermal edema (peau d'orange) of a third or more of the skin of the breast.

IBC is usually hormone receptor-negative and is more frequently HER2-positive than the usual ductal breast cancers. Studies on gene expression profiling of IBC have demonstrated that all the subtypes of IBC exist, but basal and HER2 overexpressed are more frequent.⁶⁵⁹⁻⁶⁶² According to the 7th edition of the AJCC Cancer Staging Manual, IBC is classified as stage IIIB, stage IIIC, or stage IV breast cancer, depending on the degree of nodal involvement and whether distant metastases are present. The primary tumor of IBC is classified as T4d by definition, even when no mass is specifically apparent in the breast. On radiographic imaging, findings of skin thickening and, in some cases, an underlying mass are observed. Despite use of the term “inflammatory,” the characteristic clinical features of IBC are due to blockage of dermal lymphatics by tumor emboli. Although a biopsy is required to evaluate for the presence of cancer in breast tissue and the dermal lymphatics, a diagnosis of IBC is based on clinical findings, and dermal lymphatic involvement is neither required, nor sufficient by itself, to assign a diagnosis of IBC.^{11,663} The differential diagnosis includes cellulitis of the breast and mastitis.

In the past, IBC has often been placed under the general heading of locally advanced breast cancer. There is a growing body of evidence

that IBC patients, when compared with noninflammatory forms of locally advanced breast cancer, are more likely to have a less favorable prognosis⁶⁶⁴⁻⁶⁶⁶ and to be younger at the time of disease presentation.⁶⁶⁷

The NCCN Panel acknowledges that studies focusing on genetic characterization of IBC are needed to more clearly define IBC as a disease entity and to optimize treatment.^{668,669} Nevertheless, current evidence provides justification for a separate guideline for the workup and treatment of patients diagnosed with IBC.

Stage T4d, N0- N3, M0

Workup

Women with a clinical/pathologic diagnosis of IBC without distant metastasis (stage T4d, N0-N3, M0) should undergo a thorough staging evaluation by a multidisciplinary team.

Recommendations for workup include a complete history and physical examination involving a CBC and platelet count.

A pathology review and pre-chemotherapy determinations of tumor hormone receptor and HER2 receptor status should be performed. HER2 has a predictive role in determining which patients with IBC will benefit from HER2-targeted therapy. The NCCN Panel endorses the CAP protocol for pathology reporting (www.cap.org) and endorses the ASCO CAP recommendations for quality control performance of HER2 testing and interpretation of IHC and ISH results.⁵⁷⁰

Imaging studies help facilitate image-guided biopsy, delineate locoregional disease, and identify distant metastases. Evaluation of all women suspected with IBC must include diagnostic bilateral mammogram, with the addition of ultrasound as necessary. A breast MRI scan is optional.

Evaluations for the presence of distant metastasis in the asymptomatic patient include LFTs, bone scan or sodium fluoride PET/CT (category 2B), and diagnostic CT imaging of the chest, abdomen, and pelvis (category 2B; category 2A for diagnostic CT imaging of the chest when pulmonary symptoms are present).

FDG PET/CT may be most helpful in situations where standard imaging results are equivocal or suspicious. However, there is limited evidence suggesting that PET/CT may be a useful adjunct to standard imaging of IBC due to the increased risk of regional lymph node involvement and distant spread of disease in this group of patients.^{125,126,670,671}

Nevertheless, equivocal or suspicious sites identified by FDG PET/CT scanning or other imaging methods should be biopsied for confirmation of stage IV disease whenever possible. FDG PET/CT is a category 2B recommendation. The consensus of the panel is that FDG PET/CT can be performed at the same time as diagnostic CT. If FDG PET and diagnostic CT are performed and both clearly indicate bone metastases, bone scan or sodium fluoride PET/CT may not be needed.

Genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer as defined by the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian](#).

Treatment

The treatment of patients with IBC should involve a combined modality approach⁶⁵⁷ comprising preoperative systemic therapy followed by surgery (mastectomy) and radiotherapy.

Preoperative Chemotherapy

There are no large randomized trials evaluating the optimal systemic treatment of IBC, since it is a rare disease. The systemic therapy

recommendations are based on data from retrospective analyses, small prospective studies, and data from non-IBC, locally advanced breast cancer.

The benefit of preoperative systemic therapy followed by mastectomy over preoperative systemic therapy alone in patients with IBC was shown in a retrospective analysis in which lower local recurrence rates and longer disease-specific survival were reported for the combined modality approach.⁶⁷² Results from a large retrospective study of patients with IBC performed over a 20-year period at The University of Texas M.D. Anderson Cancer Center demonstrated that initial treatment with doxorubicin-based chemotherapy followed by local therapy (ie, radiation therapy or mastectomy, or both) and additional postoperative chemotherapy resulted in a 15-year DFS rate of 28%.⁶⁷³

A retrospective study demonstrated that the addition of a taxane to an anthracycline-based regimen improved PFS and OS in patients with ER-negative IBC.⁶⁷⁴ A systematic review found evidence for an association between the intensity of preoperative therapy and the likelihood of a pCR.⁶⁷⁵ A study of IBC patients, with cytologically confirmed ALN metastases, treated with anthracycline-based chemotherapy with or without a taxane indicated that more patients receiving the anthracycline-taxane combination achieved a pCR compared with those who received only anthracycline-based therapy. In addition, patients who had a pCR in the ALNs had superior OS and DFS compared with those with residual axillary disease.⁶⁷⁶

The NCCN Panel recommends preoperative systemic therapy with an anthracycline-based regimen with or without taxanes for the *initial* treatment of patients with IBC. The panel also recommends completing the planned chemotherapy prior to mastectomy. If the chemotherapy

was not completed preoperatively, it should be completed postoperatively.

Targeted Therapy

All women with hormone receptor-positive IBC are recommended to receive endocrine therapy sequentially after completing the planned preoperative systemic therapy.

HER2-positive IBC is associated with a poor prognosis.^{661,677} For women with HER2-positive disease, the addition of trastuzumab to primary systemic chemotherapy is associated with better response rates.⁶⁷⁸⁻⁶⁸² A prospective study that randomized women with locally advanced breast cancers, including those with IBC, to neoadjuvant anthracycline-based chemotherapy with or without trastuzumab for 1 year demonstrated that the addition of trastuzumab significantly improved the response rate and event-free survival.⁶⁷⁸ The NCCN Panel recommends inclusion of trastuzumab in the chemotherapy regimen and is recommended for patients with HER2-positive disease. There are no available data to indicate the optimal duration of trastuzumab, specifically among women with IBC. However, based on the available data,⁶⁷⁸ the panel recommends continuing trastuzumab therapy for up to 1 year.

Results of small phase II trials indicate that other HER2-targeting agents such as lapatinib and pertuzumab have a clinical benefit in IBC.^{314,683} The results of the NEOSPHERE trial that included patients with IBC showed increased pCR with the pertuzumab-containing regimens. Therefore, the NCCN Panel has included in a footnote that a pertuzumab-containing regimen may be administered preoperatively in patients with HER2-positive IBC.³¹⁴

Determination of response to neoadjuvant chemotherapy in IBC should include a combination of physical examination and radiologic assessment.

Surgery

Patients with a clinical/pathologic diagnosis of IBC should always be treated with chemotherapy before surgery. It has been known for many years that surgical treatment as *primary* treatment of patients with IBC is associated with poor outcomes.⁶⁸⁴ SLN dissection is not a reliable method of assessing ALNs among women with IBC.⁶⁸⁵ Use of breast-conserving surgery in patients with IBC has been associated with poor cosmesis, and limited data suggest that rates of local recurrence may be higher when compared with mastectomy. Breast-conserving therapy is not recommended for patients with IBC.

Mastectomy with level I/II ALN dissection is the recommended surgical procedure recommended by the NCCN Panel for patients who respond to neoadjuvant chemotherapy. The NCCN Panel has listed delayed breast reconstruction as an option that can be recommended to women with IBC who have undergone a modified radical mastectomy. Reconstruction of the breasts soon after mastectomy may compromise the post-mastectomy radiation therapy outcomes.⁶⁸⁶

For patients with IBC who *do not* respond to preoperative systemic therapy, mastectomy is not generally recommended. Additional systemic chemotherapy and/or preoperative radiation should be considered for these patients. Patients with tumors responding to this secondary therapy should undergo mastectomy and subsequent treatment as described above.

Radiation

After mastectomy, radiation therapy is recommended after the completion of the planned chemotherapy.

The probability of locoregional lymph node involvement is high for women with IBC. To reduce the risk of local recurrence, the panel recommends radiation therapy to the chest wall and the supraclavicular region. If the internal mammary lymph node(s) is clinically or pathologically involved, radiation therapy should include the internal mammary nodes. If the internal mammary nodes are not clinically or pathologically involved, then including the internal mammary nodes in the radiation therapy field is at the discretion of the treating radiation oncologist (category 3). For HER2-positive disease, trastuzumab may be administered concomitantly with radiation therapy.

Stage IV or Recurrent IBC

Patients with stage IV or recurrent IBC should be treated according to the guidelines for recurrence/stage IV breast cancer (See [NCCN Guidelines for Breast Cancer](#)).

Axillary Breast Cancer

Occult breast cancer presenting with axillary metastases is an unusual presentation that can be a diagnostic and therapeutic challenge. Evidence to support recommendations on the management of patients presenting with axillary breast cancer comes from a limited number of retrospective studies involving small numbers of patients⁶⁸⁷⁻⁶⁸⁹ (see also references therein). Although treatment of women with axillary metastases from an unknown primary tumor has typically involved mastectomy and axillary nodal dissection, some of these patients have also been successfully treated with axillary nodal dissection followed by radiation therapy.^{688,689}

Patients with a suspected occult primary breast cancer will typically present to the oncologist after undergoing an initial biopsy: core needle biopsy (preferred), and/or FNA. Accurate pathologic assessment of the biopsied material is most important. Therefore, the pathologist must be consulted to determine whether the available biopsy material is adequate, or if additional biopsy material is necessary (eg, core needle, incisional, or excisional biopsy) to provide an accurate and complete diagnosis.

Workup for Possible Primary Breast Cancer

MRI of the breast can facilitate the identification of occult breast cancer, and can help select those patients most likely to benefit from mastectomy.⁶⁹⁰ For example, in a study of 40 patients with biopsy-proven breast cancer in the axilla, and a negative or indeterminate mammogram, MRI identified the primary breast lesion in 70% of the patients.⁶⁸⁸ In addition, of the 7 patients with a negative MRI who subsequently underwent ALN dissection and radiation therapy to the whole breast, no evidence of local recurrence was evident at a median follow-up of 19 months.

The [NCCN Guidelines for Occult Primary Cancer](#) provide guidance on the diagnosis and initial workup of patients with a suspicious axillary mass without any signs of a primary tumor. A small subset of these patients may have a primary cancer in the axillary tail of the breast. Adenocarcinoma with positive axillary nodes and mediastinal nodes in a woman is highly suggestive of a breast primary. Adenocarcinoma in the supraclavicular nodes, chest, peritoneum, retroperitoneum, liver, bone, or brain could also indicate primary breast cancer in women. The guidelines suggest the use of a mammogram and breast ultrasound for such patients.

Testing for immunohistochemical markers including ER/PR and HER2 is recommended. Elevated ER/PR levels provide strong evidence for a breast cancer diagnosis.⁶⁹¹ MRI of the breast should be considered for a patient with histopathologic evidence of breast cancer when mammography and ultrasound are not adequate to assess the extent of the disease. MRI may be especially helpful in women with dense breast tissue, positive axillary nodes, and suspected occult primary breast tumor or to evaluate the chest wall.⁶⁹² Breast MRI has been shown to be useful in identifying the primary site in patients with occult primary breast cancer and may also facilitate breast conservation in selected women by allowing for lumpectomy instead of mastectomy.^{688,693} In one report, the primary site was identified using MRI in about half of the women presenting with axillary metastases, irrespective of the breast density.⁶⁹⁴

The [NCCN Guidelines for Occult Primary Cancer](#) also provide recommendations for additional workup, including chest and abdominal CT to evaluate for evidence of distant metastases for patients diagnosed with adenocarcinoma (or carcinoma not otherwise specified) of the axillary nodes without evidence of a primary breast lesion. In particular, breast MRI and ultrasound are recommended. Axillary ultrasound should also be performed.

Treatment for Possible Primary Breast Cancer

Patients with MRI-positive breast disease should undergo evaluation with ultrasound or MRI-guided biopsy and receive treatment according to the clinical stage of the breast cancer. Treatment recommendations for those with MRI-negative disease are based on nodal status. For patients with T0, N1, M0 disease, options include mastectomy plus axillary nodal dissection or axillary nodal dissection plus whole breast irradiation with or without nodal irradiation. Systemic chemotherapy, endocrine therapy, or trastuzumab is given according to the

recommendations for stage II or III disease. Neoadjuvant chemotherapy, trastuzumab, and endocrine therapy should be considered for patients with T0, N2-N3, M0 disease followed by axillary nodal dissection and mastectomy as for patients with locally advanced disease.

Summary

The therapeutic options for patients with noninvasive or invasive breast cancer are complex and varied. In many situations, the patient and physician have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. With few exceptions, the evaluation, treatment, and follow-up recommendations in these guidelines are based on the results of past and present clinical trials. However, there is not a single clinical situation in which the treatment of breast cancer has been optimized with respect to either maximizing cure or minimizing toxicity and disfigurement. Therefore, patient/physician participation in prospective clinical trials allows patients to not only receive state-of-the-art cancer treatment but also to contribute to improving the treatment outcomes.

References

- Mohammad H, Forouzanfar KJF, Allyne M, Delossantos, Rafael Lozano, Alan D. Lopez, Christopher J. L. Murray, Mohsen Naghavi. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. *The Lancet* 2011;6736:61351-61352
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;66:7-30. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26742998>.
- DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. *CA Cancer J Clin* 2014;64:52-62. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24114568>.
- Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687-1717. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15894097>.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65:5-29. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25559415>.
- Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med* 2005;353:1784-1792. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16251534>.
- Gail MH, Costantino JP, Bryant J, et al. Weighing the risks and benefits of tamoxifen treatment for preventing breast cancer. *J Natl Cancer Inst* 1999;91:1829-1846. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10547390>.
- Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 1985;312:146-151. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3965932>.
- U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html.
- Edge SB, Byrd DR, Compton CC, et al., eds. *AJCC Cancer Staging Manual*, 7th Edition. New York: Springer; 2010.
- White J, Morrow M, Moughan J, et al. Compliance with breast-conservation standards for patients with early-stage breast carcinoma. *Cancer* 2003;97:893-904. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12569588>.
- Wilkinson NW, Shahryarnejad A, Winston JS, et al. Concordance with breast cancer pathology reporting practice guidelines. *J Am Coll Surg* 2003;196:38-43. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12517547>.
- Allred DC, Harvey JM, Berardo M, Clark GM. Prognostic and predictive factors in breast cancer by immunohistochemical analysis. *Mod Pathol* 1998;11:155-168. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9504686>.
- Rhodes A, Jasani B, Barnes DM, et al. Reliability of immunohistochemical demonstration of oestrogen receptors in routine practice: interlaboratory variance in the sensitivity of detection and evaluation of scoring systems. *J Clin Pathol* 2000;53:125-130. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10767828>.
- Rudiger T, Hofler H, Kreipe HH, et al. Quality assurance in immunohistochemistry: results of an interlaboratory trial involving 172 pathologists. *Am J Surg Pathol* 2002;26:873-882. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12131154>.
- Allred DC, Carlson RW, Berry DA, et al. NCCN Task Force Report: Estrogen receptor and progesterone receptor testing in breast cancer

by immunohistochemistry. J Natl Compr Canc Netw 2009;7 Suppl 6:S1-S21; quiz S22-23. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19755043>.

18. Hammond MEH, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 2010;28:2784-2795. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20404251>.

19. Hammond ME. ASCO-CAP guidelines for breast predictive factor testing: an update. Appl Immunohistochem Mol Morphol 2011;19:499-500. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22089488>.

20. Wang S, Saboorian MH, Frenkel E, et al. Laboratory assessment of the status of Her-2/neu protein and oncogene in breast cancer specimens: comparison of immunohistochemistry assay with fluorescence in situ hybridisation assays. J Clin Pathol 2000;53:374-381. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10889820>.

21. Dybdal N, Leiberman G, Anderson S, et al. Determination of HER2 gene amplification by fluorescence in situ hybridization and concordance with the clinical trials immunohistochemical assay in women with metastatic breast cancer evaluated for treatment with trastuzumab. Breast Cancer Res Treat 2005;93:3-11. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16184453>.

22. Paik S, Bryant J, Tan-Chiu E, et al. Real-world performance of HER2 testing--National Surgical Adjuvant Breast and Bowel Project experience. J Natl Cancer Inst 2002;94:852-854. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12048273>.

23. Perez EA, Suman VJ, Davidson NE, et al. HER2 testing by local, central, and reference laboratories in specimens from the North Central Cancer Treatment Group N9831 intergroup adjuvant trial. J Clin Oncol 2006;24:3032-3038. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16809727>.

24. Tubbs RR, Pettay JD, Roche PC, et al. Discrepancies in clinical laboratory testing of eligibility for trastuzumab therapy: apparent immunohistochemical false-positives do not get the message. J Clin Oncol 2001;19:2714-2721. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11352964>.

25. Press MF, Sauter G, Bernstein L, et al. Diagnostic evaluation of HER-2 as a molecular target: an assessment of accuracy and reproducibility of laboratory testing in large, prospective, randomized clinical trials. Clin Cancer Res 2005;11:6598-6607. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16166438>.

26. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 2013;31:3997-4013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24101045>.

27. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for Human Epidermal Growth Factor Receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline update. Arch Pathol Lab Med 2014;138:241-256. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24099077>.

28. Giordano SH, Buzdar AU, Hortobagyi GN. Breast cancer in men. Ann Intern Med 2002;137:678-687. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12379069>.

29. Giordano SH, Valero V, Buzdar AU, Hortobagyi GN. Efficacy of anastrozole in male breast cancer. Am J Clin Oncol 2002;25:235-237. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12040279>.

30. Rosai J. Borderline epithelial lesions of the breast. Am J Surg Pathol 1991;15:209-221. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1847606>.

31. Schnitt SJ, Connolly JL, Tavassoli FA, et al. Interobserver reproducibility in the diagnosis of ductal proliferative breast lesions

using standardized criteria. *Am J Surg Pathol* 1992;16:1133-1143. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1463092>.

32. Renshaw AA, Derhagopian RP, Martinez P, Gould EW. Lobular neoplasia in breast core needle biopsy specimens is associated with a low risk of ductal carcinoma in situ or invasive carcinoma on subsequent excision. *Am J Clin Pathol* 2006;126:310-313. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16891208>.

33. Nagi CS, O'Donnell JE, Tismenetsky M, et al. Lobular neoplasia on core needle biopsy does not require excision. *Cancer* 2008;112:2152-2158. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18348299>.

34. Hwang H, Barke LD, Mendelson EB, Susnik B. Atypical lobular hyperplasia and classic lobular carcinoma in situ in core biopsy specimens: routine excision is not necessary. *Mod Pathol* 2008;21:1208-1216. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18660792>.

35. Elsheikh TM, Silverman JF. Follow-up surgical excision is indicated when breast core needle biopsies show atypical lobular hyperplasia or lobular carcinoma in situ: a correlative study of 33 patients with review of the literature. *Am J Surg Pathol* 2005;29:534-543. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15767810>.

36. Karabakhtsian RG, Johnson R, Sumkin J, Dabbs DJ. The clinical significance of lobular neoplasia on breast core biopsy. *Am J Surg Pathol* 2007;31:717-723. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17460455>.

37. O'Neil M, Madan R, Tawfik OW, et al. Lobular carcinoma in situ/atypical lobular hyperplasia on breast needle biopsies: does it warrant surgical excisional biopsy? A study of 27 cases. *Ann Diagn Pathol* 2010;14:251-255. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20637429>.

38. Foster MC, Helvie MA, Gregory NE, et al. Lobular carcinoma in situ or atypical lobular hyperplasia at core-needle biopsy: is excisional

biopsy necessary? *Radiology* 2004;231:813-819. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15105449>.

39. Hussain M, Cunnick GH. Management of lobular carcinoma in-situ and atypical lobular hyperplasia of the breast--a review. *Eur J Surg Oncol* 2011;37:279-289. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21306860>.

40. Rendi MH, Dintzis SM, Lehman CD, et al. Lobular in-situ neoplasia on breast core needle biopsy: imaging indication and pathologic extent can identify which patients require excisional biopsy. *Ann Surg Oncol* 2012;19:914-921. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21861212>.

41. Anderson BO, Calhoun KE, Rosen EL. Evolving concepts in the management of lobular neoplasia. *J Natl Compr Canc Netw* 2006;4:511-522. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16687097>.

42. Kerlikowske K, Molinaro AM, Gauthier ML, et al. Biomarker expression and risk of subsequent tumors after initial ductal carcinoma in situ diagnosis. *J Natl Cancer Inst* 2010;102:627-637. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20427430>.

43. Stackiewicz R, Paran H, Bernheim J, et al. Prognostic significance of HER-2/neu expression in patients with ductal carcinoma in situ. *Isr Med Assoc J* 2010;12:290-295. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20929083>.

44. Zhou W, Jirstrom K, Johansson C, et al. Long-term survival of women with basal-like ductal carcinoma in situ of the breast: a population-based cohort study. *BMC Cancer* 2010;10:653. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21118480>.

45. Lari SA, Kuerer HM. Biological markers in DCIS and risk of breast recurrence: A systematic review. *J Cancer* 2011;2:232-261. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21552384>.

46. Kuhl CK, Schrading S, Bieling HB, et al. MRI for diagnosis of pure ductal carcinoma in situ: a prospective observational study. *Lancet* 2007;370:485-492. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17693177>.
47. Kowalchik KV, Vallow LA, McDonough M, et al. The role of preoperative bilateral breast magnetic resonance imaging in patient selection for partial breast irradiation in ductal carcinoma in situ. *Int J Surg Oncol* 2012;2012:206342. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22655183>.
48. Brennan ME, Turner RM, Ciatto S, et al. Ductal carcinoma in situ at core-needle biopsy: meta-analysis of underestimation and predictors of invasive breast cancer. *Radiology* 2011;260:119-128. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21493791>.
49. Cody HS, Van Zee KJ. Point: sentinel lymph node biopsy is indicated for patients with DCIS. *J Natl Compr Canc Netw* 2003;1:199-206. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19768878>.
50. Edge SB, Sheldon DG. Counterpoint: sentinel lymph node biopsy is not indicated for ductal carcinoma in situ. *J Natl Compr Canc Netw* 2003;1:207-212. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19768879>.
51. Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol* 2005;23:7703-7720. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16157938>.
52. Virnig BA, Tuttle TM, Shamliyan T, Kane RL. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. *J Natl Cancer Inst* 2010;102:170-178. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20071685>.
53. Waddell BE, Stomper PC, DeFazio JL, et al. Postexcision mammography is indicated after resection of ductal carcinoma-in-situ of the breast. *Ann Surg Oncol* 2000;7:665-668. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11034243>.
54. Bijker N, Meijnen P, Peterse JL, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853--a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *J Clin Oncol* 2006;24:3381-3387. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16801628>.
55. Emdin SO, Granstrand B, Ringberg A, et al. SweDCIS: Radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. *Acta Oncol* 2006;45:536-543. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16864166>.
56. Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. *J Clin Oncol* 1998;16:441-452. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9469327>.
57. Houghton J, George WD, Cuzick J, et al. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. *Lancet* 2003;362:95-9102. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12867108>.
58. Julien JP, Bijker N, Fentiman IS, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *Lancet* 2000;355:528-533. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10683002>.
59. Cuzick J, Sestak I, Pinder SE, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ:

long-term results from the UK/ANZ DCIS trial. *Lancet Oncol* 2011;12:21-29. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21145284>.

60. Wapnir IL, Dignam JJ, Fisher B, et al. Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. *J Natl Cancer Inst* 2011;103:478-488. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21398619>.

61. Holmberg L, Garmo H, Granstrand B, et al. Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in situ of the breast. *J Clin Oncol* 2008;26:1247-1252. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18250350>.

62. Di Saverio S, Catena F, Santini D, et al. 259 Patients with DCIS of the breast applying USC/Van Nuys prognostic index: a retrospective review with long term follow up. *Breast Cancer Res Treat* 2008;109:405-416. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17687650>.

63. Gilleard O, Goodman A, Cooper M, et al. The significance of the Van Nuys prognostic index in the management of ductal carcinoma in situ. *World J Surg Oncol* 2008;6:61-61. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18564426>.

64. Silverstein MJ, Lagios MD, Craig PH, et al. A prognostic index for ductal carcinoma in situ of the breast. *Cancer* 1996;77:2267-2274. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8635094>.

65. Silverstein MJ, Lagios MD, Groshen S, et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. *N Engl J Med* 1999;340:1455-1461. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/10320383>.

66. Hughes LL, Wang M, Page DL, et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern

Cooperative Oncology Group. *J Clin Oncol* 2009;27:5319-5324. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19826126>.

67. Wong P, Lambert C, Agnihotram RV, et al. Ductal carcinoma in situ--the influence of the radiotherapy boost on local control. *Int J Radiat Oncol Biol Phys* 2011. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21664063>.

68. Wong JS, Chen YH, Gadd MA, et al. Eight-year update of a prospective study of wide excision alone for small low- or intermediate-grade ductal carcinoma in situ (DCIS). *Breast Cancer Res Treat* 2014;143:343-350. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24346130>.

69. Goodwin A, Parker S, Gherzi D, Wilcken N. Post-operative radiotherapy for ductal carcinoma in situ of the breast--a systematic review of the randomised trials. *Breast* 2009;18:143-149. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19447038>.

70. MacDonald HR, Silverstein MJ, Mabry H, et al. Local control in ductal carcinoma in situ treated by excision alone: incremental benefit of larger margins. *Am J Surg* 2005;190:521-525. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16164913>.

71. Dunne C, Burke JP, Morrow M, Kell MR. Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ. *J Clin Oncol* 2009;27:1615-1620. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19255332>.

72. Van Zee KJ, Subhedar P, Olcese C, et al. Relationship between margin width and recurrence of ductal carcinoma in situ: Analysis of 2996 women treated with breast-conserving surgery for 30 years. *Ann Surg* 2015;262:623-631. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/26366541>.

73. Warnberg F, Garmo H, Emdin S, et al. Effect of radiotherapy after breast-conserving surgery for ductal carcinoma in situ: 20 years follow-

up in the randomized SweDCIS Trial. *J Clin Oncol* 2014;32:3613-3618. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25311220>.

74. McCormick B, Winter K, Hudis C, et al. RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma in situ comparing radiotherapy with observation. *J Clin Oncol* 2015;33:709-715. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25605856>.

75. Narod SA, Iqbal J, Giannakeas V, et al. Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ. *JAMA Oncol* 2015;1:888-896. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26291673>.

76. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 2005;97:1652-1662. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16288118>.

77. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998;90:1371-1388. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9747868>.

78. Tan-Chiu E, Wang J, Costantino JP, et al. Effects of tamoxifen on benign breast disease in women at high risk for breast cancer. *J Natl Cancer Inst* 2003;95:302-307. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12591986>.

79. Allred DC, Bryant J, Land S, et al. Estrogen receptor expression as a predictive marker of the effectiveness of tamoxifen in the treatment of DCIS: Findings from the NSABP Protocol B-24 [abstract]. *Breast Cancer Res Treat* 2002;76(Suppl 1):Abstract A30. Available at:

80. Forbes JF, Sestak I, Howell A, et al. Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial. *Lancet* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26686313>.

81. Margolese RG, Cecchini RS, Julian TB, et al. Anastrozole versus tamoxifen in postmenopausal women with ductal carcinoma in situ undergoing lumpectomy plus radiotherapy (NSABP B-35): a randomised, double-blind, phase 3 clinical trial. *Lancet* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26686957>.

82. Louie RJ, Tonneson JE, Gowarty M, et al. Complete blood counts, liver function tests, and chest x-rays as routine screening in early-stage breast cancer: value added or just cost? *Breast Cancer Res Treat* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26467045>.

83. Esserman L. Integration of imaging in the management of breast cancer. *J Clin Oncol* 2005;23:1601-1602. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15755961>.

84. Gundry KR. The application of breast MRI in staging and screening for breast cancer. *Oncology (Williston Park)* 2005;19:159-169. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15770888>.

85. Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. *J Clin Oncol* 2008;26:3248-3258. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18474876>.

86. Weber JJ, Bellin LS, Milbourn DE, et al. Selective preoperative magnetic resonance imaging in women with breast cancer: no reduction in the reoperation rate. *Arch Surg* 2012;147:834-839. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22987175>.

87. Feigelson HS, James TA, Single RM, et al. Factors associated with the frequency of initial total mastectomy: results of a multi-institutional study. *J Am Coll Surg* 2013;216:966-975. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23490543>.

88. Katipamula R, Degnim AC, Hoskin T, et al. Trends in mastectomy rates at the Mayo Clinic Rochester: effect of surgical year and

preoperative magnetic resonance imaging. *J Clin Oncol* 2009;27:4082-4088. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19636020>.

89. Sorbero ME, Dick AW, Beckjord EB, Ahrendt G. Diagnostic breast magnetic resonance imaging and contralateral prophylactic mastectomy. *Ann Surg Oncol* 2009;16:1597-1605. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19330381>.

90. Miller BT, Abbott AM, Tuttle TM. The influence of preoperative MRI on breast cancer treatment. *Ann Surg Oncol* 2012;19:536-540. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21751044>.

91. Peters NH, van Esser S, van den Bosch MA, et al. Preoperative MRI and surgical management in patients with nonpalpable breast cancer: the MONET - randomised controlled trial. *Eur J Cancer* 2011;47:879-886. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21195605>.

92. Turnbull LW, Brown SR, Olivier C, et al. Multicentre randomised controlled trial examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women with primary breast cancer scheduled for wide local excision (COMICE). *Health Technol Assess* 2010;14:1-182. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20025837>.

93. Fischer U, Zachariae O, Baum F, et al. The influence of preoperative MRI of the breasts on recurrence rate in patients with breast cancer. *Eur Radiol* 2004;14:1725-1731. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15248080>.

94. Solin LJ, Orel SG, Hwang W-T, et al. Relationship of breast magnetic resonance imaging to outcome after breast-conservation treatment with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ. *J Clin Oncol* 2008;26:386-391. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18202414>.

95. Bleicher RJ, Ciocca RM, Egleston BL, et al. Association of routine pretreatment magnetic resonance imaging with time to surgery,

mastectomy rate, and margin status. *J Am Coll Surg* 2009;209:180-187; quiz 294-185. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19632594>.

96. Turnbull L, Brown S, Harvey I, et al. Comparative effectiveness of MRI in breast cancer (COMICE) trial: a randomised controlled trial. *Lancet* 2010;375:563-571. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20159292>.

97. Baucom DH, Porter LS, Kirby JS, et al. Psychosocial issues confronting young women with breast cancer. *Breast Dis* 2005;23:103-113. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16823173>.

98. Dunn J, Steginga SK. Young women's experience of breast cancer: defining young and identifying concerns. *Psychooncology* 2000;9:137-146. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10767751>.

99. Ganz PA, Greendale GA, Petersen L, et al. Breast cancer in younger women: reproductive and late health effects of treatment. *J Clin Oncol* 2003;21:4184-4193. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14615446>.

100. Gorman JR, Bailey S, Pierce JP, Su HI. How do you feel about fertility and parenthood? The voices of young female cancer survivors. *J Cancer Surviv* 2012;6:200-209. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22179785>.

101. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. *J Natl Cancer Inst* 2012;104:386-405. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22271773>.

102. Kranick JA, Schaefer C, Rowell S, et al. Is pregnancy after breast cancer safe? *Breast J* 2010;16:404-411. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20522097>.

103. Sukumvanich P, Case LD, Van Zee K, et al. Incidence and time course of bleeding after long-term amenorrhea after breast cancer

treatment: a prospective study. *Cancer* 2010;116:3102-3111. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20564648>.

104. Quinn GP, Block RG, Clayman ML, et al. If you did not document it, it did not happen: rates of documentation of discussion of infertility risk in adolescent and young adult oncology patients' medical records. *J Oncol Pract* 2015;11:137-144. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25549654>.

105. Yee S, Abrol K, McDonald M, et al. Addressing oncofertility needs: views of female cancer patients in fertility preservation. *J Psychosoc Oncol* 2012;30:331-346. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22571247>.

106. Yeomanson DJ, Morgan S, Pacey AA. Discussing fertility preservation at the time of cancer diagnosis: dissatisfaction of young females. *Pediatr Blood Cancer* 2013;60:1996-2000. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23836521>.

107. Loren AW, Mangu PB, Beck LN, et al. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 2013;31:2500-2510. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23715580>.

108. Cruz MR, Prestes JC, Gimenes DL, Fanelli MF. Fertility preservation in women with breast cancer undergoing adjuvant chemotherapy: a systematic review. *Fertil Steril* 2010;94:138-143. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19339000>.

109. Dunn L, Fox KR. Techniques for fertility preservation in patients with breast cancer. *Curr Opin Obstet Gynecol* 2009;21:68-73. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19125006>.

110. Oktem O, Oktay K. Fertility preservation for breast cancer patients. *Semin Reprod Med* 2009;27:486-492. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19806518>.

111. Redig AJ, Brannigan R, Stryker SJ, et al. Incorporating fertility preservation into the care of young oncology patients. *Cancer* 2011;117:4-10. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21235031>.

112. Lee S, Ozkavukcu S, Heytens E, et al. Value of early referral to fertility preservation in young women with breast cancer. *J Clin Oncol* 2010;28:4683-4686. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20876425>.

113. Peate M, Meiser B, Friedlander M, et al. It's now or never: fertility-related knowledge, decision-making preferences, and treatment intentions in young women with breast cancer--an Australian fertility decision aid collaborative group study. *J Clin Oncol* 2011;29:1670-1677. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21444865>.

114. Blumenfeld Z, Evron A. Preserving fertility when choosing chemotherapy regimens - the role of gonadotropin-releasing hormone agonists. *Expert Opin Pharmacother* 2015;16:1009-1020. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25826240>.

115. Del Mastro L, Lambertini M. Temporary Ovarian Suppression With Gonadotropin-Releasing Hormone Agonist During Chemotherapy for Fertility Preservation: Toward the End of the Debate? *Oncologist* 2015;20:1233-1235. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26463868>.

116. Lambertini M, Peccatori FA, Moore HC, Del Mastro L. Reply to the letter to the editor 'Can ovarian suppression with gonadotropin releasing hormone analogs (GnRHa) preserve fertility in cancer patients?' by Rodriguez-Wallberg et al. *Ann Oncol* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26646756>.

117. Moore HC, Unger JM, Phillips KA, et al. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med* 2015;372:923-932. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25738668>.

118. Moffat R, Guth U. Preserving fertility in patients undergoing treatment for breast cancer: current perspectives. *Breast Cancer* (Dove Med Press) 2014;6:93-101. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25114587>.
119. Oktay K, Turan V, Bedoschi G, et al. Fertility Preservation Success Subsequent to Concurrent Aromatase Inhibitor Treatment and Ovarian Stimulation in Women With Breast Cancer. *Journal of Clinical Oncology* 2015;33:2424-2429. Available at: <http://jco.ascopubs.org/content/33/22/2424.abstract>.
120. Baseline staging tests in primary breast cancer: Practice guideline report # 1-14: Members of the Breast Cancer Disease Site Group. Available at: <http://www.cancercares.on.ca/common/pages/UserFile.aspx?serverId=6&path=/File%20Database/CCO%20Files/PEBC/pebc1-14f.pdf>
Accessed: May, 2016.
121. Ravaioli A, Pasini G, Polselli A, et al. Staging of breast cancer: new recommended standard procedure. *Breast Cancer Res Treat* 2002;72:53-60. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12000220>.
122. Puglisi F, Follador A, Minisini AM, et al. Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications. *Ann Oncol* 2005;16:263-266. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15668281>.
123. Brothers JM, Kidwell KM, Brown RK, Henry NL. Incidental radiologic findings at breast cancer diagnosis and likelihood of disease recurrence. *Breast Cancer Res Treat* 2016;155:395-403. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26797222>.
124. Kumar R, Chauhan A, Zhuang H, et al. Clinicopathologic factors associated with false negative FDG-PET in primary breast cancer. *Breast Cancer Res Treat* 2006;98:267-274. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16555126>.
125. Podoloff DA, Advani RH, Allred C, et al. NCCN task force report: positron emission tomography (PET)/computed tomography (CT) scanning in cancer. *J Natl Compr Canc Netw* 2007;5 Suppl 1:1-1. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17509259>.
126. Rosen EL, Eubank WB, Mankoff DA. FDG PET, PET/CT, and breast cancer imaging. *Radiographics* 2007;27 Suppl 1:S215-229. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18180228>.
127. Wahl RL, Siegel BA, Coleman RE, Gatsonis CG. Prospective multicenter study of axillary nodal staging by positron emission tomography in breast cancer: a report of the staging breast cancer with PET Study Group. *J Clin Oncol* 2004;22:277-285. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14722036>.
128. Arriagada R, Le MG, Rochard F, Contesso G. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. *J Clin Oncol* 1996;14:1558-1564. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8622072>.
129. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366:2087-2106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16360786>.
130. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002;347:1233-1241. Available at: <http://www.nejm.org/doi/full/10.1056/NEJMoa022152>.
131. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;347:1227-1232. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12393819>.

132. Early Breast Cancer Trialists' Collaborative G, Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378:1707-1716. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22019144>.

133. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *J Clin Oncol* 2014;32:1507-1515. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24516019>.

134. Fourquet A, Campana F, Zafrani B, et al. Prognostic factors of breast recurrence in the conservative management of early breast cancer: a 25-year follow-up. *Int J Radiat Oncol Biol Phys* 1989;17:719-725. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2777661>.

135. Komoike Y, Akiyama F, Iino Y, et al. Ipsilateral breast tumor recurrence (IBTR) after breast-conserving treatment for early breast cancer: risk factors and impact on distant metastases. *Cancer* 2006;106:35-41. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16333848>.

136. Zhou P, Gautam S, Recht A. Factors affecting outcome for young women with early stage invasive breast cancer treated with breast-conserving therapy. *Breast Cancer Res Treat* 2007;101:51-57. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16821084>.

137. Golshan M, Miron A, Nixon AJ, et al. The prevalence of germline BRCA1 and BRCA2 mutations in young women with breast cancer undergoing breast-conservation therapy. *Am J Surg* 2006;192:58-62. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16769276>.

138. Kroman N, Holtveg H, Wohlfahrt J, et al. Effect of breast-conserving therapy versus radical mastectomy on prognosis for young

women with breast carcinoma. *Cancer* 2004;100:688-693. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14770422>.

139. Blichert-Toft M, Nielsen M, Duing M, et al. Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. *Acta Oncol* 2008;47:672-681. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18465335>.

140. Litiere S, Werutsky G, Fentiman IS, et al. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. *Lancet Oncol* 2012;13:412-419. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22373563>.

141. Agarwal S, Pappas L, Neumayer L, et al. Effect of breast conservation therapy vs mastectomy on disease-specific survival for early-stage breast cancer. *JAMA Surg* 2014;149:267-274. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24429935>.

142. Hwang ES, Lichtensztajn DY, Gomez SL, et al. Survival after lumpectomy and mastectomy for early stage invasive breast cancer: the effect of age and hormone receptor status. *Cancer* 2013;119:1402-1411. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23359049>.

143. Hartmann-Johnsen OJ, Karesen R, Schlichting E, Nygard JF. Survival is better after breast conserving therapy than mastectomy for early stage breast cancer: A registry-based follow-up study of Norwegian women Primary operated between 1998 and 2008. *Ann Surg Oncol* 2015;22:3836-3845. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25743325>.

144. Chatterjee A, Pyfer B, Czerniecki B, et al. Early postoperative outcomes in lumpectomy versus simple mastectomy. *J Surg Res* 2015;198:143-148.

145. Recht A. Contralateral prophylactic mastectomy: caveat emptor. *J Clin Oncol* 2009;27:1347-1349. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19224834>.
146. Bedrosian I, Hu CY, Chang GJ. Population-based study of contralateral prophylactic mastectomy and survival outcomes of breast cancer patients. *J Natl Cancer Inst* 2010;102:401-409. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20185801>.
147. Jatoi I, Parsons HM. Contralateral prophylactic mastectomy and its association with reduced mortality: evidence for selection bias. *Breast Cancer Res Treat* 2014;148:389-396. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25301088>.
148. Portschy PR, Kuntz KM, Tuttle TM. Survival outcomes after contralateral prophylactic mastectomy: a decision analysis. *J Natl Cancer Inst* 2014;106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25031308>
<http://jnci.oxfordjournals.org/content/106/8/dju160.full.pdf>.
149. Fayanju OM, Stoll CR, Fowler S, et al. Contralateral prophylactic mastectomy after unilateral breast cancer: a systematic review and meta-analysis. *Ann Surg* 2014;260:1000-1010. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24950272>.
150. Rocha RD, Girardi AR, Pinto RR, de Freitas VA. Axillary ultrasound and fine-needle aspiration in preoperative staging of axillary lymph nodes in patients with invasive breast cancer. *Radiol Bras* 2015;48:345-352. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26811550>.
151. Bass SS, Lyman GH, McCann CR, et al. Lymphatic mapping and sentinel lymph node biopsy. *Breast J* 1999;5:288-295. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11348304>.
152. Cox CE. Lymphatic mapping in breast cancer: combination technique. *Ann Surg Oncol* 2001;8:67S-70S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11599905>.
153. Cox CE, Nguyen K, Gray RJ, et al. Importance of lymphatic mapping in ductal carcinoma in situ (DCIS): why map DCIS? *Am Surg* 2001;67:513-519. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11409797>.
154. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer--a multicenter validation study. *N Engl J Med* 1998;339:941-946. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9753708>.
155. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol* 2010;11:927-933. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20863759>.
156. Kuehn T, Vogl FD, Helms G, et al. Sentinel-node biopsy for axillary staging in breast cancer: results from a large prospective German multi-institutional trial. *Eur J Surg Oncol* 2004;30:252-259. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15028305>.
157. McMasters KM, Giuliano AE, Ross MI, et al. Sentinel-lymph-node biopsy for breast cancer--not yet the standard of care. *N Engl J Med* 1998;339:990-995. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9753717>.
158. O'Hea BJ, Hill AD, El-Shirbiny AM, et al. Sentinel lymph node biopsy in breast cancer: initial experience at Memorial Sloan-Kettering Cancer Center. *J Am Coll Surg* 1998;186:423-427. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9544956>.
159. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer.

N Engl J Med 2003;349:546-553. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/12904519>.

160. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst 2006;98:599-609. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16670385>.

161. Cox CE, Salud CJ, Cantor A, et al. Learning curves for breast cancer sentinel lymph node mapping based on surgical volume analysis. J Am Coll Surg 2001;193:593-600. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/11768674>.

162. Dupont E, Cox C, Shivers S, et al. Learning curves and breast cancer lymphatic mapping: institutional volume index. J Surg Res 2001;97:92-96. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/11319887>.

163. Giuliano AE, Hawes D, Ballman KV, et al. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. JAMA 2011;306:385-393. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21791687>.

164. Degnim AC, Reynolds C, Pantvaidya G, et al. Nonsentinel node metastasis in breast cancer patients: assessment of an existing and a new predictive nomogram. Am J Surg 2005;190:543-550. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16164917>.

165. Houvenaeghel G, Nos C, Giard S, et al. A nomogram predictive of non-sentinel lymph node involvement in breast cancer patients with a sentinel lymph node micrometastasis. Eur J Surg Oncol 2009;35:690-695. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19046847>.

166. Katz A, Smith BL, Golshan M, et al. Nomogram for the prediction of having four or more involved nodes for sentinel lymph node-positive

breast cancer. J Clin Oncol 2008;26:2093-2098. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18445838>.

167. Kohrt HE, Olshen RA, Bermas HR, et al. New models and online calculator for predicting non-sentinel lymph node status in sentinel lymph node positive breast cancer patients. BMC Cancer 2008;8:66-66. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18315887>.

168. Scow JS, Degnim AC, Hoskin TL, et al. Assessment of the performance of the Stanford Online Calculator for the prediction of nonsentinel lymph node metastasis in sentinel lymph node-positive breast cancer patients. Cancer 2009;115:4064-4070. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19517477>.

169. van la Parra RFD, Ernst MF, Bevilacqua JLB, et al. Validation of a nomogram to predict the risk of nonsentinel lymph node metastases in breast cancer patients with a positive sentinel node biopsy: validation of the MSKCC breast nomogram. Ann Surg Oncol 2009;16:1128-1135. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19252954>.

170. Werkoff G, Lambaudie E, Fondrinier E, et al. Prospective multicenter comparison of models to predict four or more involved axillary lymph nodes in patients with breast cancer with one to three metastatic sentinel lymph nodes. J Clin Oncol 2009;27:5707-5712. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19826125>.

171. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg 2010;252:426-432; discussion 432-423. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20739842>.

172. Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 2011;305:569-575. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21304082>.

173. Axelsson CK, Mouridsen HT, Zedeler K. Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The Danish Breast Cancer Cooperative Group (DBCG). *Eur J Cancer* 1992;28A:1415-1418. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1515262>.
174. Kiricuta CI, Tausch J. A mathematical model of axillary lymph node involvement based on 1446 complete axillary dissections in patients with breast carcinoma. *Cancer* 1992;69:2496-2501. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1568171>.
175. Fisher B, Redmond C, Fisher ER, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. *N Engl J Med* 1985;312:674-681. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3883168>.
176. Antonini N, Jones H, Horiot JC, et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. *Radiother Oncol* 2007;82:265-271. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17126434>.
177. Bartelink H, Horiot JC, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 2001;345:1378-1387. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11794170>.
178. Pignol JP, Olivetto I, Rakovitch E, et al. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. *J Clin Oncol* 2008;26:2085-2092. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18285602>.
179. Mukesh MB, Barnett GC, Wilkinson JS, et al. Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis. *J Clin Oncol* 2013;31:4488-4495. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24043742>.
180. Mulliez T, Veldeman L, van Greveling A, et al. Hypofractionated whole breast irradiation for patients with large breasts: a randomized trial comparing prone and supine positions. *Radiother Oncol* 2013;108:203-208. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24044803>.
181. Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008;371:1098-1107. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18355913>.
182. Group ST, Bentzen SM, Agrawal RK, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008;9:331-341. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18356109>.
183. Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. *Lancet Oncol* 2006;7:467-471. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16750496>.
184. Whelan TJ, Pignol JP, Levine MN, et al. Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010;362:513-520. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20147717>.
185. Haviland JS, Owen JR, Dewar JA, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013;14:1086-1094. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24055415>.
186. Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus

no boost EORTC 22881-10882 trial. J Clin Oncol 2007;25:3259-3265. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17577015>.

187. Romestaing P, Lehingue Y, Carrie C, et al. Role of a 10-Gy boost in the conservative treatment of early breast cancer: results of a randomized clinical trial in Lyon, France. J Clin Oncol 1997;15:963-968. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9060534>.

188. Vrieling C, Collette L, Fourquet A, et al. The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC 'boost vs. no boost' trial. EORTC Radiotherapy and Breast Cancer Cooperative Groups. Radiother Oncol 2000;55:219-232. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10869738>.

189. Jones HA, Antonini N, Hart AA, et al. Impact of pathological characteristics on local relapse after breast-conserving therapy: a subgroup analysis of the EORTC boost versus no boost trial. J Clin Oncol 2009;27:4939-4947. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19720914>.

190. Whelan TJ, Olivetto IA, Parulekar WR, et al. Regional nodal irradiation in early-stage breast cancer. N Engl J Med 2015;373:307-316. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26200977>.

191. Poortmans PM, Collette S, Kirkove C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. New England Journal of Medicine 2015;373:317-327. Available at: <http://www.nejm.org/doi/full/10.1056/NEJMoa1415369>.

192. McCormick B. Partial-breast radiation for early staged breast cancers: hypothesis, existing data, and a planned phase III trial. J Natl Compr Canc Netw 2005;3:301-307. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16002002>.

193. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys

2009;74:987-1001. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19545784>.

194. Shaitelman SF, Vicini FA, Beitsch P, et al. Five-year outcome of patients classified using the American Society for Radiation Oncology consensus statement guidelines for the application of accelerated partial breast irradiation: an analysis of patients treated on the American Society of Breast Surgeons MammoSite Registry Trial. Cancer 2010;116:4677-4685. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20602483>.

195. Vicini F, Arthur D, Wazer D, et al. Limitations of the American Society of Therapeutic Radiology and Oncology consensus panel guidelines on the use of accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys 2010. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20510540>.

196. Bellon JR, Come SE, Gelman RS, et al. Sequencing of chemotherapy and radiation therapy in early-stage breast cancer: updated results of a prospective randomized trial. J Clin Oncol 2005;23:1934-1940. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15774786>.

197. Recht A, Come SE, Henderson IC, et al. The sequencing of chemotherapy and radiation therapy after conservative surgery for early-stage breast cancer. N Engl J Med 1996;334:1356-1361. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8614420>.

198. Hughes KS, Schnaper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med 2004;351:971-977. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15342805>.

199. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol 2013;31:2382-2387. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23690420>.

200. Fyles AW, McCready DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med* 2004;351:963-970. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15342804>.
201. Kunkler IH, Williams LJ, Jack WJ, et al. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol* 2015;16:266-273. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25637340>.
202. Hellman S. Stopping metastases at their source. *N Engl J Med* 1997;337:996-997. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9309106>.
203. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997;337:949-955. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9395428>.
204. Overgaard M, Jensen MB, Overgaard J, et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. *Lancet* 1999;353:1641-1648. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10335782>.
205. Ragaz J, Olivotto IA, Spinelli JJ, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. *J Natl Cancer Inst* 2005;97:116-126. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15657341>.
206. Recht A, Edge SB, Solin LJ, et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001;19:1539-1569. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11230499>.
207. Early Breast Cancer Trialists' Collaborative G, McGale P, Taylor C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014;383:2127-2135. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24656685>.
208. Huang EH, Tucker SL, Strom EA, et al. Postmastectomy radiation improves local-regional control and survival for selected patients with locally advanced breast cancer treated with neoadjuvant chemotherapy and mastectomy. *J Clin Oncol* 2004;22:4691-4699. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15570071>.
209. McGuire SE, Gonzalez-Angulo AM, Huang EH, et al. Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. *Int J Radiat Oncol Biol Phys* 2007;68:1004-1009. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17418973>.
210. Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. *Radiother Oncol* 2007;82:247-253. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17306393>.
211. Nielsen HM, Overgaard M, Grau C, et al. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. *J Clin Oncol* 2006;24:2268-2275. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16618947>.
212. Jagsi R, Raad RA, Goldberg S, et al. Locoregional recurrence rates and prognostic factors for failure in node-negative patients treated with mastectomy: implications for postmastectomy radiation. *Int J*

Radiat Oncol Biol Phys 2005;62:1035-1039. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15990006>.

213. Abdulkarim BS, Cuartero J, Hanson J, et al. Increased risk of locoregional recurrence for women With T1-2N0 triple-negative breast cancer treated with modified radical mastectomy without adjuvant radiation therapy compared with breast-conserving therapy. Journal of Clinical Oncology 2011;29:2852-2858. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21670451>.

214. McLaughlin JM, Anderson RT, Ferketich AK, et al. Effect on survival of longer intervals between confirmed diagnosis and treatment initiation among low-income women with breast cancer. J Clin Oncol 2012;30:4493-4500. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23169521>.

215. Liu AS, Kao HK, Reish RG, et al. Postoperative complications in prosthesis-based breast reconstruction using acellular dermal matrix. Plast Reconstr Surg 2011;127:1755-1762. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21228744>.

216. McCarthy CM, Mehrara BJ, Riedel E, et al. Predicting complications following expander/implant breast reconstruction: an outcomes analysis based on preoperative clinical risk. Plast Reconstr Surg 2008;121:1886-1892. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18520873>.

217. Cowen D, Gross E, Rouannet P, et al. Immediate post-mastectomy breast reconstruction followed by radiotherapy: risk factors for complications. Breast Cancer Res Treat 2010;121:627-634. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20424909>.

218. Woerdeman LA, Hage JJ, Hofland MM, Rutgers EJ. A prospective assessment of surgical risk factors in 400 cases of skin-sparing mastectomy and immediate breast reconstruction with implants to establish selection criteria. Plast Reconstr Surg 2007;119:455-463. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17230076>.

219. Antony AK, McCarthy CM, Cordeiro PG, et al. Acellular human dermis implantation in 153 immediate two-stage tissue expander breast reconstructions: determining the incidence and significant predictors of complications. Plast Reconstr Surg 2010;125:1606-1614. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20517083>.

220. Ahmed S, Snelling A, Bains M, Whitworth IH. Breast reconstruction. BMJ 2005;330:943-948. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15845976>.

221. Edlich RF, Winters KL, Faulkner BC, et al. Advances in breast reconstruction after mastectomy. J Long Term Eff Med Implants 2005;15:197-207. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15777171>.

222. Pennington DG. Breast reconstruction after mastectomy: current state of the art. ANZ J Surg 2005;75:454-458. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15943736>.

223. Chang DW. Breast Reconstruction with Microvascular MS-TRAM and DIEP Flaps. Arch Plast Surg 2012;39:3-10. Available at:

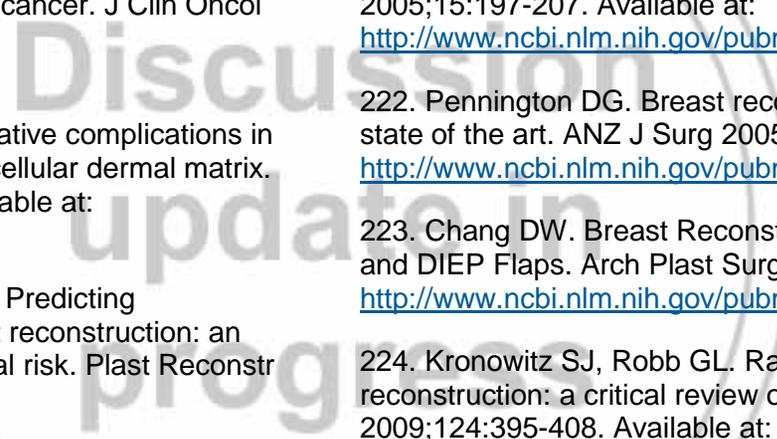
<http://www.ncbi.nlm.nih.gov/pubmed/22783484>.

224. Kronowitz SJ, Robb GL. Radiation therapy and breast reconstruction: a critical review of the literature. Plast Reconstr Surg 2009;124:395-408. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19644254>.

225. Tran NV, Chang DW, Gupta A, et al. Comparison of immediate and delayed free TRAM flap breast reconstruction in patients receiving postmastectomy radiation therapy. Plast Reconstr Surg 2001;108:78-82. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11420508>.

226. Mehta VK, Goffinet D. Postmastectomy radiation therapy after TRAM flap breast reconstruction. Breast J 2004;10:118-122. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15009038>.



227. Berry T, Brooks S, Sydow N, et al. Complication rates of radiation on tissue expander and autologous tissue breast reconstruction. *Ann Surg Oncol* 2010;17 Suppl 3:202-210. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20853034>.

228. Francis SH, Ruberg RL, Stevenson KB, et al. Independent risk factors for infection in tissue expander breast reconstruction. *Plast Reconstr Surg* 2009;124:1790-1796. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19952635>.

229. Colwell AS, Damjanovic B, Zahedi B, et al. Retrospective review of 331 consecutive immediate single-stage implant reconstructions with acellular dermal matrix: indications, complications, trends, and costs. *Plast Reconstr Surg* 2011;128:1170-1178. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22094736>.

230. Garcia-Etienne CA, Cody Iii HS, Disa JJ, et al. Nipple-sparing mastectomy: initial experience at the Memorial Sloan-Kettering Cancer Center and a comprehensive review of literature. *Breast J* 2009;15:440-449. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19496781>.

231. Petit JY, Veronesi U, Orecchia R, et al. Nipple sparing mastectomy with nipple areola intraoperative radiotherapy: one thousand and one cases of a five years experience at the European institute of oncology of Milan (EIO). *Breast Cancer Res Treat* 2009;117:333-338. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19152026>.

232. Yueh JH, Houlihan MJ, Slavin SA, et al. Nipple-sparing mastectomy: evaluation of patient satisfaction, aesthetic results, and sensation. *Ann Plast Surg* 2009;62:586-590. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19387167>.

233. Chung AP, Sacchini V. Nipple-sparing mastectomy: Where are we now? *Surg Oncol* 2008;17:261-266. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18456492>.

234. Gerber B, Krause A, Dieterich M, et al. The oncological safety of skin sparing mastectomy with conservation of the nipple-areola complex

and autologous reconstruction: an extended follow-up study. *Ann Surg* 2009;249:461-468. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19247035>.

235. Mallon P, Feron JG, Couturaud B, et al. The role of nipple-sparing mastectomy in breast cancer: a comprehensive review of the literature. *Plast Reconstr Surg* 2013;131:969-984. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23629079>.

236. Piper M, Peled AW, Foster RD, et al. Total skin-sparing mastectomy: A systematic review of oncologic outcomes and postoperative complications. *Ann Plast Surg* 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23486127>.

237. Toth BA, Forley BG, Calabria R. Retrospective study of the skin-sparing mastectomy in breast reconstruction. *Plast Reconstr Surg* 1999;104:77-84. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10597677>.

238. Carlson GW, Styblo TM, Lyles RH, et al. The use of skin sparing mastectomy in the treatment of breast cancer: The Emory experience. *Surg Oncol* 2003;12:265-269. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14998566>.

239. Downes KJ, Glatt BS, Kanchwala SK, et al. Skin-sparing mastectomy and immediate reconstruction is an acceptable treatment option for patients with high-risk breast carcinoma. *Cancer* 2005;103:906-913. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15651068>.

240. Foster RD, Esserman LJ, Anthony JP, et al. Skin-sparing mastectomy and immediate breast reconstruction: a prospective cohort study for the treatment of advanced stages of breast carcinoma. *Ann Surg Oncol* 2002;9:462-466. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12052757>.

241. Medina-Franco H, Vasconez LO, Fix RJ, et al. Factors associated with local recurrence after skin-sparing mastectomy and immediate

breast reconstruction for invasive breast cancer. *Ann Surg* 2002;235:814-819. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12035037>.

242. Newman LA, Kuerer HM, Hunt KK, et al. Presentation, treatment, and outcome of local recurrence after skin-sparing mastectomy and immediate breast reconstruction. *Ann Surg Oncol* 1998;5:620-626. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9831111>.

243. Clough KB, Kaufman GJ, Nos C, et al. Improving breast cancer surgery: a classification and quadrant per quadrant atlas for oncoplastic surgery. *Ann Surg Oncol* 2010;17:1375-1391. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20140531>.

244. Anderson BO, Masetti R, Silverstein MJ. Oncoplastic approaches to partial mastectomy: an overview of volume-displacement techniques. *Lancet Oncol* 2005;6:145-157. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15737831>.

245. Huemer GM, Schrenk P, Moser F, et al. Oncoplastic techniques allow breast-conserving treatment in centrally located breast cancers. *Plast Reconstr Surg* 2007;120:390-398. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17632339>.

246. Kaur N, Petit J-Y, Rietjens M, et al. Comparative study of surgical margins in oncoplastic surgery and quadrantectomy in breast cancer. *Ann Surg Oncol* 2005;12:539-545. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15889210>.

247. Early Breast Cancer Trialists' Collaborative G, Peto R, Davies C, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet* 2012;379:432-444. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22152853>.

248. Loprinzi CL, Thome SD. Understanding the utility of adjuvant systemic therapy for primary breast cancer. *J Clin Oncol* 2001;19:972-979. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11181659>.

249. Ravdin PM, Siminoff LA, Davis GJ, et al. Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer. *J Clin Oncol* 2001;19:980-991. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11181660>.

250. Olivetto IA, Bajdik CD, Ravdin PM, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer. *J Clin Oncol* 2005;23:2716-2725. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15837986>.

251. Loprinzi CL, Ravdin PM. Decision-making for patients with resectable breast cancer: individualized decisions for and by patients and their physicians. *J Natl Compr Canc Netw* 2003;1:189-196. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19768877>.

252. Cooke T, Reeves J, Lanigan A, Stanton P. HER2 as a prognostic and predictive marker for breast cancer. *Ann Oncol* 2001;12 Suppl 1:23-28. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11521717>.

253. Paik S, Bryant J, Park C, et al. erbB-2 and response to doxorubicin in patients with axillary lymph node-positive, hormone receptor-negative breast cancer. *J Natl Cancer Inst* 1998;90:1361-1370. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9747867>.

254. Paik S, Bryant J, Tan-Chiu E, et al. HER2 and choice of adjuvant chemotherapy for invasive breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-15. *J Natl Cancer Inst* 2000;92:1991-1998. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11121461>.

255. Piccart MJ, Di Leo A, Hamilton A. HER2: a 'predictive factor' ready to use in the daily management of breast cancer patients? *Eur J Cancer* 2000;36:1755-1761. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10974622>.

256. Pritchard KI, Shepherd LE, O'Malley FP, et al. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. *N Engl J*

Med 2006;354:2103-2111. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16707747>.

257. Thor AD, Berry DA, Budman DR, et al. erbB-2, p53, and efficacy of adjuvant therapy in lymph node-positive breast cancer. *J Natl Cancer Inst* 1998;90:1346-1360. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/9747866>.

258. Dressler LG, Berry DA, Broadwater G, et al. Comparison of HER2 status by fluorescence in situ hybridization and immunohistochemistry to predict benefit from dose escalation of adjuvant doxorubicin-based therapy in node-positive breast cancer patients. *J Clin Oncol* 2005;23:4287-4297. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/15994142>.

259. Joensuu H, Kellokumpu-Lehtinen P, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med* 2006;354:809-820. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16495393>.

260. Piccart-Gebhart M, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659-1672. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16236737>.

261. Goldhirsch A, Piccart-Gebhart M, Procter M, et al. HERA TRIAL: 2 years versus 1 year of trastuzumab after adjuvant chemotherapy in women with HER2-positive early breast cancer at 8 years of median follow up. *Cancer Research* 2012;72:S5-2. Available at:
http://cancerres.aacrjournals.org/cgi/content/meeting_abstract/72/24_MeetingAbstracts/S5-2.

262. Romond E, Perez E, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;353:1673-1684. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16236738>.

263. Romond E, Suman V, Jeong J-H, et al. Trastuzumab plus adjuvant chemotherapy for HER2-positive breast cancer: Final planned joint analysis of overall survival (OS) from NSABP B-31 and NCCTG N9831. *Cancer Research* 2012;72:S5-5. Available at:
http://cancerres.aacrjournals.org/cgi/content/meeting_abstract/72/24_MeetingAbstracts/S5-5.

264. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011;365:1273-1283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21991949>.

265. Cobleigh MA, Vogel CL, Tripathy D, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol* 1999;17:2639-2648. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/10561337>.

266. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783-792. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11248153>.

267. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002;20:719-726. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11821453>.

268. Jeffrey SS, Lonning PE, Hillner BE. Genomics-based prognosis and therapeutic prediction in breast cancer. *J Natl Compr Canc Netw* 2005;3:291-300. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16002001>.

269. Perou CM, Jeffrey SS, van de Rijn M, et al. Distinctive gene expression patterns in human mammary epithelial cells and breast cancers. *Proc Natl Acad Sci U S A* 1999;96:9212-9217. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/10430922>.

270. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001;98:10869-10874. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11553815>.

271. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 2003;100:8418-8423. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12829800>.

272. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351:2817-2826. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15591335>.

273. Dowsett M, Cuzick J, Wale C, et al. Prediction of risk of distant recurrence using the 21-gene recurrence score in node-negative and node-positive postmenopausal patients with breast cancer treated with anastrozole or tamoxifen: a TransATAC study. J Clin Oncol 2010;28:1829-1834. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20212256>.

274. Mamounas EP, Tang G, Fisher B, et al. Association between the 21-gene recurrence score assay and risk of locoregional recurrence in node-negative, estrogen receptor-positive breast cancer: results from NSABP B-14 and NSABP B-20. J Clin Oncol 2010;28:1677-1683. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20065188>.

275. Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. Lancet Oncol 2010;11:55-65. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20005174>.

276. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive

breast cancer. J Clin Oncol 2006;24:3726-3734. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16720680>.

277. Tang G, Shak S, Paik S, et al. Comparison of the prognostic and predictive utilities of the 21-gene Recurrence Score assay and Adjuvant! for women with node-negative, ER-positive breast cancer: results from NSABP B-14 and NSABP B-20. Breast Cancer Res Treat 2011;127:133-142. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21221771>.

278. Glas AM, Floore A, Delahaye LJM, et al. Converting a breast cancer microarray signature into a high-throughput diagnostic test. BMC Genomics 2006;7:278-278. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17074082>.

279. van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 2002;347:1999-2009. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12490681>.

280. van 't Veer LJ, Dai H, van de Vijver MJ, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002;415:530-536. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11823860>.

281. Knauer M, Mook S, Rutgers EJ, et al. The predictive value of the 70-gene signature for adjuvant chemotherapy in early breast cancer. Breast Cancer Res Treat 2010;120:655-661. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20204499>.

282. Kunz G. Use of a genomic test (MammaPrint) in daily clinical practice to assist in risk stratification of young breast cancer patients. Arch Gynecol Obstet 2011;283:597-602. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20383789>.

283. Ishitobi M, Goranova TE, Komoike Y, et al. Clinical utility of the 70-gene MammaPrint profile in a Japanese population. Jpn J Clin Oncol

2010;40:508-512. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20110242>.

284. Mook S, Knauer M, Bueno-de-Mesquita JM, et al. Metastatic potential of T1 breast cancer can be predicted by the 70-gene MammaPrint signature. *Ann Surg Oncol* 2010;17:1406-1413. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20094918>.

285. Drukker CA, Bueno-de-Mesquita JM, Retel VP, et al. A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study. *Int J Cancer* 2013;133:929-936. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23371464>.

286. Dowsett M, Sestak I, Lopez-Knowles E, et al. Comparison of PAM50 risk of recurrence score with oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy. *J Clin Oncol* 2013;31:2783-2790. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23816962>.

287. Gnant M, Filipits M, Greil R, et al. Predicting distant recurrence in receptor-positive breast cancer patients with limited clinicopathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone. *Ann Oncol* 2014;25:339-345. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24347518>.

288. Sestak I, Cuzick J, Dowsett M, et al. Prediction of late distant recurrence after 5 years of endocrine treatment: a combined analysis of patients from the Austrian breast and colorectal cancer study group 8 and arimidex, tamoxifen alone or in combination randomized trials using the PAM50 risk of recurrence score. *J Clin Oncol* 2015;33:916-922. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25332252>.

289. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *New England Journal of Medicine* 2015;373:2005-2014. Available at: <http://www.nejm.org/doi/full/10.1056/NEJMoa1510764>.

290. Hormone therapy with or without combination chemotherapy in treating women who have undergone surgery for node-negative breast cancer (The TAILORx Trial). Clinical Trial ID: NCT00310180. Available at:

<http://clinicaltrials.gov/ct2/show/NCT00310180?term=TAILORx&rank=2>.

291. A phase III, randomized clinical trial of standard adjuvant endocrine therapy +/-chemotherapy in patients with 1-3 positive nodes, hormone receptor-positive and HER2-negative breast cancer with recurrence score (RS) of 25 or less. RXPONDER: A clinical trial RX for positive node, endocrine responsive breast cancer. Clinical Trial ID NCT01272037. Available at: <http://clinicaltrials.gov/show/NCT01272037>.

292. MINDACT (Microarray In Node-Negative and 1 to 3 positive lymph node disease may avoid chemotherapy): A prospective, randomized study comparing the 70-Gene signature with the common clinical-pathological criteria in selecting patients for adjuvant chemotherapy in breast cancer with 0 to 3 positive nodes. Clinical Trial ID: NCT00433589. Available at: <http://clinicaltrials.gov/ct2/show/NCT00433589?term=NCT00433589&rank=1>.

293. Piccart M, Rutgers E, van't Veer L, et al. Primary analysis of the EORTC 10041/ BIG 3-04 MINDACT study: a prospective, randomized study evaluating the clinical utility of the 70-gene signature (MammaPrint) combined with common clinical-pathological criteria for selection of patients for adjuvant chemotherapy in breast cancer with 0 to 3 positive nodes [abstract]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2016 Apr 16-20; New Orleans, Louisiana: AACR; 2016. Abstract CT039 2016.

294. Swain SM, Wilson JW, Mamounas EP, et al. Estrogen receptor status of primary breast cancer is predictive of estrogen receptor status of contralateral breast cancer. *J Natl Cancer Inst* 2004;96:516-523. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15069113>.

295. Berry DA, Cirincione C, Henderson IC, et al. Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer. *JAMA* 2006;295:1658-1667. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16609087>.
296. Albain KS, Barlow WE, Ravdin PM, et al. Adjuvant chemotherapy and timing of tamoxifen in postmenopausal patients with endocrine-responsive, node-positive breast cancer: a phase 3, open-label, randomised controlled trial. *Lancet* 2009;374:2055-2063. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20004966>.
297. Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst* 2005;97:188-194. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15687361>.
298. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol* 2008;26:778-785. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18258986>.
299. Galow JR, Burstein HJ, Wood W, et al. Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease. *J Clin Oncol* 2008;26:814-819. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18258991>.
300. Killelea BK, Yang VQ, Mougalian S, et al. Neoadjuvant chemotherapy for breast cancer increases the rate of breast conservation: results from the National Cancer Database. *J Am Coll Surg* 2015;220:1063-1069. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25868410>.
301. Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J Clin Oncol* 2008;26:1275-1281. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18250347>.
302. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *Lancet* 2014;384:164-172. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24529560>.
303. von Minckwitz G, Untch M, Blohmer JU, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012;30:1796-1804. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22508812>.
304. Cataliotti L, Buzdar AU, Noguchi S, et al. Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor-positive breast cancer: the Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) trial. *Cancer* 2006;106:2095-2103. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16598749>.
305. Smith IE, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. *J Clin Oncol* 2005;23:5108-5116. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15998903>.
306. Eiermann W, Paepke S, Appfelstaedt J, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: A randomized double-blind multicenter study. *Ann Oncol* 2001;12:1527-1532. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11822750>.
307. Ellis MJ, Ma C. Letrozole in the neoadjuvant setting: the P024 trial. *Breast Cancer Res Treat* 2007;105 Suppl 1:33-43. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17912634>.
308. Ellis MJ, Suman VJ, Hoog J, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and

predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. *J Clin Oncol* 2011;29:2342-2349. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21555689>.

309. Masuda N, Sagara Y, Kinoshita T, et al. Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2012;13:345-352. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22265697>.

310. Torrisi R, Bagnardi V, Rotmensz N, et al. Letrozole plus GnRH analogue as preoperative and adjuvant therapy in premenopausal women with ER positive locally advanced breast cancer. *Breast Cancer Res Treat* 2011;126:431-441. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21221766>.

311. Fontein DB, Charehbili A, Nortier JW, et al. Efficacy of six month neoadjuvant endocrine therapy in postmenopausal, hormone receptor-positive breast cancer patients--a phase II trial. *Eur J Cancer* 2014;50:2190-2200. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24970786>.

312. Petrelli F, Borgonovo K, Cabiddu M, et al. Neoadjuvant chemotherapy and concomitant trastuzumab in breast cancer: a pooled analysis of two randomized trials. *Anticancer Drugs* 2011;22:128-135. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21218604>.

313. Piccart-Gebhart M HA, de Azambuja E, et al. . The association between event-free survival and pathological complete response to neoadjuvant lapatinib, trastuzumab or their combination in HER2-positive breast cancer. Survival follow-up analysis of the NeoALTT0 study (BIG 1-06) [abstract]. *SABCS 2013:Abstract S1-01*. Available at:

314. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial.

Lancet Oncol 2012;13:25-32. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22153890>.

315. Gianni L, Pienkowski T, Im Y-H, et al. Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P). *ASCO Meeting Abstracts* 2015;33:505. Available at: http://meeting.ascopubs.org/cgi/content/abstract/33/15_suppl/505.

316. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol* 2013;24:2278-2284. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23704196>.

317. Tamoxifen for early breast cancer: an overview of the randomised trials. *Early Breast Cancer Trialists' Collaborative Group. Lancet* 1998;351:1451-1467. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9605801>.

318. Arpino G, Green SJ, Allred DC, et al. HER-2 amplification, HER-1 expression, and tamoxifen response in estrogen receptor-positive metastatic breast cancer: a southwest oncology group study. *Clin Cancer Res* 2004;10:5670-5676. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15355892>.

319. Berry DA, Muss HB, Thor AD, et al. HER-2/neu and p53 expression versus tamoxifen resistance in estrogen receptor-positive, node-positive breast cancer. *J Clin Oncol* 2000;18:3471-3479. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11032587>.

320. De Laurentiis M, Arpino G, Massarelli E, et al. A meta-analysis on the interaction between HER-2 expression and response to endocrine treatment in advanced breast cancer. *Clin Cancer Res* 2005;11:4741-4748. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16000569>.

321. Eppenberger-Castori S, Kueng W, Benz C, et al. Prognostic and predictive significance of ErbB-2 breast tumor levels measured by enzyme immunoassay. *J Clin Oncol* 2001;19:645-656. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11157014>.

322. Knoop AS, Bentzen SM, Nielsen MM, et al. Value of epidermal growth factor receptor, HER2, p53, and steroid receptors in predicting the efficacy of tamoxifen in high-risk postmenopausal breast cancer patients. *J Clin Oncol* 2001;19:3376-3384. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11454885>.

323. Mass R. The role of HER-2 expression in predicting response to therapy in breast cancer. *Semin Oncol* 2000;27:46-52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11236028>.

324. Paik S, Shak S, Tang G, et al. Expression of the 21 genes in the Recurrence Score assay and tamoxifen clinical benefit in the NSABP study B-14 of node negative, estrogen receptor positive breast cancer [abstract]. *J Clin Oncol* 2005;23(Suppl 16):Abstract 510. Available at: http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/510.

325. Pegram MD, Pauletti G, Slamon DJ. HER-2/neu as a predictive marker of response to breast cancer therapy. *Breast Cancer Res Treat* 1998;52:65-77. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10066073>.

326. Dowsett M, Allred C, Knox J, et al. Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER-2) status with recurrence in the Arimidex, Tamoxifen, Alone or in Combination trial. *J Clin Oncol* 2008;26:1059-1065. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18227529>.

327. Early Breast Cancer Trialists' Collaborative G, Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011;378:771-784. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21802721>.

328. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687-1717. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15894097>.

329. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013;381:805-816. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23219286>.

330. Gray R, Rea D, Handley K, et al. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer [Abstract]. *J Clin Oncol* 2013;31(suppl):Abstract 5. Available at:

331. Cuzick J, Ambroisine L, Davidson N, et al. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet* 2007;369:1711-1723. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17512856>.

332. Davidson NE, O'Neill AM, Vukov AM, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). *J Clin Oncol* 2005;23:5973-5982. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16087950>.

333. Ejlertsen B, Mouridsen HT, Jensen MB, et al. Similar efficacy for ovarian ablation compared with cyclophosphamide, methotrexate, and fluorouracil: from a randomized comparison of premenopausal patients with node-positive, hormone receptor-positive breast cancer. *J Clin Oncol* 2006;24:4956-4962. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17075113>.

334. Goel S, Sharma R, Hamilton A, Beith J. LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women. *Cochrane Database Syst Rev* 2009;CD004562. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19821328>.

335. Kaufmann M, Jonat W, Blamey R, et al. Survival analyses from the ZEBRA study. goserelin (Zoladex) versus CMF in premenopausal women with node-positive breast cancer. *Eur J Cancer* 2003;39:1711-1717. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12888366>.

336. Schmid P, Untch M, Wallwiener D, et al. Cyclophosphamide, methotrexate and fluorouracil (CMF) versus hormonal ablation with leuprorelin acetate as adjuvant treatment of node-positive, premenopausal breast cancer patients: preliminary results of the TABLE-study (Takeda Adjuvant Breast cancer study with Leuprorelin Acetate). *Anticancer Res* 2002;22:2325-2332. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12174922>.

337. Thomson CS, Twelves CJ, Mallon EA, Leake RE. Adjuvant ovarian ablation vs CMF chemotherapy in premenopausal breast cancer patients: trial update and impact of immunohistochemical assessment of ER status. *Breast* 2002;11:419-429. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14965706>.

338. von Minckwitz G, Graf E, Geberth M, et al. CMF versus goserelin as adjuvant therapy for node-negative, hormone-receptor-positive breast cancer in premenopausal patients: a randomised trial (GABG trial IV-A-93). *Eur J Cancer* 2006;42:1780-1788. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16765589>.

339. Castiglione-Gertsch M, O'Neill A, Price KN, et al. Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomized trial. *J Natl Cancer Inst* 2003;95:1833-1846. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14679153>.

340. Puhalla S, Brufsky A, Davidson N. Adjuvant endocrine therapy for premenopausal women with breast cancer. *Breast* 2009;18 Suppl

3:S122-130. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19914530>.

341. Roche H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. *J Clin Oncol* 2006;24:5664-5671. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17116941>.

342. Boccardo F, Rubagotti A, Amoroso D, et al. Cyclophosphamide, methotrexate, and fluorouracil versus tamoxifen plus ovarian suppression as adjuvant treatment of estrogen receptor-positive pre-/perimenopausal breast cancer patients: results of the Italian Breast Cancer Adjuvant Study Group 02 randomized trial. *boccardo@hp380.ist.unige.it. J Clin Oncol* 2000;18:2718-2727. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10894871>.

343. Paganì O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014;371:107-118. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24881463>.

344. Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2015;372:436-446. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25495490>.

345. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007;369:559-570. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17307102>.

346. Kaufmann M, Jonat W, Hilfrich J, et al. Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 Study. *J Clin Oncol* 2007;25:2664-2670. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17563395>.

347. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005;97:1262-1271. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16145047>.

348. Forbes JF, Cuzick J, Buzdar A, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol* 2008;9:45-53. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18083636>.

349. Thurlimann B, Keshaviah A, Coates AS, et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 2005;353:2747-2757. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16382061>.

350. Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002;359:2131-2139. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12090977>.

351. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;365:60-62. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15639680>.

352. Duffy S, Jackson TL, Lansdown M, et al. The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) adjuvant breast cancer trial: first results of the endometrial sub-protocol following 2 years of treatment. *Hum Reprod* 2006;21:545-553. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16210385>.

353. Fallowfield L, Cella D, Cuzick J, et al. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. *J Clin Oncol* 2004;22:4261-4271. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15514369>.

354. Eastell R, Adams JE, Coleman RE, et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J Clin Oncol* 2008;26:1051-1057. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18309940>.

355. Dowsett M, Cuzick J, Howell A, Jackson I. Pharmacokinetics of anastrozole and tamoxifen alone, and in combination, during adjuvant endocrine therapy for early breast cancer in postmenopausal women: a sub-protocol of the 'Arimidex and tamoxifen alone or in combination' (ATAC) trial. *Br J Cancer* 2001;85:317-324. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11487258>.

356. Buzdar AU, Guastalla JP, Nabholz JM, et al. Impact of chemotherapy regimens prior to endocrine therapy: Results from the ATAC (anastrozole and tamoxifen, alone or in combination) trial. *Cancer* 2006;107:472-480. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16804925>.

357. Mouridsen H, Keshaviah A, Coates AS, et al. Cardiovascular adverse events during adjuvant endocrine therapy for early breast cancer using letrozole or tamoxifen: safety analysis of BIG 1-98 trial. *J Clin Oncol* 2007;25:5715-5722. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17998546>.

358. Rabaglio M, Sun Z, Price KN, et al. Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial. *Ann Oncol* 2009;20:1489-1498. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19474112>.

359. Mouridsen H, Giobbie-Hurder A, Goldhirsch A, et al. Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. *N Engl J Med* 2009;361:766-776. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19692688>.

360. Boccardo F, Rubagotti A, Puntoni M, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. *J*

Clin Oncol 2005;23:5138-5147. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16009955>.

361. Boccardo F, Rubagotti A, Guglielmini P, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial. Ann Oncol 2006;17 Suppl 7:10-14. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16760270>.

362. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350:1081-1092. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/15014181>.

363. Jakesz R, Jonat W, Gnant M, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 2005;366:455-462. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16084253>.

364. Jonat W, Gnant M, Boccardo F, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. Lancet Oncol 2006;7:991-996. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17138220>.

365. van de Velde CJ, Rea D, Seynaeve C, et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. Lancet 2011;377:321-331. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21247627>.

366. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003;349:1793-1802. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14551341>.

367. Goss PE, Ingle JN, Pater JL, et al. Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. J Clin Oncol 2008;26:1948-1955. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18332475>.

368. Ingle JN, Tu D, Pater JL, et al. Intent-to-treat analysis of the placebo-controlled trial of letrozole for extended adjuvant therapy in early breast cancer: NCIC CTG MA.17. Ann Oncol 2008;19:877-882. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18332043>.

369. Perez EA, Josse RG, Pritchard KI, et al. Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17. J Clin Oncol 2006;24:3629-3635. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16822845>.

370. Whelan TJ, Goss PE, Ingle JN, et al. Assessment of quality of life in MA.17: a randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women. J Clin Oncol 2005;23:6931-6940. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16157934>.

371. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. The Lancet 2012. Available at:
<http://linkinghub.elsevier.com/retrieve/pii/S0140673612619631>.

372. Jakesz R, Greil R, Gnant M, et al. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. J Natl Cancer Inst 2007;99:1845-1853. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18073378>.

373. Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. J

Clin Oncol 2010;28:509-518. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19949017>.

374. Smith IE, Dowsett M, Yap Y-S, et al. Adjuvant aromatase inhibitors for early breast cancer after chemotherapy-induced amenorrhoea: caution and suggested guidelines. J Clin Oncol 2006;24:2444-2447. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16735701>.

375. Yu B, Douglas N, Ferin MJ, et al. Changes in markers of ovarian reserve and endocrine function in young women with breast cancer undergoing adjuvant chemotherapy. Cancer 2010;116:2099-2105. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20187091>.

376. Dowsett M, Nielsen TO, A'Hern R, et al. Assessment of Ki67 in Breast Cancer: Recommendations from the International Ki67 in Breast Cancer Working Group. J Natl Cancer Inst 2011. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21960707>.

377. Dowsett M, Smith IE, Ebbs SR, et al. Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. J Natl Cancer Inst 2007;99:167-170. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17228000>.

378. . Available at: <http://www.cypalleles.ki.se/>.

379. Schroth W, Goetz MP, Hamann U, et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. JAMA 2009;302:1429-1436. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19809024>.

380. Leyland-Jones B, Regan M, Bouzyk M, et al. Outcome according to CYP2D6 genotype among postmenopausal women with endocrine-responsive early invasive breast cancer randomized in the BIG 1-98 trial [abstract]. Cancer Res 2010;70(24 Suppl):Abstract nr S1-8. Available at: http://cancerres.aacrjournals.org/cgi/content/short/70/24_MeetingAbstracts/S1-8.

381. Rae J, Drury S, Hayes D, et al. Lack of correlation between gene variants in tamoxifen metabolizing enzymes with primary endpoints in the ATAC trial [abstract]. Cancer Res 2010;70(24 Suppl):Abstract S1-7. Available at:

http://cancerres.aacrjournals.org/cgi/content/meeting_abstract/70/24_MeetingAbstracts/S1-7?sid=e2c268c0-3fe1-481b-a9c9-01b32769a3d9.

382. Higgins MJ, Stearns V. Pharmacogenetics of endocrine therapy for breast cancer. Annu Rev Med 2011;62:281-293. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21226615>.

383. Visvanathan K, Chlebowski RT, Hurley P, et al. American Society of Clinical Oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction. J Clin Oncol 2009;27:3235-3258. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19470930>.

384. Erban JK, Lau J. On the toxicity of chemotherapy for breast cancer--the need for vigilance. J Natl Cancer Inst 2006;98:1096-1097. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16912256>.

385. Henderson I, Berry D, Demetri G, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol 2003;21:976-983. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12637460>.

386. Mamounas E, Bryant J, Lembersky B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. J Clin Oncol 2005;23:3686-3696. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15897552>.

387. Citron ML, Berry DA, Cirincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of

Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431-1439. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12668651>.

388. Sparano JA, Wang M, Martino S, et al. Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node positive or high risk node negative breast cancer [abstract]. San Antonio Breast Cancer Symposium 2005:Abstract 48. Available at:

389. Sparano JA, Wang M, Martino S, et al. Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in operable breast cancer: Results of Intergroup Trial E1199 [abstract]. J Clin Oncol 2007;25 (Suppl_18) Abstract 516. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/516.

390. Sparano J, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 2008;358:1663-1671. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18420499>.

391. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research trial 9735. J Clin Oncol 2009;27:1177-1183. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19204201>.

392. Bang SM, Heo DS, Lee KH, et al. Adjuvant doxorubicin and cyclophosphamide versus cyclophosphamide, methotrexate, and 5-fluorouracil chemotherapy in premenopausal women with axillary lymph node positive breast carcinoma. Cancer 2000;89:2521-2526. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11135211>.

393. Fisher B, Brown AM, Dimitrov NV, et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant

Breast and Bowel Project B-15. J Clin Oncol 1990;8:1483-1496. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2202791>.

394. Fisher B, Anderson S, Wickerham DL, et al. Increased intensification and total dose of cyclophosphamide in a doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-22. J Clin Oncol 1997;15:1858-1869. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9164196>.

395. Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 1998;352:930-942. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9752815>.

396. Wood WC, Budman DR, Korzun AH, et al. Dose and dose intensity of adjuvant chemotherapy for stage II, node-positive breast carcinoma. N Engl J Med 1994;330:1253-1259. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8080512>.

397. Menard S, Valagussa P, Pilotti S, et al. Response to cyclophosphamide, methotrexate, and fluorouracil in lymph node-positive breast cancer according to HER2 overexpression and other tumor biologic variables. J Clin Oncol 2001;19:329-335. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11208823>.

398. Muss HB, Thor AD, Berry DA, et al. c-erbB-2 expression and response to adjuvant therapy in women with node-positive early breast cancer. N Engl J Med 1994;330:1260-1266. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7908410>.

399. Watanabe T, Kuranami M, Inoue K, et al. Phase III trial comparing 4-cycle doxorubicin plus cyclophosphamide followed by 4-cycle taxan with 8-cycle taxan as adjuvant therapy for node-positive breast cancer: Results of N-SAS-BC02 trial [abstract]. J Clin Oncol 2009;27(Suppl 15):Abstract 516. Available at: <http://meeting.ascopubs.org/cgi/content/abstract/27/15S/516>.

400. Piccart MJ, Di Leo A, Beauduin M, et al. Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. *J Clin Oncol* 2001;19:3103-3110. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11408507>.

401. Samuel JA, Wilson JW, Bandos H, et al. Abstract S3-02: NSABP B-36: A randomized phase III trial comparing six cycles of 5-fluorouracil (5-FU), epirubicin, and cyclophosphamide (FEC) to four cycles of adriamycin and cyclophosphamide (AC) in patients (pts) with node-negative breast cancer. *Cancer Research* 2015;75:S3-02. Available at: http://cancerres.aacrjournals.org/content/75/9_Supplement/S3-02.abstract.

402. Ganz PA, Wilson JW, Bandos H, et al. Abstract P3-12-01: Impact of treatment on quality of life (QOL) and menstrual history (MH) in the NSABP B-36: A randomized phase III trial comparing six cycles of 5-fluorouracil (5-FU), epirubicin, and cyclophosphamide (FEC) to four cycles of adriamycin and cyclophosphamide. *Cancer Research* 2015;75:P3-12-01. Available at: http://cancerres.aacrjournals.org/content/75/9_Supplement/P3-12-01.abstract.

403. Levine M, Pritchard K, Bramwell V, et al. Randomized trial comparing cyclophosphamide, epirubicin, and fluorouracil with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer: update of National Cancer Institute of Canada Clinical Trials Group Trial MA5. *J Clin Oncol* 2005;23:5166-5170. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16051958>.

404. Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 Randomized Trial. *J Clin Oncol* 2001;19:602-611. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11157009>.

405. Ellis P, Barrett-Lee P, Johnson L, et al. Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open-label, phase III, randomised controlled trial. *Lancet* 2009;373:1681-1692. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19447249>.

406. Martin M, Rodriguez-Lescure A, Ruiz A, et al. Randomized phase 3 trial of fluorouracil, epirubicin, and cyclophosphamide alone or followed by Paclitaxel for early breast cancer. *J Natl Cancer Inst* 2008;100:805-814. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18505968>.

407. Sparano JA ZF, Martino S, et al. Ten year update of E1199: Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer [abstract]. San Antonio Breast Cancer Symposium. Oral Presentation Abstract S3-03. 2014 Available at:

408. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med* 2005;352:2302-2313. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15930421>.

409. Swain SM, Jeong J-H, Geyer CE, et al. NSABP B-30: definitive analysis of patient outcome from a randomized trial evaluating different schedules and combinations of adjuvant therapy containing doxorubicin, docetaxel and cyclophosphamide in women with operable, node-positive breast cancer [abstract]. *Cancer Research* 2009;69 (Suppl_1):Abstract 75. Available at: http://cancerres.aacrjournals.org/cgi/content/meeting_abstract/69/2_MeetingAbstracts/75.

410. Muss HB, Berry DA, Cirincione CT, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med* 2009;360:2055-2065. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19439741>.

411. Burstein HJ. The distinctive nature of HER2-positive breast cancers. *N Engl J Med* 2005;353:1652-1654. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16236735>.

412. Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. *J Clin Oncol* 2009;27:5685-5692. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19884557>.

413. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. *J Clin Oncol* 2011;29:3366-3373. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21768458>.

414. Gianni L, Dafni U, Gelber RD, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. *Lancet Oncol* 2011;12:236-244. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21354370>.

415. Perez EA, Suman VJ, Davidson NE, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. *J Clin Oncol* 2008;26:1231-1238. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18250349>.

416. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005;23:7811-7819. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16258083>.

417. Geyer CE, Jr., Bryant JL, Romond EH, et al. Update of cardiac dysfunction on NSABP B-31, a randomized trial of sequential

doxorubicin/cyclophosphamide (AC)->paclitaxel (T) vs. AC->T with trastuzumab (H) [abstract]. *J Clin Oncol* 2006;24(Suppl 18):Abstract 581. Available at: http://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/581.

418. Telli ML, Hunt SA, Carlson RW, Guardino AE. Trastuzumab-related cardiotoxicity: calling into question the concept of reversibility. *J Clin Oncol* 2007;25:3525-3533. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17687157>.

419. Smith I, Procter M, Gelber RD, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet* 2007;369:29-36. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17208639>.

420. Spielmann M, Roché H, Delozier T, et al. Trastuzumab for patients with axillary-node-positive breast cancer: results of the FNCLCC-PACS 04 trial. *J Clin Oncol* 2009;27:6129-6134. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19917839>.

421. Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol* 2013;14:741-748. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23764181>.

422. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al. 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet* 2013;382:1021-1028. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23871490>.

423. Chia S, Norris B, Speers C, et al. Human epidermal growth factor receptor 2 overexpression as a prognostic factor in a large tissue microarray series of node-negative breast cancers. *J Clin Oncol* 2008;26:5697-5704. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19001334>.

424. Gonzalez-Angulo AM, Litton JK, Broglio KR, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2-positive, node-negative tumors 1 cm or smaller. *J Clin Oncol* 2009;27:5700-5706. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19884543>.

425. O'Sullivan C, Holmes E, Spielmann M, et al. The prognosis of small HER2+ breast cancers: A meta-analysis of the randomized trastuzumab trials [abstract]. San Antonio Breast Cancer Symposium Meeting Abstracts 2013:Abstract S 6-03 Available at:

426. Zhou Q, Yin W, Du Y, Lu J. For or against adjuvant trastuzumab for pT1a-bN0M0 breast cancer patients with HER2-positive tumors: A meta-analysis of published literatures. *PLoS One* 2014;9:e83646. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24392090>.

427. Tolaney S, Barry W, Dang C, et al. A phase II study of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC) [abstract]. San Antonio Breast Symposium Meeting Abstract 2013:Abstract S 1-04 (Oral Presentation). Available at:

428. Piccart-Gebhart MJ, Holmes AP, Baselga J, et al. First results from the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) comparing one year of anti-HER2 therapy with lapatinib alone (L), trastuzumab alone (T), their sequence (T->L), or their combination (T+L) in the adjuvant treatment of HER2-positive early breast cancer (EBC). *ASCO Meeting Abstracts* 2014;32:LBA4. Available at: http://meeting.ascopubs.org/cgi/content/abstract/32/18_suppl/LBA4.

429. Curigliano G, Viale G, Bagnardi V, et al. Clinical relevance of HER2 overexpression/amplification in patients with small tumor size and node-negative breast cancer. *J Clin Oncol* 2009;27:5693-5699. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19884553>.

430. Perez EA, Romond EH, Suman VJ, et al. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer [abstract]. *J Clin Oncol* 2007;25(Suppl 18):Abstract 512.

Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/512.

431. Untch M, Gelber RD, Jackisch C, et al. Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. *Ann Oncol* 2008;19:1090-1096. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18296421>.

432. Swain S, Kim S-B, Cortes J, et al. Confirmatory overall survival (OS) analysis of CLEOPATRA: a randomized, double-blind, placebo-controlled Phase III study with pertuzumab (P), trastuzumab (T), and docetaxel (D) in patients (pts) with HER2-positive first-line (1L) metastatic breast cancer (MBC). *Cancer Research* 2012;72:P5-18-26. Available at: http://cancerres.aacrjournals.org/cgi/content/meeting_abstract/72/24_MeetingAbstracts/P5-18-26.

433. von MG, Baselga J, Bradbury I, et al. Adjuvant Pertuzumab and Herceptin IN IniTial TherapY of Breast Cancer: APHINITY (BIG 4-11/BO25126/TOC4939g) [abstract]. *Cancer Res* 2011; 71(Suppl 24):Abstract OT1-02-04. Available at:

434. A randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer (Clinical Trial ID: NCT01358877). Available at: <http://clinicaltrials.gov/ct2/show/NCT01358877>.

435. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med* 2015;372:134-141. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25564897>.

436. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial *Lancet*

Oncol 2014;15:747-756. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24794243>.

437. Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance) [abstract]. Journal of Clinical Oncology 2014. Available at:

<http://jco.ascopubs.org/content/early/2014/08/01/JCO.2014.57.0572.abstract>.

438. Aukema TS, Straver ME, Peeters MJ, et al. Detection of extra-axillary lymph node involvement with FDG PET/CT in patients with stage II-III breast cancer. Eur J Cancer 2010;46:3205-3210. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20719497>.

439. Fuster D, Duch J, Paredes P, et al. Preoperative staging of large primary breast cancer with [¹⁸F]fluorodeoxyglucose positron emission tomography/computed tomography compared with conventional imaging procedures. J Clin Oncol 2008;26:4746-4751. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18695254>.

440. Groheux D, Moretti JL, Baillet G, et al. Effect of (¹⁸F)-FDG PET/CT imaging in patients with clinical Stage II and III breast cancer. Int J Radiat Oncol Biol Phys 2008;71:695-704. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18436392>.

441. van der Hoeven JJM, Krak NC, Hoekstra OS, et al. ¹⁸F-2-fluoro-2-deoxy-d-glucose positron emission tomography in staging of locally advanced breast cancer. J Clin Oncol 2004;22:1253-1259. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15051773>.

442. Niikura N, Costelloe CM, Madewell JE, et al. FDG-PET/CT compared with conventional imaging in the detection of distant metastases of primary breast cancer. Oncologist 2011;16:1111-1119. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21765193>.

443. Morris PG, Lynch C, Feeney JN, et al. Integrated positron emission tomography/computed tomography may render bone scintigraphy unnecessary to investigate suspected metastatic breast cancer. J Clin Oncol 2010;28:3154-3159. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20516453>.

444. Alessio AM, Kinahan PE, Cheng PM, et al. PET/CT scanner instrumentation, challenges, and solutions. Radiol Clin North Am 2004;42:1017-1032. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15488555>.

445. Wong TZ, Paulson EK, Nelson RC, et al. Practical approach to diagnostic CT combined with PET. AJR Am J Roentgenol 2007;188:622-629. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17312045>.

446. Hortobagyi GN, Singletary SE, Strom EA. Locally advanced breast cancer. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. Diseases of the Breast. Philadelphia: Lippincott Williams & Wilkins; 2004.

447. <https://www.astro.org/Clinical-Practice/Choosing-Wisely/2014-Choosing-Wisely.aspx> Aa. Available at:

448. Impact of follow-up testing on survival and health-related quality of life in breast cancer patients. A multicenter randomized controlled trial. The GIVIO Investigators. JAMA 1994;271:1587-1592. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/8182811>.

449. Rosselli Del Turco M, Palli D, Cariddi A, et al. Intensive diagnostic follow-up after treatment of primary breast cancer. A randomized trial. National Research Council Project on Breast Cancer follow-up. JAMA 1994;271:1593-1597. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/7848404>.

450. Smith TJ, Davidson NE, Schapira DV, et al. American Society of Clinical Oncology 1998 update of recommended breast cancer

surveillance guidelines. *J Clin Oncol* 1999;17:1080-1082. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10071303>.

451. Bast RC, Ravdin P, Hayes DF, et al. 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001;19:1865-1878. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11251019>.

452. Kirova YM, Stoppa-Lyonnet D, Savignoni A, et al. Risk of breast cancer recurrence and contralateral breast cancer in relation to BRCA1 and BRCA2 mutation status following breast-conserving surgery and radiotherapy. *Eur J Cancer* 2005;41:2304-2311. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16140006>.

453. Metcalfe K, Lynch HT, Ghadirian P, et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. *J Clin Oncol* 2004;22:2328-2335. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15197194>.

454. Pierce LJ, Levin AM, Rebbeck TR, et al. Ten-year multi-institutional results of breast-conserving surgery and radiotherapy in BRCA1/2-associated stage I/II breast cancer. *J Clin Oncol* 2006;24:2437-2443. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16636335>.

455. ACOG committee opinion. No. 336: Tamoxifen and uterine cancer. *Obstet Gynecol* 2006;107:1475-1478. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16738185>.

456. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet* 2000;356:2059-2063. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11145492>.

457. Boekhout AH, Vincent AD, Dalesio OB, et al. Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial. *J Clin*

Oncol 2011;29:3862-3868. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21911720>.

458. Kaplan M, Mahon S, Cope D, et al. Putting evidence into practice: evidence-based interventions for hot flashes resulting from cancer therapies. *Clin J Oncol Nurs* 2011;15:149-157. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21444282>.

459. Bordeleau L, Pritchard KI, Loprinzi CL, et al. Multicenter, randomized, cross-over clinical trial of venlafaxine versus gabapentin for the management of hot flashes in breast cancer survivors. *J Clin Oncol* 2010;28:5147-5152. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21060031>.

460. Garber K. Tamoxifen pharmacogenetics moves closer to reality. *J Natl Cancer Inst* 2005;97:412-413. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15770000>.

461. Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J Natl Cancer Inst* 2005;97:30-39. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15632378>.

462. Henry NL, Stearns V, Flockhart DA, et al. Drug interactions and pharmacogenomics in the treatment of breast cancer and depression. *Am J Psychiatry* 2008;165:1251-1255. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18829880>.

463. Ahern TP, Pedersen L, Cronin-Fenton DP, et al. No increase in breast cancer recurrence with concurrent use of tamoxifen and some CYP2D6-inhibiting medications. *Cancer Epidemiol Biomarkers Prev* 2009;18:2562-2564. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19690182>.

464. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487-497. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16079372>.

465. Dayes IS, Whelan TJ, Julian JA, et al. Randomized trial of decongestive lymphatic therapy for the treatment of lymphedema in women with breast cancer. *J Clin Oncol* 2013;31:3758-3763. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24043733>.
466. Warren AG, Brorson H, Borud LJ, Slavin SA. Lymphedema: a comprehensive review. *Ann Plast Surg* 2007;59:464-472. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17901744>.
467. Hickey M, Peate M, Saunders CM, Friedlander M. Breast cancer in young women and its impact on reproductive function. *Human Reproduction Update* 2009;15:323-339. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19174449>.
468. Moran MS, Colasanto JM, Haffty BG, et al. Effects of breast-conserving therapy on lactation after pregnancy. *Cancer J* 2005;11:399-403. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16259870>.
469. Gnant M, Mlineritsch B, Schippinger W, et al. Endocrine therapy plus zoledronic acid in premenopausal breast cancer. *N Engl J Med* 2009;360:679-691. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19213681>.
470. Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet* 2015;386:433-443. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26040499>.
471. Li CI, Daling JR, Porter PL, et al. Relationship between potentially modifiable lifestyle factors and risk of second primary contralateral breast cancer among women diagnosed with estrogen receptor-positive invasive breast cancer. *J Clin Oncol* 2009;27:5312-5318. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19738113>.
472. Pierce JP, Stefanick ML, Flatt SW, et al. Greater survival after breast cancer in physically active women with high vegetable-fruit intake regardless of obesity. *J Clin Oncol* 2007;25:2345-2351. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17557947>.
473. Chlebowski RT BG, et al. . Final survival analysis from the randomized Women's Intervention Nutrition Study (WINS) evaluating dietary intervention as adjuvant breast cancer therapy [abstract]. San Antonio Breast Cancer Symposium 2014;Abstract S5-08. Available at:
474. de Glas NA, Fontein DB, Bastiaannet E, et al. Physical activity and survival of postmenopausal, hormone receptor-positive breast cancer patients: results of the Tamoxifen Exemestane Adjuvant Multicenter Lifestyle study. *Cancer* 2014;120:2847-2854. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24840230>.
475. Courneya KS, Segal RJ, McKenzie DC, et al. Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. *Med Sci Sports Exerc* 2014;46:1744-1751. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24633595>.
476. Mishra SI, Scherer RW, Snyder C, et al. Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev* 2012;8:CD008465. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22895974>.
477. Eubank WB, Mankoff D, Bhattacharya M, et al. Impact of FDG PET on defining the extent of disease and on the treatment of patients with recurrent or metastatic breast cancer. *AJR Am J Roentgenol* 2004;183:479-486. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15269044>.
478. Moon DH, Maddahi J, Silverman DH, et al. Accuracy of whole-body fluorine-18-FDG PET for the detection of recurrent or metastatic breast carcinoma. *J Nucl Med* 1998;39:431-435. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9529287>.
479. Arslan C, Sari E, Aksoy S, Altundag K. Variation in hormone receptor and HER-2 status between primary and metastatic breast cancer: review of the literature. *Expert Opin Ther Targets* 2011;15:21-30. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21105765>.

480. Puzstai L, Viale G, Kelly CM, Hudis CA. Estrogen and HER-2 receptor discordance between primary breast cancer and metastasis. *Oncologist* 2010;15:1164-1168. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21041379>.

481. Bogina G, Bortesi L, Marconi M, et al. Comparison of hormonal receptor and HER-2 status between breast primary tumours and relapsing tumours: clinical implications of progesterone receptor loss. *Virchows Arch* 2011;459:1-10. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21643691>.

482. Fabi A, Di Benedetto A, Metro G, et al. HER2 protein and gene variation between primary and metastatic breast cancer: significance and impact on patient care. *Clin Cancer Res* 2011;17:2055-2064. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21307144>.

483. Karlsson E, Lindström LS, Wilking U, et al. Discordance in hormone receptor status in breast cancer during tumor progression [abstract]. *J Clin Oncol* 2010;28:(15_Suppl):Abstract 1009. Available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=47385.

484. Sari E, Guler G, Hayran M, et al. Comparative study of the immunohistochemical detection of hormone receptor status and HER-2 expression in primary and paired recurrent/metastatic lesions of patients with breast cancer. *Med Oncol* 2011;28:57-63. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20099049>.

485. Simmons C, Miller N, Geddie W, et al. Does confirmatory tumor biopsy alter the management of breast cancer patients with distant metastases? *Ann Oncol* 2009;20:1499-1504. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19299408>.

486. Gong Y, Booser DJ, Sneige N. Comparison of HER-2 status determined by fluorescence in situ hybridization in primary and metastatic breast carcinoma. *Cancer* 2005;103:1763-1769. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15786420>.

487. Tapia C, Savic S, Wagner U, et al. HER2 gene status in primary breast cancers and matched distant metastases. *Breast Cancer Res* 2007;9. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17511881>.

488. Lindstrom LS, Karlsson E, Wilking UM, et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. *J Clin Oncol* 2012;30:2601-2608. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22711854>.

489. Dieci MV, Barbieri E, Piacentini F, et al. Discordance in receptor status between primary and recurrent breast cancer has a prognostic impact: a single-institution analysis. *Ann Oncol* 2013;24:101-108. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23002281>.

490. Aurilio G, Disalvatore D, Pruneri G, et al. A meta-analysis of oestrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 discordance between primary breast cancer and metastases. *Eur J Cancer* 2014;50:277-289. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24269135>.

491. Katz A, Strom EA, Buchholz TA, et al. Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: implications for postoperative irradiation. *J Clin Oncol* 2000;18:2817-2827. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10920129>.

492. van Tienhoven G, Voogd AC, Peterse JL, et al. Prognosis after treatment for loco-regional recurrence after mastectomy or breast conserving therapy in two randomised trials (EORTC 10801 and DBCG-82TM). EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group. *Eur J Cancer* 1999;35:32-38. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10211085>.

493. Cox CE, Furman BT, Kiluk JV, et al. Use of reoperative sentinel lymph node biopsy in breast cancer patients. *J Am Coll Surg* 2008;207:57-61. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18589362>.

494. Aebi S, Gelber S, Anderson SJ, et al. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. *Lancet Oncol* 2014;15:156-163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24439313>.
495. Higgins MJ, Wolff AC. Therapeutic options in the management of metastatic breast cancer. *Oncology (Williston Park)* 2008;22:614-623. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18561551>.
496. Gralow JR, Biermann JS, Farooki A, et al. NCCN task force report: Bone health in cancer care. *J Natl Compr Canc Netw* 2009;7 Suppl 3:1-1. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19555589>.
497. Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol* 2003;21:4042-4057. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12963702>.
498. Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: A randomized, double-blind study. *J Clin Oncol* 2010;28:5132-5139. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21060033>.
499. Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. *Cell* 1998;93:165-176. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9568710>.
500. Woo S-B, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006;144:753-761. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16702591>.
501. Ali SM, Esteva FJ, Hortobagyi G, et al. Safety and efficacy of bisphosphonates beyond 24 months in cancer patients. *J Clin Oncol* 2001;19:3434-3437. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11454892>.
502. Berenson JR, Rosen LS, Howell A, et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. *Cancer* 2001;91:1191-1200. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11283917>.
503. Conte PF, Latreille J, Mauriac L, et al. Delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. The Aredia Multinational Cooperative Group. *J Clin Oncol* 1996;14:2552-2559. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8823335>.
504. Hortobagyi GN, Theriault RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. *J Clin Oncol* 1998;16:2038-2044. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9626201>.
505. Theriault RL. The role of bisphosphonates in breast cancer. *J Natl Compr Canc Netw* 2003;1:232-241. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19768882>.
506. Theriault RL, Lipton A, Hortobagyi GN, et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. *J Clin Oncol* 1999;17:846-854. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10071275>.
507. Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J* 2001;7:377-387. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11693896>.

508. Rosen LS, Gordon DH, Dugan W, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer* 2004;100:36-43. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/14692022>.

509. Diel IJ, Body JJ, Lichinitser MR, et al. Improved quality of life after long-term treatment with the bisphosphonate ibandronate in patients with metastatic bone disease due to breast cancer. *Eur J Cancer* 2004;40:1704-1712. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15251160>.

510. Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N Engl J Med* 1996;335:1785-1791. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/8965890>.

511. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer* 2000;88:1082-1090. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10699899>.

512. McLachlan SA, Cameron D, Murray R, et al. Safety of oral ibandronate in the treatment of bone metastases from breast cancer : long-term follow-up experience. *Clin Drug Investig* 2006;26:43-48.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17163234>.

513. Pecherstorfer M, Rivkin S, Body J-J, et al. Long-term safety of intravenous ibandronic acid for up to 4 years in metastatic breast cancer: an open-label trial. *Clin Drug Investig* 2006;26:315-322.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17163265>.

514. Hortobagyi GN, Lipton A, Chew HK, et al. Efficacy and safety of continued zoledronic acid every 4 weeks versus every 12 weeks in women with bone metastases from breast cancer: Results of the OPTIMIZE-2 trial. *ASCO Meeting Abstracts* 2014;32:LBA9500.

Available at:

http://meeting.ascopubs.org/cgi/content/abstract/32/18_suppl/LBA9500.

515. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer* 2003;98:1735-1744. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/14534891>.

516. Wilkinson GS, Kuo Y-F, Freeman JL, Goodwin JS. Intravenous bisphosphonate therapy and inflammatory conditions or surgery of the jaw: a population-based analysis. *J Natl Cancer Inst* 2007;99:1016-1024. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17596574>.

517. Klijn JG, Blamey RW, Boccardo F, et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001;19:343-353.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11208825>.

518. Bonnetterre J, Thurlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol* 2000;18:3748-3757. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11078487>.

519. Nabholz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. *J Clin Oncol* 2000;18:3758-3767. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11078488>.

520. Paridaens RJ, Dirix LY, Beex LV, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer

Cooperative Group. J Clin Oncol 2008;26:4883-4890. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18794551>.

521. Vergote I, Bonnetterre J, Thurlimann B, et al. Randomised study of anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women. Eur J Cancer 2000;36 Suppl 4:S84-85. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11056332>.

522. Gibson L, Lawrence D, Dawson C, Bliss J. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database Syst Rev 2009. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19821307>.

523. Howell A, Robertson JFR, Quaresma Albano J, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol 2002;20:3396-3403. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12177099>.

524. Osborne CK, Pippen J, Jones SE, et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol 2002;20:3386-3395. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12177098>

525. Robertson JF, Llombart-Cussac A, Rolski J, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. J Clin Oncol 2009;27:4530-4535. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19704066>.

526. Robertson JF, Lindemann JP, Llombart-Cussac A, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized 'FIRST' study. Breast Cancer Res Treat 2012;136:503-511. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23065000>.

527. Ellis MJ, Llombart-Cussac A, Feltl D, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-Line treatment of advanced breast cancer: Overall survival analysis from the phase II FIRST study. J Clin Oncol 2015;33:3781-3787. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26371134>.

528. Ingle JN, Suman VJ, Rowland KM, et al. Fulvestrant in women with advanced breast cancer after progression on prior aromatase inhibitor therapy: North Central Cancer Treatment Group Trial N0032. J Clin Oncol 2006;24:1052-1056. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16505423>.

529. Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol 2008;26:1664-1670. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18316794>.

530. Di Leo A, Jerusalem G, Petruzella L, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. J Clin Oncol 2010;28:4594-4600. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20855825>.

531. Di Leo A, Jerusalem G, Petruzella L, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. J Natl Cancer Inst 2014;106:djt337. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24317176>.

532. Bergh J, Jonsson PE, Lidbrink EK, et al. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. J Clin Oncol 2012;30:1919-1925. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22370325>.

533. Mehta RS, Barlow WE, Albain KS, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. *N Engl J Med* 2012;367:435-444. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22853014>.

534. Johnston SR, Kilburn LS, Ellis P, et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. *Lancet Oncol* 2013;14:989-998. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23902874>.

535. Buzdar A, Douma J, Davidson N, et al. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. *J Clin Oncol* 2001;19:3357-3366. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11454883>.

536. Buzdar AU, Jonat W, Howell A, et al. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on a combined analysis of data from two mature phase III trials. *Arimidex Study Group. Cancer* 1998;83:1142-1152. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9740079>.

537. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol* 2015;16:25-35. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25524798>.

538. Turner NC, Ro J, Andre F, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2015;373:209-219. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26030518>.

539. Johnston S, Pippen J, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol* 2009;27:5538-5546. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19786658>.

540. Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol* 2009;27:5529-5537. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19786670>.

541. Bachelot T, Bourgier c, Cropet C, et al. TAMRAD: A GINECO randomized phase II trial of everolimus in combination with tamoxifen versus tamoxifen alone in patients (pts) with hormone-receptor positive, HER2 negative metastatic breast Cancer (MBC) with prior exposure to aromatase inhibitors (AI) [abstract]. *Cancer Res* 2010;70(24 Supplement):Abstract: S1-6 Available at:

http://cancerres.aacrjournals.org/cgi/content/meeting_abstract/70/24_MeetingAbstracts/S1-6.

542. Chow L, Sun Y, Jassem J, et al. Phase 3 study of temsirolimus with letrozole or letrozole alone in postmenopausal women with locally advanced or metastatic breast cancer. *Breast Cancer Res Treat*. 2006;100(Suppl 1):6091. Available at:

543. Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. *Adv Ther* 2013;30:870-884. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24158787>.

544. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012;366:520-529. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22149876>.

545. Pritchard KI, Burris HA, 3rd, Ito Y, et al. Safety and efficacy of everolimus with exemestane vs. exemestane alone in elderly patients with HER2-negative, hormone receptor-positive breast cancer in BOLERO-2. *Clin Breast Cancer* 2013;13:421-432 e428. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24267730>.

546. Buzdar A, Jonat W, Howell A, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. Arimidex Study Group. *J Clin Oncol* 1996;14:2000-2011. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8683230>.

547. Dombernowsky P, Smith I, Falkson G, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol* 1998;16:453-461. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9469328>.

548. Lonning PE, Bajetta E, Murray R, et al. Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: a phase II trial. *J Clin Oncol* 2000;18:2234-2244. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10829043>.

549. Albain KS, Nag S, Calderillo-Ruiz G, et al. Global phase III study of gemcitabine plus paclitaxel (GT) vs. paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival [Abstract]. *J Clin Oncol* 2004;22:Abstract 510 Available at: http://meeting.ascopubs.org/cgi/content/abstract/22/14_suppl/510.

550. Carrick S, Parker S, Wilcken N, et al. Single agent versus combination chemotherapy for metastatic breast cancer. *Cochrane Database Syst Rev* 2005. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15846660>.

551. O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J*

Clin Oncol 2002;20:2812-2823. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12065558>.

552. Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J Clin Oncol* 2003;21:588-592. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12586793>.

553. Gennari A, Stockler M, Puntoni M, et al. Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. *J Clin Oncol* 2011;29:2144-2149. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21464403>.

554. Falkson G, Gelman RS, Pandya KJ, et al. Eastern Cooperative Oncology Group randomized trials of observation versus maintenance therapy for patients with metastatic breast cancer in complete remission following induction treatment. *J Clin Oncol* 1998;16:1669-1676. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9586877>.

555. Muss HB, Case LD, Richards F, et al. Interrupted versus continuous chemotherapy in patients with metastatic breast cancer. The Piedmont Oncology Association. *N Engl J Med* 1991;325:1342-1348. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1922236>.

556. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet* 2011;377:914-923. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21376385>.

557. Kaufman PA, Awada A, Twelves C, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol* 2015;33:594-601. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25605862>.

558. Roche H, Yelle L, Coggiotti F, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, as first-line therapy in patients with metastatic breast cancer previously treated with anthracycline chemotherapy. *J Clin Oncol* 2007;25:3415-3420. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17606972>.

559. Thomas E, Taberner J, Fornier M, et al. Phase II clinical trial of ixabepilone (BMS-247550), an epothilone B analog, in patients with taxane-resistant metastatic breast cancer. *J Clin Oncol* 2007;25:3399-3406. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17606975>.

560. Perez EA, Lerzo G, Pivot X, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine. *J Clin Oncol* 2007;25:3407-3414. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17606974>.

561. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007;357:2666-2676. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18160686>.

562. Miles DW, Chan A, Dirix LY, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol* 2010;28:3239-3247. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20498403>.

563. Robert NJ, Dieras V, Glaspy J, et al. RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC) [abstract]. *J Clin Oncol* 2009;27(Suppl 15):Abstract 1005. Available at: <http://meeting.ascopubs.org/cgi/content/abstract/27/15S/1005>.

564. Robert NJ, Dieras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth

factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J Clin Oncol* 2011;29:1252-1260. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21383283>.

565. O'Shaughnessy J, Miles D, Gray RJ, et al. A meta-analysis of overall survival data from three randomized trials of bevacizumab (BV) and first-line chemotherapy as treatment for patients with metastatic breast cancer (MBC) [abstract]. *J Clin Oncol* 2010;28(Suppl 15):Abstract 1005. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/1005.

566. BRIEFING BOOK, ONCOLOGY DRUGS ADVISORY COMMITTEE MEETING, AVASTIN (Bevacizumab). Genentech, Inc., A Member of the Roche Group; 2010. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM219228.pdf>.

567. Seidman A, Berry DA, Cirincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *J Clin Oncol* 2008;26:1642-1649. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18375893>.

568. Carlson RW, Moench SJ, Hammond ME, et al. HER2 testing in breast cancer: NCCN Task Force report and recommendations. *J Natl Compr Canc Netw* 2006;4 Suppl 3:1-22. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16813731>.

569. Roche PC, Suman VJ, Jenkins RB, et al. Concordance between local and central laboratory HER2 testing in the breast intergroup trial N9831. *J Natl Cancer Inst* 2002;94:855-857. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12048274>.

570. Wolff AC, Hammond MEH, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing

in breast cancer. J Clin Oncol 2007;25:118-145. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17159189>.

571. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109-119. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22149875>.

572. Ewer M, Baselga J, Clark E, et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in the CLEOPATRA study [abstract]. J Clin Oncol 2012;30 (Suppl_15):Abstract 533. Available at:
http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=114&abstractID=95049.

573. Cortés J, Baselga J, Im Y, et al. Quality of life assessment in CLEOPATRA, a phase III study combining pertuzumab with trastuzumab and docetaxel in metastatic breast cancer [abstract]. J Clin Oncol 2012 30 (Suppl_15) Abstract 598 Available at:
http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=114&abstractID=95084.

574. Datko F, D'Andrea G, Dickler M, et al. Phase II study of pertuzumab, trastuzumab, and weekly paclitaxel in patients with metastatic HER2-overexpressing metastatic breast cancer [abstract]. Cancer Research 2012;72:Abstract P5-18-20. Available at:
http://cancerres.aacrjournals.org/cgi/content/meeting_abstract/72/24_MeetingAbstracts/P5-18-20.

575. Paclitaxel, trastuzumab, and pertuzumab in the treatment of metastatic HER2-positive breast cancer (Clinical Trial ID: NCT01276041). Available at:
<http://clinicaltrials.gov/show/NCT01276041>.

576. Perez E, Lopez-Vega J, Mastro L, et al. A combination of pertuzumab, trastuzumab, and vinorelbine for first-line treatment of patients with HER2-positive metastatic breast cancer: An open-label, two-cohort, phase II study (VELVET) [abstract]. J Clin Oncol 2012;30

(Suppl_15):Asbtract TPS653. Available at:
http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=114&abstractID=93917.

577. Burstein HJ, Keshaviah A, Baron AD, et al. Trastuzumab plus vinorelbine or taxane chemotherapy for HER2-overexpressing metastatic breast cancer: the trastuzumab and vinorelbine or taxane study. Cancer 2007;110:965-972. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17614302>.

578. Robert N, Leyland-Jones B, Asmar L, et al. Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. J Clin Oncol 2006;24:2786-2792. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16782917>.

579. Schaller G, Bangemann N, Weber J, et al. Efficacy and safety of trastuzumab plus capecitabine in a German multicentre phase II study of pre-treated metastatic breast cancer [abstract]. J Clin Oncol 2005;23(Suppl 16):Abstract 717. Available at:
http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/717.

580. Yamamoto D, Iwase S, Kitamura K, et al. A phase II study of trastuzumab and capecitabine for patients with HER2-overexpressing metastatic breast cancer: Japan Breast Cancer Research Network (JBCRN) 00 Trial. Cancer Chemother Pharmacol 2008;61:509-514. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17516068>.

581. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20:1215-1221. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11870163>.

582. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783-1791. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23020162>.

583. Ellis PA, Barrios CH, Eiermann W, et al. Phase III, randomized study of trastuzumab emtansine (T-DM1) {+/-} pertuzumab (P) vs

trastuzumab + taxane (HT) for first-line treatment of HER2-positive MBC: Primary results from the MARIANNE study. ASCO Meeting Abstracts 2015;33:507. Available at:

http://meeting.ascopubs.org/cgi/content/abstract/33/15_suppl/507.

584. Bartsch R, Wenzel C, Altorjai G, et al. Capecitabine and trastuzumab in heavily pretreated metastatic breast cancer. J Clin Oncol 2007;25:3853-3858. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17679724>.

585. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol 2009;27:1999-2006. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19289619>.

586. Von Minckwitz G, Zielinski C, Maarteense E, et al. Capecitabine vs. capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: The TBP phase III study (GBG 26/BIG 3-05) [abstract]. J Clin Oncol 2008;26(Suppl 15):Abstract 1025. Available at:

http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/1025.

587. Baselga J, Gelmon KA, Verma S, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. J Clin Oncol 2010;28:1138-1144. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20124182>.

588. Cortes J, Fumoleau P, Bianchi GV, et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2012;30:1594-1600. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22393084>.

589. Geyer C, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med

2006;355:2733-2743. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17192538>.

590. Cameron D, Casey M, Oliva C, et al. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. Oncologist 2010;15:924-934. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20736298>.

591. Blackwell KL, Burstein HJ, Storniolo AM, et al. Randomized study of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol 2010;28:1124-1130. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20124187>.

592. Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol 2012;30:2585-2592. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22689807>.

593. Hortobagyi GN. Multidisciplinary management of advanced primary and metastatic breast cancer. Cancer 1994;74:416-423. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/8004615>.

594. Babiera GV, Rao R, Feng L, et al. Effect of primary tumor extirpation in breast cancer patients who present with stage IV disease and an intact primary tumor. Ann Surg Oncol 2006;13:776-782. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16614878>.

595. Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? Surgery 2002;132:620-626. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12407345>.

596. Rao R, Feng L, Kuerer HM, et al. Timing of surgical intervention for the intact primary in stage IV breast cancer patients. Ann Surg Oncol 2008;15:1696-1702. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18357493>.

597. Rapiti E, Verkooijen HM, Vlastos G, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. *J Clin Oncol* 2006;24:2743-2749. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16702580>.
598. Morrow M, Goldstein L. Surgery of the primary tumor in metastatic breast cancer: closing the barn door after the horse has bolted? *J Clin Oncol* 2006;24:2694-2696. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16702578>.
599. Olson JA, Marcom PK. Benefit or bias? The role of surgery to remove the primary tumor in patients with metastatic breast cancer. *Ann Surg* 2008;247:739-740. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18438109>.
600. Badwe R, Parmar V, Hawaldar R, et al. Surgical removal of primary breast tumor and axillary lymph nodes in women with metastatic breast cancer at first presentation: a randomized controlled trial. Presented at: 2013 [abstract]. San Antonio Breast Cancer Symposium 2013:Abstract S2-02. Available at:
601. Soran A, Ozmen V, Ozbas S, et al. Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (protocol MF07-01) [abstract]. San Antonio Breast Cancer Symposium 2013:Abstract S2-03. Available at:
602. Jones EL, Oleson JR, Prosnitz LR, et al. Randomized trial of hyperthermia and radiation for superficial tumors. *J Clin Oncol* 2005;23:3079-3085. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15860867>.
603. Vernon CC, Hand JW, Field SB, et al. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. International Collaborative Hyperthermia Group. *Int J Radiat Oncol Biol Phys* 1996;35:731-744. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8690639>.
604. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-247. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19097774>.
605. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207-214. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7459811>.
606. Smerage JB, Barlow WE, Hortobagyi GN, et al. Circulating tumor cells and response to chemotherapy in metastatic breast cancer: SWOG S0500. *J Clin Oncol* 2014;32:3483-3489. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24888818>.
607. Sakorafas GH, Blanchard K, Sarr MG, Farley DR. Paget's disease of the breast. *Cancer Treat Rev* 2001;27:9-18. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11237774>.
608. Kollmorgen DR, Varanasi JS, Edge SB, Carson WE. Paget's disease of the breast: a 33-year experience. *J Am Coll Surg* 1998;187:171-177. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9704964>.
609. Marcus E. The management of Paget's disease of the breast. *Curr Treat Options Oncol* 2004;5:153-160. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14990209>.
610. Morrogh M, Morris EA, Liberman L, et al. MRI identifies otherwise occult disease in select patients with Paget disease of the nipple. *J Am Coll Surg* 2008;206:316-321. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18222386>.
611. Frei KA, Bonel HM, Pelte M-F, et al. Paget disease of the breast: findings at magnetic resonance imaging and histopathologic correlation. *Invest Radiol* 2005;40:363-367. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15905723>.

612. Bijker N, Rutgers EJ, Duchateau L, et al. Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. *Cancer* 2001;91:472-477. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11169928>.

613. Kawase K, Dimaio DJ, Tucker SL, et al. Paget's disease of the breast: there is a role for breast-conserving therapy. *Ann Surg Oncol* 2005;12:391-397. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15915373>.

614. Marshall JK, Griffith KA, Haffty BG, et al. Conservative management of Paget disease of the breast with radiotherapy: 10- and 15-year results. *Cancer* 2003;97:2142-2149. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12712465>.

615. Pierce LJ, Haffty BG, Solin LJ, et al. The conservative management of Paget's disease of the breast with radiotherapy. *Cancer* 1997;80:1065-1072. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9305706>.

616. Singh A, Sutton RJ, Baker CB, Sacks NP. Is mastectomy overtreatment for Paget's disease of the nipple? *Breast* 1999;8:191-194. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14731439>.

617. Laronga C, Hasson D, Hoover S, et al. Paget's disease in the era of sentinel lymph node biopsy. *Am J Surg* 2006;192:481-483. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16978954>.

618. Sukumvanich P, Bentrem DJ, Cody HS, et al. The role of sentinel lymph node biopsy in Paget's disease of the breast. *Ann Surg Oncol* 2007;14:1020-1023. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17195914>.

619. Telli ML, Horst KC, Guardino AE, et al. Phyllodes tumors of the breast: natural history, diagnosis, and treatment. *J Natl Compr Canc Netw* 2007;5:324-330. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17439760>.

620. Anderson BO, Lawton TJ, Lehman CD, Moe RE. Phyllodes tumors. In: Harris JR, Lippman ME, Morrow M, Osborne CK, eds. *Diseases of the Breast* (ed 3rd). Philadelphia: Lippincott Williams & Wilkins; 2004.

621. Salvadori B, Cusumano F, Del Bo R, et al. Surgical treatment of phyllodes tumors of the breast. *Cancer* 1989;63:2532-2536. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2541890>.

622. Birch JM, Alston RD, McNally RJ, et al. Relative frequency and morphology of cancers in carriers of germline TP53 mutations. *Oncogene* 2001;20:4621-4628. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11498785>.

623. Chaney AW, Pollack A, McNeese MD, et al. Primary treatment of cystosarcoma phyllodes of the breast. *Cancer* 2000;89:1502-1511. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11013364>.

624. Mangi AA, Smith BL, Gadd MA, et al. Surgical management of phyllodes tumors. *Arch Surg* 1999;134:487-492. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10323420>.

625. Pandey M, Mathew A, Kattoor J, et al. Malignant phyllodes tumor. *Breast J* 2001;7:411-416. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11843853>.

626. Tse GMK, Lee CS, Kung FYL, et al. Hormonal receptors expression in epithelial cells of mammary phyllodes tumors correlates with pathologic grade of the tumor: a multicenter study of 143 cases. *Am J Clin Pathol* 2002;118:522-526. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12375638>.

627. Smith LH, Dalrymple JL, Leiserowitz GS, et al. Obstetrical deliveries associated with maternal malignancy in California, 1992 through 1997. *Am J Obstet Gynecol* 2001;184:1504-1512. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11408874>.

628. Gwyn K, Theriault R. Breast cancer during pregnancy. *Oncology (Williston Park)* 2001;15:39-46. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11271981>.
629. Middleton LP, Amin M, Gwyn K, et al. Breast carcinoma in pregnant women: assessment of clinicopathologic and immunohistochemical features. *Cancer* 2003;98:1055-1060. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12942575>.
630. Yang WT, Dryden MJ, Gwyn K, et al. Imaging of breast cancer diagnosed and treated with chemotherapy during pregnancy. *Radiology* 2006;239:52-60. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16484353>.
631. Kuerer HM, Gwyn K, Ames FC, Theriault RL. Conservative surgery and chemotherapy for breast carcinoma during pregnancy. *Surgery* 2002;131:108-110. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11812971>.
632. Annane K, Bellocq JP, Brettes JP, Mathelin C. Infiltrative breast cancer during pregnancy and conservative surgery. *Fetal Diagn Ther* 2005;20:442-444. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16113569>.
633. Khera SY, Kiluk JV, Hasson DM, et al. Pregnancy-associated breast cancer patients can safely undergo lymphatic mapping. *Breast J* 2008;14:250-254. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18476883>.
634. Mondì MM, Cuenca RE, Ollila DW, et al. Sentinel lymph node biopsy during pregnancy: initial clinical experience. *Ann Surg Oncol* 2007;14:218-221. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17066225>.
635. Filippakis GM, Zografos G. Contraindications of sentinel lymph node biopsy: are there any really? *World J Surg Oncol* 2007;5:10. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17261174>.
636. Gentilini O, Cremonesi M, Trifiro G, et al. Safety of sentinel node biopsy in pregnant patients with breast cancer. *Ann Oncol* 2004;15:1348-1351. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15319240>.
637. Keleher A, Wendt R, Delpassand E, et al. The safety of lymphatic mapping in pregnant breast cancer patients using Tc-99m sulfur colloid. *Breast J* 2004;10:492-495. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15569204>.
638. Pandit-Taskar N, Dauer LT, Montgomery L, et al. Organ and fetal absorbed dose estimates from 99mTc-sulfur colloid lymphoscintigraphy and sentinel node localization in breast cancer patients. *J Nucl Med* 2006;47:1202-1208. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16818956>.
639. Germann N, Goffinet F, Goldwasser F. Anthracyclines during pregnancy: embryo-fetal outcome in 160 patients. *Ann Oncol* 2004;15:146-150. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14679135>.
640. Johnson PH, Gwyn K, Gordon N, et al. The treatment of pregnant women with breast cancer and the outcomes of the children exposed to chemotherapy in utero [abstract]. *J Clin Oncol* 2005;23(Suppl 16):Abstract 540. Available at: http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/540.
641. Doll DC, Ringenberg QS, Yarbro JW. Antineoplastic agents and pregnancy. *Semin Oncol* 1989;16:337-346. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2678485>.
642. Ebert U, Loffler H, Kirch W. Cytotoxic therapy and pregnancy. *Pharmacol Ther* 1997;74:207-220. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9336023>.
643. Hahn KME, Johnson PH, Gordon N, et al. Treatment of pregnant breast cancer patients and outcomes of children exposed to

chemotherapy in utero. *Cancer* 2006;107:1219-1226. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16894524>.

644. Gainford MC, Clemons M. Breast cancer in pregnancy: are taxanes safe? *Clinical Oncol (R Coll Radiol)* 2006;18:159. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16523825>.

645. Garcia-Manero M, Royo MP, Espinos J, et al. Pregnancy associated breast cancer. *Eur J Surg Oncol* 2009;35:215-218. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18550321>.

646. Gonzalez-Angulo AM, Walters RS, Carpenter RJ, et al. Paclitaxel chemotherapy in a pregnant patient with bilateral breast cancer. *Clin Breast Cancer* 2004;5:317-319. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15507181>.

647. Mir O, Berveiller P, Ropert S, et al. Emerging therapeutic options for breast cancer chemotherapy during pregnancy. *Ann Oncol* 2008;19:607-613. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17921242>.

648. Bader AA, Schlembach D, Tamussino KF, et al. Anhydramnios associated with administration of trastuzumab and paclitaxel for metastatic breast cancer during pregnancy. *Lancet Oncol* 2007;8:79-81. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17196514>.

649. Fanale MA, Uyei AR, Theriault RL, et al. Treatment of metastatic breast cancer with trastuzumab and vinorelbine during pregnancy. *Clin Breast Cancer* 2005;6:354-356. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16277887>.

650. Pant S, Landon MB, Blumenfeld M, et al. Treatment of breast cancer with trastuzumab during pregnancy. *J Clin Oncol* 2008;26:1567-1569. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18349415>.

651. Sekar R, Stone PR. Trastuzumab use for metastatic breast cancer in pregnancy. *Obstet Gynecol* 2007;110:507-510. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17666645>.

652. Shrim A, Garcia-Bournissen F, Maxwell C, et al. Favorable pregnancy outcome following Trastuzumab (Herceptin) use during pregnancy--Case report and updated literature review. *Reprod Toxicol* 2007;23:611-613. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17399946>.

653. Waterston AM, Graham J. Effect of Adjuvant Trastuzumab on Pregnancy. *J Clin Oncol* 2006;24:321-322. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16401684>.

654. Watson WJ. Herceptin (trastuzumab) therapy during pregnancy: association with reversible anhydramnios. *Obstet Gynecol* 2005;105:642-643. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15738038>.

655. Witzel ID, Müller V, Harps E, et al. Trastuzumab in pregnancy associated with poor fetal outcome. *Ann Oncol* 2008;19:191-192. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18084047>.

656. Kelly H, Graham M, Humes E, et al. Delivery of a healthy baby after first-trimester maternal exposure to lapatinib. *Clin Breast Cancer* 2006;7:339-341. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17092403>.

657. Dawood, S, Cristofanilli M. What progress have we made in managing inflammatory breast cancer? *Oncology* 2007;21:673-679. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17564325>

658. Jaiyesimi IA, Buzdar AU, Hortobagyi G. Inflammatory breast cancer: a review. *J Clin Oncol* 1992;10:1014-1024. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1588366>.

659. Bertucci F, Finetti P, Rougemont J, et al. Gene expression profiling identifies molecular subtypes of inflammatory breast cancer. *Cancer Res* 2005;65:2170-2178. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15781628>.

660. Van Laere SJ, Van den Eynden GG, Van der Auwera I, et al. Identification of cell-of-origin breast tumor subtypes in inflammatory breast cancer by gene expression profiling. *Breast Cancer Res Treat* 2006;95:243-255. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16261404>.

661. Zell JA, Tsang WY, Taylor TH, et al. Prognostic impact of human epidermal growth factor-like receptor 2 and hormone receptor status in inflammatory breast cancer (IBC): analysis of 2,014 IBC patient cases from the California Cancer Registry. *Breast Cancer Res* 2009;11:R9. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19228416>.

662. Parton M, Dowsett M, Ashley S, et al. High incidence of HER-2 positivity in inflammatory breast cancer. *Breast* 2004;13:97-103.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15019688>.

663. Haagensen CD. *Inflammatory Carcinoma*. Diseases of the Breast. Philadelphia: WB Saunders; 1956:488-498.

664. Cristofanilli M, Valero V, Buzdar AU, et al. Inflammatory breast cancer (IBC) and patterns of recurrence: understanding the biology of a unique disease. *Cancer* 2007;110:1436-1444. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17694554>.

665. Panades M, Olivotto IA, Speers CH, et al. Evolving treatment strategies for inflammatory breast cancer: a population-based survival analysis. *J Clin Oncol* 2005;23:1941-1950. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15774787>.

666. Dawood S, Ueno NT, Valero V, et al. Differences in survival among women with stage III inflammatory and noninflammatory locally advanced breast cancer appear early: a large population-based study. *Cancer* 2011;117:1819-1826. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21509759>.

667. Hance KW, Anderson WF, Devesa SS, et al. Trends in inflammatory breast carcinoma incidence and survival: the surveillance, epidemiology, and end results program at the National Cancer Institute.

J Natl Cancer Inst 2005;97:966-975. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15998949>.

668. Bleicher RJ, Morrow M. Inflammatory breast cancer: Still poorly characterized. The Dawood/Cristofanilli article reviewed. *Oncology* 2007;21:679-680. Available at: <http://www.cancernetwork.com/breast-cancer/content/article/10165/61508>.

669. Nguyen DM, Sam K, Tsimelzon A, et al. Molecular heterogeneity of inflammatory breast cancer: a hyperproliferative phenotype. *Clin Cancer Res* 2006;12:5047-5054. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16951220>.

670. Carkaci S, Macapinlac HA, Cristofanilli M, et al. Retrospective study of 18F-FDG PET/CT in the diagnosis of inflammatory breast cancer: preliminary data. *J Nucl Med* 2009;50:231-238. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19164229>.

671. Chia S, Swain SM, Byrd DR, Mankoff DA. Locally advanced and inflammatory breast cancer. *J Clin Oncol* 2008;26:786-790. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18258987>.

672. Fleming RY, Asmar L, Buzdar AU, et al. Effectiveness of mastectomy by response to induction chemotherapy for control in inflammatory breast carcinoma. *Ann Surg Oncol* 1997;4:452-461.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9309333>.

673. Ueno NT, Buzdar AU, Singletary SE, et al. Combined-modality treatment of inflammatory breast carcinoma: twenty years of experience at M. D. Anderson Cancer Center. *Cancer Chemother Pharmacol* 1997;40:321-329. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9225950>.

674. Cristofanilli M, Gonzalez-Angulo AM, Buzdar AU, et al. Paclitaxel improves the prognosis in estrogen receptor negative inflammatory breast cancer: the M. D. Anderson Cancer Center experience. *Clin Breast Cancer* 2004;4:415-419. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15023242>.

675. Kim T, Lau J, Erban J. Lack of uniform diagnostic criteria for inflammatory breast cancer limits interpretation of treatment outcomes: a systematic review. *Clin Breast Cancer* 2006;7:386-395. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17239263>.
676. Hennessy BT, Gonzalez-Angulo AM, Hortobagyi GN, et al. Disease-free and overall survival after pathologic complete disease remission of cytologically proven inflammatory breast carcinoma axillary lymph node metastases after primary systemic chemotherapy. *Cancer* 2006;106:1000-1006. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16444747>.
677. Dawood S, Broglio K, Gong Y, et al. Prognostic significance of HER-2 status in women with inflammatory breast cancer. *Cancer* 2008;112:1905-1911. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18300243>.
678. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *The Lancet* 2010;375:377-384. Available at: <http://linkinghub.elsevier.com/retrieve/pii/S0140673609619644>.
679. Hurley J, Doliny P, Reis I, et al. Docetaxel, cisplatin, and trastuzumab as primary systemic therapy for human epidermal growth factor receptor 2-positive locally advanced breast cancer. *J Clin Oncol* 2006;24:1831-1838. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16549824>.
680. Burstein HJ, Harris LN, Gelman R, et al. Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2 overexpressing stage II or III breast cancer: a pilot study. *J Clin Oncol* 2003;21:46-53. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12506169>.
681. Limentani SA, Brufsky AM, Erban JK, et al. Phase II study of neoadjuvant docetaxel, vinorelbine, and trastuzumab followed by surgery and adjuvant doxorubicin plus cyclophosphamide in women with human epidermal growth factor receptor 2-overexpressing locally advanced breast cancer. *J Clin Oncol* 2007;25:1232-1238. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17296975>.
682. Van Pelt AE, Mohsin S, Elledge RM, et al. Neoadjuvant trastuzumab and docetaxel in breast cancer: preliminary results. *Clin Breast Cancer* 2003;4:348-353. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14715110>.
683. Bousсен H, Cristofanilli M, Zaks T, et al. Phase II study to evaluate the efficacy and safety of neoadjuvant lapatinib plus paclitaxel in patients with inflammatory breast cancer. *Journal of Clinical Oncology* 2010;28:3248-3255. Available at: <http://jco.ascopubs.org/content/28/20/3248.abstract>.
684. Kell MR, Morrow M. Surgical aspects of inflammatory breast cancer. *Breast Dis* 2005;22:67-73. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16735788>.
685. Stearns V, Ewing CA, Slack R, et al. Sentinel lymphadenectomy after neoadjuvant chemotherapy for breast cancer may reliably represent the axilla except for inflammatory breast cancer. *Ann Surg Oncol* 2002;9:235-242. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11923129>.
686. Motwani SB, Strom EA, Schechter NR, et al. The impact of immediate breast reconstruction on the technical delivery of postmastectomy radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;66:76-82. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16765534>.
687. Blanchard DK, Shetty PB, Hilsenbeck SG, Elledge RM. Association of surgery with improved survival in stage IV breast cancer patients. *Ann Surg* 2008;247:732-738. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18438108>.



688. Olson JA, Morris EA, Van Zee KJ, et al. Magnetic resonance imaging facilitates breast conservation for occult breast cancer. *Ann Surg Oncol* 2000;7:411-415. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10894136>.

689. Varadarajan R, Edge SB, Yu J, et al. Prognosis of occult breast carcinoma presenting as isolated axillary nodal metastasis. *Oncology* 2006;71:456-459. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17690561>.

690. Schelfout K, Kersschot E, Van Goethem M, et al. Breast MR imaging in a patient with unilateral axillary lymphadenopathy and unknown primary malignancy. *Eur Radiol* 2003;13:2128-2132. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12928964>.

691. Bhatia SK, Saclarides TJ, Witt TR, et al. Hormone receptor studies in axillary metastases from occult breast cancers. *Cancer* 1987;59:1170-1172. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3815292>.

692. Bleicher RJ, Morrow M. MRI and breast cancer: role in detection, diagnosis, and staging. *Oncology (Williston Park)* 2007;21:1521-1528, 1530; discussion 1530, 1532-1523. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18077995>.

693. Stomper PC, Waddell BE, Edge SB, Klippenstein DL. Breast MRI in the Evaluation of Patients with Occult Primary Breast Carcinoma. *Breast J* 1999;5:230-234. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11348292>.

694. Buchanan CL, Morris EA, Dorn PL, et al. Utility of breast magnetic resonance imaging in patients with occult primary breast cancer. *Ann Surg Oncol* 2005;12:1045-1053. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16244803>.

Discussion
update in
progress