National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Breast Cancer

Version 1.2022 — November 24, 2021

NCCN.org

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

Continue

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

***Meena S. Moran, MD/Vice-Chair §**
Yale Cancer Center/Smilow Cancer Hospital

Jame Abraham, MD ‡ †
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Rebecca Aft, MD, PhD ¶
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Doreen Agnese, MD ¶
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Kimberly H. Allison, MD ≠
Stanford Cancer Institute

Bethany Anderson, MD §
University of Wisconsin Carbone 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

Helen Chew, MD †
UC Davis Comprehensive Cancer Center

Chau Dang, MD †
Memorial Sloan Kettering Cancer Center

Anthony D. Elias, MD †
University of Colorado 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

Sara A. Hurvitz, MD †
UCLA Jonsson Comprehensive Cancer Center

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

Rachel C. Jankowitz, MD †
Abramson Cancer Center at the University of Pennsylvania

Sara H. Javid, MD ¶
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Jairam Krishnamurthy, MD †
Fred & Pamela Buffet Cancer Center

Marilyn Leitch, MD ¶
UT Southwestern Simmons Comprehensive Cancer Center

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

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

Joanne Mortimer, MD †
City of Hope National Medical Center

Sameer A. Patel, MD Ÿ
Fox Chase Cancer Center

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

Laura H. Rosenberger, MD, MS ¶
Duke Cancer Institute

Hope S. Rugo, MD †
UCSF Helen Diller Family Comprehensive Cancer Center

Amy Sitapati, MD Þ
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

Erica M. Stringer-Reasor, MD † ‡
O'Neal Comprehensive Cancer Center at UAB

Melinda L. Telli, MD † Þ
Stanford Cancer Institute

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

Kari B. Wisinski, MD †
University of Wisconsin Carbone Cancer Center

Jessica S. Young, MD ¶
Roswell Park Comprehensive Cancer Center

NCCN
Rashmi Kumar, PhD
Jennifer Burns, BS

Continue

‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
≠ Pathology
¥ Patient advocacy
§ Radiation oncology/ Radiotherapy
Ÿ Reconstructive surgery
¶ Surgery/Surgical oncology
* Discussion Section Writing Committee

NCCN Guidelines Panel Disclosures

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

NCCN Breast Cancer Panel Members
Summary of Guidelines Updates

Recommendations for Lobular Carcinoma In Situ were removed from the NCCN Guidelines for Breast Cancer,
See NCCN Guidelines for Breast Screening and Diagnosis

Noninvasive Breast Cancer:
Ductal Carcinoma In Situ (DCIS) Workup and Primary Treatment (DCIS-1)
DCIS Postsurgical Treatment and Surveillance/Follow-up (DCIS-2)

Invasive Breast Cancer:
Clinical Stage, Workup (BINV-1)
Locoregional Treatment of cT1–3,cN0 or N+,M0 Disease
- BCS followed by RT (BINV-2)
- Mastectomy followed by RT (BINV-3)

Systemic Adjuvant Treatment
- HR-Positive HER2-Positive Disease (BINV-5)
- HR-Positive HER2-Negative Disease:
  - Postmenopausal Patients (BINV-6)
  - Premenopausal Patients with pT1–3, pN0 (BINV-7)
  - Premenopausal Patients with pT1–3, pN+ (BINV-8)
- HR-Negative HER2-Positive Disease (BINV-9)
- HR-Negative HER2-Negative Disease (BINV-10)
- Favorable Histologies (BINV-11)

Workup Prior to Preoperative Systemic Therapy (BINV-12)
Adjuvant Systemic Therapy After Preoperative Systemic Therapy (BINV-16)
Surveillance/Follow-Up (BINV-17)
Recurrent/Stage IV (M1) Disease (BINV-18)
Treatment of Local and Regional Recurrence (BINV-19)
Systemic Treatment of Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease (BINV-20)
Principles of Biomarker Testing (BINV-A)
Principles of Dedicated Breast MRI Testing (BINV-B)
Fertility and Birth Control (BINV-C)
Considerations for Surgical Axillary Staging (BINV-D)
Axillary Lymph Node Staging (BINV-E)
Margin Status Recommendations After BCS for Invasive Cancers and DCIS (BINV-F)
Special Considerations to Breast Conservation Therapy Requiring RT (BINV-G)
Principles of Breast Reconstruction Following Surgery (BINV-H)
Principles of Radiation Therapy (BINV-I)
Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J)
Adjuvant Endocrine Therapy (BINV-K)
Preoperative/Adjuvant Therapy Regimens (BINV-L)
Principles of Preoperative Systemic Therapy (BINV-M)
Gene Expression Assays for Consideration of Adjuvant Systemic Therapy (BINV-N)
Definition of Menopause (BINV-O)
Systemic Therapy for ER- and/or PR-Positive Recurrent Unresectable (local or regional) or Stage IV (M1) Disease (BINV-P)
Systemic Therapy Regimens for Recurrent Unresectable (local or regional) or Stage IV (M1) Disease (BINV-Q)
Additional Targeted Therapies and Associated Biomarker Testing for Recurrent Unresectable (local or regional) or Stage IV (M1) Disease (BINV-R)
Principles of Monitoring Metastatic Disease (BINV-S)

Special Considerations:
Phyllodes Tumor (PHYLL-1)
Paget Disease (PAGET-1)
Breast Cancer During Pregnancy (PREG-1)
Inflammatory Breast Cancer (IBC-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.

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference:
All recommendations are considered appropriate.

See NCCN Categories of Preference.

Staging (ST-1)

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. ©2021.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Updates in Version 1.2022 of the NCCN Guidelines for Breast Cancer from Version 8.2021 include:

General
- "Lumpectomy" changed to "breast-conserving surgery."

DCIS-1
- Footnote j, modified: WBRT following BCS reduces *ipsilateral breast tumor* recurrence rates in DCIS by about 50%–*70%*.

DCIS-2
- DCIS Postsurgical Treatment, first bullet modified: Consider endocrine therapy for 5 years for *patients with ER-positive DCIS*

BINV-1
- Workup
  - Pathology review, sub-bullet added: Ki-67 test if considering adjuvant abemaciclib (see BINV-K)
  - Fifth bullet modified: Genetic counseling *and testing* if patient is at risk for hereditary breast cancer, *has triple-negative breast cancer (*TNBC*) (at any age), or is a candidate for adjuvant olaparib.*

BINV-2
- Heading added: "RT after Completion of BCS and Axillary Staging"
- Negative axillary nodes, first option modified: WBRT ± boost to tumor bed, and consider *comprehensive* regional nodal irradiation (RNI) in patients with central/medial tumors, ~~or tumors >2 cm with other high-risk features (young age or~~ *pT3 tumors, or pT2 tumors with one of the following high-risk features*: *grade 3,* extensive lymphovascular invasion [LVI], *or ER-negative*
- 1–3 positive axillary nodes
  - Criteria modified for consistency with BINV-D.
  - No after criteria, RT modified: WBRT *with inclusion of any portion of the undissected axilla at risk* ± boost to tumor bed (category 1). Strongly consider *comprehensive RNI.* ~~RT to supraclavicular/infraclavicular regions, internal mammary nodes, and any part of the axillary bed at risk~~
- ≥4 positive axillary nodes, option modified: WBRT ± boost[n] to tumor bed (category 1) + *comprehensive RNI + any portion of the undissected axilla at risk (category 1)* ~~supraclavicular/infraclavicular regions, internal mammary nodes, and any part of the axillary bed at risk (category 1).~~

BINV-3
- Heading added: "RT after Completion of Mastectomy and Axillary Staging"
- Where recommended, "RT to supraclavicular/infraclavicular regions, internal mammary nodes, and any part of the axillary bed at risk" has been changed to: "and *comprehensive RNI (including any portion of the undissected axilla at risk." (*Also on BINV-14/15, and IBC-2)

BINV-4
- Separate links added to BINV-7 and BINV-8.

BINV-5
- Footnote moved from this page to BINV-K: Evidence suggests that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal patients with HR-positive breast cancer is similar to that achieved with CMF alone. (Also on BINV-7, BINV-8, and BINV-11)
- Footnote text was moved: (Also on BINV-6 through BINV-11)
  - Moved to BINV-L, 3 of 10: Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy.
  - Moved to BINV-I (2 of 3): Available data suggest that sequential or concurrent endocrine therapy with RT is acceptable.
- Footnote removed: There are limited data to make chemotherapy recommendations for those ≥70 y of age. See NCCN Guidelines for Older Adult Oncology. (Also on BINV-6 through BINV-11)
- Footnote ee modified: Consider adjuvant bisphosphonate therapy *for risk reduction of distant metastasis for 3–5 years in postmenopausal* patients ~~with~~ (natural or induced) ~~menopause~~ *with high-risk node-negative* or *node-positive tumors.* (Also on BINV-6 through BINV-11 and BINV-16)

BINV-6
- Footnote jj added: Addition of 1 year of adjuvant olaparib is an option for select patients with germline BRCA1/2 mutation after completion of adjuvant chemotherapy. See BINV-L (1 of 8). (Also on BINV-8 and BINV-10)

BINV-12
- Clinical stage, criteria modified: c≥T2 or cN+ and M0 *or cT1,N0 HER2-positive disease or cT1,N0 TNBC* ~~and Considering preoperative systemic therapy~~ *(For* preoperative systemic therapy *criteria,* see BINV-M, 1 of 2)
- Additional workup, fourth bullet modified: Chest diagnostic CT ~~with~~ ± contrast

BINV-13
- First column, third bullet, changed "Biopsy ± clip placement..." to "Biopsy + clip placement *recommended* of suspicious and/or clinically positive axillary lymph nodes, if not previously done."

Continued

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Updates in Version 1.2022 of the NCCN Guidelines for Breast Cancer from Version 8.2021 include:

BINV-14
- First column, options modified:
  - ~~Complete response or Partial response~~ *If* BCS possible
  - ~~Partial response, lumpectomy not possible or Confirmed progressive disease at any time~~ *If* BCS not possible
- Adjuvant therapy after breast-conserving surgery, last bullet added: *Any cN0, ypN0: Adjuvant RT to whole breast ± boost to tumor bed*
- Adjuvant therapy after mastectomy, last option added: *or Adjuvant systemic therapy (see BINV-16) without adjuvant RT for any cN0,ypN0 if axilla was assessed by SLNB or axillary node dissection.*

BINV-16
- HR-positive/HER2-Negative disease
  - ypT0N0 or pCR or ypT1–4,N0 or ypN≥1, adjuvant systemic therapy modified: Adjuvant endocrine therapy (category 1) + *adjuvant olaparib if germline BRCA1/2 mutation CPS+EG score ≥3, and residual disease*
- HR-Negative/HER2-Negative disease
  - ypT0N0 or pCR, adjuvant systemic therapy added:
    - For high-risk: Adjuvant pembrolizumab (if pembrolizumab-containing regimen was given preoperatively)
  - ypT1–4,N0 or ypN≥1, adjuvant systemic therapy options modified: ~~Consider~~ *Adjuvant* capecitabine (6–8 cycles) *or Adjuvant olaparib for 1 year if germline BRCA1/2 mutation or Adjuvant pembrolizumab (if pembrolizumab-containing regimen was given preoperatively)*
- Footnote moved to BINV-I (2 of 3), and modified: *Adjuvant* HER2-targeted therapy and/or endocrine therapy may be delivered concurrently with RT. ~~, while capecitabine should follow completion of RT.~~
- Footnote zz added: High-risk criteria include stage II–III TNBC. The use of adjuvant pembrolizumab (category 2A) may be individualized.
- Footnote aaa added: Patients in the OlympiA trial did not receive capecitabine; thus, there are no data on sequencing or to guide selection of an adjuvant therapy.

BINV-17
- Endocrine therapy
  - Second bullet, first sub-bullet modified: *Age-appropriate gynecologic screening* ~~Annual gynecologic assessment every 12 mo if uterus present~~

BINV-18
- Workup
  - Imaging for systemic staging, first bullet modified: Chest diagnostic CT ~~with~~ ± contrast (Also on IBC-1)
  - Biomarker testing
    - First bullet modified: Biopsy *of at least* first recurrence of disease *(consider re-biopsy if progression)*
    - Second bullet modified: Evaluation of ER/PR and HER2 status ~~to differentiate recurrent disease from new primary~~
- Footnote eee, last line added: Since ER/PR and HER2 status can change with treatment and metastatic progression, it may be appropriate to consider repeat testing on new samples in these scenarios if management will change.

BINV-19
- Footnote iii modified: In patients with a local breast recurrence after BCS who had a prior SLNB, a repeat SLNB may be considered although the accuracy of repeat SLNB is unproven. ~~On the other hand, the prognostic significance of repeat SNB after mastectomy is unknown and its use is discouraged.~~ *After mastectomy, repeat SLNB may be considered although there are limited data in this setting.*

BINV-22
- Footnote removed from this page (it remains on BINV-P): If there is disease progression while on CDK4/6 inhibitor therapy, there are limited data to support an additional line of therapy with another CDK4/6-containing regimen. Likewise, if there is disease progression while on a everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.

BINV-23
- Option removed due to redundancy: Other HER2-targeted therapies
- Footnote vvv modified: For premenopausal patients, ~~selective ER modulators~~ *tamoxifen* alone (without ovarian ablation/suppression) + HER2-targeted therapy is also an option.

Continued

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Updates in Version 1.2022 of the NCCN Guidelines for Breast Cancer from Version 8.2021 include:

BINV-D

- Page heading modified: *Considerations for* Surgical Axillary Staging
- Top pathway, sentinel lymph node mapping and excision, and sentinel lymph node positive
  - Added pathways for "breast-conserving surgery" versus "mastectomy."
  - Added option for consideration of no further axillary surgery for those who meet all of the following criteria after mastectomy:
    - cT1–T2, cN0
    - No preoperative chemotherapy
    - 1–2 positive SLNs
    - Adjuvant RT planned with intentional inclusion of undissected axilla at risk
  - Modified option after BCS or mastectomy: Micrometastases seen in SLN ~~post-mastectomy~~
- Bottom pathway, changed "US-guided FNA or core biopsy +/- clip placement" to "US-guided FNA or core biopsy + clip placement *recommended.*"
- Footnote e added: Limited data exist for mastectomy patients.
- Footnote g added: ACOSOG Z0011: Giuliano AE, et al. JAMA. 2017 Sep 12;318(10):918-926.
- Footnote h added: EORTC AMAROS: Donker M, et al. Lancet Oncol. 2014;15(12):1303-10; Rutgers E, et al. Cancer Research. 2019;79(4 Supplement):GS4-01-GS04-01.
- Footnote i added: Limited data exist for ≥3 positive SLN.
- Footnote k modified: In the mastectomy setting, in patients who were initially cN0, who have positive nodes on SLNB, and have no axillary dissection, RT *to the chest wall* should include ~~chest wall, supraclavicular ± internal mammary nodes, and full axilla~~ *undissected axilla at risk ± RNI.*
- Footnote removed: For patients with clinically negative axilla who are undergoing mastectomy and for whom RT is planned, axillary radiation may replace axillary dissection level I/II for regional control of disease.

BINV-H (5 of 7)

- Second bullet added: Some patients may choose not to have reconstruction after mastectomy. The option to undergo mastectomy alone with a surgically optimized closure should be offered to all patients as part of a comprehensive discussion of reconstructive options. Achieving the optimal result in this scenario may require additional procedures beyond the initial mastectomy. See BINV-H (6 of 7) for patient factors influencing choice of reconstruction.

BINV-H (7 of 7)

- Nipple-Sparing Mastectomy, line modified: Nipple margin assessment ~~(ideally intraoperatively)~~ is mandatory, and the nipple margin should be clearly designated.

BINV-I (1 of 3)

- Whole Breast Radiation
  - First bullet modified: Target definition is the breast tissue *at risk* ~~in entirety~~.
  - Bullet added: Ultra-hypofractionated WBRT of 28.5 Gy delivered as 5 (once-a-week) fractions may be considered in select patients aged >50 years following BCS with pTis/T1/T2/N0, though the optimal fractionation for the boost delivery is unknown for this regimen.
  - Bullets removed:
    - For patients who require a more limited number of treatment visits for WBRT delivery, ultra-hypofractionated WBRT of 28.5 Gy delivered as 5 (once-a-week) fractions, may be considered in selected patients aged ≥50 years following BCS with pTis/T1/T2/N0 tumors. However, late toxicity effects beyond 10 years are not currently defined.
    - The optimal fractionation for the delivery of a boost is not known for this regimen.
- Footnote a added: Alternatively, 26 Gy in 5 daily fractions over one week may be considered, though data beyond 5 years for local relapse or toxicity are not yet available for this regimen. (Murray Brunt A, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 2020;395:1613-1626.)

Continued

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Updates in Version 1.2022 of the NCCN Guidelines for Breast Cancer from Version 8.2021 include:

BINV-I (2 of 3)
- Heading modified: *RT with* Preoperative or Adjuvant Systemic Therapy
- Bullet removed: Adjuvant HER2-targeted therapy and/or endocrine therapy may be delivered concurrently with RT, while capecitabine should follow completion of RT.
- Bullet and subsequent sub-bullets added on sequencing of RT with systemic therapy

BINV-I (3 of 3)
- First bullet modified: Studies of APBI suggest that rates of local control in selected low-risk patients with early-stage breast cancer ~~may be~~ *are* comparable to those treated with standard WBRT.

BINV-J (1 of 2)
- Title modified: Special Considerations for Breast Cancer in ~~men~~ *Males* (Sex Assigned at Birth)
- Added: NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

BINV-K
- Footnote d added: In patients with HR-positive/HER2-negative, high-risk breast cancer (ie, those with ≥4 positive lymph nodes, or 1–3 positive lymph nodes with one or more of the following: Grade 3 disease, tumor size ≥5 cm, or a Ki-67 score of ≥20%) 2 years of adjuvant abemaciclib can be considered.
- Footnote f added: Evidence suggests that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal patients with HR-positive breast cancer is similar to that achieved with CMF alone.
- Line added to footnote i: Patients with lymph node involvement may benefit from extended aromatase inhibitor duration (7.5–10 years total).

BINV-L (1 of 9)
- HER2-Negative
  - Useful in Certain Circumstances, added: Capecitabine (maintenance therapy for TNBC following adjuvant chemotherapy)
  - Other Recommended Regimens, Select patients with TNBC, option modified: ~~weekly~~ Paclitaxel + carboplatin *(various schedules)*
- Some footnotes have been moved to BINV-L (3 of 9), and a link has been added: See Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3 of 9)

BINV-L (2 of 9)
- HER2-Positive disease
  - Useful in Certain Circumstances, options added:
    - ◊ Neratinib (adjuvant setting only)
    - ◊ Paclitaxel + trastuzumab + pertuzumab
    - ◊ Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only)
- Some footnotes have been moved to BINV-L (3 of 9), and a link has been added: See Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3 of 9)

BINV-L (3 of 9)
- New page added: Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy

BINV-L (5 of 9)
- Other Recommended Regimens:
  - Modified: Weekly paclitaxel + carboplatin (preoperative setting only)
    - ◊ Carboplatin modified: AUC *5 or* 6 day 1
  - Added: Weekly paclitaxel + weekly carboplatin
    - ◊ Paclitaxel 80 mg/m^2 days 1, 8, and 15
    - ◊ Carboplatin AUC 1.5–2 days 1, 8, and 15
      - – Cycled every 28 days x 6 cycles
- Useful in Certain Circumstances
  - CMF chemotherapy, added "IV acceptable" beside cyclophosphamide.
  - Added: Capecitabine; 650 mg/m^2 PO twice daily on days 1–28; Cycled every 28 days for 1 year

Continued

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Updates in Version 1.2022 of the NCCN Guidelines for Breast Cancer from Version 8.2021 include:

BINV-L (8 of 9)
- HER2-Positive, Useful in Certain Circumstances, added:
  - Neratinib
    - ◊ 120 mg PO daily on days 1–7; Followed by:
    - ◊ 160 mg PO daily on days 8–14; Followed by:
    - ◊ 240 mg PO daily on days 15–28
      - – Cycled every 28 days x 1 cycle
      - – Followed by:
    - ◊ 240 mg PO daily on days 1–28
      - – Cycled every 28 days x 12 cycles beginning with cycle 2
  - Paclitaxel + trastuzumab + pertuzumab
    - ◊ Paclitaxel 80 mg/m^2 IV day 1
      - – Cycled every 7 days x 12 cycles
    - ◊ Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
    - ◊ Pertuzumab 840 mg IV day 1 followed by 420 mg IV
      - – Cycled every 21 days x 4 cycles
  - Ado-trastuzumab emtansine (T-DM1)
    - ◊ 3.6 mg/kg IV day 1
      - – Cycled every 21 days for 17 cycle

BINV-L (9 of 9)
- References have been updated.

BINV-M (1 of 2)
- Candidates for Preoperative Systemic Therapy
  - Added: Preoperative systemic therapy can be considered for cT1,N0 HER2-positive disease and TNBC

BINV-N (3 of 5)
- Treatment Implications updated for 70-gene (MammaPrint) (for pN0 and 1–3 positive nodes).

BINV-O
- This page has been significantly revised.

BINV-P
- HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression
  - All single agents that were previously listed under "Preferred Regimens" have been changed to "Other Recommended regimens: First- and Subsequent-Line Therapy."
  - Other recommended regimens for first- and subsequent-line therapy:
    - ◊ Fulvestrant was changed from a category 1 to a category 2A option.
    - ◊ Option removed: Toremifene
- Footnote b added: In phase 3 randomized controlled trials, ribociclib + endocrine therapy has shown overall survival benefit in the first-line setting.
- Footnote d added: In phase 3 randomized controlled trials, fulvestrant in combination with a CDK4/6 inhibitor (abemaciclib, palbociclib, and ribociclib) has shown overall survival benefit in the second-line setting.

BINV-Q (1 of 8)
- HER2-negative disease
  - Useful in certain circumstances, option removed: paclitaxel/bevacizumab
- Footnotes removed:
  - Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.
  - An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

Continued

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Updates in Version 1.2022 of the NCCN Guidelines for Breast Cancer from Version 8.2021 include:

BINV-Q (2 of 8)
- Systemic therapy regimens for HER2-positive, recurrent unresectable (local or regional) or stage IV (M1) disease
  - Second-line option added: Fam-trastuzumab deruxtecan-nxki; this is a category 1, preferred regimen.
  - Second-line option modified: Ado-trastuzumab emtansine (TDM-1) has been changed from a category 1, preferred regimen to a category 2A, other recommended regimen.
  - Heading modified: Third line and beyond (*optimal sequence is not known.)*
- Footnote j modified: Regimens may *also* be used as *an option for third-line and beyond* ~~or fourth-line option~~; the optimal sequence for third-line therapy and beyond is not known.
- Footnote l added: Fam-trastuzumab deruxtecan-nxki may be considered in the first-line setting as an option for select patients (ie, those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for pertuzumab-containing regimens]).
- Footnote n modified: Tucatinib + trastuzumab + capecitabine is preferred in patients with both systemic and CNS progression *in the third line setting and beyond;* ~~on ado-trastuzumab emtansine. However, tucatinib + trastuzumab + capecitabine~~ and *it* may be given in the second-line setting.
- Footnote removed: Fam-trastuzumab deruxtecan-nxki is preferred in patients with visceral metastases if progression on ado-trastuzumab emtansine.

BINV-Q (5 of 8)
- Trastuzumab + docetaxel, second bullet modified: Docetaxel 35 mg/m^2 IV days 1, 8, and 15 weekly *cycled every 28 days*

BINV-Q (6 of 8)
- Trastuzumab + lapatinib, first bullet modified: Lapatinib 1000 mg PO daily *for 21 days*

BINV-R (1 of 3)
- TNBC, biomarker modified: PD-L1 expression (*using 22C3 antibody)*

BINV-S (3 of 3)
- Bone scan, frequency modified for those receiving endocrine therapy to: Every 2–6 months.

PHYLL-1
- After excisional biopsy, moved benign phyllodes tumor to separate pathway, recommending clinical follow-up for 3 y.

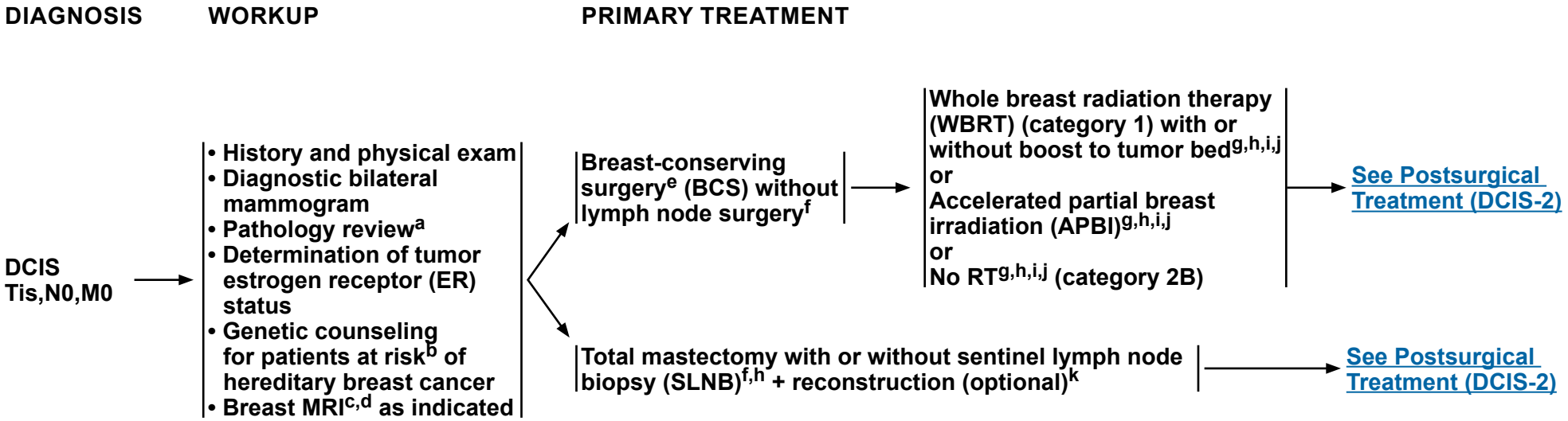
IBC-1
- Footnote removed: The accurate assessment of in-breast tumor or regional lymph node response to preoperative systemic therapy is difficult, and should include physical examination and performance of imaging studies (mammogram and/or breast MRI) that were abnormal at the time of initial tumor staging. Selection of imaging methods prior to surgery should be determined by the multidisciplinary team.

IBC-2
- Heading added for clarification: Response to Preoperative Therapy
- Added to "no response" pathway: Patients may be candidates for multiple lines of systemic therapy to palliate advanced breast cancer. At each reassessment clinicians should assess value of ongoing treatment, the risks and benefits of an additional line of systemic therapy, patient performance status, and patient preferences through a shared decision-making process.

ST-5
- Replaced Histologic Types (previously listed on ST-4) with the following: Histopathologic Type- WHO Classification 5th Edition (2019)
  - WHO Classification of Tumors Editorial Board, ed. WHO classification of tumors, 5th edition – Breast tumors. Lyon: International Agency for Research on Cancer 2019.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.



[a] The 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] For risk criteria, See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.

[c] See Principles of Dedicated Breast MRI Testing (BINV-B).

[d] The 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.

[e] Re-resection(s) may be performed in an effort to obtain negative margins in patients desiring breast-conservation therapy. Patients in whom adequate surgical margins cannot be achieved with BCS should undergo a total mastectomy. For definition of adequate surgical margins, see Margin Status Recommendations After BCS for Invasive Cancers and DCIS (BINV-F).

[f] Complete axillary lymph node dissection should not be performed in the absence of evidence of invasive cancer or proven axillary metastatic disease in patients with apparent pure DCIS. However, a small proportion of patients with apparent pure DCIS will be found to have invasive cancer at the time of their definitive surgical procedure. Therefore, the performance of a sentinel lymph node (SLN) procedure should be considered if the patient with apparent pure DCIS is to be treated with mastectomy or with excision in an anatomic location compromising the performance of a future SLN procedure.

[g] See Principles of Radiation Therapy (BINV-I).

[h] Patients found to have invasive disease at total mastectomy or re-excision should be managed as having clinical stage I or stage II disease (See ST-1), including lymph node staging.

[i] See Special Considerations to Breast-Conservation Therapy Requiring Radiation Therapy (BINV-G).

[j] WBRT following BCS reduces ipsilateral breast tumor recurrence rates in DCIS by about 50%–70%. 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, particularly if they are ER-positive and will be receiving endocrine therapy. Select patients with low-risk DCIS may be considered suitable for APBI if they meet all aspects of the definition of low-risk DCIS from the RTOG 9804 trial, including screen-detected DCIS, low to intermediate nuclear grade, tumor size ≤2.5 cm, and surgical resection with margins negative at >3 mm.

[k] See 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

DCIS POSTSURGICAL TREATMENT

Risk reduction therapy for ipsilateral breast following breast-conserving surgery (BCS):
- **Consider endocrine therapy for 5 years for patients with ER-positive DCIS, if:**
  - **Treated with BCS and RT[m] (category 1), especially for patients with ER-positive DCIS.**
  - **Treated with excision alone[l]**
- **Endocrine therapy:**
  - **Tamoxifen[m,n] for premenopausal patients**
  - **Tamoxifen[m,n] or aromatase inhibitor for postmenopausal patients with some advantage for aromatase inhibitor therapy in patients <60 years or with concerns for thromboembolism**

Risk reduction therapy for contralateral breast:
- **Counseling regarding risk reduction**

→

SURVEILLANCE/FOLLOW-UP

- **Interval history and physical exam every 6–12 mo for 5 y, then annually**
- **Mammogram every 12 mo (first mammogram 6–12 mo, after breast-conservation therapy, category 2B)**

[l] Available 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.

[m] *CYP2D6* genotype testing is not recommended for patients considering tamoxifen.

[n] The standard dose of tamoxifen is 20 mg/day for 5 years. Low-dose tamoxifen (5 mg/day for 3 years) is an option only if patient is symptomatic on the 20-mg dose or if patient is unwilling or unable to take standard-dose 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

DIAGNOSIS | **WORKUP[a]** | **CLINICAL STAGE**

Non-metastatic (M0) invasive breast cancer →

- History and physical exam
- Imaging:
  - Diagnostic bilateral mammogram
  - Ultrasound as necessary
  - Breast MRI[b] (optional), with special consideration for mammographically occult tumors
- Pathology review[c]
  - Ki-67 test if considering adjuvant abemaciclib (see BINV-K)
- Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status[d]
- Genetic counseling and testing if patient is at risk[e] for hereditary breast cancer, has triple-negative breast cancer (TNBC) (at any age), or is a candidate for adjuvant olaparib
- Address fertility and sexual health concerns as appropriate[f]
- Pregnancy test in all patients of childbearing potential[f] (If pregnant, see PREG-1)
- Assess for distress[g]
- Consider additional imaging studies only in the presence of signs and symptoms of metastatic disease[h] (see BINV-18)

cT0,N+,M0 → See NCCN Guidelines for Occult Primary

cT1–T3, ≥cN0,M0 → See criteria for preoperative systemic therapy (BINV-M)

- Not considering preoperative systemic therapy → Locoregional treatment[i]
  - See BCS Followed by RT (BINV-2)
  - or
  - See Mastectomy Followed by RT (BINV-3)
- Considering preoperative systemic therapy → See Additional Workup Prior to Preoperative Systemic Therapy (BINV-12)

Metastatic (M1) invasive breast cancer → **Stage IV (M1) or Recurrent disease** → See Workup for Recurrent or Stage IV (M1) Disease (BINV-18)

Clinical pathologic diagnosis of inflammatory breast cancer (IBC) → See Workup for IBC (IBC-1)

[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[b] Breast MRI may be useful for characterizing axillary and/or internal mammary nodal disease. See Principles of Dedicated Breast MRI Testing (BINV-B).
[c] The panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. http://www.cap.org.
[d] See Principles of Biomarker Testing (BINV-A).
[e] For risk criteria, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.
[f] For Fertility and Birth Control, see BINV-C. The general considerations for fertility and sexual health/function outlined for specific populations in NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology and NCCN Guidelines for Survivorship are applicable to all patients diagnosed with breast cancer.
[g] See NCCN Guidelines for Distress Management.
[h] Routine systemic staging is not indicated for non-metastatic (M0) cancer in the absence of systemic symptoms. If metastatic disease is suspected, see Workup on BINV-18.
[i] Patients 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-conservation therapy. These patients may be considered for prophylactic bilateral mastectomy for risk reduction. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.

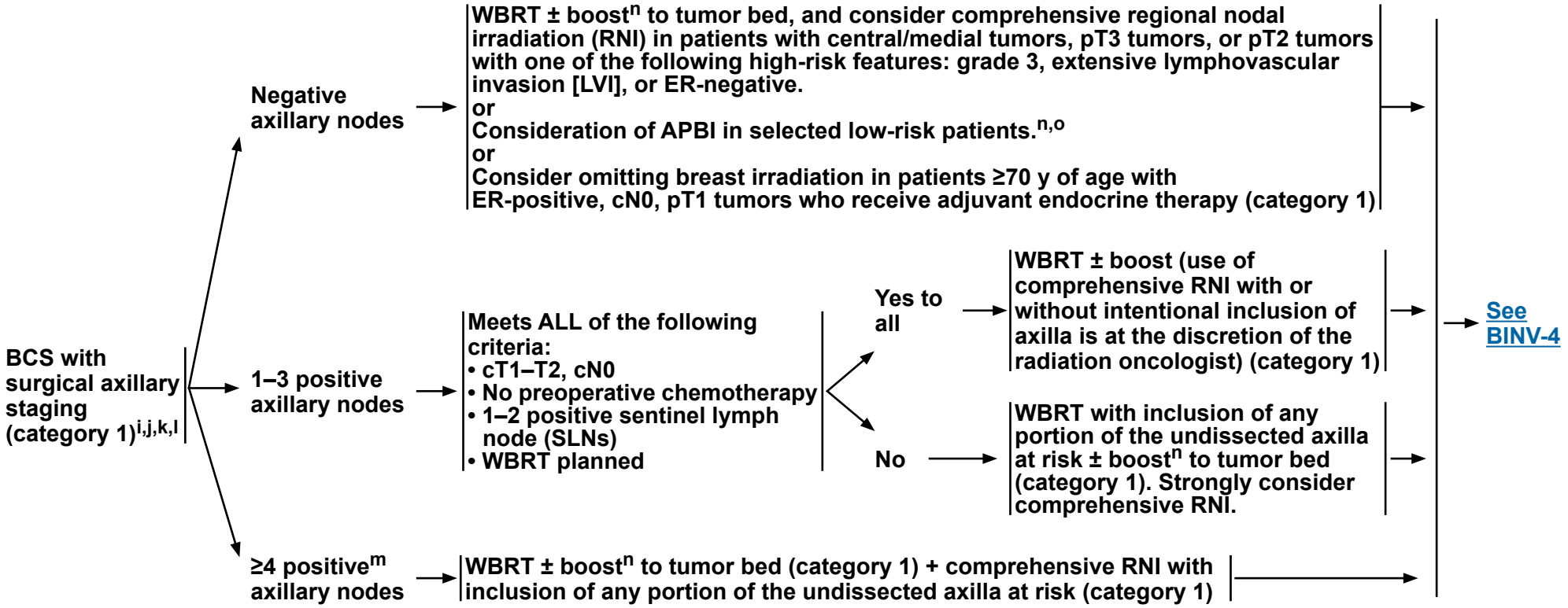
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE:[a] BREAST-CONSERVING SURGERY (BCS) FOLLOWED BY RT

RT AFTER COMPLETION OF BCS AND AXILLARY STAGING



[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.

[i] Patients 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-conservation therapy. These patients may be considered for prophylactic bilateral mastectomy for risk reduction. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.

[j] See Considerations for Surgical Axillary Staging (BINV-D).

[k] See Axillary Lymph Node Staging (BINV-E) and Margin Status Recommendations After BCS for Invasive Cancers and DCIS (BINV-F).

[l] See Special Considerations to Breast-Conservation Therapy Requiring Radiation Therapy (BINV-G).

[m] Consider imaging for systemic staging, including chest/abdominal ± pelvic diagnostic CT with contrast, bone scan, and optional FDG PET/CT.

[n] See Principles of Radiation Therapy (BINV-I).

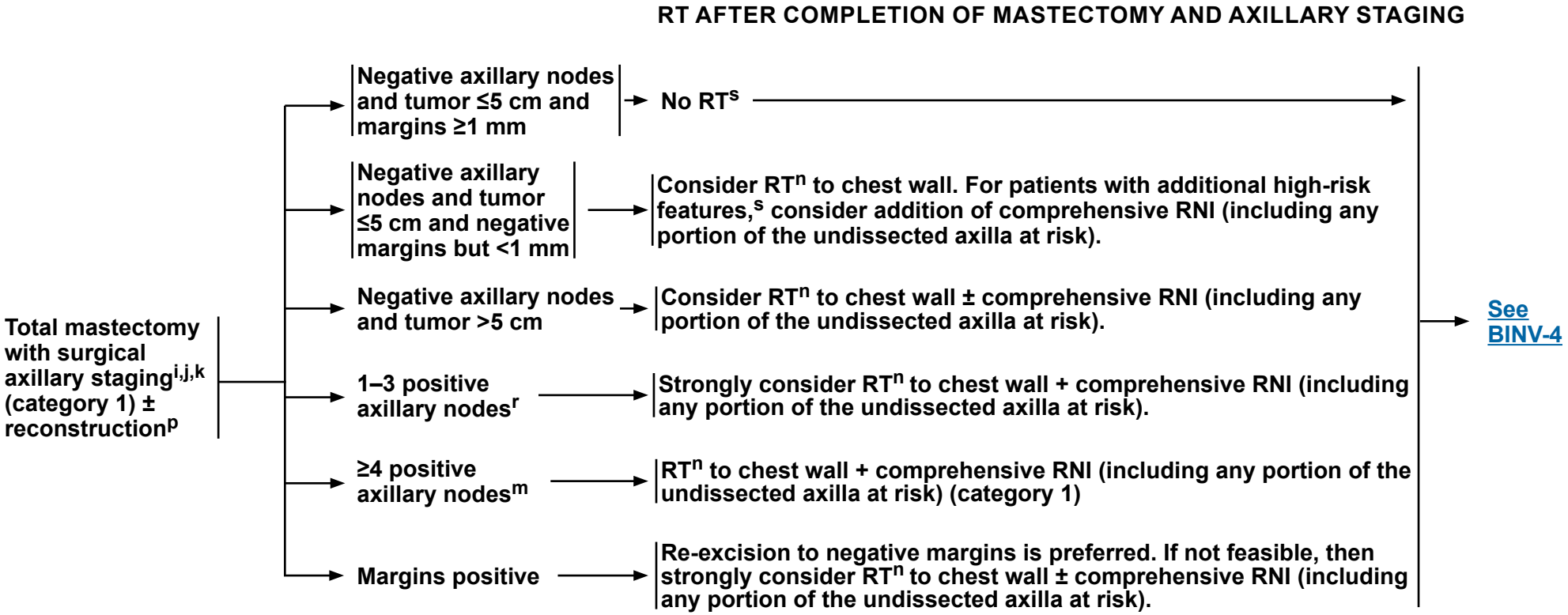
[o] APBI may be administered prior to chemotherapy.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE:[a,q] MASTECTOMY FOLLOWED BY RT

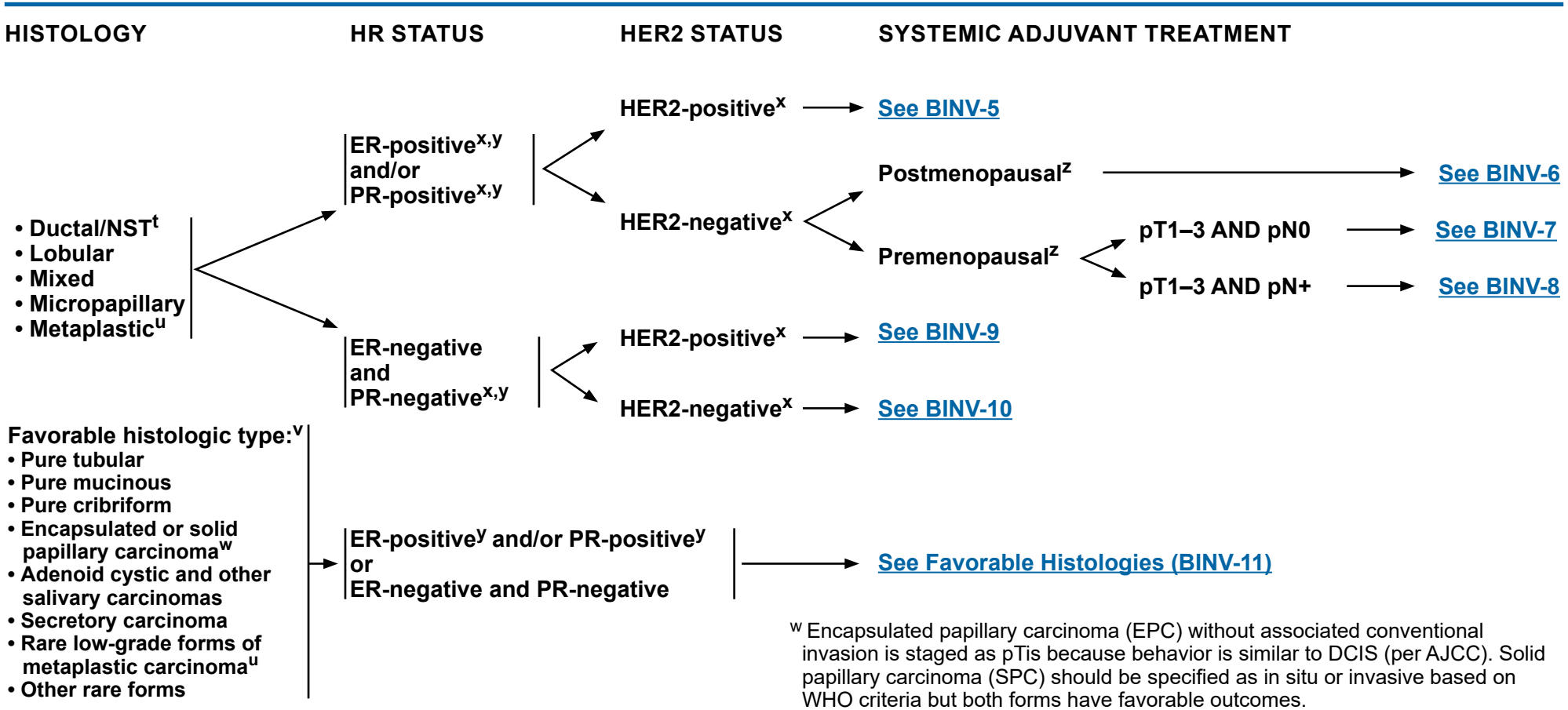


[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[i] Patients with a known or suspected genetic predisposition to breast cancer may have an increased risk of ipsilateral breast recurrence or contralateral breast cancer with breast-conservation therapy. These patients may be considered for prophylactic bilateral mastectomy for risk reduction. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.
[j] See Considerations for Surgical Axillary Staging (BINV-D).
[k] See Axillary Lymph Node Staging (BINV-E) and Margin Status Recommendations After BCS for Invasive Cancers and DCIS (BINV-F).
[m] Consider imaging for systemic staging, including chest/abdominal ± pelvic diagnostic CT with contrast, bone scan, and optional FDG PET/CT.
[n] See Principles of Radiation Therapy (BINV-I).
[p] See Principles of Breast Reconstruction Following Surgery (BINV-H).
[q] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).
[r] In the case of a micrometastasis (>0.2 to ≤2.0 mm), and no axillary dissection, evaluate other patient risk factors when considering RT.
[s] Postmastectomy RT may be considered for patients with multiple high-risk recurrence factors, including central/medial tumors or tumors ≥2 cm with <10 axillary nodes removed and at least one of the following: grade 3, ER-negative, or 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.



[t] According to WHO, carcinoma of no special type (NST) encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.

[u] There are rare subtypes of metaplastic carcinoma (eg, low-grade adenosquamous and low-grade fibromatosis-like carcinoma) that are considered to have a favorable prognosis without adjuvant systemic therapies.

[v] To be associated with favorable prognosis, the favorable histologic type should not be high grade, should be pure (>90% as classified on the surgical excision, not core biopsy alone), and should be HER2 negative. If atypical pathologic or clinical features are present, consider treating as ductal/NST.

[w] Encapsulated papillary carcinoma (EPC) without associated conventional invasion is staged as pTis because behavior is similar to DCIS (per AJCC). Solid papillary carcinoma (SPC) should be specified as in situ or invasive based on WHO criteria but both forms have favorable outcomes.

[x] Correlation of histology, hormone receptor (HR), and HER2 status should always be done with awareness of unusual/discordant or borderline results. See Principles of of Biomarker Testing (BINV-A).

[y] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus, individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).

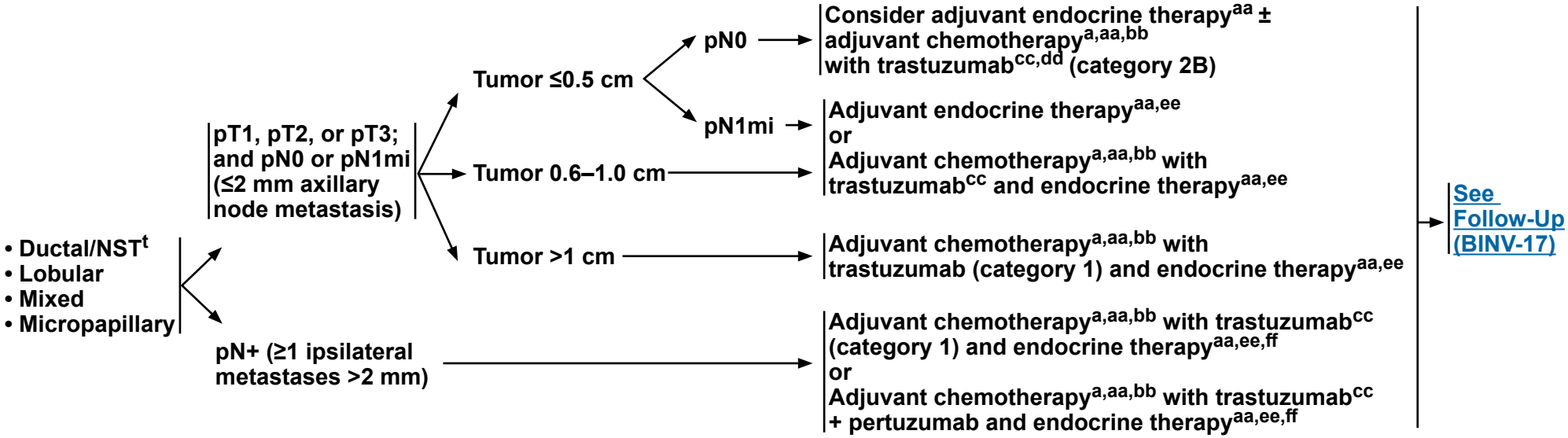
[z] See Definition of Menopause (BINV-O).

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-POSITIVE DISEASE[d,q,y]



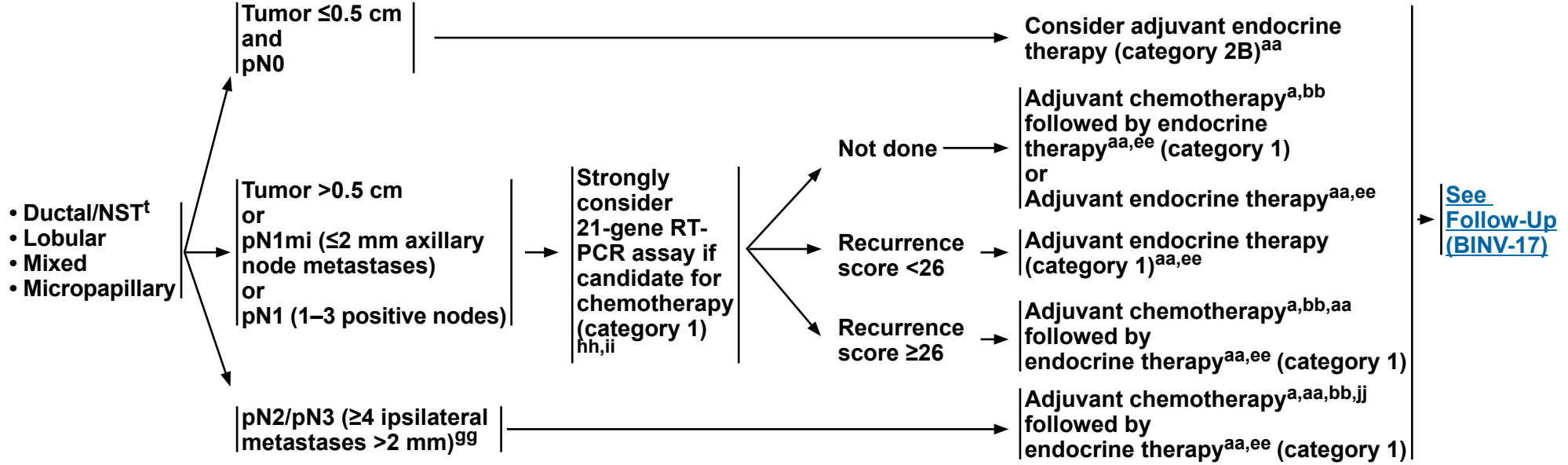
[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[d] See Principles of Biomarker Testing (BINV-A).
[q] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).
[t] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[y] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus, individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).
[aa] See Adjuvant Endocrine Therapy (BINV-K).
[bb] See Preoperative/Adjuvant Therapy Regimens (BINV-L).
[cc] The prognosis of patients with pT1a and pT1b tumors that are pN0 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.
[dd] Adjuvant chemotherapy with weekly paclitaxel and trastuzumab can be considered for pT1,N0,M0, HER2-positive cancers, particularly if the primary cancer is HR-negative. The absolute benefit of HER2-based systemic chemotherapy is likely negligible in patients with HR-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.
[ee] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.
[ff] Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab is unknown.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-NEGATIVE DISEASE[d,q,y] POSTMENOPAUSAL[z] PATIENTS with pT1–3 AND pN0 or pN+ TUMORS



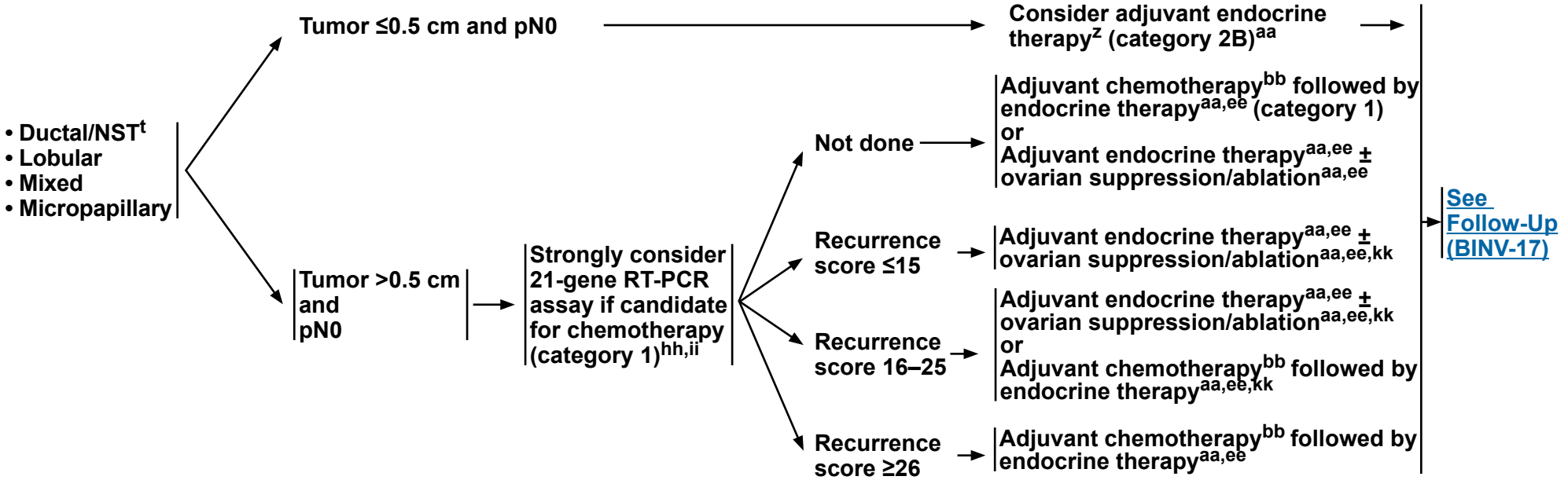
[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[d] See Principles of Biomarker Testing (BINV-A).
[q] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).
[t] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[y] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).
[z] See Definition of Menopause (BINV-O).
[aa] See Adjuvant Endocrine Therapy (BINV-K).
[bb] See Preoperative/Adjuvant Therapy Regimens (BINV-L).
[ee] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.
[gg] There are few data regarding the role of gene expression assays in those with ≥4 ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this group should be based on clinical factors.
[hh] Other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy. See Gene Expression Assays for Consideration of Adjuvant Systemic Therapy (BINV-N).
[ii] Patients with T1b tumors with low-grade histology and no lymphovascular invasion should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.
[jj] Addition of 1 year of adjuvant olaparib is an option for select patients with germline *BRCA1/2* mutation after completion of adjuvant chemotherapy. See BINV-L (1 of 8).

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-NEGATIVE DISEASE[d,q,y] PREMENOPAUSAL[z] PATIENTS with pT1–3 AND pN0 TUMORS



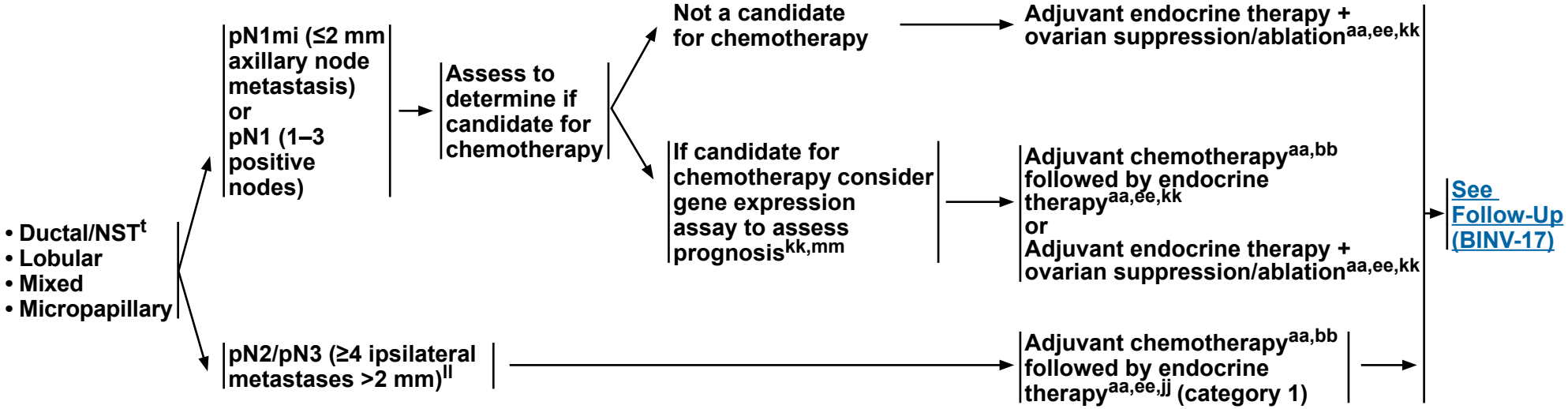
[d] See Principles of Biomarker Testing (BINV-A).
[q] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).
[t] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[y] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).
[z] See Definition of Menopause (BINV-O).
[aa] See Adjuvant Endocrine Therapy (BINV-K).
[bb] See Preoperative/Adjuvant Therapy Regimens (BINV-L).
[ee] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.
[hh] Other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy. See Gene Expression Assays for Consideration of Adjuvant Systemic Therapy (BINV-N).
[ii] Patients with T1b tumors with low-grade histology and no lymphovascular invasion should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.
[kk] In premenopausal patients with RS <26, the addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy, but it is unclear if the benefit was due to the ovarian suppression effects promoted by 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-NEGATIVE DISEASE[d,q,y] PREMENOPAUSAL[z] PATIENTS with pT1–3 AND pN+ TUMORS



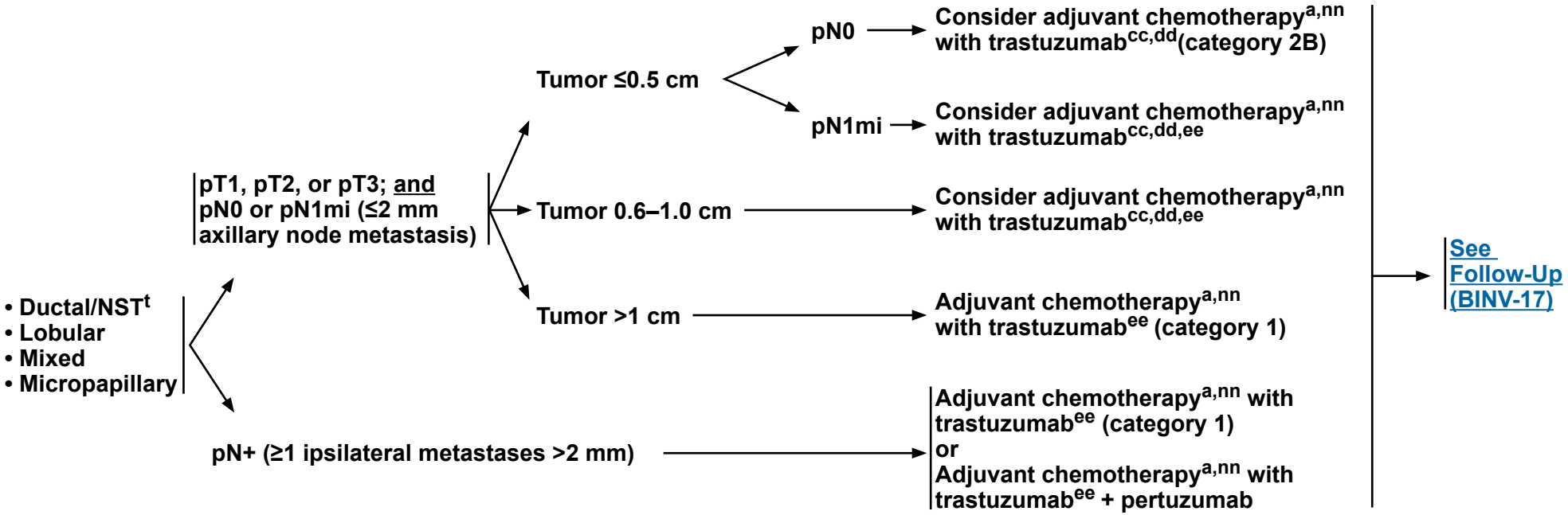
[d] See Principles of Biomarker Testing (BINV-A).
[q] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).
[t] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[y] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).
[z] See Definition of Menopause (BINV-O).
[aa] See Adjuvant Endocrine Therapy (BINV-K).
[bb] See Preoperative/Adjuvant Therapy Regimens (BINV-L).
[ee] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.
[jj] Addition of 1 year of adjuvant olaparib is an option for select patients with germline *BRCA1/2* mutation after completion of adjuvant chemotherapy. See BINV-L (1 of 8).
[kk] In premenopausal patients with RS <26, the addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy, but it is unclear if the benefit was due to the ovarian suppression effects promoted by chemotherapy.
[ll] There are few data regarding the role of gene expression assays in those with ≥4 ipsilateral axillary lymph nodes. Decisions to administer adjuvant chemotherapy for this group should be based on clinical factors.
[mm] See Gene Expression Assays for Consideration of Adjuvant Systemic Therapy (BINV-N).

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC ADJUVANT TREATMENT: HR-NEGATIVE - HER2-POSITIVE DISEASE[d,q,y]



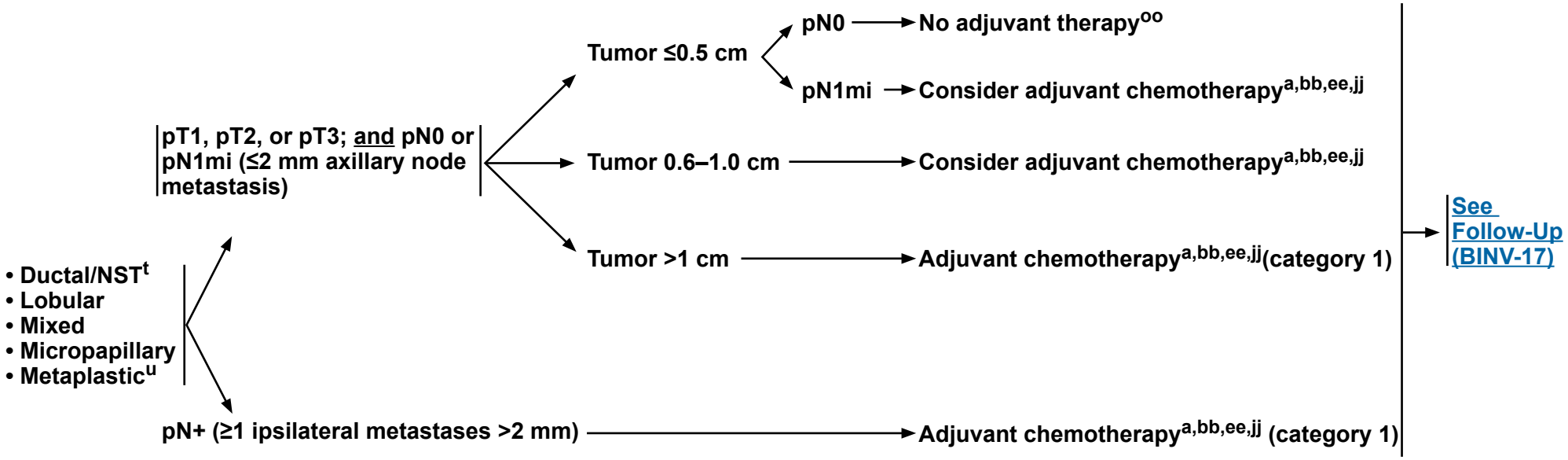
[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[d] See Principles of Biomarker Testing (BINV-A).
[q] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).
[t] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[y] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus, individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).
[cc] 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.
[dd] Adjuvant chemotherapy with weekly paclitaxel and trastuzumab can be considered for pT1,N0,M0, HER2-positive cancers, particularly if the primary cancer is HR-negative. The absolute benefit of HER2-based systemic chemotherapy is likely negligible in patients with hormone receptor-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.
[ee] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.
[nn] See Preoperative/Adjuvant Therapy Regimens (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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC ADJUVANT TREATMENT: HR-NEGATIVE - HER2-NEGATIVE DISEASE[d,q,y]



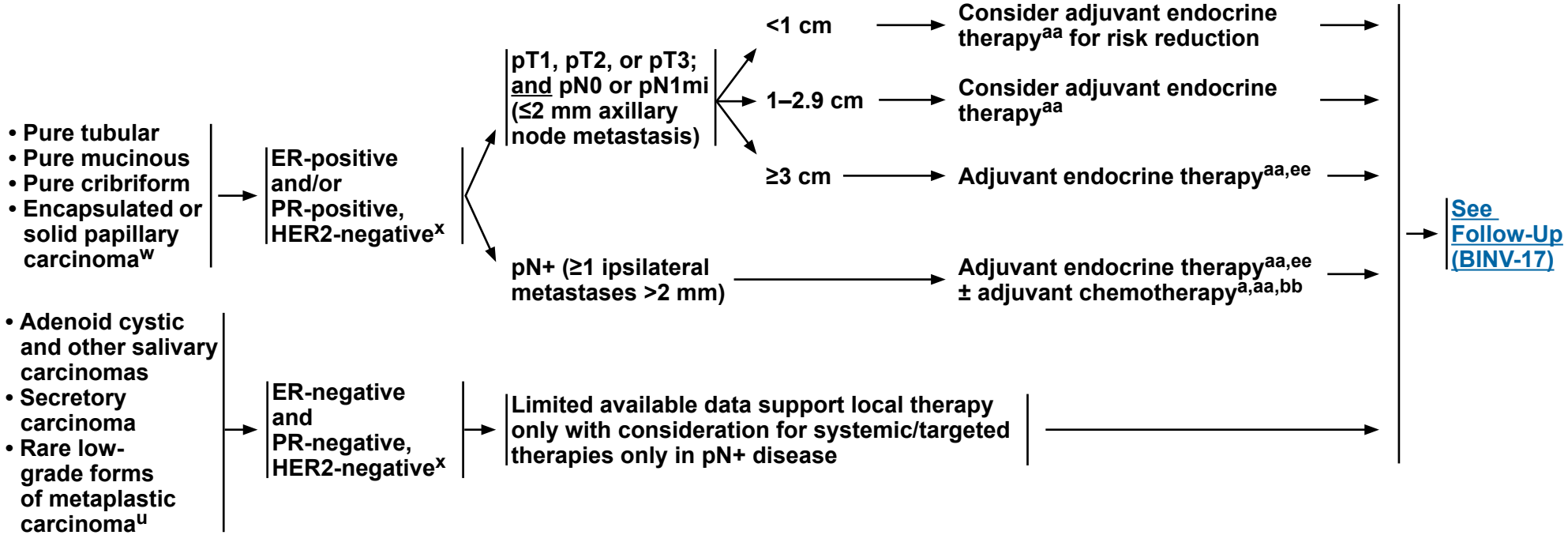
[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[d] See Principles of Biomarker Testing (BINV-A).
[q] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).
[t] According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
[u] There are rare subtypes of metaplastic carcinoma (eg, low-grade adenosquamous and low-grade fibromatosis-like carcinoma) that are considered to have a favorable prognosis without adjuvant systemic therapies.
[y] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus, individualized consideration of risks versus benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).
[bb] See Preoperative/Adjuvant Therapy Regimens (BINV-L).
[ee] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.
[jj] Addition of 1 year of adjuvant olaparib is an option for select patients with germline *BRCA1/2* mutation after completion of adjuvant chemotherapy. See BINV-L (1 of 8).
[oo] In select patients with high-risk features (eg, young patients with high-grade histology), adjuvant chemotherapy may be considered (category 2B). See (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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC ADJUVANT TREATMENT: FAVORABLE HISTOLOGIES[q,v]



[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[q] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).
[u] There are rare subtypes of metaplastic carcinoma (eg, low-grade adenosquamous and low-grade fibromatosis-like carcinoma) that are considered to have a favorable prognosis without adjuvant systemic therapies.
[v] To be associated with favorable prognosis, the favorable histologic type should not be high grade, should be pure (>90% as classified on the surgical excision, not core biopsy alone), and should be HER2 negative. If atypical pathologic or clinical features are present, consider treating as ductal/NST.
[w] EPC without associated conventional invasion is staged as pTis because behavior is similar to DCIS (per AJCC). SPC should be specified as in situ or invasive based on WHO criteria but both forms have favorable outcomes.
[x] Correlation of histology, HR, and HER2 status should always be done with awareness of unusual/discordant or borderline results. See Principles of Biomarker Testing (BINV-A).
[aa] See Adjuvant Endocrine Therapy (BINV-K).
[bb] See Preoperative/Adjuvant Therapy Regimens (BINV-L).
[ee] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

WORKUP PRIOR TO PREOPERATIVE SYSTEMIC THERAPY

CLINICAL STAGE

c≥T2[rr] or cN+ and M0
or
cT1,N0 HER2-positive disease
or
cT1,N0 TNBC
(For preoperative systemic therapy criteria, see BINV-M, 1 of 2)[pp]

→

ADDITIONAL WORKUP[a]

- Axillary assessment with exam
  - Consider ultrasound
  - Percutaneous biopsy of suspicious nodes[qq]
- CBC
- Comprehensive metabolic panel, including liver function tests and alkaline phosphatase

Additional tests to consider:[h]
- Chest diagnostic CT ± contrast
- Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast
- Bone scan or sodium fluoride PET/CT[ss] (category 2B)
- FDG PET/CT[tt] (optional)
- Breast MRI[b] (optional), with special consideration for mammographically occult tumors, if not previously done

→ For operable breast cancers: See Breast and Axillary Evaluation Prior to Preoperative Systemic Therapy (BINV-13)

→ For inoperable breast cancers: See Preoperative Systemic Therapy (BINV-15)

[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[b] Breast MRI may be useful for characterizing axillary and/or internal mammary nodal disease. See Principles of Dedicated Breast MRI Testing (BINV-B).
[h] Routine systemic staging is not indicated for non-metastatic (M0) cancer in the absence of signs or symptoms. If metastatic disease is suspected, see Workup on BINV-18.
[pp] See Principles of Preoperative Systemic Therapy (BINV-M).
[qq] At the time of axillary node sampling, a clip or tattoo should be placed to permit verification that the biopsy-positive lymph node has been removed at the time of definitive surgery.
[rr] If considering preoperative therapy, consider use of a gene expression assay during workup for postmenopausal patients with cN0, operable ER-positive, HER2-negative disease (Iwata H, et al. Breast Cancer Res Treat 2019;173,123-133; Pease AM, et al. Ann Surg Oncol 2019;26:366-371).
[ss] Bone scan or sodium fluoride PET/CT may not be needed if FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component.
[tt] FDG PET/CT may be performed at the same time as diagnostic CT, and may be helpful in situations where standard staging studies are equivocal or suspicious. FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

OPERABLE DISEASE: BREAST AND AXILLARY EVALUATION PRIOR TO PREOPERATIVE SYSTEMIC THERAPY

Prior to preoperative systemic therapy, perform:
- **Core biopsy of breast with placement of image-detectable clips or marker(s), if not previously performed, should be performed prior to preoperative therapy to demarcate the tumor bed**
- **Axillary imaging with ultrasound or MRI (if not previously done)**

  and
- **Biopsy + clip placement recommended of suspicious and/or clinically positive axillary lymph nodes, if not previously done**

→ **Preoperative systemic therapy based on HR and HER2 status**[bb,pp] → **See Surgical Treatment and Adjuvant Therapy After Preoperative Systemic Therapy (BINV-14)**

bb See Preoperative/Adjuvant Therapy Regimens (BINV-L).
pp See Principles of Preoperative Systemic Therapy (BINV-M).

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

OPERABLE DISEASE: SURGICAL TREATMENT AND ADJUVANT THERAPY AFTER PREOPERATIVE SYSTEMIC TREATMENT[uu]

SURGICAL TREATMENT | **ADJUVANT THERAPY**

BCS possible →

- **BCS with surgical axillary staging[j] (see BINV-D)** →
  - **Adjuvant systemic therapy[pp,vv] (see BINV-16) + post-lumpectomy adjuvant RT[n]**
    - **cN+ and ypN0: Adjuvant RT to the whole breast ± boost to the tumor bed;[n,ww] and strongly consider comprehensive RNI with inclusion of any portion of the undissected axilla at risk.**
    - **Any ypN+: Adjuvant RT to the whole breast ± boost to the tumor bed;[n,ww] and comprehensive RNI with inclusion of any portion of the undissected axilla at risk.**
    - **Any cN0, ypN0: Adjuvant RT to whole breast ± boost to tumor bed**

BCS not possible →

- **Mastectomy and surgical axillary staging[j] (see BINV-D) + reconstruction (optional)[p]** →
  - **Adjuvant systemic therapy[pp,vv] (see BINV-16) + post-mastectomy adjuvant RT[n]**
    - **cN+ and ypN0: Strongly consider RT to the chest wall and comprehensive RNI with inclusion of any portion of the undissected axilla at risk.**
    - **Any ypN+: RT is indicated to the chest wall + comprehensive RNI with inclusion of any portion of the undissected axilla at risk.**
  - **or**
  - **Adjuvant systemic therapy[pp,vv] (see BINV-16) without adjuvant RT for any cN0,ypN0 if axilla was assessed by SLNB or axillary node dissection[j]**

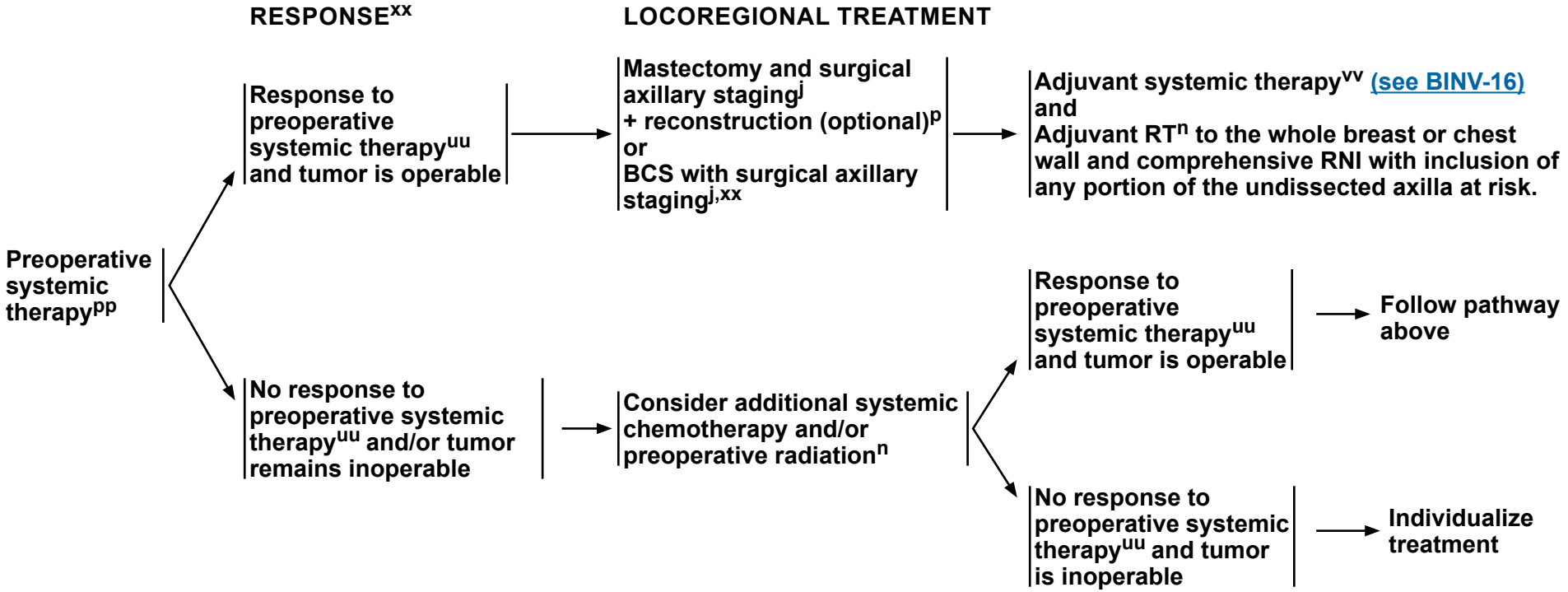
[j] See Considerations for Surgical Axillary Staging (BINV-D).
[p] See Principles of Breast Reconstruction Following Surgery (BINV-H).
[n] See Principles of Radiation Therapy (BINV-I).
[pp] See Principles of Preoperative Systemic Therapy (BINV-M).
[uu] The accurate assessment of in-breast tumor or regional lymph node response to preoperative systemic therapy is difficult, and should include physical examination and performance of imaging studies (mammogram and/or breast ultrasound 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.
[vv] Complete planned chemotherapy regimen course if not completed preoperatively.
[ww] Strongly consider RT boost for high-risk features (eg, high-grade disease, age <50 years).

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

INOPERABLE OR LOCALLY ADVANCED DISEASE (NON-INFLAMMATORY): PREOPERATIVE SYSTEMIC THERAPY AND SUBSEQUENT TREATMENT



[j] See Considerations for Surgical Axillary Staging (BINV-D).
[p] See Principles of Breast Reconstruction Following Surgery (BINV-H).
[n] See Principles of Radiation Therapy (BINV-I).
[pp] See Principles of Preoperative Systemic Therapy (BINV-M).
[uu] 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 ultrasound 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.
[vv] Complete planned chemotherapy regimen course if not completed preoperatively.
[xx] For 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

ADJUVANT SYSTEMIC THERAPY AFTER PREOPERATIVE SYSTEMIC THERAPY[ee]

	RESPONSE/PATHOLOGIC STAGE AFTER PREOPERATIVE THERAPY	ADJUVANT SYSTEMIC THERAPY[ee]
HR-positive/HER2-negative	ypT0N0 or pCR or ypT1–4,N0 or ypN≥1	Adjuvant endocrine therapy[aa,bb] (category 1) + adjuvant olaparib if germline *BRCA1/2* mutation CPS+EG score ≥3, and residual disease
HR-negative/HER2-positive	ypT0N0 or pCR	Complete up to 1 year of HER2-targeted therapy with trastuzumab (category 1) ± pertuzumab
	ypT1–4,N0 or ypN≥1	Ado-trastuzumab emtansine (category 1) alone for 14 cycles.[yy] If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete 1 year of therapy and If HR-positive, adjuvant endocrine therapy (category 1)[ff]
HR-positive/HER2-positive	ypT0N0 or pCR	Endocrine therapy[aa,bb] (category 1) + complete up to one year of HER2-targeted therapy with trastuzumab (category 1) ± pertuzumab
HR-negative/HER2-negative	ypT0N0 or pCR	For high-risk:[zz] Adjuvant pembrolizumab (if pembrolizumab-containing regimen was given preoperatively)
	ypT1–4,N0 or ypN≥1	Adjuvant capecitabine (6–8 cycles)[yy,aaa] or Adjuvant olaparib for 1 year if germline *BRCA1/2* mutation[aaa] or Adjuvant pembrolizumab (if pembrolizumab-containing regimen was given preoperatively)[aaa]

See Follow-Up (BINV-17)

[aa] See Adjuvant Endocrine Therapy (BINV-K).
[bb] See Preoperative/Adjuvant Therapy Regimens (BINV-L).
[ee] Consider adjuvant bisphosphonate therapy for risk reduction of distant metastasis for 3–5 years in postmenopausal patients (natural or induced) with high-risk node-negative or node-positive tumors.
[ff] Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab or ado-trastuzumab emtansine is unknown.
[yy] Recommendations do not apply to residual DCIS (ypTis).
[zz] High-risk criteria include stage II–III TNBC. The use of adjuvant pembrolizumab (category 2A) may be individualized.
[aaa] There are no data on sequencing or to guide selection of an adjuvant 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SURVEILLANCE/FOLLOW-UP

Exam:
- History and physical exam 1–4 times per year as clinically appropriate for 5 y, then annually

Genetic screening:
- Periodic screening for changes in family history and genetic testing indications and referral to genetic counseling as indicated, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic

Post surgical management:
- Educate, monitor, and refer for lymphedema management, see NCCN Guidelines for Survivorship: Lymphedema.

Imaging:
- Mammography every 12 mo[bbb]
- Routine imaging of reconstructed breast is not indicated
- See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic
- For patients receiving anthracycline-based therapy, see NCCN Guidelines for Survivorship for echocardiogram recommendations.

Screening for metastases:
- In the absence of clinical signs and symptoms suggestive of recurrent disease, there is no indication for laboratory or imaging studies for metastases screening.

Endocrine therapy:
- Assess and encourage adherence to adjuvant endocrine therapy
- Patients on tamoxifen:
  - Age-appropriate gynecologic screening
  - Routine annual pelvic ultrasound is not recommended
- Patients 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[ccc]

Lifestyle:
- 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

Communication:
- Coordination of care between the primary care provider and specialists is encouraged. Additionally, a personalized survivorship treatment plan including personalized treatment summary of possible long-term toxicity and clear follow-up recommendations is recommended. See NCCN Guidelines for Survivorship

Engagement:
- Patients frequently require follow-up encouragement in order to improve adherence to ongoing screening and medication adherence

→ See Recurrent Disease (BINV-18)

[bbb] Studies indicate that annual mammograms are the appropriate frequency for surveillance of breast cancer patients who have had BCS and RT with no clear advantage to shorter interval imaging. Patients should wait 6 to 12 months after the completion of RT to begin their annual mammogram surveillance. Suspicious findings on physical examination or surveillance imaging might warrant a shorter interval between mammograms.

[ccc] The use of estrogen, progesterone, or selective estrogen receptor modulators to treat osteoporosis or osteopenia in patients 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 aromatase inhibitor therapy. Optimal duration of either therapy has not been established. Duration beyond 3 years 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. There are case reports of spontaneous fractures after denosumab discontinuation. Patients 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

RECURRENT/STAGE IV (M1) DISEASE

CLINICAL STAGE

Stage IV (M1) or Recurrent →

WORKUP[a]

- History and physical exam
- Discuss goals of therapy, adopt shared decision-making, and document course of care
- CBC
- Comprehensive metabolic panel, including liver function tests and alkaline phosphatase
- Imaging for systemic staging:
  - Chest diagnostic CT ± 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[ss] (category 2B)
  - FDG PET/CT[tt] (optional)
  - X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan
- Biomarker testing:
  - Biopsy of at least first recurrence of disease (consider re-biopsy if progression)
  - Evaluation of ER/PR and HER2 status[d,ddd,eee]
  - Comprehensive germline and somatic profiling to identify candidates for additional targeted therapies, see Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease (BINV-R)
- Genetic counseling if patient is at risk[e] for hereditary breast cancer
- Assess for distress[g]

→ See Treatment of Local and Regional Recurrence (BINV-19)
and
Supportive care[fff]

→ See Systemic Treatment of Recurrent Unresectable (local or regional) or Stage IV (M1) (BINV-20)[ggg]
and
Supportive care[fff]

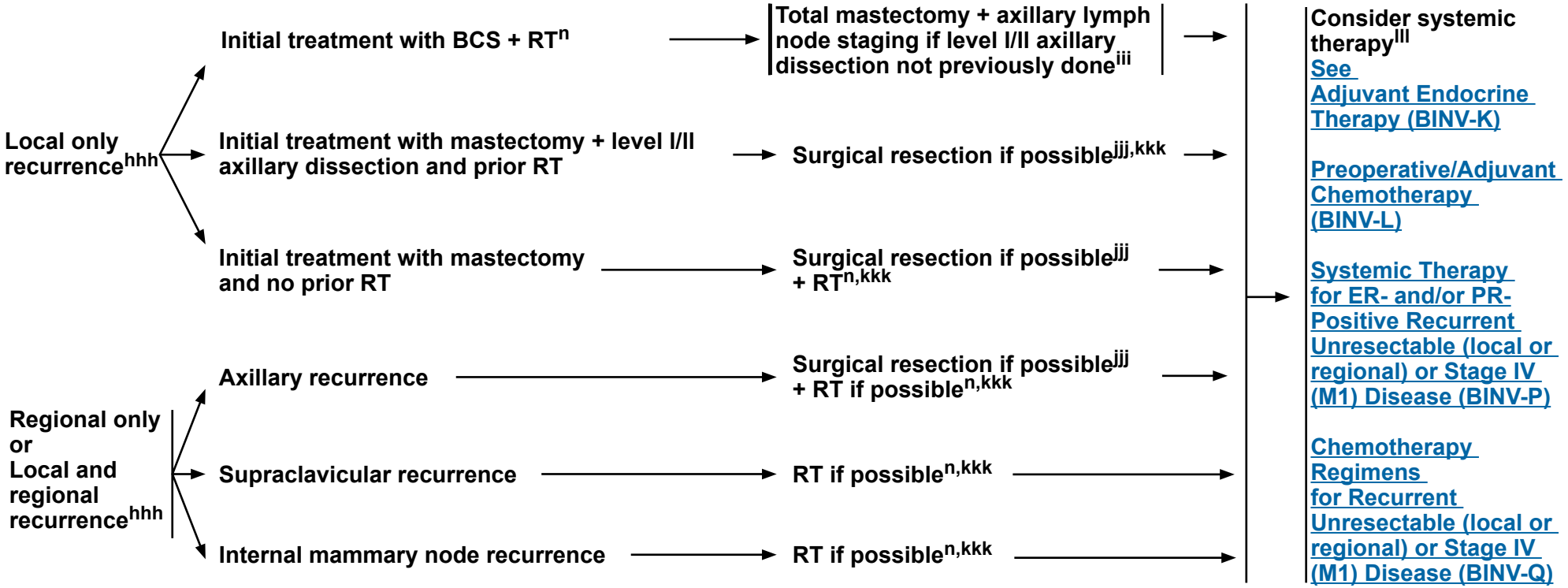
[a] For tools to aid optimal assessment and management of older adults, see NCCN Guidelines for Older Adult Oncology.
[d] See Principles of Biomarker Testing (BINV-A).
[e] For risk criteria, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.
[g] See NCCN Guidelines for Distress Management.
[ss] Bone scan or sodium fluoride PET/CT may not be needed if FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component.
[tt] 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. FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases when used in addition to standard staging studies.
[ddd] 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 HR-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).
[eee] 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. Since ER/PR and HER2 status can change with treatment and metastatic progression, it may be appropriate to consider repeat testing on new samples in these scenarios if management will change.
[fff] See NCCN Guidelines for Palliative Care and NCCN Guidelines for Supportive Care.
[ggg] For the treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

TREATMENT OF LOCAL AND REGIONAL RECURRENCE



[n] See Principles of Radiation Therapy (BINV-I).

[hhh] Multidisciplinary approach is especially important in the management of breast cancer recurrence to consider all potential treatment options for optimal outcomes.

[iii] In patients with a local breast recurrence after BCS who had a prior SLNB, a repeat SLNB may be considered although the accuracy of repeat SLNB is unproven. After mastectomy, repeat SLNB may be considered although there are limited data in this setting.

[jjj] If not technically resectable, consider systemic therapy to best response, then resect if possible.

[kkk] The decision to use RT 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.

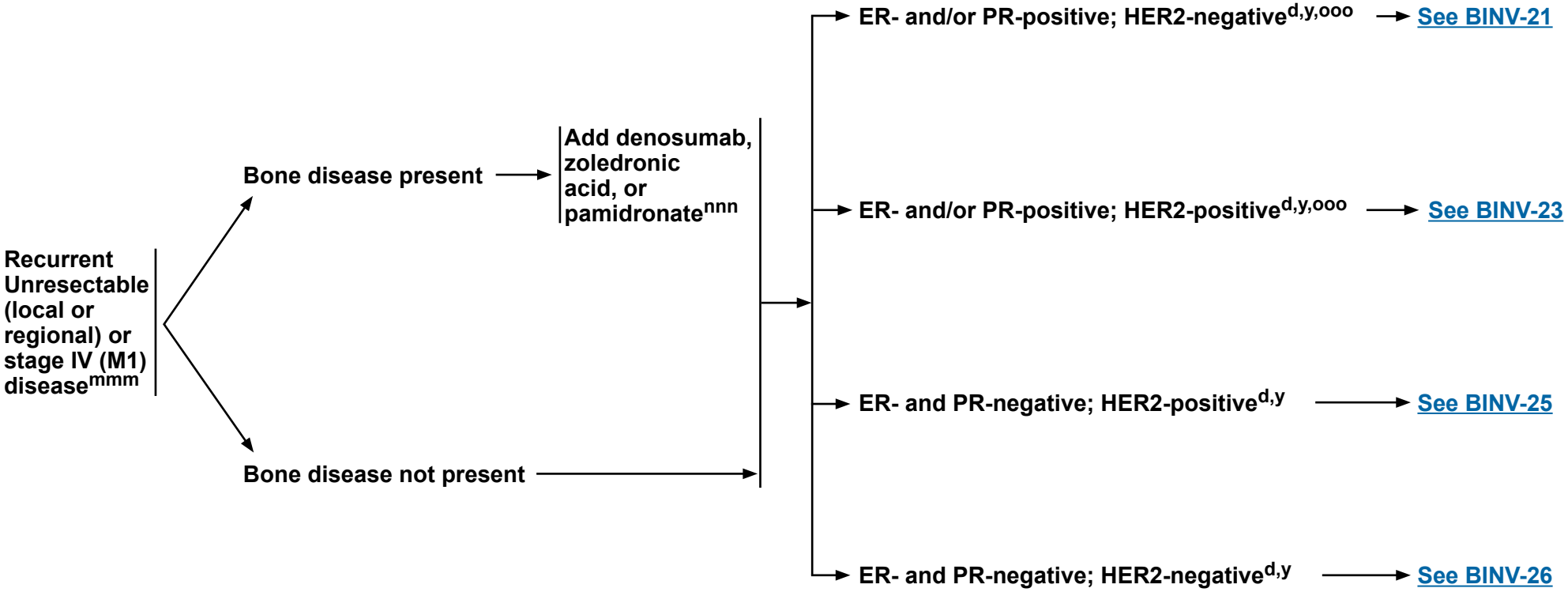
[lll] See the Discussion for additional information.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC TREATMENT OF RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE



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

[y] Although patients with cancers with 1%–100% ER IHC staining are considered ER-positive and eligible for endocrine therapies, there are more limited data on the subgroup of cancers with ER-low–positive (1%–10%) results. The ER-low–positive group is heterogeneous with reported biologic behavior often similar to ER-negative cancers; thus, individualized consideration of risks and benefits of endocrine therapy and additional adjuvant therapies should be incorporated into decision-making. See Principles of Biomarker Testing (BINV-A).

[mmm] Routine surgical resection of the primary breast tumor is generally not indicated in the management of patients presenting with de novo stage IV (M1) disease. Although there is no survival benefit, it may be considered for local control of the primary tumor. Discussion regarding management of the primary tumor in this setting must be individualized.

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

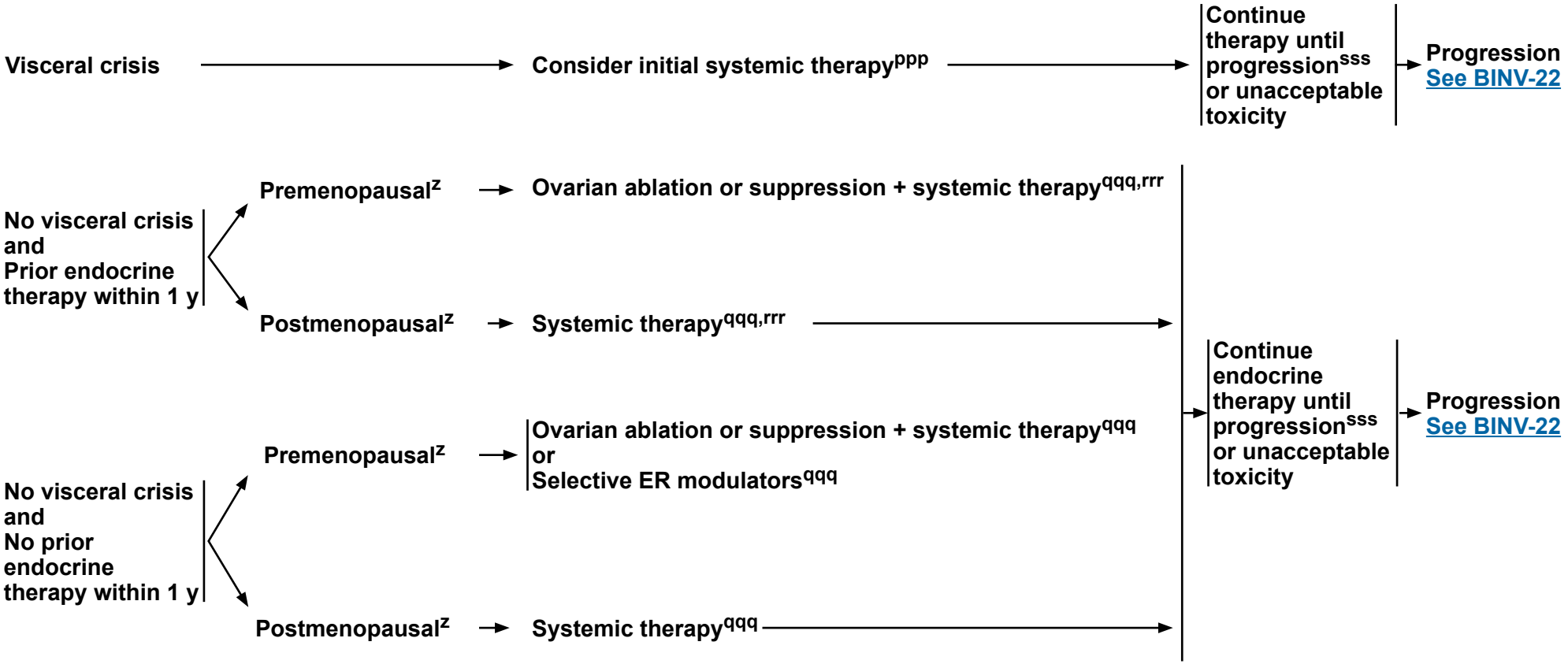
[ooo] Baseline assessment of bone density recommended for patients receiving an aromatase inhibitor who are at risk of osteoporosis (eg, age >65, family history, chronic steroids).

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC TREATMENT OF RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE: ER- AND/OR PR-POSITIVE; HER2-NEGATIVE[d]



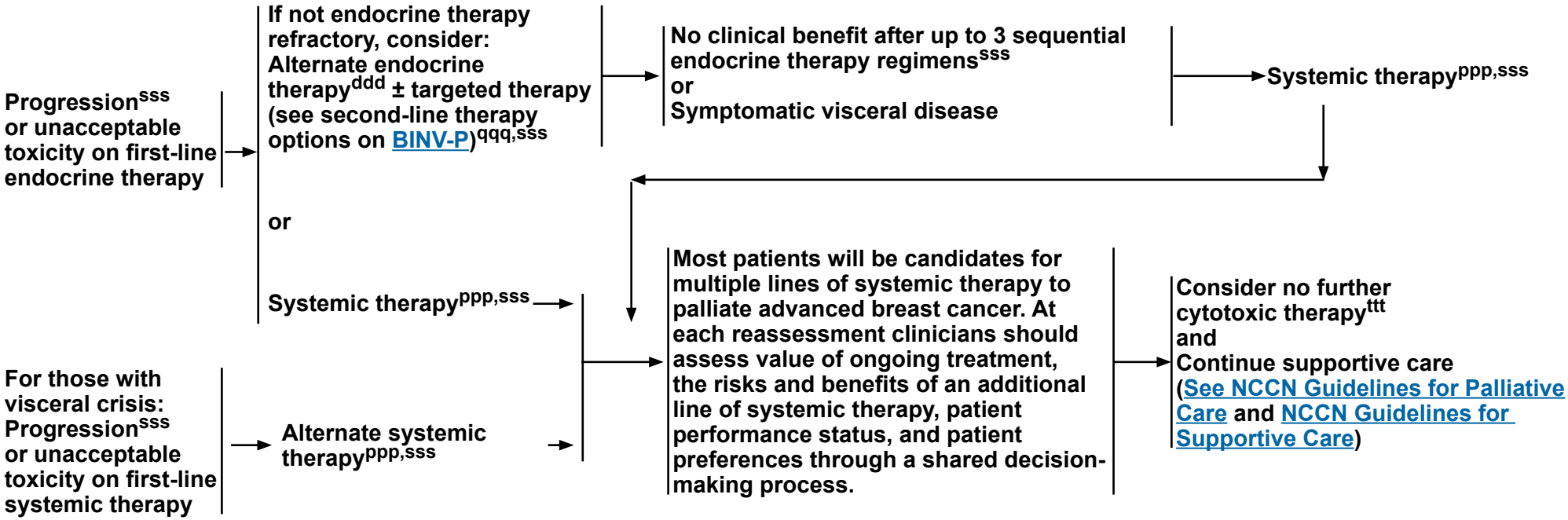
[d] See Principles of Biomarker Testing (BINV-A).
[z] See Definition of Menopause (BINV-O).
[ppp] See Systemic Therapy Regimens for Recurrent Unresectable (local or regional) or Stage IV (M1) Disease (BINV-Q).
[qqq] See Systemic Therapy for ER- and/or PR-Positive Recurrent Unresectable (local or regional)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

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC TREATMENT OF RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE: ER- AND/OR PR-POSITIVE; HER2-NEGATIVE[d,q]



[d] See Principles of Biomarker Testing (BINV-A).
[q] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).
[ddd] 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 HR-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).
[ppp] See Systemic Therapy Regimens for Recurrent Unresectable (local or regional) or Stage IV (M1) Disease (BINV-Q).
[qqq] See Systemic Therapy for ER- and/or PR-Positive Recurrent Unresectable (local or regional) or Stage IV (M1) Disease (BINV-P).
[sss] See Principles of Monitoring Metastatic Disease (BINV-S).
[ttt] The potential side effects of additional chemotherapy may outweigh any clinical benefit in a patient who has a compromised performance status. Patient preference must be taken into account.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

Systemic therapy + HER2-targeted therapy[ppp,qqq]
or
Endocrine therapy[uuu] ± HER2-targeted therapy (if premenopausal,[z] consider ovarian ablation or suppression)[qqq,vvv]

→

Continue therapy until progression[sss] or unacceptable toxicity

→

Progression
See BINV-24

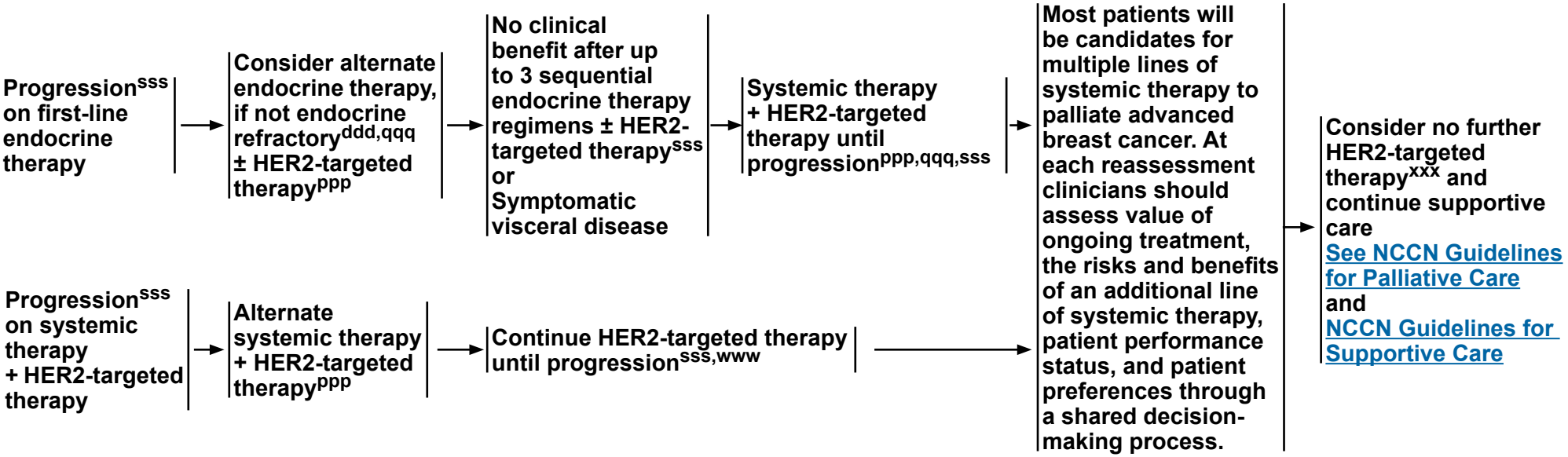
[d] See Principles of Biomarker Testing (BINV-A).
[z] See Definition of Menopause (BINV-O).
[ppp] See Systemic Therapy Regimens for Recurrent Unresectable (local or regional) or Stage IV (M1) Disease (BINV-Q).
[qqq] See Systemic Therapy for ER- and/or PR-Positive Recurrent Unresectable (local or regional) or Stage IV (M1) Disease (BINV-P).
[sss] See Principles of Monitoring Metastatic Disease (BINV-S).
[uuu] If prior endocrine therapy within 1 y, consider a different endocrine therapy.
[vvv] For premenopausal patients, tamoxifen alone (without ovarian ablation/suppression) + HER2-targeted therapy is also an 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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



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

[ddd] 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 HR-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).

[ppp] See Systemic Therapy Regimens for Recurrent Unresectable (local or regional) or Stage IV (M1) Disease (BINV-Q).

[qqq] See Systemic Therapy for ER- and/or PR-Positive Recurrent Unresectable (local or regional) or Stage IV (M1) Disease (BINV-P).

[sss] See Principles of Monitoring Metastatic Disease (BINV-S).

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

[xxx] The potential side effects of additional HER2-targeted therapy may outweigh any clinical benefit in a patient who has a compromised performance status. Patient preference must be taken into account.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC TREATMENT OF RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE: ER- and/or PR-NEGATIVE; HER2-POSITIVE[d]

Systemic therapy + HER2-targeted therapy[ppp] → **Continue therapy until progression[sss] or unacceptable toxicity** → **Progression[sss]** → **Alternate systemic therapy + HER2-targeted therapy[ppp,sss,www]** → **Most patients will be candidates for multiple lines of systemic therapy to palliate advanced breast cancer. At each reassessment clinicians should assess value of ongoing treatment, the risks and benefits of an additional line of systemic therapy, patient performance status, and patient preferences through a shared decision-making process.** → **Consider no further HER2-targeted therapy[xxx] and continue supportive care**
See NCCN Guidelines for Palliative Care
and
NCCN Guidelines for Supportive Care

[d] See Principles of Biomarker Testing (BINV-A).
[ppp] See Systemic Therapy Regimens for Recurrent Unresectable (local or regional) or Stage IV (M1) Disease (BINV-Q).
[sss] See Principles of Monitoring Metastatic Disease (BINV-S).

[www] Continue HER2-targeted therapy following progression on first-line HER2-targeted chemotherapy for metastatic breast cancer. The optimal duration of trastuzumab in patients with long-term control of disease is unknown.
[xxx] The potential side effects of additional HER2-targeted therapy may outweigh any clinical benefit in a patient who has a compromised performance status. Patient preference must be taken into account.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC TREATMENT OF RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE: ER- AND/OR PR-NEGATIVE; HER2-NEGATIVE[d]

Systemic therapy [ppp,yyy] → **Continue therapy until progression[sss] or unacceptable toxicity** → **Alternative systemic therapy[ppp,yyy]** → **Most patients will be candidates for multiple lines of systemic therapy to palliate advanced breast cancer. At each reassessment clinicians should assess value of ongoing treatment, the risks and benefits of an additional line of systemic therapy, patient performance status, and patient preferences through a shared decision-making process.** → **Consider no further cytotoxic therapy[xxx] and continue supportive care**
See NCCN Guidelines for Palliative Care
and
NCCN Guidelines for Supportive Care

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

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF BIOMARKER TESTING
HER2 TESTING[a,b]

- **HER2 testing should be performed on all new primary or newly metastatic breast cancers using methodology outlined in the ASCO/CAP HER2 testing guideline.[a]**
- **A re-review of the pathology with consideration for repeat or consultative HER2 testing should be made if a Grade 1 (any histologic type), pure mucinous, pure tubular, or pure cribriform carcinoma tests HER2-positive.[a]**
- **After a negative HER2 test result on initial biopsy sample, consider retesting on subsequent surgical or other additional sample if the initial sample was suboptimal (eg, minimal invasive cancer was present, cold ischemic time or fixation was suboptimal), testing error is expected, additional samples contain higher grade morphologically distinct cancer from the biopsy, to rule out heterogeneity in a high grade cancer, or if it will otherwise aid in clinical decision-making.[a]**

HER2 testing by validated IHC assay[b,c]

- **IHC 0,1+** → **HER2 (-)**
- **IHC 2+** → **Equivocal result** → **Must reflex test with ISH (if same specimen), or order new test with IHC or dual probe ISH (if new specimen available).**
- **IHC 3+** → **HER2 (+)**

HER2 testing by validated dual-probe[d] ISH assay[b,c]

- **HER2-Negative:**
  - **(Group 5) HER2/CEP17 ratio <2.0 AND average HER2 copy number <4.0 signals/cell)**
- **HER2-Negative[e] (Determined by concurrent IHC and ISH results):**
  - **(Group 2) HER2/CEP17 ratio ≥2.0 AND average HER2 copy number <4.0 signals/cell and concurrent IHC 0-1+ or 2+**
  - **(Group 3) HER2/CEP17 ratio <2.0 AND average HER2 copy number ≥6.0 signals/cell and concurrent IHC 0-1+**
  - **(Group 4) HER2/CEP17 ratio <2.0 AND average HER2 copy number ≥4.0 and <6.0 signals/cell and concurrent IHC 0-1+ or 2+**
- **HER2-Positive[e] (Determined by concurrent IHC and ISH results):**
  - **(Group 2) HER2/CEP17 ratio ≥2.0 AND average HER2 copy number <4.0 signals/cell and concurrent IHC 3+**
  - **(Group 3) HER2/CEP17 ratio <2.0 AND average HER2 copy number ≥6.0 signals/cell and concurrent IHC 2+ or 3+**
  - **(Group 4) HER2/CEP17 ratio <2.0 AND average HER2 copy number ≥4.0 and <6.0 signals/cell and concurrent IHC 3+**
- **HER2-Positive:**
  - **(Group 1) HER2/CEP17 ratio ≥2.0 AND average HER2 copy number ≥ 4.0 signals/cell)**

[a] NCCN endorses the ASCO/CAP HER2 testing guideline. "Principles of HER2 Testing" modified with permission from Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol 2018;36:2105-2122.

[b] Laboratory 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.

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

[d] Single-probe ISH assays are not preferentially recommended but if used, cases with average HER2 copy number ≥4.0 and <6.0 signals/cell should base final results on concurrent IHC and if 2+ reflexed to dual probe ISH testing.

[e] For ISH Groups 2–4 final ISH results are based on review of concurrent IHC, with recounting of the ISH test by a second reviewer if IHC is 2+ (per 2018 CAP/ASCO Update recommendations). Additional report comments are recommended for negative final results in these ISH Groups.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF BIOMARKER TESTING
HR TESTING

- **HR testing (ER and PR) by IHC should be performed on any new primary or newly metastatic breast cancer using methodology outlined in the latest ASCO/CAP HR testing guideline.[f] DCIS should be tested for ER (PR not required).**
- **ER testing should be used to determine if a patient is a candidate for endocrine therapies.**
  - **Cancers with 1%–100% of cells positive for ER expression are considered ER-positive. Patients with these results are considered eligible for endocrine therapies (applies to DCIS and invasive cancers).**
  - **Invasive cancers with between 1%–10% ER positivity are considered ER-low–positive. There are more limited data on the benefit of endocrine therapies in this group, but they suggest possible benefit from endocrine treatment, so patients are considered eligible for this treatment (as above). However, this group is noted to be heterogeneous and the biologic behavior of ER-low–positive cancers may be more similar to ER-negative cancers. This should be considered in decision-making for other adjuvant therapy and overall treatment pathway.**
  - **Cancers with <1% staining are considered ER-negative. Patients with cancers with these results have not been shown to benefit from endocrine therapies.**
- **Laboratories should have standard operating procedures to maximize accuracy and reproducibility of results for cases with <10% ER staining or weak intensity staining (to avoid false negatives). The status of controls should be reported for cases with these results.**
- **PR testing by IHC on invasive cancers can aid in the prognostic classification of cancers and serve as a control for possible false-negative ER results. Patients with ER-negative, PR-positive cancers may be considered for endocrine therapies, but the data on this group are noted to be limited. The same overall interpretation principles apply but PR should be interpreted as either positive (if 1%–100% of cells have nuclear staining) or negative (if <1% or 0% of cells have nuclear staining).**
- **Interpretation of any ER result by pathology should include evaluation of the concordance with the histologic findings of each case. Clinicians should be aware of when results are unusual and work with pathologists to attempt to resolve (eg, repeat testing, consultative review) or explain atypical reported findings. See table below.**

Summary of ER IHC Scoring/Interpretation

Results (following ER testing by validated IHC assay)		Interpretation/ Report As:
0% – <1% of nuclei stain		ER-negative
1%–100% of nuclei stain	1%–10% of nuclei stain	ER-low–positive (with recommended comment)
	>10% of nuclei stain	ER-positive

Correlation of ER and Histology: Highly Unusual Results

Highly Unusual ER-Negative Results	Highly Unusual ER-Positive Results
Low-grade invasive carcinomas of no special type (also known as invasive ductal carcinoma)	Metaplastic carcinomas of all subtypes
Lobular carcinomas (classic type)	Adenoid cystic carcinomas and other salivary gland-like carcinomas of the breast
Pure tubular, cribriform, or mucinous carcinomas	Secretory carcinoma
Encapsulated papillary and solid papillary carcinomas	Carcinomas with apocrine differentiation

[f] Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. J Clin Oncol 2020;38:1346-1366; Arch Pathol Lab Med 2020;144:545-563.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF DEDICATED BREAST MRI TESTING

See NCCN Guidelines for Breast Cancer Screening and Diagnosis for indications for screening MRI in patients 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-conservation therapy.**
- **May be useful in identifying otherwise clinically occult disease in patients presenting with axillary nodal metastases (cT0, cN+), with Paget 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 patients with prior breast cancer is undefined. It should generally be considered only in those whose lifetime risk of a second primary breast cancer is >20% based on models largely dependent on family history, such as in those with the risk associated with inherited susceptibility to breast cancer.**

[1] 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.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

FERTILITY AND BIRTH CONTROL

See NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology

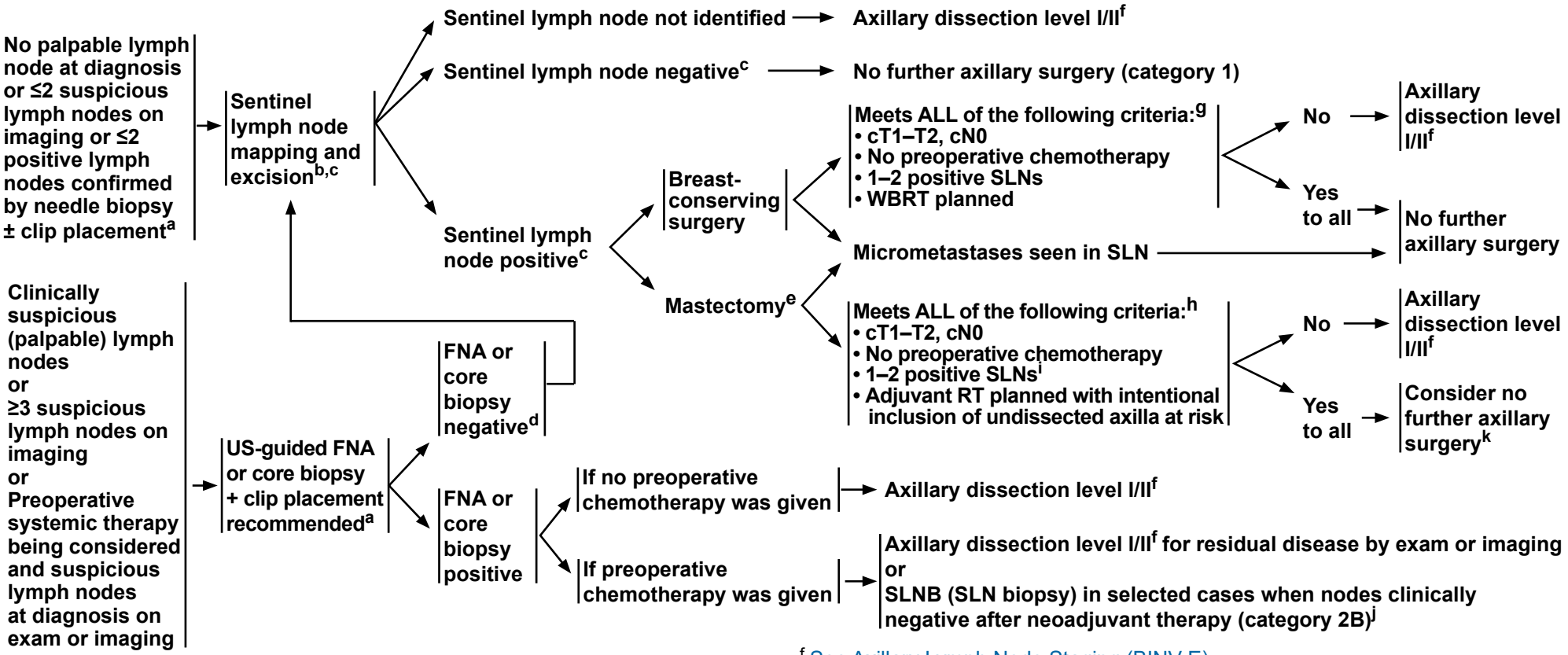
- All premenopausal patients should be informed about the potential impact of chemotherapy on fertility and asked about their desire for potential future pregnancies. Patients who may desire future pregnancies should be referred to fertility specialists before chemotherapy and/or endocrine therapy to discuss the options based on patient specifics, disease stage, and biology (which determine the urgency, 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 patients younger than 35 years resume menses within 2 years 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 infertility. 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 RT, chemotherapy, endocrine therapy, or during or within 6 months of completing trastuzumab or pertuzumab.
- Although data are limited, hormone-based birth control is discouraged regardless of the HR 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 patients with breast tumors (regardless of HR status) may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea.
- 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.
- Breastfeeding following breast-conservation cancer treatment is not contraindicated. However, the quantity and quality of breast milk produced by the conserved breast may not be sufficient or may be lacking some of the nutrients needed. Breastfeeding is not recommended during active treatment with chemotherapy and endocrine therapy or within 6 months of completing trastuzumab or pertuzumab.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

CONSIDERATIONS FOR SURGICAL AXILLARY STAGING



[a] If a positive lymph node is clipped at biopsy, every effort should be made to remove the clipped node at the time of surgery.
[b] SLN mapping injections may be peritumoral, subareolar, or subdermal.
[c] Sentinel node involvement is defined by multilevel node sectioning with hematoxylin and eosin (H&E) staining. Cytokeratin immunohistochemistry (IHC) may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is not recommended in clinical decision-making.
[d] If clinically negative axilla before chemotherapy and then have a positive sentinel node after chemotherapy, consider completion axillary lymph node dissection or multidisciplinary tumor board discussion on appropriateness of radiation of axilla without further surgery.
[e] Limited data exist for mastectomy patients.
[f] See Axillary Lymph Node Staging (BINV-E).
[g] ACOSOG Z0011: Giuliano AE, et al. JAMA. 2017 Sep 12;318(10):918-926.
[h] EORTC AMAROS: Donker M, et al. Lancet Oncol. 2014;15(12):1303-10; Rutgers E, et al. Cancer Research. 2019;79(4 Supplement):GS4-01-GS04-01.
[i] Limited data exist for ≥3 positive SLNs.
[j] Among patients shown to be N+ 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 ≥3 sentinel nodes (targeted axillary lymph node dissection). (Caudle AS, et al. J Clin Oncol 2016;34:1072-1078.)
[k] In the mastectomy setting, in patients who were initially cN0, who have positive nodes on SLNB, and have no axillary dissection, RT to the chest wall should include undissected axilla at risk ± RNI.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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 RT 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).

Lymphedema is a potential side effect after the treatment of axillary lymph node surgery resulting from damage to the lymphatic system. Early detection/diagnosis of lymphedema is key for optimal management. Consider pretreatment measurement of both arms as a baseline for patients with risk factors for lymphedema. See NCCN Guidelines for Survivorship: Lymphedema (SLYMPH-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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

MARGIN STATUS RECOMMENDATIONS AFTER BREAST-CONSERVING SURGERY (BCS) FOR INVASIVE CANCERS AND DCIS

- **Margins should be evaluated on all surgical specimens from breast-conserving surgery (BCS). 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.**
- **For mammographically detected DCIS with microcalcifications, complete resection should be documented by analysis of margins and specimen radiography. Post-excision mammography can be considered if there is uncertainty.**
- **The NCCN Panel accepts the definitions of negative margins after breast-conservation therapy from the 2014 SSO/ASTRO Margins Guideline[1] for Stage I/II Invasive Cancers and the 2016 SSO/ASTRO/ASCO Guideline for DCIS.[2] For patients with stage I or II invasive cancers after BCS, a positive margin is defined as "ink on tumor" (any invasive cancer or DCIS cells on ink). These patients generally require further surgery—either a re-excision to achieve a negative margin or a mastectomy. If re-excision is technically feasible to allow for BCS to achieve "no ink on tumor," 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. There may be select patients with stage III invasive cancers who may be eligible for BCS. For these patients, the margins status would be accessed with similar definitions.**

DCIS

- **For patients with pure DCIS treated by BCS and WBRT, a quantitative description of any tumor close to margin resection width of at least 2 mm is associated with a reduced risk of ipsilateral breast tumor recurrence (IBTR) relative to narrower negative margin widths, while the routine practice of obtaining margins greater than 2 mm to further improve outcomes is not supported by the evidence. When there is only minimal or focal DCIS involvement near the margin, clinical judgment should be utilized to weigh the risks of re-excision with risk of recurrence for an individual patient.**
- **For patients with DCIS treated with excision alone (no WBRT), regardless of margin width, there is a substantially higher rate of IBTR than treatment with excision and WBRT, even in predefined, low-risk patients. Although the optimal margin width for treatment with excision alone is unknown, it should be at least 2 mm, with some evidence suggesting improved IBTR rates with margin widths wider than 2 mm.**
- **DCIS with microinvasion (DCIS-M), defined as an invasive focus ≤1 mm in size, should refer to the DCIS margin definition when considering the optimal margin width (>2 mm), given that the majority of DCIS-M is comprised of DCIS and systemic therapy utilization for this lesion more closely reflects the treatment pattern for DCIS than for invasive carcinoma.**

Continued

[1] Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for BCS with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol 2014;32:1507-1515.
[2] Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for BCS With Whole-Breast Irradiation in Ductal Carcinoma In Situ. J Clin Oncol 2016;34:4040-4046.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

MARGIN STATUS RECOMMENDATIONS AFTER BCS FOR INVASIVE CANCERS AND DCIS

Invasive Breast Cancer

- **For invasive breast cancers that have a component of DCIS, regardless of the extent of DCIS, the negative margin definition of "no ink on tumor" should be based on the invasive margin guideline. In this setting, "no ink on tumor" is recommended for either DCIS or invasive cancer cells, primarily because the natural history, treatment, and outcomes of these lesions are more similar to invasive cancer than DCIS. For specifically challenging cases, clinical judgment and discussion with the patient should precede routine re-excision.**
- **These margin recommendations cannot be applied directly to patients undergoing APBI,[1] where data regarding local recurrence are more limited. Furthermore, individualized clinical judgment should be utilized on a case-by-case basis, using postoperative mammography to identify residual calcifications and clinical-pathologic factors such as quantitative extent of disease near margin, presence of extensive intraductal component (EIC),[3] young age, or multiple close margins to assist in identifying patients who may have an increased risk of IBTR and therefore may be selected to benefit from re-excision.**
- **For patients with invasive breast cancer after BCS, with microscopically focally positive margins (in the absence of an EIC),[3] the use of a higher radiation boost dose to the tumor bed may be considered, since generally a boost to the tumor bed is recommended for patients at higher risk of recurrence. See BINV-I.**

	No ink on tumor	2-mm margin	No margin necessary
Invasive breast cancer	X		
Invasive breast cancer + DCIS	X		
Invasive breast cancer + extensive DCIS	X		
Pure DCIS		X	
DCIS with microinvasion		X	
Pure LCIS* at surgical margin			X
Atypia at surgical margin			X

*For pleomorphic LCIS, the optimal width of margins is not known.

[1] Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for BCS with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol 2014;32:1507-1515.

[3] EIC is defined as an infiltrating ductal cancer where >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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SPECIAL CONSIDERATIONS TO BREAST-CONSERVATION THERAPY REQUIRING RT

Contraindications for breast-conservation therapy requiring RT include:

Absolute
- **RT 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 margins[a]**
- **Homozygous (biallelic inactivation) for *ATM* mutation (category 2B)**

Relative
- **Prior RT 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)**
- **Persistently positive pathologic margin[a]**
- **Patients 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-conservation therapy**
  - **May be considered for prophylactic bilateral mastectomy for risk reduction**
    (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic)
  - **May have known or suspected Li-Fraumeni syndrome (category 2B)**

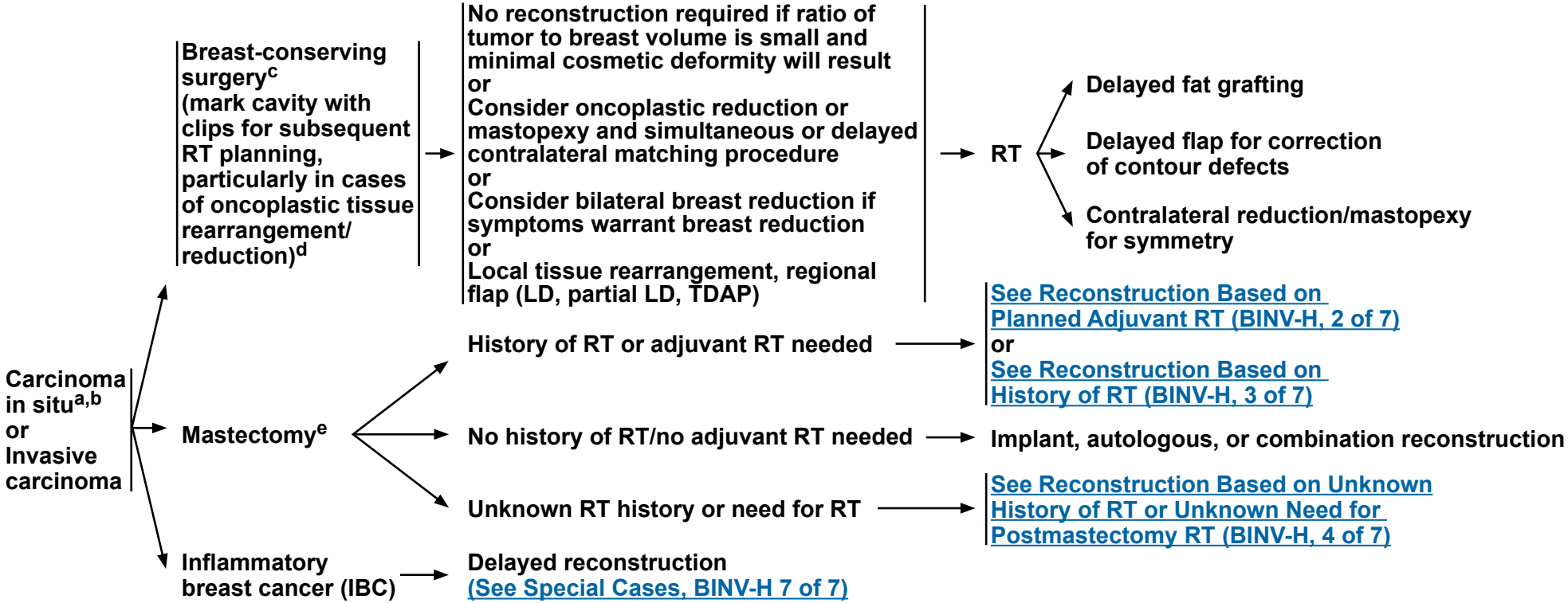
[a] See Margin Status Recommendations After BCS for Invasive Cancers and DCIS (BINV-F).

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY



[a] See General Principles of Breast Reconstruction (BINV-H 5 of 7).
[b] See Patient Factors Affecting Choice of Reconstruction (BINV-H 6 of 7).
[c] An evaluation of the likely cosmetic outcome of BCS 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 oncoplastic techniques may reduce the need for mastectomy and decrease the need for a secondary surgery to minimize breast deformity. Patients should be informed of the possibility of positive margins and potential need for secondary surgery, which could include either segmental re-excision, or mastectomy with or without loss of the nipple. Systematic oncoplastic reduction specimen orientation as well as highly specific operative documentation regarding tissue rearrangement should be conducted. Enhanced communication between the radiation oncology team and reconstructive team will be necessary for boost cavity localization for RT treatment planning (Shah C, et al. Ann Surg Oncol 2018;25:2509-2511).
[d] Consider staged partial mastectomy reconstruction (oncoplastic approaches) if preoperative margin status is unclear (lobular, multifocal/centric).
[e] As with any mastectomy, there is a risk of locoregional cancer recurrence, and evidence suggests skin-sparing or skin- and nipple-sparing mastectomy is probably equivalent to standard mastectomy in this regard. Post-mastectomy RT 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

RECONSTRUCTION BASED ON PLANNED ADJUVANT RT[a,b]

Implant-based reconstruction planned[f]

- **2 stage: tissue expander followed by permanent implant (prepectoral, partial submuscular, or total submuscular tissue expander)**
  - **Expansion followed by exchange to implant prior to the initiation of RT[k]**
  - **Expansion followed by RT and delayed exchange to implant[j,k]**
- **1 stage: direct to implant[h]**

Autologous reconstruction planned[g]

- **Immediate autologous reconstruction[i]**
- **Delayed reconstruction after the completion of RT[i]**
- **Place tissue expander at the time of surgery, followed by expansion, RT, and delayed autologous reconstruction[i,j]**

[a] See General Principles of Breast Reconstruction (BINV-H 5 of 7).
[b] See Patient Factors Affecting Choice of Reconstruction (BINV-H 6 of 7).
[f] In the setting of RT, implants are at a statistically significant increased risk of capsular contracture, aesthetic deformity, malposition, implant exposure, infection, and reconstructive failure.
[g] Common donor sites for autologous tissue include the abdomen (ie, DIEP, MS-TRAM, SIEA, free TRAM, pedicled TRAM), gluteal region (ie, SGAP, IGAP), thigh (ie, TUG, VUG, DUG, PAP), or the back (ie, LD, TDAP).
[h] Determined by preoperative size and ptosis, patient desire of postoperative size, and assessment intraoperatively of skin and soft tissue quality and perfusion, with consideration for patient-specific relative contraindications (eg, smoking, obesity) to single-stage vs. two-stage approaches. Healing issues may occur and delay initiation of RT.
[i] Consider delaying autologous reconstruction until after RT is completed, as RT to a flap may cause loss of cosmesis and/or fat necrosis.
[j] Consultation with radiation oncology may be necessary to determine if volume of contralateral tissue expander will affect RT treatment plan, because cases may require contralateral deflation. Radiation oncology consultation should also be requested in cases of an anticipated close or positive deep margin, as this may impact the optimal placement of the expander (pre- vs. subpectoral).
[k] Exchange of tissue expander to implant should be timed to avoid any delay in adjuvant RT.

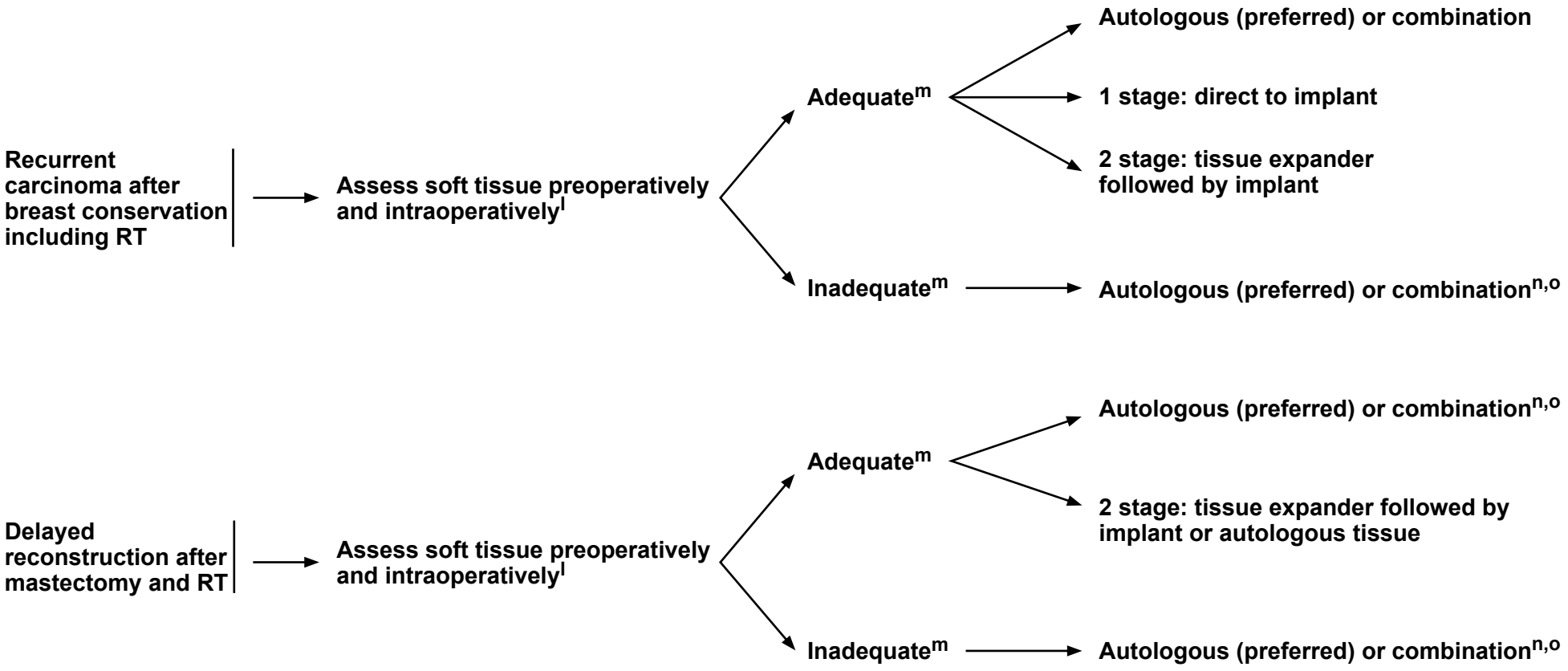
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

RECONSTRUCTION BASED ON HISTORY OF RT[a,b]



[a] See General Principles of Breast Reconstruction (BINV-H 5 of 7).
[b] See Patient Factors Affecting Choice of Reconstruction (BINV-H 6 of 7).
[l] Assessment includes clinical examination and may also include intraoperative technologies to assess perfusion.
[m] In patients with a history of RT to the breast, implant-based reconstruction carries a significantly increased risk of capsular contracture, aesthetic deformity, malposition, implant exposure, infection, and reconstructive failure.
[n] Addition of latissimus flap to prosthetics in the previously irradiated patient mitigates many of the above effects.
[o] In the delayed reconstruction patient, there is often limited soft tissue even with the addition of a latissimus flap. Therefore, latissimus flap + tissue expander placement may be required if a permanent implant cannot be accommodated under the latissimus flap.

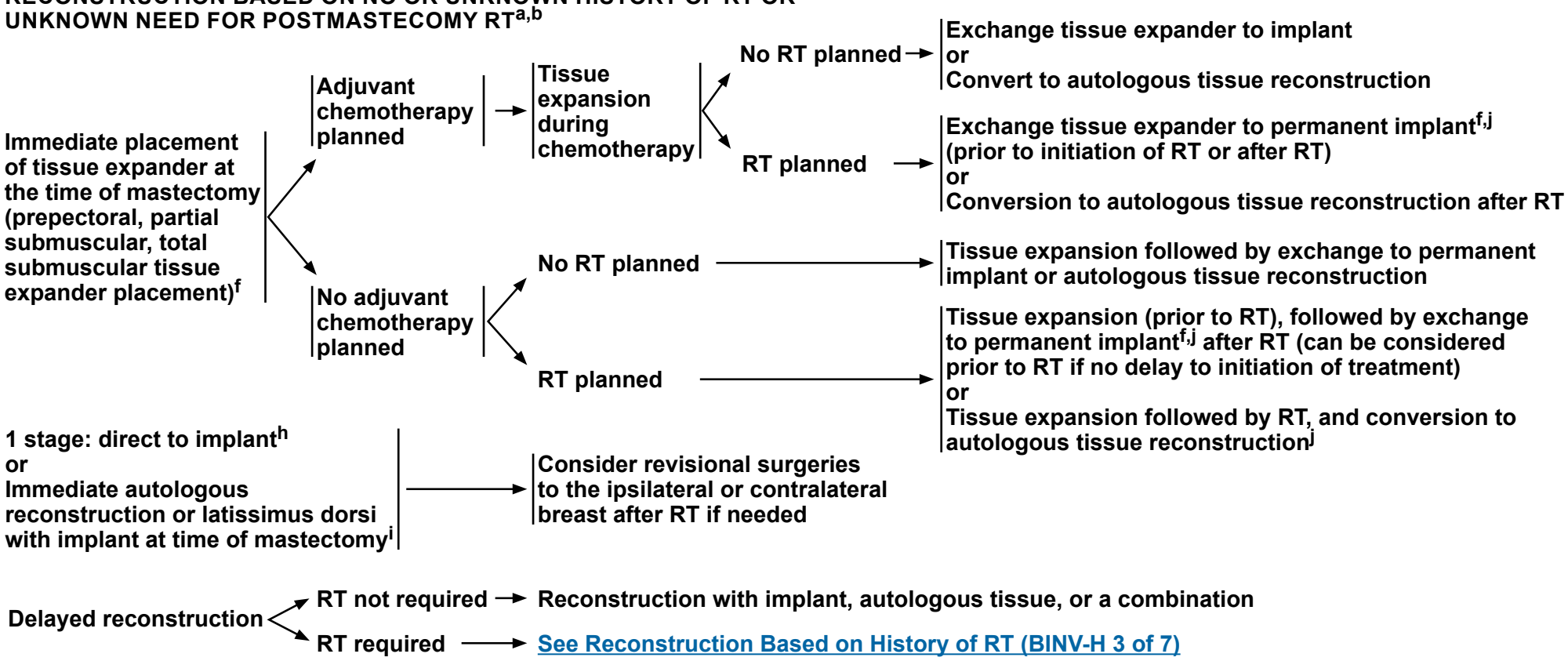
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

RECONSTRUCTION BASED ON NO OR UNKNOWN HISTORY OF RT OR UNKNOWN NEED FOR POSTMASTECOMY RT[a,b]



[a] See General Principles of Breast Reconstruction (BINV-H 5 of 7).
[b] See Patient Factors Affecting Choice of Reconstruction (BINV-H 6 of 7).
[f] In the setting of RT, implants are at a statistically significant increased risk of capsular contracture, aesthetic deformity, malposition, implant exposure, infection, and reconstructive failure.
[h] Determined by preoperative size and ptosis, patient desire of postoperative size, and assessment intraoperatively of skin and soft tissue quality and perfusion, with consideration for patient-specific relative contraindications (eg, smoking, obesity) to single-stage vs. two-stage approaches. Healing issues may occur and delay initiation of RT.
[i] Consider delaying autologous reconstruction until after RT is completed, as RT to a flap may cause loss of cosmesis and/or fat necrosis.
[j] Consultation with radiation oncology may be necessary to determine if volume of contralateral tissue expander will affect RT treatment plan, because cases may require contralateral deflation. Radiation oncology consultation should also be requested in cases of an anticipated close or positive deep margin, as this may impact the optimal placement of the expander (pre- vs. subpectoral).

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

General Principles of Breast Reconstruction

- **Breast reconstruction may be an option for any patient receiving surgical treatment for breast cancer. All patients 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.**
- **Some patients may choose not to have reconstruction after mastectomy. The option to undergo mastectomy alone with a surgically optimized closure should be offered to all patients as part of a comprehensive discussion of reconstructive options. Achieving the optimal result in this scenario may require additional procedures beyond the initial mastectomy. See BINV-H (6 of 7) for patient factors influencing choice of reconstruction.**
- **Selection of reconstruction option is based on an assessment of cancer treatment, patient body habits, obesity, smoking history, comorbidities, and patient concerns. Smoking and obesity (WHO Class 2 and 3) increase the risk of preoperative complications for all types of breast reconstruction, whether with implant or flap prosthetic or autologous. Patients with these risk factors should be counseled about their increased risk for complications following breast reconstruction, including donor site complications/hernias and bulges of the abdominal wall, delayed healing, mastectomy skin flap necrosis, total flap failure (obesity), and implant failure (smoking).**
- **Nipple areolar reconstruction should be offered to patients if the nipple-areolar complex (NAC) has been removed as part of their cancer treatment. Various techniques are available for nipple reconstruction. Three-dimensional (3-D) tattooing can be offered to patients as an option for NAC reconstruction.**
- **Additionally, patients who are not satisfied with the cosmetic outcome following completion of breast cancer treatment should be offered reconstructive surgery consultation.**
- **Patients known to harbor genetic mutations that increase the risk of breast cancer may opt to undergo bilateral prophylactic mastectomies with reconstruction. Reconstruction can be performed with prosthetic, autologous tissue, or a combination of implant with autologous tissue.**
- **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.**
- **Revisional surgery may be necessary after breast reconstruction. This may include procedures such as fat grafting, mastopexy, direct excision/suction-assisted lipectomy, contralateral procedures (in cases of unilateral reconstruction), and others. Patients should be informed before reconstruction that revision surgery may be necessary.**

Continued

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

Patient Factors Influencing Breast Reconstruction

- Breast reconstruction is elective and patients may choose to not have breast reconstruction. Individual patients present preoperatively with a variety of factors that may impact the choice of reconstruction, the risk of complications, donor site morbidity, and aesthetic result. Each of these factors must be taken into account, along with patient desire, to choose the optimal method of reconstruction.
- Patient desire
  - The patient may have a strong feeling towards one form of reconstruction after being given the options. Breast reconstruction should be a shared decision.
- Medical comorbidities
  - Medical comorbidities may preclude longer reconstructive procedures such as autologous tissue reconstruction in some patients.
  - The selection of the reconstructive method of choice should take into consideration patient comorbidities.
  - Poorly controlled diabetes is a risk factor for postoperative complications in both implant and autologous tissue reconstruction.
  - Patients should be screened for personal or familial thrombophilia. Thrombophilia may result in reconstructive failure of microsurgical reconstruction or thromboembolic events.
- Tobacco use
  - Smoking has been associated with increased risk of delayed wound healing, mastectomy flap necrosis, NAC necrosis in the setting of nipple-sparing mastectomy, infection, and failure of implant-based reconstruction. In free flap reconstruction, smoking increases the risk of donor complications. Patients should be encouraged to stop smoking prior to reconstruction.
  - Smoking has not definitively been shown to increase the risk of microvascular thrombosis in free flap breast reconstruction.
- Breast size/shape
  - If patient has significant macromastia or ptosis, consideration can be given to a reduction pattern mastectomy with either implant-based or autologous tissue reconstruction, or oncoplastic reduction techniques.
  - The volume limitations of implants may preclude an acceptable reconstruction in patients with macromastia if preservation of volume is a priority.
- BMI
  - Patients with a markedly elevated BMI may be at increased risk of infectious complications and seromas as well as donor site complications from autologous reconstruction, including delayed healing and hernia formation. Immediate reconstruction can be performed, but delayed reconstruction can be considered if the patient is motivated to lose weight. Oncoplastic reduction techniques can be considered if the breast is large/ptotic.
- Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL)
  - There exists an association between certain types of textured breast implants and BIA-ALCL. The risk appears to vary based on the method of texturing. Patients with a past or current history of textured implants should follow up with their reconstructive surgeon. See NCCN Guidelines for T-Cell Lymphomas.

Continued

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

Special Cases

- **Nipple-sparing mastectomy**
  - **Historically, the NAC has been 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 early-stage breast cancer, DCIS, risk-reduction procedures, and in some locally advanced invasive cancers (ie, with complete clinical response to preoperative chemotherapy and no nipple involvement with cancer). Preoperative clinical or radiographic evidence of nipple involvement, including Paget disease, bloody nipple discharge associated with malignancy, IBC, 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. Preoperative breast size, shape, and nipple position should also be considered in the decision to perform NAC-sparing mastectomy. Patients with small to moderate breast volume with good nipple position are ideal candidates. In patients with large or significantly ptotic breasts, NAC-sparing mastectomies may be offered in select cases by using various reduction patterns or delay techniques to augment the NAC perfusion, either in an immediate or delayed fashion, as long as it does not delay oncologic care. Intraoperative assessment of the NAC perfusion should also guide the decision to preserve the NAC or remove it.**
  - **Patients should be counseled on the risk of delayed healing, nipple necrosis, loss of pigmentation, loss of sensation, loss of projection, and need for subsequent removal of the NAC.**
- **Inflammatory breast cancer**
  - **Delayed reconstruction after mastectomy for IBC remains the clinical standard, for several reasons. The need to resect involved skin negates the benefit of skin-sparing mastectomy for immediate reconstruction, and high rates of local and distant recurrence warrant comprehensive, regional nodal irradiation in a timely fashion, which may be technically more challenging or subject to delay after immediate reconstruction.**
  - **Advances in multimodal therapy have improved 5-year survival in IBC patients, justifying clinical studies to see if immediate reconstruction may be appropriate for certain patients with IBC, but neither the outcomes nor the clinical features to predict such outcomes are known at this time.**
  - **In the uncommon clinical circumstance that the extent of skin excision at the time of mastectomy precludes primary or local closure, reconstruction of the chest wall defect with autologous tissue is necessary, and concomitant immediate reconstruction may be accomplished.**

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF RADIATION THERAPY

Optimizing Delivery of Individual Therapy

- It is important to individualize RT planning and delivery.
  - 3-D CT-based treatment planning should be routinely utilized to delineate target volumes and adjacent organs at risk.
  - Radiation to the breast/chest wall and nodal regions is generally delivered with single energy or mixed energy photons ± electrons.
  - Improved homogeneity of the target dose and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments, and intensity-modulated RT (IMRT).
  - Additional techniques such as respiratory control (deep inspiration breath-hold), prone positioning, and cardiac blocks may also be used to try to further reduce dose to heart, lung, and adjacent normal tissue.
  - Verification of treatment setup consistency is done with weekly imaging. When using certain techniques (ie, prone breast), more frequent imaging may be appropriate. Standard utilization of daily imaging is not recommended.
  - When treating the internal mammary nodes, dose-volume histograms (DVHs) should be used to evaluate dose constraints, dose to normal tissues (ie, heart, lung), and planning target volumes (PTVs).
- It is common for RT to follow chemotherapy when chemotherapy is indicated.

Whole Breast Radiation

- Target definition is the breast tissue at risk.
- RT dosing:
  - The whole breast should receive a hypofractionated dose of 40–42.5 Gy in 15–16 fractions; in selected cases 45–50.4 Gy in 25–28 fractions may be considered.
  - 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.
- Lumpectomy cavity boost can be delivered using enface electrons, photons, or brachytherapy.
- Ultra-hypofractionated WBRT of 28.5 Gy delivered as 5 (once-a-week) fractions may be considered in select patients aged >50 years following BCS with pTis/T1/T2/N0, though the optimal fractionation for the boost delivery is unknown for this regimen.[a,b]
- 3-D planning to minimize inhomogeneity and exposure to heart and lung is essential when using this regimen.

[a] Alternatively, 26 Gy in 5 daily fractions over one week may be considered, though data beyond 5 years for local relapse or toxicity are not yet available for this regimen. [Murray Brunt A, Haviland JS, Wheatley DA, et al. Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. Lancet 2020;395:1613-1626.]

[b] Brunt AM, Haviland JS, Sydenham M, et al. Ten-year results of FAST: A randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. J Clin Oncol 2020;38:3261-3272.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF RADIATION THERAPY

Chest Wall Radiation (including breast reconstruction)

- The target includes the ipsilateral chest wall, mastectomy scar, and drain sites when indicated.
  - Depending on whether or not the patient has had breast reconstruction, several techniques using photons and/or electrons are appropriate.
  - Special consideration should be given to the use of bolus material to ensure that the skin dose is adequate, particularly in the case of IBC.
  - RT dosing:
    - Dose is 45–50.4 Gy in 25–28 fractions to the chest wall ± scar boost, at 1.8–2 Gy per fraction, to a total dose of approximately 60–66 Gy.
- Chest wall scar boost may be delivered with or without bolus using electrons or photons.

Regional Nodal Radiation

- For paraclavicular and axillary nodes, prescription depth varies based on the patient anatomy.
- Regional nodes should be contoured when considering regional nodal RT. Refer to breast atlases for contouring guidelines.[c,d]
- RT dosing:
  - Dose is 45–50.4 Gy in 25–28 fractions to the regional nodal fields.
  - A supplemental boost of RT can be delivered to grossly involved or enlarged lymph nodes (ie, internal mammary or clavicular) that have not been surgically addressed.

RT with Preoperative or Adjuvant Systemic Therapy

- In patients treated with preoperative systemic therapy, adjuvant RT is based on the maximal disease stage (ie, clinical stage, pathologic stage, tumor characteristics) at diagnosis (before preoperative systemic therapy) and pathology results after preoperative systemic therapy.
- Sequencing of RT with systemic therapy:
  - It is common for RT to follow chemotherapy when chemotherapy is indicated. However,
    - CMF (cyclophosphamide/methotrexate/fluorouracil) and RT may be given concurrently, or CMF may be given first.
    - Capecitabine should be given after completion of RT.
    - Adjuvant olaparib can be given concurrently with RT (and endocrine therapy).
  - Adjuvant HER2-targeted therapy and/or endocrine therapy may be delivered concurrently with RT.
  - Available data suggest that sequential or concurrent endocrine therapy with RT is acceptable. Due to compounding side effects, initiating endocrine therapy at the completion of RT may be preferred.

[c] Offersen BV, Boersma LJ, Kirkove C, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiother Oncol 2015;114:3-10.
[d] Gentile MS, Usman AA, Neuschler EI, et al. Contouring guidelines for the axillary lymph nodes for the delivery of radiation therapy in breast cancer: Evaluation of the RTOG Breast Cancer Atlas. Int J Radiat Oncol Biol Phys 2015;93:257-265.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF RADIATION THERAPY

Accelerated Partial Breast Irradiation (APBI)

- **Studies of APBI suggest that rates of local control in selected low-risk patients with early-stage breast cancer are comparable to those treated with standard WBRT. However, compared to standard WBRT, several studies document an inferior cosmetic outcome with external beam delivery methods of 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 consensus statement, which now defines patients age ≥50 years to be considered "suitable" for APBI if:**
    - **Invasive ductal carcinoma measuring ≤2 cm (pT1 disease) with negative margin widths of ≥2 mm, no LVI, ER-positive, and *BRCA* negative; or**
    - **Low/intermediate nuclear grade, screening-detected DCIS measuring size ≤2.5 cm with negative margin widths of ≥3 mm.**
- **RT dosing**

Regimen	Method	Reference
30 Gy/5 fractions QOD (preferred)	**External beam RT (EBRT)[e]**	Livi L, Meattini I, Marrazzo L, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur J Cancer 2015;51:451-463. Meattini I, Marrazzo L, Saieva C, et al. Accelerated partial-breast irradiation compared with whole-breast irradiation for early breast cancer: Long-term results of the randomized phase III APBI-IMRT-Florence Trial. J Clin Oncol 2020;38:4175-4183.
40 Gy/15 fractions	**EBRT**	Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet 2017;390:1048-1060.
34 Gy/10 fractions BID	**Balloon/ Interstitial**	Vicini FA, Cecchini RS, White JR, et al. Long-term primary results of accelerated partial breast irradiation after BCS for early-stage breast cancer: a randomised, phase 3, equivalence trial. Lancet 2019;394:2155-2164.
38.5 Gy/10 fractions BID	**EBRT**	Whelan TJ, Julian JA, Berrang TS, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. Lancet 2019;394:2165-2172.

[e] The protocol mandated IMRT.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SPECIAL CONSIDERATIONS FOR BREAST CANCER IN MALES (SEX ASSIGNED AT BIRTH)

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

- **Few males have been included in breast cancer trials.[1] Therefore, recommendations regarding management of breast cancer in males are generally extrapolated from findings of clinical trials focusing on breast cancer in females.**
- **Although there are some biologic and clinical differences between breast cancer in males and females, management of breast cancer in males is similar overall to management of breast cancer in females, with the following special considerations pertinent to male patients:[2]**
  - **Genetics: The NCCN Panel recommends consideration of genetic testing for all males with breast cancer (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic).**
  - **Breast surgery: Historically, males with breast cancer have undergone mastectomy more often than breast-conserving surgery. However, breast-conservation therapy is increasingly being performed in males and evolving data indicate that breast conservation in males is associated with equivalent outcomes to mastectomy and that it is safe and feasible. Decisions about breast conservation versus mastectomy in males should be made according to similar criteria as for females.[2-9]**
  - **Axillary lymph node surgery: As in females, SLNB should be performed in the setting of male breast cancer with a clinically node-negative axilla.[2,4]**
  - **RT: Indications for radiation after breast surgery in males with breast cancer are the same as for females with breast cancer.[2,5,10,11]**
  - **Use of molecular assays: Data are limited regarding the use of molecular assays to assess prognosis and to predict benefit from chemotherapy in males with breast cancer.[2] Available data suggest the 21-gene assay recurrence score provides prognostic information in males with breast cancer.[12,13]**
  - **Preoperative/adjuvant systemic therapy: Chemotherapy with/without HER2-targeted therapy should be recommended for males with breast cancer according to guidelines for females with breast cancer.[2] Options for adjuvant endocrine therapy for males with breast cancer include tamoxifen for 5–10 years or, if tamoxifen is contraindicated, a GnRH analog plus an aromatase inhibitor. In males, single-agent adjuvant treatment with an aromatase inhibitor has been associated with inferior outcomes compared to tamoxifen alone, likely due to inadequate estradiol suppression, and is not recommended.[2,14-17]**
  - **Follow-up after treatment for early-stage disease: There are only limited data to support screening for breast cancer in males.[2] The NCCN Panel recommends that bone density be assessed at baseline and every 2 years in males with breast cancer who receive adjuvant GnRH analog therapy. Low bone density should be managed according to standard guidelines.[18]**
  - **Systemic therapy for advanced disease: Management of advanced breast cancer in males is similar to that in females; however, it is preferred that when an aromatase inhibitor is used, a GnRH analog should be given concurrently.[2] Available data suggest single-agent fulvestrant has similar efficacy in males as in females.[19] Newer agents such as CDK4/6 inhibitors in combination with an aromatase inhibitor or fulvestrant, mTOR inhibitors, and *PIK3CA* inhibitors have not been systematically evaluated in clinical trials in males with breast cancer. However, available real-world data suggest comparable efficacy and safety profiles and it is reasonable to recommend these agents to males based on extrapolation of data from studies comprised largely of female participants with advanced breast cancer. Indications for and recommendations regarding chemotherapy, HER2-targeted therapy, immunotherapy, and PARP inhibitors for advanced breast cancer in males are similar to those for advanced breast cancer in females.[1]**

References

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SPECIAL CONSIDERATIONS FOR BREAST CANCER IN MALES (SEX ASSIGNED AT BIRTH)
REFERENCES

[1] Duma N, Hoversten KP, Ruddy KJ. Exclusion of male patients in breast cancer clinical trials. JNCI Cancer Spectr 2018;2:pky018.
[2] Gao Y, Goldberg JE, Young TK, et al. Breast cancer screening in high-risk men: A 12-year longitudinal observational study of male breast imaging utilization and outcomes. Radiology 2019;293:282-291.
[3] Cardoso F, Bartlett JMS, Slaets L, et al. Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program. Ann Oncol 2018;29:405-417.
[4] Cloyd JM, Hernandez-Boussard T, Wapnir IL. Outcomes of partial mastectomy in male breast cancer patients: analysis of SEER, 1983-2009. Ann Surg Oncol 2013;20:1545-1550.
[5] Bateni SB, Davidson AJ, Arora M, et al. Is breast-conserving therapy appropriate for male breast cancer patients? A National Cancer Database analysis. Ann Surg Oncol 2019;26:2144-2153.
[6] Zaenger D, Rabatic BM, Dasher B, Mourad WF. Is breast conserving therapy a safe modality for early-stage male breast cancer? Clin Breast Cancer 2016;16:101-104.
[7] Leone J, Zwenger AO, Leone BA, et al. Overall survival of men and women with breast cancer according to tumor subtype: A population-based study. Am J Clin Oncol 2019;42:215-220.
[8] Elmi M, Sequeira S, Azin A, et al. Evolving surgical treatment decisions for male breast cancer: an analysis of the National Surgical Quality Improvement Program (NSQIP) database. Breast Cancer Res Treat 2018;171:427-434.
[9] Fields EC, DeWitt P, Fisher CM, Rabinovitch R. Management of male breast cancer in the United States: a surveillance, epidemiology and end results analysis. Int J Radiat Oncol Biol Phys 2013;87:747-752.
[10] Flynn LW, Park J, Patil SM, et al. Sentinel lymph node biopsy is successful and accurate in male breast carcinoma. J Am Coll Surg 2008;206:616-621.
[11] Jardel P, Vignot S, Cutuli B, et al. Should adjuvant radiation therapy be systematically proposed for male breast cancer? A systematic review. Anticancer research. 2018;38:23-31.
[12] Massarweh SA, Sledge GW, Miller DP, et al. Molecular characterization and mortality from breast cancer in men. J Clin Oncol 2018;36:1396-1404.
[13] Grenader T, Yerushalmi R, Tokar M, et al. The 21-gene recurrence score assay (Oncotype DX) in estrogen receptor-positive male breast cancer: experience in an Israeli cohort. Oncology 2014;87:1-6.
[14] Hayes FJ, Seminara SB, Decruz S, et al. Aromatase inhibition in the human male reveals a hypothalamic site of estrogen feedback. J Clin Endocrinol Metab 2000;85:3027-3035.
[15] Mauras N, O'Brien KO, Klein KO, Hayes V. Estrogen suppression in males: metabolic effects. J Clin Endocrinol Metab 2000;85:2370-2377.
[16] Eggemann H, Ignatov A, Smith BJ, et al. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. Breast Cancer Res Treat 2013;137:465-4670.
[17] Harlan LC, Zujewski JA, Goodman MT, Stevens JL. Breast cancer in men in the United States: a population-based study of diagnosis, treatment, and survival. Cancer 2010;116:3558-3568.
[18] Gralow JR, Biermann JS, Farooki A, et al. NCCN Task Force Report: Bone Health In Cancer Care. J Natl Compr Canc Netw 2013;11 Suppl 3:S1-50; quiz S51.
[19] Zagouri F, Sergentanis TN, Chrysikos D, et al: Fulvestrant and male breast cancer: a case series. Ann Oncol 2013;24:265-266.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

ADJUVANT ENDOCRINE THERAPY[a,b,c,d]

Premenopausal at diagnosis[e,f]

- **Tamoxifen[g] for 5 y (category 1) ± ovarian suppression or ablation[f,h] (category 1)**
  - **Postmenopausal[e]** → **Aromatase inhibitor for 5 y[i] (category 1) or Consider tamoxifen[g] for an additional 5 y to complete 10 y**
  - **Premenopausal[e]** → **Consider tamoxifen[g] for an additional 5 y to complete 10 y or No further endocrine therapy**
- **or**
- **Aromatase inhibitor for 5 y[i] + ovarian suppression or ablation[f,h] (category 1)** → **Consider aromatase inhibitor for an additional 3–5 y[i]**

Postmenopausal at diagnosis[e]

- **Aromatase inhibitor[i] for 5 y (category 1)** → **Consider aromatase inhibitor for an additional 3–5 y[i]**
- **or**
- **Aromatase inhibitor[i] for 2–3 y (category 1)** → **Tamoxifen[g] to complete 5 y of endocrine therapy (category 1)**
- **or**
- **Tamoxifen[g] for 2–3 y** → **Aromatase inhibitor to complete 5 y[i] of endocrine therapy (category 1) or Up to 5 y of an aromatase inhibitor[i] (category 2B)**
- **Tamoxifen[g] for 4.5–6 y** → **Aromatase inhibitor for 5 y[i] (category 1) or Consider tamoxifen[g] for an additional 5 y to complete 10 y**
- **Patients with a contraindication to aromatase inhibitors, who decline aromatase inhibitors, or who are intolerant to aromatase inhibitors** → **Tamoxifen[g] for 5 y (category 1) or Consider tamoxifen[g] for up to 10 y**

[a] If patient is not postmenopausal, sequential evaluation of hormonal status is recommended to consider an alternative endocrine agent.
[b] Baseline assessment of bone density recommended for patients receiving an aromatase inhibitor who are at risk of osteoporosis (eg, age >65, family history, chronic steroids).
[c] 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 aromatase inhibitor therapy.
[d] In patients with HR-positive/HER2-negative, high-risk breast cancer (ie, those with ≥4 positive lymph nodes, or 1–3 positive lymph nodes with one or more of the following: Grade 3 disease, tumor size ≥5 cm, or a Ki-67 score of ≥20%) 2 years of adjuvant abemaciclib can be considered.
[e] See Definition of Menopause (BINV-O).
[f] Evidence suggests that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal patients with HR-positive breast cancer is similar to that achieved with CMF alone.
[g] Some SSRIs like fluoxetine and paroxetine decrease the formation of endoxifen, 4-OH tamoxifen, and active metabolites of tamoxifen, and may impact its efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, SNRIs (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 patients being considered for tamoxifen therapy.
[h] A balanced discussion of the risks and benefits associated with ovarian suppression therapy is critical. Aromatase inhibitor or tamoxifen for 5 y plus ovarian suppression should be considered, based on SOFT and TEXT clinical trial outcomes, for premenopausal patients at higher risk of recurrence (ie, young age, high-grade tumor, lymph node involvement). Coadministration of strong inhibitors of *CYP2D6* should be used with caution.
[i] 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. Patients with lymph node involvement may benefit from extended aromatase inhibitor duration (7.5–10 years total).

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Negative[b]	
Preferred Regimens: • Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks[c] • Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel[c] • TC (docetaxel and cyclophosphamide) • Olaparib, if germline *BRCA1/2* mutations[d,e] • High-risk[f] triple-negative breast cancer (TNBC): Preoperative pembrolizumab + carboplatin + paclitaxel, followed by preoperative pembrolizumab + cyclophosphamide + doxorubicin or epirubicin, followed by adjuvant pembrolizumab • TNBC and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy:[e] Capecitabine	
Useful in Certain Circumstances: • Dose-dense AC (doxorubicin/cyclophosphamide) • AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B) • CMF (cyclophosphamide/methotrexate/fluorouracil) • AC followed by weekly paclitaxel[c] • Capecitabine (maintenance therapy for TNBC after adjuvant chemotherapy)	**Other Recommended Regimens:** • AC followed by docetaxel every 3 weeks[c] • EC (epirubicin/cyclophosphamide) • TAC (docetaxel/doxorubicin/cyclophosphamide) • Select patients with TNBC:[g] ▸ Paclitaxel + carboplatin[g] (various schedules) ▸ Docetaxel + carboplatin[g] (preoperative setting only)

See Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3 of 9)

[a] Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m2.

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

[c] It is acceptable to change the administration sequence to taxane (with or without HER2-targeted therapy) followed by AC.

[d] Consider addition of adjuvant olaparib for 1 y for those with germline BRCA1/2 mutations and:
- TNBC, if 1) ≥pT2 or ≥pN1 disease after adjuvant chemotherapy, or 2) residual disease after preoperative chemotherapy
- HR-positive, HER2-negative tumors, if 1) ≥4 positive lymph nodes after adjuvant chemotherapy (category 2A), or 2) residual disease after preoperative therapy and a clinical stage, pathologic stage, estrogen receptor status, and tumor grade (CPS+EG) score ≥3 (category 2A).

Adjuvant olaparib can be used concurrently with endocrine therapy.

[e] Patients in the OlympiA trial did not receive capecitabine; thus, there are no data on sequencing or to guide selection of one agent over the other.

[f] High-risk criteria include stage II–III TNBC. The use of adjuvant pembrolizumab (category 2A) may be individualized.

[g] The inclusion of platinum agents as neoadjuvant chemotherapy for TNBC remains controversial. Several studies have shown improved pCR rates with incorporation of platinum. However, long-term outcomes remain unknown. The routine use of platinum agents as part of neoadjuvant therapy for TNBC is not recommended for most patients (including BRCA mutation carriers), but it may be considered in select patients (such as those for whom achieving better local control is necessary). The use of platinum agents in the adjuvant setting is not recommended. If platinum agents are included in an anthracycline-based regimen, the optimal sequence of chemotherapy and choice of taxane agent is not established.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PREOPERATIVE/ADJUVANT THERAPY REGIMENS[a]

HER2-Positive	
Preferred Regimens: • Paclitaxel + trastuzumab[h] • TCH (docetaxel/carboplatin/trastuzumab) • TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab) • If no residual disease after preoperative therapy or no preoperative therapy: Complete up to one year of HER2-targeted therapy with trastuzumab[j] (category 1) ± pertuzumab. • If residual disease after preoperative therapy: Ado-trastuzumab emtansine (category 1) alone. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (category 1) ± pertuzumab to complete one year of therapy.[i,j]	
Useful in Certain Circumstances: • Docetaxel + cyclophosphamide + trastuzumab • AC followed by T[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules) • AC followed by T[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab, various schedules) • Neratinib[i] (adjuvant setting only) • Paclitaxel + trastuzumab + pertuzumab[j] • Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only)	**Other Recommended Regimens:** • AC followed by docetaxel[c] + trastuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab) • AC followed by docetaxel[c] + trastuzumab + pertuzumab[j] (doxorubicin/cyclophosphamide followed by docetaxel + trastuzumab + pertuzumab)

See Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy (BINV-L, 3 of 9)

[a] Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m2.

[c] It is acceptable to change the administration sequence to taxane (with or without HER2-targeted therapy) followed by AC.

[h] Paclitaxel + trastuzumab may be considered for patients with low-risk T1,N0,M0, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.

[i] Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab or ado-trastuzumab emtansine is unknown.

[j] 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.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PREOPERATIVE/ADJUVANT THERAPY REGIMENS

Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy

- **Consider scalp cooling to reduce incidence of chemotherapy-induced alopecia for patients receiving neoadjuvant/adjuvant chemotherapy. Results may be less effective with anthracycline-containing regimens.**
- **Sequence of therapies in the adjuvant setting:**
  - **Chemotherapy and endocrine therapy should be given sequentially, with endocrine therapy given after chemotherapy.**
  - **Adjuvant olaparib can be given concurrently with endocrine therapy.**
  - **For sequencing of RT with systemic therapy, see BINV-I (2 of 3).**
- **Considerations for HER2-positive disease:**
  - **An FDA-approved biosimilar is an appropriate substitute for trastuzumab.**
  - **Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine.**
  - **Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use may be substituted anywhere that the combination of intravenous pertuzumab and intravenous trastuzumab are given as part of systemic therapy. Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use has different dosing and administration instructions compared to the intravenous products.**

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PREOPERATIVE/ADJUVANT THERAPY REGIMENS

HER2-Negative
Preferred Regimens

- **Dose-dense AC followed by paclitaxel[1]**
  - Doxorubicin 60 mg/m^2 IV day 1
  - Cyclophosphamide 600 mg/m^2 IV day 1
    - ◊ Cycled every 14 days for 4 cycles.[k]
    - ◊ Followed by:
  - Paclitaxel 175 mg/m^2 by 3 h IV infusion day 1
    - ◊ Cycled every 14 days for 4 cycles.[k]
- **Dose-dense AC followed by weekly paclitaxel[1]**
  - Doxorubicin 60 mg/m^2 IV day 1
  - Cyclophosphamide 600 mg/m^2 IV day 1
    - ◊ Cycled every 14 days for 4 cycles.[k]
    - ◊ Followed by:
  - Paclitaxel 80 mg/m^2 by 1 h IV infusion weekly for 12 weeks.
- **TC[2]**
  - Docetaxel 75 mg/m^2 IV day 1
  - Cyclophosphamide 600 mg/m^2 IV day 1
    - ◊ Cycled every 21 days for 4 cycles.[k]
- **Preoperative pembrolizumab + chemotherapy followed by adjuvant pembrolizumab[3]**
  - Preoperative:
    - ◊ Pembrolizumab 200 mg IV Day 1
    - ◊ Paclitaxel 80 mg/m^2 IV Days 1, 8, 15
    - ◊ Carboplatin AUC 5 IV Day 1
      - – Cycled every 21 days x 4 cycles (cycles 1-4)
    - Followed by:
    - ◊ Pembrolizumab 200 mg IV Day 1
    - ◊ Doxorubicin 60 mg/m^2 IV Day 1 or Epirubicin 90 mg/m^2 IV Day 1
    - ◊ Cyclophosphamide 600 mg/m^2 IV Day 1
      - – Cycled every 21 days x 4 cycles (cycles 5–8)
    - Followed by:
  - Adjuvant pembrolizumab 200 mg IV Day 1
    - ◊ Cycled every 21 days x 9 cycles
- **Capecitabine[4]**
  - 1,000–1,250 mg/m^2 PO twice daily on days 1–14
    - ◊ Cycled every 21 days for 6–8 cycles
- **Olaparib[5,l]**
  - 300 mg PO twice daily
  - Cycled every 28 days for 1 y

[k] All cycles are with myeloid growth factor support. See NCCN Guidelines for Hematopoietic Growth Factors.
[l] There is also a capsule formulation available. However, do not substitute the capsules for the tablets on a mg-per-mg basis due to differences in dosing and bioavailability.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PREOPERATIVE/ADJUVANT THERAPY REGIMENS

HER2-Negative
Other Recommended Regimens

- **AC followed by docetaxel every 3 weeks[6]**
  - 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.
- **EC chemotherapy[7]**
  - Epirubicin 100 mg/m² IV day 1
  - Cyclophosphamide 830 mg/m² IV day 1
    - ◊ Cycled every 21 days for 8 cycles.
- **TAC chemotherapy[8]**
  - 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.[k]
- **Paclitaxel + carboplatin**
  - **Weekly paclitaxel + carboplatin[9] (preoperative setting only)**
    - ◊ Paclitaxel 80 mg/m² days 1, 8, and 15
    - ◊ Carboplatin AUC 5 or 6 day 1;
      - – Cycled every 21 days x 4 cycles
  - **Weekly paclitaxel + weekly carboplatin[10,11]**
    - ◊ Paclitaxel 80 mg/m² days 1, 8, and 15
    - ◊ Carboplatin AUC 1.5–2 days 1, 8, and 15
      - – Cycled every 28 days x 6 cycles
- **Docetaxel + carboplatin (4–6 cycles) (preoperative setting only)[12,13,k]**
  - Docetaxel 75 mg/m² day 1
  - Carboplatin AUC 6 day 1
    - ◊ Cycled every 21 days x 4–6 cycles.

HER2-Negative
Useful in Certain Circumstances

- **Dose-dense AC[1]**
  - Doxorubicin 60 mg/m² IV day 1
  - Cyclophosphamide 600 mg/m² IV day 1
    - ◊ Cycled every 14 days for 4 cycles.[l]
- **AC[14]**
  - Doxorubicin 60 mg/m² IV on day 1
  - Cyclophosphamide 600 mg/m² IV day 1
    - ◊ Cycled every 21 days for 4 cycles.
- **CMF chemotherapy[15]**
  - Cyclophosphamide 100 mg/m² PO days 1–14 (IV acceptable)
  - 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 weekly paclitaxel[16]**
  - 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 weeks.
- **Capecitabine (maintenance therapy)[17]**
  - 650 mg/m² PO twice daily on days 1–28
  - Cycled every 28 days for 1 year

[k] All cycles are with myeloid growth factor support. See NCCN Guidelines for Hematopoietic Growth Factors.
[l] There is also a capsule formulation available. However, do not substitute the capsules for the tablets on a mg-per-mg basis due to differences in dosing and bioavailability.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PREOPERATIVE/ADJUVANT THERAPY REGIMENS

HER2-Positive[m,n,o] Preferred Regimens		
Paclitaxel + trastuzumab[18] ▸ Paclitaxel 80 mg/m^2 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.	**TCH[19]** ▸ Docetaxel 75 mg/m^2 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 ◊ Cycled every 21 days to complete 1 y of therapy.[p] OR ▸ Trastuzumab 8 mg/kg IV wk 1 ◊ Followed by: ▸ Trastuzumab 6 mg/kg IV ◊ Cycled every 21 days to complete 1 y of therapy.[p]	**TCH + pertuzumab[20]** ▸ Docetaxel 75 mg/m^2 IV day 1 ▸ Carboplatin AUC 6 IV day 1 ◊ Cycled every 21 days for 6 cycles With: ▸ Trastuzumab 8 mg/kg IV day 1 ▸ Pertuzumab 840 mg IV day 1 ◊ Followed by: ▸ Trastuzumab 6 mg/kg IV on day 1 ▸ Pertuzumab 420 mg IV day 1 ◊ Cycled every 21 days to complete 1 y of therapy.[o]

[m] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

[n] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine.

[o] Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use may be substituted anywhere that the combination of intravenous pertuzumab and intravenous trastuzumab are given as part of systemic therapy. Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use has different dosing and administration instructions compared to the intravenous products.

[p] Evaluate left ventricular ejection fraction (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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PREOPERATIVE/ADJUVANT THERAPY REGIMENS

HER2-Positive[m,n,o] Useful in Certain Circumstances			
AC followed by T + trastuzumab[21] ▸ Doxorubicin 60 mg/m^2 IV day 1 ▸ Cyclophosphamide 600 mg/m^2 IV day 1 ◊ Cycled every 21 days for 4 cycles. ◊ Followed by: ▸ Paclitaxel 80 mg/m^2 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.[p]	**Dose-dense AC followed by paclitaxel + trastuzumab[22]** ▸ Doxorubicin 60 mg/m^2 IV day 1 ▸ Cyclophosphamide 600 mg/m^2 IV day 1 ◊ Cycled every 14 days for 4 cycles. ◊ Followed by: ▸ Paclitaxel 175 mg/m^2 by 3 h IV infusion day 1 ◊ Cycled every 14 days for 4 cycles.[k] ◊ 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.[p]	**AC or Dose-Dense AC followed by T + trastuzumab + pertuzumab[23]** ▸ Doxorubicin 60 mg/m^2 IV day 1 ▸ Cyclophosphamide 600 mg/m^2 IV day 1 ◊ Cycled every 21 days for 4 cycles or For dose-dense: Cycle every 14 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/m^2 IV days 1, 8, and 15 ◊ Cycled every 21 days for 4 cycles ◊ Followed by: ▸ Trastuzumab 6 mg/kg IV day 1 ▸ Pertuzumab 420 mg IV day 1 ◊ Cycled every 21 days to complete 1 y of therapy[p]	**Docetaxel/cyclophosphamide + trastuzumab[24]** ▸ Docetaxel 75 mg/m^2 IV day 1 ▸ Cyclophosphamide 600 mg/m^2 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 ◊ Cycled every 21 days to complete 1 y of therapy of trastuzumab therapy.[p] 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[p]

[k] All cycles are with myeloid growth factor support. See NCCN Guidelines for Hematopoietic Growth Factors.

[m] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

[n] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine.

[o] Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use may be substituted anywhere that the combination of intravenous pertuzumab and intravenous trastuzumab are given as part of systemic therapy. Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use has different dosing and administration instructions compared to the intravenous products.

[p] 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PREOPERATIVE/ADJUVANT THERAPY REGIMENS

HER2-Positive[m,n,o] Other Recommended Regimens

AC followed by docetaxel + trastuzumab[18,25]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 IV day 1
  - ◊ Cycled every 21 days for 4 cycles
  - ◊ Followed by:
- Docetaxel 100 mg/m^2 IV day 1
  - ◊ Cycled every 21 days for 4 cycles
  - ◊ With:
- Trastuzumab
  - ◊ 4 mg/kg IV wk 1; Followed by:
  - ◊ 2 mg/kg IV weekly for 11 wks; Followed by:
  - ◊ 6 mg/kg IV
  - ◊ Cycled every 21 days to complete 1 y of trastuzumab therapy.[p]

AC followed by docetaxel + trastuzumab + pertuzumab[26]
- Doxorubicin 60 mg/m^2 IV day 1
- Cyclophosphamide 600 mg/m^2 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/m^2 IV day 1
  - ◊ Cycled every 21 days for 4 cycles
  - ◊ Followed by:
- Trastuzumab 6 mg/kg IV
- Pertuzumab 420 mg IV day 1
  - ◊ Cycled every 21 days to complete 1 y of therapy.[p]

HER2-Positive[l,m,n] Useful in Certain Circumstances

Neratinib[27]
- 120 mg PO daily on days 1–7; Followed by:
- 160 mg PO daily on days 8–14; Followed by:
- 240 mg PO daily on days 15–28
  - ◊ Cycled every 28 days x 1 cycle
  - ◊ Followed by:
- 240 mg PO daily on days 1–28
  - ◊ Cycled every 28 days x 12 cycles beginning with cycle 2

Paclitaxel + trastuzumab + pertuzumab[28]
- Paclitaxel 80 mg/m^2 IV day 1
  - ◊ Cycled every 7 days x 12 cycles
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
  - ◊ Cycled every 21 days x 4 cycles

Ado-trastuzumab emtansine (T-DM1)[29]
- 3.6 mg/kg IV day 1
  - ◊ Cycled every 21 days for 17 cycles

[m] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[n] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine.
[o] Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use may be substituted anywhere that the combination of intravenous pertuzumab and intravenous trastuzumab are given as part of systemic therapy. Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use has different dosing and administration instructions compared to the intravenous products.
[p] 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PREOPERATIVE/ADJUVANT THERAPY REGIMENS - REFERENCES

[1] Citron ML, Berry DA, Cirrincione 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.
[2] Jones 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.
[3] Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. N Engl J Med, 2020;382:810-821.
[4] Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med 2017;376:2147-2159.
[5] Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med 2021;384:2394-2405.
[6] von 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 GEPARDUO study of the German Breast Group. J Clin Oncol 2005;23:2676-2685.
[7] 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.
[8] Martin, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005;352:22.
[9] Sharma P, Kimler BF, O'Dea A, et al. Randomized phase II trial of anthracycline-free and anthracycline-containing neoadjuvant carboplatin chemotherapy regimens in stage I-III triple-negative breast cancer (NeoSTOP). Clin Cancer Res 2021;27:975-982.
[10] Yu KD, Ye FG, He M, et al. Effect of adjuvant paclitaxel and carboplatin on survival in women with triple-negative breast cancer: A phase 3 randomized clinical trial. JAMA Oncol 2020;6:1390-1396.
[11] 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.
[12] Sharma P, Lopez-Tarruella S, Garcia-Saenz J, et al. Efficacy of neoadjuvant carboplatin plus docetaxel in triple-negative breast cancer: Combined analysis of two cohorts. Clin Cancer Res 2017;23:649-657.
[13] Zhang L, Wu ZY, Li J, et al. Neoadjuvant Docetaxel Plus Carboplatin Versus Epirubicin Plus Cyclophosphamide Followed by Docetaxel in Triple-Negative, Early-Stage Breast Cancer (NeoCART): Results from a Multicenter, Randomized Controlled, Open-Label Phase II Trial. Int J Cancer 2021, Sep 30.
[14] 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.
[15] Goldhirsch 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;9:489-493.
[16] Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in adjuvant treatment of breast cancer. N Engl J Med 2008;258:1663-1671.
[17] Wang X, Wang SS, Huang H, et al. Effect of Capecitabine Maintenance Therapy Using Lower Dosage and Higher Frequency vs Observation on Disease-Free Survival Among Patients With Early-Stage Triple-Negative Breast Cancer Who Had Received Standard Treatment: The SYSUCC-001 Randomized Clinical Trial. JAMA. 2021;325(1):50-58.
[18] Tolaney S, Barry W, Dang C, et al. Adjuvant paclitaxel and trastuzumab for node-negative HER2-positive breast cancer. N Engl J Med 2015;372:134-141.
[19] Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2011;365:1273-1283.
[20] 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.
[21] Romond 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.
[22] Dang 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;26:1216-1222.
[23] Swain SM, Ewer MS, Viale G, et al. Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study. Ann Oncol 2018;29:646-653.
[24] Jones 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;14:1121-1128.
[25] Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med 2006;354:809-820.
[26] 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.
[27] Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2016;17:367-377.
[28] Nitz UA, Gluz O, Christgen M, et al. De-escalation strategies in HER2-positive early breast cancer (EBC): final analysis of the WSG-ADAPT HER2+/HR- phase II trial: efficacy, safety, and predictive markers for 12weeks of neoadjuvant dual blockade with trastuzumab and pertuzumab ± weekly paclitaxel. Ann Oncol 2017;28:2768-2772.
[29] Tolaney SM, Tayob N, Dang C, et al. Adjuvant trastuzumab emtansine versus paclitaxel in 8combination with trastuzumab for stage I HER2-positive breast cancer (ATEMPT): A randomized clinical trial. J Clin Oncol 2021;39:2375-2385.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF PREOPERATIVE SYSTEMIC THERAPY

Known Benefits of Preoperative Systemic Therapy
- Facilitates breast conservation
- Can render inoperable tumors operable
- Treatment response provides important prognostic information at an individual patient level, particularly in patients with TNBC or HER2-positive breast cancer
- Identifies patients with residual disease at higher risk for relapse to allow for the addition of supplemental adjuvant regimens, particularly in patients with TNBC or HER2-positive breast cancer.
- Allows time for genetic testing
- Allows time to plan breast reconstruction in patients electing mastectomy
- Allows time for delayed decision-making for definitive surgery

Opportunities
- May allow SLNB alone if initial cN+ becomes cN0 after preoperative therapy
- May provide an opportunity to modify systemic treatment if no preoperative therapy response or progression of disease
- May allow for more limited radiation fields in patients with cN+ who become cN0/pN0 after preoperative therapy
- Provides 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:
  - IBC
  - Bulky or matted cN2 axillary nodes
  - cN3 nodal disease
  - cT4 tumors
- In select patients with operable breast cancer
  - Preoperative systemic therapy is preferred for:
    - ◊ HER2-positive disease and TNBC, if cT ≥2 or cN ≥1
    - ◊ Large primary tumor relative to breast size in a patient who desires breast conservation
    - ◊ cN+ disease likely to become cN0 with preoperative systemic therapy
  - Preoperative systemic therapy can be considered for cT1,N0 HER2-positive disease and TNBC
- Patients in whom definitive surgery may be delayed.

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
- 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF PREOPERATIVE SYSTEMIC THERAPY

- **Randomized trials of chemotherapy demonstrate similar long-term outcomes when patients are given the same treatment preoperatively compared with postoperatively.[a]**
- **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 TNBC, somewhat less so for HER2-positive disease, and least for ER-positive disease.[b,c]**
- **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-L).**
- **Preoperative endocrine therapy alone may be considered for patients with ER-positive disease based on comorbidities or low-risk luminal biology based on clinical characteristics and/or genomic signatures.**
- **Patients with HER2-positive tumors should be treated with preoperative systemic therapy incorporating trastuzumab.[d] A pertuzumab-containing regimen may be administered preoperatively to patients with ≥ pT2 or ≥ pN1, HER2-positive early-stage breast cancer. See Preoperative/Adjuvant Therapy Regimens (BINV-L).**
- **Some studies suggest an increased risk of locoregional recurrence following use of preoperative chemotherapy.[e] These trials delivered chemotherapy regimens that are no longer standard, did not include targeted therapies, did not use modern imaging techniques, and/or used non-standard locoregional management. Care should be taken to follow the procedures outlined in BINV-12 and BINV-14 to assure appropriate locoregional management. 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 Potentially Operable Disease: Breast and Axillary Evaluation Prior to Preoperative Systemic Therapy (BINV-12).**
- **Tumor response should be routinely assessed by clinical exam and imaging studies (see footnote uu on BINV-13) during delivery of preoperative therapy. It is preferred that the standard regimen is completed prior to surgery. If all intended treatment is not completed prior to surgery, the remainder may be given in the adjuvant setting. Patients with operable breast cancer experiencing progression of disease during preoperative systemic therapy may be given an alternate systemic regimen or proceed to surgery if deemed resectable. Locoregional therapy principles should be applied in the same manner as in patients treated with adjuvant systemic therapy.**

[a] 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.

[b] 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.

[c] 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.

[d] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

[e] Early Breast Cancer Trialists' Collaborative Group (EBTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: metaanalysis of individual patient data from ten randomised trials. Lancet Oncol 2018;19:27-39.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY[a,b]

Assay	Predictive	Prognostic	NCCN Category of Preference	NCCN Category of Evidence and Consensus	Recurrence Risk and Treatment Implications
21-gene (Oncotype Dx) (for pN0)	Yes	Yes	Preferred	1	BINV-N (2 of 5)
21-gene (Oncotype Dx) for pN1 (1–3 positive nodes)[c]	Yes	Yes	Postmenopausal: Preferred	1	BINV-N (2 of 5)
			Premenopausal: Other	2A	
70-gene (MammaPrint) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	1	BINV-N (3 of 5)
50-gene (Prosigna) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A	BINV-N (3 of 5)
12-gene (EndoPredict) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A	BINV-N (3 of 5)
Breast Cancer Index (BCI)	Predictive of benefit of extended adjuvant endocrine therapy	Yes	Other	2A	BINV-N (4 of 5)

[a] Gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. Use of these assays is not required for staging. The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown.
[b] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).
[c] In the overall study population of the RxPONDER trial, 10.3% had high-grade disease and 9.2% had 3 involved 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.

References

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY[a,b]

Assay	Recurrence Risk	Treatment Implications
21-gene (Oncotype Dx) (for postmenopausal patients with pN0 and pN1 [1–3 positive nodes])[c]	<26	Patients with T1b/c–2, pN0, HR-positive, HER2-negative tumors, with risk scores (RS) between 0–10 have a risk of distant recurrence of <4% and those with RS 11–25 derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study.[1] Postmenopausal patients with pT1–3, pN1, HR-positive, HER2-negative, with RS <26 derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective RxPONDER study.[2]
	≥26	In postmenopausal patients with pT1–3, HR-positive, HER2-negative, and pN0 and pN1 (1–3 positive nodes) tumors and an RS ≥26, the addition of chemotherapy to endocrine therapy is recommended.[1,2]
21-gene (Oncotype Dx) (for premenopausal patients: pN0)	≤15	Premenopausal patients with T1b/c –2, pN0, HR-positive, HER2-negative tumors with RS <16 derived no benefit from the addition of chemotherapy to endocrine therapy in the prospective TAILORx study.[1]
	16–25	In premenopausal patients with RS between 16–25, a small benefit from the addition of chemotherapy could not be ruled out, but it is unclear if the benefit was due to the ovarian suppression effect promoted by chemotherapy in premenopausal patients.[1,2] For this group, consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an AI.
	≥26	In premenopausal patients with HR-positive, HER2-negative, and pN0 tumors and an RS ≥26, the addition of chemotherapy to endocrine therapy is recommended.[1]
21-gene (Oncotype Dx) (for premenopausal patients with 1–3 positive nodes)[c]	<26	In premenopausal patients with pT1–3 and pN1 (1–3 positive nodes) tumors and an RS <26, the addition of chemotherapy to endocrine therapy was associated with a lower rate of distant recurrence compared with endocrine monotherapy[2] but it is unclear if the benefit was due to the ovarian suppression effects promoted by chemotherapy. For this group of patients, consider chemotherapy followed by endocrine therapy or alternatively, ovarian function suppression combined with either tamoxifen or an AI.[2]
	≥26	In premenopausal patients with HR-positive, HER2-negative, pT1–3 and pN1 (1–3 positive nodes) tumors and an RS ≥26, the addition of chemotherapy to endocrine therapy is recommended.[2]

[a] Gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. Use of these assays is not required for staging. The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown.
[b] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).
[c] In the overall study population of the RxPONDER trial, 10.3% had high-grade disease and 9.2% had 3 involved 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.

References

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY[a,b]

Assay	Recurrence Risk	Treatment Implications
70-gene (MammaPrint) (for pN0 and 1–3 positive nodes)	Low	Patients with high clinical risk and low genomic risk were randomly assigned to receive chemotherapy (n = 749) or not (n = 748); this was the intention-to-treat population. The 8-year estimates for distant metastasis-free survival in the intention-to-treat population were 92.0% (95% CI, 89.6–93.8) for chemotherapy versus 89.4% (86.8–91.5) for no chemotherapy (HR, 0.66; 95% CI, 0.48–0.92). An exploratory analysis confined to the subset of patients with HR-positive, HER2-negative disease (1358 [90.7%] of 1497 randomly assigned patients, of whom 676 received chemotherapy and 682 did not) shows different effects of chemotherapy administration on 8-year distant metastasis-free survival according to age: 93.6% (95% CI, 89.3–96.3) with chemotherapy versus 88.6% (83.5–92.3) without chemotherapy in 464 patients aged 50 years or younger (absolute difference 5.0 percentage points [SE, 2.8; 95% CI, −0.5–10.4]) and 90.2% (86.8–92.7) versus 90.0% (86.6–92.6) in 894 females older than 50 years (absolute difference 0.2 percentage points [2.1, −4.0–4.4]). The 8-year distant metastasis-free survival in the exploratory analysis by nodal status in these patients was 91.7% (95% CI, 88.1–94.3) with chemotherapy and 89.2% (85.2–92.2) without chemotherapy in 699 node-negative patients (absolute difference 2.5 percentage points [SE, 2.3; 95% CI, −2.1 –7.2]) and 91.2% (87.2–94.0) versus 89.9% (85.8–92.8) for 658 patients with one to three positive nodes (absolute difference 1.3 percentage points [2.4, −3.5–6.1]).[3]
	High	
50-gene (Prosigna) (for pN0 and 1–3 positive nodes)	Node negative: Low (0–40), Intermediate (41–60), High (61–100)	For patients with T1 and T2 HR-positive, HER2-negative, pN0 tumors, a risk of recurrence score in the low range, regardless of T size, places the tumor into the same prognostic category as T1a–T1b,N0,M0.[4]
	Node positive: Low (0–40)	In patients with HR-positive, HER2-negative, pN+ tumors (1–3 positive lymph nodes) with low risk of recurrence score, treated with endocrine therapy alone, the distant recurrence risk was less than 3.5% at 10 years and no distant recurrence was seen at 10 years in the TransATAC study in a similar group.[5]
	Node positive: High (41–100)	
12-gene (EndoPredict) (pN0 and 1–3 positive nodes)	Low (≤3.3)	For patients with T1 and T2 HR-positive, HER2-negative, and pN0 tumors, a 12-gene low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a–T1b,N0,M0.[6] In ABCSG 6/8, patients in the low-risk group had risk of distant recurrence of 4% at 10 years and in the TransATAC study, patients with 1–3 positive nodes in the low-risk group had a 5.6% risk of distant recurrence at 10 years.[6,7] The assay is prognostic in endocrine and chemo-endocrine treated patients.[7]
	High (>3.3)	

[a] Gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. Use of these assays is not required for staging. The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown.

[b] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).

References

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY[a,b]

Assay	Recurrence Risk/ Predictive Result	Treatment Implications
Breast Cancer Index (BCI)	BCI (H/I) Low	• For patients with T1 and T2 HR-positive, HER2-negative, and pN0 tumors, a BCI (H/I) in the low-risk range (0–5), regardless of T size, places the tumor into the same prognostic category as T1a–T1b, N0,M0. • Patients with BCI (H/I) low demonstrated a lower risk of distant recurrence (compared to BCI [H/I] high) and no significant improvement in DFS or OS compared to the control arm in terms of extending endocrine therapy duration.[8]
	BCI (H/I) High	• For patients with T1 HR-positive, HER2-negative, and pN0 tumors, a BCI (H/I) high (5.1–10) demonstrated significant rates of late distant recurrence. • In secondary analyses of the MA.17, Trans-aTTom, and IDEAL trials, patients with HR-positive, T1–T3, pN0 or pN+ who had a BCI (H/I) high demonstrated significant improvements in DFS when adjuvant endocrine therapy was extended, compared to the control arm.[8-11] • In contrast, BCI (H/I) low patients derived no benefit from extended adjuvant therapy.[8]

[a] Gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. Use of these assays is not required for staging. The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown.

[b] See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (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.

References

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY
REFERENCES

[1] Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. N Engl J Med 2018;379:111-121.
[2] Kalinsky K, Barlow WE, Meric-Bernstam F, et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) < 25: SWOG S1007 (RxPonder). SABCS 2021;81(4): Abstract GS3-00.
[3] Piccart M, van 't Veer LJ, Poncet C, et al. 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol. 2021;22:476-488.
[4] Laenkholm AV, Jensen MB, Eriksen JO, et al. PAM50 risk of recurrence score predicts 10-year distant recurrence in a comprehensive Danish cohort of postmenopausal women allocated to 5 years of endocrine therapy for hormone receptor-positive early breast cancer. J Clin Oncol 2018;36:735-740.
[5] Sestak I, Buus R, Cuzick J, et al. Comparison of the performance of 6 prognostic signatures for estrogen receptor–positive breast cancer: A secondary analysis of a randomized clinical trial. JAMA Oncol 2018;4:545-553.
[6] Filipits M, Rudas M, Jakesz R, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clin Cancer Res 2011;17:6012-6020.
[7] Sestak I, Martín M, Dubsky P, et al. Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone. Breast Cancer Res Treat 2019;176:377-386.
[8] Noordhoek I, Treuner K, Putter H, et al. Breast cancer index predicts extended endocrine benefit to individualize selection of patients with HR(+) early-stage breast cancer for 10 years of endocrine Therapy. Clin Cancer Res 2021;27:311-319.
[9] Sgroi DC, Carney E, Zarrella E, et al. Prediction of late disease recurrence and extended adjuvant letrozole benefit by the HOXB13/IL17BR biomarker. J Natl Cancer Inst 2013;105:1036-1042.
[10] Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, et al. Optimal duration of extended adjuvant endocrine therapy for early breast cancer; Results of the IDEAL Trial (BOOG 2006-05). J Natl Cancer Inst 2017;110:40-48.
[11] Bartlett JMS, Sgroi DC, Treuner K, et al. Breast cancer index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen-To Offer More? (aTTom) trial. Ann Oncol 2019;30:1776-1783.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

DEFINITION OF MENOPAUSE

- Menopause is the permanent cessation of menses and includes a profound and permanent decrease in ovarian estrogen synthesis.
- Determination of menopausal status may be required to guide selection of endocrine therapy for breast cancer.
- Menopause is usually a clinical diagnosis made after ≥12 months of amenorrhea. Natural menopause is experienced between ages 42–58 years.
- Breast cancer treatments may affect ovarian function and menses.
  - In those who are pre-menopausal at the beginning of chemotherapy and who develop chemotherapy-induced amenorrhea, ovarian function may still be intact despite amenorrhea or may resume over time. The likelihood of ovarian function resuming after chemotherapy is higher among those aged <40 years.
  - Tamoxifen may cause amenorrhea without inducing menopause in pre-menopausal individuals.
  - Ovarian function suppression induces amenorrhea and reduces ovarian estrogen synthesis without causing permanent menopause.
- Twelve months of amenorrhea alone is insufficient to diagnose menopause with chemotherapy-induced amenorrhea or with tamoxifen ± ovarian suppression. Follicle-stimulating hormone (FSH) and estradiol levels are used to support the diagnosis of menopause; however, clear criteria to guide interpretation of FSH and estradiol in this population is lacking.
  - Tamoxifen may alter FSH levels, limiting its utility in determination of menopausal status.
  - FSH and estradiol should be repeated serially to ensure menopausal status in breast cancer patients with chemotherapy-induced amenorrhea.
- Evidence-based criteria for the diagnosis of menopause in patients with breast cancer are lacking. Clinical trials in breast cancer have utilized a variety of definitions of menopause. Reasonable criteria for determining menopause in patients with breast cancer include any of the following:
  - Prior bilateral oophorectomy
  - Age ≥60 years
  - Age <60 with amenorrhea for ≥12 months in the absence of prior chemotherapy, receipt of tamoxifen, toremifene, or ovarian suppression and estradiol and FSH in the post-menopausal range
  - Age <60 years: chemotherapy-induced amenorrhea for ≥12 months with FSH and estradiol in post-menopausal range on serial assessments
  - Age <60 years: on tamoxifen with FSH and estradiol level in post-menopausal range
- Menopausal status cannot be determined in those receiving ovarian function suppression

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

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

Preferred Regimens
First-Line Therapy
- Aromatase inhibitor + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)[b]
- Selective ER down-regulator (fulvestrant, category 1)[c] + non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[c]
- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)[b]

Preferred Regimens
Second- and Subsequent-Line Therapy
- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[d,e]
- For *PIK3CA*-mutated tumors, see additional targeted therapy options (see BINV-R)[e,f]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[e,g]

Other Recommended Regimens
First- and Subsequent-Line Therapy
- Selective ER down-regulator
  - Fulvestrant[c]
- Non-steroidal aromatase inhibitor
  - Anastrozole
  - Letrozole
- Selective estrogen receptors modulator
  - Tamoxifen
- Steroidal aromatase inactivator
  - Exemestane

Useful in Certain Circumstances[f]
Subsequent-Line Therapy
- Megestrol acetate
- Estradiol
- Abemaciclib[e,h]

HER2-Positive and Postmenopausal[i,j,k] or Premenopausal Receiving Ovarian Ablation or Suppression

- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

[a] Baseline assessment of bone density recommended for patients receiving an aromatase inhibitor who are at risk of osteoporosis (eg, age >65, family history, chronic steroids).
[b] In phase 3 randomized controlled trials, ribociclib + endocrine therapy has shown overall survival benefit in the first-line setting.
[c] A single study (S0226) in patients with HR-positive breast cancer and no prior chemotherapy, biological therapy, or endocrine therapy for metastatic disease demonstrated that the addition of fulvestrant to anastrozole resulted in prolongation of time to progression and overall survival. Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. Two studies with similar design (FACT and SOFEA) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole.
[d] In phase 3 randomized controlled trials, fulvestrant in combination with a CDK4/6 inhibitor (abemaciclib, palbociclib, and ribociclib) has shown overall survival benefit in the second-line setting.
[e] If there is disease progression while on a CDK4/6 inhibitor, there are limited data to support the use of another CKD4/6 inhibitor. If there is progression while on a PI3K inhibitor, there are limited data to support another line of therapy with a PIK3CA-containing regimen. If there is disease progression while on an everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.
[f] See Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease (BINV-R).
[g] A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal aromatase inhibitor).
[h] Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting.
[i] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[j] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine or fam-trastuzumab deruxtecan-nxki.
[k] If treatment was initiated with chemotherapy and trastuzumab + pertuzumab, and the chemotherapy was stopped, endocrine therapy may be added to trastuzumab + pertuzumab.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

HER2-Negative		
Preferred Regimens	**Other Recommended Regimens[g]**	**Useful in Certain Circumstances[g]**
• Anthracyclines ▸ Doxorubicin ▸ Liposomal doxorubicin • Taxanes ▸ Paclitaxel • Anti-metabolites ▸ Capecitabine ▸ Gemcitabine • Microtubule inhibitors ▸ Vinorelbine ▸ Eribulin • Sacituzumab govitecan-hziy (for TNBC)[d] • For germline *BRCA1/2* mutations[d] see additional targeted therapy options (BINV-R)[e] • Platinum (for TNBC and germline *BRCA1/2* mutation)[e] ▸ Carboplatin ▸ Cisplatin • For PD-L1–positive TNBC see additional targeted therapy options (BINV-R)[f]	• Cyclophosphamide • Docetaxel • Albumin-bound paclitaxel • Epirubicin • Ixabepilone	• AC (doxorubicin/cyclophosphamide) • EC (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/ methotrexate/fluorouracil) • Docetaxel/capecitabine • GT (gemcitabine/paclitaxel) • Gemcitabine/carboplatin • Carboplatin + paclitaxel or albumin-bound paclitaxel

HER2-Positive Disease, see BINV-Q (2 of 8)

[a] Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m^2.

[b] Consider scalp cooling to reduce incidence of chemotherapy-induced alopecia for patients receiving chemotherapy. Results may be less effective with anthracycline-containing regimens.

[c] For treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.

[d] For adult patients with metastatic TNBC who received at least two prior therapies, with at least one line for metastatic disease.

[e] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy.

[f] See Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease (BINV-R).

[g] Sequential single agents are preferred, but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[h]

HER2-Positive			
Setting	**Regimen**	**NCCN Category of Preference**	**NCCN Category of Evidence**
First line[i]	Pertuzumab + trastuzumab + docetaxel[k]	Preferred Regimen	1
	Pertuzumab + trastuzumab + paclitaxel[k]	Preferred Regimen	2A
Second line[j]	Fam-trastuzumab deruxtecan-nxki[j,l,m]	Preferred Regimen	1
	Ado-trastuzumab emtansine (T-DM1)[j]	Other Recommended Regimen	2A
Third line and beyond (optimal sequence is not known)	Tucatinib + trastuzumab + capecitabine[k,n]	Other Recommended Regimen[n]	1
	Trastuzumab + docetaxel or vinorelbine[k,o]	Other Recommended Regimen	2A
	Trastuzumab + paclitaxel ± carboplatin[k,o]	Other Recommended Regimen	2A
	Capecitabine + trastuzumab or lapatinib[k,o]	Other Recommended Regimen	2A
	Trastuzumab + lapatinib[k,o] (without cytotoxic therapy)	Other Recommended Regimen	2A
	Trastuzumab + other agents[k,o,p,q]	Other Recommended Regimen	2A
	Neratinib + capecitabine[o]	Other Recommended Regimen	2A
	Margetuximab-cmkb + chemotherapy[o] (capecitabine, eribulin, gemcitabine, or vinorelbine)	Other Recommended Regimen	2A
Additional targeted therapy options (See BINV-R)			

[h] See additional considerations for those receiving systemic HER2-targeted therapy (BINV-Q 3 of 8).
[i] Maintenance trastuzumab/pertuzumab after response (with concurrent endocrine therapy if ER+ and HER2+ metastatic breast cancer).
[j] Regimens may also be used as an option for third-line and beyond; the optimal sequence for third-line therapy and beyond is not known.
[k] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[l] Fam-trastuzumab deruxtecan-nxki may be considered in the first-line setting as an option for select patients (ie, those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for pertuzumab-containing regimens]).
[m] Fam-trastuzumab deruxtecan-nxki is contraindicated for patients with pneumonitis or interstitial lung disease (ILD).
[n] Tucatinib + trastuzumab + capecitabine is preferred in patients with both systemic and CNS progression in the third-line setting and beyond; and it may be given in the second-line setting.
[o] Multiple lines of concurrent chemotherapy with anti-HER2 therapy (trastuzumab or a TKI) offer clinical benefit for recurrent unresectable HER2+ metastatic breast cancer and have been studied in phase 2 or 3 trials. Clinical experience suggests frequent clinical benefit for such treatment. However, there are no meaningful data for use of any of these regimens among patients previously treated with pertuzumab-based chemotherapy, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki, or trastuzumab/capecitabine/tucatinib regimens. Thus, the optimal sequence or true benefit of therapy is not known.
[p] 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.
[q] Trastuzumab may be safely combined with all non-anthracycline containing preferred and other single agents listed on BINV-Q (1 of 8) 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Additional Considerations for Those Receiving Systemic Therapy for HER2-Positive Disease

- **Alternative taxanes (ie, docetaxel, paclitaxel, albumin-bound paclitaxel) may be substituted for select patients due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of albumin-bound paclitaxel should not exceed 125 mg/m^2.**
- **Consider scalp cooling to reduce incidence of chemotherapy-induced alopecia for patients receiving chemotherapy. Results may be less effective with anthracycline-containing regimens.**
- **An FDA-approved biosimilar is an appropriate substitute for trastuzumab.**
- **Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine or fam-trastuzumab deruxtecan-nxki.**
- **Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use may be substituted anywhere that the combination of intravenous pertuzumab and intravenous trastuzumab are given as part of systemic therapy. Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use has different dosing and administration instructions compared to the intravenous products.**
- **Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.**
- **For treatment of brain metastases, see NCCN Guidelines for Central Nervous System Cancers.**

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

HER2-Negative Regimens:

- **Anthracyclines:**
  - Doxorubicin 60–75 mg/m² IV day 1; cycled every 21 days[1]
  - Doxorubicin 20 mg/m² IV day 1 weekly[2]
  - Liposomal doxorubicin[3] 50 mg/m² IV day 1; cycled every 28 days
- **Taxanes:**
  - Paclitaxel 175 mg/m² IV day 1; cycled every 21 days[4]
  - Paclitaxel 80 mg/m² IV day 1 weekly[5]
- **Antimetabolites:**
  - Capecitabine[6] 1000–1250 mg/m² PO twice daily days 1–14; cycled every 21 days
  - Gemcitabine[7] 800–1200 mg/m² IV days 1, 8, and 15; cycled every 28 days
- **Microtubule inhibitors:**
  - Vinorelbine[8,9]
    - ◊ 25 mg/m² IV day 1 weekly; or
    - ◊ 20–35 mg/m² IV days 1 and 8; cycled every 21 days; or
    - ◊ 25–30 mg/m² IV days 1, 8, and 15; cycled every 28 days
  - Eribulin[10] 1.4 mg/m² IV days 1 and 8; cycled every 21 days
- **Platinum (for TNBC and germline *BRCA1/2* mutation)**
  - Carboplatin[11] AUC 6 IV on day 1
    - ◊ Cycled every 21–28 days
  - Cisplatin[12] 75 mg/m² IV on day 1
    - ◊ Cycled every 21 days
- **Cyclophosphamide[13]**
  - 50 mg PO daily on days 1–21
  - Cycled every 28 days
- **Docetaxel[14,15]**
  - 60–100 mg/m² IV day 1
  - Cycled every 21 days
- **Docetaxel[16]**
  - 35 mg/m² IV weekly for 6 weeks followed by a 2-week rest, then repeat
- **Albumin-bound paclitaxel[17,18]**
  - 100 mg/m² or 125 mg/m² IV days 1, 8, and 15
  - Cycled every 28 days
- **Albumin-bound paclitaxel[17]**
  - 260 mg/m² IV
  - Cycled every 21 days
- **Epirubicin[19]**
  - 60–90 mg/m² IV day 1
  - Cycled every 21 days
- **Ixabepilone[20]**
  - 40 mg/m² IV day 1
  - Cycled every 21 days
- **Sacituzumab govitecan-hziy (for TNBC)[21]**
  - 10 mg/kg IV on days 1 and 8
  - Cycled every 21 days
- **AC[22]**
  - Doxorubicin 60 mg/m² IV day 1
  - Cyclophosphamide 600 mg/m² IV day 1
    - ◊ Cycled every 21 days
- **EC[23]**
  - Epirubicin 75 mg/m² IV day 1
  - Cyclophosphamide 600 mg/m² IV day 1
    - ◊ Cycled every 21 days
- **CMF[24]**
  - Cyclophosphamide 100 mg/m² PO days 1–14
  - Methotrexate 40 mg/m² IV days 1 and 8
  - 5-fluorouracil 600 mg/m² IV days 1 and 8
    - ◊ Cycled every 28 days
- **Docetaxel/capecitabine[25]**
  - Docetaxel 75 mg/m² IV day 1
  - Capecitabine 950 mg/m² PO twice daily days 1–14
    - ◊ Cycled every 21 days
- **GT[26]**
  - Paclitaxel 175 mg/m² IV day 1
  - Gemcitabine 1250 mg/m² IV days 1 and 8 (following paclitaxel on day 1)
    - ◊ Cycled every 21 days
- **Gemcitabine/carboplatin[27]**
  - Gemcitabine 1000 mg/m² on days 1 and 8
  - Carboplatin AUC 2 IV on days 1 and 8
    - ◊ Cycled every 21 days
- **Carboplatin/albumin-bound paclitaxel[28]**
  - Carboplatin AUC 2 IV on days 1 and 8
  - Albumin-bound paclitaxel 125 mg/m² IV on days 1 and 8
  - Cycled every 21 days
- **Carboplatin/paclitaxel[29,30]**
  - Paclitaxel 175–200 mg/m² IV day 1
  - Carboplatin AUC 6 IV day 1
  - Cycled every 21 days
    or
  - Paclitaxel 100 mg/m² IV days 1, 8, and 15
  - Carboplatin AUC 2 IV days 1, 8, and 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.

Continued

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

HER2-Positive Regimens:[k,r,s]

- **Pertuzumab + trastuzumab + docetaxel**[31]
  - Pertuzumab 840 mg IV day 1 followed by 420 mg IV
  - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV day 1 every 21 days
  - Docetaxel 75–100 mg/m^2 IV day 1
    - ◊ Cycled every 21 days

- **Pertuzumab + trastuzumab + paclitaxel**[32,33]
  - 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
  - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV day 1 every 21 days[33]
  - Paclitaxel 80 mg/m^2 IV day 1 weekly[32]or
  - Paclitaxel 175 mg/m^2 day 1
    - ◊ Cycled every 21 days

- **Tucatinib + trastuzumab + capecitabine**[34]
  - Tucatinib 300 mg orally twice daily on days 1–21
  - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV day 1 every 21 days
  - Capecitabine 1000 mg/m^2 orally twice daily on days 1–14
  - Cycled every 21 days

- **Ado-trastuzumab emtansine (T-DM1)**[35]
  - 3.6 mg/kg IV day 1
    - ◊ Cycled every 21 days

- **Fam-trastuzumab deruxtecan-nxki**[36]
  - 5.4 mg/kg IV day 1
    - ◊ Cycled every 21 days

- **Paclitaxel/carboplatin + trastuzumab**[37]
  - Carboplatin AUC 6 IV day 1
  - Paclitaxel 175 mg/m^2 IV day 1
    - ◊ Cycled every 21 days
  - Trastuzumab 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV day 1 every 21 days[33]

- **Weekly paclitaxel/carboplatin + trastuzumab**[38]
  - Paclitaxel 80 mg/m^2 IV days 1, 8, and 15
  - Carboplatin AUC 2 IV days 1, 8, and 15
    - ◊ Cycled every 28 days
  - Trastuzumab 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV day 1 every 21 days[33]

- **Trastuzumab + paclitaxel**[39,40]
  - Paclitaxel 175 mg/m^2 IV day 1 cycled every 21 days[39]
    or
  - Paclitaxel 80–90 mg/m^2 IV day 1 weekly[41]
  - Trastuzumab 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV day 1 every 21 days[33]

- **Trastuzumab + docetaxel**[41,42]
  - Docetaxel 80–100 mg/m^2 IV day 1 cycled every 21 days[41]
    or
  - Docetaxel 35 mg/m^2 IV days 1, 8, and 15 weekly cycled every 28 days[42]
  - Trastuzumab 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV day 1 every 21 days[33]

[k] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[r] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine or fam-trastuzumab deruxtecan-nxki.
[s] Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use may be substituted anywhere that the combination of intravenous pertuzumab and intravenous trastuzumab are given as part of systemic therapy. Pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use has different dosing and administration instructions compared to the intravenous products.

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.

Continued

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

HER2-Positive Regimens (continued):[k,r]

- **Trastuzumab + vinorelbine**[9,43,44]
  - Vinorelbine
    - ◊ 25 mg/m^2 IV day 1 weekly; or
    - ◊ 20–35 mg/m^2 IV days 1 and 8; cycled every 21 days; or
    - ◊ 25–30 mg/m^2 IV days 1, 8, and 15; cycled every 28 days
  - Trastuzumab 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV day 1 every 21 days[33]
- **Trastuzumab + capecitabine**[45,46,47]
  - Capecitabine 1000–1250 mg/m^2 PO twice daily days 1–14 cycled every 21 days
  - Trastuzumab 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly[39,46]
    or
  - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV day 1 every 21 days[31,33]
- **Lapatinib + capecitabine**[48]
  - Lapatinib 1250 mg PO daily days 1–21
  - Capecitabine 1000 mg/m^2 PO twice daily days 1–14
    - ◊ Cycled every 21 days
- **Trastuzumab + lapatinib**[49]
  - Lapatinib 1000 mg PO daily for 21 days
  - Trastuzumab 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV day 1 every 21 days[33]
- **Neratinib + capecitabine**[50]
  - Neratinib 240 mg PO daily on days 1–21
  - Capecitabine 750 mg/m^2 PO twice daily on days 1–14
    - ◊ Cycled every 21 days
- **Margetuximab-cmkb + capecitabine**[51]
  - Margetuximab 15 mg/kg IV day 1
  - Capecitabine 1000 mg/m^2 po twice daily days 1–14
    - ◊ Cycled every 21 days
- **Margetuximab-cmkb + eribulin**[51]
  - Margetuximab 15 mg/kg IV day 1
  - Eribulin 1.4 mg/m^2 IV days 1 and 8
    - ◊ Cycled every 21 days
- **Margetuximab-cmkb + gemcitabine**[51]
  - Margetuximab 15 mg/kg IV day 1
  - Gemcitabine 1000 mg/m^2 IV days 1 and 8
    - ◊ Cycled every 21 days
- **Margetuximab-cmkb + vinorelbine**[51]
  - Margetuximab 15 mg/kg IV day 1
  - Vinorelbine 25–30 mg/m^2 IV days 1 and 8
    - ◊ Cycled every 21 days

[k] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[r] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine or fam-trastuzumab deruxtecan-nxki.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE REFERENCES

[1] Chan 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.
[2] Gasparini 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.
[3] O'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.
[4] Seidman 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.
[5] Perez 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.
[6] Bajetta 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.
[7] Seidman AD. Gemcitabine as single-agent therapy in the management of advanced breast cancer. Oncology (Williston Park) 2001;15:11-14.
[8] Zelek 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.
[9] Esfahani K, Ferrario C, Le P, Panasci L. The trastuzumab and vinorelbine combination: an alternative to taxane-based chemotherapy for early-stage and locally advanced her2-positive breast cancer. Curr Oncol 2014;21:e723-e727.
[10] 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.
[11] Isakoff 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 2015;33:1902-1909.
[12] Silver DP, Richardson AL, Eklund AC, et al. Efficacy of neoadjuvant cisplatin in triple-negative breast cancer. J Clin Oncol 2010;28:1145-1153.
[13] Licchetta A, Correale P, Migali C, et al. Oral metronomic chemo-hormonal-therapy of metastatic breast cancer with cyclophosphamide and megestrol acetate. J Chemother 2010;22:201-204.
[14] Burris HA, 3rd. Single-agent docetaxel (Taxotere) in randomized phase III trials. Semin Oncol 1999;26:1-6.
[15] Harvey 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;24:4963-4970.
[16] Rivera 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;112:1455-1461.
[17] Gradishar 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.
[18] Gradishar 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;27:3611-3619.
[19] Bastholt 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.
[20] Perez 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;25:3407-3414.
[21] Bardia A, Mayer IA, Vahdat LT, et al. Sacituzumab govitecan-hziy in refractory metastatic triple negative breast cancer. N Engl J Med 2019;380:741-751.
[22] Nabholtz 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;21:968-975.
[23] Langley 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.
[24] Bonadonna 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.
[25] Mavroudis 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 2010;21:48-54.
[26] Albain 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;26:3950-3957.
[27] O'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.
[28] Yardley DA, Coleman R, Conte P, et al. nab-Paclitaxel plus carboplatin or gemcitabine versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative metastatic breast cancer: results from the tnAcity trial. Ann Oncol 2018;29:1763-1770.

Continued

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE REFERENCES

[29] Perez EA, Hillman DW, Stella PJ, et al. A phase II study of paclitaxel plus carboplatin as first-line chemotherapy for women with metastatic breast carcinoma. Cancer 2000;88:124-131.
[30] Loesch D, Robert N, Asmar L, et al. Phase II multicenter trial of a weekly paclitaxel and carboplatin regimen in patients with advanced breast cancer. J Clin Oncol 2002;20:3857-3864.
[31] 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.
[32] 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.
[33] Leyland-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.
[34] Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med 2020;382(7):597-609.
[35] Verma 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.
[36] Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med 2020;382:610-621.
[37] 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.
[38] Perez 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.
[39] 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.
[40] Seidman A, Berry DA, Cirrincione 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.
[41] Marty 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.
[42] Esteva 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.
[43] 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.
[44] Andersson 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.
[45] 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.
[46] 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.
[47] Bartsch R, Wenzel C, Altorjai G, et al. Capecitabine and trastuzumab in heavily pretreated metastatic breast cancer. J Clin Oncol 2007;25:3853-3858.
[48] 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.
[49] Blackwell KL, Burstein H, Storniolo A, 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.
[50] Saura C, Oliveira M, Feng YH, et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer previously treated with ≥2 HER2-directed regimens: Findings from the multinational, randomized, phase 3 NALA trial. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting. May 31-June 4, 2019; Chicago, IL. J Clin Oncol 2019;37:(suppl; abstr 1002).
[51] Rugo HS, Im S, Cardoso F, et al. Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer. JAMA Oncol 2021;7573-584.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
Any[a]	*BRCA1* mutation *BRCA2* mutation	Germline sequencing	Olaparib Talazoparib	Category 1 Category 1	Preferred
HR-positive/ HER2-negative[b]	*PIK3CA* activating mutation	PCR (blood or tissue block if blood negative), molecular panel testing	Alpelisib + fulvestrant[c]	Category 1	Preferred second- or subsequent-line therapy
TNBC	PD-L1 expression (using 22C3 antibody) Threshold for positivity combined positive score ≥10	IHC	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[d]	Category 1	Preferred first-line therapy[h]
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[e] Entrectinib[e]	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, PCR (tissue block)	Pembrolizumab[d,f] Dostarlimab-gxly[g]	Category 2A	
Any	TMB-H (≥10 mut/mb)	NGS	Pembrolizumab[d,f]	Category 2A	

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

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

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

[d] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

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

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

[g] Dostarlimab-gxly is indicated for adult patients with MSI-H/dMMR unresectable or metastatic tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

[h] While available data are in the first-line setting, this regimen can be used for second and subsequent lines of therapy if PD-1/PD-L1 inhibitor therapy has not been previously used. If there is disease progression while on a PD-1/PD-L1 inhibitor, there are no data to support an additional line of therapy with another PD-1/PD-L1 inhibitor.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

Dose Schedules for Additional Targeted Therapies

Preferred Regimens:

- **Olaparib[1] tablet[i]**
  - 300 mg PO twice daily
  - Cycled every 28 days
- **Talazoparib[2] tablet**
  - 1 mg PO daily
  - Cycled every 28 days
- **Alpelisib + fulvestrant[3]**
  - Alpelisib 300 mg PO daily on days 1–28; fulvestrant 500 mg IM on days 1 and 15
    - ◊ 28-day cycle for 1 cycle
  - Followed by alpelisib 300 mg PO daily on days 1–28; fulvestrant 500 mg IM on day 1
    - ◊ Cycled every 28 days until disease progression or unacceptable toxicity
- **Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)[4]**
  - Pembrolizumab 200 mg IV day 1 (given every 21 days)
  - Albumin-bound paclitaxel 100 mg/m^2 days 1, 8, 15 (given every 28 days)
    OR
  - Paclitaxel 90 mg/m^2 IV days 1, 8, 15 (given every 28 days)
    OR
  - Pembrolizumab 200 mg IV day 1
  - Gemcitabine 1000 mg/m^2 IV days 1 and 8
  - Carboplatin AUC 2 IV days 1 and 8
    - ◊ Given every 21 days

Useful in Certain Circumstances:

- **Larotrectinib[5]**
  - 100 mg PO twice daily on days 1–28
  - Cycled every 28 days until disease progression or unacceptable toxicity
- **Entrectinib[6]**
  - 600 mg PO daily on days 1–28
  - Cycled every 28 days until disease progression or unacceptable toxicity
- **Pembrolizumab[7-10]**
  - 200 mg IV on day 1, every 21 days until disease progression or unacceptable toxicity
    or
  - 400 mg IV on day 1, every 6 weeks until disease progression or unacceptable toxicity, or up to 24 months
- **Dostarlimab-gxly[11]**
  - 500 mg IV on day 1
    - ◊ Cycled every 21 days for cycles 1–4
  - Followed by 1000 mg IV on day 1 of cycle 5
    - ◊ Cycled every 42 days starting with cycle 5

[i] There is also a capsule formulation available. However, do not substitute the capsules for the tablets on a mg-per-mg basis due to differences in dosing and bioavailability.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

[1] Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med 2017;377:523-533.
[2] Litton J, Rugo H, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med 2018;379:753-763.
[3] Andre F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 2019;380:1929-1940.
[4] Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet 2020;396:1817-1828.
[5] Drilon A, Laetsch TW, Kummar W, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731-739.
[6] Drilon A, Siena S, Ou SI, et al. Safety and antitumor activity of the multitargeted pan-TRK, ROS1, and ALK inhibitor entrectinib: Combined results from two phase I trials (ALKA-372-001 and STARTRK-1). Cancer Discov 2017;7:400-409.
[7] Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017;357:409-413.
[8] Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-2520.
[9] Lala M, Li TR, De Alwis DP, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. Eur J Cancer 2020;131:68-75.
[10] Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol 2020;21:1353-1365.
[11] Berton D, Banerjee S, Curigliano G, et al. Antitumor activity of dostarlimab in patients with mismatch repair–deficient (dMMR) tumors: a combined analysis of 2 cohorts in the GARNET study. Poster presented at American Society for Clinical Oncology (ASCO), Virtual Meeting, June 4–8, 2021. [Abstract ID: 2564].

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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. Clinicians should take into account patient preferences through a shared decision-making process.

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, alanine aminotransferase (ALT), aspartate transaminase (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, carcinoembryonic antigen [CEA], CA 15-3, CA 27.29)[a]**

[a] Rising tumor markers (eg, CEA, CA 15-3, CA 27.29) 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.

Continued

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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, 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

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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 Disease[b]

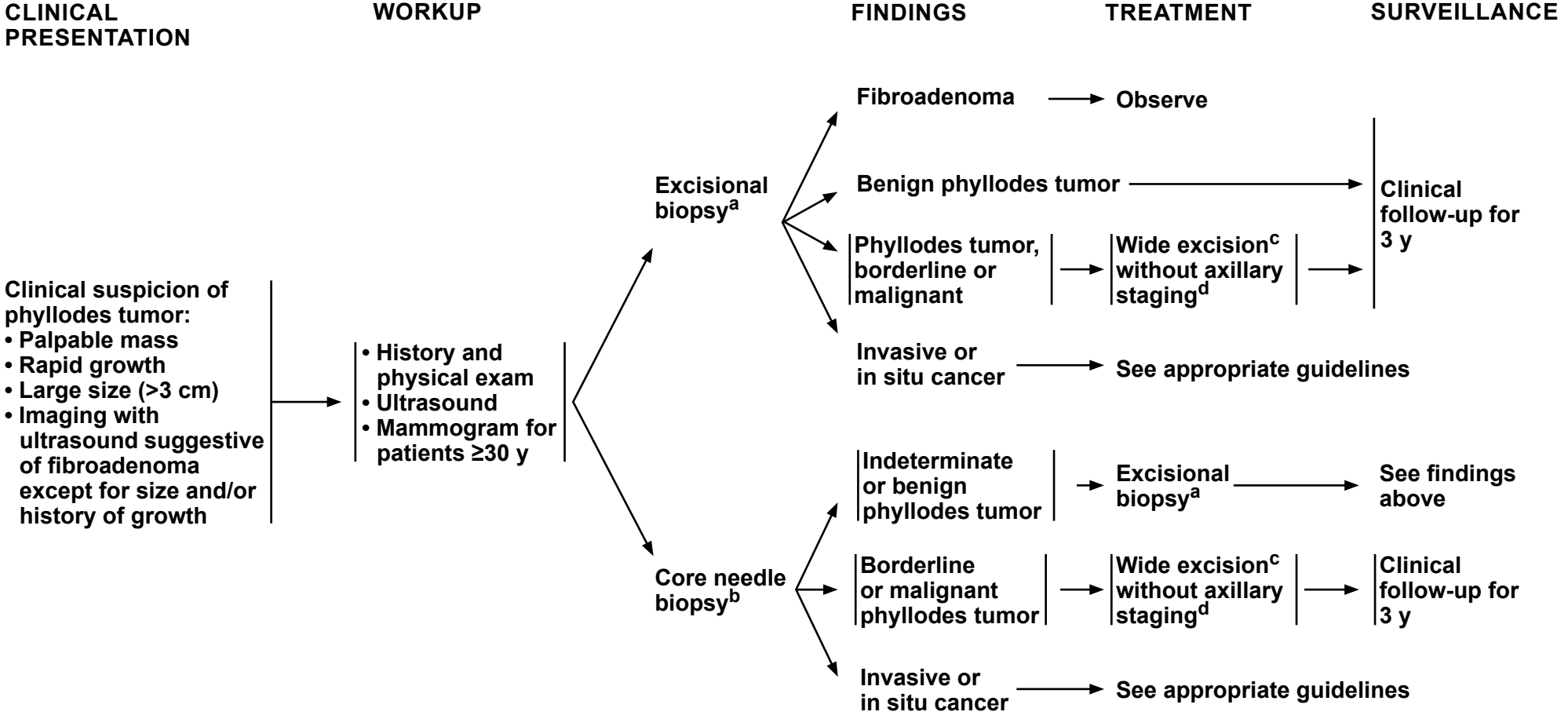
	Baseline Prior to New Therapy	Chemotherapy	Endocrine Therapy	Restaging if Concern for Progression of Disease
Symptom Assessment	Yes	Prior to each cycle	Every 1–3 months	Yes
Physical Examination	Yes	Prior to each cycle	Every 1–3 months	Yes
Performance Status	Yes	Prior to each cycle	Every 1–3 months	Yes
Weight	Yes	Prior to each cycle	Every 1–3 months	Yes
LFTs, CBC	Yes	Prior to each cycle, as indicated	Every 1–3 months	Yes
CT Chest/Abdomen/ Pelvis with Contrast	Yes	Every 2–4 cycles	Every 2–6 months	Yes
Bone Scan	Yes	Every 4–6 cycles	Every 2–6 months	Yes
PET/CT	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated
Tumor Markers	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated

[b] In 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.



[a] Excisional biopsy includes complete mass removal, but without the intent of obtaining surgical margins.

[b] FNA 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.

[c] For malignant or borderline disease, wide excision means excision with the intention of obtaining surgical margins ≥1 cm. Narrow surgical margins are associated with heightened local recurrence risk, but are not an absolute indication for mastectomy when partial mastectomy fails to achieve a margin width ≥1 cm.

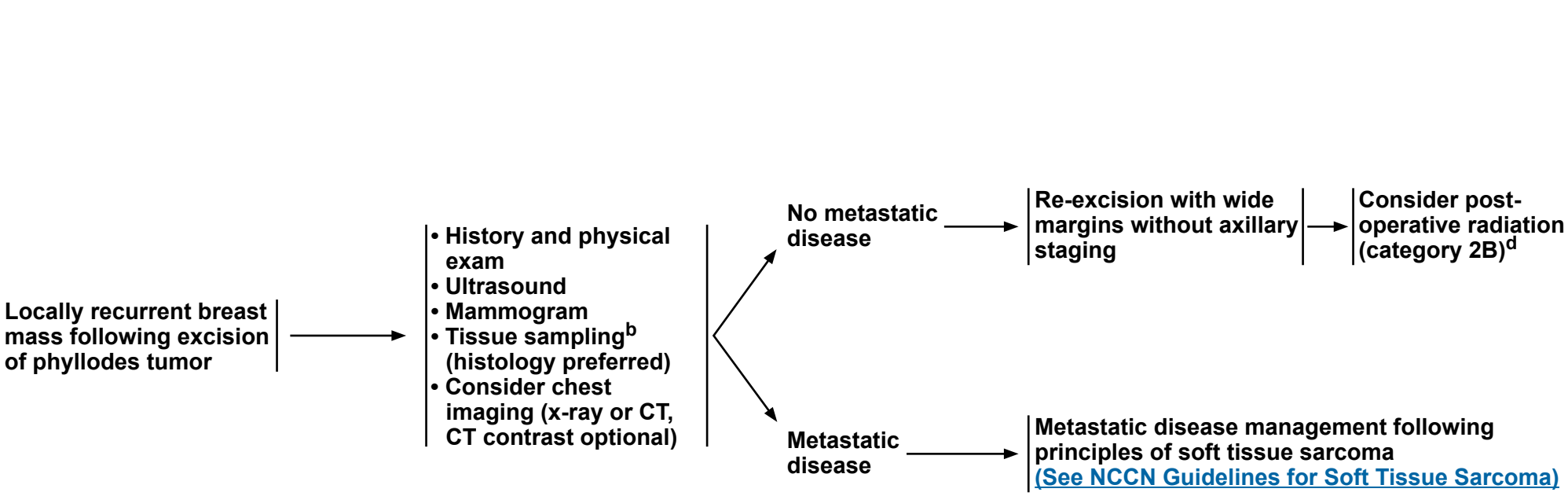
[d] There are no prospective randomized data supporting the use of RT for phyllodes tumors. However, in the setting where additional recurrence would create significant morbidity (eg, chest wall recurrence following mastectomy), RT may be considered following the same principles that are applied to the 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PHYLLODES TUMOR RECURRENCE



[b] FNA 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.

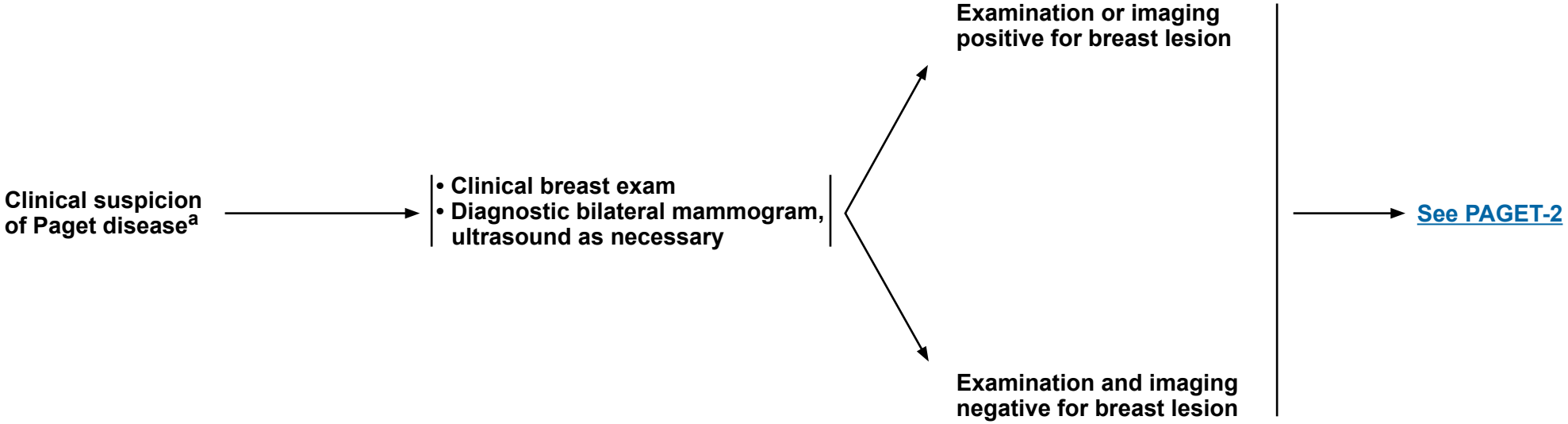
[d] There are no prospective randomized data supporting the use of RT for phyllodes tumors. However, in the setting where additional recurrence would create significant morbidity (eg, chest wall recurrence following mastectomy), RT may be considered following the same principles that are applied to the 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

CLINICAL PRESENTATION | **WORKUP**

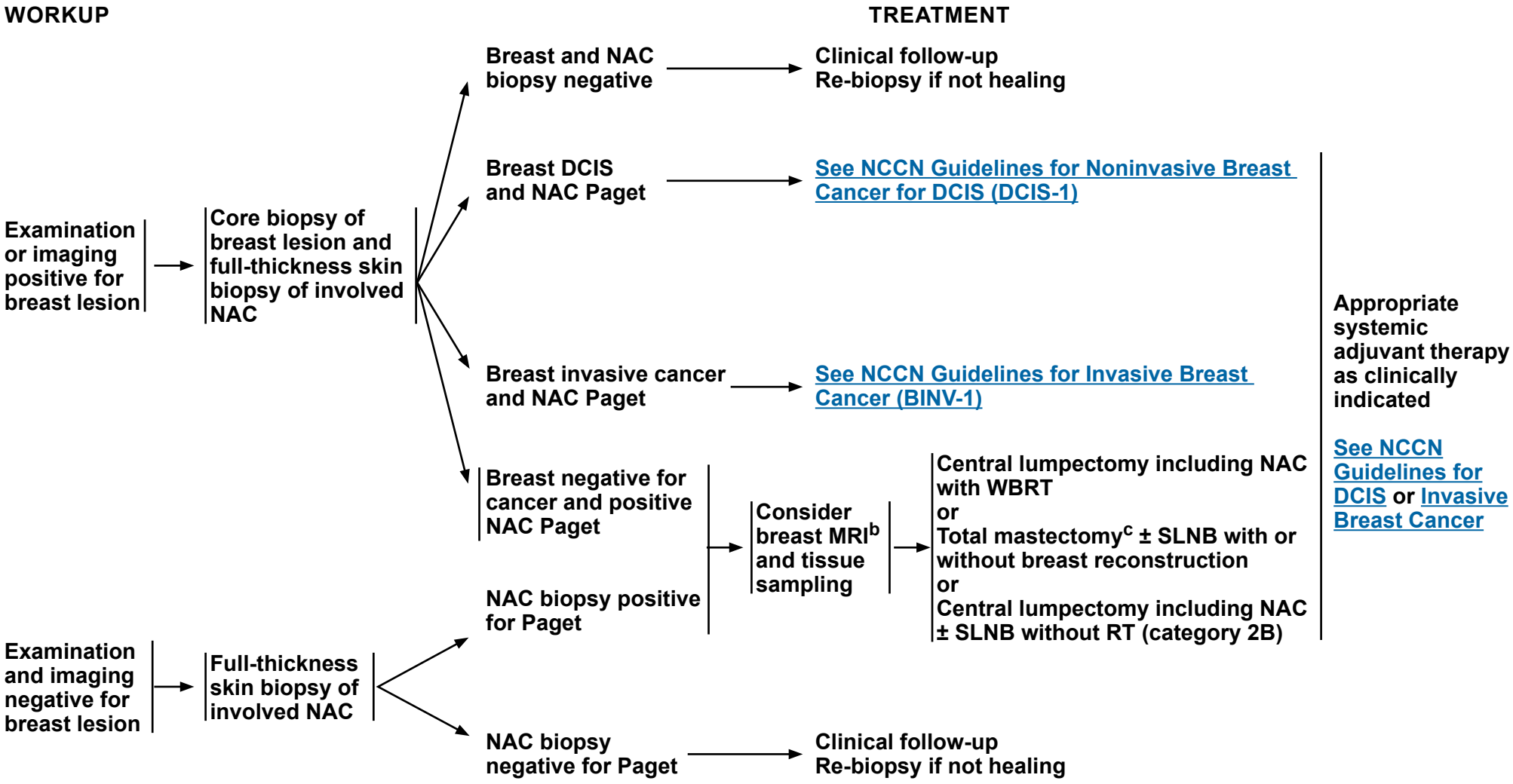


[a] Nipple or areolar eczema, ulceration, bleeding, or itching.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

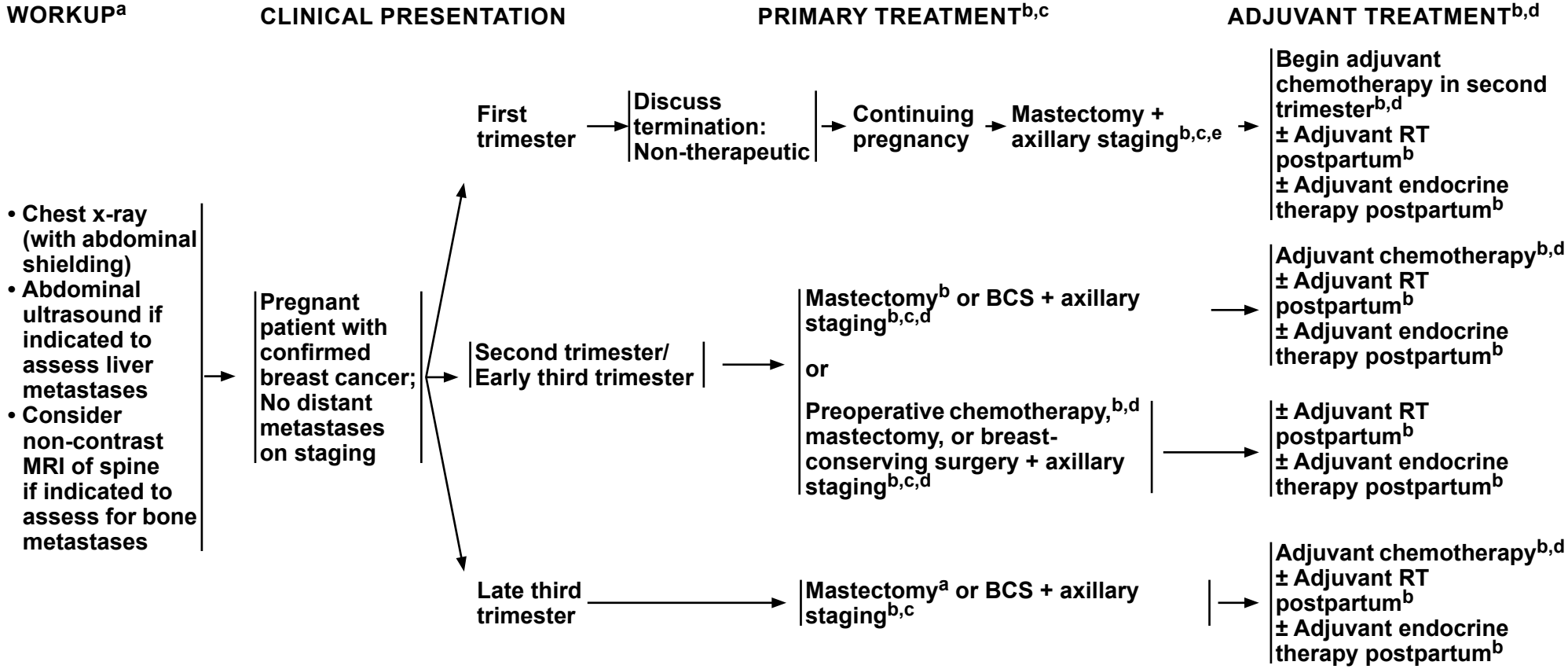


[b] See Principles of Dedicated Breast MRI Testing (BINV-B).
[c] Mastectomy is always an option with any manifestation of Paget disease (See Discussion).

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.



[a] CT scans and nuclear imaging are contraindicated during pregnancy.

[b] Considerations and selection of optimal local therapy and systemic therapy are similar to that recommended in non–pregnancy-associated breast cancer; see other sections of this guideline. However, the selection and timing of chemotherapy, endocrine therapy, and RT is different in the pregnant versus non-pregnant patient (See Discussion). Chemotherapy should not be administered during the first trimester of pregnancy, and RT should not be administered during any trimester of pregnancy. Coordination is recommended between the oncology and obstetrics teams to plan the optimal timing of systemic therapy administration during 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.

[c] Use of blue dye is contraindicated in pregnancy; radiolabeled sulfur colloid appears to be safe for SLNB in pregnancy. See Considerations for Surgical Axillary Staging (BINV-D).

[d] There are limited data on the use of taxanes during pregnancy. If used, the NCCN Panel recommends weekly administration of paclitaxel after the first trimester if clinically indicated by disease status. The use of anti-HER2 therapy is contraindicated during pregnancy.

[e] If late first trimester, may consider preoperative chemotherapy in the second trimester.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

CLINICAL PRESENTATION[a]

Clinical pathologic diagnosis of IBC →

WORKUP

- **History and physical exam by multidisciplinary team and obtain medical photography**
- **CBC**
- **Comprehensive metabolic panel, including liver function tests and alkaline phosphatase**
- **Pathology review[b]**
- **Determination of tumor ER/PR status and HER2 status[c]**
- **Fertility counseling if premenopausal[d]**
- **Genetic counseling if patient is at risk[e] for hereditary breast cancer**
- **Imaging:**
  - **Bilateral diagnostic mammogram, ultrasound as necessary**
  - **Chest diagnostic CT ± contrast**
  - **Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast**
  - **Bone scan or FDG-PET/CT[f,g]**
  - **Breast MRI (optional)**

→ **Preoperative systemic therapy,[h] anthracycline + taxane (preferred).[h] If tumor HER2-positive, HER2-targeted therapy[i]** → **See IBC-2**

[a] IBC is a clinical syndrome in patients 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 IBC.

[b] The panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. http://www.cap.org.

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

[d] See Fertility and Birth Control (BINV-C).

[e] For risk criteria, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.

[f] If 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.

[g] 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. FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases when used in addition to standard staging studies.

[h] See Preoperative/Adjuvant Therapy Regimens (BINV-L).

[i] A pertuzumab-containing regimen may be administered preoperatively to patients with HER2-positive IBC.

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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

RESPONSE TO PREOPERATIVE THERAPY | **TREATMENT[k]**

Response[j] → **Total mastectomy + level I/II axillary dissection + RT to chest wall and comprehensive RNI with inclusion of any portion of the undissected axilla at risk ± delayed breast reconstruction[l]** →

- **Complete planned chemotherapy regimen course if not completed preoperatively plus endocrine treatment if ER-positive and/or PR-positive (sequential chemotherapy followed by endocrine therapy).[n]**
- **Complete up to one year of HER2-targeted therapy if HER2-positive (category 1). May be administered concurrently with RT[o] and with endocrine therapy if indicated.**

No response[j] → **Consider additional systemic chemotherapy[m] and/or preoperative radiation.** → **Patients may be candidates for multiple lines of systemic therapy to palliate advanced breast cancer. At each reassessment clinicians should assess value of ongoing treatment, the risks and benefits of an additional line of systemic therapy, patient performance status, and patient preferences through a shared decision-making process.**

- **Response[j]** → **See above pathway**
- **No response[j]** → **Individualized treatment**

[j] 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.
[k] Patients with recurrent IBC should be treated according to the guideline for recurrence/stage IV (M1) disease (BINV-19).
[l] See Principles of Breast Reconstruction Following Surgery (BINV-H).
[m] See Systemic Therapy Regimens for Recurrent Unresectable (local or regional) or Stage IV (M1) Disease (BINV-Q).
[n] See Adjuvant Endocrine Therapy (BINV-K).
[o] 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.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

Primary Tumor (T) The T category of the primary tumor is defined by the same criteria regardless of whether it is based on clinical or pathological criteria, or both. The T category is based primarily on the size of the invasive component of the cancer. The maximum size of a tumor focus is used as an estimate of disease volume. The largest contiguous dimension of a tumor focus is used, and small satellite foci of noncontiguous tumor are not added to the size. The cellular fibrous reaction to invasive tumor cells is generally included in the measurement of a tumor prior to treatment; however, the dense fibrosis observed following neoadjuvant treatment is generally not included in the pathological measurement because its extent may overestimate the residual tumor volume. The clinical size of a primary tumor (T) can be measured based on clinical findings (physical examination and imaging modalities, such as mammography, ultrasound, and MR imaging) and pathological findings (gross and microscopic measurements). Clinical tumor size (cT) should be based on the clinical findings that are judged to be most accurate for a particular case, although it may still be somewhat inaccurate because the entent of some breast cancers is not always apparent with current imaging techniques and because tumors are composed of varying proportions of noninvasive and invasive disease, which these techniques are currently unable to distinguish. 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 the size should be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 4.9 mm is reported as 5 mm, or a size of 2.04 cm is reported as 2.0 cm (20 mm). The exception to this rounding rule is for a breast tumor sized between 1.0 and1.4 mm. These sizes are rounded up to 2 mm, because rounding down would result in the cancer's being categorized as microinvasive carcinoma (T1mi) defined as a size of 1.0 mm or less.

***Table 1.* Definitions for T, N, M**

TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis (DCIS)*		Ductal carcinoma *in situ*
Tis (Paget)		Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted
T1		Tumor ≤20 mm in greatest dimension
	T1mi	Tumor ≤1 mm in greatest dimension
	T1a	Tumor >1 mm but ≤5 mm in greatest dimension (round any measurement >1.0–1.9 mm to 2 mm)
	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 macroscopic nodules); invasion of the dermis alone does not qualify as T4
	T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures does not qualify as T4
	T4b	Ulceration and/or ipsilateral macrosopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
	T4c	Both T4a and T4b are present
	T4d	Inflammatory carcinoma

*Note: Lobular carcinoma *in situ* (LCIS) is a benign entity and is removed from TNM staging in the AJCC Cancer Staging Manual, 8th Edition.

Continued

Used with the permission of the American College of Surgeons, Chicago Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. For complete information and data supporting the staging tables, visit www.springer.com.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Table 1. **Definitions for T, N, M (continued)**

Regional Lymph Nodes (N)

Clinical (cN)

cNX*	Regional lymph nodes cannot be assessed (e.g., previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
cN1mi**	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
cN2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; *or* in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; *or* in ipsilateral internal mammary lymph node(s) with 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
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or fine needle aspiration/core needle biopsy respectively.
*The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examination of the axilla.
**cN1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy.

Pathologic (pN)

pNX	Regional lymph nodes cannot be assessed (e.g., not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cells clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (RT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined.
pN2	Metastases in 4–9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes

Continued

Used with the permission of the American College of Surgeons, Chicago Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. For complete information and data supporting the staging tables, visit www.springer.com.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Table 1. **Definitions for T, N, M (continued)**

Pathologic (pN)

pN3	Metastases in 10 or more axillary lymph nodes; *or* in infraclavicular (level III axillary) lymph nodes; *or* positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive level I, II axillary lymph nodes; *or* in more than three axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; *or* in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm); *or* metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging); *or* pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or FNA/core needle biopsy respectively, with NO further resection of nodes

Distant Metastasis (M)

M0	No clinical or radiographic evidence of distant metastases*
cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits no larger than 0.2 mm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
cM1	Distant metastases detected by clinical and radiographic means
pM1	Any histologically proven metastases in distant organs; or if in non-regional nodes, metastases greater than 0.2 mm

Table 2. **AJCC Anatomic Stage Groups**

The Anatomic Stage Group table should only be used in global regions where biomarker tests are not routinely available.
Cancer registries in the U.S. must use the Clinical and Pathological Prognostic Stage Group tables for case reporting.

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

Notes:
1. T1 includes T1mi.
2. T0 and T1 tumors with nodal micrometastases (N1mi) are staged as Stage IB.
3. T2, T3, and T4 tumors with nodal micrometastases (N1mi) are staged using the N1 category.
4. M0 includes M0(i+).
5. The designation pM0 is not valid; any M0 is clinical.
6. If a patient presents with M1 disease prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
7. Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided the studies are performed within 4 months of diagnosis in the absence of disease progression, and provided the patient has not received neoadjuvant therapy.
8. Staging following neoadjuvant therapy is designated with “yc” or “yp” prefix to the T and N classification. There is no anatomic stage group assigned if there is a complete pathological response (pCR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

Continued

Used with the permission of the American College of Surgeons, Chicago Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. For complete information and data supporting the staging tables, visit www.springer.com.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Table 2. **AJCC Anatomic Stage Groups (continued)**

Histologic Grade (G)

All invasive breast carcinomas should be assigned a histologic grade. The Nottingham combined histologic grade (Nottingham modification of the SBR grading system) is recommended and is stipulated for use by the College of American Pathologists (see www.cap.org). The grade for a tumor is determined by assessing morphologic features (tubule formation, nuclear pleomorphism, and calibrated mitotic count), assigning a value from 1 (favorable) to 3 (unfavorable) for each feature, and totaling 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. The use of subjective grading alone is discouraged.

Invasive Cancer (Scarff-Bloom-Richardson [SBR] Grading System, Nottingham Modification)

GX Grade cannot be assessed

G1 Low combined histologic grade (favorable); SBR score of 3–5 points

G2 Intermediate combined histologic grade (moderately favorable); SBR score of 6–7 points

G3 High combined histologic grade (unfavorable); SBR score of 8–9 points

Ductal Carcinoma *in situ*: Nuclear Grade
The grade that should be used for ductal carcinoma in situ is nuclear grade (www.cap.org)

GX Grade cannot be assessed

G1 Low nuclear grade

G2 Intermediate nuclear grade

G3 High nuclear grade

Continued

Used with the permission of the American College of Surgeons, Chicago Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. For complete information and data supporting the staging tables, visit www.springer.com.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Histopathologic Type - WHO Classification 5th Edition (2019)

In situ carcinomas

- Ductal carcinoma in situ (DCIS) (low nuclear grade, intermediate nuclear grade, and high nuclear grade)
- In situ papillary neoplasms (papillary DCIS, encapsulated papillary carcinoma, solid papillary carcinoma in situ)

Invasive Carcinomas

- Invasive breast carcinoma of no special type (ductal and other special patterns)
- Microinvasive carcinoma
- Invasive lobular carcinoma
- Tubular carcinoma
- Cribriform carcinoma
- Mucinous carcinoma
- Mucinous cystadenocarcinoma
- Invasive micropapillary carcinoma
- Invasive papillary carcinoma
- Invasive solid papillary carcinoma
- Carcinoma with apocrine differentiation
- Metaplastic carcinoma (spindle cell, squamous, with heterologous differentiation, low-grade adenosquamous carcinoma, low-grade fibromatosis-like and mixed metaplastic)
- Neuroendocrine tumor (NET)
- Neuroendocrine carcinoma (NEC)
- Salivary gland-type (acinic cell, adenoid cystic, secretory, mucoepidermoid, polymorphous adenocarcinoma)
- Tall cell carcinoma with reversed polarity

Favorable Histologic Types

- Tubular carcinoma
- Cribriform carcinoma
- Mucinous carcinoma
- Adenoid cystic
- Low-grade adenosquamous carcinoma metaplastic carcinoma
- Low-grade fibromatosis-like metaplastic carcinoma

Continued

WHO Classification of Tumors Editorial Board, ed. WHO Classification of Tumors, 5th Edition – Breast Tumors. Lyon: International Agency for Research on Cancer 2019.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

***Table 3.* Clinical Prognostic Stage**

Clinical Prognostic Stage applies to ALL patients with breast cancer for clinical classification and staging. It uses clinical tumor (T), node (N) and metastases (M) information based on history, physical examination, any imaging performed (not necessary for clinical staging) and relevant biopsies. Genomic profile information is not included in Clinical Prognostic Stage as pathologic information from surgery is necessary to ascertain the prognosis using these tools.

TNM	Grade	HER2	ER	PR	Stage
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	
				Negative	IB
	G2	Positive	Positive	Positive	IA
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	
				Negative	IB
	G3	Positive	Positive	Positive	IA
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	IB
			Negative	Positive	
				Negative	

TNM	Grade	HER2	ER	PR	Stage
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	IIB
	G3	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	IIB
			Negative	Positive	
				Negative	

Continued

*T1 includes T1mi.

**N1 does not include N1mi. T1 N1mi M0 and T0 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status.

Used with the permission of the American College of Surgeons, Chicago Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. For complete information and data supporting the staging tables, visit www.springer.com.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Table 3. **Clinical Prognostic Stage (continued)**

TNM	Grade	HER2	ER	PR	Stage
T2 N1*** M0 T3 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	
				Negative	
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	
				Negative	IIIB
	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	IIIA
			Negative	Positive	
				Negative	IIIB

TNM	Grade	HER2	ER	PR	Stage
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1*** M0 T3 N2 M0	G1	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	
				Negative	IIIB
	G2	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	
				Negative	IIIB
	G3	Positive	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	IIIB
			Negative	Positive	
				Negative	IIIC

Continued

*T1 includes T1mi.
***N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1 and T4 N1, respectively.

Used with the permission of the American College of Surgeons, Chicago Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. For complete information and data supporting the staging tables, visit www.springer.com.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Table 3. **Clinical Prognostic Stage (continued)**

TNM	Grade	HER2	ER	PR	Stage
T4 N0 M0 T4 N1*** M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	
				Negative	IIIC
	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	
				Negative	IIIC
	G3	Positive	Positive	Positive	IIIB
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	IIIC
			Negative	Positive	
				Negative	
Any T Any N M1	Any	Any	Any	Any	IV

Notes:
1. Because N1mi categorization requires evaluation of the entire node, and cannot be assigned on the basis of an FNA or core biopsy, N1mi can only be used with Clinical Prognostic Staging when clinical staging is based on a resected lymph node in the absence of resection of the primary cancer, such as the situation where sentinel node biopsy is performed prior to receipt of neoadjuvant chemotherapy or endocrine therapy.
2. For cases with lymph node involvement with no evidence of primary tumor (e.g. T0 N1, etc.) or with breast ductal carcinoma *in situ* (e.g. Tis N1, etc.), the grade, HER2, ER, and PR information from the tumor in the lymph node should be used for assigning stage group.
3. For cases where HER2 is determined to be “equivocal” by ISH (FISH or CISH) testing under the 2013 ASCO/CAP HER2 testing guidelines, the HER2 “negative” category should be used for staging in the Clinical Prognostic Stage Group.
4. The prognostic value of these Prognostic Stage Groups is based on populations of persons with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy).

Continued

***N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1 and T4 N1, respectively.

Used with the permission of the American College of Surgeons, Chicago Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. For complete information and data supporting the staging tables, visit www.springer.com.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Table 4. **Pathological Prognostic Stage**

Pathological Prognostic Stage applies to patients with breast cancer treated with surgery as the initial treatment. It includes all information used for clinical staging plus findings at surgery and pathological findings from surgical resection. Pathological Prognostic Stage does not apply to patients treated with systemic or radiation prior to surgical resection (neoadjuvant therapy).

TNM	Grade	HER2	ER	PR	Stage
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	
				Negative	
	G2	Positive	Positive	Positive	
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	
				Negative	IB
	G3	Positive	Positive	Positive	IA
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	
			Negative	Positive	
				Negative	IB
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	
				Negative	IIA
	G2	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	
				Negative	
	G3	Positive	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	
				Negative	

Continued

*T1 includes T1mi.

**N1 does not include N1mi. T1 N1mi M0 and T0 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status.

Used with the permission of the American College of Surgeons, Chicago Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. For complete information and data supporting the staging tables, visit www.springer.com.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Table 4. **Pathological Prognostic Stage (continued)**

TNM	Grade	HER2	ER	PR	Stage
T2 N1*** M0 T3 N0 M0	G1	Positive	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	
				Negative	
	G2	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	
				Negative	
	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	
				Negative	IIIA

TNM	Grade	HER2	ER	PR	Stage
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1*** M0 T3 N2 M0	G1	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	
				Negative	
	G2	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	
				Negative	IIIB
	G3	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	
				Negative	IIIC

Continued

*T1 Includes T1mi.
***N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1 and T4 N1, respectively.

Used with the permission of the American College of Surgeons, Chicago Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. For complete information and data supporting the staging tables, visit www.springer.com.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Table 4. **Pathological Prognostic Stage (continued)**

TNM	Grade	HER2	ER	PR	Stage
T4 N0 M0 T4 N1*** M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	
				Negative	
	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	
				Negative	IIIC
	G3	Positive	Positive	Positive	IIIB
				Negative	
			Negative	Positive	
				Negative	
		Negative	Positive	Positive	
				Negative	IIIC
			Negative	Positive	
				Negative	
Any T Any N M1	Any	Any	Any	Any	IV

Notes:
1. For cases with lymph node involvement with no evidence of primary tumor (e.g. T0 N1, etc.) or with breast ductal carcinoma *in situ* (e.g. Tis N1, etc.), the grade, HER2, ER and PR information from the tumor in the lymph node should be used for assigning stage group.
2. For cases where HER2 is determined to be “equivocal” by ISH (FISH or CISH) testing under the 2013 ASCO/CAP HER2 testing guidelines, HER2 “negative” category should be used for staging in the Pathological Prognostic Stage Group.
3. The prognostic value of these Prognostic Stage Groups is based on populations of persons with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy).

Table 5. **Genomic Profile for Pathologic Prognostic Staging**

When Oncotype DX Score is Less than 11...

TNM	Grade	HER2	ER	PR	Stage
T1 N0 M0 T2 N0 M0	Any	Negative	Positive	Any	IA

Notes:
1. Obtaining genomic profiles is NOT required for assigning Pathological Prognostic Stage. However genomic profiles may be performed for use in determining appropriate treatment. If the OncotypeDx® test is performed in cases with a T1N0M0 or T2N0M0 cancer that is HER2-negative and ER-positive, and the recurrence score is less than 11, the case should be assigned Pathological Prognostic Stage Group IA.
2. If OncotypeDx® is not performed, or if it is performed and the OncotypeDx® score is not available, or is 11 or greater for patients with T1–2 N0 M0 HER2–negative, ER-positive cancer, then the Prognostic Stage Group is assigned based on the anatomic and biomarker categories shown above.
3. OncotypeDx® is the only multigene panel included to classify Pathologic Prognostic Stage because prospective Level I data supports this use for patients with a score less than 11. Future updates to the staging system may include results from other multigene panels to assign cohorts of patients to Prognostic Stage Groups based on the then available evidence. Inclusion or exclusion in this staging table of a genomic profile assay is not an endorsement of any specific assay and should not limit appropriate clinical use of any genomic profile assay based on evidence available at the time of treatment.

***N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1 and T4 N1, respectively.

Used with the permission of the American College of Surgeons, Chicago Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. For complete information and data supporting the staging tables, visit www.springer.com.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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 indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Version 1.2022, 11/24/21 © 2021 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Discussion

The Discussion section on management of recurrent/Stage IV breast cancer was updated on 03/06/20. The rest of the discussion update is in progress.

Table of Contents

Overview MS-2
Literature Search Criteria and Guidelines Update Methodology MS-2
Staging MS-2
Pathology Assessment MS-3
Treatment Approach MS-5
Ductal Carcinoma in Situ (Tis, N0, M0) MS-6
- Primary Treatment for DCIS MS-6
- Management of DCIS after Primary Treatment MS-10

Invasive Breast Cancer (T0–3,N1,M0 and T1–3,N0–1,M0) MS-12
- Workup MS-12
- Locoregional Treatment MS-14
- Breast Reconstruction MS-22
- Systemic Therapies (Preoperative and Adjuvant) MS-26
- Staging and Workup Prior to Preoperative Chemotherapy MS-46
- Post-Therapy Surveillance and Follow-up MS-48

Recurrent/Stage IV Breast Cancer MS-51
- Staging and Workup for Recurrent/Stage IV Breast Cancer MS-51
- Management of Locally Recurrent Disease MS-52
- Management of Recurrent or Stage IV Disease MS-53
- Monitoring Metastatic Disease MS-72

Special Situations MS-74
- Paget's Disease MS-74
- Phyllodes Tumors of the Breast MS-76
- Breast Cancer During Pregnancy MS-77
- Inflammatory Breast Cancer MS-79
- Axillary Breast Cancer MS-83

Summary MS-84
References MS-85

Discussion update in progress

Version 1.2022 © 2021 National Comprehensive Cancer Network© (NCCN©), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Overview

Breast cancer is the most common malignancy in women in the United States and is second only to lung cancer as a cause of cancer death. The American Cancer Society has estimated that 279,100 Americans will be diagnosed with breast cancer and 42,690 will die of disease in the United States in 2020[1]. The therapeutic options for patients with noninvasive or invasive breast cancer are complex and varied. These NCCN Clinical Practice Guidelines for Breast Cancer include up-to-date guidelines for clinical management of patients with carcinoma in situ, invasive breast cancer, Paget's disease, Phyllodes tumor, inflammatory breast cancer, and breast cancer during pregnancy. These guidelines are developed by a multi-disciplinary panel of representatives from NCCN member institutions with breast cancer-focused expertise in the fields of medical oncology, surgical oncology, radiation oncology, pathology, reconstructive surgery, and patient advocacy.

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: Breast Cancer, Breast Neoplasms, DCIS, Inflammatory Breast Cancer OR Phyllodes. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[2]

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.

Discussion update in progress

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+);

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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 (HR) 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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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-positive[21-24] 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 (C*EP)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 and <6.0 signals/cell) must be confirmed by reflex

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Ductal Carcinoma in Situ (Tis, N0, M0)

The recommended workup and staging of DCIS includes history and physical examination; bilateral diagnostic mammography; pathology review; determination of tumor estrogen receptor (ER) status; and MRI as indicated.

For pathology reporting, the NCCN panel endorses the College of American Pathologists Protocol for both invasive and noninvasive carcinomas of the breast.[3]

The NCCN panel recommends testing for ER status in order to determine the benefit of adjuvant endocrine therapy or risk reduction. Although the tumor 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.[4-7] The NCCN Panel has concluded that knowing the HER2 status of DCIS does not alter the management strategy and is not required DCIS.

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 role of MRI in management of DCIS remains unclear. MRI has been prospectively shown to have a sensitivity of up to 98% for high-grade DCIS.[8] In a prospective, observational study of 193 women with pure DCIS who 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.[8] However, other studies suggest that MRI can overestimate the extent of disease.[9] Therefore, surgical decisions should not be not be solely based on MRI results especially when mastectomy is being contemplated. If MRI findings suggest more extensive disease than is seen on mammography such that a markedly larger resection is required for complete excision, the findings should be verified histologically through MRI-guided biopsy of the more extensive enhancement.

Studies have also been performed to determine whether the use of MRI reduces re-excision rates and decreases local recurrence in women with DCIS. No reduction in re-excision rates was seen in women undergoing lumpectomy following MRI compared with those who did not undergo preoperative MRI.[10,11]

The NCCN Panel recommends only performing breast MRI for DCIS in select circumstances where additional information is warranted during the initial workup, noting that the use of MRI has not been shown to increase likelihood of negative margins or decrease conversion to mastectomy for DCIS.

Primary Treatment for DCIS

The goal of primary therapy for DCIS is to prevent progression to invasive breast carcinoma. Management strategies for DCIS treatment include surgery (mastectomy or lumpectomy), radiation therapy, and adjuvant endocrine therapy to reduce risk of recurrence.

Surgery: Excision of DCIS using a breast-conserving approach (lumpectomy) with or without whole breast radiation therapy (WBRT) or alternatively, mastectomy, are the primary treatment options for individuals with DCIS.

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. Post-excision mammography is valuable in confirming that an adequate excision of

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

DCIS has been performed particularly for DCIS patients who initially present with microcalcifications.[12]

Mastectomy: Patients with DCIS and evidence of widespread disease (ie, disease involving two or more quadrants) on diagnostic mammography or other imaging, physical examination, or biopsy may require mastectomy.

Mastectomy permanently alters the lymphatic drainage pattern to the axilla, so that future performance of a sentinel lymph node biopsy (SLNB) is not technically feasible.[13,14] Therefore, for DCIS patients who intend on treatment with mastectomy, or alternatively, for local excision in an anatomic location that could compromise the lymphatic drainage pattern to the axilla (eg, tail of the breast), a SLNB procedure should *strongly* be considered at the time of definitive surgery to avoid necessitating a full axillary lymph node dissection for evaluation of the axilla.[13-16]

Complete axillary lymph node dissection (ALND) is *not* recommended unless there is pathologically documented invasive cancer or axillary lymph node metastatic disease in patients (by either biopsy or SNLB). However, a small proportion of women (about 25%) with seemingly pure DCIS on initial biopsy will have invasive breast cancer at the time of the definitive surgical procedure[17] and thus will ultimately require ALN staging.

Lumpectomy plus Whole Breast Radiation Therapy (WBRT): Breast conserving therapy (BCT) includes lumpectomy to remove the tumor with negative surgical margins followed by WBRT to eradicate any residual microscopic disease.

Several prospective randomized trials of pure DCIS have shown that the addition of WBRT after lumpectomy decreases the rate of in-breast disease recurrence, [18-25] or distant metastasis-free survival.[26] In the long term follow-up of the RTOG 9804 trial, 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.[25] A meta-analysis of four large multicenter randomized trials confirms the results of the individual trials, demonstrating that the addition of WBRT after lumpectomy for DCIS provides a statistically and clinically significant reduction in ipsilateral breast events (HR [hazard ratio], 0.49; 95% CI; 0.41–0.58, $P < .00001$).[27] However, these trials did not show that the addition of RT has an overall survival benefit. 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, $P < .001$).[24] However, overall survival (OS) and cumulative all-cause mortality rates through 15 years were similar between the two groups (HR for death, 1.08; 95% CI, 0.79–1.48).[24] Similar findings were reported by a large observational study of the SEER database that included 108,196 patients with DCIS.[28] In a subgroup analysis at 10 years, of 60,000 women treated with breast-conserving therapy, with or without radiation therapy, radiation therapy was associated with a 50% reduction in the risk of ipsilateral recurrence (adjusted HR, 0.47 [95% CI, 0.42–0.53]; $P < .001$), however, breast cancer-specific mortality was found to be similar (HR, 0.86 [95% CI, 0.67–1.10]; $P = .22$).[28]

More recently, in a population-based study, the use of WBRT in patients with higher-risk DCIS (eg higher nuclear grade, younger age, and larger tumor size) was demonstrated to be associated with a modest, but statistically significant improvement in survival.[29]

RT Boost: The use of RT boost has been demonstrated to provide a small but statistically significant reduction in IBTR risk (4% at 20 years) in all age groups for invasive breast cancers.[30-33]

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

ecently, a pooled analysis of patient-level data from 10 academic institutions evaluated outcomes of pure DCIS patients, all treated with lumpectomy and WBRT (n = 4131) who either received RT boost with a median dose of 14 Gy (n = 2661) or received no boost (n = 1470). The median follow-up of patients was 9 years. A decrease in IBTR was seen in patients who received boost compared with those who did not at 5 years (97.1% vs 96.3%), 10 years (94.1% vs 92.5%), and 15 years (91.6% vs 88.0%) (*P* = .0389 for all). The use of RT boost was associated with significantly decreased IBTR across the entire cohort of patients (hazard ratio [HR], 0.73; 95% CI, 0.57-0.94; *P* = .01).[34] In a multivariate analysis that took into account factors associated with lower IBTR, including grade, ER positive status, use of adjuvant tamoxifen, margin status, and age, the benefit of RT boost still remained statistically significant (hazard ratio, 0.69; 95% confidence interval [CI], 0.53 - 0.91; *P* < .010).[34] Even in patients considered very low risk based on negative margins status (defined as no ink on tumor as per National Surgical Adjuvant Breast and Bowel Project definition, or margins <2 mm as per SSO/ASTRO/ASCO definition), the RT boost remained statistically significant for decreasing the rate of local relapse. Similar to invasive cancers, though RT boost was beneficial in all age groups studied, the magnitude of the absolute benefit of the boost was greatest in younger patients. Two ongoing randomized, phase 3 trials are studying whether an RT boost reduces recurrence in patients with DCIS (ClinicalTrials.gov Identifiers: NCT00470236 and NCT00907868).

While considering RT boost for DCIS, the NCCN panel recommends an individualized approach based on patient preference and other factors such as longevity.

Lumpectomy alone without WBRT: Several trials have examined omission of RT after lumpectomy in carefully selected, low-risk patients. There are retrospective series suggesting that selected patients have a low risk of in-breast recurrence when treated with excision alone (without WBRT).[35-38] For example, in one retrospective review, 10-year disease-free survival (DFS) rates of 186 patients with DCIS treated with lumpectomy alone was 94% for patients with low-risk DCIS and 83% for patients with both intermediate- and high-risk DCIS.[35]

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.[36]

A multi-Institutional, non-randomized, 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.[39] Patients were enrolled onto one of two low-risk cohorts: a) low- or intermediate-grade DCIS, tumor size 2.5 cm or smaller (n = 561); or b) high-grade DCIS, tumor size 1 cm or smaller (n = 104). Protocol specifications included excision of the DCIS tumor with a minimum negative margin width of at least 3 mm. Only 30% of the patients received tamoxifen. Of note, margins were substantially wider than the 3 mm protocol requirement in many patients (ie- the low/intermediate-risk patient group margins were ≥ 5 mm in 62% of patients and >10 mm or no tumor on re-excision in 48 % of patients).[39] Although the rate of IBTR were acceptably low for the low-/intermediate grade group at the 5 years, at a median follow-up time of 12.3 years, the rates of developing an IBTR were 14.4% for low/intermediate-grade and 24.6% for high grade DCIS (*P* = .003). This suggests that IBTR events may be delayed but not prevented in the seemingly low-risk population. Therefore, the NCCN panel concluded that for DCIS patients treated with lumpectomy alone (without radiation), irrespective of margin width, the risk of IBTR is substantially higher than treatment with excision followed by whole breast radiation therapy (even for predefined low-risk subsets of DCIS patients).

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Margin status after breast conserving therapy: Prospective randomized trials have not been carried out to analyze whether wider margins can replace the need for radiation therapy for DCIS. 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.[40] 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 IBTR 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.[41]

A fairly recent 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.[42] 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 ($P = .95$).[42]

According to the 2016 guidelines by SSO/ASTRO/ASCO, the use of at least 2 mm margin in DCIS treated with WBRT is associated with low rates of ipsilateral breast tumor recurrence (IBTR).[43] Additional factors to consider in assessing adequacy of excision for DCIS include presence of residual calcifications, which margin is close (anterior against skin or posterior against muscle versus medial, superior, inferior or lateral), and life expectancy of the patient. Notably, in situations where DCIS is admixed with invasive carcinoma, SSO/ASTRO/ASCO guidelines support “no tumor on ink” as an adequate margin applying to both the invasive and noninvasive components in this mixed tumor scenario.

NCCN Recommendations for Primary Treatment of DCIS

Trials are ongoing to determine if there might be a selected favorable biology DCIS sub-group where surgical excision is not required. Until such time that definitive evidence regarding the safety of this non-surgical approach is demonstrated, the NCCN panel continues to recommend surgical excision for 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 with or without boost (category 1); total mastectomy, with or without SLNB with optional reconstruction (category 2A); or lumpectomy alone (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.

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). Women treated with mastectomy are appropriate candidates for breast reconstruction (see *Principles of Breast Reconstruction Following Surgery* in the NCCN Guidelines for Breast Cancer).

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.

The NCCN Panel accepts the definitions of negative margins after BCS from the 2016 SSO/ASTRO/ASCO Guidelines for DCIS.[43] For pure DCIS treated by BCS and whole breast radiation therapy treatment (WBRT), 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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

negative margin widths wider than 2 mm is not supported by the evidence. 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).

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.[44,45] These data also showed that tamoxifen led to a substantial reduction in the risk of developing benign breast disease.[46] 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.[47]

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. At a median follow-up of 13.6 years, patients who received 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; $P = .023$).[24] 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.[48]

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.[23] 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-positive 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.[49] 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, $P = .78$).[49] 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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[50] 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.[50] 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 while the anastrozole group had slightly more cases of arthralgia and myalgia.[50]

The results of the IBIS-II and the NSAP-B-35 studies indicate that anastrozole provides at least a comparable benefit as adjuvant treatment for postmenopausal women with hormone-receptor-positive DCIS, with a different toxicity profile.

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.

Surveillance after treatment for DCIS helps early recognition of disease recurrences (either DCIS or invasive disease) and evaluation and management of therapy-related complications. The majority of recurrences of DCIS are in-breast recurrences after breast-conserving therapy, and recurrences mostly occur in close proximity to the location of the prior disease. Overall, approximately one-half of the local recurrences after initial treatment for a pure DCIS are invasive in nature, whereas the remainder recur as pure DCIS. 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.

Discussion update in progress

Version 1.2022 © 2021 National Comprehensive Cancer Network© (NCCN©), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Invasive Breast Cancer (T0–3,N1,M0 and T1–3,N0–1,M0)

Workup

he recommended workup of localized invasive breast cancer includes: history and physical exam; bilateral diagnostic mammography; breast ultrasonography, if necessary; determination of tumor HR 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.[51] 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[52-54] MRI findings tend to overestimate extent of disease[55] resulting in increase in frequency of mastectomies.[56-59]

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.[59]

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.[60,61] Retrospective review of utility MRI showed conflicting outcome results, one with benefit[62] and another without.[63] One systematic review[54] documented that breast MRI staging altered surgical treatment in 7.8% to 33.3% of women,[54] 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.[64,65]

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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

missing some elements critical to patient management.[66,67] 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.[68-72] 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.[73] 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.[74] 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 cancer[75-77] 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.[78] 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.[78-84]

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.[85-87] In one trial goserelin improved the probability of pregnancy from 11% to 21% in patients with HR-negative early-stage breast cancer.[88] Smaller historical experiences in patients with HR-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.[89,90]

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[91] These recommendations are based on studies showing no additional value of these tests in patients with early-stage disease.[92-94] 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.[92] For patients with stage III breast cancer, the prevalence of a positive liver ultrasound and positive chest x-ray was 6% and 7%, respectively.[92]

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.[95-98]

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.

Discussion update in progress

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 overall survival as primary breast local treatment for the majority of women with stage I and stage II breast cancers (category 1).[99-103]

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.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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).[104]

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.[105-107] Risk factors, such as a family history of breast cancer or a genetic predisposition for breast cancer (i.e., 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.[108] Studies have shown that survival outcomes for young women with breast cancer receiving either lumpectomy or mastectomy are similar.[101,102,109-111] Some recent studies show improved survival[112-114] and fewer post-surgical complications[115] 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.[116] 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; $P = .004$).[117] 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%).[117] These differences observed in retrospective analysis could be due to selection bias among patients who chose risk reducing contralateral mastectomy.[118] A statistical simulation of survival outcomes after risk reducing contralateral mastectomy among women with stage I or II breast

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[119] Data from a recent meta-analysis found no absolute reduction in risk of distant metastases with RRM.[120] 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.[120]

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

Axillary lymph node dissection is the standard of care for patients with clinically positive nodes. However, ALND is associated with lymphedema and other significant morbidities,[121-123] and therefore sentinel lymph node biopsy (SLNB) has replaced axillary evaluation for clinically node negative patients.

Based on several randomized trials, it is now accepted that patients with a negative sentinel node do not need an ALND.[124-127]

The ACOSOG Z0011 trial randomized women greater than or equal to 18 years of age with T1/T2 tumors, fewer than 3 positive sentinel lymph nodes (SLNs), undergoing lumpectomy and whole breast radiation therapy (WBRT) to SLNB alone (n = 436) or to ALND (n = 420). In this study, there was no difference in local recurrence, disease-free survival (DFS), or overall survival (OS) between women with positive SLN undergoing a completion ALND versus no ALND. Only ER-negative status, age less than 50, and lack of adjuvant systemic therapy were associated with decreased OS.[128] At a median follow-up of 6.3 years, locoregional recurrences were noted in 4.1% of patients in the ALND group and 2.8% of patients in the SLNB patients (P = .11). Median OS was approximately 92% in each group.[129] Long term follow-up (median 9.25 years) results of the ACOSOG Z0011 study showed no statistically significant difference in local recurrence-free survival (RFS) between arms of the trial (P = .13).[130] The cumulative incidence of ipsilateral axillary recurrences at 10 years was 0.5% (2 patients) in those who underwent ALND and 1.5% (5 patients) in those who underwent SLNB-alone (P = .28).[130] The 10-year cumulative incidence of local regional recurrences was 6.2% with ALND and 5.3% with SLNB alone (P = .36).[130] The results of the ACOSOG Z0011 trial show that that ALND is not needed in women with early-stage breast cancer who have only one or two sentinel lymph node metastases who will receive whole-breast RT as part of breast-conserving therapy.

Another randomized trial (IBCSG 23-01) was specifically designed to compare outcomes in patients with sentinel micrometastases (≤2 mm) treated with ALND versus no ALND.[131] While the ACOSOG Z0011 trial was limited to those undergoing BCT, this trial included patients

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

undergoing mastectomy (9%).[131] Between the group treated with ALND versus the group that was not treated with ALND, there were no differences in 5 year DFS (84.4%; 95% CI 80.7%–88.1% versus 87.8%; 95% CI 84.4%–91.2%), cumulative incidence of breast cancer events - including local, regional, contralateral breast, and distant recurrence (10.8%; 95% CI 7.6–14.0 versus 10.6%; 95% CI 7.5–13.8) or OS (97.6%; 95% CI 96.0%–99.2% versus 97.5%; 95% CI 95.8%–99.1%).[131] Regional recurrence was less than 1 % for those who underwent ALND and 1% for those who did not undergo ALND.[131] The results of this trial show that in patients with only micrometastases in the sentinel nodes, ALND is not needed.

The results of a trial by the European EORTC group (AMAROS) assessed whether axillary RT provides regional control with fewer side-effects compared with ALND.[132] This trial included patients (n = 4823) with T1 or T2 breast cancer and positive SLN (micrometastatic or macrometastatic) and included a small fraction of patients (n = 248) treated with mastectomy.[132] The results reported no difference in five-year OS or DFS for patients randomized to ALND versus axillary radiation.[132] The 5-year DFS was 86.9% (95% CI 84.1–89.3) in the ALND group and 82.7% (79.3–85.5) in the axillary radiotherapy group. The 5-year OS was 93.3% (95% CI 91.0–95.0) in the ALND group and 92.5% (90.0–94.4) in the axillary radiotherapy group.[132] At the end of 5 years, lymphedema was less frequent in the group treated with axillary RT versus ALND (11% vs. 23%).[132] The results of this trial show that axillary radiation is an acceptable alternative to ALND for axillary control in patients found to have positive sentinel nodes, with significantly less lymphedema related morbidity.

NCCN Recommendations for Surgical Axillary Staging: In patients with clinically positive nodes, to determine whether axillary lymph node ALND is needed, the panel recommends pathologic confirmation of malignancy using ultrasound-guided fine-needle aspiration (FNA)[133] or core biopsy of suspicious nodes. According to the NCCN panel, the recommendation for axillary dissection of level I and II nodes is limited to patients with biopsy proven axillary metastases. Traditional level I and level II axillary lymph nodes (ALN) requires that at least 10 lymph nodes be provided for pathologic evaluation to accurately stage the axilla.[134,135] ALND should be extended to include level III nodes only if gross disease is apparent in the level II and III nodes. In the absence of gross disease in level II nodes, lymph node dissection should include tissue inferior to the axillary vein from the latissimus dorsi muscle laterally to the medial border of the pectoralis minor muscle (level I and II).

If axillary lymph nodes are clinically negative at the time of diagnosis or if FNA/core biopsy results of suspicious nodes is negative, the panel recommends SLN mapping and excision. 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.[136] In the uncommon situation in which H&E staining is equivocal, reliance on the results of cytokeratin IHC is appropriate.

Based on the ACOSOG Z0011 trial results, for patients with T1 or T2 tumors, 1 to 2 positive SLNs, treated with lumpectomy but *no* preoperative systemic therapy and for whom receive WBRT, the NCCN panel recommends no further axillary surgery. If any of the above criteria are not

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

met, the panel recommends level I and II axillary dissection. In the 2017 version of the NCCN guidelines, based on the results of the IBCSG 23-01 trial, the NCCN panel recommends no ALND for patients with positive SLN when that disease is *only* micrometastatic. According to the American Joint Committee on Cancer (AJCC) staging, micrometastatic nodal involvement is defined as a metastatic deposit >0.2 mm but ≤ 2.0 mm.[137]

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

For patients undergoing mastectomy with clinically negative axillae but with positive SLNs, the panel notes that for regional control of disease axillary radiation may replace ALND.

Radiation Therapy

Principles of 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, 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 set up 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.[100,103] 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.[138,139] The panel recommends whole breast irradiation to include breast tissue in 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 intensity-modulated radiation therapy (IMRT) may be used.[140,141] 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.[142] 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.[143-146] The 10-year follow-up data from the START trials[147] are consistent with the 10-year results of the Canadian trial,[146] 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.[146] The START trials reported radiation-related effects to normal breast tissue such as breast shrinkage, telangiectasia, and breast edema as less

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

common with the hypofractionated fraction regimen.[147] The NCCN Panel recommends for whole breast irradiation, a dose of 46–50 Gy in 23-25 fractions or 40–42.5 Gy in 15–16 fractions. Based on convenience and the data from the START trials,[147] the short course of radiation therapy (40–42.5 Gy in 15–16 fractions) is the NCCN preferred option in patients being given radiation treatment to the 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.[30,32,139,147-149] 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, several techniques using photons and/or electrons are appropriate. The NCCN panel recommends dose of 46-50 Gy in 23-25 fractions to the chest wall. A boost at the scar at the 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.[150] The distant recurrences were reduced from 17.3% to 13.4%.[150] An improvement in disease-free survival was seen from 77% to 82% at 10 years in those who received regional nodal irradiation compared to those who did not.[150] 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.[151]

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.[152] 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.[153] 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.[154,155] Follow-up is limited and studies are ongoing.

Radiation Therapy in Patients Receiving Preoperative Systemic Therapy

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.

Adjuvant 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 2 A 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).[103] 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.[103]

Regional Nodal Irradiation after lumpectomy

The reduction in recurrence the risk of locoregional and distant recurrence and improvement in disease-free survival seen in the MA.20 and EORTC 22922/10925 trials, support the importance of regional nodal irradiation after lumpectomy.[150,151] 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 greater than or equal to 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.[156,157] 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;[157] however, differences in rates of distant or local recurrence were not statistically significant when the two arms were compared at 135-month follow-up.[156]

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.[158] These results were confirmed in an updated analysis of this study with a median follow-up of 12.6 years.[159] At 10 years, a statistically significant reduction in IBTR 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 were free from locoregional recurrence.[159] Similar results were obtained in other studies of similar design.[160,161] 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).

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Adjuvant 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.[162-166] In these trials, the ipsilateral chest wall and the ipsilateral locoregional lymph nodes were irradiated. The results of EBCTCG meta-analyses[167] 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. [151] Based on these studies, the current guidelines recommend postmastectomy chest wall irradiation in women 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.[168,169]

Regional Nodal Irradiation after mastectomy

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.[170] 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 greater than or equal to 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.[171] Consideration should be given to radiation to the ipsilateral supraclavicular area and to the ipsilateral internal mammary lymph nodes, especially in patients 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.[172] 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.[173]

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[174] 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.[175-179] 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 (i.e., 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.[180-182] 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 (i.e., 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.[183] Several procedures using autologous tissue are available including transverse rectus abdominis myocutaneous flap, latissimus dorsi flap, and gluteus maximus myocutaneous flap reconstruction.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[184,185] Some studies, however, have not found a significant compromise in reconstruction cosmesis after radiation therapy.[186] 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.[187] Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis, implant exposure, and failed reconstruction.[188,189] 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.[190-192] 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.[191,193,194] 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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 (i.e., 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).[195,196] 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,[197] 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.[198-202] 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.[203] The evolving field of oncoplastic surgery includes the use of "volume displacement" techniques performed in conjunction with a large partial mastectomy.[204] 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.[204,205]

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.[206]

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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Systemic Therapies (Preoperative and Adjuvant)

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 HR-positive tumors.[207-214] 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.[215] 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.[216-218] 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; $P = .0141$).[218] 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%.[219] The mean change in left ventricular ejection fraction was similar in all treatment arms.[219] 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.

Preoperative Systemic therapy

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.[220,221] 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.[222] Results from large clinical trials and retrospective reviews indicate that breast conservation rates are improved with preoperative systemic therapy.[221,223] 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.[224-226]

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.

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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Adjuvant Systemic Therapy

After surgical treatment, adjuvant systemic therapy should be considered. In patients with early-stage breast cancer, systemic adjuvant therapy is administered to reduce risk of cancer recurrence. The decision is often based on individual risk of relapse and predicted sensitivity to a particular treatment (eg, ER/PR and HER2 status). 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. The decision-making process requires collaboration between the health care team and patient.

Stratification for Systemic Adjuvant Therapy

The NCCN Guidelines stratify patients with breast cancer based on their HR- 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).

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,[227] 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.[228,229] 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.[230]

Adjuvant Systemic therapy for hormone receptor-positive, HER2-negative tumors

Women with HR positive, HER2-negative tumors, receive adjuvant endocrine therapy to reduce the risk of recurrence and those deemed at high risk for distant recurrence despite adjuvant endocrine therapy, receive adjuvant chemotherapy. The incremental benefit of adding adjuvant chemotherapy to endocrine therapy in patients with low clinical risk of recurrence such as those with very small, low grade, lymph node-negative tumors is relatively small.[231] The decision whether or not to administer adjuvant chemotherapy in patients with HR-positive, HER2-negative tumors is based on many factors including lymph node status, size, grade, lymphovascular invasion, age, comorbid conditions and/or the results of a gene expression profile test using multigene assays.

Multigene Assays

Several commercially-available gene-based assays are useful in determining prognosis by predicting distant recurrence, local recurrence, or survival. Of these, only one, the 21-gene assay (Oncotype Dx) has been clinically validated for predicting the benefit of adding adjuvant chemotherapy to further reduce the risk of recurrence.

21-gene assay (Oncotype DX) in Node-negative, HR-positive, HER2-negative disease: The 21-gene recurrence score (RS) is one of the most validated multigene assays. The RS is helpful in determining the prognosis in women with HR-positive, HER2-negative tumors treated with endocrine therapy alone by predicting locoregional and distant recurrence.[232-234] This assay has also been validated to predict the benefit from adding adjuvant chemotherapy to adjuvant endocrine therapy for

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

women with HR-positive, HER2-negative, node-negative breast cancer.[235-237]

Among patients with T1b/c and T2, lymph node-negative, HR-positive, HER2-negative tumors with RS between 0-10, the risk of distant recurrence is low and these patients derive no incremental benefit from the addition of adjuvant chemotherapy to endocrine therapy.[236,238] At the other end of the spectrum, patients with lymph node-negative, HR-positive, HER2-negative cancers with high RS (≥ 31) have a higher risk of distant recurrence and secondary analyses of prospective studies demonstrate a clear benefit from adjuvant chemotherapy.[236,238]

For those with intermediate RS (11-25), the recently reported TAILORx trial of postmenopausal women (n= 6711) with lymph node-negative, HR-positive, HER-2 negative breast cancer, showed similar disease-free survival rates at 9-years in those who received adjuvant chemotherapy followed by endocrine therapy compared with endocrine therapy alone.[238] However, in a subset analysis, women 50 years of age or younger with RS 16-25 had significantly lower rates of distance recurrence with the addition of adjuvant chemotherapy to endocrine therapy.[238] The cutoff for low, intermediate, and high RS was different in TAILORx versus NSABP B-20. The NSABP-B20 was the first trial to validate the 21-gene assay both as a prognostic as well as a predictive tool and identified RS cut-offs to predict the magnitude of chemotherapy benefit in patients with node-negative, HR-positive breast cancer.[7]

21-gene assay (Oncotype DX) in Node- positive, HR-positive, HER2-negative disease: In the West German Plan B study, women (n = 110) with lymph node-positive, HR-positive, HER2-negative tumors, and a RS of ≤11, were found to have a 5-year disease-free survival was 94.4% when treated with endocrine therapy alone.[239] In a secondary analysis of a prospective registry of women with HR-positive, HER2-negative, lymph node-positive tumors, the 5-year risk of distant recurrence in patients with a RS of <18, treated with endocrine therapy alone was 2.7%.[240] These results suggest that in patients with limited nodal disease (1-3 positive lymph nodes) and a low RS, the absolute benefit from chemotherapy is likely to be very small.[240,241]

There is a clear benefit from adjuvant chemotherapy in patients with node positive, HR-positive, HER2-negative tumors, if the RS is high (≥ 31). In a secondary analysis of the SWOG 8814 trial of women with HR-positive, lymph node-positive tumors, high RS (≥31) was predictive of chemotherapy benefit. This study evaluated breast cancer specimens from node-positive, HR-positive postmenopausal women (n= 367) randomized to endocrine therapy with tamoxifen alone or chemotherapy with CAF followed by tamoxifen.[235] Compared with tamoxifen alone, treatment with CAF among women with a high RS (≥31) resulted in improved 10-year DFS (55% vs. 43%; HR 0.59, 95% CI 0.35-1.01) and OS (73% vs. 54%; HR 0.56, 95% CI 0.31-1.02).[235]

The absolute benefit of chemotherapy in patients with limited lymph node involvement and a RS ≤25 remains to be determined. The ongoing Southwest Oncology Group (SWOG) S1007 RxPONDER trial,[242] assigned women with 1-3 lymph node-positive nodes, HR-positive, HER2-negative breast cancer and a RS ≤ 25 to standard endocrine therapy with or without adjuvant chemotherapy. The results of this trial are expected to determine the benefit (if any) for chemotherapy in this group of patients.

70-gene assay (MammaPrint): Results from the randomized MINDACT trial,[243] demonstrated that the 70-gene assay can identify a subset of patients who have a low likelihood of distant recurrence despite high-risk clinical features (based on tumor size, grade, nodal status). In this trial, 79% had lymph node-negative disease and 21% had 1-3 positive lymph nodes and all patients underwent risk assessment by clinical criteria (using Adjuvant! Online) and genomic risk assessment by the 70-gene assay.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Patients with low-risk disease according to both clinical criteria and genomic assay results did not receive adjuvant chemotherapy, whereas patients categorized as high-risk by both assessments received chemotherapy. Patients with discordant results (i.e., either high clinical risk/low genomic risk or low clinical risk/high genomic risk) were randomized to the chemotherapy group or the no-chemotherapy group on the basis of either the clinical result or the genomic result. The primary outcome of the study was met with the demonstration that among those with high clinical risk/low genomic risk, the 5-year rate of survival without distant metastasis in those did not receive adjuvant chemotherapy was 94.7% (95% CI, 92.5 to 96.2).[243]

In the intention-to-treat population, among patients at high clinical risk/low genomic risk by the 70-gene assay, the 5-year rate of survival with no distant metastasis in those who received chemotherapy was 95.9% (95% CI, 94.0 to 97.2) versus 94.4% (95% CI, 92.3 to 95.9) in those who did not receive chemotherapy (adjusted HR for distant metastasis or death with chemotherapy vs.no chemotherapy 0.78; 95% CI, 0.50 to 1.21)[243] Among patients at low clinical risk/ high genomic risk, 5-year survival with no distant metastasis was 95.8% with chemotherapy (95% CI, 92.9 to 97.6), compared with a rate of 95.0% (95% CI, 91.8 to 97.0%) without chemotherapy (adjusted HR for distant metastasis or death with chemotherapy vs. no chemotherapy,1.17; 95% CI, 0.59 to 2.28). These data suggest that the results of the 70-gene signature do not provide evidence for making recommendations regarding chemotherapy for patients at low clinical risk.[243]

In a subgroup analysis by nodal status, among node-negative patients with high clinical risk/low genomic risk, the 5-year rate of survival with no distant metastasis was 95.7% (95% CI, 93.0 to 97.4) in those who received adjuvant chemotherapy compared with 93.2% (95% CI, 90.1 to 95.4) in those who did not receive chemotherapy.[243] Among patients with 1-3 positive lymph nodes, the rates of survival without distant metastases were 96.3% (95% CI, 93.1 to 98.1) in those who received adjuvant chemotherapy versus 95.6 (95% CI, 92.7 to 97.4) in those who did not receive adjuvant chemotherapy.[243] These data suggest that the additional benefit of adjuvant chemotherapy in patients with high-clinical risk/low genomic risk is likely to be small.

50-gene assay (PAM50): The 50-gene assay (PAM-50) risk of recurrence (ROR) score stratifies patients with HR-positive disease into high, medium, and low risk groups. Several studies have demonstrated the prognostic value of ROR score in estimating risk of disease recurrence.[244-246]

In a study from the Danish Breast Cancer Cooperative Group database, patients with lymph node node-negative tumors and low ROR had a distant recurrence risk of 5.0% (95% CI, 2.9% to 8.0%) whereas tumors with high ROR had a distant recurrence risk of 17.8% (95% CI, 14.0% to 22.0%).[245] Based on these analyses, patients with T1 and T2, HR-positive, HER2- negative, lymph node-negative tumors, a ROR score in the low range, regardless of tumor size, places the individual into the same prognostic category as those with T1a–T1b, N0, M0 tumors.[245]

In patients with 1-3 lymph-node positive, HR-positive, HER2-negative disease with low-risk of recurrence score, the distant recurrence risk was less than 3.5% at 10 years with endocrine therapy alone. [245] In TransATAC study, no distant recurrence was seen at 10 years in a similar group.[246]

12-gene assay (EndoPredict): This assay utilizes 12-genes to calculate a prognostic score. This assay appears to be useful in identifying a subgroup of patients with ER-positive, HER2-negative tumors with very low risk of recurrence without adjuvant chemotherapy and helpful in identifying patients at low risk for a late recurrence.[247] Based on results of

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

two Austrian Breast Cancer Study Group trials- ABCSG-6 and ABCSG-8, patients with HR-positive, HER-2 negative, and lymph-node node-negative disease with a low-risk score by the 12-gene assay had risk of distant recurrence of 4% at 10 years.[247] The prognostic value of the risk score rom the 12-gene assay was found to be independent of conventional clinicopathological factors. Patients with T1 and T2 HR-positive, HER2-negative, and lymph node-negative tumors, a 12-gene low-risk score, regardless of T size, places the tumor into the same prognostic category as T1a–T1b, N0, M0.

In TransATAC study, patients with 1-3 positive nodes in the low-risk group had a 5.6% risk of distant recurrence at 10 years,[246] suggesting that chemotherapy would be of limited benefit in these women.

Breast Cancer Index: The Breast Cancer Index (BCI) is a combination of two profiles, the HOXB13-to-IL17BR expression ratio (H:I ratio) and the Molecular Grade Index (MGI). Compared with clinical prognostic factors (eg, age, tumor size, tumor grade, and lymph node status), the H:I ratio has been shown to be prognostic in the setting of adjuvant tamoxifen monotherapy.[248,249] The addition of MGI to H:I was determined provide additional prognostic discrimination, leading to the BCI assay.[248] In a secondary analysis of the ATAC trial, BCI was prognostic in node negative breast cancer for both early (years 0-5) and late (years 5-10) distant recurrence.[250] For patients with T1 and T2 HR-positive, HER2-negative, and lymph node-negative tumors, a BCI in the low-risk range, regardless of T size, places the tumor into the same prognostic category as T1a-T1b, N0, M0. There are limited data as to the role of BCI in HR-positive, HER2-negative, and lymph node-positive breast cancer.

NCCN Recommendations for Use of Multigene Assays: Considering the ability of the multigene assays to predict benefit of adjuvant systemic chemotherapy and ability to determine prognosis by predicting risk of distant recurrence, the NCCN Panel has summarized the treatment implications based on risk scores and nodal status. The Panel notes that the multigene assays provide prognostic and therapy-predictive information that complements TNM and biomarker information.

Use of Multigene Assays in Axillary Lymph Node-Negative HR-Positive, HER2-Negative Tumors

Small tumors (up to 0.5 cm in greatest diameter) that do not involve the lymph nodes have a favorable prognosis so adjuvant chemotherapy is not recommended. According to the NCCN Panel, adjuvant endocrine therapy may be considered in this group of patients to reduce the risk for a second contralateral breast cancer, as well as the small benefit in reducing the risk of local/regional and distant recurrence.(Category 2B).

For patients with invasive ductal or lobular tumors greater than 0.5 cm in diameter and no lymph node involvement (lymph node node-negative), the NCCN panel recommends strongly considering the 21-gene RT-PCR assay to help estimate likelihood of recurrence *and* benefit from chemotherapy (category 1). The panel has noted that on an exploratory analysis from the TAILORx study,[238] adjuvant chemotherapy may be considered in women 50 years of age or younger with a 21-gene RS of 16-25. Also, patients with T1b tumors with low grade histology should be considered for endocrine monotherapy, as the TAILORx study[238] did not include patients with such tumors.

The panel notes that other prognostic multigene assays may be considered to help estimate risk of recurrence but these assays have not been validated to predict the benefit of systemic chemotherapy. Also, amongst the other assays, the panel has listed the 70-gene assay as a category 1 option based on the results of the prospective MINDACT[243] trial demonstrating the ability of the 70-gene assay to identify a good genomic risk population despite a high clinical risk, in whom chemotherapy may be omitted without a detrimental effect. High clinical risk in the MINDACT trial

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

was defined for grade 1 tumors as >3 cm N0 or T2N1, for grade 2 tumors T2N0-1, and for grade 3 tumors T1c-2N0-1.

urthermore, given no difference in outcomes with or without chemotherapy in the discordant low clinical risk/high genomic risk group, the MINDACT study suggests that the 70-gene panel is not useful guiding systemic chemotherapy decisions in this subgroup of patients.

Since results of different assays may not be concordant with each other and these assays have not been compared head-to-head prospectively, clinicians should only order one of the available assays for a specific patient and tumor.

Use of Multigene Assays in Axillary Lymph Node-Positive HR- Positive, HER2-Negative Tumors

For patients with four or more involved nodes the panel recommends systemic adjuvant chemotherapy followed by endocrine therapy (category 1).

Patients with less than four involved nodes or with pN1mi and less than or equal to 2 mm axillary node metastasis, are most often candidates for chemotherapy in addition to endocrine therapy. The panel recommends that clinical decision making for adjuvant chemotherapy be based on elements of clinical risk stratification such as clinical characteristics, tumor stage, pathology and comorbid conditions. If the patient is not a candidate for chemotherapy, the panel recommends adjuvant endocrine therapy alone (category 2A).

For those who are candidates for systemic adjuvant chemotherapy based on clinical characteristics, tumor stage, and pathology, the panel recommends consideration of multigene assays to assess prognosis as a tool to assist with treatment decision making. The panel notes in those with N1mi and N1 tumors, while multigene assays have yet to be proven to be predictive for adjuvant chemotherapy benefit, they are prognostic and can be used to identify low-risk patients who are likely to derive little or no absolute benefit from addition of adjuvant chemotherapy to adjuvant endocrine therapy. While a secondary analysis of the prospective SWOG 8814 trial demonstrated no benefit for chemotherapy for women with 1-3 involved ipsilateral axillary lymph nodes and a low RS, there was benefit for the addition of adjuvant chemotherapy in those with high-RS (≥ 31) from the 21-gene assay,[235] At this time, the optimal RS cut-off (< 11 vs < 18) to withhold chemotherapy for HR-positive, HER2-negative, 1-3 lymph node-positive tumors is still unknown. The results of the RxPONDER trial,[242] are expected determine the benefit (if any) of chemotherapy goog. In the MINDACT trial, among patients with 1-3 positive nodes who had a high clinical risk of recurrence but low risk by the 70-gene assay, the rates of survival were similar between those who received adjuvant chemotherapy in addition to adjuvant endocrine therapy versus those received adjuvant endocrine therapy alone, suggesting that chemotherapy could be omitted in this group.[243] Other multigene assays have not proven to be predictive of benefit from chemotherapy.

For those who are candidates for systemic adjuvant chemotherapy based on clinical characteristics, tumor stage, and pathology, if multigene assay is not available, the panel recommends systemic adjuvant chemotherapy followed by endocrine therapy (category 1).

Adjuvant Endocrine Therapy

The NCCN Guidelines call for the determination of ER and PR content in all primary invasive breast cancers.[251] 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.[252] Selected studies suggest that HER2-positive breast cancers may be less sensitive to some endocrine therapies, although other studies have failed to confirm this

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

finding.[253-261] 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.[262] 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 HR-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.[47] 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.[47] In patients receiving both tamoxifen and chemotherapy, chemotherapy should be given first, followed by sequential tamoxifen.[263] Prospective randomized trials have demonstrated that 5 years of tamoxifen is more effective than 1 to 2 years of tamoxifen.[264,265]

The ATLAS trial randomly allocated pre- and postmenopausal women to 5 or 10 years (extended therapy) of tamoxifen. 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.[266] The risk of recurrence during years 5 to 14 was 21.4% for women receiving tamoxifen versus 25.1% for controls (absolute recurrence reduction 3.7%). Patients who received tamoxifen for 10 years had a greater reduction in risk of progression, possibly due to a “carryover effect.” The reduction in risk of recurrence was 0.90 (95% CI, 0.79–1.02) during 5 to 9 years of tamoxifen treatment and 0.75 (0.62–0.90) after 10 years of treatment. There were alsodecreases in the incidence of contralateral breast cancer. Furthermore, reduced mortality was also 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 with 10 years of tamoxifen treatment were an increased risk for endometrial cancer and pulmonary embolism.[266] The results of the aTTom trial confirm the significant reduction in recurrence and death from breast cancer seen in the ATLAS trial with 10 versus 5 years of tamoxifen therapy.[267]

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 dosed monthly or every 3 months.

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).[268] In addition, data on ovarian suppression with tamoxifen, chemotherapy, or both showed no significant reduction in 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 HR-positive tumors and superior outcomes with CMF in patients with HR-negative tumors.[268-276] 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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

ablation/suppression plus tamoxifen versus chemotherapy alone generally demonstrate no difference in rates of recurrence or survival.[277-279]

A large intergroup study in premenopausal women with HR-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).[269] 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*.[277] 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.

In two randomized trials (TEXT and SOFT), premenopausal women with HR-positive early-stage breast cancer were assigned to receive exemestane plus ovarian suppression or tamoxifen plus ovarian suppression for a period of 5 years.[280] 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; $P < .001$).[280] 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; $P = .37$).[280] In the SOFT trial,[281] 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; $P = .10$).[282] 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.[282] 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.[281] 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).

Aromatase inhibitors: 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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[283,284] 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.[285] However, no survival differences have been reported for patients receiving initial adjuvant therapy with an aromatase inhibitor versus first-line tamoxifen.[286,287] 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 HR-positive breast cancer.[288,289] With a median of 100 months follow-up, results in 5216 postmenopausal women with HR-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.[286] 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.[289] ATAC trial sub-protocols show a lesser effect of anastrozole compared with tamoxifen on endometrial tissue;[290] similar effects of anastrozole and tamoxifen on quality of life, with most patients reporting that overall quality of life was not significantly impaired;[291] a greater loss of bone mineral density with anastrozole;[292] a small pharmacokinetic interference of anastrozole in the presence of tamoxifen of unclear significance;[293] and no evidence for an interaction between prior chemotherapy and anastrozole.[294]

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.[287] 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.[295] 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%).[296] 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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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).[297]

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.[298] 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).[298] 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.[299] 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.[300] 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 ARNO 95 trial has also been reported.[301] 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).[284] 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.[302]

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.[303] 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,[297] 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.

The NCCN panel finds no compelling evidence that there is meaningful efficacy or toxicity differences between the available aromatase inhibitors: anastrozole, letrozole, and exemestane. All three have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant settings.

Duration of adjuvant endocrine therapy

Adjuvant endocrine therapy is recommended for a minimum of 5 years. A recent retrospective analysis by the Oxford University studied risk of recurrence for years 5 through 20 after 5 years of endocrine therapy. [304] These data showed a considerable risk of recurrence between years 5 and 20 in these patients treated with initial 5 years of endocrine therapy.[304] Data has now emerged showing benefit of extended endocrine therapy in improving DFS.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

ata from the ATLAS trial (discussed above)[266] and the aTTom trial confirm greater reduction in recurrence and death from breast cancer with 10 versus 5 years of tamoxifen therapy.[267]

For those treated initially with adjuvant tamoxifen, there is evidence for benefit from extended adjuvant endocrine therapy from several randomized trials. 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 HR-positive, early-stage breast cancer.[285,305] With a median follow-up of 64 months, letrozole was associated with improved DFS (HR 0.52, 95% CI 0.45-0.61) and an improved OS (HR 0.61, 95% CI 0.52-0.71) compared with placebo.[306]

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.[307,308] 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.[309,310] 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.[311] 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, HR-positive postmenopausal patients received 5 years of adjuvant tamoxifen and were randomized to 3 years of anastrozole or no further therapy.[312] 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).[312]

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.[313] It is not known whether initial, sequential, or extended use of adjuvant aromatase inhibitors is the optimal strategy.

In women initially treated with an AI, a randomized phase III trial (MA17.R) evaluated the effects of extending adjuvant AI therapy from 5 to 10 years.[314] Postmenopausal women who had completed 4.5 to 6 years of therapy with an AI (with a median duration of prior tamoxifen of 5 years), were randomized to letrozole or placebo for an additional 5 years.[314] Improvement was seen in five-year DFS in those receiving letrozole compared to those who received placebo (95% [95% CI 93 - 96%] vs. 91% [95% CI 89 -93%]). The annual rate of contralateral breast cancer reported was lower with letrozole (0.49% vs. 0.21%; HR 0.42, 95% CI 0.22-0.81%). However, longer duration of AI resulted in more frequent bone-related adverse effects compared with those who received placebo and no improvement was observed with respect to OS. Bone-related adverse effects included bone pain (18% vs. 14%), fractures (14% vs. 9%), and new-onset osteoporosis (11% vs. 6%).[314]

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[315,316]

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 NCCNPanel 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.[317] 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.[318] 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. 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.[319] 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.[320] The study found no correlation between CYP2D6 allelic status and disease outcome or between CYP2D6 allelic status and tamoxifen-related adverse effects.[320] A genetic analysis of the ATAC trial found no association between CYP2D6

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

genotype and clinical outcomes.[321] Given the limited and conflicting evidence at this time,[322] 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.[323] 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 bisphosphonate therapy

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

Bisphosphonates: In the Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12) trial, for patients older than 40 years, zoledronic acid significantly reduced the risk of recurrence by 34% (HR, 0.66; *P*=.014) and the risk of death by 49% (HR, 0.51; *P*=.020). However, no improvement was seen in either DFS or OS in this post hoc analysis among patients younger than 40 years.[324] In a planned subgroup analysis of the AZURE trial, zoledronic acid improved DFS in women who were more than 5 years since menopause at trial entry.[325] A meta-analysis of data from seven adjuvant bisphosphonate trials (AZURE, ABCSG-12, ZO-FAST, Z-FAST, EZO-FAST, NSABP-B34, GAIN), including only those known to be aged 50 years or older, postmenopausal, or with ovarian suppression, showed a significant benefit for the use of adjuvant bisphosphonates in patients with a low-estrogen state and early-stage breast cancer.[326] More recently, the Early Breast Cancer Trialists' Collaborative Group (EBTCG) conducted a meta-analysis of all randomized adjuvant bisphosphonate studies (26 studies) and reported convincing evidence that adjuvant bisphosphonates provide benefits to postmenopausal (natural or induced) patients with breast cancer.[327] With bisphosphonate therapy, the greatest improvement was seen in bone recurrence (RR=0.83, *P* = .004) and bone fractures (RR=0.85, *P* = .02). No effect was seen on distant recurrence outside bone (RR =0.98, *P* =0.69).[327] In premenopausal patients, bisphosphonate therapy did not seem to have a significant effect on bone recurrence. However, in postmenopausal patients, zoledronic acid significantly reduced bone recurrence (3.4% vs. 4.5%, RR=0.73, 99% CI 0.53 to 1.00); the difference in breast cancer mortality was not statistically significant (7.1% vs. 7.9%, RR=0.88, 99% CI 0.69 to 1.11).[327]

Denosumab: In the adjuvant setting, the ABCSG-18 trial studied the effect of denosumab in postmenopausal patients treated with adjuvant AIs and showed a reduction in clinical fractures (HR 0.5, *P* < .0001), which was the primary endpoint of this study.[328] Subsequently in an interim analysis, an improvement in DFS, a secondary end point of the trial was reported.[329] However unlike the bisphosphonates which have demonstrated an OS benefit when used as adjuvant therapy, there is no available data showing an OS benefit with denosumab. Results of the ABCSG-18 and the ongoing D-CARE[330] trials may provide evidence for use of denosumab in the adjuvant setting.

NCCN recommendations for use of bisphosphonates as adjuvant therapy: Based on the EBTCG metaanalysis.[327], the panel recommends considering adjuvant bisphosphonate therapy for postmenopausal (natural or induced) women receiving adjuvant endocrine therapy.

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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[331] 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.[332,333] 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.[334]

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.[335-337] 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.[337] 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,[334] 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.[338] 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).

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

The AC regimen for four cycles has been studied in randomized trials, resulting in relapse-free survival and OS equivalent to CMF chemotherapy.[339,340] No benefit from dose escalation of either doxorubicin or cyclophosphamide was shown.[332,341]

Studies of CMF chemotherapy versus no chemotherapy have shown DFS and OS advantages with CMF chemotherapy.[47,342] Studies using FAC/CAF chemotherapy have shown that the use of full-dose chemotherapy regimens is important.[343] 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.[342] 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.[258,344-349] 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.[350] 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.[351] Patient and tumor characteristics were equally distributed between both arms (<50 years of age: 40%, lumpectomy: 68%, and hormone positivity: 65%).[351] 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.[351] Five deaths resulted from the toxicity of FEC treatment, compared to the death of two women on the AC treatment.[351]

The quality-of-life impact and menstrual history of women on the NSABP (NRG) B-36 was also investigated in a phase III trial.[352] Women on FEC treatment experienced a worse quality of life at six months and higher rate of post-chemotherapy amenorrhea.[352]

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.[353] The second trial compared FEC given intravenously every 3 weeks at 2 dose levels of epirubicin (50 mg/m^2 vs. 100 mg/m^2) in premenopausal and

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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/m^2 arm.[354] 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.[278] 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.[355]

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.[356] 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, the10-year DFS rate with weekly paclitaxel was 69% and the 10-year OS rate was 75%.[357]

Final results from a randomized trial of TAC versus FAC chemotherapy in ALN-positive breast cancer demonstrated that TAC is superior to FAC.[358] 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.[359]

Several retrospective studies have evaluated the potential interaction of chemotherapy benefit and ER status.[47,231] 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.[231]

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,[360] the enrollment in that study was discontinued early.[360] Therefore, there is also a possibility that AC/CMF is not superior to any chemotherapy in this cohort. The panel

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[361]Results of several randomized trials testing trastuzumab as adjuvant therapy have been reported.[362-370]

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.[369] 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.[366,371,372] 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).[362,364,366,368,371,372] 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.[371] 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.[373,374]

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.[364] 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; $P = .0115$).[375] 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.[370] 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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

years compared with 1 year.[365] 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.[368] 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).[368] 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.[362] 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.[362] 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.[363]

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.[366,367] 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.[376] 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 effective[377] 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.[378]

Retrospective analyses of low-risk patients with small tumors demonstrate that in T1a-bN0 breast cancers, HER2 overexpression added a 15% to

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

30% risk for recurrence.[379-382] 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.[383] 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.[216,217,219]

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.[384] 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.[384]

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.[379] 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.[380] 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).[385] Subgroup analyses from several of the randomized trials have shown consistent benefit of trastuzumab irrespective of tumor size or nodal status.[368,386,387]

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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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,[368] and docetaxel plus trastuzumab followed by FEC[362] (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 setting[388] and the significant improvement in pCR seen in the neoadjuvant setting,[217,219] 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.[389,390]

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%).[391]

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.[251] 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.

Staging and Workup Prior to Preoperative Chemotherapy

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[96,97,392-396] support a potential role for FDG

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[397] 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.[398] 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.[398] 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 breath-holding, 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 breath-holding 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.[399] 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.[399] It may be convenient to perform PET/CT and diagnostic CT at the same time.

Operable Locally Advanced Breast Cancer

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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

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.[400] 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 HR-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 tumors 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 HR-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 T0-3, N1, M0 and T1-3, N0-1, M0 tumors

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.[401] 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.[402-404] In addition, the panel notes no evidence to support the use of "tumor

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[96,405]

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.[406-408]

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.[409] 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.[315] 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.[410-413] 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.[414,415] 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.[315,416,417]

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.[418] 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.[419,420] 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 HR status of the tumor.[421] Alternative birth

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[421,422]

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.[423] 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.[328]

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.[424] 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.[425] 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.[426]

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.[427-429]

For management of issues related to survivorship including late/long-term effects of cancer and its treatment, see the NCCN Guidelines for Survivorship.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

The section on management of recurrent/Stage IV breast cancer was updated on 03/06/20.

Recurrent/Stage IV Breast Cancer

Staging and Workup for Recurrent and Stage IV Breast Cancer

The staging evaluation of women who present with recurrent or stage IV breast cancer includes history and physical exam; the performance of a complete blood count, liver function tests, chest diagnostic CT, bone scan, and radiographs of any long or weight-bearing bones that are painful or appear abnormal on bone scan; 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 NCCN Panel generally discourages the use of sodium fluoride PET or PET/CT scans for the evaluation of patients with recurrent disease. 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.[96,97,430,431] In general, the non-diagnostic CT scans used for PET under-evaluate the lungs and the liver compared with contrast-enhanced diagnostic CT scans. 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 NCCN Panel is that FDG PET/CT is optional and most helpful in situations where standard imaging results are equivocal or suspicious. The NCCN Panel recommends bone scan or sodium fluoride PET/CT (category 2B) to detect bone metastases. 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. Soft tissue tumor biopsy is preferred over bone sites unless a portion of the biopsy can be protected from harsh decalcification solution to preserve more accurate assessment of biomarkers.

Determination of HR 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.[432,433] 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.[433] 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.[434-443]

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 HR–positive breast cancer, or with prior positive HR 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 HR 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.

Genetic testing: In the metastatic setting, results from genetic testing may have therapeutic implications. Germline mutations in BRCA1/2 have proven clinical utility and therapeutic impact. Therefore, germline BRCA1/2 mutations should be assessed in all patients with recurrent or metastatic

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

breast cancer to identify candidates for poly adenosine diphosphate ribose polymerase (PARP)-inhibitor therapy.

Management of Locally Recurrent Disease

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 plus radiation 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.[444] 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.[445]

According to the NCCN Panel, mastectomy-treated patients should undergo surgical resection of the local recurrence (if it can be accomplished with limited morbidity) 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.

In women with a local breast recurrence after breast-conserving surgery and radiation therapy who had a prior sentinel lymph node (SLN) biopsy, a repeat SLN biopsy may be considered although the accuracy of repeat SNB is unproven, and the prognostic significance of repeat SNB after mastectomy is unknown and its use is discouraged.[446,447] On the other hand, the prognostic significance of repeat SLN biopsy after mastectomy is unknown and its use is discouraged. The consensus recommendation of the panel for most women with a local recurrence following breast-conserving therapy and SLN biopsy is mastectomy and a level I/II axillary dissection.

The results of the CALOR trial found that after complete resection in patients with isolated locoregional recurrence, adjuvant chemotherapy improves both DFS and OS.[448] 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).[448] Five-year OS in all patients in the study was also significantly improved with chemotherapy (88% vs. 76%, P = .024).[448] 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).[448] However these women received endocrine therapy.

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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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 Recurrent or Stage IV Disease

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

Surgery for Recurrent or Stage IV Disease

The primary treatment approach recommended by the NCCN Panel for women with metastatic breast cancer and an intact primary tumor is systemic therapy, with consideration of surgery after initial systemic treatment for those women requiring palliation of symptoms or with impending complications, such as skin ulceration, bleeding, fungation, and pain.[449] *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.[450-453] Substantial selection biases exist in all of these studies and are likely to confound the study results.[454,455]

Two 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.[456,457] In the first prospective trial, women (n =350) with de-novo metastatic breast cancer who achieved a partial or complete response to anthracycline-based chemotherapy were randomly assigned to either surgery of the primary tumor plus adjuvant radiation versus no locoregional treatment.[456] There was no difference in the overall survival (OS) between the group that received surgery and the group that did not (19.2 vs. 20.5 months, hazard ratio [HR] 1.04, 95% CI 0.81-1.34).[456] In a separate multiple center prospective registry study women who responded to first-line systemic therapy were randomized to management of the primary tumor by surgery or not. [458] Preliminary data showed no difference in OS between the two groups [458]

However, another trial by the Turkish Federation, MF07-01 of women (n=274) with de-novo metastatic breast cancer randomized to local management (mastectomy, or BCS with radiation) followed by systemic therapy versus systemic therapy only, observed a benefit with surgery.[459] While no difference in survival was seen at 36 months, at 40 months, patients treated with local management showed an improvement in survival with locoregional treatment (46.4% vs. 26.4%; HR 0.66, 95% CI 0.49-0.88). [459] The design of this trial is different from the other the first being two prospective studies described above in which patients were included only if they had experienced a response to systemic therapy. Second, randomization in the Turkish trial was not balanced. Patients who received surgery had lower rates of triple-negative disease (7% vs. 17%), visceral metastases (29% vs. 45%), and many had solitary bone metastases only (33% vs. 20%).[459] In an unplanned subgroup analysis, patients who appeared to derive the greatest OS benefit from local management included those with HR-positive disease, (HR 0.63; 95% CI 0.44–0.89; P = .008); HER2-negative disease (HR 0.64; 95% CI 0.45–0.91; P = .01); those younger than 55 years HR 0.57; 95% CI 0.38–0.86; P = .007; and those with solitary bone metastases (HR 0.47; 95% CI 0.23–0.98; P = 0.04). [459]

Discussion update progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

Guideline Stratification for Systemic Therapy for Stage IV/Recurrent Disease

The systemic treatment of breast cancer recurrence or stage IV disease prolongs survival and enhances quality of life (QOL) but is not curative. Therefore, treatments associated with minimal toxicity are preferred. Thus, the use of the minimally toxic endocrine therapies is preferred to the use of cytotoxic therapy whenever reasonable.[460] Guidance for treatment of patients with breast cancer and brain metastases is included the NCCN Guidelines for Central Nervous System.

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

Therapy for Bone Metastases

Complications from bone metastases include pain, decreased performance status, and decreased QOL, as well as skeletal-related events (SREs), which are defined as the need for radiation or surgery to bone, pathologic fractures, spinal cord compression, and hypercalcemia of malignancy.

The NCCN Panel recommends treatment with a bone modifying agent such as zoledronic acid, pamidronate or denosumab (category 1) in addition to chemotherapy or endocrine therapy if bone metastasis is present, expected survival is ≥3 months. Patients should undergo a dental examination with preventive dentistry prior to initiation of this therapy. The bisphosphonates and denosumab are associated with a risk of development of osteonecrosis of the jaw (ONJ). Poor baseline dental health or dental procedures during treatment are known risk factors for ONJ. Thus, a dental examination with preventive dentistry intervention is recommended prior to treatment with intravenous bisphosphonate or denosumab, and dental procedures invasive of gum or bone during treatment should be avoided if at all possible. Additional risk factors for the development of ONJ include administration of chemotherapy or corticosteroids and poor oral hygiene with periodontal disease and dental abscess.[461]

Bisphosphonates

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.[462-469] In metastatic bone disease, bisphosphonate treatment is associated with fewer SREs, fewer pathologic fractures, and less need for radiation therapy and surgery to treat bone pain.

The use of bisphosphonates in metastatic disease is a palliative care measure. No impact on OS has been observed in patients treated with bisphosphonates.

The data indicate that zoledronic acid and pamidronate may be given on a 3- to 4-week schedule in conjunction with antineoplastic therapy (i.e., endocrine therapy, chemotherapy, biologic therapy) or every 12 weeks. Three randomized trials have compared zoledronic acid dosed every 4 weeks versus every 12 weeks.[470-472] Data from these trials show that among women with breast cancer and bone metastases zoledronic acid administered once every 12 weeks versus once every four weeks does not

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

compromise efficacy and has similar rates of SREs.[470,471,473] In the ZOOM trial,[470] the rate of skeletal morbidities was 0.22 (95% CI, 0.14 to 0.29) in those receiving zoledronic acid every 4 weeks versus and 0.26 (95% CI, 0.15 to 0.37) those receiving zoledronic acid every 12 weeks. In the CALGB 70604 trial,[471] the rate of SRE rate in the 4-week arm was 29.5% versus 28.6% in the 12-week arm. In OPTIMIZE-2 trial,[472] the rate of SREs was 22% of the in the 4-week arm and 23.2% in the 12-week arm.[472] The NCCN Panel recommends an optimal dosing of every 12 weeks.

The use of bisphosphonates should be accompanied by calcium and vitamin D supplementation with daily doses of calcium of 1200 to 1500 mg and vitamin D_3 of 400 to 800 IU. Recommended agents for use in the United States are pamidronate 90 mg intravenously over 2 hours or zoledronic acid 4 mg intravenously over 15 minutes. The original studies continued treatment for up to 24 months; however, there are limited long-term safety data indicating treatment can continue beyond that time.[465,467,474] 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.

Denosumab

Women with metastatic breast cancer to bone who are candidates for bisphosphonate therapy may also be considered for treatment with denosumab. This recommendation is based on the results of a single randomized trial comparing denosumab to zoledronic acid.[475] 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.[475] Dosing of denosumab outside of every 3-6 weeks has not been studied.

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

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

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

Many premenopausal and postmenopausal women with HR-positive breast cancer benefit from sequential use of endocrine therapies at disease progression. Therefore, women with breast cancers who respond to an endocrine-based therapy with either shrinkage of the tumor or long-term disease stabilization (clinical benefit) should receive additional endocrine therapy at disease progression. Those who progress on or within 12 months of completing adjuvant endocrine or patients who progress on first-line endocrine therapy for metastatic disease are eligible for second-line endocrine therapy either as monotherapy or in combination with a targeted agent. The optimal sequence for endocrine therapy is not well defined. The choice would depend on previous, tolerance of treatment, and patient preference.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

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

Aromatase inhibitor in combination with CDK 4/6 inhibitor: In postmenopausal women or premenopausal women receiving ovarian ablation or ovarian function suppression with an LHRH agonist, combinations of aromatase inhibitors (AI) with CDK 4/6 inhibitors (palbociclib, ribociclib, or abemaciclib) have demonstrated improved PFS relative to an AI alone.

Palbociclib in combination with letrozole was studied in a phase III study that included postmenopausal patients (n =666) with metastatic, HR-positive, HER2-negative breast cancer who had not received prior treatment for advanced disease.[476] An improvement in PFS (24.8 vs. 14.5 months; hazard ratio [HR] 0.58, 95% CI 0.46-0.72) and objective response rate (ORR; 42 vs. 35 percent) was seen with the combination of palbociclib and letrozole compared with letrozole alone.[476] Grade 3 and 4 adverse effects seen with the combination of palbociclib and letrozole included neutropenia (66.5% vs. 1.4%), leukopenia (24.8% vs. 0%), anemia (5.4% vs. 1.8%) and fatigue (1.8% vs. 0.5%).[476]

Ribociclib in combination with letrozole was also studied as first-line therapy in a phase III study of postmenopausal women (n=668) with HR-positive, HER2-negative recurrent/Stage IV breast cancer. At a median follow-up of 26.4 months, an improvement in PFS (25.3 vs. 16.0 months; HR for progression or death was 0.56, 95% CI 0.45-0.70) and improved ORR of 43% vs. 29% was seen with ribociclib plus letrozole compared with letrozole alone.[477] Grade 3 or 4 adverse events were more common with the combination included neutropenia (62% vs. 1.2%), leukopenia (21.3% vs. 0.9%), and abnormal liver function tests (10.2% vs. 2.4%).[477]

The phase III MONARCH trial studied the combination of abemaciclib with either an AI (letrozole or anastrozole) versus AI monotherapy as first-line treatment of women with advanced HR-positive, HER2-negative breast cancer. The combination of abemaciclib with the AI improved PFS, compared with AI alone (median not reached versus 14.7 months, respectively; HR 0.54, 95% CI 0.41-0.72).[478] The ORR was higher with the combination compared with AI monotherapy (59% vs. 44 %).[478] The most frequent grade 3 or higher adverse events for abemaciclib versus placebo included diarrhea (9.5% vs.1.2%), neutropenia (21.1% vs. 1.2%), leukopenia (8% vs. 0.6%) and fatigue (2% versus 0%).[478]

Most trials studying CDK 4/6 inhibitor with an AI have mainly included postmenopausal women and only a small subset of premenopausal women on ovarian suppression. However, in the phase III MONALEESA-7 trial, 672 pre- or perimenopausal women with HR-positive, HER2-negative, advanced breast cancer were randomly assigned to first-line treatment with ribociclib or placebo with goserelin plus either a non-steroidal AI or tamoxifen.[479] An improvement in PFS was seen with the addition of ribociclib (median PFS, 24 versus 13 months; HR 0.55, 95% CI 0.4-0.69).[479]

At 3.5 years, an improvement in OS was reported with ribociclib (70% vs. 46%; HR 0.71, 95% CI 0.54-0.95).[480] Grade 3 and 4 adverse events reported in greater than 10% of patients in either group included neutropenia (61% vs. 4%) and leukopenia (14% vs. 1%).[479]

Based on the above data, the NCCN panel has included AI in combination with CDK 4/6 inhibitors as a category 1 first-line option for

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

postmenopausal women and premenopausal women with ovarian ablation/suppression with HR-positive, HER2-negative recurrent/stage IV breast cancer.

Single agent fulvestrant: Fulvestrant is an estrogen receptor (ER) antagonist and was originally approved as a monthly intramuscular injection (250 mg per month); higher dose has been proven to be more effective in subsequent randomized trials. In the first-line setting, fulvestrant was found to be as effective as anastrozole in terms of ORR (36.0% vs. 35.5%; odds ratio, 1.02; 95% CI, 0.56 –1.87).[481] An improved time to progression was seen with fulvestrant compared to anastrozole (median time to progression was 23.4 months for fulvestrant versus 13.1 months for anastrozole; HR, 0.63; 95% CI, 0.39– 1.00; *P* = .0496).[482] This study also used a higher loading dose of 500 mg every 2 weeks for 3 doses and then maintenance dose of 500 mg monthly.[481] 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).[483]

A separate phase III randomized study in postmenopausal women with metastatic HR-positive breast cancer compared fulvestrant 500 mg every 2 weeks for 3 doses followed by 500 mg monthly versus fulvestrant 250 mg monthly. The PFS was superior with the fulvestrant 500 mg regimen (HR, 0.80; 95% CI, 0.68–0.94; *P* = .006),[484] 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).[485]

Results from another phase III trial (FALCON) of first-line treatment with fulvestrant compared with anastrozole in endocrine therapy-naive patients with metastatic ER-positive breast cancer, demonstrated improved PFS with fulvestrant (at the higher dose, 500 mg) over anastrozole at a median follow-up of 25.0 months (16.6 vs. 13.8 months, HR for progression or death 0.797, 95% CI 0.637-0.999).[486] The QOL outcomes were similar between the two groups, with the most common adverse effects being arthralgia (17% vs. 10%) and hot flashes (11% vs. 10%) for fulvestrant and anastrozole, respectively.[486]

Fulvestrant + CDK 4/6 inhibitor: In the phase III trial MONALEESA-3, patients (n = 726) with advanced HR-positive breast cancer who had no prior endocrine therapy or had progressed on prior therapy, the combination of ribociclib with fulvestrant showed improved in PFS versus fulvestrant alone (21 vs. 13 months; HR 0.59, 95% CI 0.48-0.73).[487] The PFS benefits were consistent across patients with and without prior endocrine treatment. In a subsequent analysis, a significant improvement in OS was observed.[488] At 42 months the estimated OS was 57.8% (95% confidence interval [CI], 52.0 to 63.2) in the ribociclib group and 45.9% (95% CI,36.9 to 54.5) in the placebo group.[488]

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

Fulvestrant + non-steroidal AI: Combination of two endocrine agents as first-line treatment in postmenopausal women with HR-positive, metastatic breast cancer has been reported from studies comparing single-agent anastrozole versus anastrozole plus fulvestrant.

In one study (FACT), combination of fulvestrant with anastrozole was not superior to single-agent anastrozole (time to progression HR, 0.99; 95%

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

CI, 0.81–1.20; *P* = .91).[489] In a second phase III trial (SoFEA), the effect of fulvestrant alone or in combination with anastrozole or exemestane was studied in patients with advanced breast cancer with acquired resistance to an non-steroidal AI.[490] An AI had been given as adjuvant treatment to 18% of patients for a median of 27.9 months, and to 82% of patients for locally advanced/metastatic disease for a median of 19.3 months. Median PFS was 4.8 months, 4.4 months, and 3.4 months for patients treated with fulvestrant alone, anastrozole plus fulvestrant, and fulvestrant plus exemestane, respectively. No differences were observed for ORR, clinical benefit rate, and OS.

In the trial by the Southwest Oncology Group (SWOG), S0226, PFS (HR, 0.80; 95% CI, 0.68–0.94; stratified log-rank *P* = .007) and OS (HR, 0.81; 95% CI, 0.65–1.00; stratified *P* = .049) were superior with combination anastrozole plus fulvestrant.[491] In a subgroup analysis in this trial suggested that patients without prior adjuvant tamoxifen experienced the greatest OS benefit with combination therapy compared with monotherapy (median, 52.2 months vs.40.3 months, respectively; hazard ratio, 0.73; 95% CI, 0.58 to 0.92).[492]

The reasons for the divergent outcomes in the above trials is not very clear. The three trials discussed above had slightly different patient populations- there were more cases of patients with no prior endocrine exposure (with de novo stage IV metastatic disease) in the SWOG S0226 trial compared with the FACT trial. The FACT trial included a more heterogeneous population of both premenopausal and postmenopausal women with locally advanced and metastatic disease. The SoFEA trial only enrolled patients with acquired endocrine resistance (who had disease progression while they were receiving an aromatase inhibitor). Further studies are needed to confirm the results of the SWOG S0226 trial.

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

Monotherapy with endocrine agents: In postmenopausal women there is evidence supporting the use of an AI as first-line therapy for their recurrent disease.[493,494]

Prospective randomized trials comparing the AI head-to-head have demonstrated that all AI's are the same.[495] Tamoxifen is the commonly used SERM for premenopausal women.[496] In postmenopausal women, AI monotherapy has been shown to have superior outcome compared with tamoxifen, although the differences are modest.[497-501] 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 PFS or OS between the two arms.[499]

NCCN recommendations for first-line therapy: For postmenopausal women with HR-positive, HER2-negative recurrent/stage IV breast cancer, NCCN category 1, preferred regimens include a cyclin-dependent kinase (CDK) 4/6 inhibitor with an aromatase inhibitor (AI); fulvestrant with or without a CDK 4/6 inhibitor; Fulvestrant with a non-steroidal AI. The NCCN category 2A, preferred regimen includes non-steroidal AI (anastrozole, letrozole); steroidal aromatase inhibitor (exemestane), and selective estrogen receptor modulator (tamoxifen or toremifene). For premenopausal women, first-line endocrine treatment includes ovarian suppression/ablation and endocrine therapy listed above for postmenopausal women or alternately with a selective estrogen- receptor modulator (SERM) alone.

Preferred regimens for Second and Subsequent Lines of therapy for HR- Positive, HER2-Negative Breast Cancer

Fulvestrant containing regimens

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Fulvestrant + CDK 4/6 inhibitors: Fulvestrant in combination with a CDK 4/6 inhibitor may be offered to patients who experienced progression during prior treatment with AIs with or without one line of prior chemotherapy (category 1), because PFS was improved compared with fulvestrant alone in a phase III trial (PALOMA-3).[502] The NCCN panel notes that treatment should be limited to those *without* prior exposure to CDK 4/6 inhibitors

The phase III trial (PALOMA-3) compared the combination of palbociclib and fulvestrant to fulvestrant in pre- or post-menopausal HR-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 9.5 months for the combination compared to 4.6 months for fulvestrant (HR 0.46, $P <$ .000001)[503] Grade 3/4 adverse events of palbociclib and fulvestrant were mainly confined to neutropenia (in 65% of patients).

In the MONARCH 2 phase III trial, patients who had progressed while receiving endocrine therapy were randomly assigned to fulvestrant with or without abemaciclib.[504] Those receiving combination therapy experienced an improved PFS relative to those receiving fulvestrant alone (16.4 versus 9.3 months; HR 0.55, 95% CI 0.45-0.68). The ORR was higher in those receiving abemaciclib and fulvestrant (48% vs. 21%).[504] In addition, am improvement was seen in OS with abemaciclib plus fulvestrant compared with fulvestrant alone (46.7 versus 37.3 months; HR 0.757 95% CI 0.606-0.945).[505]

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

Fulvestrant monotherapy: Fulvestrant monotherapy appears to be at least as effective as anastrozole in patients whose disease progressed on previous tamoxifen.[506,507] A randomized phase II study compared anastrozole versus fulvestrant in over 200 patients with advanced breast cancer.[481,482] In the initial analysis, fulvestrant was as effective as anastrozole in terms of ORR (36.0% vs. 35.5%; odds ratio, 1.02; 95% CI, 0.56 –1.87; P = .947) in evaluable patients (n = 89 for fulvestrant and n = 93 for anastrozole).[481] 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).[482] This study used a higher 500 mg loading dose every 2 weeks for 3 doses and then 500 mg monthly.[481] 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).[483]

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.[508] The clinical benefit rates of exemestane versus fulvestrant observed in a phase III trial of postmenopausal women with HR-positive advanced breast cancer who experienced disease progression on prior nonsteroidal aromatase inhibitor therapy were comparable (32.2% vs. 31.5%; P = .853).[509] 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.[509]

Fulvestrant plus alpelisib: In a randomized phase III trial of patients (n=572) with advanced HR-positive breast cancer and confirmed

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) status, all of whom had received a prior AI either for local or advanced disease. Patients were enrolled into either *PIK3CA* mutant (n=341) cohort or the *PIK3CA* non-mutant cohort and each cohort was randomized to receive fulvestrant plus the phosphoinositide 3-kinase (PI3K) inhibitor, alpelisib versus fulvestrant plus placebo. Patients with *PIK3CA* mutation, receiving alpelisib showed improved PFS compared to fulvestrant alone. At a median follow-up of 20 months PFS was 11.0 months (95% confidence interval [CI], 7.5 to 14.5) in the alpelisib group compared with 5.7 months (95% CI, 3.7 to 7.4) in the group that received fulvestrant alone (HR for progression or death, 0.65; 95% CI, 0.50 to 0.85; P < .001); in the cohort without PIK3CA-mutated tumors, the HR was 0.85 (95% CI, 0.58 to 1.25). In the overall population, the most frequently reported grade 3 or 4 adverse events seen with alpelisib and fulvestrant versus fulvestrant alone were hyperglycemia (36.6% vs.0.7%); rash (9.9% vs. 0.3%) and diarrhea (grade 3) (6.7% vs. 0.3%); no diarrhea or rash of grade 4 was reported.[510]

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

A randomized phase II study estimated the efficacy of tamoxifen alone versus tamoxifen combined with everolimus, an oral inhibitor of mTOR, in women with HR-positive, HER2-negative metastatic breast cancer previously treated with an aromatase inhibitor.[511] 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.[511]

A phase III trial in postmenopausal women with advanced, HR-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.[512] In this study, PFS was not different between the treatment arms (HR, 0.89; 95% CI, 0.75–1.05; log-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[512,513] is uncertain, but may be related to the issues of patient selection and extent of prior endocrine therapy.

A phase III study (BOLERO-2) randomized postmenopausal women with HR-positive advanced breast cancer that had progressed or recurred during treatment with a nonsteroidal aromatase inhibitor to exemestane with or without the mTOR inhibitor everolimus.[514] 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).[513] The adverse events (all grades) that occurred more frequently in those receiving everolimus included stomatitis, infections, rash, pneumonitis, and hyperglycemia.[513,514] 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.[515] Based on the evidence from the BOLERO-2 trial, the NCCN Panel has included everolimus plus exemestane as an option for women who fulfill the entry criteria for BOLERO-2. Tamoxifen or fulvestrant in combination with everolimus have also been included as options. The NCCN panel also notes that if there is

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

disease progression while on an everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.

Aromatase inhibitors: Aromatase Inhibitors as monotherapy are options as subsequent-line therapy. The three AIs (anastrozole, letrozole, and exemestane) have shown similar efficacy in the second-line setting.[495,516,517] AI monotherapy maybe be useful in patients desiring single-agent treatment, if they have not received an AI as first-line treatment or in patients who may not be suitable for combination therapy. Patients who have received a prior nonsteroidal AI may benefit from a steroidal AI as subsequent -line of therapy or vice-versa.

Selective estrogen receptors modulator: An analysis of two randomized studies of first-line treatment with anastrozole followed by second-line tamoxifen and vice versa showed that tamoxifen is effective as second-line option.[518]

NCCN recommendations for second-line: For postmenopausal women with HR-positive, HER2-negative recurrent/stage IV breast cancer, the preferred options available include fulvestrant with a CDK 4/6 inhibitor (palbociclib, ribociclib, abemaciclib) (category1), or for those with tumor *PIK3CA* mutations, fulvestrant with alpelisib, everolimus with either an AI, tamoxifen or fulvestrant; monotherapy with fulvestrant, non-steroidal or steroidal AI, or SERM. Estrogen receptor 1 (ESR1) activating mutations are frequently detected in patients with prior exposure to AIs. Tumors with these mutations are generally resistant to both AIs and tamoxifen. Certain tumors with these mutations retain sensitivity to fulvestrant. All may benefit by adding one of the following to fulvestrant - a CDK 4/6-inhibitor, or an mTOR-inhibitor, or alpelisib, if the tumor has *PIK3CA* mutation.

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

Megestrol acetate,[493,519-521] estradiol[522] androgens such as fluoxymesterone, and single agent abemaciclib have been listed as options useful in certain circumstances.

The phase II MONARCH 1 trial, evaluated the activity of abemaciclib as a single agent in patients (n =132) with refractory HR-positive, HER2-negative metastatic breast cancer who had progressed on endocrine therapy and already received multiple systemic therapies (average of three prior systemic regimens).[523] Ninety percent of patients had visceral disease and 50.8% had more than three sites of metastases.[523] Single-agent abemaciclib induced partial response in 26 (19.7%) and demonstrated an ORR of 19.7% (95% CI: 13.3–27.5).[523] Median PFS was 6 months (95% CI: 4.2–7.5). At the final analysis, at 18 months, median OS was 22.3 months (95% CI: 17.7–not reached).[523] Diarrhea was the most frequent adverse event reported in 90.2% patients. Other common adverse events were fatigue (65.2%), nausea (64.4%) and decreased appetite (45.5%). Grade 3 and 4 neutropenia occurred in 26.9% of patients.[523] The NCCN panel has included single agent abemaciclib as an option for those with disease progression on prior endocrine therapy and prior chemotherapy in the metastatic setting.

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

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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

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

Preferred Regimens for Stage IV/Recurrent HER2-Positive Breast Cancer
A randomized, double-blind, phase III study (CLEOPATRA) compared the efficacy and safety of pertuzumab in combination with trastuzumab and docetaxel versus trastuzumab and docetaxel as first-line treatment for 808 women (n=808) with HER2-positive metastatic breast cancer.[524] This trial included patients (about 10%) who had previously received trastuzumab in the adjuvant or neoadjuvant setting. At a median follow-up of 19 months, the addition of pertuzumab to docetaxel plus trastuzumab resulted in improvement in PFS compared with placebo (median, 18.5 versus 12.4 months; hazard ratio [HR] 0.62, 95% CI 0.51-0.75, $P < .001$).[524] 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; $P = .0008$).[388] The most common adverse reactions reported in the pertuzumab group compared to the control group were diarrhea (67% vs. 46%), rash(34% vs. 24%), mucosal inflammation (27% vs. 20%), febrile neutropenia (14% vs. 8%), and dry skin(10% vs. 4%). Peripheral edema and constipation were greater in the control group.[524] Cardiac adverse events or left ventricular systolic dysfunction were reported slightly more frequently in the control group.[525] Health-related QOL was not different in the two treatment groups.[526] In the PERUSE study, patients (n=1436) with advanced HER2-positive breast cancer and no prior systemic therapy (except endocrine therapy) received docetaxel, paclitaxel or nab-paclitaxel with trastuzumab and pertuzumab until disease progression or unacceptable toxicity. The preliminary results after 52 months median follow-up, show that median PFS was comparable between docetaxel, paclitaxel and nab-paclitaxel (median PFS reported was19.6, 23.0 and 18.1 months with docetaxel, paclitaxel and nab-paclitaxel, respectively).[527] Compared with docetaxel-containing therapy, paclitaxel-containing therapy was associated with more neuropathy (31% vs. 16%), but less febrile neutropenia (1% vs. 11%) and mucositis (14% vs. 25%).
Phase II trials have also found activity and tolerability for pertuzumab, pertuzumab with trastuzumab, and for other regimens combining pertuzumab and trastuzumab together with other active cytotoxic agents (i.e., paclitaxel, vinorelbine).[528,529,530] Phase III trials of pertuzumab plus chemotherapy without trastuzumab have not been reported.

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

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

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

In a phase III trial (MARIANNE), 1,095 patients with locally advanced or metastatic breast cancer were randomized to first-line treatment with T-DM1 with or without pertuzumab or trastuzumab plus a taxane. The

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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).[531] 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).[531] The incidence of Grade 3–5 adverse events was 54.1%, 45.4%, and 46.2% in the trastuzumab plus a taxane arm, T-DM1 arm, and T-DM1 plus pertuzumab arm, respectively. Health-related QOL was maintained for a longer duration with a median of 7.7 months for T-DM1 (HR, 0.70; 95% CI, 0.57–0.86) and a median of 9 months for T-DM1 plus pertuzumab (HR, 0.68; 95% CI, 0.55–0.84) compared with a median of 3.9 months for trastuzumab and a taxane.[531]

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,[531] the NCCN Panel included T-DM1 as an option for treatment of patients with HER2-positive metastatic breast cancer. Pertuzumab, trastuzumab, and a taxane, however, remains the preferred first-line regimen for HER2-positive metastatic disease based on data demonstrating improved OS compared to trastuzumab and a taxane. TDM-1 as first-line therapy should be considered only in those not suitable for the preferred treatment.

First-line trastuzumab in combination with selected chemotherapy[532] are additional options for HER2-positive metastatic breast cancer patients. Randomized trials demonstrate benefit from adding trastuzumab to other agents including paclitaxel with or without carboplatin,[532-535] docetaxel,[533] and vinorelbine,[533] for patients with HER2-positive metastatic disease. In addition, the combination of trastuzumab and capecitabine has also shown efficacy as a first-line trastuzumab-containing regimen in this setting.[536,537] The NCCN panel believes the 27% frequency of significant cardiac dysfunction in patients treated with the combination of trastuzumab and doxorubicin/cyclophosphamide chemotherapy in the metastatic setting is too high for use of this combination outside the confines of a prospective clinical trial.[532,537,538]

In those with disease progression on first-line trastuzumab-containing regimens, the NCCN Panel recommends continuation of HER2 blockade. This recommendation also applies to patients who are diagnosed with HER2-positive metastatic disease after prior exposure to trastuzumab in the adjuvant setting. Several trials have demonstrated benefit of continuation of trastuzumab therapy following disease progression on a trastuzumab-containing regimen.[539-541] However, the optimal duration of trastuzumab in patients with long-term control of disease is unknown.

Pertuzumab is active in patients beyond the first-line setting. The results of a multicenter, open-label, single-arm, phase II study (n = 66) show that the combination of pertuzumab and trastuzumab is active and well tolerated in patients with HER2-positive metastatic breast cancer that has progressed on prior trastuzumab therapy.[542] The trial reported an objective response rate of 24.2% (16 patients out of 66). The median PFS time observed with pertuzumab and trastuzumab combination was 15.5 months (range, 0.9–17.0 months; 80% CI, 18-31 months.[542] The reported median duration of response with the combination was 5.8 months (range, 2.9–15.3 months).[542]

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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[543]

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

T-DM1 also has also shown activity in the second-line setting. A randomized, international, multicenter, open-label, phase III study (EMILIA) evaluated the safety and efficacy of T-DM1 compared with lapatinib plus capecitabine for HER2-positive patients with locally advanced breast cancer or metastatic breast cancer previously treated with trastuzumab and a taxane.[544] 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; $P = .0005$).[544] 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.[544]

A phase II single-arm study evaluated fam-trastuzumab deruxtecan-nxki, a HER2 antibody conjugated with a topoisomerase I inhibitor, in adults (n=184) with pathologically documented HER2-positive metastatic breast cancer who had received multiple previous treatments including treatment with T-DM1.[545] After a median duration of follow-up of 11.1 months (range 0.7- to 19.9), the median response duration with fam-trastuzumab deruxtecan-nxki was 14.8 months (95% CI, 13.8 to 16.9), and the median PFS was 16.4 months (95% CI, 12.7 to not reached).[545] Most commonly reported adverse events (grade 3 or higher) were a decreased neutrophil count (20.7%), anemia (in 8.7%), nausea (in 7.6%), and fatigue (6%).[545] Interstitial lung disease (ILD) was reported in 13.6% of the patients (grade 1 or 2 - 10.9%; grade 3 or 4 - 0.5%; and grade 5 - 2.2%). Based on this study and the approval from the U.S. FDA, the NCCN panel has included this as an option for HER-2 positive metastatic disease noting that it is indicated in patients after two or more lines of prior HER2-targeted therapy regimens in the metastatic setting and contraindicated for those with a history of or active ILD.

Lapatinib in combination with capecitabine or trastuzumab are options 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.[546] 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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

a trend toward a survival advantage with lapatinib plus capecitabine.[547] 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).[547]

Results from a phase III trial in which patients with heavily pretreated metastatic breast cancer and disease progression on trastuzumab therapy randomly assigned to trastuzumab plus lapatinib or lapatinib monotherapy showed that PFS was increased from 8.1 weeks to 12 weeks (*P* = .008) with the combination.[548] 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). [549] 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.[549] Based on the absence of data, the panel does not recommend the addition of chemotherapy to the trastuzumab and lapatinib combination.

In a phase II trial of patients (n=49) with progressive, HER2-positive disease and brain metastases (92% received CNS surgery and/or radiotherapy),[550] were treated with capecitabine plus neratinib, a second-generation (irreversible) pan-HER TKI inhibitor of the tyrosine kinase domains of EGFR, HER2 and HER4. The patients were separated based on prior lapatinib treatment. The combination therapy resulted in a CNS objective response rate of 49% (95% CI, 32% to 66%), among lapatinib-naïve patients, and 33% (95% CI, 10% to 65%) among those with prior lapatinib treatment.[550] Median PFS and OS among lapatinib-naïve patients was 5.5 and 13.3 months, and 3.1 and 15.1 months among those with prior lapatinib treatment. Grade 3 diarrhea occurred in 29% of patients.[550]

A prospective randomized phase III trial (NALA) randomized patients (n = 621) with HER2-positive to neratinib in combination with capecitabine or lapatinib plus capecitabine until disease progression.[551] All enrolled patients received a least two lines of prior HER2-targeted treatment in the metastatic setting. Approximately 30% had received ≥3 prior treatment lines. About a third of all patients had received prior treatment with trastuzumab, pertuzumab and T-DM1.

The ORR (32.8 % vs. 26.7%; *P* = .1201), the clinical benefit rate (44.5% vs 35.6%; *P* = .0328), and median duration of response (8.5 vs 5.6 months) all favored the neratinib arm. Fewer patients required intervention for CNS metastases with neratinib. The risk of progression was reduced by 24% in the neratinib group (HR 0.76; 95% CI 0.63–0.93; *P* = .0059). There was a non-significant trend towards improved survival. The OS rates at 6 and 12 months were 90.2% vs 87.5% with neratinib + capecitabine compared with 72.5% vs 66.7% for lapatinib in combination with capecitabine (HR = 0.88; 95% CI 0.72–1.07; *P*= .2086). Diarrhea was the most frequent side effect in the NALA trial in both arms, but a higher rate was observed in patients in the neratinib group (any grade diarrhea 83% vs. 66%; grade 3/4 diarrhea 24% vs. 13%).

Based on the results of the NALA trial and the recent FDA approval, NCCN has included neratinib plus capecitabine as a category 2A option in this setting.

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

Women with Stage IV or recurrent disease characterized by tumors that are HR-positive, HER2-positive tumors have the option of receiving HER2-directed therapy as a component of their treatment plan. Options include, treatment with a HER2-targeted therapy plus chemotherapy or endocrine therapy alone or in combination with HER2-targeted therapy. Endocrine therapy alone or in combination with HER2- targeted therapy is a less toxic approach compared with HER2-targeted therapy combined

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

with chemotherapy. Premenopausal women treated with HER2-targeted therapy *and* endocrine therapy should receive ovarian suppression or ablation.

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

In the TAnDEM study, postmenopausal women (n =207) with metastatic HR-positive and HER2-positive tumors were randomized to receive anastrozole alone or anastrozole plus trastuzumab.[552] Compared with single-agent anastrozole, an improvement in PFS was seen with combination therapy (4.8 vs. 2.4 months; HR 0.63, 95% CI 0.47-0.84, *P* = .0016). The combination was associated with a higher incidence of toxicities (all grades) fatigue (21% vs. 9%), diarrhea (20% vs. 8%), vomiting (21% vs. 4%), and pyrexia (18% vs. 7%); serious (grade 3/4) toxicities were rare in both treatment arms.

The phase III eLEcTRA trial studied the efficacy and safety of trastuzumab plus letrozole in patients (n=93) with HER2-positive and HR-positive metastatic breast cancer. Median time to progression was 3.3 months with letrozole and 14.1 months with trastuzumab plus letrozole. The results are consistent with the TAnDEM trial, however, due to smaller numbers of patients enrolled in this trial, this was not statistically significant (HR, 0.67; 95% CI, 0.35 to 1.29; *P* = .23).[553]

In a phase III study of postmenopausal patients (n=219) with HER2–positive and HR–positive disease, first-line treatment with lapatinib plus letrozole reduced the risk of disease progression compared to treatment with letrozole alone (median PFS, 8.2 months v 3.0 months; HR, 0.71, 95% CI, 0.53 to 0.96; *P* = .019).[554] The combination of letrozole plus trastuzumab was associated with a higher rate of grade 3 or grade 4 toxicities, including diarrhea (10% vs. 1%) and rash (1% vs. 0%).[554]

In the randomized phase II study (PERTAIN), postmenopausal women (n=258) were randomly assigned to either first-line pertuzumab plus trastuzumab and an AI (anastrozole or letrozole) or trastuzumab plus an AI. There was an improvement in PFS with the three-drug combination (18.9 versus 15.8 months; HR 0.65, 95% CI 0.48-0.89).[555] Grade 3 or higher adverse events observed were higher trastuzumab and pertuzumab versus pertuzumab alone (50% vs. 39%). Of note, about half of women received induction therapy with a taxane for 18 to 24 weeks prior to the initiation of endocrine therapy. Based on the results of the PERTAIN trial,[555] the NCCN panel notes that if treatment was initiated with chemotherapy and trastuzumab plus pertuzumab, and the chemotherapy was stopped, endocrine therapy may be added to the trastuzumab plus pertuzumab.

In the ALTERNATIVE trial, postmenopausal women (n=355) with HER2-positive, HR-positive metastatic breast cancer were randomized to receive lapatinib plus trastuzumab plus an AI, lapatinib plus an AI, or trastuzumab plus AI without chemotherapy.[556] All patients in the trial received prior trastuzumab and prior endocrine therapy, either in the adjuvant or metastatic disease setting. AI in combination with lapatinib plus trastuzumab demonstrated significant increase in PFS compared with trastuzumab without lapatinib (11 vs. 5.7 months; HR 0.62, 95% CI 0.45-0.88, *P* = .0064).[556] Most common adverse events with the combination compared with trastuzumab or lapatinib monotherapy were diarrhea (69%, 9%, 51%), rash (36%, 2%, 28%), nausea (22%, 9%, 22%), and paronychia (30%, 0, 15%).

The NCCN Panel has also included other combinations of available endocrine therapies such as fulvestrant or tamoxifen with trastuzumab as options for HR-positive and HER2-positive metastatic disease. These options would be mostly considered after completion of chemotherapy plus HER2-therapy or in a few patients with indolent or asymptomatic

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

disease based on the need for continuing HER2-targeted therapy for disease control. The selection of appropriate endocrine therapy would depend on agents the patient has already received and/or progressed on.

Systemic Therapy for Recurrent or Stage IV Disease with germline BRCA1/2 mutations

About 5% of all patients with breast cancer carry the germline breast cancer susceptibility gene (*BRCA)* mutations and rates of these mutations are higher rates among those with HER2-negative disease. [557,558]

PARP inhibitors: The phase III OlympiAD trial randomized patients (n= 302) with metastatic breast cancer harboring the germline BRCA mutations to the PARP inhibitor, olaparib (n=205) or physicians choice (n=97) of non-platinum chemotherapy (capecitabine, eribulin or vinorelbine).[559] An improvement in PFS was seen in those receiving olaparib relative to those receiving chemotherapy [7.0 vs. 4.2 months; HR: 0.58; 95% CI: 0.43–0.80; *P*< .001].[559] The study, included all subtypes- those with HR-positive, HER2-negative and positive disease, and triple negative. The PFS improvements noted with olaparib were noted in all subtypes and greatest in the triple-negative population. Subsequent follow-up did not show a statistically significant difference in OS between treatment arms and the study was also not powered to evaluate OS. The median OS with olaparib compared with treatment of physician's choice was 19.3 months versus 17.1 months, respectively (HR 0.90, 95% CI 0.66-1.23; *P* = .513).[560] The QOL was significantly better in the olaparib arm. It is interesting to note that patients who had not received prior chemotherapy in the metastatic setting achieved a 7.9-month longer median OS with olaparib compared with treatment of physician's choice.[560]

The phase III EMBRACA trial patients with advanced breast cancer harboring the germline *BRCA* mutations and no prior exposure to a PARP inhibitor, were randomized to talazoparib (n=287) or to physicians choice of single agent chemotherapy (n=144).[561] The median PFS among patients in the talazoparib group was longer than the control group (8.6 months [95% CI, 7.2 to 9.3] vs. 5.6 months [95% CI, 4.2 to 6.7]; HR for disease progression or death, 0.54; 95% CI, 0.41 to 0.71; *P* <.001).[561]

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

Platinums: The phase III, TNT trial compared docetaxel with carboplatin in the first-line setting in women (n=376) with triple negative breast cancer. In the unselected population, carboplatin was not more active than docetaxel (ORR, 31.4% vs. 34.0%; P = .66). [562] Patients with a germline BRCA1/2 mutation had a significantly better response to carboplatin than docetaxel (ORR, 68.0% vs. 33.3%, absolute difference 34.7%, *P* =.03). [562] PFS was also improved with carboplatin treatment in patients with a germline BRCA1/2 mutation (median PFS 6.8 months vs. 4.4 months), no difference was found in OS. However, patients with somatic BRCA 1/2 mutation in the tumor DNA did not appear to have the same advantage.

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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

In a randomized trial (IMpassion 130), patients (n= 902) with triple negative breast cancer who had not received treatment in the metastatic setting were randomized to the programmed cell death ligand 1 (PD-L1) inhibitor, atezolizumab plus albumin-bound paclitaxel or placebo plus albumin-bound paclitaxel.[563]

All patients enrolled in the trial had to have completed previous chemotherapy (preoperative or adjuvant) at least 12 months before randomization and not received any chemotherapy in the metastatic setting. At a median follow-up of 12.9 months, there was statistically significant difference in PFS in those receiving atezolizumab plus albumin-bound paclitaxel than in the placebo plus albumin-bound paclitaxel (7.2 vs. 5.5 months; HR for progression or death 0.80, 95% CI 0.69-0.92), and a nonsignificant trend towards improved OS (21.3 vs. 17.6 months; HR for death 0.84, 95% CI 0.69-1.02).[563] However, in a planned subset analysis of patients with PD-L1-expressing tumors, treatment with atezolizumab plus albumin-bound paclitaxel showed statistically significant improvement in PFS (7.5 vs. 5 months; HR 0.62, 95% CI 0.49-0.78), and OS (25 vs. 15.5 months; HR 0.62, 95% CI 0.45-0.86).[563] Grade 3 or higher adverse events occurred in 48.7% receiving atezolizumab plus albumin-bound paclitaxel versus 42.2% receiving placebo plus albumin-bound paclitaxel. Grade 3 or 4 neuropathy was more frequently seen among those receiving atezolizumab (5.5% vs. 2.7%). There were 3 treatment-related deaths among the patients who received atezolizumab, consistent with other studies of checkpoint inhibitors. Adverse events led to treatment discontinuation in 16% in the atezolizumab arm versus 8% in the control arm.[563] PD-L1-positive expression in tumor-infiltrating immune cells of 1% or more has been associated with a better outcome with PD-L1 inhibitor treatment.[564] A subsequent 18-month follow-up analysis confirmed PFS and OS benefits among those with PD-L1-expressing tumors.[565] Atezolizumab plus albumin-bound paclitaxel is included as a preferred option for those with advanced triple negative breast cancer with PD-L1 expression in ≥1% tumor-infiltrating immune cells.

Systemic Chemotherapy for Recurrent or Stage IV Disease

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

A variety of chemotherapy regimens are felt to be appropriate, as outlined in the treatment algorithm. Combination chemotherapy generally provides higher rates of objective response and longer time to progression, in comparison to single-agent chemotherapy. Combination chemotherapy is, however, associated with an increase in toxicity and is of little survival benefit.[566-570] Furthermore, administering single agents sequentially decreases the likelihood that dose reductions will be needed. Thus, the NCCN Panel finds no compelling evidence that combination chemotherapy is superior to sequential single agents. Therefore, sequential monotherapy is the preferred and combination therapy is useful in patients with rapid clinical progression or need for rapid symptom and/or disease control.

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

The NCCN panel recommends considering scalp cooling to reduce incidence of chemotherapy-induced alopecia for patients receiving chemotherapy. The data on efficacy of scalp cooling is mainly from the

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

adjuvant setting and also show that results may be less effective with anthracycline-containing regimens.[571-575]

A metanalyses showed favorable impact on OS by prolonging treatment until disease progression.[576] In this analysis, data from four studies involving 666 patients, indicated that median OS was increased by 23% (95% confidence interval [CI] 9–38%, *P* = .01) in women receiving longer durations of chemotherapy versus a limited number of cycles.[576] In a systematic review, longer durations of chemotherapy demonstrated a marginal increase in OS (HR, 0.91, 95% CI 0.84–0.99) and a significant improvement in PFS (HR 0.66, 95% CI 0.6–0.72), compared with shorter durations.[570]

A more recent study of patients (n=420) with HER2-negative, advanced breast cancer showed that intermittent first-line treatment with paclitaxel plus bevacizumab was not inferior to continuous treatment. The median overall PFS for intermittent versus continuous was 7.4 months and 9.7 months respectively (HR of 1.17 (95% CI 0.88–1.57).). Median OS was 17.5 months versus 20.9 months for intermittent versus continuous treatment, with a HR of 1.38 (95% CI 1.00-1.91).[577]

Determining the duration of chemotherapy in an individual patient typically depends on the efficacy and tolerability and shared decision-making between the treating physician and patient.

Most patients will be candidates for multiple lines of systemic therapies for palliation. At each reassessment clinicians should assess value of ongoing treatment, the risks and benefits of an additional line of systemic therapy, patient performance status, and patient preferences through a shared decision-making process.

Preferred Chemotherapy Regimens for Stage IV or Recurrent Metastatic Disease

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

Among preferred single agents, the NCCN Panel has included taxanes (paclitaxel), anthracyclines (doxorubicin and liposomal doxorubicin), anti-metabolites (capecitabine and gemcitabine), microtubule inhibitors (eribulin and vinorelbine), platinum agents for patients with triple negative tumors and germline BRCA 1/2 mutations.

Paclitaxel can be administered weekly (80 mg/m^2)[578] or every three weeks (175 mg/m^2).[579] A meta-analysis of randomized controlled trials that compared weekly and every three weeks taxanes regimens in advanced breast cancer showed that compared with every three-week treatment, weekly administration of paclitaxel resulted in an improvement in OS (HR 0.78, 95% CI 0.67-0.89).[580]

Doxorubicin (60 to 75 mg/m^2) every three weeks, or 20 mg/m2 weekly has shown an ORR between 30 to 47%.[581-584] Liposomal doxorubicin (50 mg/m^2 every 4 weeks) has been shown to have efficacy similar to doxorubicin (60 mg/m^2 every 3 weeks).[585] It has also been shown to have efficacy in the second-line setting for patients with metastatic breast cancer.[585] Compared with doxorubicin, the liposomal doxorubicin has a less frequent dosing schedule and decreased risk of cardiotoxicity 7% vs. 26%, HR 3.16; 95% CI 1.58-6.31), decreased rate of nausea (37 % vs. 53%) and vomiting (19% vs. 31%), lower rates of alopecia (20% vs. 66%), and neutropenia (4% vs. 10%).[585] However, compared with doxorubicin it was associated with a higher rate of palmar-plantar erythrodysesthesia (48% vs. 2%), stomatitis (22% vs. 15%), and mucositis (23% vs 13%).[585]

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

The benefit of capecitabine as a treatment option for patients with metastatic breast cancer has been demonstrated in multiple phase II trials. Results of one study of patients (n=126) treated with capecitabine showed ORR of 28%, median TTP of 4.9 months and median OS of15.2 months (95% CI: 13.5-19.6 months). [586] In another study, women (n=95) were randomized to capecitabine or cyclophosphamide, methotreaxate and fluorouracil (CMF). [587] Treatment with single agent capecitabine resulted in a higher ORR compared with CMF (30% vs. 16%). The median TTP and OS were similar in both groups.[587]

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, patients (n=762) with metastatic breast cancer were randomized 2:1 to eribulin or treatment of physicians' choice. The OS was improved in women assigned to eribulin (median 13.1 months, 95% CI 11.8-14.3) compared with those receiving other treatments (10.6 months, 9.3-12.5;), a 19% statistically significant risk reduction (HR 0·81, 95% CI 0.66-0.99; *P*=.041).[588]

A phase III trial compared eribulin with capecitabine in patients with metastatic breast cancer and showed that both treatments were similar with respect to OS and PFS.[589] The median PFS times for eribulin and capecitabine were 4.1 and 4.2 months, respectively (HR, 1.08; 95% CI, 0.93 to 1.25; *P*= .30) and the OS with eribulin versus capecitabine was 15.9 months versus 14.5 months; HR 0.88, 95% CI 0.77-1.00). [589]

In addition to the above, gemcitabine[590] and vinorelbine are both active as a single agents even in heavily pretreated patients with metastatic breast cancer.[591-593]

Among other recommended single agents, the NCCN Panel has included taxanes (docetaxel,[594] albumin-bound paclitaxel[595-597]), anthracyclines (epirubicin) [598]), and ixabepilone.[599-601] as other recommended regimens.

Ixabepilone as monotherapy has been evaluated in several phase II trials of women with metastatic breast cancer: in a first-line setting in patients previously treated with anthracycline chemotherapy [599]; in patients with taxane-resistant metastatic breast cancer[600]; and in patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine.[601] 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;[599] 12% (95% CI, 4.7%– 26.5%), 10.4 months, and 7.9 months for the taxane-resistant patients;[600] 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.[601] In the study by Perez et al,[601] grade 3/4 treatment-related toxicities included peripheral sensory neuropathy (14%) and neutropenia (54%).

The NCCN Panel had included combination chemotherapy regimens as useful in certain circumstances. The combination regimen options include doxorubicin/cyclophosphamide (AC);[602,603] epirubicin/cyclophosphamide (EC)[604]; docetaxel and capecitabine;[568] gemcitabine and paclitaxel (GT);[605]; cyclophosphamide/methotrexate/fluorouracil (CMF);[606] gemcitabine/ carboplatin;[607-609] carboplatin with paclitaxel or albumin-bound paclitaxel;[610-612] and paclitaxel/bevacizumab.[613-615]

For the doublet regimens that are included, randomized phase III trials have shown that the ORR with first-line AC treatment ranges from 47% to 54%) and OS is around 20 months.[602,603] For first-line EC, a phase III trial reported the ORR of 55%, PFS 7.1 months, and OS of 14 months.[604] For first-line capecitabine/docetaxel, a phase III trial reported an ORR of 53%

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

and time-to-progression of 11 months.[616] In the second-line setting, another phase III trial compared the efficacy and tolerability of capecitabine/docetaxel therapy in anthracycline-pretreated patients and showed significantly superior efficacy in time to disease progression (HR, 0.652; 95% CI, 0.545 to 0.780; P =.0001; median, 6.1 vs. 4.2 months), OS (HR, 0.775; 95% CI, 0.634 to 0.947; P =.0126; median, 14.5 vs. 11.5 months), and ORR (42% v 30%, P =.006) compared with single agent docetaxel.[568]

Combination chemotherapy regimens containing a platinum agent or a taxane have been shown to be efficacious in patients with metastatic triple negative breast cancer. A randomized phase II study compared the addition of iniparib to gemcitabine/carboplatin versus gemcitabine/carboplatin in patients with triple negative breast cancer who had received no more than two prior chemotherapies. ORR was similar in both groups - 30.2% (95% CI, 24.6 to 35.8) with gemcitabine/carboplatin.[607] and the median OS was 11.1 months with gemcitabine/carboplatin [HR of 0.88 (95% CI, 0.69 to 1.12)].[607]

Several phase II studies have evaluated the efficacy of paclitaxel/carboplatin as first-line for patients with metastatic breast cancer and found the combination to be an effective therapeutic option in this setting.[611,612] The randomized the trial, tnAcity, evaluated the efficacy and safety of first-line albumin-bound paclitaxel plus carboplatin, albumin-bound paclitaxel plus gemcitabine, and gemcitabine plus carboplatin in patients with metastatic triple negative breast cancer.[610] The results of this trial reported that median PFS was significantly longer with albumin-bound paclitaxel plus carboplatin versus albumin-bound paclitaxel/ gemcitabine (8.3 vs. 5.5 months; HR, 0.59 [95% CI, 0.38–0.92]; *P* = .02) or gemcitabine/carboplatin (8.3 vs. 6.0 months; HR, 0.58 [95% CI, 0.37–0.90]; *P* = 0.02). The median OS was also longer with albumin-bound paclitaxel plus carboplatin versus albumin-bound paclitaxel/ gemcitabine (16.8 vs. 12.1 months; HR, 0.73 [95% CI, 0.47–1.13]; *P* = .16) or gemcitabine/carboplatin (16.8 vs. 12.6 months; HR, 0.80 [95% CI, 0.52–1.22]; *P* = .29). The ORR was 73%, 39%, and 44%, respectively.[610]

A series of trials have sought to define the role for bevacizumab in the treatment of metastatic breast cancer. The E2100 trial randomized 722 women with recurrent or metastatic breast cancer to first-line chemotherapy with paclitaxel with or without bevacizumab.[613] 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.[617] 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.[614,615] In a subset analysis of the phase III CALGB 40502 trial, patients (*n* = 201) with metastatic triple negative breast cancer, first-line albumin-bound paclitaxel in combination with bevacizumab resulted in a median PFS of 7.4 months.[618]

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

The data from the above-mentioned randomized trials, document that the addition of bevacizumab to first- or second-line chemotherapy agents

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

modestly improves time to progression and response rates. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel. None of these studies demonstrates an increase in OS or QOL when analyzed alone or in a meta-analyses of the trials.[619] Therefore, the NCCN Panel has included bevacizumab in combination with paclitaxel as an option useful in only select circumstances.

The only triplet regimen listed as an option in the metastatic setting is CMF. This regimen was compared in the first-line setting with capecitabine monotherapy, and results show similar ORR and PFS.[606] However, CMF resulted in a shorter OS (median, 22 versus 18 months; HR 0.72, 95% CI 0.55-0.94) compared to capecitabine.

Additional Targeted Therapies for Stage IV disease Useful in Certain Circumstances

Neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusions are seen in of a few rare types of cancer, such as secretory carcinoma of the breast or salivary gland and infantile fibrosarcoma and also infrequently in some common cancers, such as melanoma, glioma and carcinomas of the thyroid, lung and colon.[620] *NTRK* fusions are identified by fluorescence *in situ* hybridization (FISH), Next Generation Sequencing (NGS) or polymerase chain reaction (PCR). Larotrectinib[621-623] and entrectinib[623,624] are two NTRK-inhibitors that are U.S FDA approved for the treatment of solid tumors that have an NTRK gene fusion without a known acquired resistance mutation and have no satisfactory alternative treatments or that have progressed following treatment. If patient with recurrent/stage IV breast presents with a tumor with an *NTRK* fusion, treatment with a NTRK-inhibitor is an option if no satisfactory alternative treatments exists or that have progressed following treatment.

Pembrolizumab is U.S FDA approved for the treatment of patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options.[625-627] Pembrolizumab has demonstrated anti-tumor activity in heavily pre-treated patients with metastatic breast cancer and high tumor mutation burden (greater than or equal to 9 mutations/megabase) determined by commercially available tests.[628] If patient with recurrent/stage IV breast cancer presents has a tumor with MSI-H/MMR mutation, whose disease has progressed following prior treatments and no satisfactory alternative treatment options, treatment pembrolizumab is an option.

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 decide on 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 decide, along with the patient, whether disease is being controlled and the toxicity of treatment is acceptable. Sometimes individual pieces of information can be conflicting with regards to disease response, and clinical judgement along with patient input is critical.

The NCCN Panel recommends using widely accepted criteria for reporting response, stability, and progression of disease such as the RECIST criteria[629] and the WHO criteria.[630] The Panel also recommends using the

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

same method of response 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) or circulating DNA (ctDNA) 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.[631] 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. [631] 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.[631]

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[632] 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.[633-635] 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.[635,636]

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.[634] 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.[637-641] 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.[642,643] Patients treated with breast conservation should

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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 HR status.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[644] 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.[645] 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.[646] 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.[646] 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.[647] 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.[648] 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.[649] 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).[650]

While the epithelial component of most phyllodes tumors contains ER (58%) and/or PR (75%),[651] 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[652] 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.[653,654] 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%.[655] 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.[655] 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 HR 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,[656] and breast-conserving therapy during pregnancy does not appear to have a negative impact on survival.[656,657] 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,[658,659] 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.[660] There are limited data with only case reports and estimations of fetal radiation dose regarding use of radioactive tracer (eg, technetium 99m sulfur colloid).[661-663] Isosulfan blue or

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[664,665] Collected data of chemotherapy exposure in utero indicate that the first trimester has the greatest risk of fetal malformation.[666,667] 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/m^2 IV days 1 and 4, doxorubicin 50 mg/m^2 by IV infusion over 72 hours, and cyclophosphamide 500 mg/m^2 IV day 1) may be given with relative safety during the second and third trimesters of pregnancy.[665] 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.[653] 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.[665,668] 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.[669-672] 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.[673-680] 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.[681]

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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[682,683] 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 HR-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.[684-687] 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.[688,689] 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 prognosis[690-692] and to be younger at the time of disease presentation.[693]

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.[694,695] Nevertheless, current evidence provides justification for a separate guideline for the workup and treatment of patients diagnosed with IBC.

StageT4d, 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 HR- and HER2- 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.[696]

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).

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[96,97,697,698] 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 approach[682] 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.[699] 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%.[700]

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.[701] A systematic review found evidence for an association between the intensity of preoperative therapy and the likelihood of a pCR.[702] 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.[703]

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 HR-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.[686,704] For women with HER2-positive disease, the addition of trastuzumab to primary systemic chemotherapy is associated with better response rates.[705-709] A

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[705] 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,[705] 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.[217,710] 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.[217]

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.[711] SLN dissection is not a reliable method of assessing ALNs among women with IBC.[712] 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.[713]

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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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).

Discussion update in progress

Version 1.2022 © 2021 National Comprehensive Cancer Network© (NCCN©), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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 patients[714-716](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.[715,716]

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.[717] 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.[715] 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.[718] 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.[719] 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.[715,720] 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.[721]

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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.

Discussion update in progress

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.

Version 1.2022 © 2021 National Comprehensive Cancer Network© (NCCN©), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31912902

2. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html.

3. http://www.cap.org. Accessed January, 2019.

4. 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.

5. Stackievicz 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.

6. 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.

7. 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.

8. 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.

9. Allen LR, Lago-Toro CE, Hughes JH, et al. Is there a role for MRI in the preoperative assessment of patients with DCIS? Ann Surg Oncol 2010;17:2395-2400. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20217259.

10. Davis KL, Barth RJ, Jr., Gui J, et al. Use of MRI in preoperative planning for women with newly diagnosed DCIS: risk or benefit? Ann Surg Oncol 2012;19:3270-3274. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22911365.

11. Pilewskie M, Olcese C, Eaton A, et al. Perioperative breast MRI is not associated with lower locoregional recurrence rates in DCIS patients treated with or without radiation. Ann Surg Oncol 2014;21:1552-1560. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24385207.

12. 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.

13. 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.

14. 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.

15. 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.

16. 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.

17. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

18. 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.

19. 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.

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

25. 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: https://www.ncbi.nlm.nih.gov/pubmed/25605856.

26. 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.

27. Goodwin A, Parker S, Ghersi 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.

28. 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: https://www.ncbi.nlm.nih.gov/pubmed/26291673.

29. Sagara Y, Freedman RA, Vaz-Luis I, et al. Patient Prognostic Score and Associations With Survival Improvement Offered by Radiotherapy After Breast-Conserving Surgery for Ductal Carcinoma In Situ: A Population-Based Longitudinal Cohort Study. J Clin Oncol 2016;34:1190-1196. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26834064.

30. 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.

31. Bartelink H, Maingon P, Poortmans P, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Lancet Oncol 2015;16:47-56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25500422.

32. 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.

33. Polgar C, Fodor J, Orosz Z, et al. Electron and high-dose-rate brachytherapy boost in the conservative treatment of stage I-II breast cancer first results of the randomized Budapest boost trial. Strahlenther Onkol 2002;178:615-623. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12426672.

34. Moran MS, Zhao Y, Ma S, et al. Association of Radiotherapy Boost for Ductal Carcinoma In Situ With Local Control After Whole-Breast Radiotherapy. JAMA Oncol 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28358936.

35. 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.

36. 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.

37. 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.

38. 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.

39. 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.

40. 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.

41. 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.

42. 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.

43. Morrow M, Van Zee KJ, Solin LJ, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma in Situ. Pract Radiat Oncol 2016;6:287-295. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27538810.

44. 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.

45. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

46. 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.

47. 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.

48. 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:

49. 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.

50. 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.

51. 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.

52. 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.

53. 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.

54. 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.

55. 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.

56. 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.

57. 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.

58. 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.

59. 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.

60. 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.

61. 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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

2010;14:1-182. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20025837.

62. 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.

63. 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.

64. 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.

65. 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.

66. 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.

67. Wilkinson NW, Shahryarinejad 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.

68. 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.

69. 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.

70. 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.

71. 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.

72. 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.

73. 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.

74. 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.

75. 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.

76. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

77. 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.

78. 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.

79. 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.

80. 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.

81. 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.

82. 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.

83. 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.

84. 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.

85. 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.

86. 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.

87. 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.

88. 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:

89. 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.

90. 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. J Clin Oncol 2015;33:2424-2429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26101247.

91. Baseline staging tests in primary breast cancer: Practice guideline report # 1-14: Members of the Breast Cancer Disease Site Group.

92. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

93. 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.

94. 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.

95. 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.

96. 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.

97. 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.

98. 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.

99. 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.

100. 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.

101. 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.

102. 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.

103. 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.

104. 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.

105. 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.

106. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

107. 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.

108. 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.

109. 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.

110. Blichert-Toft M, Nielsen M, During 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.

111. 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.

112. 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.

113. 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.

114. 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.

115. Chatterjee A, Pyfer B, Czerniecki B, et al. Early postoperative outcomes in lumpectomy versus simple mastectomy. J Surg Res 2015;198:143-148. Available at:

116. Recht A. Contralateral prophylactic mastectomy: caveat emptor. J Clin Oncol 2009;27:1347-1349. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19224834.

117. 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.

118. 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.

119. 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

120. 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.

121. Deutsch M, Land S, Begovic M, Sharif S. The incidence of arm edema in women with breast cancer randomized on the National Surgical Adjuvant Breast and Bowel Project study B-04 to radical mastectomy versus total mastectomy and radiotherapy versus total mastectomy alone. Int J Radiat Oncol Biol Phys 2008;70:1020-1024. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18029105.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

122. Fleissig A, Fallowfield LJ, Langridge CI, et al. Post-operative arm morbidity and quality of life. Results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. Breast Cancer Res Treat 2006;95:279-293. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16163445.

123. Lucci A, McCall LM, Beitsch PD, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. J Clin Oncol 2007;25:3657-3663. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17485711.

124. Ashikaga T, Krag DN, Land SR, et al. Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. J Surg Oncol 2010;102:111-118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20648579.

125. Land SR, Kopec JA, Julian TB, et al. Patient-reported outcomes in sentinel node-negative adjuvant breast cancer patients receiving sentinel-node biopsy or axillary dissection: National Surgical Adjuvant Breast and Bowel Project phase III protocol B-32. J Clin Oncol 2010;28:3929-3936. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20679600.

126. 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.

127. 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.

128. 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.

129. 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.

130. Giuliano AE, Ballman K, McCall L, et al. Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients With Sentinel Lymph Node Metastases: Long-term Follow-up From the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 Randomized Trial. Ann Surg 2016;264:413-420. Available at:

131. Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol 2013;14:297-305. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23491275.

132. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014;15:1303-1310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25439688.

133. 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.

134. 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.

135. Kiricuta CI, Tausch J. A mathematical model of axillary lymph node involvement based on 1446 complete axillary dissections in patients with

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

breast carcinoma. Cancer 1992;69:2496-2501. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1568171.

136. 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.

137. American Joint Committee on Cancer (AJCC) Cancer staging manual, Seventh Edition (2010) published by Springer Science+Business Media, LLC.

138. 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.

139. 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.

140. Pignol JP, Olivotto 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.

141. 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.

142. 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.

143. 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.

144. 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.

145. 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.

146. 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.

147. 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.

148. 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.

149. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

150. Whelan TJ, Olivotto 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.

151. 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.

152. 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.

153. 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.

154. 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.

155. 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.

156. 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.

157. 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.

158. 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.

159. 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.

160. 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.

161. 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: https://www.ncbi.nlm.nih.gov/pubmed/25637340.

162. 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.

163. 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.

164. 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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

randomised trial. Lancet 1999;353:1641-1648. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10335782.

165. 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.

166. 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.

167. 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.

168. 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.

169. 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.

170. 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.

171. 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.

172. 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.

173. 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.

174. 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.

175. 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.

176. 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.

177. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

178. 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.

179. 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.

180. 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.

181. 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.

182. 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.

183. 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.

184. 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.

185. 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.

186. 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.

187. 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.

188. 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.

189. 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.

190. 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.

191. 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.

192. 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.

193. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

194. 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.

195. 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.

196. Piper M, Peled AW, Foster RD, et al. Total skin-sparing mastectomy: A aystematic review of oncologic outcomes and postoperative complications. Ann Plast Surg 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23486127.

197. 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.

198. 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.

199. 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.

200. 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.

201. 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.

202. Newman LA, Kuerer HM, Hunt KK, et al. Presentation, treatment, and outcome of local recurrence afterskin-sparing mastectomy and immediate breast reconstruction. Ann Surg Oncol 1998;5:620-626. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9831111.

203. 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.

204. 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.

205. 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.

206. 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.

207. 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.

208. 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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

trial. J Clin Oncol 2005;23:5108-5116. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15998903.

209. 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.

210. 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.

211. 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.

212. 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.

213. 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.

214. 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.

215. 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.

216. 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 NeoALTTO study (BIG 1-06) [abstract]. SABCS 2013:Abstract S1–01. Available at:

217. 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.

218. 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.

219. 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.

220. 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.

221. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

B-18 and B-27. J Clin Oncol 2008;26:778-785. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18258986.

222. Gralow 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.

223. 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.

224. 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: https://www.ncbi.nlm.nih.gov/pubmed/18250347.

225. 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.

226. 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: https://www.ncbi.nlm.nih.gov/pubmed/22508812.

227. 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.

228. Olivotto 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.

229. 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.

230. 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.

231. Berry DA, Cirrincione 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.

232. 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.

233. 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.

234. 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.

235. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

236. 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.

237. 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.

238. Sparano J, Gray, RJ, Wood, WC, Makower, DF, Lively, TG, Saphner, TJ et al. TAILORx: Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score [Abstract]. J Clin Oncol 2018;36 (suppl; abstr LBA1) Available at: http://abstracts.asco.org/214/AbstView_214_212997.html.

239. Nitz U, Gluz O, Christgen M, et al. Reducing chemotherapy use in clinically high-risk, genomically low-risk pN0 and pN1 early breast cancer patients: five-year data from the prospective, randomised phase 3 West German Study Group (WSG) PlanB trial. Breast Cancer Res Treat 2017;165:573-583. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28664507.

240. Stemmer SM, Steiner M, Rizel S, et al. Clinical outcomes in ER+ HER2 -node-positive breast cancer patients who were treated according to the Recurrence Score results: evidence from a large prospectively designed registry. NPJ Breast Cancer 2017;3:32. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28900632.

241. Gluz O, Nitz UA, Christgen M, et al. West German Study Group Phase III PlanB Trial: First Prospective Outcome Data for the 21-Gene Recurrence Score Assay and Concordance of Prognostic Markers by Central and Local Pathology Assessment. J Clin Oncol 2016;34:2341-2349. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26926676.

242. https://clinicaltrials.gov/ct2/show/NCT01272037 {Identifier: NCT01272037}.

243. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-gene signature as an aid to treatment decisions in early-stage breast cancer. New England Journal of Medicine 2016;375:717-729. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa1602253.

244. 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.

245. Laenkholm AV, Jensen MB, Eriksen JO, et al. PAM50 Risk of Recurrence Score Predicts 10-Year Distant Recurrence in a Comprehensive Danish Cohort of Postmenopausal Women Allocated to 5 Years of Endocrine Therapy for Hormone Receptor-Positive Early Breast Cancer. J Clin Oncol 2018;36:735-740. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29369732.

246. Sestak I, Buus R, Cuzick J, et al. Comparison of the performance of 6 prognostic signatures for estrogen receptor–positive breast cancer: A secondary analysis of a randomized clinical trial. JAMA Oncology 2018;4:545-553. Available at: http://dx.doi.org/10.1001/jamaoncol.2017.5524.

247. Filipits M, Rudas M, Jakesz R, et al. A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors. Clin Cancer Res 2011;17:6012-6020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21807638.

248. Ma XJ, Wang Z, Ryan PD, et al. A two-gene expression ratio predicts clinical outcome in breast cancer patients treated with tamoxifen. Cancer Cell 2004;5:607-616. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15193263.

249. Sestak I, Buus R, Cuzick J, et al. Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor-Positive Breast Cancer: A

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Secondary Analysis of a Randomized Clinical Trial. JAMA Oncol 2018;4:545-553. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29450494.

250. Sgroi DC, Sestak I, Cuzick J, et al. Prediction of late distant recurrence in patients with oestrogen-receptor-positive breast cancer: a prospective comparison of the breast-cancer index (BCI) assay, 21-gene recurrence score, and IHC4 in the TransATAC study population. Lancet Oncol 2013;14:1067-1076. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24035531.

251. 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.

252. 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.

253. 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.

254. 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.

255. 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.

256. 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.

257. 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.

258. 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.

259. 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.

260. 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.

261. 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.

262. 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.

263. 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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

trial. Lancet 2009;374:2055-2063. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20004966.

264. 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: https://www.ncbi.nlm.nih.gov/pubmed/21802721.

265. 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.

266. 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.

267. 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.

268. 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.

269. 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.

270. 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.

271. 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.

272. 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.

273. 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.

274. 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.

275. 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.

276. Castiglione-Gertsch M, O'Neill A, Price KN, et al. Adjuvant chemotherapy followed by goserelin versus either modality alone for

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.

277. 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.

278. 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.

279. 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.

280. Pagani 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.

281. Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med 2015;372:436-446.

282. Bear HD, Tang G, Rastogi P, et al. Neoadjuvant plus adjuvant bevacizumab in early breast cancer (NSABP B-40 [NRG Oncology]): secondary outcomes of a phase 3, randomised controlled trial. Lancet Oncol 2015;16:1037-1048.

283. 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.

284. 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.

285. 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.

286. 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.

287. 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.

288. 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.

289. 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.

290. 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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Reprod 2006;21:545-553. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16210385.

291. 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.

292. 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.

293. 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.

294. Buzdar AU, Guastalla JP, Nabholtz 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.

295. 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.

296. 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.

297. 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.

298. 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.

299. 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.

300. 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.

301. 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.

302. 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.

303. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

304. Pan H, Gray R, Davies C, et al. Predictors of recurrence during years 5-14 in 46,138 women with ER+ breast cancer allocated 5 years only of endocrine therapy (ET) {Abstract}. J Clin Oncol 34, 2016 (suppl; abstract 505) 2016. Available at: http://meetinglibrary.asco.org/content/166053-176.

305. 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.

306. Jin H, Tu D, Zhao N, et al. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. J Clin Oncol 2012;30:718-721. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22042967.

307. 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.

308. 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.

309. 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.

310. 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.

311. Davies C, Pan H, Godwin J, et al. ATLAS - 10 v 5 years of adjuvant tamoxifen (TAM) in ER+ disease: Effects on outcome in the first and in the second decade after diagnosis. Cancer Research 2012;72:S1-2. Available at: http://cancerres.aacrjournals.org/cgi/content/meeting_abstract/72/24_MeetingAbstracts/S1-2.

312. 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.

313. 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.

314. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N Engl J Med 2016;375:209-219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27264120.

315. 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.

316. 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.

317. 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.

318. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

319. 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.

320. 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.

321. 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.

322. 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.

323. 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.

324. Gnant M, Mlineritsch B, Stoeger H, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. The Lancet. Oncology 2011;12:631-641. Available at: https://pubmed.ncbi.nlm.nih.gov/21641868.

325. Coleman RE, Marshall H, Cameron D, et al. Breast-cancer adjuvant therapy with zoledronic acid. N Engl J Med 2011;365:1396-1405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21995387.

326. Gregory W, Marshall H, Bell R, et al. Adjuvant zoledronic acid (ZOL) in postmenopausal women with breast cancer and those rendered postmenopausal: Results of a meta-analysis. ASCO Meeting Abstracts 2012;30:513. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/513.

327. Early Breast Cancer Trialists' Collaborative G, Coleman R, Powles T, et al. Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 2015;386:1353-1361. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26211824.

328. 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:

329. Gnant M, Pfeiler G, Dubsky PC, et al. The impact of adjuvant denosumab on disease-free survival: Results from 3,425 postmenopausal patients of the ABCSG-18 trial [Abstract} Cancer Res. 2016;76(4 Suppl):Abstract S2- 02 2015. Available at: http://www.abstracts2view.com/sabcs15/view.php?nu=SABCS15L_443.

330. Goss PE, Barrios CH, Chan A, et al. Denosumab versus placebo as adjuvant treatment for women with early-stage breast cancer at high risk of disease recurrence (D-CARE): A global, placebo-controlled, randomized, double-blind, phase 3 clinical trial [Abstract]. Cancer Res. 2013;73(24 Suppl):Abstract OT2-6-02 2013. Available at: http://cancerres.aacrjournals.org/content/73/24_Supplement/OT2-6-02.

331. 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.

332. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

333. 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.

334. Citron ML, Berry DA, Cirrincione 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.

335. 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:

336. 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.

337. 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.

338. 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.

339. 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.

340. 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.

341. 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.

342. 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.

343. 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.

344. 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.

345. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

346. 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.

347. 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.

348. 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.

349. 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.

350. 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.

351. 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.

352. 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.

353. 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.

354. 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.

355. 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.

356. 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.

357. 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.

358. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

359. 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.

360. Muss HB, Berry DA, Cirrincione 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.

361. 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.

362. 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.

363. 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.

364. 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.

365. 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.

366. 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.

367. 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.

368. 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.

369. 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.

370. 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.

371. 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.

372. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.

373. 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.

374. 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.

375. 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.

376. 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.

377. 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.

378. 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.

379. 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.

380. 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.

381. 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:

382. 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.

383. 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 ; Abstract S 1-04 (Oral Presentation. 2013. Available at:

384. 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.

385. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

386. 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.

387. 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.

388. 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.

389. 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.

390. 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.

391. 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: https://www.ncbi.nlm.nih.gov/pubmed/25564897.

392. 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.

393. Fuster D, Duch J, Paredes P, et al. Preoperative staging of large primary breast cancer with [^{18}F]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.

394. Groheux D, Moretti JL, Baillet G, et al. Effect of (^{18})F-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.

395. van der Hoeven JJM, Krak NC, Hoekstra OS, et al. ^{18}F-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.

396. 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.

397. 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.

398. 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.

399. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

400. 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.

401. https://www.astro.org/Clinical-Practice/Choosing-Wisely/2014-Choosing-Wisely.aspx Aa. Available at:

402. 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.

403. 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.

404. 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.

405. 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.

406. 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.

407. 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.

408. 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.

409. 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.

410. 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.

411. 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.

412. 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.

413. 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.

414. 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.

415. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

416. 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.

417. 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.

418. 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.

419. 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.

420. 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.

421. 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.

422. 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.

423. 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.

424. 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.

425. 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.

426. 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:

427. 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.

428. 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.

429. 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.

430. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

431. 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.

432. 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.

433. Pusztai 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.

434. 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.

435. 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.

436. 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.

437. 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.

438. 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.

439. 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.

440. 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.

441. 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.

442. 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.

443. 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.

444. 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.

445. 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-

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.

446. 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.

447. Poodt IGM, Vugts G, Schipper RJ, Nieuwenhuijzen GAP. Repeat sentinel lymph node biopsy for ipsilateral breast tumor recurrence: A systematic review of the results and impact on prognosis. Ann Surg Oncol 2018;25:1329-1339. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29468606.

448. 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.

449. 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.

450. 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.

451. 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.

452. 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.

453. 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.

454. 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.

455. 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.

456. Badwe R, Hawaldar R, Nair N, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. Lancet Oncol 2015;16:1380-1388. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26363985.

457. King TA, Lyman JP, Gonen M, et al. Prognostic Impact of 21-Gene Recurrence Score in Patients With Stage IV Breast Cancer: TBCRC 013. J Clin Oncol 2016;34:2359-2365. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27001590.

458. King TA, Lyman J, Gonen M, et al. A prospective analysis of surgery and survival in stage IV breast cancer (TBCRC 013). Journal of Clinical Oncology 2016;34:1006-1006. Available at: https://doi.org/10.1200/JCO.2016.34.15_suppl.1006.

459. Soran A, Ozmen V, Ozbas S, et al. Randomized Trial Comparing Resection of Primary Tumor with No Surgery in Stage IV Breast Cancer at Presentation: Protocol MF07-01. Ann Surg Oncol 2018;25:3141-3149. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29777404.

460. 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.

461. Woo S-B, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

2006;144:753-761. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16702591.

462. 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.

463. 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.

464. 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.

465. 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.

466. 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.

467. 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.

468. 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.

469. 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.

470. Amadori D, Aglietta M, Alessi B, et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial. Lancet Oncol 2013;14:663-670. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23684411.

471. Himelstein AL, Foster JC, Khatcheressian JL, et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases: A Randomized Clinical Trial. JAMA 2017;317:48-58. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28030702.

472. Hortobagyi GN, Van Poznak C, Harker WG, et al. Continued Treatment Effect of Zoledronic Acid Dosing Every 12 vs 4 Weeks in Women With Breast Cancer Metastatic to Bone: The OPTIMIZE-2 Randomized Clinical Trial. JAMA Oncol 2017;3:906-912. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28125763.

473. 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.

474. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

475. 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.

476. Finn RS, Martin M, Rugo HS, et al. Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 2016;375:1925-1936. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27959613.

477. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol 2018;29:1541-1547. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29718092.

478. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. J Clin Oncol 2017;35:3638-3646. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28968163.

479. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol 2018;19:904-915. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29804902.

480. Im SA, Lu YS, Bardia A, et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. N Engl J Med 2019;381:307-316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31166679.

481. 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.

482. 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.

483. 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.

484. Di Leo A, Jerusalem G, Petruzelka 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.

485. Di Leo A, Jerusalem G, Petruzelka 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.

486. Robertson JFR, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. Lancet 2016;388:2997-3005. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27908454.

487. Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol 2018:Jco2018789909.

488. Slamon DJ, Neven P, Chia S, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. N Engl J Med 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31826360.

489. 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

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

2012;30:1919-1925. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22370325.

490. 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.

491. 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.

492. Mehta RS, Barlow WE, Albain KS, et al. Overall Survival with Fulvestrant plus Anastrozole in Metastatic Breast Cancer. N Engl J Med 2019;380:1226-1234. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30917258.

493. 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.

494. 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.

495. Campos SM, Guastalla JP, Subar M, et al. A comparative study of exemestane versus anastrozole in patients with postmenopausal breast cancer with visceral metastases. Clin Breast Cancer 2009;9:39-44. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19299239.

496. Sunderland MC, Osborne CK. Tamoxifen in premenopausal patients with metastatic breast cancer: a review. J Clin Oncol 1991;9:1283-1297.

497. Bonneterre 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.

498. Nabholtz 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.

499. 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.

500. Vergote I, Bonneterre 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.

501. Mauri D, Pavlidis N, Polyzos NP, Ioannidis JP. Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. J Natl Cancer Inst 2006;98:1285-1291. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16985247.

502. 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:

503. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Oncol 2016;17:425-439. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26947331.

504. Sledge GW, Jr., Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. J Clin Oncol 2017;35:2875-2884. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28580882.

505. Sledge GW, Jr., Toi M, Neven P, et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. JAMA Oncol 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31563959.

506. 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.

507. 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

508. 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.

509. 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.

510. Andre F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med 2019;380:1929-1940. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31091374.

511. 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.

512. 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:

513. 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.

514. 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.

515. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

516. Dixon JM, Renshaw L, Langridge C, et al. Anastrozole and letrozole: an investigation and comparison of quality of life and tolerability. Breast Cancer Res Treat 2011;125:741-749. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20821047.

517. Rose C, Vtoraya O, Pluzanska A, et al. An open randomised trial of second-line endocrine therapy in advanced breast cancer. comparison of the aromatase inhibitors letrozole and anastrozole. Eur J Cancer 2003;39:2318-2327. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14556923.

518. Thurlimann B, Robertson JF, Nabholtz JM, et al. Efficacy of tamoxifen following anastrozole ('Arimidex') compared with anastrozole following tamoxifen as first-line treatment for advanced breast cancer in postmenopausal women. Eur J Cancer 2003;39:2310-2317. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14556922.

519. Abrams J, Aisner J, Cirrincione C, et al. Dose-response trial of megestrol acetate in advanced breast cancer: cancer and leukemia group B phase III study 8741. J Clin Oncol 1999;17:64-73. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10458219.

520. Willemse PH, van der Ploeg E, Sleijfer DT, et al. A randomized comparison of megestrol acetate (MA) and medroxyprogesterone acetate (MPA) in patients with advanced breast cancer. Eur J Cancer 1990;26:337-343. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2141491.

521. 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.

522. Ellis MJ, Gao F, Dehdashti F, et al. Lower-dose vs high-dose oral estradiol therapy of hormone receptor-positive, aromatase inhibitor-resistant advanced breast cancer: a phase 2 randomized study. JAMA 2009;302:774-780. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19690310.

523. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR(+)/HER2(-) Metastatic Breast Cancer. Clin Cancer Res 2017;23:5218-5224. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28533223.

524. 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.

525. 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.

526. 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.

527. Bachelot T, Ciruelos E, Schneeweiss A, et al. Preliminary safety and efficacy of first-line pertuzumab combined with trastuzumab and taxane therapy for HER2-positive locally recurrent or metastatic breast cancer (PERUSE). Ann Oncol 2019;30:766-773. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30796821.

528. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

529. Paclitaxel, trastuzumab, and pertuzumab in the treatment of metastatic HER2-positive breast cancer (Clinical Trial ID: NCT01276041). Available at: http://clinicaltrials.gov/show/NCT01276041. .

530. 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.

531. 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.

532. 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.

533. 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.

534. 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.

535. Seidman A, Berry DA, Cirrincione 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.

536. 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.

537. 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.

538. 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.

539. 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.

540. 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.

541. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

542. 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.

543. 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.

544. 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.

545. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31825192.

546. 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.

547. 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.

548. 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.

549. 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.

550. Freedman RA, Gelman RS, Anders CK, et al. TBCRC 022: A phase II trial of neratinib and capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. J Clin Oncol 2019;37:1081-1089. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30860945.

551. Saura C, Oliveira M, Feng Y-H, et al. Neratinib + capecitabine versus lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: Findings from the multinational, randomized, phase III NALA trial. Journal of Clinical Oncology 2019;37:1002-1002. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.1002.

552. 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: https://www.ncbi.nlm.nih.gov/pubmed/19786670.

553. Huober J, Fasching PA, Barsoum M, et al. Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer - results of the eLEcTRA trial. Breast 2012;21:27-33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21862331.

554. 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.

555. Rimawi M, Ferrero JM, de la Haba-Rodriguez J, et al. First-Line trastuzumab plus an aromatase inhibitor, with or without pertuzumab, in human epidermal growth factor receptor 2-positive and hormone receptor-

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

positive metastatic or locally advanced breast cancer (PERTAIN): A randomized, open-label phase II trial. J Clin Oncol 2018;36:2826-2835. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30106636.

556. Gradishar WJ, Hegg R, Im S-A, et al. Phase III study of lapatinib (L) plus trastuzumab (T) and aromatase inhibitor (AI) vs T+AI vs L+AI in postmenopausal women (PMW) with HER2+, HR+ metastatic breast cancer (MBC): ALTERNATIVE. Journal of Clinical Oncology 2017;35:1004-1004. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.1004.

557. Malone KE, Daling JR, Doody DR, et al. Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years. Cancer Res 2006;66:8297-8308. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16912212.

558. Kurian AW, Gong GD, John EM, et al. Performance of prediction models for BRCA mutation carriage in three racial/ethnic groups: findings from the Northern California Breast Cancer Family Registry. Cancer Epidemiol Biomarkers Prev 2009;18:1084-1091. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19336551.

559. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med 2017;0:null. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28578601.

560. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol 2019;30:558-566. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30689707.

561. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med 2018;379:753-763. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30110579.

562. Tutt A, Tovey H, Cheang MCU, et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. Nat Med 2018;24:628-637. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29713086.

563. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med 2018;379:2108-2121. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30345906.

564. Emens LA, Cruz C, Eder JP, et al. Long-term Clinical Outcomes and Biomarker Analyses of Atezolizumab Therapy for Patients With Metastatic Triple-Negative Breast Cancer: A Phase 1 Study. JAMA Oncol 2019;5:74-82. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30242306.

565. Schmid P, Adams S, Rugo HS, et al. IMpassion130: updated overall survival (OS) from a global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab (atezo) + nab-paclitaxel (nP) in previously untreated locally advanced or metastatic triple-negative breast cancer (mTNBC). Journal of Clinical Oncology 2019;37:1003-1003. Available at: https://doi.org/10.1200/JCO.2019.37.15_suppl.1003.

566. 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.

567. 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.

568. 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: https://www.ncbi.nlm.nih.gov/pubmed/12065558.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

569. 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.

570. 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: https://www.ncbi.nlm.nih.gov/pubmed/21464403.

571. Giarratano T, Frezzini S, Zanocco M, et al. Use of scalp cooling device to prevent alopecia for early breast cancer patients receiving chemotherapy: A prospective study. Breast J 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31837103.

572. Kruse M, Abraham J. Management of Chemotherapy-Induced Alopecia With Scalp Cooling. J Oncol Pract 2018;14:149-154. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29529389.

573. Nangia J, Wang T, Osborne C, et al. Effect of a Scalp Cooling Device on Alopecia in Women Undergoing Chemotherapy for Breast Cancer: The SCALP Randomized Clinical Trial. JAMA 2017;317:596-605. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28196254.

574. Rugo HS, Klein P, Melin SA, et al. Association Between Use of a Scalp Cooling Device and Alopecia After Chemotherapy for Breast Cancer. Jama 2017;317:606-614.

575. Rugo HS, Melin SA, Voigt J. Scalp cooling with adjuvant/neoadjuvant chemotherapy for breast cancer and the risk of scalp metastases: systematic review and meta-analysis. Breast Cancer Res Treat 2017;163:199-205. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28275922.

576. Stockler MR, Wilcken NJC, Coates AS. Chemotherapy for Advanced Breast Cancer – How Long Should it Continue? Breast Cancer Research and Treatment 2003;81:49-52. Available at: https://doi.org/10.1023/A:1026316806601.

577. Claessens AKM, Bos M, Lopez-Yurda M, et al. Intermittent versus continuous first-line treatment for HER2-negative metastatic breast cancer: the Stop & Go study of the Dutch Breast Cancer Research Group (BOOG). Breast Cancer Res Treat 2018;172:413-423. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30121808.

578. Perez 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11709565.

579. Seidman AD, Berry D, Cirrincione 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: https://www.ncbi.nlm.nih.gov/pubmed/18375893.

580. Mauri D, Kamposioras K, Tsali L, et al. Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: A meta-analysis. Cancer Treat Rev 2010;36:69-74. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19945225.

581. Chan 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561296.

582. Gasparini 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1987737.

583. Norris B, Pritchard KI, James K, et al. Phase III comparative study of vinorelbine combined with doxorubicin versus doxorubicin alone in disseminated metastatic/recurrent breast cancer: National Cancer Institute of Canada Clinical Trials Group Study MA8. J Clin Oncol 2000;18:2385-2394.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

584. Andersson M, Daugaard S, von der Maase H, Mouridsen HT. Doxorubicin versus mitomycin versus doxorubicin plus mitomycin in advanced breast cancer: a randomized study. Cancer Treat Rep 1986;70:1181-1186.

585. O'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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14998846.

586. Fumoleau P, Largillier R, Clippe C, et al. Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer 2004;40:536-542. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14962720.

587. Oshaughnessy JA, Blum J, Moiseyenko V, et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. Ann Oncol 2001;12:1247-1254. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11697835.

588. 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.

589. 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.

590. Vernieri C, Prisciandaro M, Milano M, et al. Single-Agent Gemcitabine vs. Carboplatin-Gemcitabine in Advanced Breast Cancer: A Retrospective Comparison of Efficacy and Safety Profiles. Clin Breast Cancer 2019;19:e306-e318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30635175.

591. Jones S, Winer E, Vogel C, et al. Randomized comparison of vinorelbine and melphalan in anthracycline-refractory advanced breast cancer. J Clin Oncol 1995;13:2567-2574. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7595708.

592. Fumoleau P, Delgado FM, Delozier T, et al. Phase II trial of weekly intravenous vinorelbine in first-line advanced breast cancer chemotherapy. J Clin Oncol 1993;11:1245-1252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8315421.

593. Martin M, Ruiz A, Munoz M, et al. Gemcitabine plus vinorelbine versus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. Lancet Oncol 2007;8:219-225. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17329192.

594. Jones SE, Erban J, Overmoyer B, et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 2005;23:5542-5551. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16110015.

595. Ibrahim NK, Samuels B, Page R, et al. Multicenter phase II trial of ABI-007, an albumin-bound paclitaxel, in women with metastatic breast cancer. J Clin Oncol 2005;23:6019-6026. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16135470.

596. Gradishar 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16172456.

597. Gradishar WJ, Krasnojon D, Cheporov S, et al. Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

first-line therapy for metastatic breast cancer. J Clin Oncol 2009;27:3611-3619. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19470941.

598. Bastholt 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8648369.

599. Roche H, Yelle L, Cognetti 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.

600. Thomas E, Tabernero 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.

601. 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.

602. Nabholtz 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;21:968-975. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12637459.

603. Biganzoli L, Cufer T, Bruning P, et al. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial. J Clin Oncol 2002;20:3114-3121. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12118025.

604. Langley RE, Carmichael 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 National Cancer Research Institute trial AB01. J Clin Oncol 2005;23:8322-8330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16293863.

605. Albain KS, Nag SM, 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;26:3950-3957. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18711184.

606. Stockler MR, Harvey VJ, Francis PA, et al. Capecitabine versus classical cyclophosphamide, methotrexate, and fluorouracil as first-line chemotherapy for advanced breast cancer. J Clin Oncol 2011;29:4498-4504. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22025143.

607. O'Shaughnessy J, Schwartzberg L, Danso MA, et al. Phase III study of iniparib plus gemcitabine and carboplatin versus gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer. J Clin Oncol 2014;32:3840-3847. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25349301.

608. Yardley DA, Brufsky A, Coleman RE, et al. Phase II/III weekly nab-paclitaxel plus gemcitabine or carboplatin versus gemcitabine/carboplatin as first-line treatment of patients with metastatic triple-negative breast cancer (the tnAcity study): study protocol for a randomized controlled trial. Trials 2015;16:575. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26673577.

609. Nelli F, Moscetti L, Natoli G, et al. Gemcitabine and carboplatin for pretreated metastatic breast cancer: the predictive value of immunohistochemically defined subtypes. Int J Clin Oncol 2013;18:343-349. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22350024.

610. Yardley DA, Coleman R, Conte P, et al. nab-Paclitaxel plus carboplatin or gemcitabine versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative metastatic breast cancer: results from the tnAcity trial. Ann Oncol 2018;29:1763-1770. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29878040.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

611. Perez EA, Hillman DW, Stella PJ, et al. A phase II study of paclitaxel plus carboplatin as first-line chemotherapy for women with metastatic breast carcinoma. Cancer 2000;88:124-131. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10618614.

612. Fountzilas G, Kalofonos HP, Dafni U, et al. Paclitaxel and epirubicin versus paclitaxel and carboplatin as first-line chemotherapy in patients with advanced breast cancer: a phase III study conducted by the Hellenic Cooperative Oncology Group. Ann Oncol 2004;15:1517-1526. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15367413.

613. 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.

614. 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.

615. 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.

616. Mavroudis 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 2010;21:48-54. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19906761.

617. 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.

618. Rugo HS, Barry WT, Moreno-Aspitia A, et al. Randomized Phase III Trial of Paclitaxel Once Per Week Compared With Nanoparticle Albumin-Bound Nab-Paclitaxel Once Per Week or Ixabepilone With Bevacizumab As First-Line Chemotherapy for Locally Recurrent or Metastatic Breast Cancer: CALGB 40502/NCCTG N063H (Alliance). J Clin Oncol 2015;33:2361-2369. Available at:

619. 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.

620. Stransky N, Cerami E, Schalm S, et al. The landscape of kinase fusions in cancer. Nat Commun 2014;5:4846.

621. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med 2018;378:731-739. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29466156.

622. Meric-Bernstam F, Shukla N, Peled N, et al. Abstract P6-20-02: Activity of larotrectinib, a highly selective inhibitor of tropomyosin receptor kinase, in TRK fusion breast cancers. Cancer Research 2019;79:P6-20-02.

623. Drilon A. TRK inhibitors in TRK fusion-positive cancers. Ann Oncol 2019;30:viii23-viii30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31738426.

624. Demetri GD, Paz-Ares L, Farago AF, et al. Efficacy and safety of entrectinib in patients with NTRK fusion-positive tumours: Pooled analysis of STARTRK-2, STARTRK-1, and ALKA-372-001. Annals of Oncology 2018;29. Available at: https://doi.org/10.1093/annonc/mdy483.003.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

625. Adams S, Loi S, Toppmeyer D, et al. Pembrolizumab monotherapy for previously untreated, PD-L1-positive, metastatic triple-negative breast cancer: cohort B of the phase II KEYNOTE-086 study. Ann Oncol 2019;30:405-411. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30475947.

626. Phan K, Charif M. Pembrolizumab for PD-L1-Positive Breast Cancer Refractory to Chemotherapy. Am J Ther 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31219807.

627. Nanda R, Chow LQ, Dees EC, et al. Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study. J Clin Oncol 2016;34:2460-2467. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27138582.

628. Alva AS, Mangat PK, Garrett-Mayer E, et al. Pembrolizumab (P) in patients (pts) with metastatic breast cancer (MBC) with high tumor mutational burden (HTMB): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) Study. Journal of Clinical Oncology 2019;37:1014-1014. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.1014.

629. 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.

630. 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.

631. 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.

632. 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.

633. 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.

634. 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.

635. 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.

636. 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.

637. 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.

638. 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.

639. 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.

640. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

641. 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.

642. 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.

643. 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.

644. 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.

645. 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.

646. 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.

647. 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.

648. 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.

649. 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.

650. 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.

651. 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.

652. 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.

653. 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.

654. 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.

655. 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.

656. 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.

657. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

658. 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.

659. Mondi 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.

660. 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.

661. 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.

662. 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.

663. 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.

664. 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.

665. 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.

666. 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.

667. 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.

668. 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.

669. 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.

670. 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.

671. 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.

672. 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.

673. 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.

674. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

675. 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.

676. 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.

677. 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.

678. 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.

679. 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.

680. 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.

681. 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.

682. 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

683. 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.

684. 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.

685. 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.

686. 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.

687. 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.

688. Edge SB, Byrd DR, Compton CC, et al., eds. AJCC Cancer Staging Manual, 7th Edition. New York: Springer; 2010.

689. Haagensen CD. Inflammatory Carcinoma. Diseases of the Breast. Philadelphia: WB Saunders; 1956:488-498.

690. 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.

691. 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.

692. Dawood S, Ueno NT, Valero V, et al. Differences in survival among women with stage III inflammatory and noninflammatory locally advanced

Discussion Update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

breast cancer appear early: a large population-based study. Cancer 2011;117:1819-1826. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21509759.

693. 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.

694. 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.

695. 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.

696. 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.

697. 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.

698. 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.

699. 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.

700. 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.

701. 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.

702. 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.

703. 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.

704. 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.

705. 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.

706. 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.

Discussion update in progress

Printed by Efrain Salas on 11/29/2021 10:17:16 PM. For personal use only. Not approved for distribution. Copyright © 2021 National Comprehensive Cancer Network, Inc., All Rights Reserved.

707. 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.

708. 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.

709. 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.

710. Boussen 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.

711. 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.

712. 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.

713. 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.

714. 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.

715. 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.

716. 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.

717. 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.

718. 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.

719. 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.

720. 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.

721. 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