



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Poland Edition

Breast Cancer

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NCCN.org

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[NCCN Breast Cancer Panel Members](#)

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[NCCN Guidelines: Poland Edition Definitions \(DEF-1\)](#)

[Principles of Breast Cancer Care \(POLAND-INTRO\)](#)

Recommendations for Lobular Carcinoma In Situ were removed from the NCCN Guidelines for Breast Cancer. [See NCCN Guidelines for Breast Cancer Screening and Diagnosis](#)

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

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[Definition of Menopause \(BINV-O\)](#)

[Systemic Therapy for ER- and/or PR-Positive Recurrent Unresectable \(Local or Regional\) or Stage IV \(M1\) Disease \(BINV-P\)](#)

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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](#).

[See International Adaptations Table of Contents for other NCCN Guidelines: Poland Edition.](#)

Most recent version of the NCCN Guidelines is available at www.NCCN.org.

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NCCN GUIDELINES: POLAND EDITION — DEFINITIONS

THE NCCN GUIDELINES: POLAND EDITION IS REPRESENTED AS FOLLOWS:
Black Text: Recommendations that are applicable for the specific country/region
<i>Italicized Blue Text:</i> <i>Regional modifications that are appropriate/feasible in the specific country/region</i>
Gray Text with Strikethrough: Recommendations that are not feasible or available in the specific country/region at this time

Note: Drugs and biologics included in the NCCN Guidelines® are approved by the United States Food and Drug Administration (FDA). Alternate agents based on the local regulations and availability may be substituted provided evidence supports their efficacy and safety. Generic drugs should be used only when studies have proven bioequivalence and the drugs have met the same standards for identity, strength, purity, and quality as the innovator drugs. The WHO Model Lists of Essential Medicines can be found here: <http://www.who.int/medicines/publications/essentialmedicines/en/>.



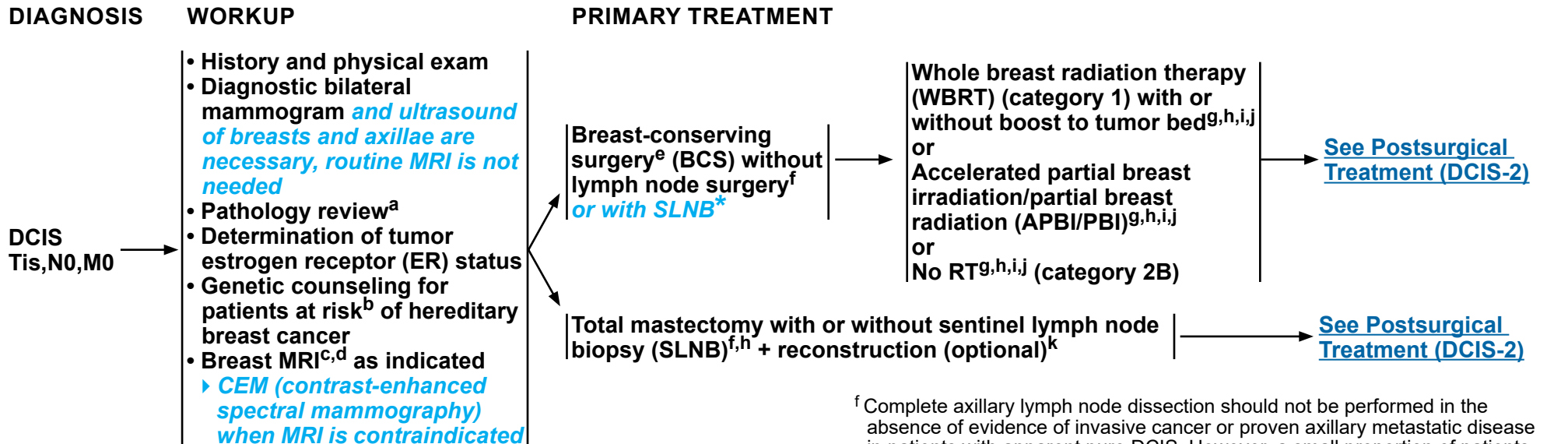
PRINCIPLES OF BREAST CANCER CARE

- *Patients should be referred to centers that provide the highest level of competence – BREAST CANCER UNIT.*
- *Standards of care are based on best reported achievable outcomes. Multidisciplinary care is always recommended.*
- *Delays in treatment reduce the effectiveness of treatment, so efforts should be made to expedite investigations and referrals to reduce the waiting time before treatment initiation.*

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*** Indications for SLNB in DCIS:**

- 1) Mastectomy with/without simultaneous reconstruction;
- 2) Clinically palpable tumor;
- 3) Suspicion of microinvasion within DCIS (in core needle biopsy);
- 4) DCIS with "risk factors": microcalcifications over 50 mm; DCIS in biopsy without microcalcifications in imaging studies; location of the tumor which may impair the performance of a possible SLNB in the case of identifying an invasive cancer.

^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/PBI 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 \(BINV-H\)](#).

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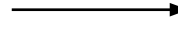
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**DCIS POSTSURGICAL TREATMENT****SURVEILLANCE/FOLLOW-UP****Risk reduction therapy for ipsilateral breast following BCS:**

- Consider endocrine therapy for 5 years for patients with ER-positive DCIS, if:
 - ▶ Treated with BCS and RT^m (category 1)
 - ▶ Treated with excision alone^l
- Endocrine therapy:ⁿ
 - ▶ Tamoxifen^{m,o} for premenopausal patients
 - ▶ Tamoxifen^{m,o} 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



- 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.

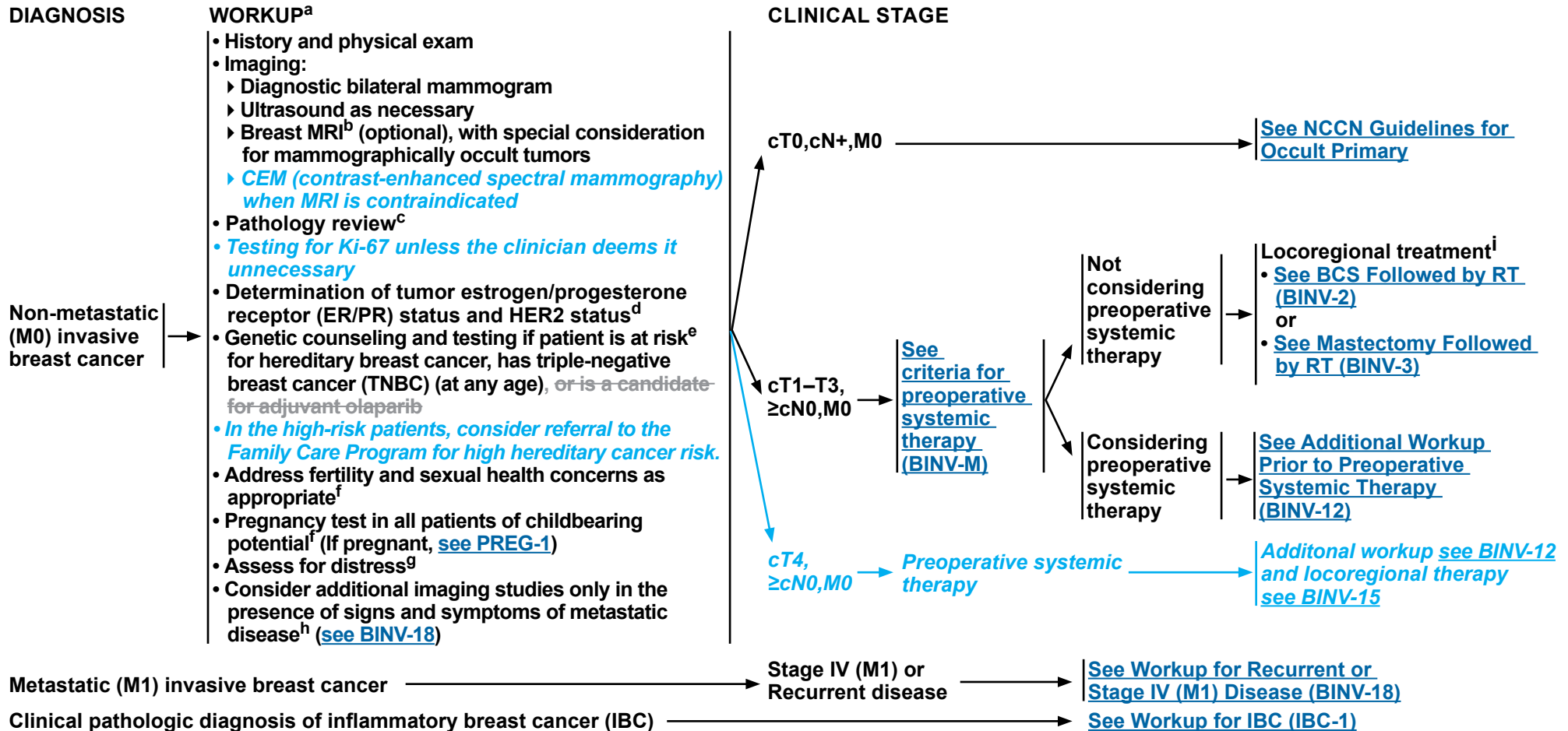
ⁿ The use of a bisphosphonate (PO/IV) or denosumab is acceptable to maintain or improve bone mineral density and reduce risk of fractures in postmenopausal (natural or induced) patients receiving adjuvant aromatase inhibitor therapy. Optimal duration of either therapy has not been established. Benefits from duration beyond 3 years or optimal 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.

^o 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.

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^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](#).

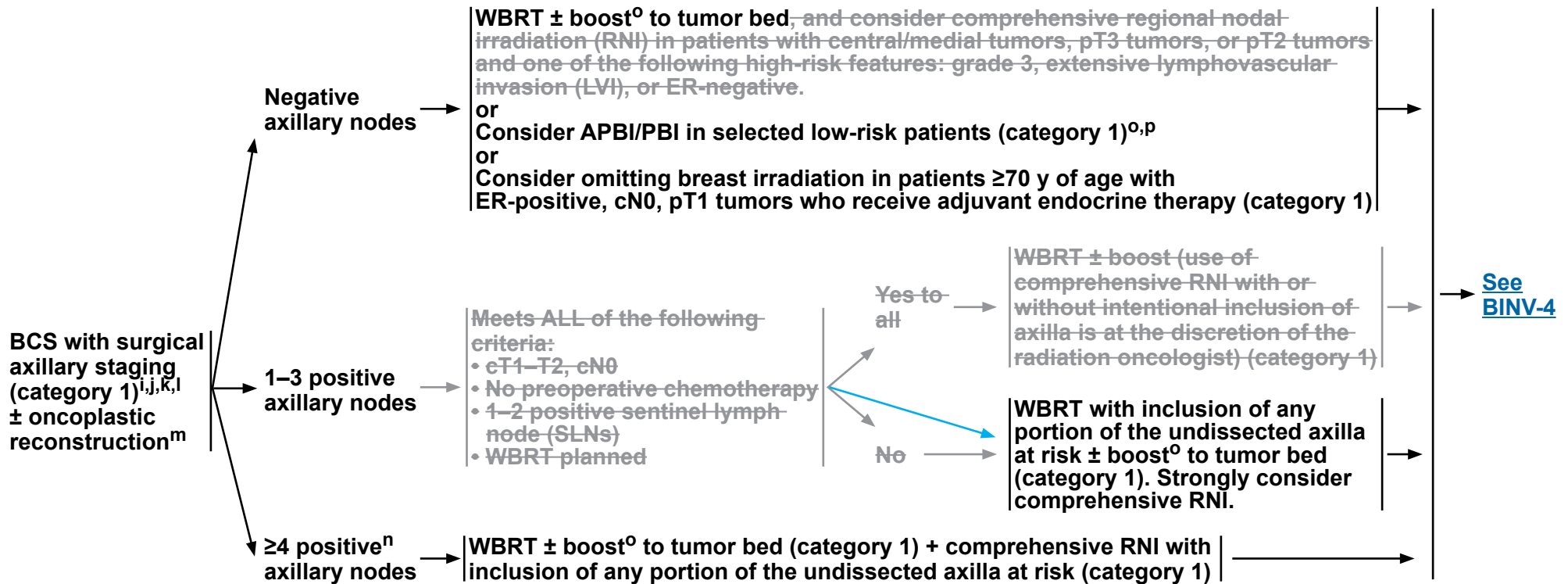
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**LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE:^a
BREAST-CONSERVING SURGERY (BCS) FOLLOWED BY RT**

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 Includes techniques such as local tissue rearrangement, local flaps, regional flaps, breast reduction and mastopexy to allow for greater volumes of resection while optimizing aesthetic outcomes in patients undergoing BCS

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

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

^p APBI/PBI may be administered prior to chemotherapy.

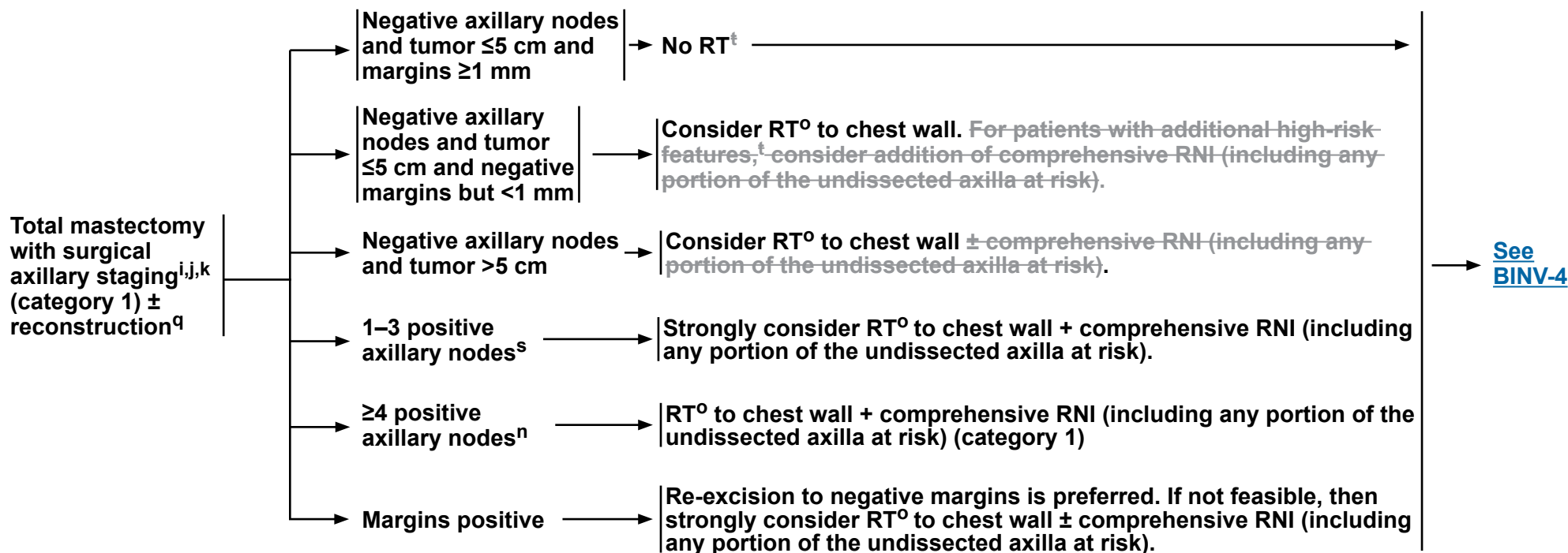
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**LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE:^{a,r}
 MASTECTOMY FOLLOWED BY RT**

RT AFTER COMPLETION OF MASTECTOMY 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 \(BINV-F\)](#).

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

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

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

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

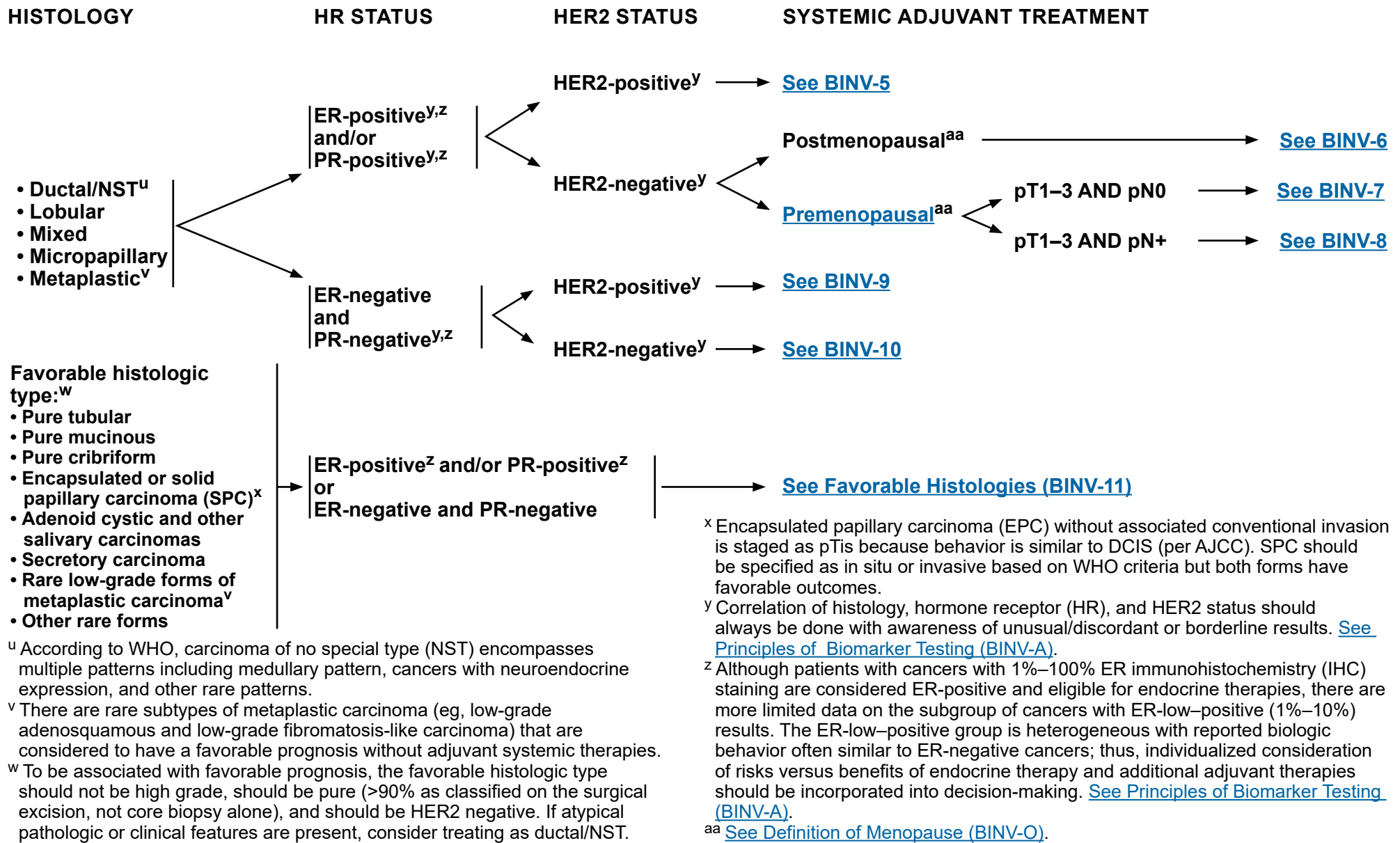
^s In the case of a micrometastasis (>0.2 to ≤2.0 mm), and no axillary dissection, evaluate other patient risk factors when considering RT.

^t Postmastectomy RT may be considered for patients with multiple high-risk recurrence factors, including central/medial tumors or tumors ≥2 cm and at least one of the following: grade 3, ER-negative, or LVI.

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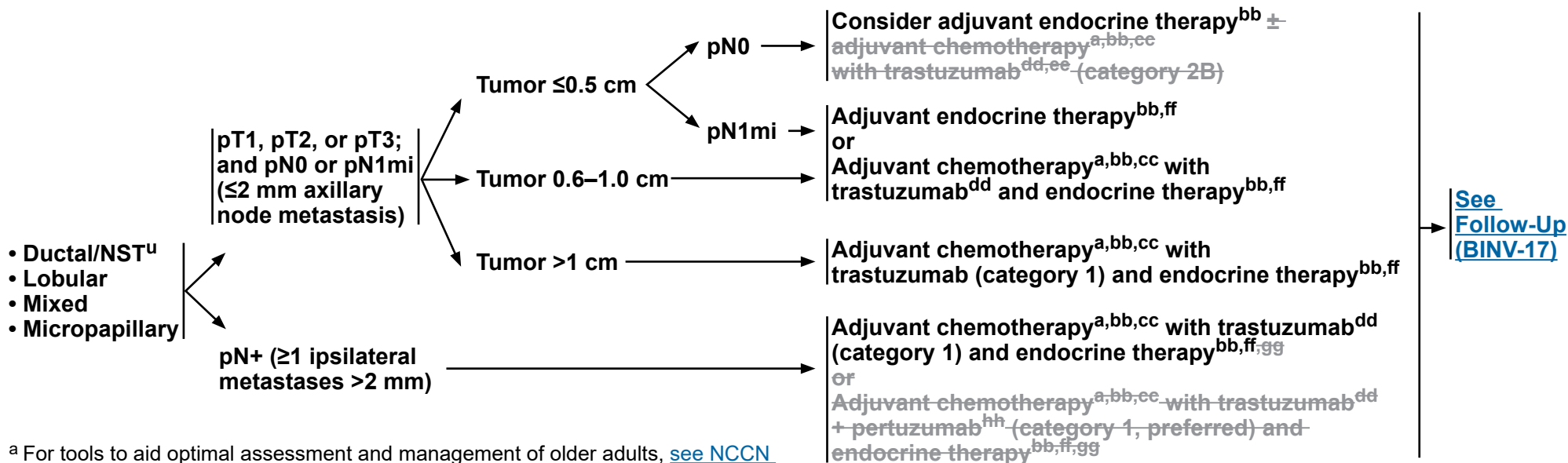
^u According to WHO, carcinoma of no special type (NST) encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.
^v There are rare subtypes of metaplastic carcinoma (eg, low-grade adenosquamous and low-grade fibromatosis-like carcinoma) that are considered to have a favorable prognosis without adjuvant systemic therapies.
^w 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.

^x Encapsulated papillary carcinoma (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.
^y Correlation of histology, hormone receptor (HR), and HER2 status should always be done with awareness of unusual/discordant or borderline results. [See Principles of Biomarker Testing \(BINV-A\)](#).
^z Although patients with cancers with 1%–100% ER immunohistochemistry (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 Definition of Menopause \(BINV-O\)](#).

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SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-POSITIVE DISEASE^{d,r,z}



^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 \(BINV-A\)](#).

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

^u According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.

^z 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 Adjuvant Endocrine Therapy \(BINV-K\)](#).

^{cc} [See Preoperative/Adjuvant Therapy Regimens \(BINV-L\)](#).

^{dd} 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.

^{ee} 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.

^{ff} 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} 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.

^{hh} Updated results from the adjuvant APHINITY trial in HER2-positive early breast cancer, with a median follow-up of 8.4 years, have confirmed the benefit of adding pertuzumab to trastuzumab plus chemotherapy in preventing recurrences.

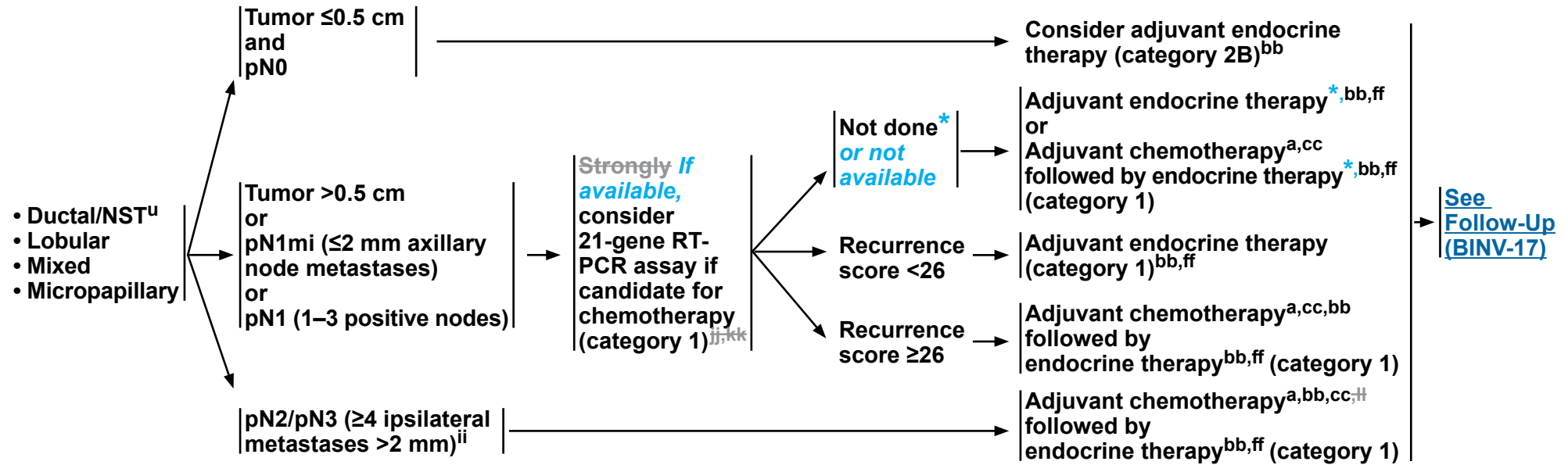
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SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-NEGATIVE DISEASE^{d,r,z} POSTMENOPAUSAL^{aa} PATIENTS with pT1–3 AND pN0 or pN+ TUMORS



* Recommendations reordered for NCCN Guidelines: Poland Edition.

^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 \(BINV-A\)](#).

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

^u According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.

^z 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 Definition of Menopause \(BINV-O\)](#).

^{bb} [See Adjuvant Endocrine Therapy \(BINV-K\)](#).

^{cc} [See Preoperative/Adjuvant Therapy Regimens \(BINV-L\)](#).

^{ff} 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.

ⁱⁱ 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.

^{jj} ~~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 \(BINV-N\)](#).~~

^{kk} ~~Patients with T1b tumors with low-grade histology and no LVI should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.~~

^{ff} ~~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](#).~~

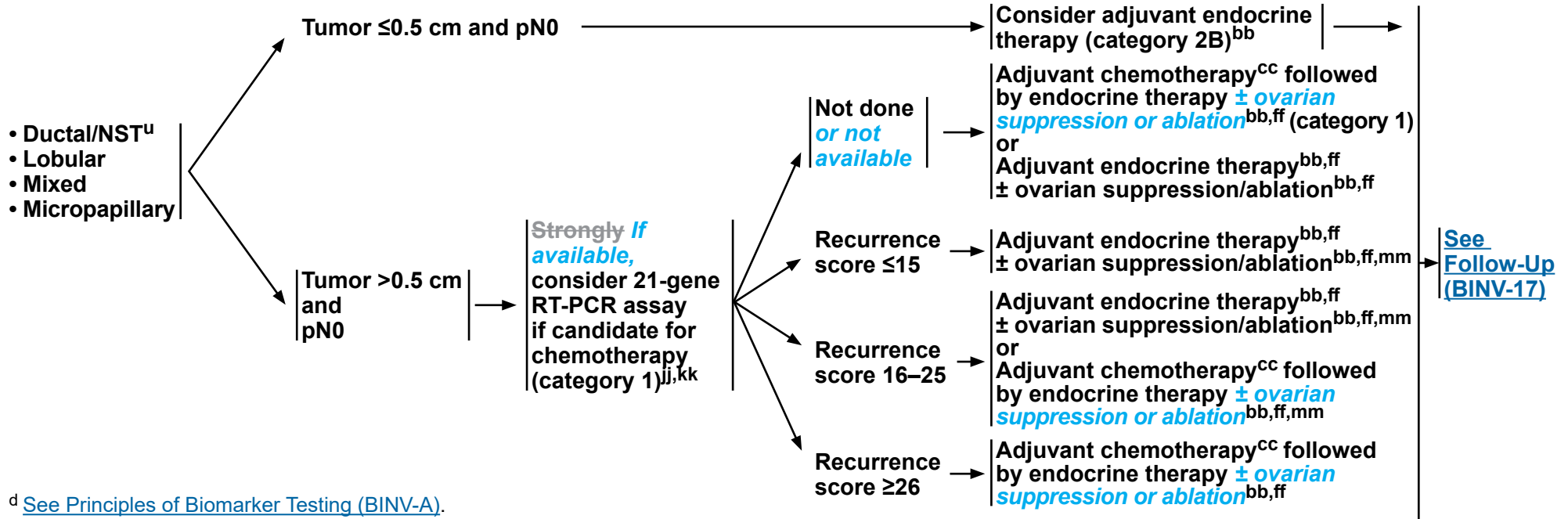
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SYSTEMIC ADJUVANT TREATMENT: HR-POSITIVE - HER2-NEGATIVE DISEASE^{d,r,z} PREMENOPAUSAL^{aa} PATIENTS with pT1–3 AND pN0 TUMORS



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

^q See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).

^u According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.

^z 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).

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^{ff} 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} 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).

^{kk} Patients with T1b tumors with low-grade histology and no LVI should be treated with endocrine monotherapy as the TAILORx trial did not include patients with such tumors.

^{mm} In premenopausal patients with recurrence score <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.

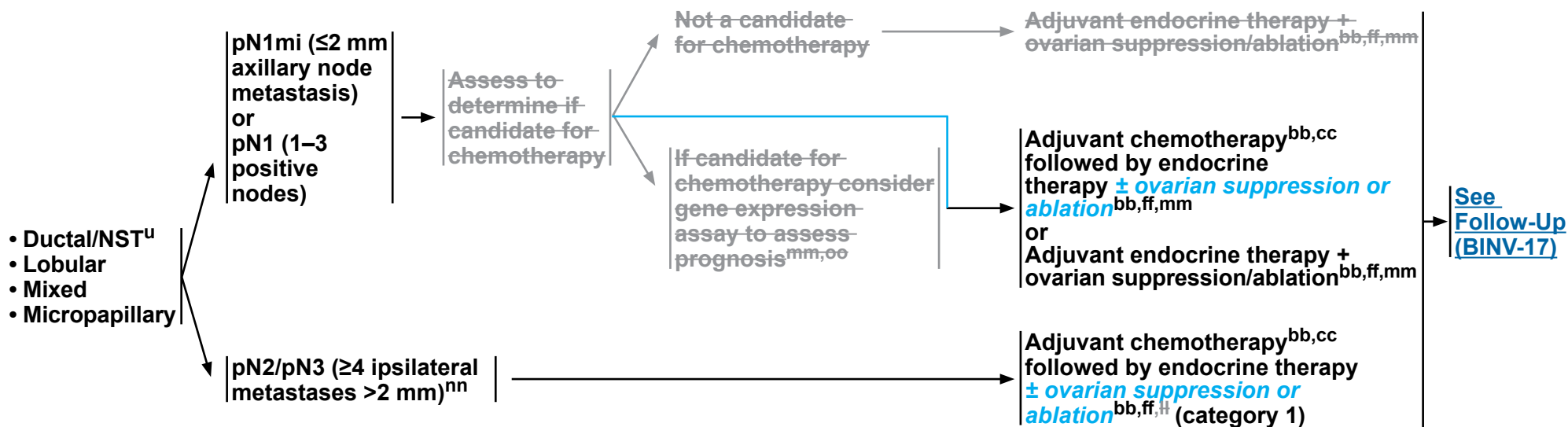
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^q See Special Considerations for Breast Cancer in Males (Sex Assigned at Birth) (BINV-J).

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^{ff} 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.

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ⁿⁿ 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.

^{oo} See Gene Expression Assays for Consideration of Adjuvant Systemic Therapy (BINV-N).

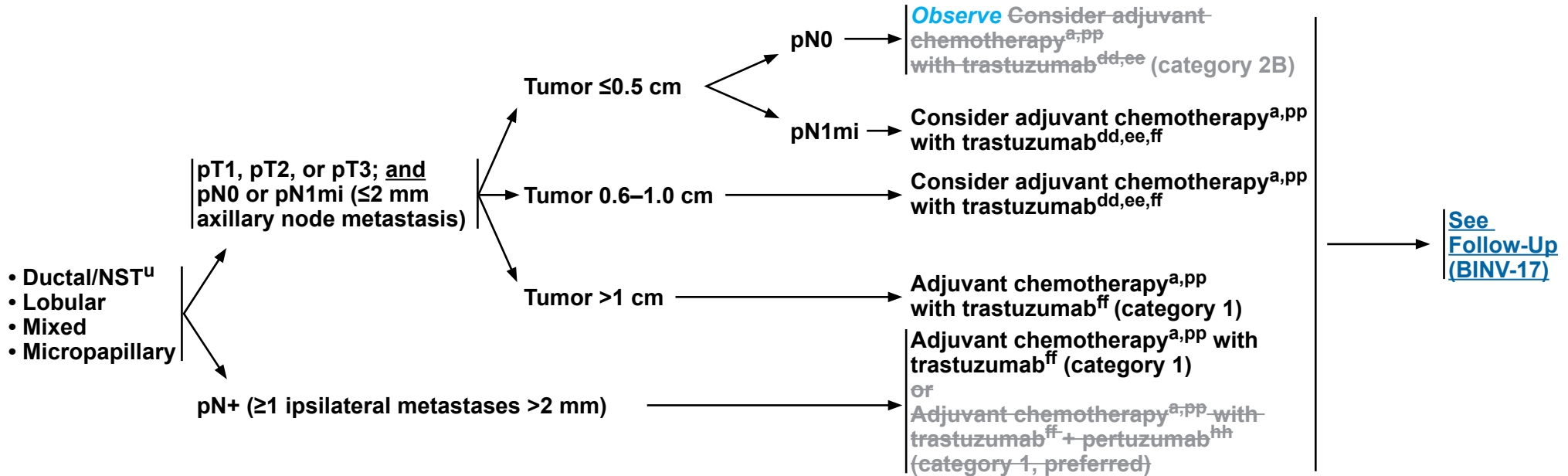
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SYSTEMIC ADJUVANT TREATMENT: HR-NEGATIVE - HER2-POSITIVE DISEASE^{d,r,z}



^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 \(BINV-A\)](#).

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

^u According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.

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^{dd} 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.

^{ee} 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.

^{ff} 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} Updated results from the adjuvant APHINITY trial in HER2-positive early breast cancer, with a median follow-up of 8.4 years, have confirmed the benefit of adding pertuzumab to trastuzumab plus chemotherapy in preventing recurrences. [Pertuzumab is unavailable in Poland](#).

^{pp} [See Preoperative/Adjuvant Therapy Regimens \(BINV-L\)](#).

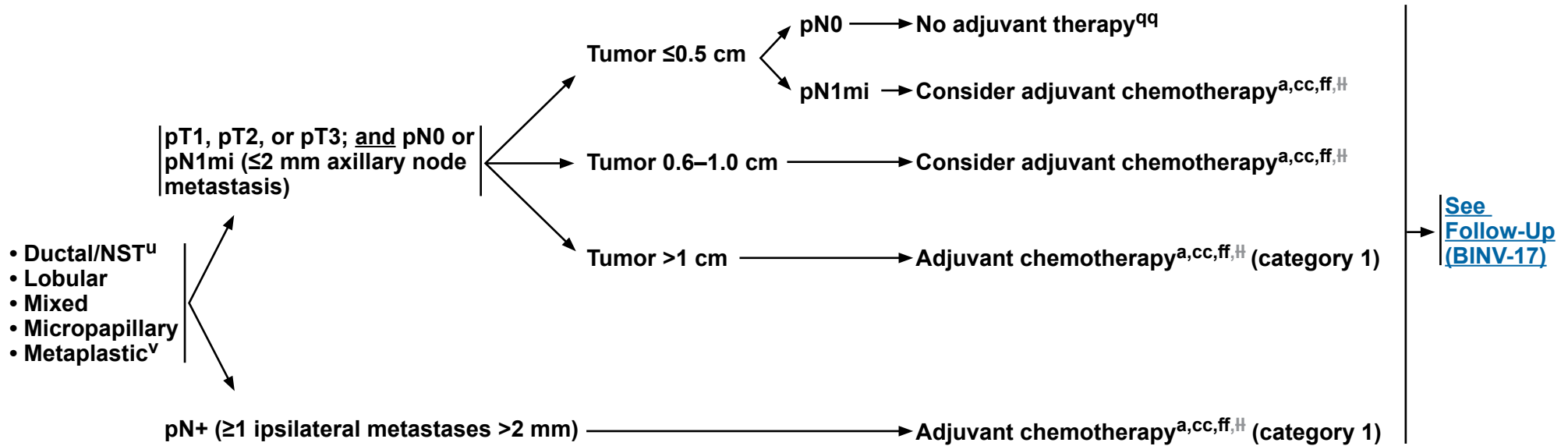
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^d [See Principles of Biomarker Testing \(BINV-A\)](#).

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

^u According to WHO, carcinoma of NST encompasses multiple patterns including medullary pattern, cancers with neuroendocrine expression, and other rare patterns.

^v 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.

^z 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} [See Preoperative/Adjuvant Therapy Regimens \(BINV-L\)](#).

^{ff} 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.

^h 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](#).

^{qq} In select patients with high-risk features (eg, young patients with high-grade histology), adjuvant chemotherapy may be considered (category 2B). [See BINV-L](#).

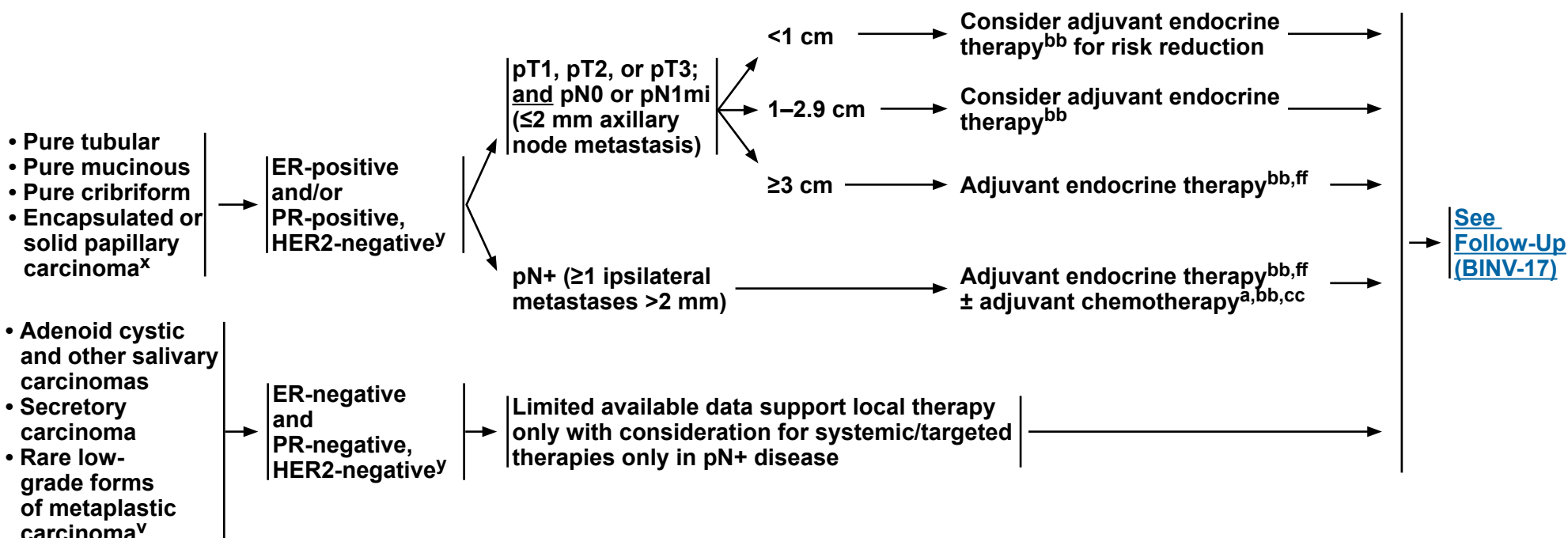
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SYSTEMIC ADJUVANT TREATMENT: FAVORABLE HISTOLOGIES^{r,w}



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

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

^v 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.

^w 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.

^x 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.

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

^{bb} [See Adjuvant Endocrine Therapy \(BINV-K\)](#).

^{cc} [See Preoperative/Adjuvant Therapy Regimens \(BINV-L\)](#).

^{ff} 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.

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WORKUP PRIOR TO PREOPERATIVE SYSTEMIC THERAPY

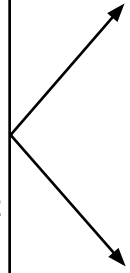
CLINICAL STAGE

ADDITIONAL WORKUP^a

c≥T2^{tt} or cN+ and M0
or
cT1c, cN0 HER2-positive
disease
or
cT1c, cN0 TNBC
(For preoperative
systemic therapy criteria,
see [BINV-M 1](#))^{rr}



- Axillary assessment with exam
 - ▶ **Consider TAD**
 - ▶ **Consider Ultrasound**
 - ▶ **Consider percutaneous biopsy of suspicious nodes^{ss}**
- CBC
- Comprehensive metabolic panel, including liver function tests and alkaline phosphatase
- Additional tests ~~to consider as~~ **if clinically indicated**
 - Chest diagnostic CT ± contrast
 - Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast
 - Bone scan ~~or sodium fluoride PET/CT~~ (category 2B)
 - FDG PET/CT (useful in certain circumstances)^{uu}
 - Breast MRI^b (optional), with special consideration for mammographically occult tumors, ~~if not previously done*~~
 - ▶ **CEM (if breast MRI is contraindicated or not available)**



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

For inoperable breast cancers: [See Preoperative Systemic Therapy \(BINV-15\)](#)

* *Basic indications for preoperative MRI include:*
 (1) Patients newly diagnosed with invasive lobular cancer (LoE-2a, DoR-B). Preoperative MRI changes therapy by 28% and significantly reduces the number of re-operations.
 (2) Patients under 60 years of age with discrepancy in size >1 cm between XRM and US with expected impact on treatment decision (LoE-2b, DoR-B).
 (3) Patients eligible for PBI based on CBE and conventional imaging (LoE-3b, DoR-B).

^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 \(BINV-B\)](#).
^{rr} [See Principles of Preoperative Systemic Therapy \(BINV-M\)](#).
^{ss} 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.

^{tt} 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).
^{uu} FDG PET/CT is most beneficial and accurate for advanced disease (stage III) and invasive ductal (compared to lobular) histology, but may be useful in selected circumstances of earlier stage disease (stage IIA disease: T1N1, T2N0) such as: equivocal CT+ bone scan results; suspicion of undetected nodal and/or distant disease; and treatment response assessment. An FDG-PET/CT may be utilized as an adjunct to, or in lieu of, initial standard staging and may be performed simultaneously with diagnostic CT. Conversely, a bone scan ~~or sodium fluoride PET/CT~~ may not be needed if an upfront FDG PET/CT clearly indicates consistent findings on both PET and CT components.

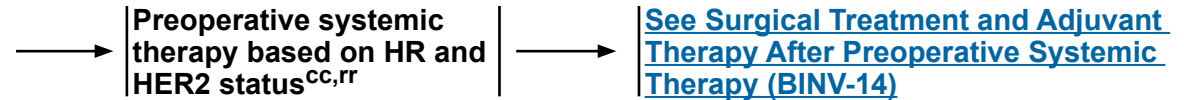
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OPERABLE DISEASE: BREAST AND AXILLARY EVALUATION PRIOR TO PREOPERATIVE SYSTEMIC THERAPY

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



^{cc} [See Preoperative/Adjuvant Therapy Regimens \(BINV-L\)](#).

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

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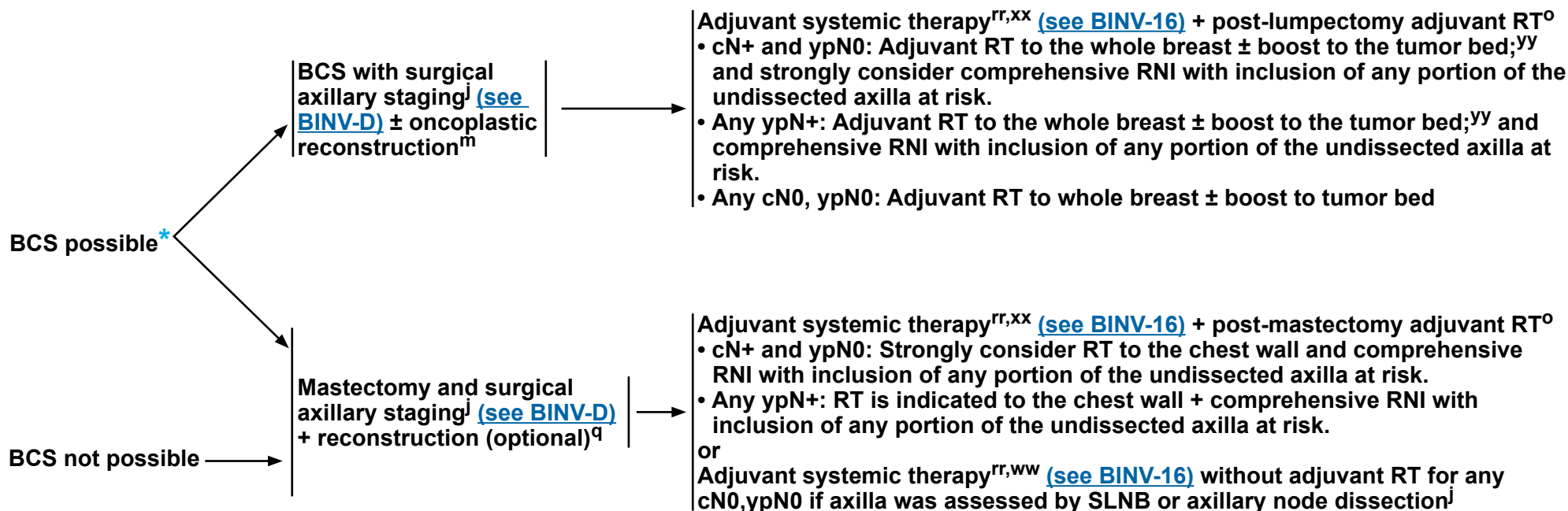
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OPERABLE DISEASE:*

SURGICAL TREATMENT AND ADJUVANT THERAPY AFTER PREOPERATIVE SYSTEMIC TREATMENT^{VV}

SURGICAL TREATMENT

ADJUVANT THERAPY



* The optimum timing of surgery post-completion of NACT is 4–8 weeks.

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

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

^m Includes techniques such as local tissue rearrangement, local flaps, regional flaps, breast reduction and mastopexy to allow for greater volumes of resection while optimizing aesthetic outcomes in patients undergoing BCS.

^o See Principles of Radiation Therapy (BINV-I).

^{rr} See Principles of Preoperative Systemic Therapy (BINV-M).

^{VV} 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. MRI is more accurate than mammography for assessing tumor response to adjuvant therapy. *MRI is not mandatory in patients undergoing preoperative systemic therapy.*

^{xx} Complete planned systemic therapy regimen course if not completed preoperatively.

^{yy} Strongly consider RT boost for high-risk features (eg, high-grade disease, age <50 years).

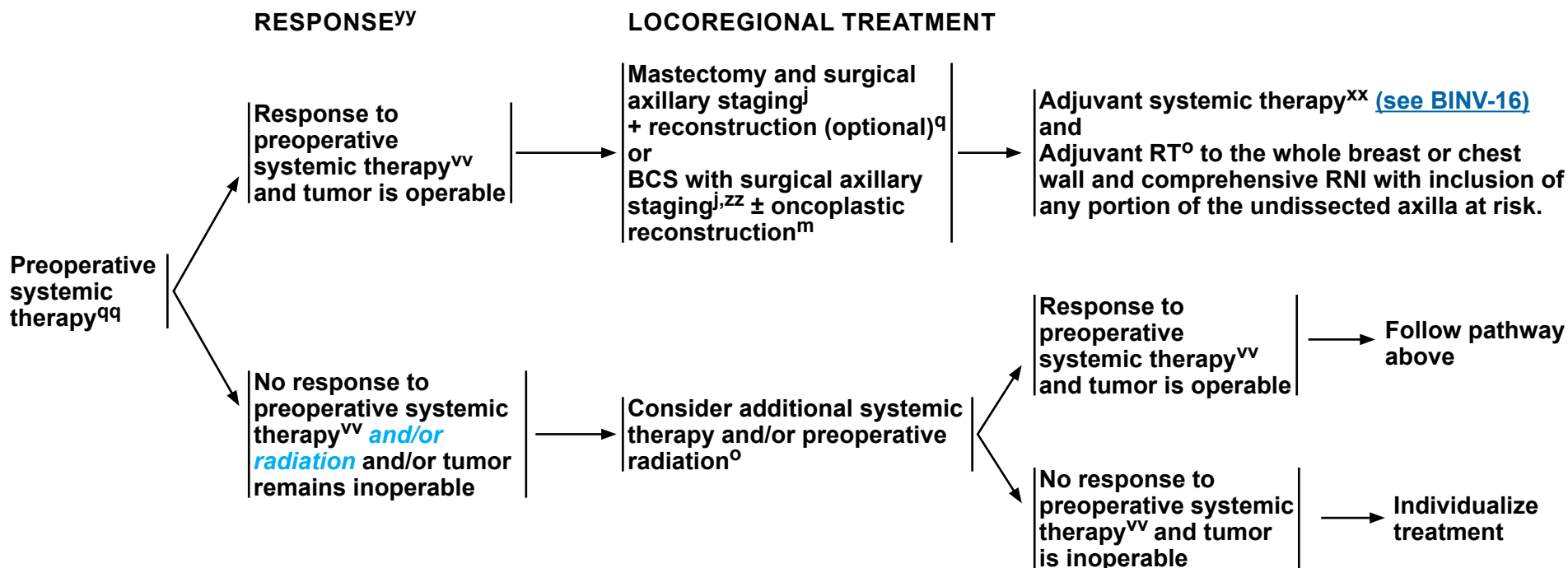
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INOPERABLE OR LOCALLY ADVANCED DISEASE (NON-INFLAMMATORY): PREOPERATIVE SYSTEMIC THERAPY AND SUBSEQUENT TREATMENT



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

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

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

^m Includes techniques such as local tissue rearrangement, local flaps, regional flaps, breast reduction and mastopexy to allow for greater volumes of resection while optimizing aesthetic outcomes in patients undergoing BCS.

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

^{vv} 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. MRI is more accurate than mammography for assessing tumor response to adjuvant therapy.

^{xx} Complete planned systemic therapy regimen course, if not completed preoperatively.

^{zz} 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.

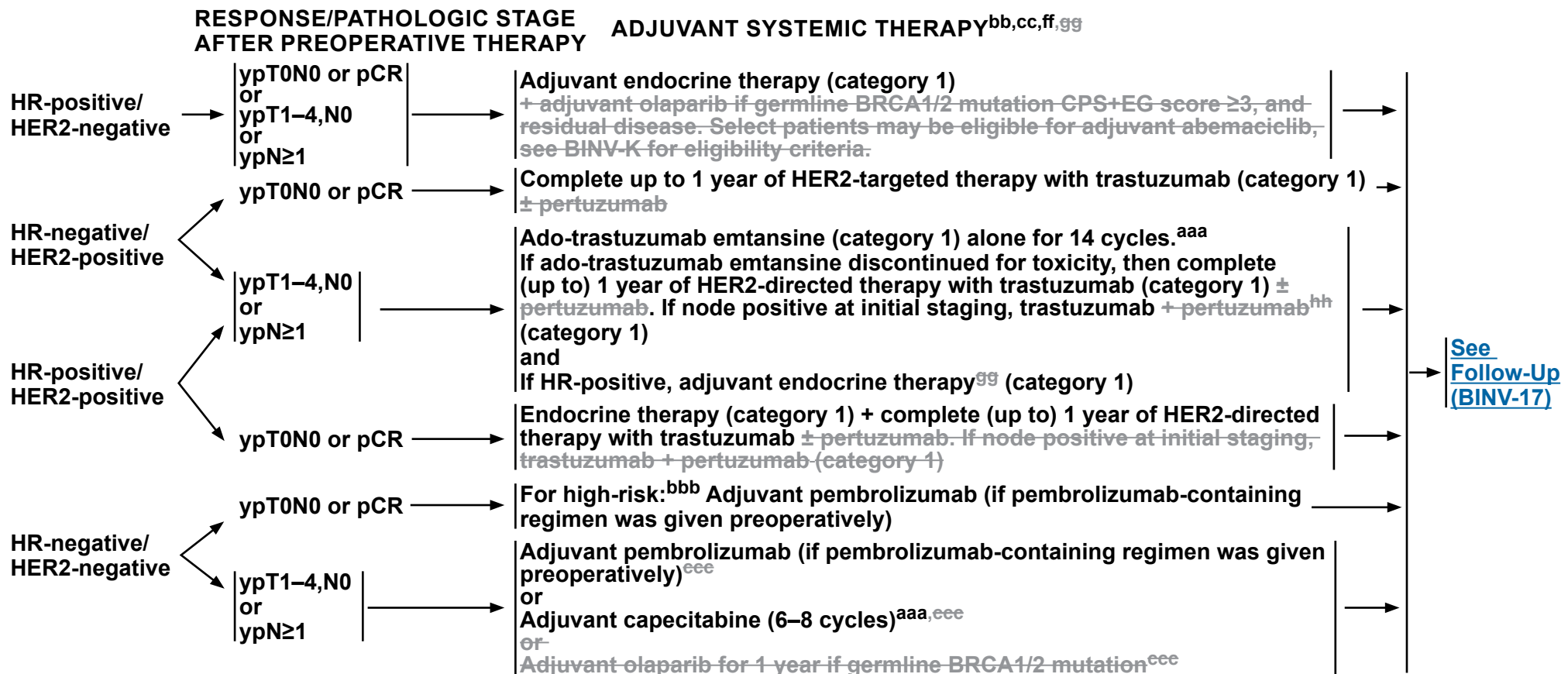
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ADJUVANT SYSTEMIC THERAPY AFTER PREOPERATIVE SYSTEMIC THERAPY^{ff}



^{bb} See Adjuvant Endocrine Therapy (BINV-K).

^{cc} See Preoperative/Adjuvant Therapy Regimens (BINV-L).

^{ff} 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} 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.

^{hh} Updated results from the adjuvant APHINITY trial in HER2-positive early breast cancer, with a median follow-up of 8.4 years, have confirmed the benefit of adding pertuzumab to trastuzumab plus chemotherapy in preventing recurrences.

^{aaa} Recommendations do not apply to residual DCIS (ypTis).

^{bbb} High-risk criteria include stage II–III TNBC. The use of adjuvant pembrolizumab (category 2A) may be individualized.

^{eee} There are no data on sequencing or combining adjuvant capecitabine, pembrolizumab and/or olaparib in patients who meet criteria for treatment with one or more of these agents. However, their sequential/combined use may be considered in certain patients with high-risk of recurrence.

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**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^{ddd}
- Routine imaging of reconstructed breast is not indicated
- For patients with germline mutations or family history of breast cancer, please refer to [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.

Post treatment monitoring:

- Cardiotoxicity monitoring for patients who received left-sided radiation therapy, anthracyclines, or HER2-targeted therapy. For anthracycline-induced toxicity, [See NCCN Guidelines for Survivorship](#)
- Provide guidance on risk of comorbidities

Endocrine therapy:

- *Patients administered aromatase inhibitors with treatment-induced menopause should have estrogen levels checked on a regular basis*
- 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^{eee}

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 should be provided access to rehabilitation and psychological support at all steps of treatment and follow-up*
- Patients frequently require follow-up encouragement in order to improve adherence to ongoing screening and medication adherence

[See Recurrent Disease \(BINV-18\)](#)

^{ddd} 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.

^{eee} The use of estrogen, progesterone, or selective ER 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. Benefits of duration beyond 3 years or optimal 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.

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RECURRENT/STAGE IV (M1) DISEASE CLINICAL WORKUP^a STAGE

Stage IV (M1)
or
Recurrent

- 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 (*preferred*) or brain CT if suspicious CNS symptoms
 - ▶ Spine MRI with contrast if back pain or symptoms of cord compression
 - ▶ Bone scan ~~or sodium-fluoride PET/CT~~ (category 2B)
 - ▶ Useful in certain circumstances:
 - ◊ FDG PET/CT (~~consider FES PET/CT for ER-positive disease~~)
 - ▶ 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,fff,999}
 - ▶ Comprehensive germline and somatic profiling to identify candidates for additional targeted therapies,ⁱⁱⁱ [see Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV \(M1\) Disease \(BINV-Q 6\)](#)
- 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^{hhh}

[See Systemic Treatment of Recurrent Unresectable \(local or regional\) or Stage IV \(M1\) \(BINV-20\)](#)ⁱⁱⁱ and Supportive care^{jjj}

^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](#).

^{fff} 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, *In case of discordant ER and/or PR determination between primary and metastatic tumor(s)*, 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 an HR-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).

⁹⁹⁹ 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.

^{hhh} [See NCCN Guidelines for Palliative Care](#) and [NCCN Guidelines for Supportive Care](#).

ⁱⁱⁱ Tissue or plasma-based circulating tumor DNA (ctDNA) assays may be used. Tissue-based assays have greater sensitivity, but ctDNA may reflect tumor heterogeneity more accurately.

^{jjj} For the treatment of brain metastases, see [NCCN Guidelines for Central Nervous System Cancers](#).

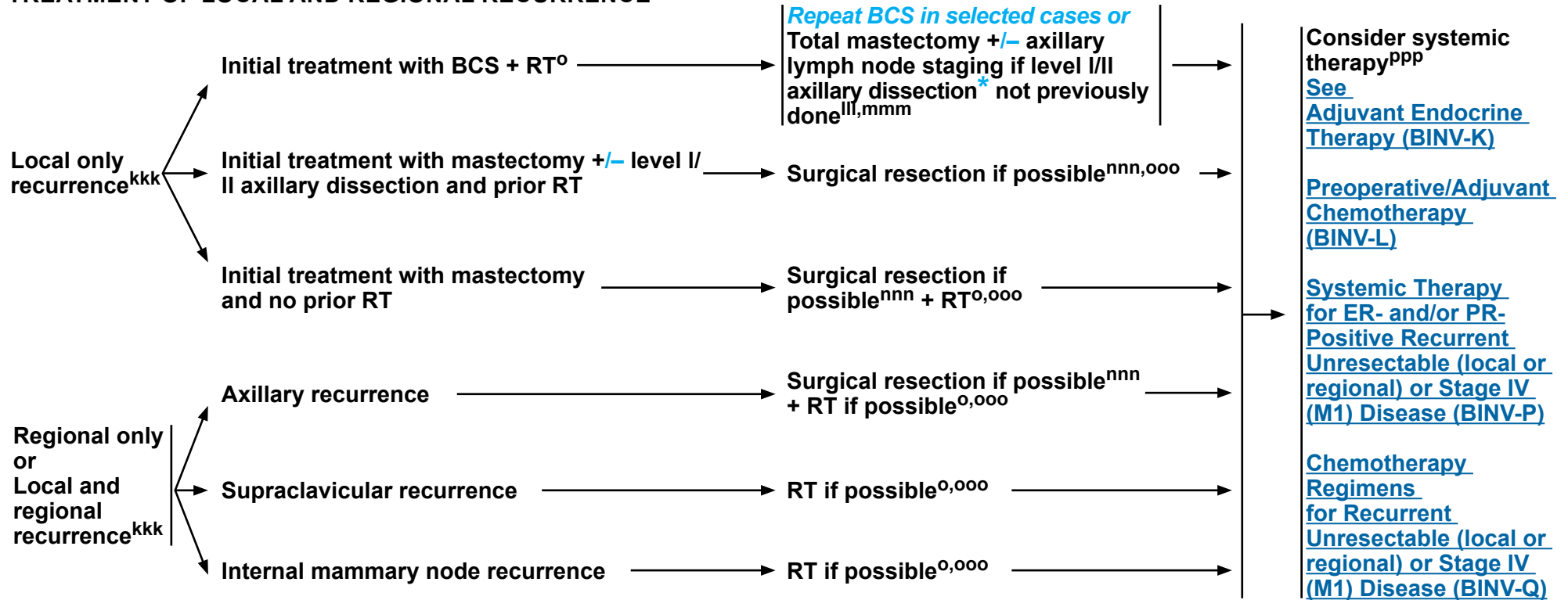
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TREATMENT OF LOCAL AND REGIONAL RECURRENCE



* In case of recurrence in the breast gland and rcN0:
 - after mastectomy, R0 resection is recommended;
 - after BCS+RT, simple R0 mastectomy (if possible) or R0 re-BCS with partial breast irradiation are recommended;
 - re-BCS without radiotherapy is allowed in selected situations.
 For rcN0:
 - after prior axillary dissection, axillary fossa intervention is not recommended;
 - after prior SLNB, re-SLNB is not recommended but is conditionally acceptable.
 For axillary rcN+:
 - re-axillary dissection R0 or other R0 salvage procedure in the axillary fossa is recommended (if possible).

^o See Principles of Radiation Therapy (BINV-I).

^{kkk} Multidisciplinary approach is especially important in the management of breast cancer recurrence to consider all potential treatment options for optimal outcomes.

^{lll} 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.

^{mmm} In selected patients who decline mastectomy and otherwise meet consensus criteria for radiotherapy omission or APBI/PBI, repeat BCS +/- adjuvant APBI/PBI may be considered. There are limited data for a repeat BCS in this setting.

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

^{ooo} 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.

^{ppp} See the [Discussion](#) for additional information.

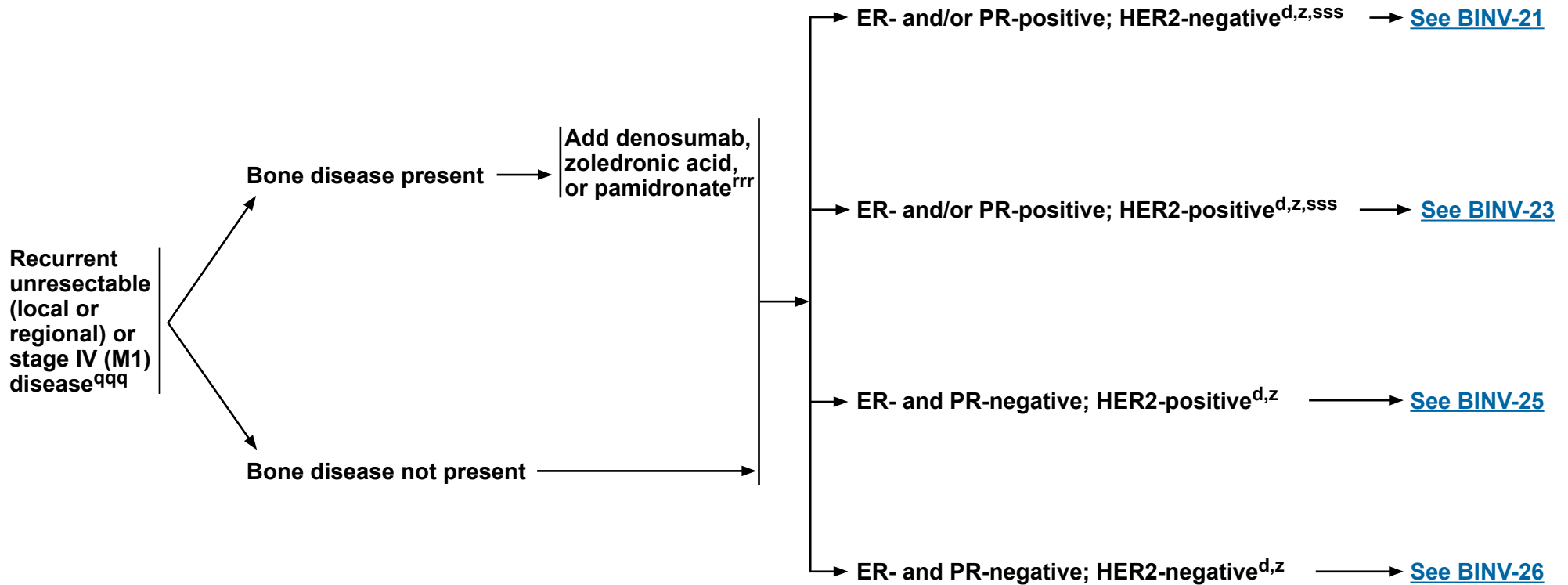
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SYSTEMIC TREATMENT OF RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE



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

^z 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).

^{qqq} 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.

^{rrr} Denosumab, zoledronic acid, or pamidronate (all with calcium and vitamin D supplementation) should be given (category 1) in addition to systemic therapy 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.

^{sss} 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).

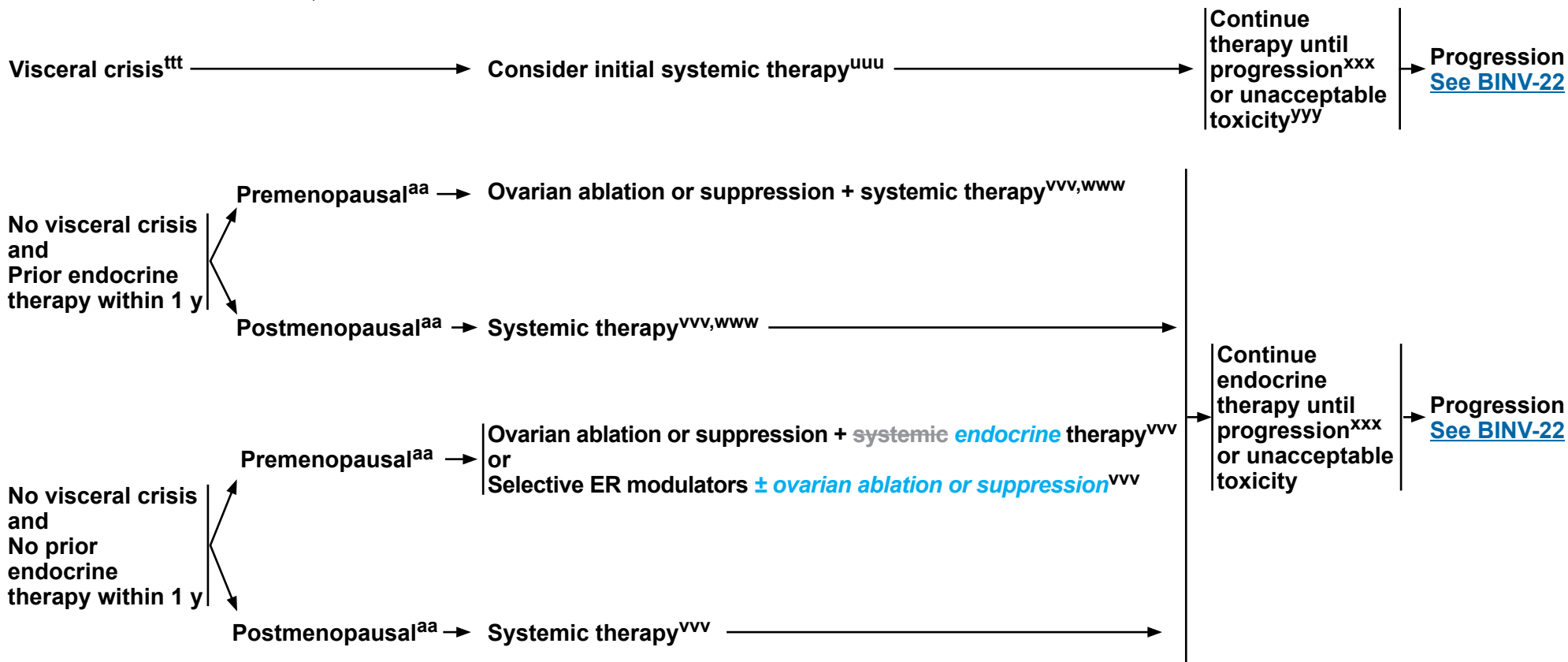
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SYSTEMIC TREATMENT OF RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE: ER- AND/OR PR-POSITIVE; HER2-NEGATIVE^d



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

^{aa} See Definition of Menopause (BINV-O).

^{ttt} According to the 5th ESO-ESMO international consensus guidelines (Cardoso F, et al. Ann Oncol 2020;31:1625) for advanced breast cancer visceral crisis is defined as: “severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy.”

^{uuu} See Systemic Therapy Regimens for Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease (BINV-Q).

^{vvv} See Systemic Therapy for ER- and/or PR-Positive Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease (BINV-P).

^{www} If progression on initial endocrine therapy, switch to a different endocrine therapy option.

^{xxx} See Principles of Monitoring Metastatic Disease (BINV-T).

^{yyy} It is acceptable to switch to endocrine-based therapy (see BINV-P) after disease stabilizes or response is observed

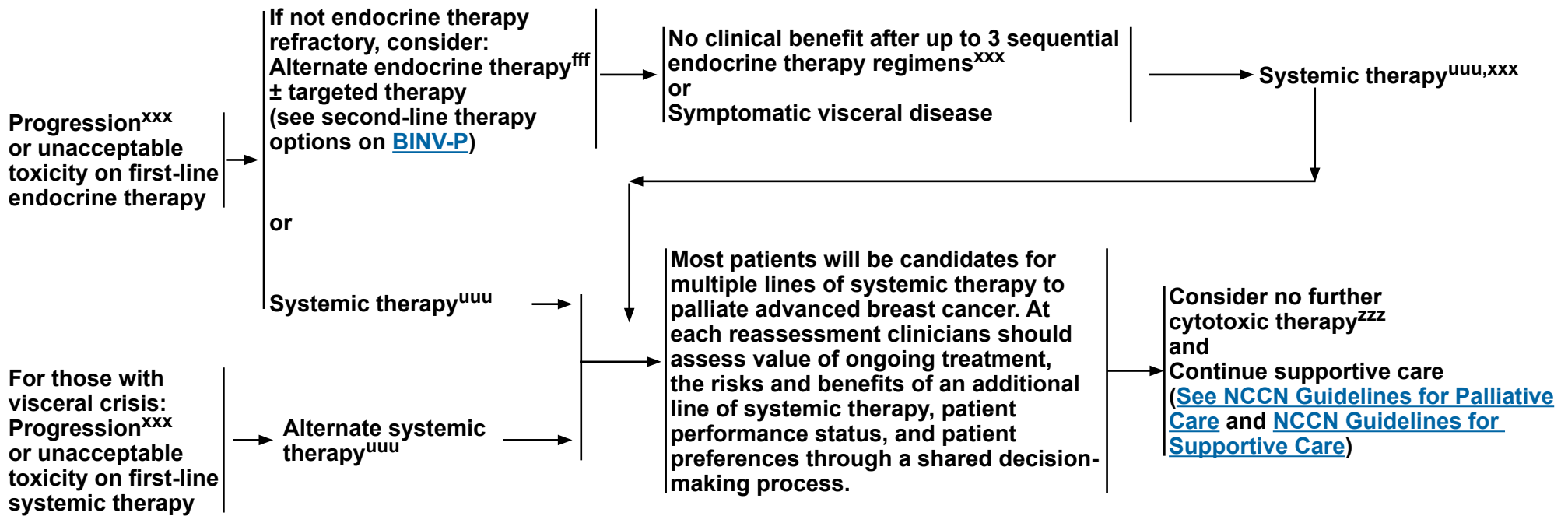
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^d See [Principles of Biomarker Testing \(BINV-A\)](#).

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

^{fff} 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).

^{uuu} See [Systemic Therapy Regimens for Recurrent Unresectable \(Local or Regional\) or Stage IV \(M1\) Disease \(BINV-Q\)](#).

^{vvv} See [Systemic Therapy for ER- and/or PR-Positive Recurrent Unresectable \(Local or Regional\) or Stage IV \(M1\) Disease \(BINV-P\)](#).

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

^{zzz} The potential side effects of additional line of therapy may outweigh any clinical benefit in a patient who has a compromised performance status. Patient preference must be taken into account.

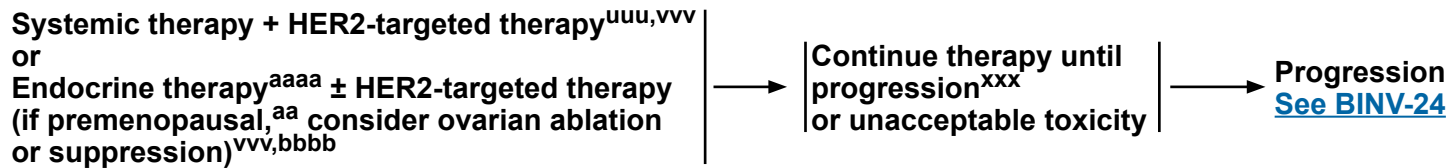
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^d See Principles of Biomarker Testing (BINV-A).

^{aa} See Definition of Menopause (BINV-O).

^{uuu} See Systemic Therapy Regimens for Recurrent Unresectable (local or regional) or Stage IV (M1) Disease (BINV-Q).

^{vvv} See Systemic Therapy for ER- and/or PR-Positive Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease (BINV-P).

^{xxx} See Principles of Monitoring Metastatic Disease (BINV-T).

^{aaaa} If prior endocrine therapy within 1 y, consider a different endocrine therapy.

^{bbbb} For premenopausal patients, tamoxifen alone (without ovarian ablation/suppression) + HER2-targeted therapy is also an option.

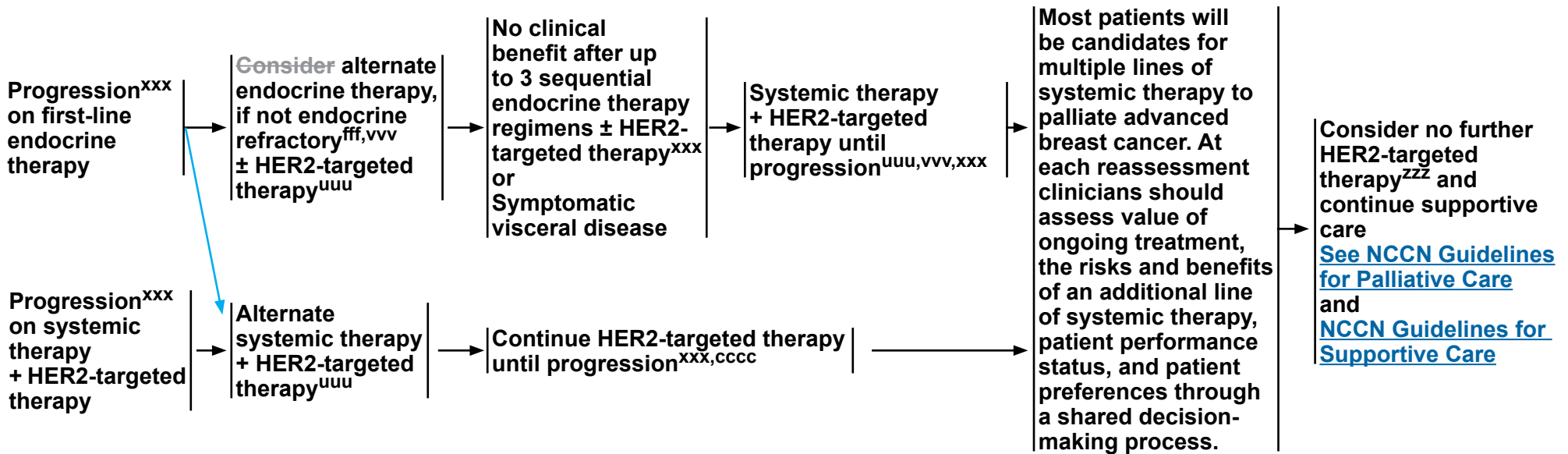
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^d See Principles of Biomarker Testing (BINV-A).

^{fff} 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).

^{uuu} See Systemic Therapy Regimens for Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease (BINV-Q).

^{vvv} See Systemic Therapy for ER- and/or PR-Positive Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease (BINV-P).

^{xxx} See Principles of Monitoring Metastatic Disease (BINV-T).

^{zzz} The potential side effects of additional line of therapy may outweigh any clinical benefit in a patient who has a compromised performance status. Patient preference must be taken into account.

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

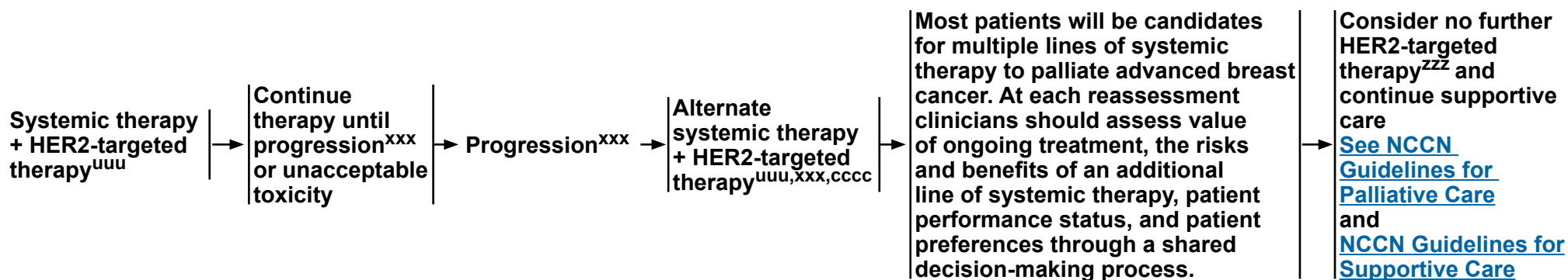
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SYSTEMIC TREATMENT OF RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE: ER- and/or PR-NEGATIVE; HER2-POSITIVE^d



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

^{uuu} See Systemic Therapy Regimens for Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease (BINV-Q).

^{xxx} See Principles of Monitoring Metastatic Disease (BINV-T).

^{zzz} The potential side effects of additional line of therapy may outweigh any clinical benefit in a patient who has a compromised performance status. Patient preference must be taken into account.

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

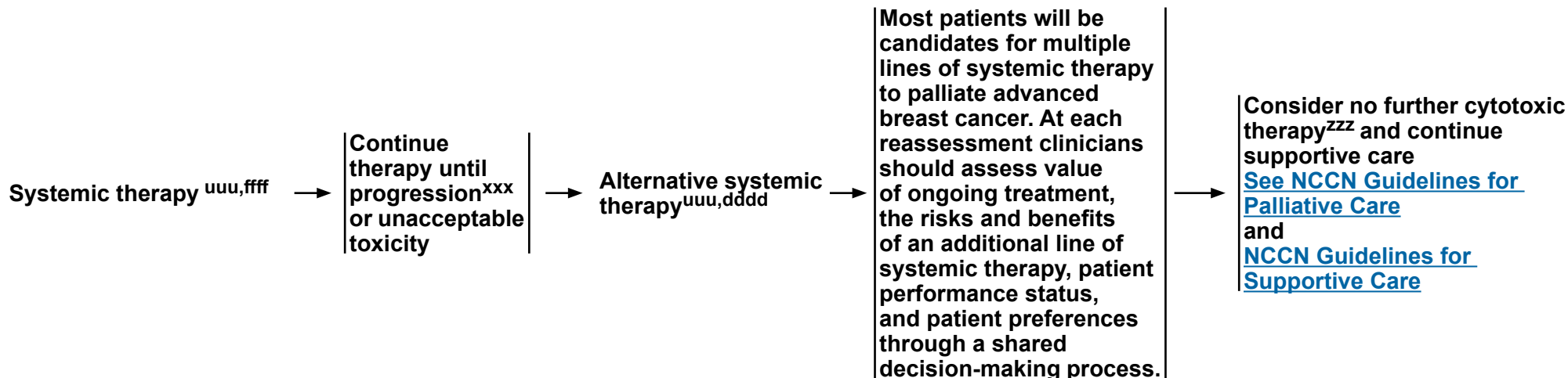
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^d See Principles of Biomarker Testing (BINV-A).

^{xx} See Systemic Therapy Regimens for Recurrent Unresectable (local or regional) or Stage IV (M1) Disease (BINV-Q).

^{xxx} See Principles of Monitoring Metastatic Disease (BINV-T).

^{zzz} The potential side effects of additional line of therapy may outweigh any clinical benefit in a patient who has a compromised performance status. Patient preference must be taken into account.

^{dddd} See Additional Targeted Therapies and Associated Biomarker Testing for Recurrent Unresectable (Local or Regional) or Stage IV (M1) Disease BINV-Q (6).

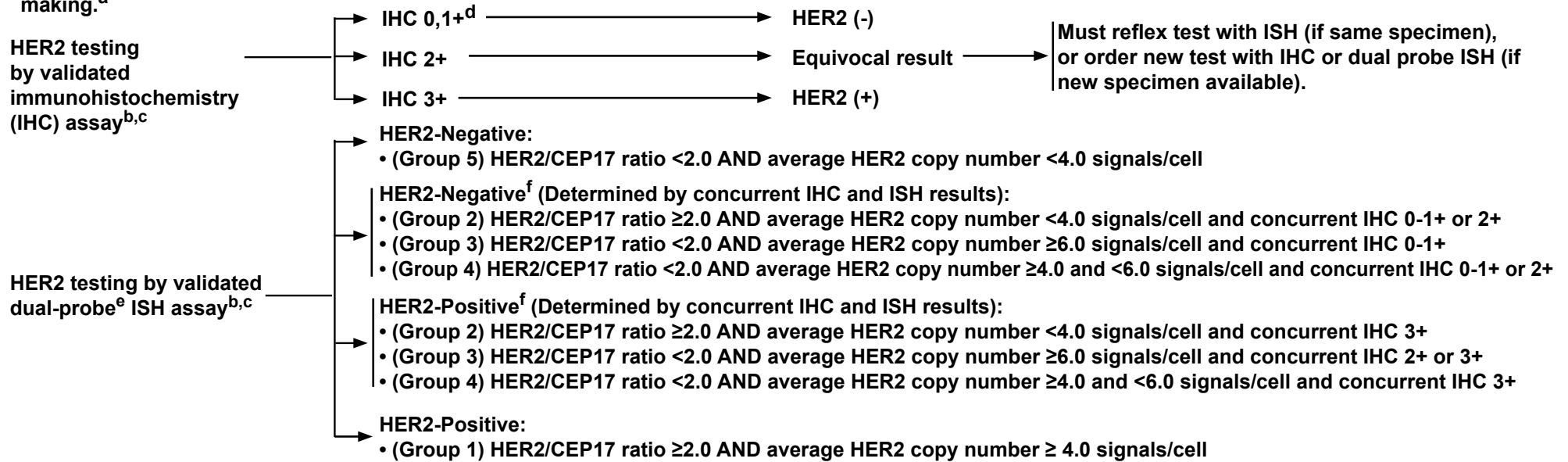
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PRINCIPLES OF BIOMARKER TESTING
HER2 TESTING^{a,b}

- **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**



^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 specimens 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 The distinction between HER2 IHC 0 and 1+ is currently clinically relevant in the metastatic setting since patients with HER2 1+ or 2+/ISH negative results (on primary or metastatic samples) may be eligible for treatment targeting non-amplified levels of HER2 expression.

^e 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.

^f 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.

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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.⁹ 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

⁹ 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.

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**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 for:~~
 - ~~1) Patients with dense breasts treated with BCS + RT~~
 - ~~2) Those diagnosed before the age of 50~~
 - ~~3) 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.²~~
- **Routine annual MRI is not indicated for follow-up screening of women with a history of breast cancer, except for those with a high lifetime risk of a second primary breast cancer.^{2,3,4}**

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.

² Monticciolo DL, Newell MS, Moy L, et al. Breast cancer screening in women at higher-than-average risk: Recommendations from the ACR. *J Am Coll Radiol* 2018;15:408-414.

² *Sardanelli F et al. Magnetic Resonance Imaging of the Breast: Recommendations from the EUSOMA Working Group. Eur J Cancer* 2010;46:1296-316.

³ *Consensus Guideline on Diagnostic and Screening Magnetic Resonance Imaging of the Breast. The American Society of Breast Surgeons. June 22, 2017.*

⁴ *Forrai G et al. Use of Diagnostic Imaging Modalities in Modern Screening, Diagnostics and Management of Breast Tumours 1st Central-Eastern European Professional Consensus Statement on Breast Cancer. Pathol Oncol Res.* 2022;28:1610382.

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FERTILITY AND BIRTH CONTROL

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

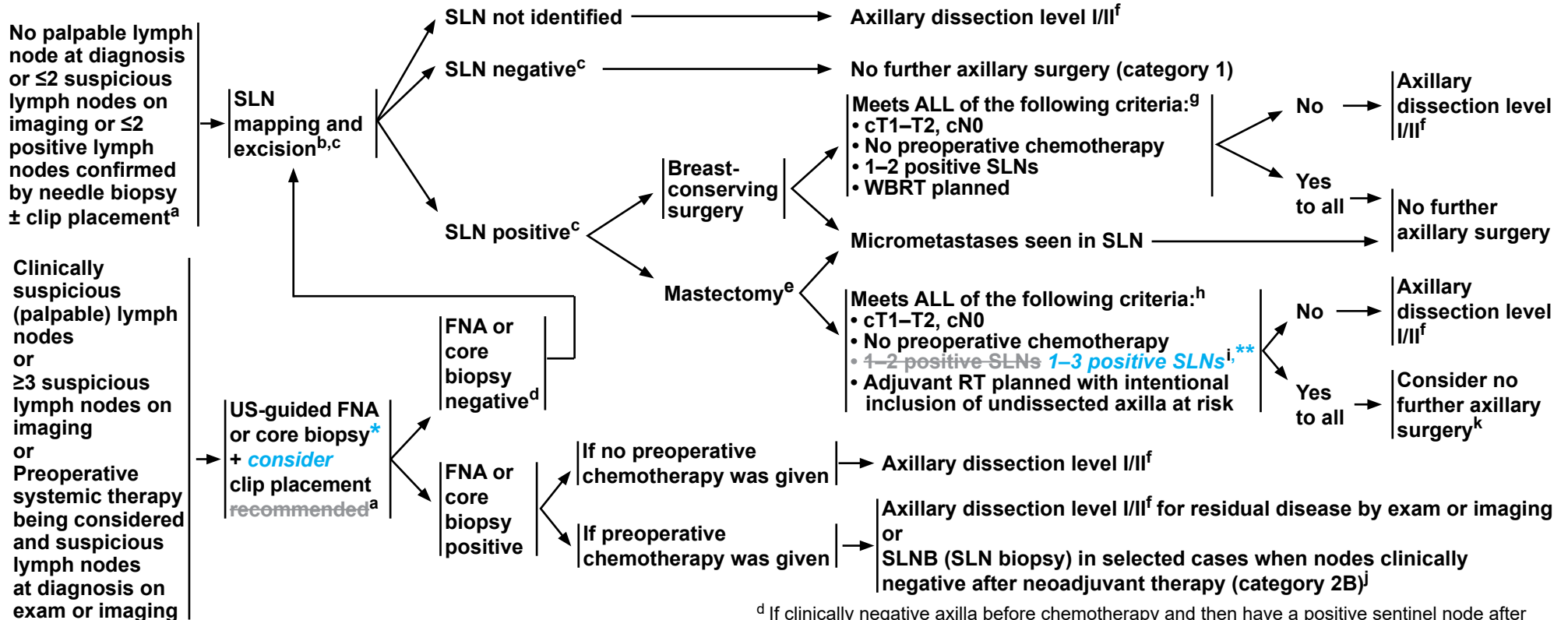
- All premenopausal patients should be informed about the potential impact of chemotherapy on fertility and asked about their desire for potential future pregnancies. Patients who may desire future pregnancies should be referred to fertility specialists before chemotherapy and/or endocrine therapy to 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 <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.

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CONSIDERATIONS FOR SURGICAL AXILLARY STAGING



* *Lymph node biopsy may be foregone in patients presenting with clinically unequivocal nodal involvement or metastatic disease.*
 ** *cT1-2N0 (palpably node-negative) cancer undergoing mastectomy, with 1-3 SLN+ and receiving axillary RT.*

^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 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;318:918-926.
^h EORTC AMAROS: Donker M, et al. Lancet Oncol 2014;15:1303-10; Rutgers E, et al. Cancer Research 2019;79-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 (optimal) or at least 2 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.

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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 \(SLYMPH-1\).](#)

For patients aged 70 years with clinically node-negative early-stage (cT1-2N0) invasive breast cancer that is hormone receptor-positive and HER2-negative, SLNB is not required.

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

- Margins should be evaluated on all surgical specimens from 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 Guideline¹ 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.

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**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/PBI,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 Lobular Carcinoma In Situ (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.

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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 \(BINV-F\)](#).

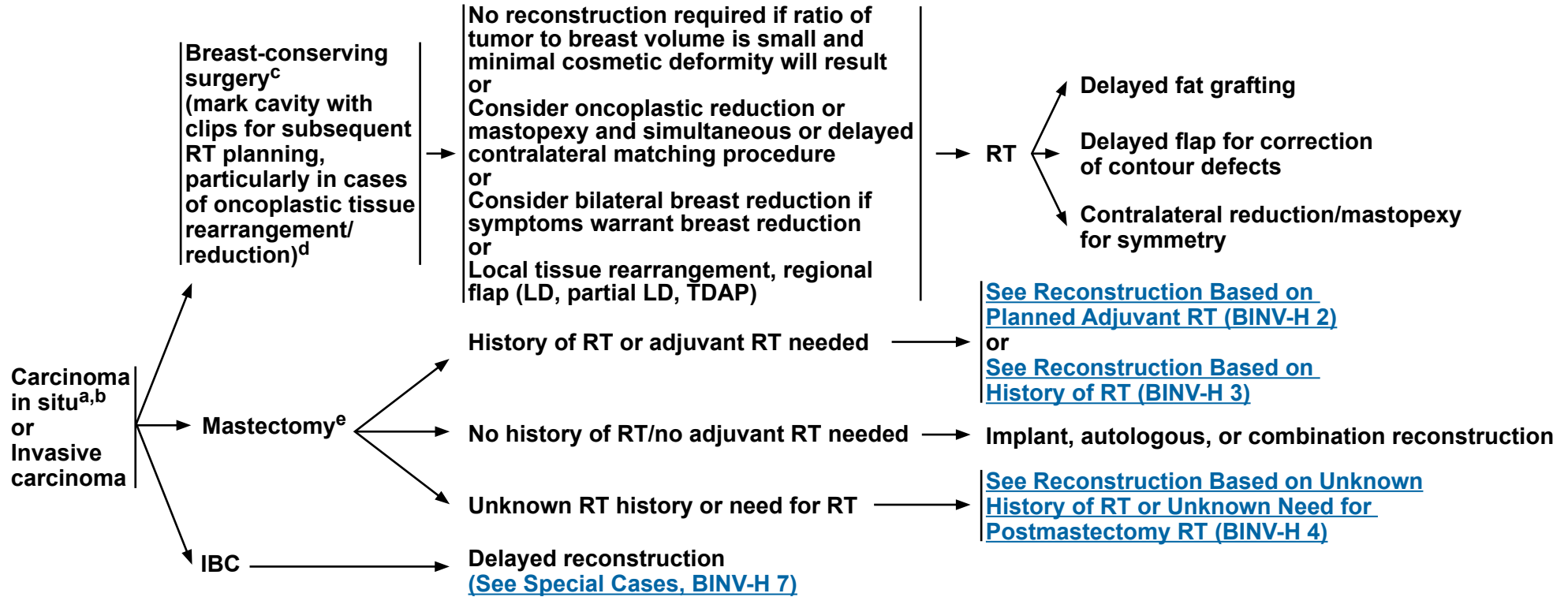
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PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY



^a See [General Principles of Breast Reconstruction \(BINV-H 5\)](#).

^b See [Patient Factors Affecting Choice of Reconstruction \(BINV-H 6\)](#).

^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.

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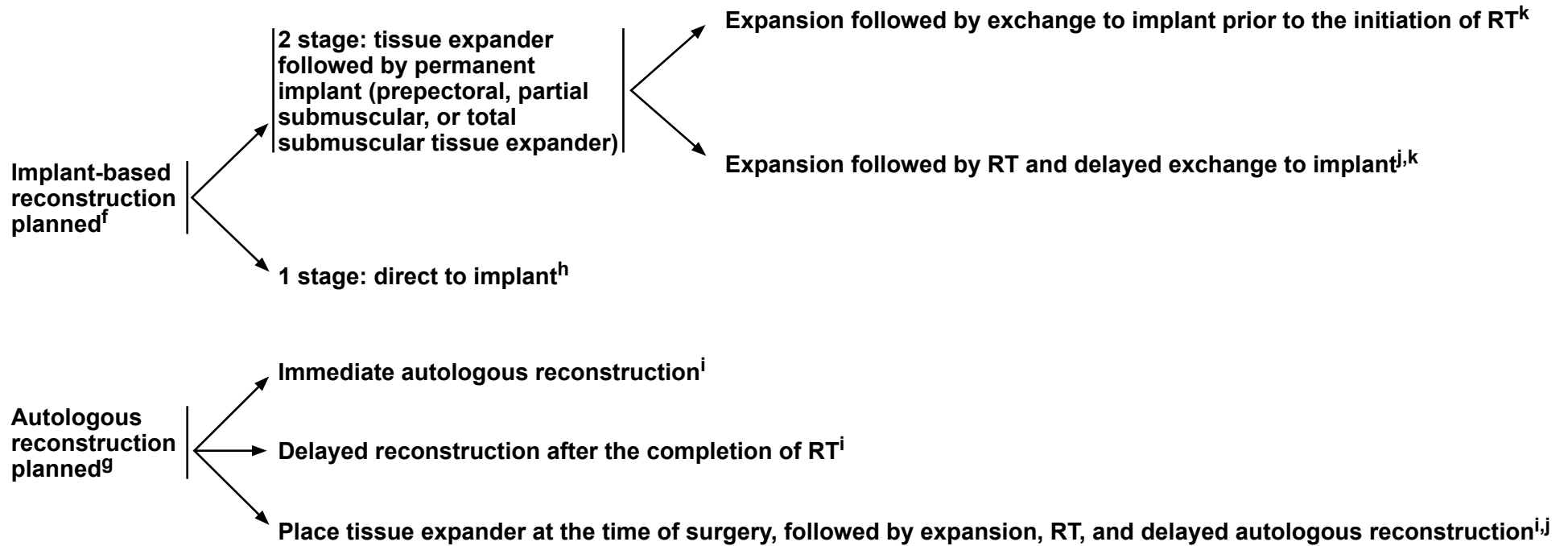
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PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

RECONSTRUCTION BASED ON PLANNED ADJUVANT RT^{a,b}



^a See [General Principles of Breast Reconstruction \(BINV-H 5\)](#).

^b See [Patient Factors Affecting Choice of Reconstruction \(BINV-H 6\)](#).

^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.

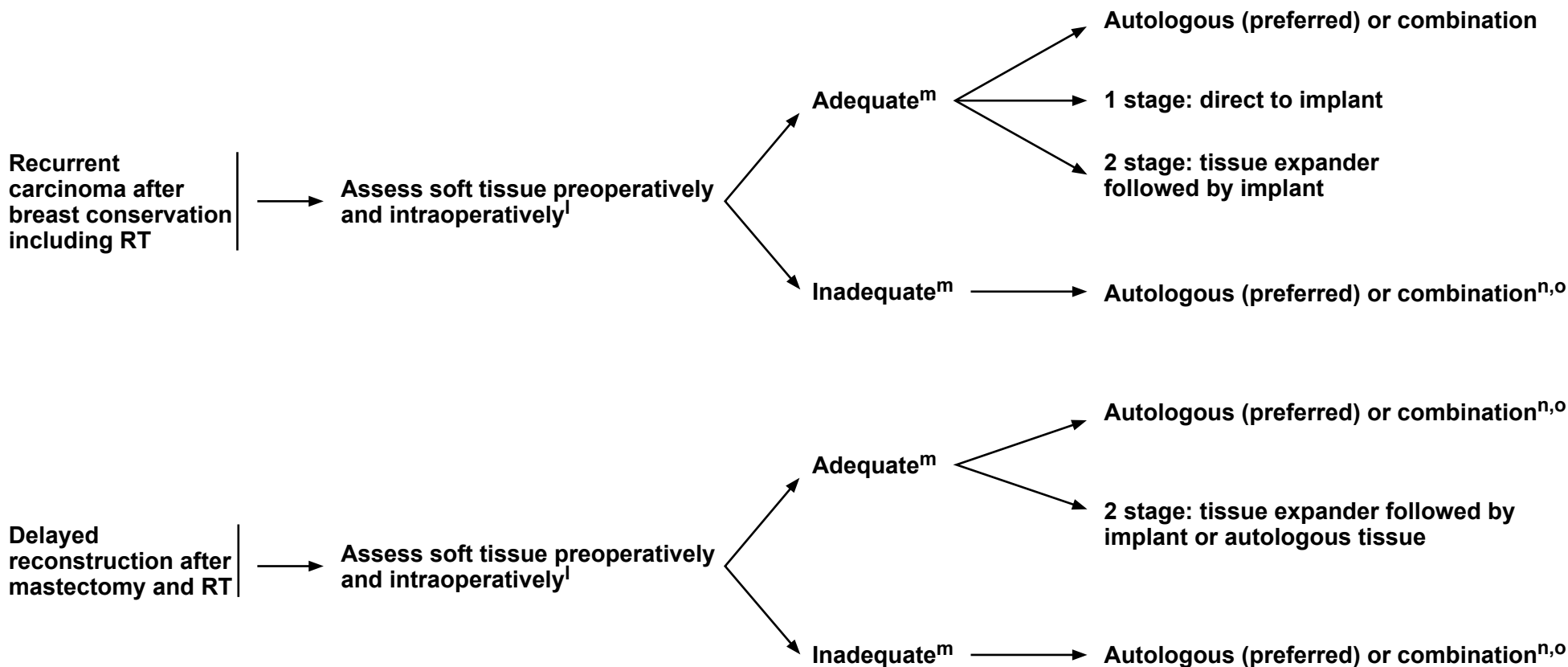
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PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

RECONSTRUCTION BASED ON HISTORY OF RT^{a,b}



^a See General Principles of Breast Reconstruction (BINV-H 5).

^b See Patient Factors Affecting Choice of Reconstruction (BINV-H 6).

^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.

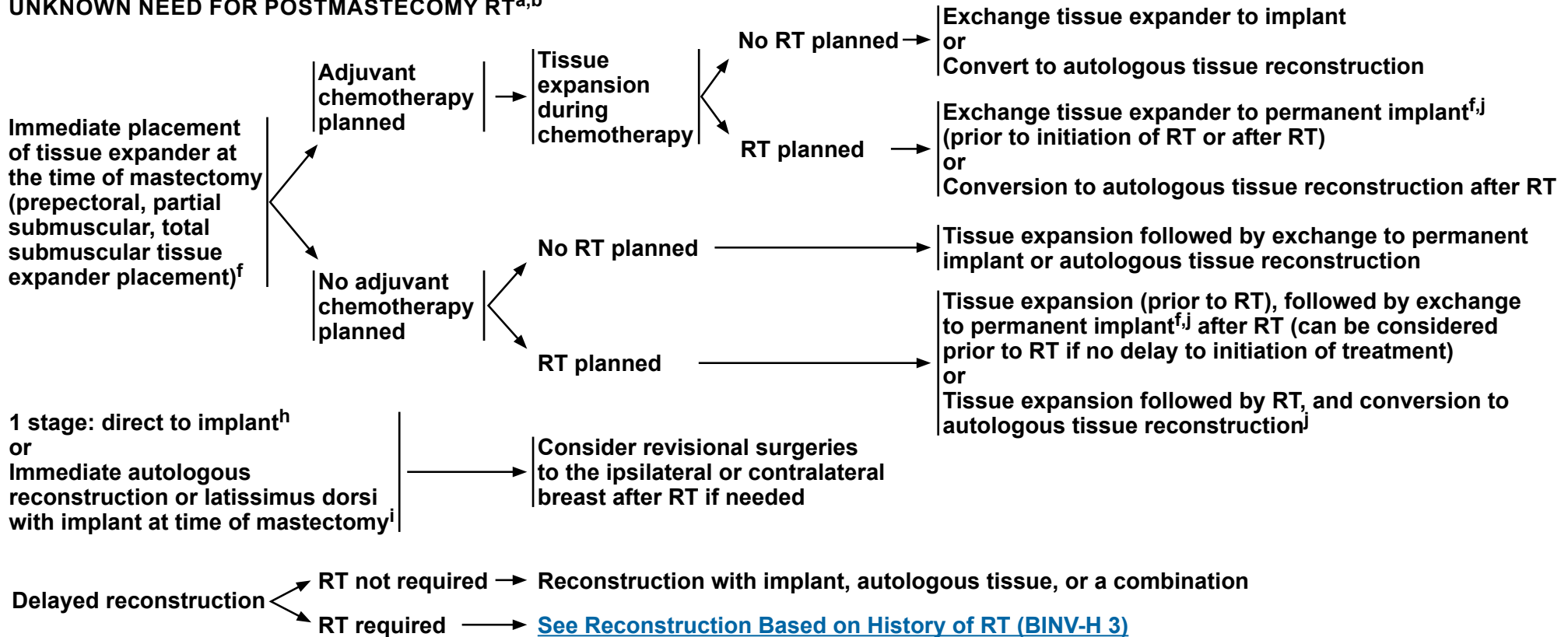
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PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY

RECONSTRUCTION BASED ON NO OR UNKNOWN HISTORY OF RT OR UNKNOWN NEED FOR POSTMASTECTOMY RT^{a,b}



^a See [General Principles of Breast Reconstruction \(BINV-H 5\)](#).

^b See [Patient Factors Affecting Choice of Reconstruction \(BINV-H 6\)](#).

^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).

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**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 \(6\)](#) 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.**

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**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)~~ *squamous cell carcinoma (SCC) and various lymphomas***
 - ▶ **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.](#)**

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**PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING SURGERY****Special Cases****• Nipple-sparing mastectomy**

- ▶ **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.**
- ▶ **Topical 2% nitroglycerine (45 mg total dose) used prophylactically has been shown to reduce mastectomy skin flap necrosis in both skin-sparing mastectomy and nipple sparing mastectomy in one randomized control trial.**

• 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, **RN** *locoregional 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.**

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**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 routinely be utilized to delineate target volumes & organs at risk, and assess dose distribution across the entire treatment volume.
 - ▶ Radiation to the breast/chest wall and nodal regions is generally delivered with single energy or mixed energy photons ± electrons.
 - ▶ Treatment planning should be optimized to maximally improve homogeneity across the target volume while minimizing dose to organs at risk.
 - ▶ 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.
 - ▶ At a minimum, weekly imaging to verify treatment setup should be utilized. More frequent imaging may be needed for selected cases with inconsistent reproducibility. *Imaging before each ultra-hypofractionated radiotherapy fraction is recommended.* Image-guided radiation therapy (IGRT) may be utilized with deep inspiration breath-hold (DIBH) technique to reduce normal tissue exposure of the heart, lung or liver.
 - ▶ Dose-volume histograms (DVHs) should be used to evaluate, dose and constraints 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~~; *in selected patients 26 Gy in 5 fractions may be considered though the optimal fractionation for the boost delivery is unknown for this regimen. The dose of 45–50.4 Gy in 25–28 fractions is not recommended, unless radiotherapy volume includes regional lymph nodes.*
 - ▶ 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.~~ *Boost may be delivered after WBR (10–16 Gy in 4–8 fractions) or as a simultaneous integrated boost (36–40 Gy in 15 fractions to the whole breast, 40 Gy in 15 fractions to the partial breast, and 48 Gy in 15 fractions to the tumor bed).**
- Lumpectomy cavity boost can be delivered using enface electrons, photons, or brachytherapy.^a
 - ▶ Ultra-hypofractionated WBRT of 28.5 Gy in 5 (once-a-week) fractions may be considered for selected pts over 50 yrs following BCS with early-stage, node-negative disease, particularly those in whom a boost is not intended.^{a,b}

* Coles CE, Havilan JS, Kirby AM, et al. Dose-escalated simultaneous integrated boost radiotherapy in early breast cancer (IMPORT HIGH): a multicentre, phase 3, non-inferiority, open-label, randomised controlled trial. *Lancet* 2023;24:2124-2137.

^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.

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**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:
 - ▶ Chest wall RT dose is 45-50.4 Gy at 1.8–2 Gy/fx in 25–28 fractions ~~patients not undergoing breast reconstruction may alternatively receive 40 Gy at 2.67 Gy/fx or 42.5 Gy at 2.66 Gy/fx~~ **irrespective of breast reconstruction**.
 - ◊ Boost: 10–16 Gy at 1.8 to 2.0 Gy/fx total 5–8 fractions.
 - ▶ Chest wall scar boost of 10–16 Gy/fx 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:
 - ▶ Regional node dose is 45–50.4 Gy at 1.8–2 Gy/fx; ~~patients not undergoing breast reconstruction may alternatively receive~~ **or 40 Gy at 2.67 Gy/fx or 42.5 Gy at 2.66 Gy/fx.**
 - ▶ A supplemental boost of RT can be delivered to grossly involved or enlarged lymph nodes (i.e. internal mammary or supraclavicular) that have not been surgically addressed.
 - ◊ 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 ~~is typically~~ **may be given concurrently or** after completion of RT.
 - Olaparib should be given after completion of RT.
 - ◊ Available data suggest that ~~sequential or concurrent endocrine therapy with RT is acceptable~~ **preferred to sequential approach**. ~~Due to compounding side effects, initiating endocrine therapy at the completion of RT may be preferred.~~ Endocrine therapy may be delivered concurrently with RT or started after the completion of RT.
 - ◊ Adjuvant HER2-targeted therapy ± endocrine therapy may be delivered concurrently with RT.

^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.

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**PRINCIPLES OF RADIATION THERAPY****Accelerated Partial Breast Irradiation (APBI)/Partial Breast Irradiation (PBI)**

- APBI/PBI offers comparable local control to WBRT in selected low-risk patients with early-stage breast cancer. However, the optimal external beam-APBI/PBI technique/fractionation for minimizing long-term cosmesis effects has not been determined.
 - ▶ Patients are encouraged to participate in clinical trials.
 - ▶ The NCCN Panel recommends APBI/PBI *may be considered* for any patient who is *BRCA* negative and meets the 2016 ASTRO criteria. The 2016 ASTRO criteria define patients aged ≥ 50 years to be considered "suitable" for APBI/PBI if:
 - ◊ Invasive ductal carcinoma measuring ≤ 2 cm (pT1 disease) with negative margin widths of ≥ 2 mm, no LVI, and ER-positive 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. <i>Eur J Cancer</i> 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. <i>J Clin Oncol</i> 2020;38:4175-4183.
40 Gy/15 fractions	EBRT	Goles CE, Griffin GL, 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. <i>Lancet</i> 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. <i>Lancet</i> 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. <i>Lancet</i> 2019;394:2165-2172.
<i>26 Gy/5 fractions QD</i>	<i>EBRT</i>	<i>ESTRO recommendations: Meattini I, Becherini C, Boersma L, et al. European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. <i>Lancet Oncol.</i> 2022;23:e21-e31.</i>

^e The protocol mandated IMRT.

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**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 BCS. 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

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[References](#)

**SPECIAL CONSIDERATIONS FOR BREAST CANCER IN MALES (SEX ASSIGNED AT BIRTH)**
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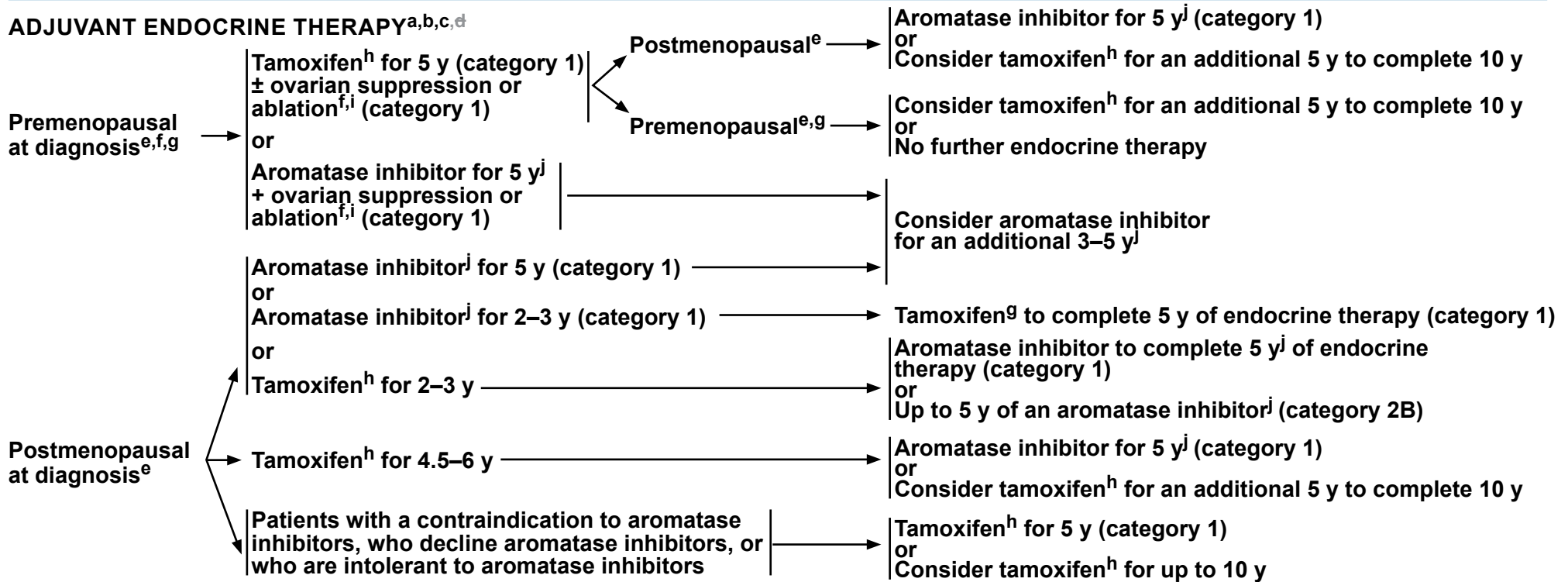
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ADJUVANT ENDOCRINE THERAPY^{a,b,c,d}



^a *In case of uncertain menopausal status*, if patient is not postmenopausal, sequential evaluation of hormonal status is recommended to consider an alternative endocrine agent *for patients treated with an aromatase inhibitor*.

^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 (confirmed preoperatively and/or at surgery), or 1–3 positive lymph nodes with one or more of the following: grade 3 disease, tumor size ≥5 cm (on pre-operative imaging and/or at surgery) 2 years of adjuvant abemaciclib can be considered in combination with endocrine therapy (category 1). In patients eligible for both adjuvant olaparib and abemaciclib, the optimal sequence is not known.

^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 Safety data support administration of GnRH agonists before or with chemotherapy, especially if there is a goal to enhance fertility preservation. They can also be initiated after chemotherapy in patients who remain premenopausal.

^h 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.

ⁱ A balanced discussion of the risks and benefits associated with ovarian suppression therapy is critical, including the potential side effects of premature menopause. 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).

^j 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).

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PREOPERATIVE/ADJUVANT THERAPY REGIMENS^a

HER2-Negative^b	
<p>Preferred Regimens:</p> <ul style="list-style-type: none"> • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by paclitaxel every 2 weeks^c • Dose-dense AC (doxorubicin/cyclophosphamide) followed or preceded by weekly paclitaxel^c • TC (docetaxel and cyclophosphamide) • Olaparib, if germline BRCA1/2 mutations^{d,e} • High-risk^f 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:^g Capecitabine 	
<p>Useful in Certain Circumstances:</p> <ul style="list-style-type: none"> • 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) 	<p>Other Recommended Regimens:</p> <ul style="list-style-type: none"> • AC followed by docetaxel every 3 weeks^c <i>or AC followed by weekly paclitaxel^c</i> • EC (epirubicin/cyclophosphamide) <i>(useful in certain circumstances)</i> • TAC (docetaxel/doxorubicin/cyclophosphamide) • Select patients with TNBC:^{g,1} <ul style="list-style-type: none"> ▶ Paclitaxel + carboplatin (various schedules) ▶ Docetaxel + carboplatin^{g,1} (preoperative setting only)

[See Additional Considerations for Those Receiving Preoperative/Adjuvant Therapy \(BINV-L, 3\)](#)

^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. *Docetaxel and paclitaxel may be used interchangeably.*

^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, ER 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 *and improved EFS/DFS* rates with incorporation of platinum. However, *overall survival outcomes remain uncertain* 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) *may be considered*. 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. Carboplatin may be used as part of the pembrolizumab regimen.

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PREOPERATIVE/ADJUVANT THERAPY REGIMENS^a

HER2-Positive	
<p>Preferred Regimens:</p> <ul style="list-style-type: none"> • Paclitaxel + trastuzumab^h • TCH (docetaxel/carboplatin/trastuzumab) • TCHP (docetaxel/carboplatin/trastuzumab/pertuzumab) (<i>preoperative setting only</i>) • 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} If node positive at initial staging, trastuzumab + pertuzumab (category 1)^k 	
<p>Useful in Certain Circumstances:</p> <ul style="list-style-type: none"> • 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) (<i>preoperative setting only</i>) • Neratinibi (adjuvant setting only) • Paclitaxel + trastuzumab + pertuzumab <i>PCTP</i> (paclitaxel/carboplatin/trastuzumab/pertuzumab)^j • Ado-trastuzumab emtansine (TDM-1) (adjuvant setting only) 	<p>Other Recommended Regimens:</p> <ul style="list-style-type: none"> • 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 \(BINV-L, 3\)](#)

^a *Paclitaxel and docetaxel may be used interchangeably* 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.

^k Updated results from the adjuvant APHINITY trial in HER2-positive early breast cancer, with a median follow-up of 8.4 years, have confirmed the benefit of adding pertuzumab to trastuzumab plus chemotherapy in preventing recurrences in those with node positive disease.

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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 \(2\)](#).
- Considerations for HER2-positive disease:
 - ▶ ~~An FDA-approved biosimilar~~ ***A biosimilar validated with the reference biologic product*** 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.~~

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**DOSING: PREOPERATIVE/ADJUVANT THERAPY REGIMENS****HER2-Negative
Preferred Regimens**

- **Dose-dense AC followed by paclitaxel²**
 - ▶ Doxorubicin 60 mg/m² IV day 1
 - ▶ Cyclophosphamide 600 mg/m² IV day 1
 - ◊ Cycled every 14 days for 4 cycles.¹
 - ◊ Followed by:
 - ▶ Paclitaxel 175 mg/m² by 3 h IV infusion day 1
 - ◊ Cycled every 14 days for 4 cycles.¹
- **Dose-dense AC followed by weekly paclitaxel²**
 - ▶ Doxorubicin 60 mg/m² IV day 1
 - ▶ Cyclophosphamide 600 mg/m² IV day 1
 - ◊ Cycled every 14 days for 4 cycles.¹
 - ◊ Followed by:
 - ▶ Paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 weeks.
- **TC³**
 - ▶ Docetaxel 75 mg/m² IV day 1
 - ▶ Cyclophosphamide 600 mg/m² IV day 1
 - ◊ Cycled every 21 days for 4-6 cycles.¹
- **Preoperative pembrolizumab + chemotherapy followed by adjuvant pembrolizumab⁴**
 - ▶ Preoperative:
 - ◊ Pembrolizumab 200 mg IV Day 1
 - ◊ Paclitaxel 80 mg/m² IV Days 1, 8, 15
 - ◊ Carboplatin AUC 5 IV Day 1
 - Or
 - ◊ Carboplatin AUC 1.5 IV Days 1, 8, 15
 - Cycled every 21 days x 4 cycles (cycles 1–4)
 - Followed by:
 - ◊ Pembrolizumab 200 mg IV Day 1
 - ◊ Doxorubicin 60 mg/m² IV Day 1 or Epirubicin 90 mg/m² IV Day 1
 - ◊ Cyclophosphamide 600 mg/m² 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^{5,*}**
 - ▶ 1,000–1,250 mg/m² PO twice daily on days 1–14
 - ◊ Cycled every 21 days for 6–8 cycles
- **Olaparib⁶**
 - ▶ 300 mg PO twice daily
 - ▶ Cycled every 28 days for 1 y

* *In patients without pCR after preoperative chemotherapy.*

¹ All cycles are with myeloid growth factor support. [See NCCN Guidelines for Hematopoietic Growth Factors.](#)

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

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**DOSING: PREOPERATIVE/ADJUVANT THERAPY REGIMENS**

HER2-Negative Other Recommended Regimens	HER2-Negative Useful in Certain Circumstances
<ul style="list-style-type: none"> • AC followed by docetaxel every 3 weeks⁷ <ul style="list-style-type: none"> ▶ Doxorubicin 60 mg/m² IV on day 1 ▶ Cyclophosphamide 600 mg/m² IV day 1 <ul style="list-style-type: none"> ◊ Cycled every 21 days for 4 cycles. ◊ Followed by: ▶ Docetaxel 75–100 mg/m² IV on day 1 <ul style="list-style-type: none"> ◊ Cycled every 21 days for 4 cycles. • EC chemotherapy⁸ <ul style="list-style-type: none"> ▶ Epirubicin 100 mg/m² IV day 1 ▶ Cyclophosphamide 830 mg/m² IV day 1 <ul style="list-style-type: none"> ◊ Cycled every 21 days for 8 cycles. • TAC chemotherapy⁹ <ul style="list-style-type: none"> ▶ Docetaxel 75 mg/m² IV day 1 ▶ Doxorubicin 50 mg/m² IV day 1 ▶ Cyclophosphamide 500 mg/m² IV day 1 <ul style="list-style-type: none"> ◊ Cycled every 21 days for 6 cycles.¹ • AC followed by weekly paclitaxel¹⁸ <ul style="list-style-type: none"> ▶ Doxorubicin 60 mg/m² IV day 1 ▶ Cyclophosphamide 600 mg/m² IV day 1 <ul style="list-style-type: none"> ◊ Cycled every 21 days for 4 cycles. ◊ Followed by: ▶ Paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 weeks. • Paclitaxel + carboplatin <ul style="list-style-type: none"> ▶ Weekly paclitaxel + carboplatin^{1,10} (preoperative setting only) <ul style="list-style-type: none"> ◊ Paclitaxel 80 mg/m² days 1, 8, and 15 ◊ Carboplatin AUC 5 or 6 day 1; <ul style="list-style-type: none"> – Cycled every 21 days for 4 cycles. ▶ Weekly paclitaxel + weekly carboplatin^{11,12} <ul style="list-style-type: none"> ◊ Paclitaxel 80 mg/m² days 1, 8, and 15 ◊ Carboplatin AUC 1.5–2 days 1, 8, and 15 <ul style="list-style-type: none"> – Cycled every 28 days for 6 cycles. • Docetaxel + carboplatin (4–6 cycles) (preoperative setting only)^{1,13,14,1} <ul style="list-style-type: none"> ▶ Docetaxel 75 mg/m² day 1 ▶ Carboplatin AUC 6 day 1 <ul style="list-style-type: none"> ◊ Cycled every 21 days for 4–6 cycles. 	<ul style="list-style-type: none"> • Dose-dense AC² <ul style="list-style-type: none"> ▶ Doxorubicin 60 mg/m² IV day 1 ▶ Cyclophosphamide 600 mg/m² IV day 1 <ul style="list-style-type: none"> ◊ Cycled every 14 days for 4 cycles.¹ • AC¹⁵ <ul style="list-style-type: none"> ▶ Doxorubicin 60 mg/m² IV on day 1 ▶ Cyclophosphamide 600 mg/m² IV day 1 <ul style="list-style-type: none"> ◊ Cycled every 21 days for 4 cycles. • CMF^{16,17} <ul style="list-style-type: none"> ▶ Cyclophosphamide 100 mg/m² PO days 1–14 ▶ Methotrexate 40 mg/m² IV days 1 & 8 ▶ 5-fluorouracil 600 mg/m² IV days 1 & 8 <ul style="list-style-type: none"> ◊ Cycled every 28 days for 6 cycles. Or <ul style="list-style-type: none"> ▶ Cyclophosphamide 600 mg/m² IV day 1 ▶ Methotrexate 40 mg/m² IV day 1 ▶ 5-fluorouracil 600 mg/m² IV day 1 <ul style="list-style-type: none"> ◊ Cycled every 21 days for 8 cycles. • AC followed by weekly paclitaxel¹⁸ <ul style="list-style-type: none"> ▶ Doxorubicin 60 mg/m² IV day 1 ▶ Cyclophosphamide 600 mg/m² IV day 1 <ul style="list-style-type: none"> ◊ Cycled every 21 days for 4 cycles. ◊ Followed by ▶ Paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 weeks. • EC <ul style="list-style-type: none"> ▶ Epirubicin 75–90 mg/m² IV day 1 ▶ Cyclophosphamide 600 mg/m² IV day 1 <ul style="list-style-type: none"> ◊ Cycled every 21 days for 8 cycles. • Capecitabine (maintenance therapy)¹⁹ <ul style="list-style-type: none"> ▶ 650 mg/m² PO twice daily on days 1–28 ▶ Cycled every 28 days for 1 year

¹ All cycles are with myeloid growth factor support. [See NCCN Guidelines for Hematopoietic Growth Factors.](#)

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

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DOSING: PREOPERATIVE/ADJUVANT THERAPY REGIMENS

HER2-Positive^{m,n,⊖} Preferred Regimens		
<p>Paclitaxel + trastuzumab²⁰</p> <ul style="list-style-type: none"> ▶ Paclitaxel 80 mg/m² IV weekly for 12 weeks <ul style="list-style-type: none"> ◊ With: ▶ Trastuzumab 4 mg/kg IV with first dose of paclitaxel <i>Trastuzumab 8 mg/kg IV wk 1</i> <ul style="list-style-type: none"> ◊ 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>TCH²¹</p> <ul style="list-style-type: none"> ▶ Docetaxel 75 mg/m² IV day 1 ▶ Carboplatin AUC 6 IV day 1 <ul style="list-style-type: none"> ◊ Cycled every 21 days for 6 cycles ◊ With: ▶ Trastuzumab 4 mg/kg IV wk 1 <ul style="list-style-type: none"> ◊ Followed by: ▶ Trastuzumab 2 mg/kg IV for 17 wks <ul style="list-style-type: none"> ◊ Followed by: ▶ Trastuzumab 6 mg/kg IV <ul style="list-style-type: none"> ◊ Cycled every 21 days to complete 1 y of therapy.^P <p>OR</p> <ul style="list-style-type: none"> ▶ Trastuzumab 8 mg/kg IV wk 1 <ul style="list-style-type: none"> ◊ Followed by: ▶ Trastuzumab 6 mg/kg IV <ul style="list-style-type: none"> ◊ Cycled every 21 days to complete 1 y of therapy.^P 	<p>TCH + pertuzumab²²</p> <ul style="list-style-type: none"> ▶ Docetaxel 75 mg/m² IV day 1 ▶ Carboplatin AUC 6 IV day 1 <ul style="list-style-type: none"> ◊ Cycled every 21 days for 6 cycles ◊ With: ▶ Trastuzumab 8 mg/kg IV day 1 ▶ Pertuzumab 840 mg IV day 1 <ul style="list-style-type: none"> ◊ Followed by: ▶ Trastuzumab 6 mg/kg IV on day 1 ▶ Pertuzumab 420 mg IV day 1 <ul style="list-style-type: none"> ◊ Cycled every 21 days to complete 1 y of therapy.^P

^m An FDA-approved biosimilar *A biosimilar validated with the reference biologic product* 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.

[⊖] 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.

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**DOSING: PREOPERATIVE/ADJUVANT THERAPY REGIMENS****HER2-Positive^{m,n,⊖}****Useful in Certain Circumstances****AC followed by T + trastuzumab²³**

- ▶ Doxorubicin 60 mg/m² IV day 1
- ▶ Cyclophosphamide 600 mg/m² IV day 1
 - ◊ Cycled every 21 days for 4 cycles.
 - ◊ Followed by:
- ▶ Paclitaxel 80 mg/m² by 1 h IV weekly for 12 wks
 - ◊ With:
- ▶ Trastuzumab 4 mg/kg IV with first dose of paclitaxel
 - ◊ Followed by:
- ▶ Trastuzumab 2 mg/kg IV weekly to complete 1 y of treatment. As an alternative, trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel, and given to complete 1 y of trastuzumab treatment.^P

Dose-dense AC followed by paclitaxel + trastuzumab²⁴

- ▶ Doxorubicin 60 mg/m² IV day 1
- ▶ Cyclophosphamide 600 mg/m² IV day 1
 - ◊ Cycled every 14 days for 4 cycles.
 - ◊ Followed by:
- ▶ Paclitaxel 175 mg/m² by 3 h IV infusion day 1
 - ◊ Cycled every 14 days for 4 cycles.¹
 - ◊ With:
- ▶ Trastuzumab 4 8 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 + pertuzumab²⁵

- ▶ Doxorubicin 60 mg/m² IV day 1
- ▶ Cyclophosphamide 600 mg/m² IV day 1
 - ◊ Cycled every 21 days for 4 cycles or
 - ◊ For dose-dense: Cycle every 14 days for 4 cycles
 - ◊ Followed by:
- ▶ Paclitaxel 80 mg/m² IV by 1h IV weekly for 12 wks
 - ◊ With:
- ▶ Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- ▶ Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- ▶ Paclitaxel 80 mg/m² IV days 1, 8, and 15
 - ◊ Cycled every 21 days for 4 cycles
 - ◊ Followed by:
- ▶ 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 + trastuzumab²⁶

- ▶ Docetaxel 75 mg/m² IV day 1
 - ▶ Cyclophosphamide 600 mg/m² IV day 1
 - ◊ Cycled every 21 days for 4 cycles
 - ◊ With:
 - ▶ Trastuzumab 4 mg/kg IV wk 1
 - ◊ Followed by:
 - ▶ Trastuzumab 2 mg/kg IV weekly for 41 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

¹ All cycles are with myeloid growth factor support. [See NCCN Guidelines for Hematopoietic Growth Factors.](#)

^m An FDA-approved biosimilar [A biosimilar validated with the reference biologic product](#) 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.

[⊖] 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.

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**DOSING: PREOPERATIVE/ADJUVANT THERAPY REGIMENS****HER2-Positive^{m,†,‡}****Other Recommended Regimens****AC followed by docetaxel + trastuzumab^{20,27}**

- ▶ Doxorubicin 60 mg/m² IV day 1
- ▶ Cyclophosphamide 600 mg/m² IV day 1
 - ◊ Cycled every 21 days for 4 cycles
 - ◊ Followed by:
- ▶ Docetaxel 100 mg/m² IV day 1
 - ◊ Cycled every 21 days for 4 cycles
 - ◊ With:
- ▶ Trastuzumab
 - ◊ 4 mg/kg IV wk 1; Followed by:
 - ◊ 2 mg/kg IV weekly for 11 wks; Followed by:
8 mg/kg IV day 1; Followed by:
 - ◊ 6 mg/kg IV
 - ◊ Cycled every 21 days to complete 1 y of trastuzumab therapy.^P

AC followed by docetaxel + trastuzumab + pertuzumab²⁸

- ▶ Doxorubicin 60 mg/m² IV day 1
- ▶ Cyclophosphamide 600 mg/m² IV day 1
 - ◊ Cycled every 21 days for 4 cycles
 - ◊ Followed by:
- ▶ Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- ▶ Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- ▶ Docetaxel 75–100 mg/m² IV day 1
 - ◊ Cycled every 21 days for 4 cycles
 - ◊ Followed by:
- ▶ Trastuzumab 6 mg/kg IV
- ▶ Pertuzumab 420 mg IV day 1
 - ◊ Followed by:
- ▶ *Docetaxel 75–100 mg/m² IV day 1*
 - ◊ *Cycled every 21 days for 4 cycles*
 - ◊ *With:*
- ▶ *Pertuzumab 840 mg IV day 1 followed by 420 mg IV*
 - ◊ *Cycled every 21 days (preoperatively only)*
- ▶ *Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV*
 - ◊ *Cycled every 21 days to complete 1 y of therapy.^P*

PCTP (paclitaxel/carboplatin/trastuzumab/pertuzumab) (preoperative)

- ▶ Paclitaxel; 80 mg/m² IV day 1 and 8
- ▶ Carboplatin IV; AUC 6; day 1 or AUC 3; day 1, 8
 - ◊ Cycled every 21 days
 - ◊ With:
- ▶ Pertuzumab 840 mg IV day 1 followed by 420 mg IV
 - ◊ Cycled every 21 days (preoperative only)
- ▶ Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
 - ◊ Cycled every 21 days to complete 1 y of trastuzumab treatment^P

^m An FDA-approved biosimilar *A biosimilar validated with the reference biologic product* is an appropriate substitute for trastuzumab.

[†] Trastuzumab and hyaluronidase-ozxk 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-ozxk for or with ado-trastuzumab emtansine.

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.

[‡] 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.

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DOSING: PREOPERATIVE/ADJUVANT THERAPY REGIMENS (continued)

HER2-Positive ^{m,n,o} Useful in Certain Circumstances		
<p>Neratinib²⁹</p> <ul style="list-style-type: none"> ▶ 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 <ul style="list-style-type: none"> ◊ Cycled every 28 days x 1 cycle ◊ Followed by: ▶ 240 mg PO daily on days 1–28 <ul style="list-style-type: none"> ◊ Cycled every 28 days x 12 cycles beginning with cycle 2 	<p>Paclitaxel + trastuzumab + pertuzumab³⁰</p> <ul style="list-style-type: none"> ▶ Paclitaxel 80 mg/m² IV day 1 <ul style="list-style-type: none"> ◊ 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 <ul style="list-style-type: none"> ◊ Cycled every 21 days x 4 cycles ◊ Followed by:- ▶ Trastuzumab 6 mg/kg IV;- ▶ Pertuzumab 420 mg IV day 1;- <ul style="list-style-type: none"> ◊ Cycled every 21 days to complete 1 y of therapy^p 	<p>Ado-trastuzumab emtansine (T-DM1)³¹</p> <ul style="list-style-type: none"> ▶ 3.6 mg/kg IV day 1 <ul style="list-style-type: none"> ◊ Cycled every 21 days for 17 14 cycles (<i>post-operatively in patients with residual disease</i>)

^m An FDA-approved biosimilar *A biosimilar validated with the reference biologic product* is an appropriate substitute for trastuzumab.

ⁿ Trastuzumab and hyaluronidase-ozyk 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-ozyk for or with ado-trastuzumab emtansine.

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.

^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.

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PREOPERATIVE/ADJUVANT THERAPY REGIMENS - REFERENCES

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**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 \geq cT2 or \geq cN1
 - ◇ 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 cT1c, cN0 HER2-positive disease and TNBC
- Patients in whom definitive surgery may be delayed.

Non-candidates for Preoperative Systemic Therapy *if the only aim is to decrease the extent of surgery*

- 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

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**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 (OS), 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 \geq pT2 or \geq 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.

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^d An FDA-approved biosimilar *A biosimilar validated with the reference biologic product* 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.

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**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)
21-gene (Oncotype Dx) for pN1 (1–3 positive nodes)^c	Yes	Yes	Postmenopausal: Preferred	1	BINV-N (2)
			Premenopausal: Other	2A	
70-gene (MammaPrint) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	1	BINV-N (3)
50-gene (Prosigna) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A	BINV-N (3)
12-gene (EndoPredict) for pN0 and pN1 (1–3 positive nodes)	Not determined	Yes	Other	2A	BINV-N (3)
Breast Cancer Index (BCI)	Predictive of benefit of extended adjuvant endocrine therapy	Yes	Other	2A	BINV-N (4)

^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.

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References



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.

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**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)	High	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 (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 >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
	Low ^c	
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 \(Sex Assigned at Birth\) \(BINV-J\)](#).

^c Postmenopausal patients with UltraLow risk in the Stockholm Tamoxifen trial had a 20-year breast cancer specific survival of 97% with 2-5 years of Tamoxifen (Esserman LJ, et al. JAMA Oncology 2017;3:1503-1510). Patients with an ultralow-risk in the MINDACT trial have shown 8-year breast cancer specific survival above 99%. (Lopes Cardozo JMN, et al. J Clin Oncol 2022;40:1335-1345).

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References



GENE EXPRESSION ASSAYS FOR CONSIDERATION OF EXTENDED ADJUVANT SYSTEMIC THERAPY^{a,b}

Assay	Recurrence Risk/ Predictive Result	Treatment Implications
Breast Cancer Index (BCI)	BCI (H/I) Low	<ul style="list-style-type: none"> 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 disease-free survival (DFS) or OS compared to the control arm in terms of extending endocrine therapy duration.⁸
	BCI (H/I) High	<ul style="list-style-type: none"> 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 \(Sex Assigned at Birth\) \(BINV-J\).](#)

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References

**GENE EXPRESSION ASSAYS FOR CONSIDERATION OF ADJUVANT SYSTEMIC THERAPY**
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- 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.
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**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 premenopausal 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 premenopausal 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 \pm 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 patients with breast cancer 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

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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	
<p>Preferred Regimens</p> <p>First-Line Therapy</p> <ul style="list-style-type: none"> • Aromatase inhibitor + CDK4/6 inhibitor^b <ul style="list-style-type: none"> ▶ Aromatase inhibitor + ribociclib (category 1)^c ▶ Aromatase inhibitor + abemaciclib ▶ Aromatase inhibitor + palbociclib • Fulvestrant^d + CDK4/6 inhibitor^b <ul style="list-style-type: none"> ▶ Fulvestrant + ribociclib (category 1)^e ▶ Fulvestrant + abemaciclib (category 1)^e ▶ Fulvestrant + palbociclib <p>Second- and Subsequent-Line Therapy</p> <ul style="list-style-type: none"> • Fulvestrant <i>or AI if fulvestrant was used in the first line</i> + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)^{f,9} • For <i>PIK3CA</i>-mutated tumors, see additional targeted therapy options, see BINV-Q (6)^h • Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)^{i,j} 	<p>Other Recommended Regimens</p> <p>First- and/or Subsequent-Line Therapy</p> <ul style="list-style-type: none"> • Selective ER down-regulator <ul style="list-style-type: none"> ▶ Fulvestrant^k <ul style="list-style-type: none"> ▶ For <i>ESR1</i> mutated tumors, see BINV-Q (6) • Selective ER down-regulator (fulvestrant, category 1) + non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)^k • Non-steroidal aromatase inhibitor <ul style="list-style-type: none"> ▶ Anastrozole ▶ Letrozole • Selective ER modulator <ul style="list-style-type: none"> ▶ Tamoxifen • Steroidal aromatase inactivator <ul style="list-style-type: none"> ▶ Exemestane <p>Useful in Certain Circumstances</p> <p>Subsequent-Line Therapy</p> <ul style="list-style-type: none"> • Megestrol acetate • Estradiol • Abemaciclib^l • Additional targeted therapy options, see BINV-Q (6)

HER2-Positive and Postmenopausal ^{m,n} or Premenopausal Receiving Ovarian Ablation or Suppression
<ul style="list-style-type: none"> • 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 There is controversy on the choice of CDK4/6 inhibitor as there are no head to head comparisons between the agents and there are some differences in the study populations in the phase 3 randomized studies.

^c In phase 3 randomized controlled trials, ribociclib + endocrine therapy has shown OS benefit in the first-line setting.

^d Consider for disease progression on adjuvant endocrine therapy or with early disease relapse within 12 months of adjuvant endocrine therapy completion

^e In phase 3 randomized controlled trials, fulvestrant + ribociclib or abemaciclib has shown OS benefit in the first-line setting

^f In phase 3 randomized controlled trials, fulvestrant in combination with a CDK4/6 inhibitor (abemaciclib, ~~palbociclib~~, and ribociclib) has shown OS benefit in the second-line setting.

⁹ If there is disease progression while on palbociclib, there are limited phase II data to support the use of ribociclib in the second line setting

^h If there is progression while on a PI3K inhibitor, there are limited data to support another line of therapy with a PI3K-pathway inhibitor-containing regimen.

ⁱ 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.

^j 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).

^k 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 OS. 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.

^l Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting.

^m An FDA-approved biosimilar *A biosimilar validated with the reference biologic product* 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~~.

ⁿ If treatment was initiated with chemotherapy and trastuzumab + pertuzumab, and the chemotherapy was stopped, endocrine therapy may be added to trastuzumab + pertuzumab.

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

HR-Positive and HER2-Negative with Visceral Crisis [†] or Endocrine Refractory		
Setting	Subtype/Biomarker	Regimen
First Line	No germline <i>BRCA1/2</i> mutation ^b	Systemic chemotherapy see BINV-Q (5)
	Germline <i>BRCA1/2</i> mutation ^b	PARPi (olaparib, talazoparib) ^c (Category 1, preferred)
Second Line	HER2 IHC 1+ or 2+/ISH negative ^d	Fam-trastuzumab deruxtecan-nxki ^e (Category 1, preferred)
	Germline <i>BRCA1/2</i> mutation^b	PARPi (talazoparib)^c (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan-nxki No germline <i>BRCA1/2</i> mutation^b	Sacituzumab govitecan ^f (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
Third Line and beyond	Any	Systemic chemotherapy see BINV-Q (5)
	Germline <i>BRCA1/2</i> mutation^b	Talazoparib
	NTRK fusion	Larotrectinib
	Biomarker positive (ie, MSI-H, NTRK-, RET, TMB-H)	Targeted agents see BINV-Q (6)

[†] According to the 5th ESO-ESMO international consensus guidelines (Cardoso F, et al. Ann Oncol 2020;31:1625) for advanced breast cancer visceral crisis is defined as: “severe organ dysfunction, as assessed by signs and symptoms, laboratory studies and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important organ compromise leading to a clinical indication for the most rapidly efficacious therapy.”

^a For treatment of brain metastases, [see NCCN Guidelines for Central Nervous System Cancers](#).

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

^c PARPi can be considered for a later line for those with *BRCA1/2* mutation, however available evidence suggests it is more effective if used earlier.

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

^e Fam-trastuzumab deruxtecan may be considered in a later line for HER2 IHC 1+ or 2+/ISH negative, if not used in second-line. Fam-trastuzumab deruxtecan-nxki is associated with interstitial lung disease (ILD)/pneumonitis. Regular monitoring for this serious side effect is recommended. For patients with a history of ILD/pneumonitis, there are no data on managing safety or toxicity of this drug in a trial.

^f Sacituzumab govitecan-hziy may be used for adult patients with HR-positive, HER2-negative metastatic/locally advanced unresectable breast cancer after prior treatment including endocrine therapy, a CDK4/6 inhibitor, and at least two lines of chemotherapy, one of which was a taxane, and at least one of which was in the metastatic setting. It may be considered for later line if not used as second-line therapy.

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

HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
Setting	Subtype/Biomarker	Regimen
First Line	PD-L1 CPS $\geq 10^g$ regardless of germline <i>BRCA</i> mutation status ^b	Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin) ^h (Category 1, preferred)
	PD-L1 CPS $< 10^g$ and no germline <i>BRCA1/2</i> mutation ^b	Systemic chemotherapy see BINV-Q (5)
	PD-L1 CPS $< 10^g$ and germline <i>BRCA1/2</i> mutation ^b	<ul style="list-style-type: none"> • PARPi (olaparib, talazoparib) (Category 1, preferred) • Platinum (cisplatin or carboplatin) (Category 1, preferred)
Second Line	Germline <i>BRCA1/2</i> mutation ^b	PARPi (olaparib, talazoparib) (Category 1, preferred)
	Any	Sacituzumab govitecan ⁱ (Category 1, preferred) Systemic chemotherapy see BINV-Q (5)
	No germline <i>BRCA1/2</i> mutation ^b and HER2 IHC 1+ or 2+/ <i>ISH</i> negative ^d	Fam-trastuzumab deruxtecan-nxki ^e (Category 1, preferred)
Third Line and beyond	Biomarker positive (ie, MSI-H, NTRK <i>fusion</i> , RET, TMB-H)	Targeted agents see BINV-Q (6) <i>larotrectinib</i>
	Any	Systemic chemotherapy see BINV-Q (5) or sacituzumab govitecan if not previously used (Category 1, preferred)

^a For treatment of brain metastases, [see NCCN Guidelines for Central Nervous System Cancers](#).

^b Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy

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

^e Fam-trastuzumab deruxtecan may be considered in a later line for HER2 IHC 1+ or 2+/*ISH* negative, if not used in second-line. Fam-trastuzumab deruxtecan-nxki is associated with interstitial lung disease (ILD)/pneumonitis. Regular monitoring for this serious side effect is recommended. For patients with a history of ILD/pneumonitis, there are no data on managing safety or toxicity of this drug in a trial.

^g PD-L1 expression is assessed using 22C3 antibody. Threshold for positivity combined positive score ≥ 10 .

^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.

ⁱ Sacituzumab govitecan-hzyj may be used for adult patients with metastatic TNBC who have received at least 2 prior therapies, at least one of which was for metastatic disease. It may be considered for later line if not used as second line therapy.

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

HR-Positive or -Negative and HER2-Positive ^{j,k}	
Setting	Regimen
First Line ^l	Pertuzumab + trastuzumab + docetaxel (Category 1, preferred)
	Pertuzumab + trastuzumab + paclitaxel (preferred)
Second-Line ^m	Fam-trastuzumab deruxtecan-nxki ^m (Category 1, preferred)
Third-Line <i>Second Line</i>	Tucatinib + trastuzumab + capecitabine ⁿ (Category 1, preferred)
	Ado-trastuzumab emtansine (T-DM1) ^o
Fourth <i>Third Line and Beyond</i> (optimal sequence is not known) ^p	Trastuzumab + docetaxel or vinorelbine
	Trastuzumab + paclitaxel ± carboplatin
	Capecitabine + trastuzumab or lapatinib
	Trastuzumab + lapatinib (without cytotoxic therapy)
	Trastuzumab + other chemotherapy agents ^{q,r}
	Neratinib + capecitabine
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)
Additional Targeted Therapy Options see BINV-Q (6)	

^j See additional considerations for those receiving systemic HER2-targeted therapy ([BINV-Q 4](#)).

^k 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 *is* are FDA-indicated in HER2-negative disease, the panel supports use in any breast cancer subtype associated with a germline mutation. There is lower-level evidence for HER2-positive tumors, therefore category 2A for this setting. (Note: *olaparib is not approved in Poland for HER2-negative disease*).

^l Maintenance trastuzumab/pertuzumab after response (with concurrent endocrine therapy if ER+ and HER2+ metastatic breast cancer).

^m 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]). Fam-trastuzumab deruxtecan-nxki is associated with interstitial lung disease (ILD)/pneumonitis. Regular monitoring for this serious side effect is recommended. For patients with a history of ILD/pneumonitis, there are no data on managing safety or toxicity of this drug in a trial.

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 May be used as an option for third-line and beyond; the optimal sequence for third-line therapy and beyond is not known. If not a candidate fam-trastuzumab T-DM1 could be considered in the second-line.

^p 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.

^q 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.

^r Trastuzumab may be safely combined with all non-anthracycline-containing preferred and other single agents listed on ([BINV-Q 5](#)) for recurrent or metastatic breast cancer.

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

- **When receiving taxane-containing regimen:**
 - ▶ **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.~~**
 - ▶ **Consider cryotherapy of hands and feet to decrease the risk of peripheral neuropathy.**
- **~~An FDA-approved biosimilar~~ [A biosimilar validated with the reference biologic product](#) 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](#).**

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Systemic Chemotherapy for HR-Positive or -Negative and HER2-Negative ^{a,s,t,u}		
Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<ul style="list-style-type: none"> • Anthracyclines <ul style="list-style-type: none"> ▶ Doxorubicin ▶ Liposomal doxorubicin • Taxanes <ul style="list-style-type: none"> ▶ Paclitaxel • Anti-metabolites <ul style="list-style-type: none"> ▶ Capecitabine ▶ Gemcitabine • Microtubule inhibitors <ul style="list-style-type: none"> ▶ Vinorelbine ▶ Eribulin 	<ul style="list-style-type: none"> • Cyclophosphamide • Docetaxel • Albumin-bound paclitaxel • Epirubicin • ixabepilone 	<ul style="list-style-type: none"> • AC (doxorubicin/cyclophosphamide) • EC (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/methotrexate/fluorouracil) • Docetaxel/capecitabine • GT (gemcitabine/paclitaxel) • Gemcitabine/carboplatin • Carboplatin + paclitaxel or albumin-bound paclitaxel

- For specific lines of systemic therapy options for HR-positive and HER2-negative with visceral crisis or endocrine refractory, [see BINV-Q \(1\)](#).
- For specific lines of systemic therapy options for HR-negative and HER2-negative (TNBC), [see BINV-Q \(2\)](#).
- For specific lines of systemic therapy options for HR-negative or -positive and HER2-positive, [see BINV-Q \(3\)](#).

^a For treatment of brain metastases, [see NCCN Guidelines for Central Nervous System Cancers](#).

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

^s 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.~~

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

^u Consider cryotherapy of hands and feet to decrease the risk of peripheral neuropathy when receiving taxane therapies.

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**ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING
FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE****Biomarkers Associated with FDA-Approved Targeted Therapies**

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Targeted Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive/ HER2-negative ^v	PIK3CA activating mutation	PCR (blood or tissue block if blood negative)	Alpelisib + fulvestrant ^w	Category 1	Preferred second- or subsequent-line therapy
HR-positive/ HER2-negative ^x	ESR1 mutation	NGS, PCR (blood)	Elacestrant	Category 2A	Other-recommended regimen
Any	NTRK fusion	FISH, NGS, PCR (tissue block)	Larotrectinib ^y Entrectinib ^y	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR (tissue block)	Pembrolizumab ^{z,aa} Dostarlimab-gxly ^{bb}	Category 2A	
Any	TMB-H (≥10 mut/mb)	NGS	Pembrolizumab ^{z,aa}	Category 2A	
Any	RET-fusion	NGS	Selpercatinib ^{cc}	Category 2A	

^v 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.

^w The safety of alpelisib in patients with Type 1 or uncontrolled Type 2 diabetes has not been established.

^x For postmenopausal females or adult males with ER-positive, HER2-negative, ESR1-mutated disease after progression on one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor.

^y 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.

^z See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

^{aa} 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.

^{bb} 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.

^{cc} Selpercatinib is indicated for adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

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**EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH STAGE-
IV (M1) DISEASE**

Breast Cancer Subtype	Emerging Biomarkers	Detection	Potential targeted therapy ^{dd}	NCCN Category of Evidence	NCCN Category of Preference
ER+/HER2- ER-/HER2-	HER2 activating mutations	NGS ^{ee}	Neratinib ± fulvestrant ^{ff} Neratinib ± trastuzumab/ fulvestrant ^{gg}	Category 2B	Useful in certain circumstances • If ER+/HER2-, in patients who have already received CDK4/6 inhibitor therapy.
Any	Somatic <i>BRCA1/2</i> mutations	NGS ^{ee}	Olaparib ^{hh}	Category 2B	Useful in certain circumstances
Any	Germline <i>PALB2</i>	Germline sequencing	Olaparib ^{hh}	Category 2B	Useful in certain circumstances

^{dd}At the present time, the data for the emerging biomarkers for the potential targeted agents noted in the table are promising but limited.

^{ee}Tumor tissue or ctDNA.

^{ff}Ma CX, Luo J, Freedman RA, et al. The phase II MuthHER study of neratinib alone and in combination with fulvestrant in HER2-mutated, non-amplified metastatic breast cancer. *Clin Cancer Res* 2022; 28:1258-1267.

^{gg}Jhaveri KL, Goldman JW, Hurvitz SA, et al. Neratinib plus fulvestrant plus trastuzumab (N+F+T) for hormone receptor-positive (HR+), HER2-negative, HER2-mutant metastatic breast cancer (MBC): Outcomes and biomarker analysis from the SUMMIT trial. *Journal of Clinical Oncology* 2022;40:1028-1028.

^{hh}Tung NM, Robson ME, Ventz S, et al. TBCRC 048: phase II study of olaparib for metastatic breast cancer and mutations in homologous recombination-related genes. *J Clin Oncol* 2020;38:4274-4282.

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**DOISING: 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 days¹
- ▶ Doxorubicin 20 mg/m² IV day 1 weekly²
- ▶ Liposomal doxorubicin³ 50 mg/m² IV day 1; cycled every 28 days

• Taxanes:

- ▶ Paclitaxel 175 mg/m² IV day 1; cycled every 21 days⁴
- ▶ Paclitaxel 80 mg/m² IV day 1 weekly⁵

• Antimetabolites:

- ▶ Capecitabine⁶ 1000–1250 mg/m² PO twice daily days 1–14; cycled every 21 days
- ▶ Gemcitabine⁷ 800–1200 mg/m² IV days 1, 8, and 15; cycled every 28 days

• 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
 - ◊ **25–30 mg/m² IV days 1, 8, cycled every 21 days; or**
 - ◊ **60–80 mg/m² PO day 1 weekly**
- ▶ Eribulin¹⁰ 1.4 mg/m² IV days 1 and 8; cycled every 21 days

• Platinum (for TNBC and germline BRCA1/2 mutation)

- ▶ Carboplatin¹¹ AUC 6 IV on day 1
 - ◊ Cycled every 21–28 days; **or**
 - ◊ **Carboplatin AUC 2 IV on day 1 weekly**
- ▶ Cisplatin¹² 75 mg/m² IV on day 1
 - ◊ Cycled every 21 days

• Cyclophosphamide¹³

- ▶ 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^{14,16}

- ▶ 35 mg/m² IV weekly for 6 weeks followed by a 2-week rest, then repeat

• Albumin-bound paclitaxel^{17,18}

- ▶ 400 mg/m² or 125 mg/m² IV days 1, 8, and 15
 - ◊ Cycled every 28 days

• Albumin-bound paclitaxel¹⁷

- ▶ 260 mg/m² IV
 - ◊ Cycled every 21 days

• Epirubicin¹⁹

- ▶ 60–90 mg/m² IV day 1
 - ◊ Cycled every 21 days

• Irabepitone²⁰

- ▶ 40 mg/m² IV day 1
 - ◊ Cycled every 21 days

• Sacituzumab govitecan-hzjy (for TNBC or HR+/HER2-)^{21,22}

- ▶ 10 mg/kg IV on days 1 and 8
 - ◊ Cycled every 21 days

• Fam-trastuzumab deruxtecan-nxki (for HER2 IHC 1+ or 2+/*ISH* negative)²³

- ▶ 5.4 mg/kg IV day 1
 - ◊ Cycled every 21 days

• AC²⁴

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

• EC²⁵

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

• CMF²⁶

- ▶ 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/capecitabine²⁷

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

• GT²⁸

- ▶ 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/carboplatin²⁹

- ▶ 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 paclitaxel³⁰

- ▶ 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^{31,32}

- ▶ Paclitaxel 175–200 mg/m² IV day 1
- ▶ Carboplatin AUC 6 IV day 1
 - ◊ Cycled every 21 days
 - or
 - ▶ Paclitaxel ~~100~~ **80** mg/m² IV days 1, 8, and 15
 - ▶ Carboplatin AUC 2 IV days 1, 8, and 15
 - ◊ Cycled every 28 days

See dosing for additional targeted therapies on [BINV-Q \(13\)](#)

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.

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[Continued](#)

**BINV-Q
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**DOSING: SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE****HER2-Positive Regimens:**^{ii,jj,kk}

- **Pertuzumab + trastuzumab + docetaxel**³³
 - ▶ 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/m² IV day 1
 - ◊ Cycled every 21 days
- **Pertuzumab + trastuzumab + paclitaxel**^{34,35}
 - ▶ 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 days³⁵
 - ▶ Paclitaxel 80 mg/m² IV day 1 weekly³⁴
 - or
 - ▶ Paclitaxel 175 mg/m² day 1
 - ◊ Cycled every 21 days
- **Tucatinib + trastuzumab + capecitabine**³⁶
 - ▶ 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/m² orally twice daily on days 1–14
 - ◊ Cycled every 21 days
- **Ado-trastuzumab emtansine (T-DM1)**³⁷
 - ▶ 3.6 mg/kg IV day 1
 - ◊ Cycled every 21 days
- **Fam-trastuzumab deruxtecan-nxki**³⁸
 - ▶ 5.4 mg/kg IV day 1
 - ◊ Cycled every 21 days
- **Paclitaxel/carboplatin + trastuzumab**³⁹
 - ▶ Carboplatin AUC 6 IV day 1
 - ▶ Paclitaxel 175 mg/m² IV day 1
 - ◊ Cycled every 21 days
 - ▶ Trastuzumab 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
 - or
 - ▶ Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV day 1 every 21 days³⁵
- **Weekly paclitaxel/carboplatin + trastuzumab**⁴⁰
 - ▶ Paclitaxel 80 mg/m² 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 days³⁵
- **Trastuzumab + paclitaxel**^{41,42}
 - ▶ Paclitaxel 175 mg/m² IV day 1 cycled every 21 days⁴¹
 - or
 - ▶ Paclitaxel 80–90 mg/m² IV day 1 weekly⁴³
 - ▶ 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 days³⁵
- **Trastuzumab + docetaxel**^{43,44}
 - ▶ Docetaxel 80–100 mg/m² IV day 1 cycled every 21 days⁴³
 - or
 - ▶ Docetaxel 35 mg/m² IV days 1, 8, and 15 weekly cycled every 28 days⁴⁴
 - ▶ 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 days³⁵

ⁱⁱ An FDA-approved biosimilar [A biosimilar validated with the reference biologic product](#) is an appropriate substitute for trastuzumab.

^{jj} 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.

^{kk} 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.

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See dosing for additional targeted therapies on [BINV-Q \(13\)](#)

[Continued](#)

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**DOSING: SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE****HER2-Positive Regimens (continued):^{ii,ji}**• **Trastuzumab + vinorelbine^{9,45,46}**

- ▶ Vinorelbine
 - ◊ 25 mg/m² IV day 1 weekly; or
 - ◊ 20–35 30 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
- ▶ 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 days³⁵

• **Trastuzumab + capecitabine^{47,48,49}**

- ▶ Capecitabine 1000–1250 mg/m² PO twice daily days 1–14 cycled every 21 days
- ▶ Trastuzumab 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly^{41,48}
- or
- ▶ Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV day 1 every 21 days^{33,35}

• **Lapatinib + capecitabine⁵⁰**

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

• **Trastuzumab + lapatinib⁵⁴**

- ▶ 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 days³⁵

• **Neratinib + capecitabine⁵²**

- ▶ Neratinib 240 mg PO daily on days 1–21
- ▶ Capecitabine 750 mg/m² PO twice daily on days 1–14
 - ◊ Cycled every 21 days
- or
- ▶ 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 15–21
- ▶ Capecitabine 750 mg/m² PO twice daily on days 1–14
 - ◊ Cycled every 21 days x 1 cycle
- Followed by
- ▶ Neratinib 240 mg PO daily on days 1–21
- ▶ Capecitabine 750 mg/m² PO twice daily on days 1–14
 - ◊ Cycled every 21 days beginning with cycle 2

• **Margetuximab-cmkb + capecitabine⁵³**

- ▶ Margetuximab 15 mg/kg IV day 1
- ▶ Capecitabine 1000 mg/m² po twice daily days 1–14
 - ◊ Cycled every 21 days

• **Margetuximab-cmkb + eribulin⁵³**

- ▶ Margetuximab 15 mg/kg IV day 1
- ▶ Eribulin 1.4 mg/m² IV days 1 and 8
 - ◊ Cycled every 21 days

• **Margetuximab-cmkb + gemcitabine⁵³**

- ▶ Margetuximab 15 mg/kg IV day 1
- ▶ Gemcitabine 1000 mg/m² IV days 1 and 8
 - ◊ Cycled every 21 days

• **Margetuximab-cmkb + vinorelbine⁵³**

- ▶ Margetuximab 15 mg/kg IV day 1
- ▶ Vinorelbine 25–30 mg/m² IV days 1 and 8
 - ◊ Cycled every 21 days

See dosing for additional targeted therapies on [BINV-Q \(13\)](#)

ⁱⁱ An FDA-approved biosimilar [A biosimilar validated with the reference biologic product](#) is an appropriate substitute for trastuzumab.

^{ji} 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.

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**SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE**
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**SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE**
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**DOSING: ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING
FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE****• Alpelisib + fulvestrant¹**

- ▶ 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

• Dostarlimab-gxly²

- ▶ 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

• Elacestrant³

- ▶ 345 mg PO daily on days 1–28
- ▶ Cycled every 28 days until disease progression or unacceptable toxicity

• Entrectinib⁴

- ▶ 600 mg PO daily on days 1–28
- ▶ Cycled every 28 days until disease progression or unacceptable toxicity

• Larotrectinib⁵

- ▶ 100 mg PO twice daily on days 1–28
- ▶ Cycled every 28 days until disease progression or unacceptable toxicity

• Olaparib⁶ tablet

- ▶ 300 mg PO twice daily
- ▶ Cycled every 28 days

• Pembrolizumab⁷⁻¹⁰

- ▶ 200 mg IV on day 1, every 21 days until disease progression or unacceptable toxicity, or up to 24 months or
- ▶ 400 mg IV on day 1, every 6 weeks until disease progression or unacceptable toxicity, or up to 24 months

• Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine and carboplatin)¹¹

- ▶ Pembrolizumab 200 mg IV day 1 (given every 21 days)
- ▶ Albumin-bound paclitaxel 100 mg/m² days 1, 8, 15 (given every 28 days) or
- ▶ Paclitaxel 90 mg/m² IV days 1, 8, 15 (given every 28 days) or
- ▶ Pembrolizumab 200 mg IV day 1
- ▶ Gemcitabine 1000 mg/m² IV days 1 and 8
- ▶ Carboplatin AUC 2 IV days 1 and 8
 - ◊ Given every 21 days

• Selpercatinib¹²

- ▶ Patients < 50 kg: 120 mg PO twice daily until disease progression or unacceptable toxicity
- ▶ Patients ≥ 50 kg: 160 mg PO twice daily until disease progression or unacceptable toxicity

• Talazoparib¹³ tablet

- ▶ 1 mg PO daily
- ▶ Cycled every 28 days

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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.

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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.

Note: This is the NCCN Guidelines: Poland Edition, For definitions, see page DEF-1.

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

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[Continued](#)

BINV-R
2 OF 3

**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 <i>As clinically indicated</i>	Every 4–6 cycles	Every 2–6 months	Yes <i>As clinically indicated</i>
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

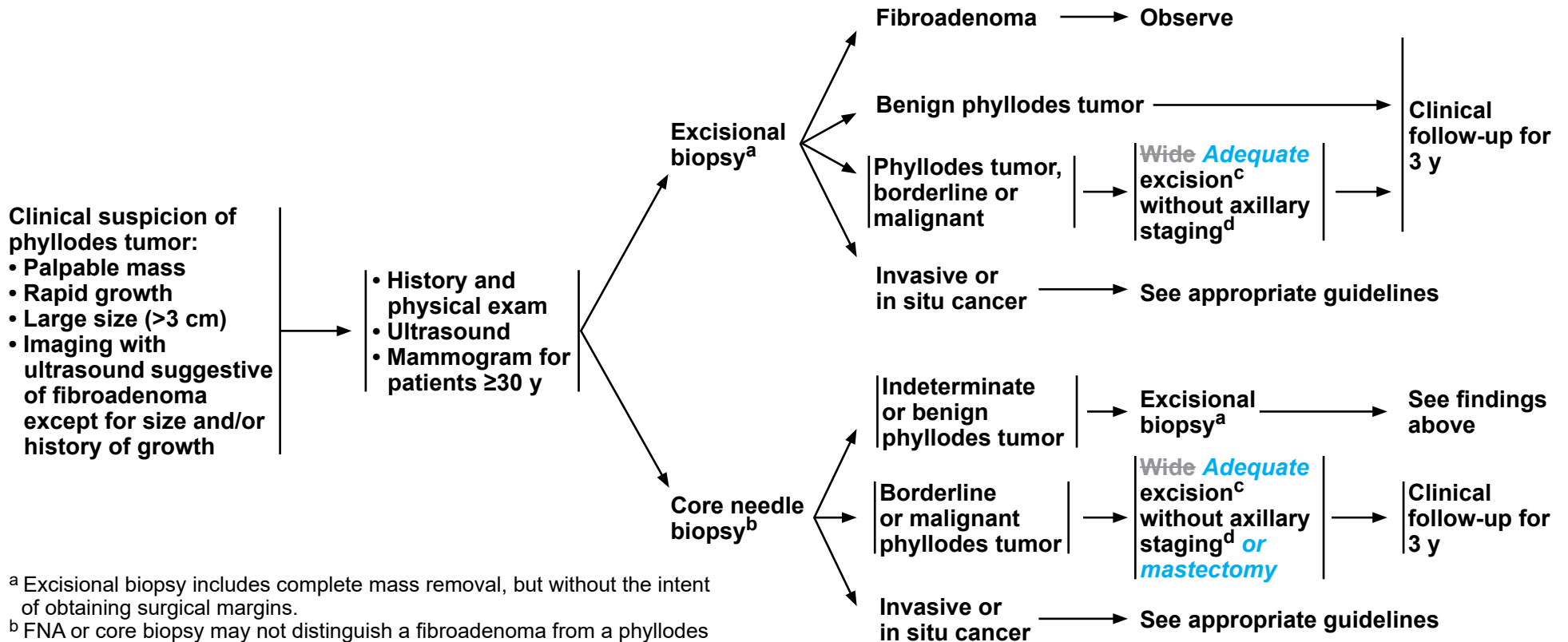
^b In patients who have long-term stable disease, the frequency of monitoring can be reduced.

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CLINICAL PRESENTATION WORKUP FINDINGS TREATMENT SURVEILLANCE



^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 *adequate* excision means excision with the intention of obtaining surgical margins ≥ 1 cm > 1 mm. 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. *The use of radiotherapy for phyllodes tumors should be considered in malignant or borderline tumors at younger age, or tumor diameter >5 cm, or narrow resection margin. In the post-mastectomy setting, chest wall radiotherapy should be considered in patients with high risk of local recurrence.*

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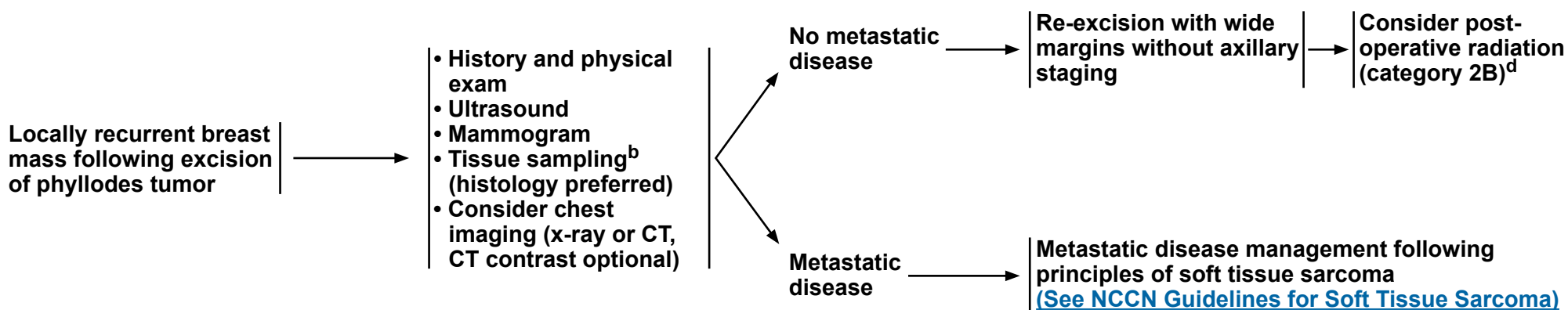
PHYLLODES TUMOR RECURRENCE

CLINICAL PRESENTATION

WORKUP

FINDINGS

TREATMENT



^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.

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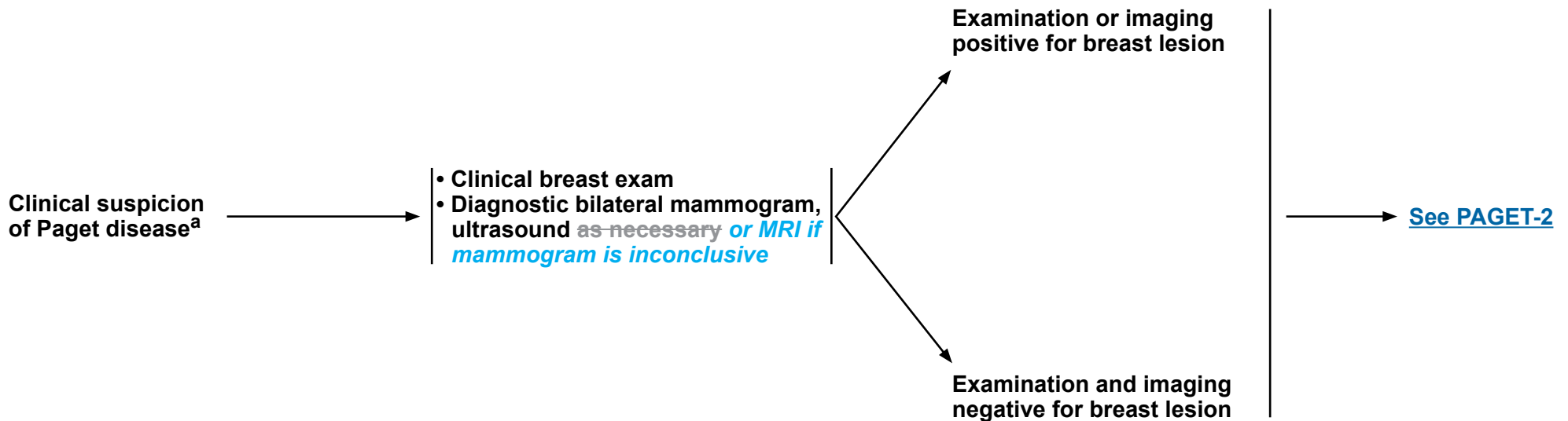
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CLINICAL PRESENTATION

WORKUP



^a Nipple or areolar eczema, ulceration, bleeding, or itching.

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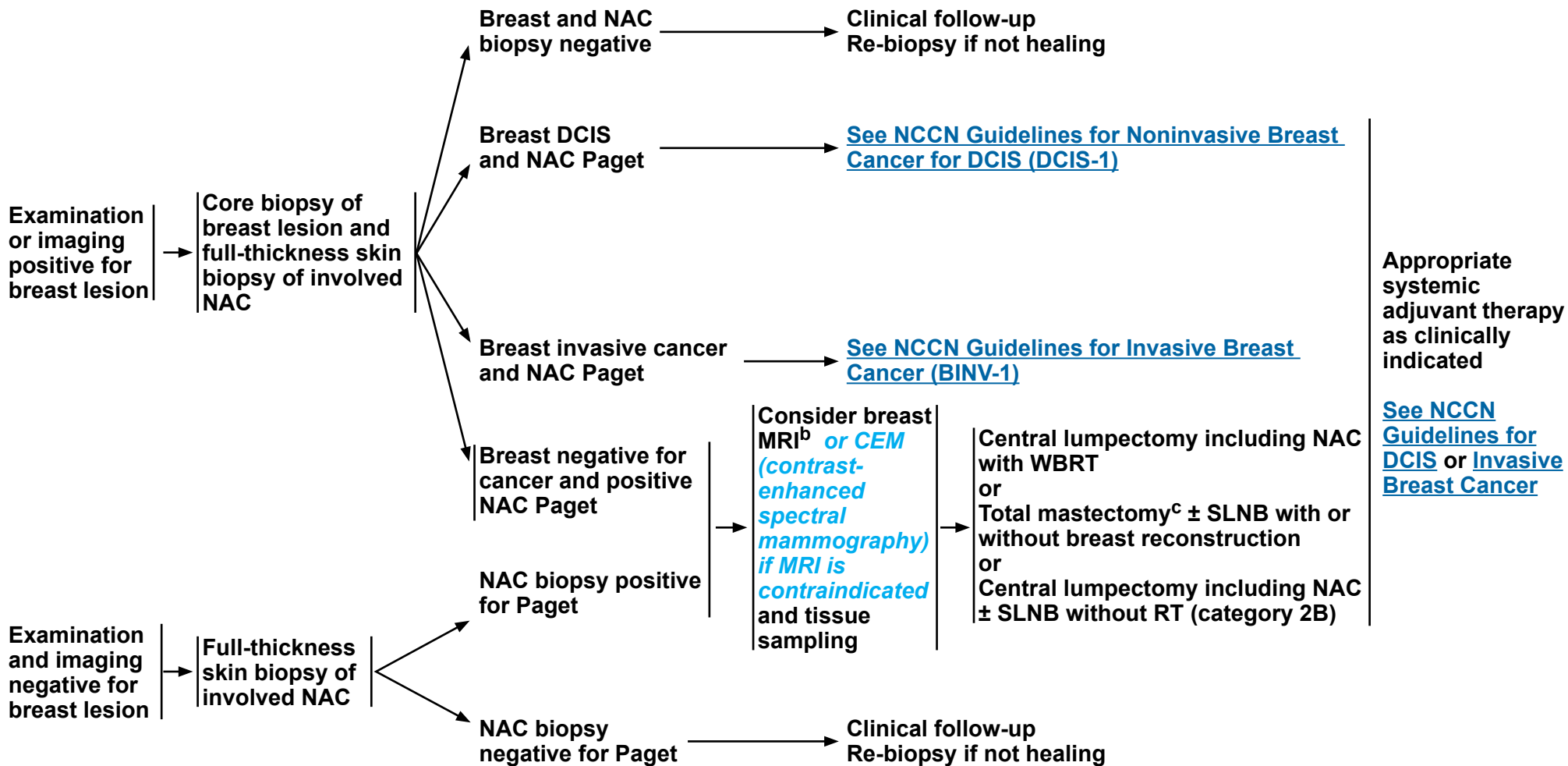


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Paget Disease

WORKUP

TREATMENT



^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: This is the NCCN Guidelines: Poland Edition, For definitions, see page DEF-1.

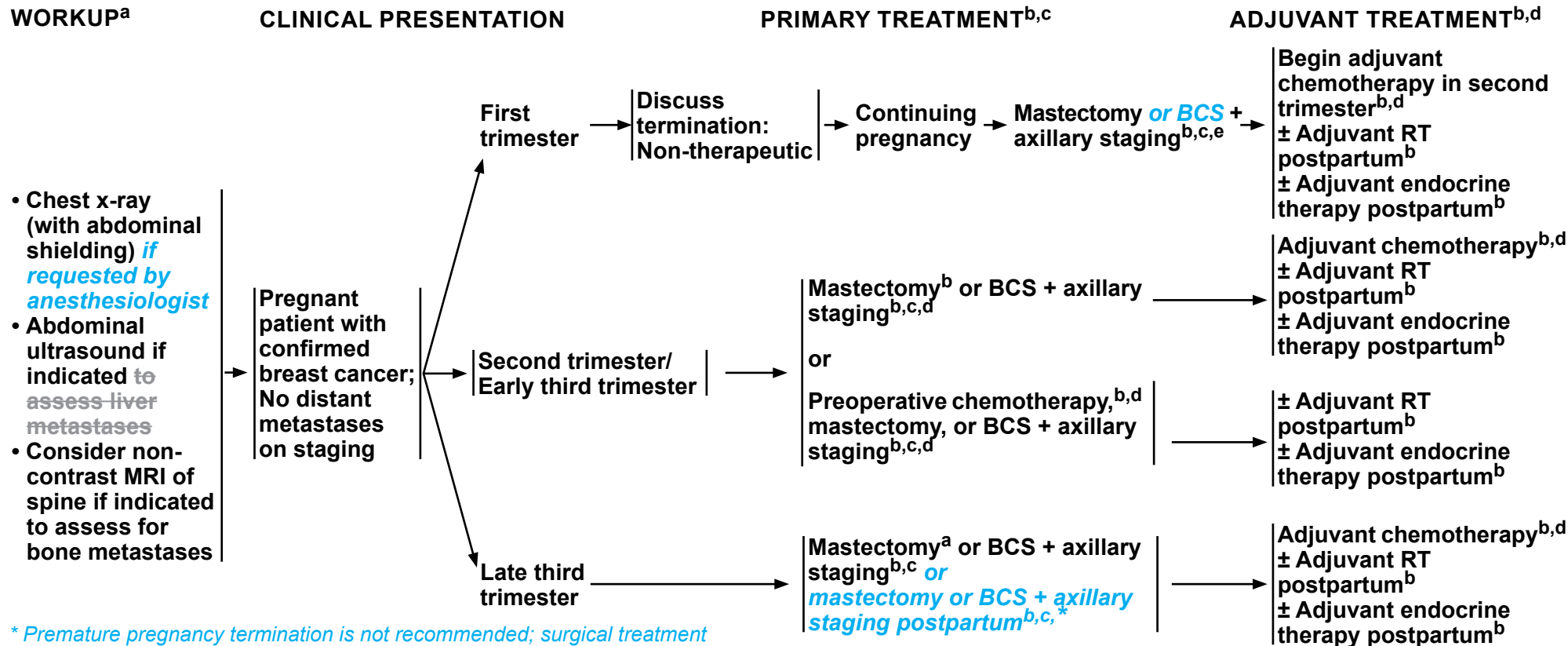
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Breast Cancer During Pregnancy



* Premature pregnancy termination is not recommended; surgical treatment may be postponed in the late third trimester in selected cases.

^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 *Safe and recommended* chemotherapy during pregnancy for breast cancer is from regimens that utilize various combinations of doxorubicin, cyclophosphamide, and fluorouracil *paclitaxel*. 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. The optimal schedule of *paclitaxel during pregnancy* is unclear. If used, the NCCN Panel recommends weekly administration of paclitaxel *Weekly administration* after the first trimester *is recommended* 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.

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CLINICAL PRESENTATION^a

WORKUP

Clinical pathologic diagnosis of IBC

- History and physical exam by multidisciplinary team and obtain medical photography
- CBC
- Comprehensive metabolic panel, including LFTs 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} *as an alternative to chest, abdominal, pelvic and bone imaging*
 - ▶ Breast MRI (optional)

[See Preoperative/Adjuvant Therapy Regimens \(BINV-L\)](#)

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

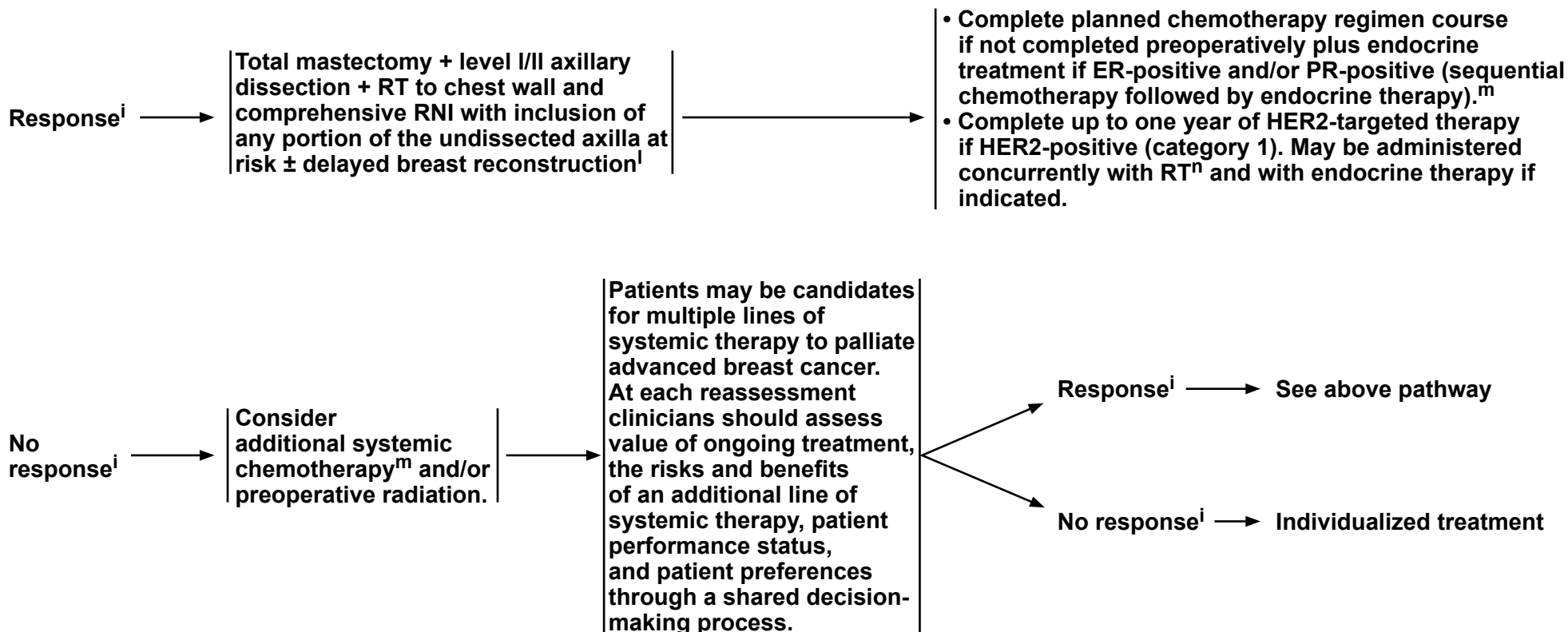
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RESPONSE TO PREOPERATIVE THERAPY

TREATMENT^j



ⁱ 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.

^j Patients with recurrent IBC should be treated according to the guideline for recurrence/stage IV (M1) disease ([BINV-19](#)).

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

^l See [Systemic Therapy Regimens for Recurrent Unresectable \(Local or Regional\) or Stage IV \(M1\) Disease \(BINV-Q\)](#).

^m See [Adjuvant Endocrine Therapy \(BINV-K\)](#).

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

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**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 intent 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 and 1.4 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	T2	Tumor >20 mm but ≤50 mm in greatest dimension
T0	No evidence of primary tumor	T3	Tumor >50 mm in greatest dimension
Tis (DCIS)*	Ductal carcinoma <i>in situ</i>	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
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma <i>in situ</i> (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	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
T1	Tumor ≤20 mm in greatest dimension	T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T1mi	Tumor ≤1 mm in greatest dimension	T4c	Both T4a and T4b are present
T1a	Tumor >1 mm but ≤5 mm in greatest dimension (round any measurement >1.0–1.9 mm to 2 mm)	T4d	Inflammatory carcinoma
T1b	Tumor >5 mm but ≤10 mm in greatest dimension		
T1c	Tumor >10 mm but ≤20 mm in greatest dimension		

*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](#)

**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](#)



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](#)

**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](#)



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](#)



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		IB
			Negative	Negative		
	G2	Positive	Positive	Positive	IA	
				Negative		
				Positive		
			Negative	Positive		IB
				Negative		
				Positive		
G3		Positive	Positive	IA		
			Negative			
			Positive			
		Negative	Positive	IB		
			Negative			
			Positive			

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

*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.

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[Continued](#)



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	IIB
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
	Negative		Positive	IIB	
			Negative	IIB	
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
	Negative		Positive	IIB	
			Negative	IIIB	
	G3	Positive	Positive	Positive	IB
				Negative	IIB
Negative			Positive	IIB	
			Negative		IIB
Negative		Positive	Positive	IIIA	
			Negative		IIIB
	Negative	Positive	IIIB		
		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	IIIA
		Negative	Positive	Positive	
				Negative	IIB
	Negative		Positive	IIIA	
			Negative	IIIB	
	G2	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	
				Negative	IIIB
		Negative	Positive	Positive	
				Negative	IIIA
	Negative		Positive	IIIB	
			Negative	IIIB	
	G3	Positive	Positive	Positive	IIB
				Negative	IIIA
Negative			Positive	IIIA	
			Negative		IIIA
Negative		Positive	Positive	IIIB	
			Negative		IIIC
	Negative	Positive	IIIB		
		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.

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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		IIIC
			Negative	Negative		
	G2	Positive	Positive	Positive	IIIA	
				Negative	IIIB	
			Negative	Positive		
				Negative		
		Negative	Positive	Positive		IIIC
			Negative	Negative		
G3			Positive	Positive	Positive	IIIB
					Negative	
	Negative	Positive		Positive	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.

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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	IA
							Negative	
			Negative			Positive		
						Negative		
	Negative		Positive		Positive			
					Negative			
			Negative	Positive				
				Negative				
			G3	Positive	Positive	Positive	IA	
						Negative		
	Negative				Positive			
				Positive	Positive			
		Negative						
	Negative	Positive		Positive	IB			
			Negative					
		Negative						

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

*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.

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[Continued](#)



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		IA
		Negative		IIB		
		G2			Positive	Positive
			Negative	IIB		
	Negative		Positive			IB
			Negative	IIB		
			G3		Positive	Positive
	Negative			IIB		
	Negative	Positive				IIA
		Negative		IIB		
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		IB
		Negative		IIIA		
		G2			Positive	Positive
			Negative	IIIA		
	Negative		Positive			IB
			Negative	IIIB		
			G3		Positive	Positive
	Negative			IIIA		
	Negative	Positive				IIB
		Negative		IIIA		
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.

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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	Negative	IIIB	
		Negative	Positive	Positive		IIIA
			Negative	Negative	IIIB	
	G2	Positive	Positive	Positive	IIIA	
			Negative	Negative	IIIB	
		Negative	Positive	Positive		IIIA
			Negative	Negative	IIIB	
		G3	Positive	Positive	Positive	IIIB
				Negative	Negative	
			Negative	Positive	Positive	IIIC
				Negative	Negative	
Any T Any N M1	Any	Any	Any	Any	IV	

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

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Notes:

- 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.
- 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.
- 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:

- 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.
- 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.
- 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.



ABBREVIATIONS

APBI	accelerated partial breast irradiation	LFTs	liver function tests	TNBC	triple-negative breast cancer
BCS	breast-conserving surgery	LVEF	left ventricular ejection fraction	WBRT	whole breast radiation therapy
CPS	combined positive score	NAC	nipple-areolar complex		
ctDNA	circulating tumor deoxyribonucleic acid	NST	no special type		
DCIS	ductal carcinoma in situ	OS	overall survival		
ER	estrogen receptor	PBI	partial breast irradiation		
EPC	encapsulated papillary carcinoma	pCR	complete pathological response		
FNA	fine-needle aspiration	PR	Progesterone Receptor		
HER2	human Epidermal Growth Factor Receptor 2	RNI	regional nodal irradiation		
HR	hormone receptor	RS	recurrence score		
IBC	inflammatory breast cancer	SLN	sentinel lymph node		
IBTR	ipsilateral breast tumor recurrence	SLNB	sentinel lymph node biopsy		
IHC	immunohistochemistry	SPC	solid papillary carcinoma		
IMRT	intensity modulated radiation therapy	SNRI	selective serotonin reuptake inhibitors		
ISH	in situ hybridization	SSRI	serotonin and norepinephrine reuptake inhibitors		



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.



Discussion

This discussion corresponds to the NCCN Guidelines for Breast Cancer. The section for DCIS and Locoregional Management of Invasive Breast Cancer was updated on May 7th, 2022. The update to the rest of the Discussion is in progress.

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Overview

Breast cancer is the most common malignancy in females in the United States and is second only to lung cancer as a cause of cancer death. The American Cancer Society has estimated that 290,560 Americans will be diagnosed with breast cancer and 43,780 will die of disease in the United States in 2022.¹ 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, 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](#).



Ductal Carcinoma in Situ (Tis, N0, M0)

The diagnosis of DCIS has increased since the introduction and increased utilization of screening mammography. According to the American Cancer Society, over 50,000 cases of DCIS of the female breast will be diagnosed in 2022 in United States.¹

Workup for DCIS

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 (CAP) 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. This is in accordance with the American Society for Clinical Oncology (ASCO)/CAP guidelines,⁴ which recommend that ER testing of newly diagnosed DCIS to determine potential benefit of endocrine therapies for breast cancer risk reduction and progesterone receptor (PR) testing be considered optional. Although the tumor HER2 status is of prognostic significance in invasive cancer, its importance in DCIS has not been established. To date, studies have either found unclear or weak evidence of HER2 status as a prognostic indicator in DCIS,⁵⁻⁸ and no statistically significant benefit to the use of trastuzumab concurrently with radiation in HER2-amplified DCIS.⁹ The NCCN Panel has concluded that HER2 status for DCIS does not alter the management strategy and therefore is not recommended for 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, Ovarian, and Pancreatic.](#)

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.¹⁰ In a prospective, observational study of 193 patients with pure DCIS who underwent both mammography and MRI imaging preoperatively; 93 (56%) patients were diagnosed by mammography and 153 (92%) were diagnosed by MRI ($P < .0001$). Of the 89 patients with high-grade DCIS, 43 (48%) who were not diagnosed by mammography were diagnosed by MRI alone.¹⁰ However, other studies suggest that MRI can overestimate the extent of disease.¹¹ Therefore, the surgical decisions for performing a mastectomy for DCIS should not be solely based on MRI findings alone. 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 performed to determine whether the use of MRI reduces re-excision rates and decreases local recurrence in patients with DCIS show conflicting results. While several studies suggest no reduction in re-excision rates in patients with pure DCIS undergoing breast-conserving surgery (BCS) following MRI compared with those who did not undergo preoperative MRI,^{12,13} some have demonstrated a reduction in re-excision rate with use of preoperative MRI for DCIS.^{14,15} One study showed an additional cancer detection rate of 6.2% with preoperative MRI.¹⁵ Therefore, the use of preoperative MRI remains controversial. 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 BCS), and/or radiation therapy (RT), followed by adjuvant endocrine therapy in eligible patients to reduce risk of recurrence.

The choice of local treatment does not impact overall disease-related survival; therefore, the individual's preferences for risk-reduction must be considered.

Several prospective randomized trials of pure DCIS have shown that the addition of whole breast radiation therapy (WBRT) after BCS decreases the rate of in-breast disease recurrence,¹⁶⁻²³ but not distant metastasis-free survival.²⁴ A meta-analysis of four large multicenter randomized trials confirmed the results of the individual trials, demonstrating that the addition of WBRT after BCS for DCIS provides a statistically and clinically significant reduction in ipsilateral breast events (hazard ratio [HR], 0.49; 95% confidence interval [CI]; 0.41–0.58, $P < .00001$).²⁵ However, these trials did not show that the addition of RT has an overall survival (OS) benefit. The long-term follow-up of the NSABP B-17 showed that at 15 years, RT resulted in a 52% reduction of ipsilateral invasive recurrence compared with excision alone (HR, 0.48; 95% CI, 0.33–0.69, $P < .001$).²² The 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).²² Similar findings were reported by a large observational study of the SEER database that included 108,196 patients with DCIS.²⁶ In a subgroup analysis at 10 years, of 60,000 patients treated with BCS, with or without WBRT, a 50% reduction in the risk of ipsilateral recurrence (adjusted HR, 0.47 [95% CI, 0.42–0.53]; $P < .001$) was associated with the addition of WBRT. However, in this study, breast cancer-specific mortality was found to be similar (HR, 0.86 [95% CI, 0.67–1.10]; $P = .22$).²⁶

In contrast, several population-based studies suggest beneficial effects of WBRT for DCIS after BCS, for example, the use of WBRT in patients with higher-risk DCIS (eg, higher nuclear grade, younger age, larger tumor size) was demonstrated to be associated with a modest but statistically significant improvement in OS.²⁷ In another observational study of the SEER database including 140,366 patients with DCIS, the 15-year breast cancer mortality rate was 1.7% for those treated with breast-conserving therapy (BCT) versus 2.3% for patients treated with BCS alone (HR, 0.77; 95% CI, 0.67–0.88; $P < .001$), demonstrating a small but significant reduction in breast cancer mortality with BCS and WBRT compared with BCS alone.²⁸

RT Boost: The use of RT boost has been demonstrated to provide a small but statistically significant reduction in ipsilateral breast tumor recurrence (IBTR) risk (4% at 20 years) in all age groups for invasive breast cancers.²⁹⁻³²

A pooled analysis of patient-level data from 10 academic institutions evaluated outcomes of pure DCIS patients, all treated with BCS 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 a 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 (HR, 0.73; 95% CI, 0.57–0.94; $P = .01$).³³ 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 (HR, 0.69; 95% CI, 0.53–0.91; $P < .010$).³³ 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 (NSABP) definition, or margins >2 mm as per Society of Surgical Oncology [SSO]/American Society for Radiation Oncology [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 randomized phase III trials are studying whether an RT boost reduces recurrence in patients with DCIS (ClinicalTrials.gov Identifiers: NCT00470236 and NCT00907868).

These trials have completed accrual and are now in active follow-up. A recent publication on the health-related quality of life (HRQOL) in patients enrolled in the BIG 3-07/TROG 07.01 phase III trial (NCT00470236) showed that after 2 years, the cosmetic status was impacted negatively with the boost versus no boost, suggesting the importance of informed shared decision-making regarding addition of boost until data related to impact on local recurrence and OS are published.³⁴ According to the 5-year data from this trial, presented at the 2021 annual San Antonio Breast Cancer Symposium (SABCS) meeting, 93% of patients in the group who did not receive a boost were free from local recurrence compared with 97% in the group who received an RT boost (HR, 0.47; 95% CI, 0.31–0.72; $P < .001$).³⁵ The peer-reviewed publication of these data is awaited.

Breast Conserving Surgery Alone Without WBRT: RT adds to treatment cost and is accompanied by adverse effects. Therefore, in an attempt to de-escalate treatment and limit morbidity and preserve quality of life (QOL), several trials have examined omission of RT 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).³⁶⁻³⁹ For example, in one retrospective review, 10-year disease-free survival (DFS) rates of 186 patients with DCIS treated with

BCS alone were 94% for patients with low-risk DCIS and 83% for patients with both intermediate- and high-risk DCIS.³⁶ In another retrospective study of 215 patients with DCIS treated with BCS without RT, or systemic risk reduction therapy, the recurrence rates over 8 years were 0%, 21.5%, and 32.1% in patients with low-, intermediate-, or high-risk DCIS, respectively.³⁷ The stratification for risk of recurrence in this retrospective study was calculated using the modified Van Nuys Prognostic Index based on tumor grade, size, absence of comedo necrosis, margin width, and age at diagnosis.³⁷

A multi-institutional, non-randomized, prospective study of selected patients with low-risk DCIS treated without radiation has also provided some support for BCS alone without radiation.⁴⁰ Patients were enrolled onto one of two low-risk cohorts: 1) low- or intermediate-grade DCIS, tumor size 2.5 cm or smaller ($n = 561$); or 2) 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).⁴⁰ Although the rate of IBTR was acceptably low for the low-/intermediate-grade group at 5 years, at a median follow-up 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.

The RTOG 9804 trial investigated outcomes of RT omission in the setting of low-risk DCIS, randomizing 636 patients with low-risk disease to either RT or observation after surgery.²³ In this study, low risk consisted of low- to intermediate-grade DCIS measuring less than 2.5 cm, with negative margins of greater than or equal to 3 mm. With a median follow-up of 7



years, a reduced risk of local recurrence was seen with use of RT compared with observation (0.9% vs. 6.7%; HR, 0.11; 95% CI, 0.03–0.47). No difference was seen in either DFS or OS. With a follow-up of 15 years, local recurrence rates were reduced by 50% with RT versus without RT (7.1% vs. 15.1%; HR, 0.36; 95% CI, 0.20–0.66).⁴¹

The available evidence from four randomized trials (NSABP B-39/RTOG 0413,⁴² OCOG-RAPID,⁴³ University of Florence,⁴⁴ and GEC-ESTRO⁴⁵) of patients with breast cancer (tumors ≤ 3 cm) has shown that accelerated partial breast irradiation (APBI) delivered with multi-catheter brachytherapy is non-inferior in local control compared with WBRT, with similar toxicity and breast cosmetic outcomes. Patients with DCIS constituted 25%, 18%, 8.8%, and 6% of patients in the NSABP B-39/RTOG 0413, OCOG RAPID, University of Florence, and GEC-ESTRO trials, respectively. Per the ASTRO guideline for APBI, patients with screen-detected DCIS measuring less than 2.5 cm, with grade I or II disease, and with negative margins of 3 mm or more are “suitable” candidates for APBI.⁴⁶

Margin Status After Breast-Conserving Therapy: Prospective randomized trials have not been carried out to analyze whether wider margins can replace the need for RT 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 compared to greater than or equal to 10 mm.⁴⁷ In a meta-analysis of 4660 patients with DCIS treated with BCS 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.⁴⁸

A study retrospectively reviewed a database of 2996 patients with DCIS who underwent BCS to investigate the association between margin width and recurrence, controlling all other characteristics.⁴⁹ Wider margins were significantly associated with a lower rate of recurrence only in patients who did not receive RT ($P < .0001$), but not in those treated with radiation ($P = .95$).⁴⁹

According to the DCIS Consensus Guideline on Margins by SSO/ASTRO/ASCO, the use of at least a 2-mm margin in DCIS treated with WBRT is associated with low rates of IBTR.⁴⁶ 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, the SSO/ASTRO/ASCO Consensus Guideline on Margins for invasive breast cancer should be utilized, which supports “no tumor on ink” as an adequate margin applying to both the invasive and noninvasive components in this mixed tumor scenario.

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.

For DCIS patients undergoing mastectomy, or for local excision in an anatomic location that could compromise the lymphatic drainage pattern to the axilla (eg, tail of the breast), a sentinel lymph node biopsy (SLNB) procedure should *strongly* be considered at the time of definitive surgery to avoid necessitating a full axillary lymph node (ALN) dissection for evaluation of the axilla.⁵⁰⁻⁵³ Since only a small proportion of patients (about 25%) with seemingly pure DCIS on initial biopsy will have invasive breast cancer at the time of the definitive surgical procedure⁵⁴ and will ultimately require ALN staging, ALN dissection (ALND) is *not* recommended unless



there is pathologically documented invasive cancer or ALN metastatic disease in patients (by either biopsy or SNLB).

NCCN Recommendations for Primary Treatment of DCIS

Trials are ongoing to determine if there might be a selected favorable biology DCIS subgroup 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 all DCIS.

According to the NCCN Panel, primary treatment options for patients with DCIS along with their respective categories of consensus are:

- 1) BCS plus WBRT with or without boost (category 1). While considering RT boost for DCIS, the NCCN Panel recommends an individualized approach based on patient preference and other factors such as longevity. The NCCN Panel notes that WBRT following BCS reduces IBTR rates in DCIS by about 50% to 70%. For DCIS patients treated with BCS alone (without radiation), irrespective of margin width, the risk of IBTR is substantially higher than treatment with excision followed by WBRT (even for predefined low-risk subsets of DCIS patients).
- 2) Total mastectomy, with or without SLNB with optional reconstruction (category 2A).
- 3) BCS plus APBI in carefully selected cases (category 2A). According to the panel, select patients with low-risk DCIS may be considered suitable for APBI if they meet all aspects of the definition of RTOG 9804 low-risk DCIS or ASTRO “suitable” DCIS for APBI.
- 4) BCS alone (category 2B). The option of BCS alone should be considered only in cases where the patient and the physician view the individual as having a low risk of disease recurrence. For patients with low-risk disease that has been fully resected with negative margins and particularly if they are ER-positive and will be receiving endocrine therapy,

the absolute reduction of in-breast recurrence may not be large enough to justify the risks associated with RT. Therefore, according to the NCCN Panel, it may be reasonable to omit RT in such cases.

Contraindications to BCT are listed in the algorithm (*Special Considerations to Breast Conservation Therapy Requiring RT*). Patients treated with mastectomy are appropriate candidates for breast reconstruction (see *Principles of Breast Reconstruction Following Surgery*).

According to the NCCN Panel, complete resection should be documented by analysis of margins and specimen radiography. Post-excision mammography can be considered for any uncertainty about adequacy of the excision remains (eg, the mass and/or microcalcifications are not clearly within the specimen). Clips may be used to delineate the tumor bed and ensure adequate coverage with radiation, provide design of boost and APBI fields, and provide markers should additional surgery be required pending the pathologic margin status review.

For patients with pure DCIS treated by BCS and WBRT, a quantitative description of any tumor close to margin is helpful as a resection width of at least 2 mm is associated with a reduced risk of IBTR relative to narrower negative margin widths. 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.

For DCIS with microinvasion (DCIS-M), defined as an invasive focus 1 mm or smaller in size, the optimal margin width should refer to the DCIS margin definition (≥ 2 mm), given that the majority of DCIS-M is comprised of DCIS and the natural history and systemic therapy utilization for DCIS-M more closely reflect the treatment pattern for pure DCIS than for invasive carcinoma.

Management of DCIS After Primary Treatment

Tamoxifen: DCIS falls between atypical ductal hyperplasia (ADH) and invasive ductal carcinoma within the spectrum of breast proliferative abnormalities. The Breast Cancer Prevention Trial performed by NSABP showed a 75% reduction in the occurrence of invasive breast cancer in patients with ADH treated with tamoxifen.^{55,56} These data also showed that tamoxifen led to a substantial reduction in the risk of developing invasive breast disease.⁵⁷ The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview analysis showed that, with 5 years of tamoxifen therapy, patients with ER-positive or receptor-unknown invasive tumors had a 39% reduction in the annual odds of recurrence of invasive breast cancer.⁵⁸

Similarly, the NSABP B-24 trial found a benefit from tamoxifen for patients with DCIS after treatment with breast conservation surgery and RT. In that study, patients with DCIS who were treated with BCT 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; $P = .023$).²² The patients 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% invasive and 7.2% noninvasive recurrences for those treated with placebo. 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 BCT.⁵⁹

A phase III trial randomized patients with excised DCIS to receive WBRT or no WBRT and tamoxifen versus no tamoxifen.²¹ The randomization was independent for each of the two treatments (RT and tamoxifen). 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 WBRT (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 WBRT (ipsilateral HR, 0.93; 95% CI, 0.50–1.75; $P = .80$; contralateral HR, 0.99; 95% CI, 0.39–2.49; $P = 1.0$).

The standard dose of tamoxifen is 20 mg/day for 5 years. The phase III TAM-01 trial studied a lower dose of tamoxifen (5 mg for 3 years) in 501 patients with breast intraepithelial neoplasia including DCIS, lobular carcinoma in situ (LCIS), and ADH. The rate of recurrence of either intraepithelial neoplasia or invasive breast cancer was 5.7% among those receiving tamoxifen 5 mg daily versus 11.9% for those receiving placebo (HR, 0.48; 95% CI, 0.25–0.89) at a median follow-up of 5.1 years.⁶⁰ The relative risk (RR) reduction with low-dose tamoxifen seen in the TAM-01 trials is consistent with that seen in trials that used a higher dose of tamoxifen, but the rate of severe toxicity compared with placebo was less.

Anastrozole: In patients with ER-positive and/or PR-positive DCIS treated by wide local excision with or without RT, 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.⁶¹ 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 of 33 deaths were recorded for anastrozole and 36 for tamoxifen (HR, 0.9393; 95% CI, 0.58–1.50; *P* = .78).⁶¹ Although the number of patients reporting any adverse event was similar between anastrozole (n = 1323, 91%) and tamoxifen (n = 1379, 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, gynecologic cancers and symptoms, vasomotor symptoms, and deep vein thromboses reported with tamoxifen. The NSABP B-35 study randomly assigned 3104 postmenopausal patients with hormone-positive DCIS treated with lumpectomy and radiation to either tamoxifen or anastrozole for 5 years. Prior to being randomly assigned, patients were stratified by age—under 60 years or over 60 years. The primary endpoint was breast cancer-free interval.⁶² 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.⁶² In addition, anastrozole resulted in further improvement in breast cancer-free interval in younger postmenopausal patients (<60 years of age). 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.⁶²

Results of the IBIS-II and the NSABP-B-35 studies indicate that anastrozole provides at least a comparable benefit as adjuvant treatment

for postmenopausal patients with hormone receptor (HR)-positive DCIS treated with BCS and RT, with a different toxicity profile.

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 BCT, 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.

NCCN Recommendations for Management of DCIS After Primary Treatment

According to the NCCN Panel, in patients with ER-positive DCIS treated with BCT, endocrine therapy with tamoxifen (for premenopausal and postmenopausal patients) or an aromatase inhibitor (for postmenopausal patients, especially those < 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 (category 1 for those undergoing BCT followed by RT; category 2A for those undergoing excision alone). The benefit of endocrine therapy for ER-negative DCIS is not known. Low-dose tamoxifen (5 mg/day for 3 years) is an option only if the 20-mg standard-dose of tamoxifen is not tolerated (see DCIS-2).

Follow-up of patients 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 BCT, the first follow-up mammogram should be performed 6 to 12 months after the completion of RT (category 2B) (see DCIS-2). Patients receiving endocrine therapy for risk reduction should be monitored as described in the [NCCN Guidelines for Breast Cancer Risk Reduction](#).



Invasive Breast Cancer

Workup for Non-metastatic (M0) Invasive Breast Cancer

The recommended workup of localized invasive breast cancer (listed on BINV-1) includes a history and physical exam. Complete blood count (CBC) and liver function tests (LFTs) have no added benefit in the detection of underlying metastatic disease in patients with asymptomatic early-stage breast cancers.⁶³ In addition, monitoring of disease relapse with any tumor markers is *not* recommended.

Imaging: Imaging with bilateral diagnostic mammography is recommended; breast ultrasonography is recommended only if necessary.

The use of MRI in the workup remains controversial. 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—including MRI-guided biopsy—in many circumstances.⁶⁴⁻⁶⁶ MRI findings tend to overestimate extent of disease,⁶⁷ resulting in increased frequency of mastectomies.⁶⁸⁻⁷¹

MRI findings alone are not sufficient to determine whether BCT is optimal, as additional tissue sampling is needed to verify true malignant disease warranting excision. MRI use may increase mastectomy rates by identifying areas of mammographically occult disease that may have been adequately treated with radiation after BCS had the disease remained undiscovered without MRI.⁷¹

Two prospective randomized studies have examined the utility of preoperative MRI in determining disease extent, and neither demonstrated improvement in rates of re-excision after initial BCS.^{72,73} Retrospective

review of the utility of MRI showed conflicting outcome results—one with benefit⁷⁴ and another without.⁷⁵ One systematic review⁶⁶ documented that breast MRI staging altered surgical treatment in 7.8% to 33.3% of patients;⁶⁶ however, no differences in local recurrence or survival have been demonstrated. In addition, there is no evidence that use of breast MRI increases rates of margin-negative resection.^{76,77}

Breast MRI may assist with identification and management of clinically occult primary tumors presenting with axillary nodal metastases.⁷⁸ In patients with Paget disease not identifiable on mammography, breast MRI may help determine the extent of disease.^{79,80} Breast MRI also has utility in screening patients with higher than average risk based on family history.⁸¹

If breast MRI imaging is performed, a dedicated breast coil, an imaging team experienced with reading breast MRI and performing MRI-guided biopsy, and multidisciplinary management are the standard of care.

According to the NCCN Panel, the use of MRI is optional and is not universally recommended by experts in the field. Breast MRI may be used for staging evaluation to define extent of cancer, in the adjuvant or neoadjuvant setting, to detect the presence of multifocal or multicentric cancer in the ipsilateral breast, or as screening of the contralateral breast cancer at time of initial diagnosis. Additional indications for breast MRI include: clinical axillary metastasis with an occult primary cancer; Paget disease of the nipple with breast primary not identified by other breast imaging modalities or physical examination; follow-up screening of patients with prior mammographically undetected breast cancers; and those whose lifetime risk of a second primary breast cancer is greater than 20% (based on models largely dependent on family history).

Pathology Assessment: A central component of the treatment of breast cancer is full knowledge of extent of disease and biologic features. Full



knowledge of extent of disease and biologic features is central to the treatment of breast cancer.

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 panel also recommends testing for Ki-67 if HR-positive, HER2-negative, and considering adjuvant abemaciclib.

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. 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. The NCCN Breast Cancer Panel endorses the

use of the CAP protocols for reporting the pathologic analysis of all breast cancer specimens.⁴

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, Ovarian, and Pancreatic](#), 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 patients have higher rates of psychosocial distress than patients diagnosed at older ages.⁸²⁻⁸⁶ The NCCN Breast Cancer Panel recommends assessing for distress in patients newly diagnosed with breast cancer using guidance from [NCCN Guidelines for Distress Management](#).

Fertility and Sexual Health:

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. The panel recommends referring to those guidelines for guidance.

Numerous epidemiologic studies have demonstrated that childbearing after treatment for invasive breast cancer does not increase rates of recurrence or death from breast cancer.⁸⁷ 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 and fertility may wane during the 5 to 10 years of adjuvant endocrine therapy.



While the potential to regain menstrual function within 2 years of completing chemotherapy is possible, especially for those younger than age 35,⁸⁸ resumption of menses does not correlate with fertility, and conversely, fertility may be preserved without menses. Therefore, all premenopausal patients should be informed about the potential impact of chemotherapy on fertility and offered the option of fertility preservation if future childbearing is desired.

Considerations for fertility preservation should incorporate 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 cancer⁸⁹⁻⁹¹ 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.⁹² The NCCN Panel recommends that all treating physicians should have a discussion with their patients of childbearing potential regarding the options for fertility preservation. Patients who desire to bear children after systemic therapy should be referred to a fertility specialist prior to initiating systemic (chemotherapy or endocrine) therapy.⁹²⁻⁹⁸

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.⁹⁹⁻¹⁰¹ In one trial goserelin improved the probability of pregnancy from 11% to 21% in patients with HR-negative early-stage breast cancer.¹⁰² 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 including hormonal interventions, ovarian stimulation, embryo or oocyte cryopreservation, and other investigational options, as well as the probability of successful gestation and childbirth.^{103,104}

Combining the various modalities for a specific patient may increase the odds of preservation of future fertility. It is important for fetal safety that patients actively avoid becoming pregnant during breast cancer treatment.

Additional Diagnostic Workup

The panel has reiterated that routine systemic imaging is *not* indicated for patients with early-stage breast cancer *in the absence* of signs/symptoms of metastatic disease. Recommendations for additional metastatic workup should be performed for those patients with signs or symptoms suspicious for metastatic disease, based on lack of evidence to demonstrate any benefits with metastatic workup in early-stage disease.¹⁰⁵⁻¹⁰⁷ 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.¹⁰⁵ For patients with stage III breast cancer, the prevalence of a positive liver ultrasound and positive chest x-ray was 6% and 7%, respectively.¹⁰⁵

CBC, comprehensive metabolic panel, liver function, and alkaline phosphatase tests should be considered only if the patient is a candidate for preoperative or adjuvant systemic therapy (BINV-12). A bone scan or sodium fluoride PET/CT is indicated in patients presenting with localized bone pain or elevated alkaline phosphatase. 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.

A diagnostic chest CT is indicated only if pulmonary symptoms (ie, cough or hemoptysis) are present. Likewise, abdominal and pelvic 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.

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. The routine use of FDG PET/CT scanning is not recommended in the staging of clinical stage I, II, or operable III (T3,N1) breast cancer, due to its high false-negative rate for the detection of lesions that are small (<1 cm) and/or low-grade disease, the high rate of false-positive scans in patients without locally advanced disease, the low sensitivity for detection of axillary nodal metastases, and the low probability of these patients having detectable metastatic disease.¹⁰⁸⁻¹¹¹

Locoregional Treatment of cT1–3, cN0 or cN+, M0 Disease

Surgery

Patients with early-stage operable breast cancer initially undergo upfront definitive surgery (BCS or mastectomy), and adjuvant systemic therapy, if indicated, based on primary tumor characteristics, such as tumor size, grade, lymph node involvement, ER/PR status, expression of HER2 receptor, and tumor genomics. Some patients with early-stage operable HER2-positive or triple-negative disease may be treated with preoperative systemic therapy first, followed by surgery. For NCCN Panel recommendations and consideration for preoperative systemic therapy,

refer to www.NCCN.org. Radiation is typically sequenced after definitive surgery and after systemic chemotherapy (if delivered).

Several randomized trials document that mastectomy is equivalent to BCT, which includes BCS with WBRT with respect to OS as primary treatment for the majority of patients with stage I and stage II breast cancers (category 1).¹¹²⁻¹¹⁶ The optimal choice of surgery is based on a shared decision made by the patient and clinician after discussing benefits and risks of mastectomy versus BCT in regards to long-term survival, risk of local recurrence, and the impact on cosmetic outcome and overall QOL.

Breast Conserving Surgery

BCS allows patients to preserve their breast without sacrificing oncologic outcome. BCS 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 of a single region or segment of the breast tissue with a satisfactory cosmetic result; have diffusely positive pathologic margins; or have homozygous (biallelic) inactivation for ATM mutation (category 2B). Relative contraindications to lumpectomy include previous RT to the breast or chest wall; active connective tissue disease involving the skin (especially scleroderma and lupus); persistently positive pathologic margin; or in those with a known or suspected genetic predisposition to breast cancer who may have an increased risk of ipsilateral breast recurrence or contralateral breast cancer with BCT or who may be considered for prophylactic bilateral mastectomy for risk reduction as per the criteria in the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#) or may have known or suspected Li-Fraumeni syndrome (category 2B).



Several studies of patients with early-stage breast cancer treated with BCS have identified young age as a significant predictor of an increased likelihood of IBTRs after BCT.¹¹⁷⁻¹¹⁹ Risk factors, such as a family history of breast cancer or a genetic predisposition for breast cancer (ie, *BRCA1/2* or other cancer predisposing mutation), are more likely to exist in the population of young patients with breast cancer, thereby confounding the independent contributions of age and treatment to clinical outcome.¹²⁰

With respect to OS outcomes for young patients with breast cancer, BCT or mastectomy are similar.^{114,115,121-123} Some studies have shown improved survival¹²⁴⁻¹²⁶ and fewer post-surgical complications¹²⁷ with BCS.

Mastectomy

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

Only limited data are available on the survival impact of risk-reducing contralateral mastectomy in patients with a unilateral breast cancer.¹²⁸ Analysis of patients included in the SEER database treated with mastectomy for a unilateral breast cancer from 1998 to 2003 showed that contralateral risk-reducing 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 patients (18–49 years of age) with stage I/II, ER-negative breast cancer (HR, 0.68; 95% CI, 0.53–0.88; *P* = .004).¹²⁹ The 5-year breast cancer survival for this group was only *slightly* improved with contralateral risk-reducing mastectomy versus without (88.5% vs. 83.7%, difference = 4.8%).¹²⁹ These differences observed in retrospective analysis could be due to selection bias among patients who chose risk-reducing contralateral mastectomy.¹³⁰ A statistical simulation of survival outcomes after risk-reducing contralateral mastectomy among patients with stage I or II breast cancer with no *BRCA* mutation found that the absolute 20-year survival benefit from risk-reducing contralateral mastectomy was less than 1%

among all age, ER status, and cancer stage groups.¹³¹ Data from another meta-analysis found no absolute reduction in risk of distant metastases with risk-reducing mastectomy.¹³² Furthermore, among patients with unilateral breast cancer who have an increased familial/genetic risk, a decrease in metastatic contralateral breast cancer incidence was observed in those who received risk-reducing contralateral mastectomy, although no improvement was seen in OS of these patients.¹³²

The panel recommends that patients 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, Ovarian, and Pancreatic](#)). 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 [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic](#), risk reduction mastectomy of the contralateral breast to a known unilateral breast cancer treated with mastectomy or BCT is discouraged by the panel.

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

Margin Assessment: After surgical resection, a careful histologic assessment of resection margins is essential. The NCCN Panel notes that benefit of BCS is predicated on achieving pathologically negative margins after resection. The NCCN Panel accepts the most recent definition outlined in the guidelines established by the SSO/ASTRO as the standard for negative surgical margins for invasive cancer.¹³³



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). Patients with positive margins generally require further surgery—either a re-excision to achieve a negative margin or a mastectomy. If re-excision is technically feasible 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 margin status would be assessed with similar definitions. 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.

For invasive breast cancers that have a component of DCIS, the negative margin definition of “no ink on tumor” should be utilized based on the SSO/ASTRO Consensus Guideline on Margins unless it is DCIS with microinvasion, which behaves more like pure DCIS and 2-mm margins are recommended. 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.

The same margin recommendations cannot be applied directly to patients undergoing APBI, where data regarding local recurrence are more limited

than WBRT. 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), young age, or multiple close margins to assist in identifying patients who may have an increased risk of ipsilateral recurrence and therefore may benefit from re-excision.

Surgical Axillary Staging

Axillary status is important for planning systemic adjuvant treatment and RT. The lymphatic pathways from the breast go to the ALNs, internal mammary, infraclavicular, and/or supraclavicular lymph nodes.

Traditional level I and level II ALNDs require 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 I 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).

Historically, ALND has been the standard of care for axillary staging.¹³⁶ However, ALND is associated with lymphedema and other significant morbidities.¹³⁷⁻¹³⁹ This has been largely replaced with SLNB.

SLN mapping injections may be peritumoral, subareolar, or subdermal. SLNs can be assessed for the presence of metastases by both hematoxylin and eosin (H&E) staining and cytokeratin immunohistochemistry (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.¹⁴⁰ In the uncommon situation in which H&E staining is equivocal, reliance on the results of cytokeratin IHC is appropriate.

Two randomized trials compared SLNB alone versus ALND. The Milan trial (1998–1999) randomized 516 patients treated with BCS with tumors up to 2 cm to two arms, one receiving immediate axillary dissection and the other receiving the dissection only if the sentinel node was involved.¹⁴¹ After 79 months follow-up, there was no difference in OS and DFS.¹⁴²

Another similar study, (NSABP) B-32, conducted between 1999 and 2004, randomized 5611 patients with invasive breast cancer up to 2 cm to either ALND or SLNB alone with ALND performed only if the SLN was positive.¹⁴³ After 95.6 months of follow-up, OS and DFS were similar in the two groups. Results of a subgroup analysis of this study showed patients with ALND had significantly higher arm morbidity and significantly more restricted work and social activity and impaired QOL.^{144,145}

The ALMANAC trial studied the QOL in patients with SLNB versus ALND in 1031 patients.¹⁴⁶ After 12 months, lymphedema and sensory loss were higher in the ALND group. Operative time, drainage use, hospitalization, and resumption of normal life were much longer in ALND compared to the SLNB group. The SNAC trial¹⁴⁷ and the DBCCG trial¹⁴⁸ also showed less morbidity with SLNB compared with ALND.

Based on the results of the above studies, it was clarified that for *negative* sentinel nodes, ALND is not needed.

The ACOSOG Z0011 trial addressed the role of ALND in those with a clinically negative axilla but pathologically positive lymph nodes from an SLNB. This trial randomized patients greater than or equal to 18 years of age with clinical T1/T2 tumors, fewer than 3 positive SLNs, undergoing BCS and WBRT, to SLNB alone (n = 436) or to a completion ALND (n = 420). In this study, there was no difference in local recurrence, DFS, or OS between patients 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.¹⁴⁹ 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 group ($P = .11$). Median OS was approximately 92% in each group.¹⁵⁰ 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 trial arms ($P = .13$).¹⁵¹ 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 ($P = .28$).¹⁵¹ The 10-year cumulative incidence of locoregional recurrences was 6.2% with ALND and 5.3% with SLNB alone ($P = .36$).¹⁵¹

The results of the ACOSOG Z0011 trial demonstrate that there is no benefit to ALND in patients with early-stage breast cancer who have only one or two SLN metastases (minimal nodal burden) on SLNB after receiving WBRT as part of BCT. Mastectomy patients were not enrolled in the ACOSOG Z0011 trial since these patients do not routinely receive radiation.

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.¹⁵² While the ACOSOG Z0011 trial was limited to those undergoing BCT, this trial included patients undergoing mastectomy (9%).¹⁵² Between the group treated with SLNB



plus ALND versus the group that had SLNB alone, there were no differences in 5-year DFS (84.4%; 95% CI, 80.7%–88.1% vs. 87.8%; 95% CI, 84.4%–91.2%); cumulative incidence of breast cancer events, including local, regional, contralateral breast, and distant recurrence (10.8%; 95% CI, 7.6–14.0 vs. 10.6%; 95% CI, 7.5–13.8); or OS (97.6%; 95% CI, 96.0%–99.2% vs. 97.5%; 95% CI, 95.8%–99.1%).¹⁵² Regional recurrence was less than 1% for those who underwent ALND and 1% for those who did not undergo ALND.¹⁵² The results of this trial show that in patients with micrometastases on SLNB, 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.¹⁵³ This trial included patients (n = 4823) with T1 or T2 breast cancer with positive SLNs randomized to an ALND or axillary RT. One thousand four hundred twenty-five patients had positive SLNs (micrometastatic or macrometastatic), which included a small fraction of patients (n = 248) treated with mastectomy (17%).¹⁵³ The results reported no difference in 5-year OS or DFS for patients randomized to ALND versus axillary radiation.¹⁵³ 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 RT 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 RT group.¹⁵³ At the end of 5 years, lymphedema was less frequent in the group treated with axillary RT versus ALND (11% vs. 23%).¹⁵³ The 10-year follow-up results presented at the 2021 SABCS showed no significant differences between the two arms with respect to OS (with ALND, OS was 84.6% vs. 81.4% with axillary RT), distant metastasis-free survival (with ALND was 81.7% vs. 78.2% with axillary RT), or locoregional recurrence rate (3.59% with ALND vs. 4.07% with axillary RT). The axillary recurrence with axillary RT was 1.8% versus 0.93% with ALND.¹⁵⁴

The OTOASAR trial was designed similarly to the AMAROS trial; patients (n = 2100) with tumors less than or equal to 3.0 cm who were clinically node negative were randomized to receive either ALND or axillary RT if they had 1 to 2 positive SLNs.¹⁵⁵ The results showed no difference in axillary recurrence with ALND compared with SLNB plus RT to the axilla.¹⁵⁵

In the setting of preoperative chemotherapy, the question that is being explored is whether ALND may be omitted in patients with complete pathologic response after preoperative therapy.

Several prospective studies have evaluated patients with positive lymph nodes before preoperative systemic therapy who had clinical complete response to preoperative therapy and underwent SLNB and ALND. The results of these studies have shown that in those with node-positive disease prior to preoperative systemic therapy, SLNB has a greater than 10% false-negative rate when performed after preoperative systemic therapy. In the SENTINA study,¹⁵⁶ the overall false-negative rate was 14.2%. In the ACOSOG-Z1071 trial,¹⁵⁷ the false-negative rate was 12.6% and in the SN FNAC trial,¹⁵⁸ the false-negative rate was 13.3%.

Subgroup analyses from studies have shown that 1) using dual-agent lymphatic mapping (radiotracer and blue dye); 2) identifying three or more SLNs; and 3) marking the metastatic lymph node with a clip before neoadjuvant therapy and then resecting it at the time of surgery reduces false-negative rates to less than 10%.

A subgroup analysis of the ACOSOG Z1071 trial showed lower false-negative rates in patients who had a clip placed in the positive lymph nodes at the time of initial biopsy followed by removal of the clipped node during SLN surgery after preoperative systemic therapy.¹⁵⁹ A another study of selective localization and removal of clipped nodes with SLN biopsy, known as targeted axillary dissection (TAD), showed false-



negative rates reduced to approximately 2% compared with 4% with removal of the clipped lymph node alone.¹⁶⁰

Several ongoing clinical trials are examining further de-escalation of axillary surgery in those who have positive nodes after preoperative systemic treatment. The Alliance A011202/MAC19 trial (NCT01901094) is randomly assigning patients who have sentinel node–positive disease after neoadjuvant chemotherapy to ALND versus no further axillary surgery. Both arms will receive regional nodal radiation. The SLNB alone arm will include axillary RT to the undissected axilla (levels I–III), whereas the ALND arm will not include RT to levels I or II axillae.

NCCN Recommendations for Surgical Axillary Staging: If ALNs are clinically negative (no palpable nodes) at the time of diagnosis, 2 or fewer suspicious lymph nodes are found on imaging, or 2 or fewer positive lymph nodes are confirmed by needle biopsy, the panel recommends SLN mapping.

If SLN is negative, no further surgery is needed in these patients. If SLN is positive, based on the ACOSOG Z 0011 data, no further surgery is recommended only if all of the following criteria are met: the patients have cT1-2, N0 tumors, have not received preoperative systemic therapy, only have 1 or 2 positive SLNs, and will undergo BCT (BCS + WBRT). If any of the above criteria are not met, the panel recommends level I and II axillary dissection.

Based on the AMAROS and OTASAR trial data, no further surgery is recommended only if all of the following criteria are met: the patients have cT1-2, N0 tumors, have not received preoperative systemic therapy, have 1 to 2 positive SLNs, and will undergo lumpectomy or mastectomy along with adjuvant RT with *intentional* inclusion of undissected axilla at risk. If any of the above criteria are not met, the panel recommends level I and II axillary dissection. In select patients undergoing mastectomy with clinically

negative axillae but 1 to 2 positive SLNs, the panel notes that axillary radiation may replace ALND for regional control of disease. Based on the results of the IBCSG 23-01 trial, the NCCN Panel recommends no ALND for patients with positive SLNs when that disease is limited to *only* micrometastatic. According to the American Joint Committee on Cancer (AJCC) staging, micrometastatic nodal involvement is defined as a metastatic deposit or greater than 0.2 mm but less than or equal to 2.0 mm.¹⁶¹

In patients with clinically suspicious (palpable) lymph nodes or 3 or more suspicious lymph nodes on imaging, or if preoperative systemic therapy is being considered for patients with suspicious lymph nodes at diagnosis on exam or imaging, the panel recommends pathologic confirmation of malignancy using ultrasound-guided fine-needle aspiration (FNA)¹⁶² or core biopsy of suspicious nodes with clip placement.

According to the NCCN Panel, the recommendation for ALND of level I and II nodes is limited to patients with biopsy-proven axillary metastases (in those who did not receive preoperative systemic therapy) or who have residual disease after preoperative chemotherapy. Highly selected patients with biopsy-proven axillary metastases, who then converted to clinically node negative *after* preoperative systemic therapy, may undergo SLNB with removal of the clipped lymph node. This is a currently a category 2B recommendation as the rate of false negatives is high when SLN is performed after preoperative systemic therapy.

According to the NCCN Panel, based on available data, the false-negative rate can be reduced by marking biopsied lymph nodes to document their removal, using dual tracer, and by removing 3 or more sentinel nodes (targeted ALND). When sentinel nodes are *not* successfully identified, the panel recommends level I and II axillary dissection be performed for axillary staging.

**Radiation Therapy***Principles of Radiation Therapy*

It is important to individualize RT 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 RT (IMRT). Respiratory control techniques including deep inspiration breath-hold and prone positioning may be used to try to further reduce dose to adjacent normal tissues, particularly the heart and lung.¹⁶³ 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. Radiation to the breast/chest wall and nodal regions is generally delivered with single-energy or mixed-energy photons with or without electrons. Dose-volume histograms (DVHs) should be used to evaluate dose constraints, evaluate dose to normal tissues (ie, heart, lung), and ensure adequate coverage to the intended planning target volumes (PTVs), including the breast/chest wall, supraclavicular fossa, axillary levels I–III, and internal mammary nodes.

Whole Breast Radiation Therapy

WBRT reduces the risk of local recurrence and has shown to have a beneficial effect on survival.^{113,116} 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.^{164,165} For greater homogeneity of target dose and to spare normal tissues using compensators such as tissue wedges, forward planning using segments and IMRT may be used.^{166,167}

Four randomized clinical trials have investigated hypofractionated WBRT 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.^{168–171} The 10-year follow-up data from the START trials¹⁷² are consistent with the 10-year results of the Canadian trial,¹⁷¹ 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 the standard dose of 50 Gy in 25 fractions over 5 weeks.¹⁷¹ The START trials reported radiation-related effects to normal breast tissue such as breast shrinkage, telangiectasia, and breast edema as less common with the hypofractionated regimen.¹⁷²

Another randomized trial showed similar outcomes among patients receiving a hypofractionated schedule (40 Gy in 15 fractions) compared with standard fractionation (50 Gy in 25 fractions) in patients (n = 1854) with node-negative breast cancer (n = 1608) or DCIS (n = 246).¹⁷³ The 9-year risk of locoregional recurrence was 3.3% in the 50-Gy group and 3.0% in the 40-Gy group. The 9-year OS was 93.4% in the 50-Gy group and 93.4% in the 40-Gy group. Radiation-associated cardiac and lung disease were comparable between the groups.

Other shorter schedules of delivering WBRT have also been studied with similar results. The FAST trial compared patients over 50 years of age with low-risk invasive breast carcinoma (pT1–2, pN0) randomly assigned to the standard schedule of 50 Gy in 25 fractions over 5 weeks or 30 Gy or 28.5 Gy in 5 fractions once weekly. After 10-year follow-up, there were no significant differences reported in normal tissue effects for the standard 50 Gy in 25 fractions schedule versus a once-weekly schedule for 5 weeks totaling 28.5 Gy, but normal tissue effects were higher with a weekly schedule for 5 weeks totaling 30 Gy.¹⁷⁴

The FAST Forward trial randomized patients with non-metastatic breast cancer (n = 4096) after BCS or mastectomy to one of the following: 40 Gy in 15 fractions over 3 weeks; 27 Gy in 5 fractions over 1 week; or 26 Gy in 5 fractions over 1 week to either whole breast or chest wall.¹⁷⁵ The 5-year incidence of ipsilateral breast tumor relapse was 2.1% with the standard



40 Gy in 15 fractions over 3 weeks versus 1.7% with 27 Gy in 5 fractions over 1 week (5.4 Gy per fraction; HR, 0.86; 95% CI, 0.51–1.44) and 1.4% with 26 Gy in 5 fractions over 1 week (5.2 Gy per fraction; HR, 0.67; 95% CI, 0.38–1.16).¹⁷⁵ The moderate or marked tissue effects in the breast or chest wall were 15% with 27 Gy, 12% with 26 Gy, and 10% with 40 Gy, but differences between the 40 Gy and 26 Gy groups were not statistically different.¹⁷⁵

RT Boost to Tumor Bed: In patients with higher risk characteristics (such as age <50 years, high-grade disease, or patients with focally positive margins) an RT boost has been shown to reduce local relapse.^{29,31,165,172,176-178} RT boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy.¹⁷⁹

NCCN Recommendations for WBRT: The panel has defined the target as breast tissue at risk. The NCCN Panel recommends a dose of 40 to 42.5 Gy in 15 to 16 fractions for all patients getting whole breast radiation without regional nodal radiation, based on its equivalence in efficacy and toxicity demonstrated in the moderately hypofractionated trials.¹⁷² While these abbreviated courses of RT of 40 to 42.5 Gy in 15 to 16 fractions are the NCCN Panel's preferred fractionation schema for whole breast radiation, the conventionally fractionated regimen of 46 to 50 Gy in 23 to 25 fractions may be utilized in selected patients. The RT boost doses intended to decrease rate of local recurrence are 10 to 16 Gy in 4 to 8 fractions.

Ultra-hypofractionated WBRT of 28.5 Gy delivered as 5 (once weekly) fractions may be considered in select patients with pTis/T1/T2/N0 aged greater than 50 years after BCS, though the optimal fractionation for the boost delivery is unknown for this regimen. 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 and

should be discussed with patients prior to its use. The panel also notes that when using ultra-hypofractionated dosing, it is essential to utilize 3-D planning to minimize inhomogeneity and exposure to heart and lung.

Chest Wall Radiation:

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. Chest wall scar boost may be delivered with or without bolus using electrons or photons.

NCCN Recommendations for Chest Wall Radiation: The NCCN Panel recommends a dose of 45 to 50.4 Gy in 25 to 28 fractions to the chest wall. A boost at the scar of 1.8 to 2 Gy per fraction to a total dose of approximately 60 to 66 Gy may be considered in some cases based on risk. Special consideration should be given to the use of bolus material to ensure that the skin dose is adequate, particularly in the case of inflammatory breast cancer.

Regional Nodal Irradiation

Two studies, MA.20 and EORTC 22922/10925, evaluated the addition of regional nodal irradiation (RNI) to the internal mammary nodes and the upper axillary nodes including the supraclavicular region, in addition to WBRT or chest wall irradiation after BCS 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.¹⁸⁰ The distant recurrences were reduced from 17.3% to 13.4%.¹⁸⁰ An improvement in DFS was seen from 77% to 82% at 10 years in those who received RNI compared to those who did not.¹⁸⁰ In EORTC 22922/10925, regional RT 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.¹⁸¹ Results of 15.7 years follow-up showed that breast cancer mortality (19.8% vs. 16%; 95% CI, 0.70–0.94) and



breast cancer recurrence (27.1% vs. 24.5%; 95% CI, 0.77%–0.98%) were reduced with internal mammary and medial supraclavicular RT.¹⁸²

The independent contribution of internal mammary nodal RT as a component of RNI continues to be debated as it is associated with higher risk of cardiac and lung toxicity, and data regarding its benefits are conflicting (discussed in detail below).

NCCN Recommendation for RNI: When considering RNI, anatomic variations across patients result in significant differences in prescription depth and field design. The NCCN Panel therefore recommends contouring the individual nodal basins that are at-risk using one of the various breast atlases, to ensure adequate RT coverage.^{183,184}

The recommended dose for RNI is 45 to 50.4 Gy in 25 to 28 fractions to the regional nodal fields. A supplemental RT boost can be delivered to grossly involved or enlarged lymph nodes (ie, internal mammary or clavicular) that have not been surgically addressed.

Accelerated Partial Breast Irradiation

Several large, randomized trials have been published using various forms of APBI rather than WBRT after BCS. Most of these studies have found that rates of local control in selected low-risk patients with early-stage breast cancer are equal to those treated with WBRT.^{43,45,185-187} In the NSABP B-39 trial, 10-year cumulative incidence of IBTR with APBI was 4.6% compared with 3.9% with WBRT, yielding an absolute difference of 0.7% with an HR of 1.22 (90% CI, 0.94–1.58) that did not meet the prespecified criteria for equivalence.⁴² However, given the small magnitude in IBTR differences between WBRT and APBI, it is not likely to be of clinical significance in appropriately selected patients.

QOL, toxicity, and cosmetic outcomes have generally been comparable or slightly favored APBI in randomized trials. For example, the IMPORT-LOW study compared WBRT with partial breast irradiation delivered as 40 Gy in

15 once-daily fractions using reduced-size breast tangents and found less breast firmness, less change in breast appearance, and lower average number of adverse events per person with partial breast irradiation.^{185,188} The University of Florence compared WBRT with intensity-modulated APBI (30 Gy in 5 fractions, delivered every other day), and 10-year results have shown that APBI produced less acute and late toxicity and better cosmetic outcomes.¹⁸⁶ However, the RAPID trial found significantly higher rates of fair/poor cosmetic outcome with 3-D conformal APBI delivered as 38.5 Gy in 10 twice-daily fractions.^{43,189} The majority of APBI patients on NSABP B-39 were treated with the same external beam regimen, and treatment-related toxicities were not different for APBI versus WBRT as currently reported.⁴² Cosmetic outcome analysis, however, is pending.

NCCN Recommendation for APBI: The panel accepts the updated ASTRO APBI consensus statement for guidance on APBI use.¹⁹⁰ The NCCN Panel recommends APBI for any *BRCA*-negative patient who meets the ASTRO 2016 “suitable” criteria defined as over age 50 years, ER-positive invasive ductal carcinoma measuring less than or equal to 2 cm (pT1 disease) with negative margin widths of greater than or equal to 2 mm, and no lymphovascular invasion (LVI), and also permits APBI in patients over the age of 50 with screen-detected low- or intermediate-grade DCIS measuring less than or equal to 2.5 cm, resected with greater than or equal to 3 mm margins. The panel prefers the APBI regimen and method followed in the trial by University of Florence (30 Gy/5 fractions QOD delivered using IMRT).¹⁸⁶ The panel encourages participation in clinical trials for patients who do not meet the above criteria.

Adjuvant Radiation Therapy After BCS

Those who have a positive lymph node have a high risk of recurrence. Therefore, after BCS WBRT is strongly recommended with or without boost to tumor bed for node-positive disease (category 1 for those with positive nodes; category 2A for those with negative axillary nodes). This



recommendation is supported by the results of a meta-analysis by the EBCTCG showing reduction in 10-year risk of recurrence in those who received WBRT versus those who did not (19% vs. 35%; RR, 0.52; 95% CI 0.48–0.56).¹¹⁶ 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.¹¹⁶

For patients with a pathologically confirmed, focally positive margin without EIC, who do not undergo re-excision after BCS, 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.

Regional Nodal Irradiation After BCS

The reduction in the risk of locoregional and distant recurrence and improvement in DFS seen in the MA.20 and EORTC 22922/10925 trials,^{180,181} and the reduction in breast cancer mortality with 15-year follow-up of the EORTC 22922 patients,¹⁸² support the importance of RNI after BCS.

As mentioned previously, routine inclusion of the internal mammary nodes as a component of RNI remains somewhat controversial due to the associated cardiac and lung toxicities. A Korean trial KROG 08-06 studied independent effect on DFS of RT to internal mammary nodes after BCS or mastectomy for node-positive disease,¹⁹¹ randomizing patients to RNI with internal mammary RT versus RNI without internal mammary RT. Radiation to the internal mammary nodes did not significantly improve the DFS in patients with node-positive breast cancer. However, there was a statistically significant benefit in outcomes with internal mammary nodal RT for patients with medially or centrally located tumors.¹⁹¹ Conflicting data have arisen from the Danish Breast Cancer Cooperative Group that recently reported 15-year follow-up of their study on RT to internal

mammary nodes in patients (n = 3089) with positive nodes and early-stage breast cancer.¹⁹² In this study, RT to the internal mammary nodes was delivered to right-sided patients (n = 1,491), while no RT to internal mammary nodes was delivered to left-sided patients (n = 1,598). The study reported a 15-year improved OS rate of 60.1% with RT to internal mammary nodes compared to 55.4% with no RT to internal mammary nodes. Improvements were also seen with respect to risk of developing distant recurrence and breast cancer-specific mortality favoring RT to internal mammary nodes.¹⁹²

Clinical judgment is needed when determining inclusion of the internal mammary nodes during RNI. Therefore, the NCCN Panel no longer specifies the fields that should be included for RNI and refers to it as comprehensive RNI. According to the panel, patient selection should consider risks versus benefits including long-term organ (cardiac and lung) toxicities, comorbidities of the patient, age, and life expectancy. In including RT to the internal mammary nodes, meticulous treatment planning with normal tissue dose constraints is mandatory.

RNI After BCS for Node-Negative Disease: The NCCN Panel recommends consideration of comprehensive RNI in patients with central/medial tumors (in accordance with EORTC 22922 trial criteria) and in accordance with the MA.20 criteria: 3 tumors, as well as those with T2 tumors who have undergone limited axillary dissection (<10 lymph nodes) and also have other risk factors, including high-grade histology, ER-negative disease, or LVI.¹⁸⁰

RNI After BCS for Node-Positive Disease: For those with 1 to 3 positive nodes, if a patient meets all of the following criteria—has cT1–T2, cN0; did not receive preoperative chemotherapy; and has 1 to 2 positive SLNs—the use of comprehensive RNI with or without the intentional inclusion of the axilla is at the discretion of the radiation oncologist. If the patients do not meet all the criteria listed, the NCCN Panel recommends WBRT with



inclusion of any portion of the undissected axilla at risk (category 1) with strong consideration of comprehensive RNI.

For those with 4 or more positive nodes, the NCCN Panel recommends comprehensive RNI with inclusion of any portion of the undissected axilla at risk (category 1).

Radiation Therapy After BCS in Older Adults with ER-Positive Tumors

WBRT as a component of BCT does not affect breast cancer-specific survival in selected patients over 70 years of age with more indolent disease. In a study of patients 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 BCS with WBRT or BCS alone, both with tamoxifen for 5 years. Locoregional recurrence rates were 1% in the BCS, radiation, and tamoxifen arm and 4% in the BCS plus tamoxifen arm. There were no differences in OS, DFS, or need for mastectomy.¹⁹³ These results were confirmed in an updated analysis of this study with a median follow-up of 12.6 years.¹⁹⁴ At 10 years, a statistically significant reduction in IBTR was seen with RT with 90% of patients in the BCS and tamoxifen arm compared with 98% in the BCS plus radiation and tamoxifen arm.¹⁹⁴ Concordant results have been demonstrated in other studies of similar design.^{195,196} Whether the increase in local relapse without RT is relevant for an individual patient should be individualized after a discussion of the risks and benefits of RT and patient commitment to 5 years of endocrine therapy if RT omission is being considered.

The NCCN Guidelines allow for the use of BCS (pathologically negative margin required) with 5 years of tamoxifen or an aromatase inhibitor, without breast irradiation, for patients over 70 years of age with clinically negative lymph nodes and ER-positive, T1 breast cancers (category 1).

Adjuvant Radiation Therapy After Mastectomy

Post-Mastectomy RT for 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 patients with positive ALNs after mastectomy and ALN dissection.¹⁹⁷⁻²⁰¹ In these trials, the ipsilateral chest wall and the ipsilateral locoregional lymph nodes were irradiated. The results of EBCTCG meta-analyses show that RT after mastectomy and axillary node dissection reduced both recurrence and breast cancer mortality in the patients with 1 to 3 positive lymph nodes even when systemic therapy was administered.^{181,202} According to the NCCN Panel, post-mastectomy radiation to the chest wall is recommended in all of these patients (category 1). Data from the EORTC 22922/10925 trial support the inclusion of RNI in patients undergoing post-mastectomy radiation. The trial assessed the independent effects of including RNI versus no RNI when treating the chest wall after mastectomy. Based on the benefits demonstrated in this trial, the NCCN Panel recommends comprehensive RNI to include any undissected axilla at risk (category 1 for 1 or more positive nodes).

Post-Mastectomy RT for Node-Negative Disease:

In patients with negative nodes, tumor less than or equal to 5 cm, and clear margins (≥ 1 mm), post-mastectomy RT is typically not recommended. However, the panel has noted that it may be considered in subsets of these patients with high-risk features. Based on the inclusion criteria of node-negative patients enrolled onto the RNI trials (MA-20 and EORTC 22922), any patients with the following high-risk features, including central/medial tumors, T3 tumors, or tumors greater than or equal to 2 cm with fewer than 10 axillary nodes removed and at least one of the following: grade 3, ER-negative, or LVI, should be considered for PMRT with RNI to include any undissected axilla at risk. Features in node-negative tumors that predict a high rate of local recurrence include primary tumors greater than 5 cm or positive pathologic margins.²⁰³



In patients with positive pathologic margin, if re-resection to negative margins is not possible, the panel recommends strongly considering chest wall irradiation with the addition of comprehensive RNI including any portion of the axilla at risk. Chest wall irradiation should be considered with addition of comprehensive RNI, including any portion of the axilla at risk in those with tumors greater than 5 cm. 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 with consideration of comprehensive RNI including any portion of the undissected axilla at risk *only* in those with high-risk features.

Considerations for RT in Patients Receiving Preoperative Systemic Therapy

The panel recommends that decisions related to administration of adjuvant RT for patients receiving preoperative systemic chemotherapy should be made based on maximal stage (ie, clinical/anatomic stage, tumor characteristics) at diagnosis (before preoperative systemic therapy) and pathologic stage at definitive surgery (after preoperative systemic therapy). Data from numerous studies in patients with stage III disease suggest that postoperative RT improves local control even for patients who have a pathologic complete response (pCR) to neoadjuvant chemotherapy.²⁰⁴⁻²⁰⁷

RT After Preoperative Therapy and BCS:

Those who have clinically negative nodes at diagnosis, that remain pathologically node-negative at definitive surgery (after systemic therapy), should receive adjuvant RT to the whole breast with the addition of boost to the tumor bed after SLNB.

Patients who have clinically/radiographically positive nodes at diagnosis and convert to clinically/radiographically node negative after preoperative chemotherapy are candidates for the NSABP B-51 trial assessing the

benefit of RNI. Until the results of this trial become available, the existing data suggest that node-positive disease at presentation is at high risk for locoregional recurrence and should be considered to receive comprehensive RNI with inclusion of any portion of the undissected axilla at risk.

Patients who have clinically/radiographically positive nodes at diagnosis who convert to clinically/radiographically negative nodes after preoperative chemotherapy, but are found to have persistent nodal disease on SLNB, are candidates for the ALLIANCE 11202 trial assessing whether ALND can be safely replaced with axillary RT. ALND is the standard arm of this trial; however, in the event that a neoadjuvant therapy patient with node-positive disease (ypN1+) does not undergo a complete axillary dissection, all levels of the undissected axilla should be included with the radiation treatment.

RT After Preoperative Therapy and Mastectomy:

Those who have clinically positive nodes at diagnosis that respond to preoperative systemic therapy and become node-negative should be strongly considered to receive RT to the chest wall and comprehensive RNI with inclusion of any portion of the undissected axilla at risk based on the discussion above.

For those with positive nodes (ypN1+) after preoperative systemic therapy, axillary dissection is the standard treatment arm of the ongoing Alliance 11202 trial; however, if RT is indicated it should include chest wall along with comprehensive RNI with inclusion of any portion of the undissected axilla at risk.

Those who have node-negative disease at diagnosis and after preoperative systemic therapy and whose axilla was assessed by SLNB or axillary node dissection may forego RT.



Two prospective trials are ongoing and will prospectively evaluate the benefit of RT in patients treated with neoadjuvant therapy (NSABP B-51/RTOG 1304 [NCT01872975] and the Alliance A011202/MAC19 trial [NCT01901094]).

Sequencing of RT and Systemic Therapy:

If chemotherapy and radiation are indicated after surgery, adjuvant radiation is typically delivered after the completion of chemotherapy.^{208,209} This recommendation is based on results of the “Upfront-Outback” trial in which patients who had undergone BCS and axillary dissection were randomly assigned to receive chemotherapy following RT or RT following chemotherapy. The initial results showed an increased rate of local recurrence in the group with delayed RT at a median follow-up of 58 months;²⁰⁹ however, differences in rates of distant or local recurrence were not statistically significant when the two arms were compared at 135-month follow-up.²⁰⁸ While it is common for RT to follow chemotherapy when chemotherapy is indicated, based on data from prospective and retrospective studies, CMF (cyclophosphamide/methotrexate/fluorouracil) and RT may be given concurrently.

Data from multiple studies of patients treated with endocrine therapy either before, during, or after RT suggest no difference in outcomes or toxicity.²¹⁰⁻²¹³ Therefore, according to the NCCN Panel, sequential or concurrent endocrine therapy with RT is acceptable. However, due to compounding side effects, initiating endocrine therapy at the completion of RT may be preferred.

When adjuvant capecitabine²¹⁴ is indicated, since it is a known radiosensitizing agent with potential to increase toxicity to normal tissue, it should be given after completion of adjuvant RT.

When adjuvant olaparib is used, the panel recommends that olaparib be given after completion of RT. In the OlympiA trial,²¹⁵ olaparib was not administered concurrently with RT and there are limited data on safety of concurrent administration.

Adjuvant HER2-targeted therapy may be delivered concurrently with RT. Data from clinical trials in the adjuvant setting do not suggest an increased complication rate with the concurrent administration of HER2-targeted therapies with adjuvant RT.²¹⁶



Breast Reconstruction

Breast reconstruction may be an option for any woman receiving surgical treatment for breast cancer. Therefore, all patients 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.²¹⁷ 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.²¹⁸⁻²²² 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.

Those 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.²²³⁻²²⁵

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.²²⁶ Several procedures using autologous tissue are available including transverse rectus abdominis myocutaneous flap, latissimus dorsi flap, and gluteus maximus myocutaneous flap reconstruction.



Composite reconstruction techniques use implants in combination with autogenous tissue reconstruction to provide volume and symmetry. Patients with underlying diabetes or who smoke tobacco have increased rates of complications following autogenous tissue breast cancer reconstruction, presumably because of underlying microvascular disease.

Reconstruction can be performed either at the time of the mastectomy known as “immediate breast reconstruction” and under the same anesthetic or in a delayed fashion any time, known as “delayed breast reconstruction.” In many cases, breast reconstruction involves a staged approach requiring more than one procedure such as surgery on the contralateral breast to improve symmetry, revision surgery involving the breast and/or donor site, and/or nipple and areola reconstruction and tattoo pigmentation.

Plans for post-mastectomy radiation therapy can impact decisions related to breast reconstruction since there is a significantly increased risk of implant capsular contracture following irradiation of an implant. Furthermore, postmastectomy irradiation may have a negative impact on breast cosmesis when autologous tissue is used in immediate breast reconstruction, and may interfere with the targeted delivery of radiation when immediate reconstruction is performed using either autologous tissue or breast implants.^{227,228} Some studies, however, have not found a significant compromise in reconstruction cosmesis after radiation therapy.²²⁹ 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.²³⁰ Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis, implant exposure, and failed reconstruction.^{231,232} 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.²³³⁻²³⁵ 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.^{234,236,237} NAC-sparing procedures may be an option in patients who are carefully selected by experienced multidisciplinary teams. According to the NCCN Panel, when considering a NAC-sparing procedure, assessment of nipple margins is mandatory.



Retrospective data support the use of NAC-sparing procedures for patients with breast cancer with low rates of nipple involvement and low rates of local recurrence due to early-stage, biologically favorable (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).^{238,239}

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,²⁴⁰ 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.²⁴¹⁻²⁴⁵

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 those 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.²⁴⁶ The evolving field of oncoplastic surgery includes the use of "volume displacement" techniques performed in conjunction with a large partial mastectomy.²⁴⁷ 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.^{247,248}

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.²⁴⁹

Limitations of oncoplastic volume displacement techniques include lack of standardization among centers, performance at only a limited number of sites in the United States, and the possible necessity for subsequent mastectomy if pathologic margins are positive when further



breast-conserving attempts are deemed impractical or unrealistic. Nevertheless, the consensus of the panel is that these issues should be considered prior to surgery for individuals who are likely to have a surgical defect that is cosmetically unsatisfactory. Those 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

**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.²⁵⁰⁻²⁵⁷ According to the NCCN Panel, the endocrine therapy options include an aromatase inhibitor (with ovarian suppression for premenopausal patients) or tamoxifen. The preferred endocrine therapy option for postmenopausal patients 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.²⁵⁸ 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.²⁵⁹⁻²⁶¹ 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; $P = .0141$).²⁶¹ 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%.²⁶² The mean change in left ventricular ejection fraction was similar in all treatment arms.²⁶² 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.^{263,264} 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.²⁶⁵ Results from large clinical trials and retrospective reviews indicate that breast conservation rates are improved with preoperative systemic therapy.^{264,266} 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.²⁶⁷⁻²⁶⁹



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 patients 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.

**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,²⁷⁰ 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.^{271,272} 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.²⁷³

Adjuvant Systemic therapy for hormone receptor-positive, HER2-negative tumors

Patients 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.²⁷⁴ 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 patients with HR-positive, HER2-negative tumors treated with endocrine therapy alone by predicting locoregional and distant recurrence.²⁷⁵⁻²⁷⁷ This assay has also been validated to predict the benefit from adding adjuvant chemotherapy to adjuvant endocrine therapy for



patients with HR-positive, HER2-negative, node-negative breast cancer.²⁷⁸⁻²⁸⁰

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.^{279,281} 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.^{279,281}

For those with intermediate RS (11-25), the recently reported TAILORx trial of postmenopausal patients (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.²⁸¹ However, in a subset analysis, patients 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.²⁸¹ 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, patients (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.²⁸² In a secondary analysis of a prospective registry of patients 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%.²⁸³ 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.^{283,284}

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 patients 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 patients (n= 367) randomized to endocrine therapy with tamoxifen alone or chemotherapy with CAF followed by tamoxifen.²⁷⁸ Compared with tamoxifen alone, treatment with CAF among patients 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).²⁷⁸

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,²⁸⁵ assigned patients 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,²⁸⁶ 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.



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).²⁸⁶

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).²⁸⁶ 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.²⁸⁶

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.²⁸⁶ 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.²⁸⁶ 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.²⁸⁷⁻²⁸⁹

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%).²⁸⁸ 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.²⁸⁸

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.²⁸⁸ In TransATAC study, no distant recurrence was seen at 10 years in a similar group.²⁸⁹

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.²⁹⁰ Based on results of



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.²⁹⁰ The prognostic value of the risk score from 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,²⁸⁹ suggesting that chemotherapy would be of limited benefit in these patients.

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.^{291,292} The addition of MGI to H:I was determined provide additional prognostic discrimination, leading to the BCI assay.²⁹¹ 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.²⁹³ 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,²⁸¹ adjuvant chemotherapy may be considered in patients 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 study²⁸¹ 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 MINDACT²⁸⁶ 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



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.

Furthermore, 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 patients 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.²⁷⁸ 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,²⁸⁵ are expected determine the benefit (if any) of chemotherapy. 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 who received adjuvant endocrine therapy alone, suggesting that chemotherapy could be omitted in this group.²⁸⁶ 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.²⁹⁴ 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.²⁹⁵ Selected studies suggest that HER2-positive breast cancers may be less sensitive to some endocrine therapies, although other studies have failed to confirm this



finding.²⁹⁶⁻³⁰⁴ 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.³⁰⁵ However, given the favorable toxicity profile of the available endocrine therapies, the panel recommends the use of adjuvant endocrine therapy in the majority of patients 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 patients.⁵⁸ In patients 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.⁵⁸ In patients receiving both tamoxifen and chemotherapy, chemotherapy should be given first, followed by sequential tamoxifen.³⁰⁶ Prospective randomized trials have demonstrated that 5 years of tamoxifen is more effective than 1 to 2 years of tamoxifen.^{307,308}

The ATLAS trial randomly allocated pre- and postmenopausal patients to 5 or 10 years (extended therapy) of tamoxifen. The outcome analyses of 6846 patients with ER-positive disease showed that by extending adjuvant treatment to 10 years, the risk of relapse and breast cancer-related mortality was reduced.³⁰⁹ The risk of recurrence during years 5 to 14 was 21.4% for patients 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 decreases in the incidence of contralateral breast cancer as well. 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 patients in the

ATLAS trial after with 10 years of tamoxifen treatment were an increased risk for endometrial cancer and pulmonary embolism.³⁰⁹ 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.³¹⁰

In patients 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).³¹¹ In addition, data on ovarian suppression with tamoxifen, chemotherapy, or both showed no significant reduction in recurrence or death.

Studies in premenopausal patients 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.³¹¹⁻³¹⁹ There is also the suggestion that the benefits of ovarian suppression/ablation may be greater in the younger premenopausal group. Studies in premenopausal patients of ovarian



ablation/suppression plus tamoxifen versus chemotherapy alone generally demonstrate no difference in rates of recurrence or survival.³²⁰⁻³²²

A large intergroup study in premenopausal patients 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).³¹² 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*.³²⁰ They identified no statistically significant reduction in annual rates of recurrence or death with the addition of ovarian suppression or ablation to chemotherapy in patients less than 40 years or 40 to 49 years of age.

In two randomized trials (TEXT and SOFT), premenopausal patients 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.³²³ 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; $P < .001$).³²³ 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; $P = .37$).³²³ In the SOFT trial,³²⁴ premenopausal patients 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; $P = .10$).³²⁵ In a subgroup analysis, patients 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.³²⁵ In the subgroup of patients with no prior chemotherapy, no meaningful benefit was seen from ovarian suppression, as patients who received tamoxifen alone demonstrated a 95% chance of remaining disease-free for 5 years.³²⁴ 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 patients 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 patients 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 patients with functioning ovaries and should not be used in patients whose ovarian



function cannot reliably be assessed owing to treatment-induced amenorrhea.

The results from two prospective, randomized, clinical trials have provided evidence of an OS benefit for patients with early-stage breast cancer receiving initial endocrine therapy with tamoxifen followed sequentially by anastrozole (HR, 0.53; 95% CI, 0.28–0.99; $P = .045$) or exemestane (HR, 0.83; 95% CI, 0.69–1.00; $P = .05$ [excluding patients with ER-negative disease]) when compared with tamoxifen as the only endocrine therapy.^{326,327} In addition, the NCIC-CTG MA-17 trial demonstrated a survival advantage with extended therapy with letrozole compared with placebo in patients with ALN-positive (but not lymph node-negative), ER-positive breast cancer.³²⁸ However, no survival differences have been reported for patients receiving initial adjuvant therapy with an aromatase inhibitor versus first-line tamoxifen.^{329,330} 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 patients with HR-positive breast cancer.^{331,332} With a median of 100 months follow-up, results in 5216 postmenopausal patients 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.³²⁹ 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.³³² ATAC trial sub-protocols show a lesser effect of anastrozole compared with tamoxifen on endometrial tissue;³³³ similar effects of anastrozole and tamoxifen on quality of life, with most patients reporting that overall quality of life was not significantly impaired;³³⁴ a greater loss of bone mineral density with anastrozole;³³⁵ a small pharmacokinetic interference of anastrozole in the presence of tamoxifen of unclear significance;³³⁶ and no evidence for an interaction between prior chemotherapy and anastrozole.³³⁷

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.³³⁰ With 8010 patients included in the analysis, DFS was superior in the letrozole-treated patients (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.³³⁸ In addition, a higher incidence of bone fracture was observed for patients in the letrozole arm compared with those in the tamoxifen arm (9.5% vs. 6.5%).³³⁹ After a longer follow-up (median 71 months) no significant improvement in DFS was noted with either tamoxifen followed by letrozole or the reverse sequence



as compared with letrozole alone (HR for tamoxifen followed by letrozole, 1.05; 99% CI, 0.84–1.32; HR for letrozole followed by tamoxifen, 0.96; 99% CI, 0.76–1.21).³⁴⁰

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 patients. The Italian Tamoxifen Anastrozole (ITA) trial randomized 426 postmenopausal patients 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.³⁴¹ 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 ($P = .10$).³⁴¹ 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 0.1.³⁴² The IES trial randomized 4742 postmenopausal patients 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.³⁴³ 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.³⁴⁴ 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; $P = .045$).³²⁷ 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.³⁴⁵

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.³⁴⁶ 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,³⁴⁰ 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.³⁴⁷ These data showed a considerable risk of recurrence between years 5 and 20 in these patients treated with initial 5 years of endocrine therapy.³⁴⁷ Data has now emerged showing benefit of extended endocrine therapy in improving DFS.



Data from the ATLAS trial (discussed above)³⁰⁹ and the aTTom trial confirm greater reduction in recurrence and death from breast cancer with 10 versus 5 years of tamoxifen therapy.³¹⁰

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 patients who had completed 4.5 to 6 years of adjuvant tamoxifen demonstrated that extended therapy with letrozole provides benefit in postmenopausal patients with HR-positive, early-stage breast cancer.^{328,348} 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.³⁴⁹

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 patients who had been randomly assigned to placebo after 4.5 to 6 years of tamoxifen.^{350,351} 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 patients may experience ongoing menopausal symptoms and loss of bone mineral density.^{352,353} 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 patients.³⁵⁴ 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.³⁵⁵ At a median follow-up of 62.3 months, patients who received anastrozole (n = 387) were reported to have a statistically significantly reduced risk of recurrence compared with patients who received no further treatment (n = 469; HR, 0.62; 95% CI, 0.40–0.96; *P* = .031).³⁵⁵

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.³⁵⁶ It is not known whether initial, sequential, or extended use of adjuvant aromatase inhibitors is the optimal strategy.

In patients 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.³⁵⁷ Postmenopausal patients 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.³⁵⁷ 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%).³⁵⁷

***NCCN Recommendations for Adjuvant Endocrine Therapy for***

Postmenopausal Patients: The NCCN Guidelines for Breast Cancer recommend the following adjuvant endocrine therapy options for patients 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 patients, 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 Patients: If 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). Patients 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 patients is to be considered for therapy with an aromatase inhibitor.^{358,359}

After 5 years of initial endocrine therapy, for patients who are postmenopausal at that time (including those who have become postmenopausal during the 5 years of tamoxifen therapy), the NCCN Panel recommends considering extended therapy with an aromatase inhibitor for up to 5 years (category 1) or based on the data from the ATLAS trial considering tamoxifen for an additional 5 years. For those who

remain premenopausal after the initial 5 years of tamoxifen, the panel recommends considering continuing up to 10 years of tamoxifen therapy.

Response to Adjuvant Endocrine Therapy: The measurement of the nuclear antigen, Ki-67 by IHC, gives an estimate of the tumor cells in the proliferative phase (G1, G2, and M phases) of the cell cycle. Studies have demonstrated the prognostic value of Ki-67 as a biomarker and its usefulness in predicting response and clinical outcome.³⁶⁰ 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.³⁶¹ 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.³⁶² 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.³⁶³ The study found no correlation between CYP2D6 allelic status and disease outcome or between CYP2D6 allelic status and tamoxifen-related adverse effects.³⁶³ A genetic analysis of the ATAC trial found no association between CYP2D6



genotype and clinical outcomes.³⁶⁴ Given the limited and conflicting evidence at this time,³⁶⁵ 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.³⁶⁶ 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 over 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 under 40 years.³⁶⁷ In a planned subgroup analysis of the AZURE trial, zoledronic acid improved DFS in patients who were more than 5 years since menopause at trial entry.³⁶⁸ 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 over 50 years, postmenopausal, or with ovarian suppression, showed a significant benefit for the use of adjuvant bisphosphonates in patients with a low-estrogen state and early-stage breast cancer.³⁶⁹ 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.³⁷⁰ 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, $P =0.69$).³⁷⁰ 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).³⁷⁰

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.³⁷¹ Subsequently in an interim analysis, an improvement in DFS, a secondary end point of the trial was reported.³⁷² 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-CARE³⁷³ 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,³⁷⁰ the panel recommends considering adjuvant bisphosphonate therapy for postmenopausal (natural or induced) patients 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 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.³⁷⁴ 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 patients 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.^{375,376} On retrospective analysis, the apparent advantage of the paclitaxel-containing regimen appears greater in patients 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.³⁷⁷

The ECOG E1199 study was a four-arm trial that randomized 4950 patients to receive AC chemotherapy followed by either paclitaxel or docetaxel given by either an every-3-week schedule or a weekly schedule.³⁷⁸⁻³⁸⁰ 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.³⁸⁰ 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,³⁷⁷ 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 patients with stage I to III breast cancer.³⁸¹ At a median follow-up of 7 years, overall DFS (81% vs. 75%; HR, 0.74; 95% CI, 0.56–0.98; $P = .033$) and OS (87% vs. 82%; HR, 0.69; 95% CI, 0.50–0.97; $P = .032$) were significantly improved with TC compared with AC.

Other Regimens

Other regimens included in the guidelines are: AC; epirubicin and cyclophosphamide (EC); CMF; AC with sequential docetaxel administered every 3 weeks; AC with sequential weekly paclitaxel; FEC/CEF followed by docetaxel or weekly paclitaxel; FAC followed by weekly paclitaxel; and docetaxel, doxorubicin, and cyclophosphamide (TAC).

The AC regimen for four cycles has been studied in randomized trials, resulting in relapse-free survival and OS equivalent to CMF



chemotherapy.^{382,383} No benefit from dose escalation of either doxorubicin or cyclophosphamide was shown.^{375,384}

Studies of CMF chemotherapy versus no chemotherapy have shown DFS and OS advantages with CMF chemotherapy.^{58,385} Studies using FAC/CAF chemotherapy have shown that the use of full-dose chemotherapy regimens is important.³⁸⁶ 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.³⁸⁵ 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.^{301,387-392} 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 patients with node-positive breast cancer.³⁹³ 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.³⁹⁴ Patient and tumor characteristics were equally distributed between both arms (<50 years of age: 40%, lumpectomy: 68%, and hormone positivity: 65%).³⁹⁴ The results reported that DFS after eight years was not greater for those patients who had been on the longer FEC chemotherapy treatment and that the patients 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.³⁹⁴ Five deaths resulted from the toxicity of FEC treatment, compared to the death of two patients on the AC treatment.³⁹⁴

The quality-of-life impact and menstrual history of patients on the NSABP (NRG) B-36 was also investigated in a phase III trial.³⁹⁵ Patients on FEC treatment experienced a worse quality of life at six months and higher rate of post-chemotherapy amenorrhea.³⁹⁵

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 patients 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.³⁹⁶ The second trial compared FEC given intravenously every 3 weeks at 2 dose levels of epirubicin (50 mg/m² vs. 100 mg/m²) in premenopausal and



postmenopausal patients with node-positive breast cancer. Five-year DFS (55% vs. 66%; $P = .03$) and OS (65% vs. 76%; $P = .007$) both favored the epirubicin 100 mg/m² arm.³⁹⁷ Another randomized trial in patients with ALN-positive breast cancer compared 6 cycles of FEC with 3 cycles of FEC followed by 3 cycles of docetaxel.³²¹ 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 patients with node-positive or high-risk, node-negative, operable breast cancer.³⁹⁸

The addition of weekly paclitaxel after FEC was shown to be superior to FEC alone in a randomized study of 1246 patients with early-stage breast cancer.³⁹⁹ The former regimen was associated with a 23% reduction in the risk of relapse compared with FEC (HR, 0.77; 95% CI, 0.62–0.95; $P = .022$), although no significant difference in OS was seen when the two arms were compared at a median follow-up of 66 months.

The phase III E1199 trial compared patients with node-positive or high-risk node-negative breast cancer who received 4 cycles of AC every 3 weeks, followed by either paclitaxel or docetaxel, either weekly or every 3 weeks. The 10-year updated results of this trial showed that incorporation of weekly paclitaxel and docetaxel every 3 weeks was associated with significant improvements in DFS, and marginal improvements in OS, compared with paclitaxel given every 3 weeks. Among patients with triple-negative disease, the 10-year DFS rate with weekly paclitaxel was 69% and the 10-year OS rate was 75%.⁴⁰⁰

Final results from a randomized trial of TAC versus FAC chemotherapy in ALN-positive breast cancer demonstrated that TAC is superior to FAC.⁴⁰¹

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.⁴⁰²

Several retrospective studies have evaluated the potential interaction of chemotherapy benefit and ER status.^{58,274} 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.²⁷⁴

For patients 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 patients aged greater than or equal to 65 years with early-stage breast cancer,⁴⁰³ the enrollment in that study was discontinued early.⁴⁰³ Therefore, there is also a possibility that AC/CMF is not superior to any chemotherapy in this cohort. The panel



recommends that treatment should be individualized for patients 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 HER2.⁴⁰⁴ Results of several randomized trials testing trastuzumab as adjuvant therapy have been reported.⁴⁰⁵⁻⁴¹³

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.⁴¹² 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.^{409,414,415} 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).^{405,407,409,411,414,415} 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.⁴¹⁴ 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.^{416,417}

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.⁴⁰⁷ 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; $P = .0115$).⁴¹⁸ 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.⁴¹³ The primary endpoint of DFS continued to be significantly higher in the trastuzumab-treated group (78.6%) versus the observation group (72.2; HR, 0.76; 95% CI, 0.66–0.87; $P < .0001$). At a median follow-up of 8 years, the study reported no significant difference in DFS, a secondary endpoint, in patients treated with trastuzumab for 2



years compared with 1 year.⁴⁰⁸ Therefore, 1 year of adjuvant trastuzumab remains the current standard of treatment.

The BCIRG 006 study randomized 3222 patients 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.⁴¹¹ 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).⁴¹¹ In the FinHer trial, 1010 patients 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.⁴⁰⁵ 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.⁴⁰⁵ 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.⁴⁰⁶

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.^{409,410} In the FNCLCC-PACS-04 trial, 528 patients 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.⁴¹⁹ 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 effective⁴²⁰ 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.⁴²¹

Retrospective analyses of low-risk patients with small tumors demonstrate that in T1a-bN0 breast cancers, HER2 overexpression added a 15% to



30% risk for recurrence.⁴²²⁻⁴²⁵ 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.⁴²⁶ 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.^{259,260,262}

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.⁴²⁷ 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.⁴²⁷

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 patients 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.⁴²² Ten-year breast cancer-specific survival and 10-year recurrence-free survival were 85% and 75%, respectively, in patients with tumors characterized as HER2-positive, ER-positive tumors, and 70% and 61%, respectively, in patients 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.⁴²³ In the other retrospective study of patients 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).⁴²⁸ Subgroup analyses from several of the randomized trials have shown consistent benefit of trastuzumab irrespective of tumor size or nodal status.^{411,429,430}

NCCN-Recommended HER-Targeted Regimens

The panel recommends AC followed by paclitaxel with trastuzumab for 1 year commencing with the first dose of paclitaxel as a preferred HER2-targeting adjuvant regimen. The TCH regimen is also a preferred regimen, especially for those with risk factors for cardiac toxicity, given the results of the BCIRG 006 study that demonstrated superior DFS in



patients receiving TCH or AC followed by docetaxel plus trastuzumab compared with AC followed by docetaxel alone.

Other trastuzumab-containing regimens included in the NCCN Guidelines are: AC followed by docetaxel and trastuzumab,⁴¹¹ and docetaxel plus trastuzumab followed by FEC⁴⁰⁵ (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 setting⁴³¹ and the significant improvement in pCR seen in the neoadjuvant setting,^{260,262} 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.^{432,433}

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%).⁴³⁴

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 1.²⁹⁴ 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.

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 2014.⁴³⁵ 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.⁴³⁶⁻⁴³⁸ In addition, the panel notes no evidence to support the use of “tumor markers” for breast cancer, and routine bone scans, CT scans, MRI scans, PET scans, or ultrasound examinations in the asymptomatic patient provide no advantage in survival or ability to palliate recurrent disease and are, therefore, not recommended.^{109,439}

The use of breast MRI in follow-up of patients with prior breast cancer is undefined. It may be considered as an option in patients 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 patients with *BRCA1/2* mutations when compared with patients with sporadic breast cancer.⁴⁴⁰⁻⁴⁴²

The panel recommends that patients 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 patients.⁴⁴³ 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 patients. The vast majority of patients with tamoxifen-associated uterine carcinoma have early vaginal spotting.

If an adjuvant aromatase inhibitor is considered in patients 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.³⁵⁸ Bilateral oophorectomy assures postmenopausal status in young patients with therapy-induced amenorrhea and may be considered prior to initiating therapy with an aromatase inhibitor in a young woman.

Symptom management for patients 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.⁴⁴⁴⁻⁴⁴⁷ 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.^{448,449} 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.^{358,450,451}

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.⁴⁵² 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.^{453,454} The panel recommends educating the patients on lymphedema, monitoring for lymphedema, and referring for lymphedema management as needed.

Many young patients treated for breast cancer maintain or regain premenopausal status following treatment for breast cancer. For these



patients, the NCCN Panel discourages the use of hormonal birth control methods, regardless of the HR status of the tumor.⁴⁵⁵ Alternative birth control methods are recommended, including intrauterine devices, barrier methods, and, for those with no intent of future pregnancy, tubal ligation or vasectomy for the partner. Breastfeeding during endocrine or chemotherapy treatment is not recommended by the NCCN Panel because of risks to the infant. Breastfeeding after breast-conserving treatment for breast cancer is not contraindicated. However, lactation from an irradiated breast may not be possible, or may occur only with a diminished capacity.^{455,456}

The panel recommends that patients 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 patients 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 patients receiving endocrine therapy with ovarian suppression.⁴⁵⁷ Use of bisphosphonates in such patients and in other subgroups remains controversial. Denosumab has shown to significantly reduce fractures in postmenopausal patients receiving adjuvant therapy aromatase inhibitors, and improves bone mineral density.³⁷¹

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. Patients 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 patients 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.⁴⁵⁸ A prospective study of 1490 patients diagnosed with stage I–III breast cancer showed an association between high fruit and vegetable consumption, physical activity, and improved survivorship, regardless of obesity.⁴⁵⁹ 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.⁴⁶⁰

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.⁴⁶¹⁻⁴⁶³

For management of issues related to survivorship including late/long-term effects of cancer and its treatment, see the [NCCN Guidelines for Survivorship](#).



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 patients 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.^{109,110,464,465} 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.^{466,467} 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.⁴⁶⁷ 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 HER2.⁴⁶⁸⁻⁴⁷⁷

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



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 patients 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.⁴⁷⁸ 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.⁴⁷⁹

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 patients 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.^{480,481} 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 patients 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.⁴⁸² 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, $P = .046$).⁴⁸² Five-year OS in all patients in the study was also significantly improved with chemotherapy (88% vs. 76%, $P = .024$).⁴⁸² The benefit of adjuvant chemotherapy was mostly seen in patients with ER-negative disease. Among patients 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).⁴⁸² However these patients received endocrine therapy.

According to the NCCN Panel, after local treatment, patients with local recurrences only should be considered for limited duration systemic chemotherapy or endocrine therapy similar to that outlined in the adjuvant



chemotherapy section. The panel emphasized the importance of individualizing treatment strategies in patients with a recurrence of disease limited to a local site.

Management of 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 patients with metastatic breast cancer and an intact primary tumor is systemic therapy, with consideration of surgery after initial systemic treatment for those requiring palliation of symptoms or with impending complications, such as skin ulceration, bleeding, fungation, and pain.⁴⁸³ 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.⁴⁸⁴⁻⁴⁸⁷ Substantial selection biases exist in all of these studies and are likely to confound the study results.^{488,489}

Two prospective, randomized studies assessed whether or not surgery on the primary tumor in the breast is necessary for patients who are diagnosed with metastatic/stage IV breast cancer.^{490,491} In the first

prospective trial, patients (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.⁴⁹⁰ 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).⁴⁹⁰ In a separate multiple center prospective registry study patients who responded to first-line systemic therapy were randomized to management of the primary tumor by surgery or not.⁴⁹² Preliminary data showed no difference in OS between the two groups.⁴⁹²

However, another trial by the Turkish Federation, MF07-01 of patients (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.⁴⁹³ 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).⁴⁹³ 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%).⁴⁹³ 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).⁴⁹³



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.⁴⁹⁴ Guidance for treatment of patients with breast cancer and brain metastases is included in 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.⁴⁹⁵

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.⁴⁹⁶⁻⁵⁰³ 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.⁵⁰⁴⁻⁵⁰⁶ Data from these trials show that among patients with breast cancer and bone metastases zoledronic acid administered once every 12 weeks versus once every four weeks does not



compromise efficacy and has similar rates of SREs.^{504,505,507} In the ZOOM trial,⁵⁰⁴ 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,⁵⁰⁵ 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,⁵⁰⁶ the rate of SREs was 22% of the in the 4-week arm and 23.2% in the 12-week arm.⁵⁰⁶ 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 D₃ of 400 to 800 IU. Recommended agents for use in the United States are pamidronate 90 mg intravenously over 2 hours or zoledronic acid 4 mg intravenously over 15 minutes. The original studies continued treatment for up to 24 months; however, there are limited long-term safety data indicating treatment can continue beyond that time.^{499,501,508} 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

Patients 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.⁵⁰⁹ 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.⁵⁰⁹ 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

Patients 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.

Patients 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 patients with HR-positive breast cancer benefit from sequential use of endocrine therapies at disease progression. Therefore, patients 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. For disease progression on or within 12 months of completing adjuvant endocrine or for disease progression 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.



Many trials in HR-positive patients have not included premenopausal patients. The NCCN Panel that recommends patients with HR-positive disease should have adequate ovarian suppression/ablation and then be treated in the same way as post-menopausal patients. 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 patients or premenopausal patients 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.⁵¹⁰ 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.⁵¹⁰ 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%).⁵¹⁰

Ribociclib in combination with letrozole was also studied as first-line therapy in a phase III study of postmenopausal patients (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.⁵¹¹ 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%).⁵¹¹

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 patients 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).⁵¹² The ORR was higher with the combination compared with AI monotherapy (59% vs. 44 %).⁵¹² 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%).⁵¹²

Most trials studying CDK 4/6 inhibitor with an AI have mainly included postmenopausal patients and only a small subset of premenopausal patients on ovarian suppression. However, in the phase III MONALEESA-7 trial, 672 pre- or perimenopausal patients 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.⁵¹³ 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).⁵¹³

At 3.5 years, an improvement in OS was reported with ribociclib (70% vs. 46%; HR 0.71, 95% CI 0.54-0.95).⁵¹⁴ 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%).⁵¹³

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



postmenopausal patients and premenopausal patients 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).⁵¹⁵ 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; $P = .0496$).⁵¹⁶ 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.⁵¹⁵ 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; $P = .041$).⁵¹⁷

A separate phase III randomized study in postmenopausal patients 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; $P = .006$),⁵¹⁸ 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; $P = .02$).⁵¹⁹

Results from another phase III trial (FALCON) of first-line treatment with fulvestrant compared with anastrozole in endocrine therapy-naïve 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).⁵²⁰ 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.⁵²⁰

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 disease progression 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).⁵²¹ The PFS benefits were consistent across patients with and without prior endocrine treatment. In a subsequent analysis, a significant improvement in OS was observed.⁵²² 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.⁵²²

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 patients and premenopausal patients 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 patients 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%



CI, 0.81–1.20; $P = .91$).⁵²³ 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 a non-steroidal AI.⁵²⁴ 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.⁵²⁵ 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).⁵²⁶

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 patients 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 patients there is evidence supporting the use of an AI as first-line therapy for their recurrent disease.^{527,528}

Prospective randomized trials comparing the AI head-to-head have demonstrated that all AI's are the same.⁵²⁹ Tamoxifen is the commonly used SERM for premenopausal patients.⁵³⁰ In postmenopausal patients, AI monotherapy has been shown to have superior outcome compared with tamoxifen, although the differences are modest.⁵³¹⁻⁵³⁵ A randomized phase III trial comparing tamoxifen with exemestane as first-line endocrine therapy for postmenopausal patients with metastatic breast cancer showed no significant differences PFS or OS between the two arms.⁵³³

NCCN recommendations for first-line therapy: For postmenopausal patients 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 patients, first-line endocrine treatment includes ovarian suppression/ablation and endocrine therapy listed above for postmenopausal patients 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



Fulvestrant + CDK 4/6 inhibitors: Fulvestrant in combination with a CDK 4/6 inhibitor may be offered to patients who experienced disease 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).⁵³⁶ 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, $P < .000001$)⁵³⁷ 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 disease progression while receiving endocrine therapy were randomly assigned to fulvestrant with or without abemaciclib.⁵³⁸ 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%).⁵³⁸ In addition, an 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).⁵³⁹

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 patients and premenopausal patients with ovarian ablation/suppression with HR-positive, HER2- negative

recurrent/stage IV breast cancer. The panel notes 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.^{540,541} A randomized phase II study compared anastrozole versus fulvestrant in over 200 patients with advanced breast cancer.^{515,516} 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).⁵¹⁵ 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; $P = .0496$).⁵¹⁶ This study used a higher 500 mg loading dose every 2 weeks for 3 doses and then 500 mg monthly.⁵¹⁵ 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; $P = .041$).⁵¹⁷

A phase II study of fulvestrant in postmenopausal patients 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.⁵⁴² The clinical benefit rates of exemestane versus fulvestrant observed in a phase III trial of postmenopausal patients with HR-positive advanced breast cancer who experienced disease progression on prior nonsteroidal aromatase inhibitor therapy were comparable (32.2% vs. 31.5%; $P = .853$).⁵⁴³ 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.⁵⁴³

Fulvestrant plus alpelisib: In a randomized phase III trial of patients (n=572) with advanced HR-positive breast cancer and confirmed



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.⁵⁴⁴

Everolimus plus endocrine therapy: Resistance to endocrine therapy in patients 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 patients with HR-positive, HER2-negative metastatic breast cancer previously treated with an aromatase inhibitor.⁵⁴⁵ 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.⁵⁴⁵

A phase III trial in postmenopausal patients 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.⁵⁴⁶ 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^{546,547} 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 patients with HR-positive advanced breast cancer that had disease progression or recurrence during treatment with a nonsteroidal aromatase inhibitor to exemestane with or without the mTOR inhibitor everolimus.⁵⁴⁸ 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; $P < .0001$).⁵⁴⁷ The adverse events (all grades) that occurred more frequently in those receiving everolimus included stomatitis, infections, rash, pneumonitis, and hyperglycemia.^{547,548} 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.⁵⁴⁹ Based on the evidence from the BOLERO-2 trial, the NCCN Panel has included everolimus plus exemestane as an option for patients 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 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.^{529,550,551} AI monotherapy may 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.⁵⁵²

NCCN recommendations for second-line: For postmenopausal patients 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) (category 1), 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,^{527,553-555} estradiol⁵⁵⁶ 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 disease progression while on endocrine therapy and already received multiple systemic therapies (average of three prior systemic regimens).⁵⁵⁷ Ninety percent of patients had visceral disease and 50.8% had more than three sites of metastases.⁵⁵⁷ Single-agent abemaciclib induced partial response in 26 (19.7%) and demonstrated an ORR of 19.7% (95% CI: 13.3–27.5).⁵⁵⁷ 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).⁵⁵⁷ 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.⁵⁵⁷ 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.



Patients with disease progression while being treated with HER2-targeted therapy should be offered additional line of 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-targeted 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 patients (n=808) with HER2-positive metastatic breast cancer.⁵⁵⁸ 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, $P < .001$).⁵⁵⁸ 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; $P = .0008$).⁴³¹ 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.⁵⁵⁸ Cardiac adverse events or left ventricular systolic dysfunction were reported slightly more frequently in the control group.⁵⁵⁹ Health-related QOL was not different in

the two treatment groups.⁵⁶⁰ 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 was 19.6, 23.0 and 18.1 months with docetaxel, paclitaxel and nab-paclitaxel, respectively).⁵⁶¹ 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).^{562,563,564} 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 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; $P = .14$).⁵⁶⁵ 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; $P = .31$).⁵⁶⁵ 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.⁵⁶⁵

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,⁵⁶⁵ 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 chemotherapy⁵⁶⁶ 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,⁵⁶⁶⁻⁵⁶⁹ docetaxel,⁵⁶⁷ and vinorelbine,⁵⁶⁷ 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.^{570,571} 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.^{566,571,572}

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.⁵⁷³⁻⁵⁷⁵ 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.⁵⁷⁶ 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).⁵⁷⁶ The reported median duration of response with the combination was 5.8 months (range, 2.9–15.3 months).⁵⁷⁶

To determine whether the clinical benefit seen in the study was from pertuzumab alone or was a result of the combined effect of pertuzumab and trastuzumab, a cohort of patients ($n = 29$) whose disease progressed during prior trastuzumab-based therapy received pertuzumab monotherapy until progressive disease or unacceptable toxicity. Of these, patients with disease progression ($n = 17$) continued to receive pertuzumab with the addition of trastuzumab. In the 29 patients who received pertuzumab monotherapy, the objective response rate and



clinical benefit rate reported were 3.4% and 10.3%, respectively, whereas in the patients who received dual blockade after disease progression while on pertuzumab, the objective response rate and clinical benefit rate were 17.6% and 41.2%, respectively.⁵⁷⁷

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.⁵⁷⁸ 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; $P = .0005$).⁵⁷⁸ 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.⁵⁷⁸

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-DM1.⁵⁷⁹ 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).⁵⁷⁹ 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%).⁵⁷⁹ 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 disease progression on a trastuzumab-containing regimen.

A phase III study compared lapatinib plus capecitabine with capecitabine alone in patients 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.⁵⁸⁰ 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 had disease progression on monotherapy were allowed to cross over to the combination arm. This resulted in insufficient power to detect significant differences in OS; an exploratory analysis



demonstrated a trend toward a survival advantage with lapatinib plus capecitabine.⁵⁸¹ 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; $P = .210$).⁵⁸¹

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.⁵⁸² 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; $P = .026$).⁵⁸³ 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.⁵⁸³ 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),⁵⁸⁴ 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.⁵⁸⁴ 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.⁵⁸⁴

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.⁵⁸⁵ 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

Patients 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



with chemotherapy. Premenopausal patients 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 patients with stage IV or recurrent HR-positive, HER2-positive tumors.

In the TAnDEM study, postmenopausal patients (n =207) with metastatic HR-positive and HER2-positive tumors were randomized to receive anastrozole alone or anastrozole plus trastuzumab.⁵⁸⁶ 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; $P = .23$).⁵⁸⁷

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; $P = .019$).⁵⁸⁸ 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%).⁵⁸⁸

In the randomized phase II study (PERTAIN), postmenopausal patients (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).⁵⁸⁹ Grade 3 or higher adverse events observed were higher with trastuzumab and pertuzumab versus pertuzumab alone (50% vs. 39%). Of note, about half of patients 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,⁵⁸⁹ 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 patients (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.⁵⁹⁰ 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, $P = .0064$).⁵⁹⁰ 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



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.

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.^{591,592}

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 physician's choice (n=97) of non-platinum chemotherapy (capecitabine, eribulin or vinorelbine).⁵⁹³ 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; $P < .001$].⁵⁹³ 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; $P = .513$).⁵⁹⁴ 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.⁵⁹⁴

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 physician's choice

of single agent chemotherapy (n=144).⁵⁹⁵ 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; $P < .001$).⁵⁹⁵

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 patients (n=376) with triple negative breast cancer. In the unselected population, carboplatin was not more active than docetaxel (ORR, 31.4% vs. 34.0%; $P = .66$).⁵⁹⁶ 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%, $P = .03$).⁵⁹⁶ 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.

**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.⁵⁹⁷

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).⁵⁹⁷ 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).⁵⁹⁷ 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.⁵⁹⁷ 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.⁵⁹⁸ A subsequent 18-month follow-up analysis confirmed PFS and OS benefits among those with PD-L1-expressing

tumors.⁵⁹⁹ Atezolizumab plus albumin-bound paclitaxel is included as a preferred option for those with advanced triple negative breast cancer with PD-L1 expression in $\geq 1\%$ tumor-infiltrating immune cells.

Systemic Chemotherapy for Recurrent or Stage IV Disease

Patients 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.⁶⁰⁰⁻⁶⁰⁴ 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



adjuvant setting and also show that results may be less effective with anthracycline-containing regimens.⁶⁰⁵⁻⁶⁰⁹

A meta-analysis showed favorable impact on OS by prolonging treatment until disease progression.⁶¹⁰ 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 patients receiving longer durations of chemotherapy versus a limited number of cycles.⁶¹⁰ 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.⁶⁰⁴

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).⁶¹¹

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/m²)⁶¹² or every three weeks (175 mg/m²).⁶¹³ 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).⁶¹⁴

Doxorubicin (60 to 75 mg/m²) every three weeks, or 20 mg/m² weekly has shown an ORR between 30 to 47%.⁶¹⁵⁻⁶¹⁸ Liposomal doxorubicin (50 mg/m² every 4 weeks) has been shown to have efficacy similar to doxorubicin (60 mg/m² every 3 weeks).⁶¹⁹ It has also been shown to have efficacy in the second-line setting for patients with metastatic breast cancer.⁶¹⁹ 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%).⁶¹⁹ 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%).⁶¹⁹



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 of 15.2 months (95% CI: 13.5-19.6 months).⁶²⁰ In another study, patients (n=95) were randomized to capecitabine or cyclophosphamide, methotrexate and fluorouracil (CMF).⁶²¹ 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.⁶²¹

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 patients 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; $P=.041$).⁶²²

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.⁶²³ 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).⁶²³

In addition to the above, gemcitabine⁶²⁴ and vinorelbine are both active as single agents even in heavily pretreated patients with metastatic breast cancer.⁶²⁵⁻⁶²⁷

Among other recommended single agents, the NCCN Panel has included taxanes (docetaxel,⁶²⁸ albumin-bound paclitaxel⁶²⁹⁻⁶³¹), anthracyclines (epirubicin)⁶³², and ixabepilone.⁶³³⁻⁶³⁵ as other recommended regimens.

Ixabepilone as monotherapy has been evaluated in several phase II trials of patients with metastatic breast cancer: in a first-line setting in patients previously treated with anthracycline chemotherapy⁶³³; in patients with taxane-resistant metastatic breast cancer⁶³⁴; and in patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine.⁶³⁵ 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;⁶³³ 12% (95% CI, 4.7%–26.5%), 10.4 months, and 7.9 months for the taxane-resistant patients,⁶³⁴ 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.⁶³⁵ In the study by Perez et al,⁶³⁵ 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);^{636,637} epirubicin/cyclophosphamide (EC)⁶³⁸; docetaxel and capecitabine;⁶⁰² gemcitabine and paclitaxel (GT);⁶³⁹ cyclophosphamide/methotrexate/fluorouracil (CMF);⁶⁴⁰ gemcitabine/ carboplatin;⁶⁴¹⁻⁶⁴³ carboplatin with paclitaxel or albumin-bound paclitaxel;⁶⁴⁴⁻⁶⁴⁶ and paclitaxel/bevacizumab.⁶⁴⁷⁻⁶⁴⁹

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.^{636,637} For first-line EC, a phase III trial reported the ORR of 55%, PFS 7.1 months, and OS of 14 months.⁶³⁸ For first-line capecitabine/docetaxel, a phase III trial reported an ORR of 53%



and time-to-progression of 11 months.⁶⁵⁰ 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.⁶⁰²

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.⁶⁴¹ and the median OS was 11.1 months with gemcitabine/carboplatin [HR of 0.88 (95% CI, 0.69 to 1.12)].⁶⁴¹

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.^{645,646} The randomized 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.⁶⁴⁴ 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.⁶⁴⁴

A series of trials have sought to define the role for bevacizumab in the treatment of metastatic breast cancer. The E2100 trial randomized 722 patients with recurrent or metastatic breast cancer to first-line chemotherapy with paclitaxel with or without bevacizumab.⁶⁴⁷ 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.⁶⁵¹ 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.^{648,649} 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.⁶⁵²

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/m².

The data from the above-mentioned randomized trials, document that the addition of bevacizumab to first- or second-line chemotherapy agents



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-analysis of the trials.⁶⁵³ 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.⁶⁴⁰ 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 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.⁶⁵⁴ *NTRK* fusions are identified by fluorescence *in situ* hybridization (FISH), Next Generation Sequencing (NGS) or polymerase chain reaction (PCR). Larotrectinib⁶⁵⁵⁻⁶⁵⁷ and entrectinib^{657,658} 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 exist or that have disease progression 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.⁶⁵⁹⁻⁶⁶¹ 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.⁶⁶² 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 criteria⁶⁶³ and the WHO criteria.⁶⁶⁴ The Panel also recommends using the



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.⁶⁶⁵ 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.⁶⁶⁵ 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.⁶⁶⁵



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.⁶⁶⁶ 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.⁶⁶⁷⁻⁶⁶⁹ The associated cancers are not necessarily located adjacent to the NAC and may be either DCIS or invasive cancer.

Patients 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.^{669,670}

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.⁶⁶⁸ 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.⁶⁷¹⁻⁶⁷⁵ 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.^{676,677} Patients treated with breast conservation should



receive whole breast radiation. Extended-field radiation to regional lymph nodes should be used in cases of an associated invasive breast cancer with involved lymph nodes as for any breast cancer as described in [the initial sections of the NCCN Guidelines](#). A radiation boost should be considered for the site of the resected NAC and any associated resected cancer site, if applicable.

Patients with an associated invasive cancer have substantial risk of developing metastases. Adjuvant systemic therapy should be administered according to the stage of the cancer. Patients 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



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.⁶⁷⁸ 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.⁶⁷⁹ 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 40.⁶⁸⁰ 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.⁶⁸⁰ 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.⁶⁸¹ 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.⁶⁸² 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.⁶⁸³ 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).⁶⁸⁴

While the epithelial component of most phyllodes tumors contains ER (58%) and/or PR (75%),⁶⁸⁵ endocrine therapy has no proven role in the treatment of phyllodes tumors. Similarly, there is no evidence that adjuvant cytotoxic chemotherapy provides benefit in reduction of recurrences or death. In the rare patient who experiences a systemic recurrence (usually in the lung), treatment should be as recommended in the [NCCN Guidelines for Soft Tissue Sarcoma](#).



Breast Cancer During Pregnancy

Breast cancer occurring concurrently with pregnancy is an infrequent clinical event. In a California registry study, there were 1.3 breast cancers diagnosed per 10,000 live births.⁶⁸⁶ 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.^{687,688} 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%.⁶⁸⁹

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.⁶⁸⁹ 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,⁶⁹⁰ and breast-conserving therapy during pregnancy does not appear to have a negative impact on survival.^{690,691} 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,^{692,693} 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 patients. 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 patients under 30 weeks gestation.⁶⁹⁴ There are limited data with only case reports and estimations of fetal radiation dose regarding use of radioactive tracer (eg, technetium 99m sulfur colloid).⁶⁹⁵⁻⁶⁹⁷ Isosulfan blue



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Breast Cancer

or methylene blue dye for sentinel node biopsy procedures is discouraged during pregnancy.

The indications for systemic chemotherapy are the same in the pregnant patient as in the non-pregnant breast cancer patient, although chemotherapy should not be administered at any point during the first trimester of pregnancy. The largest experience in pregnancy has been with anthracycline and alkylating agent chemotherapy.^{698,699} Collected data of chemotherapy exposure in utero indicate that the first trimester has the greatest risk of fetal malformation.^{700,701} Fetal malformation risks in the second and third trimester are approximately 1.3%, not different than that of fetuses not exposed to chemotherapy during pregnancy. If systemic therapy is initiated, fetal monitoring prior to each chemotherapy cycle is appropriate. Chemotherapy during pregnancy should not be given after week 35 of pregnancy or within 3 weeks of planned delivery in order to avoid the potential for hematologic complications during delivery. Data from a single-institution prospective study indicate that FAC chemotherapy (5-FU 500 mg/m² IV days 1 and 4, doxorubicin 50 mg/m² by IV infusion over 72 hours, and cyclophosphamide 500 mg/m² IV day 1) may be given with relative safety during the second and third trimesters of pregnancy.⁶⁹⁹ 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.⁶⁸⁷ An update of this experience reported on 57 patients 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.^{699,702} 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.⁷⁰³⁻⁷⁰⁶ 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.⁷⁰⁷⁻⁷¹⁴ 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.⁷¹⁵

Endocrine therapy and radiation therapy are contraindicated during pregnancy. Endocrine therapy and radiation therapy, if indicated, should thus not be initiated until the postpartum period.

Communication between the oncologist and maternal fetal medicine specialist is essential at every visit and for every treatment decision point for the patient.

**Inflammatory Breast Cancer**

Inflammatory breast cancer (IBC) is a rare, aggressive form of breast cancer estimated to account for 1% to 6% of breast cancer cases in the United States.^{716,717} 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.⁷¹⁸⁻⁷²¹ 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.^{722,723} 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 prognosis⁷²⁴⁻⁷²⁶ and to be younger at the time of disease presentation.⁷²⁷

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.^{728,729} Nevertheless, current evidence provides justification for a separate guideline for the workup and treatment of patients diagnosed with IBC.

Stage T4d, N0- N3, M0**Workup**

Patients 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.⁷³⁰

Imaging studies help facilitate image-guided biopsy, delineate locoregional disease, and identify distant metastases. Evaluation of all patients suspected with IBC must include diagnostic bilateral mammogram, with the addition of ultrasound as necessary. A breast MRI scan is optional.

Evaluations for the presence of distant metastasis in the asymptomatic patient include LFTs, bone scan or sodium fluoride PET/CT (category 2B), and diagnostic CT imaging of the chest, abdomen, and pelvis (category 2B; category 2A for diagnostic CT imaging of the chest when pulmonary symptoms are present).



FDG PET/CT may be most helpful in situations where standard imaging results are equivocal or suspicious. However, there is limited evidence suggesting that PET/CT may be a useful adjunct to standard imaging of IBC due to the increased risk of regional lymph node involvement and distant spread of disease in this group of patients.^{109,110,731,732}

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 approach⁷¹⁶ 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.⁷³³ 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%.⁷³⁴

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.⁷³⁵ A systematic review found evidence for an association between the intensity of preoperative therapy and the likelihood of a pCR.⁷³⁶ 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.⁷³⁷

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 patients 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.^{720,738} For patients with HER2-positive disease, the addition of trastuzumab to primary systemic chemotherapy is associated with better response rates.⁷³⁹⁻⁷⁴³ A



prospective study that randomized patients 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.⁷³⁹ 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 patients with IBC. However, based on the available data,⁷³⁹ 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.^{260,744} 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.²⁶⁰

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.⁷⁴⁵ SLN dissection is not a reliable method of assessing ALNs among patients with IBC.⁷⁴⁶ 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 patients with IBC who have undergone a modified radical mastectomy. Reconstruction of the breasts soon after mastectomy may compromise the post-mastectomy radiation therapy outcomes.⁷⁴⁷

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 patients with IBC. To reduce the risk of local recurrence, the panel recommends radiation therapy to the chest wall and the supraclavicular region. If the internal mammary lymph node(s) is clinically or pathologically involved, radiation therapy should include the internal mammary nodes. If the internal mammary nodes are not clinically or pathologically involved, then including the internal mammary nodes in the radiation therapy field is at the discretion of the treating radiation oncologist (category 3). For HER2-positive disease, trastuzumab may be administered concomitantly with radiation therapy.

**Stage IV or Recurrent IBC**

Patients with stage IV or recurrent IBC should be treated according to the guidelines for recurrence/stage IV breast cancer (See [NCCN Guidelines for Breast Cancer](#)).

Axillary Breast Cancer

Occult breast cancer presenting with axillary metastases is an unusual presentation that can be a diagnostic and therapeutic challenge. Evidence to support recommendations on the management of patients presenting with axillary breast cancer comes from a limited number of retrospective studies involving small numbers of patients⁷⁴⁸⁻⁷⁵⁰ (see also references therein). Although treatment of patients 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.^{749,750}

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.⁷⁵¹ 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.⁷⁴⁹ 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 patients. 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.⁷⁵² 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 patients with dense breast tissue, positive axillary nodes, and suspected occult primary breast tumor or to evaluate the chest wall.⁷⁵³ 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 patients by allowing for lumpectomy instead of mastectomy.^{749,754} In one report, the primary site was identified using MRI in about half of the patients presenting with axillary metastases, irrespective of the breast density.⁷⁵⁵

The [NCCN Guidelines for Occult Primary Cancer](#) also provide recommendations for additional workup, including chest and abdominal CT to evaluate for evidence of distant metastases for patients diagnosed



with adenocarcinoma (or carcinoma not otherwise specified) of the axillary nodes without evidence of a primary breast lesion. In particular, breast MRI and ultrasound are recommended. Axillary ultrasound should also be performed.

Treatment for Possible Primary Breast Cancer

Patients with MRI-positive breast disease should undergo evaluation with ultrasound or MRI-guided biopsy and receive treatment according to the clinical stage of the breast cancer. Treatment recommendations for those with MRI-negative disease are based on nodal status. For patients with T0, N1, M0 disease, options include mastectomy plus axillary nodal dissection or axillary nodal dissection plus whole breast irradiation with or without nodal irradiation. Systemic chemotherapy, endocrine therapy, or trastuzumab is given according to the recommendations for stage II or III disease. Neoadjuvant chemotherapy, trastuzumab, and endocrine therapy should be considered for patients with T0, N2-N3, M0 disease followed by axillary nodal dissection and mastectomy as for patients with locally advanced disease.

Summary

The therapeutic options for patients with noninvasive or invasive breast cancer are complex and varied. In many situations, the patient and physician have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. With few exceptions, the evaluation, treatment, and follow-up recommendations in these guidelines are based on the results of past and present clinical trials. However, there is not a single clinical situation in which the treatment of breast cancer has been optimized with respect to either maximizing cure or minimizing toxicity and disfigurement. Therefore, patient/physician participation in prospective clinical trials allows patients to not only receive state-of-the-art cancer treatment but also to contribute to improving the treatment outcomes.



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Discussion
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