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NCCN Clinical Practice Guidelines in Oncology™

Breast Cancer

V.2.2008

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The change in the 2.2008 version of the Breast Guidelines from the 1.2008 version is the addition of the updated manuscript.

Summary of changes in the 1.2008 version of the Breast Guidelines from the 2.2007 version include:

DCIS-1 - Primary treatment of DCIS now includes 3 options: lumpectomy without lymph node surgery plus whole breast radiation (category 1); total mastectomy with or without sentinel node biopsy with or without reconstruction (category 2A); lumpectomy without lymph node surgery without radiation (category 2B).

BINV-1 - Workup for patients with clinical stage I, IIA, IIB, or T3,N1,M0 disease was reorganized to distinguish optional additional studies from those recommended for all of these patients.

BINV-3 - Recommendation for locoregional treatment for patients with clinical stage I, IIA, IIB, or T3,N1,M0 disease with 1-3 positive axillary nodes following total mastectomy was changed from "Consider" to "Strongly consider" postmastectomy radiation therapy.

BINV-6 - For patients with hormone receptor-positive, HER2-negative tumors that are 0.6-1.0 cm and moderately/poorly differentiated or with unfavorable features, or > 1 cm, the recommendation for use of a 21-gene RT-PCR assay (category 2B) was added to the systemic adjuvant treatment decision pathway as an option for guiding chemotherapy treatment decisions.

BINV-9 - Systemic adjuvant treatment for patients with tubular or colloid tumors that are hormone receptor-positive and node-positive was changed from "adjuvant hormonal therapy + adjuvant chemotherapy" to "adjuvant hormonal therapy ± adjuvant chemotherapy". For hormone receptor-positive, node negative tubular/colloid tumors that are ≥ 1 cm, the recommendation for use or consideration of adjuvant chemotherapy was removed.

BINV-13 - The heading for workup for patients with locally advanced invasive cancer was modified to specify "Noninflammatory" disease and reorganized to distinguish optional additional studies from those recommended for all of these patients.

BINV-14 - Heading was modified to indicate that these recommendations apply to patients with "noninflammatory" locally advanced invasive disease.

Surgical axillary staging was changed to "level I/II axillary dissection"; recommendation for radiation therapy to internal mammary nodes was expanded to include "internal mammary nodes if involved, consider internal mammary nodes if not clinically involved (category 3)".

BINV-16 - BINV-20 - Recommendations for treatment of Recurrence/Stage IV disease is stratified according to whether bone disease is present and then further stratified according to hormone receptor and HER2 tumor status.

BINV-G - "Principles of Breast Reconstruction Following Mastectomy" section is new to the guidelines.

BINV-H - "Principles of Radiation Therapy" section is new to the guidelines.

BINV-I - Throughout the adjuvant hormonal therapy guideline, names of specific aromatase inhibitors were replaced with the term "aromatase inhibitor".

BINV-J - Added to the Adjuvant chemotherapy guideline, was the TC (docetaxel/cyclophosphamide) regimen.

BINV-M Capecitabine is listed as a preferred chemotherapy agent in combination with lapatinib for patients with HER2-positive recurrent or metastatic disease. Based on FDA approval and data from recent studies, ixabepilone (category 2A) + capecitabine (category 2B) were added under "Other active options" for the treatment of metastatic breast cancer

PHYLL-1 - Phyllodes tumor further described as including "benign, borderline, and malignant" disease.

PREG-1 - The term "core biopsy preferred" was added as clarification for confirming cancer diagnosis; added statement "methylene blue dye should not be used in pregnant patients" to footnote "c".

IBC-1 - Inflammatory Breast Cancer is a new algorithm to the NCCN Breast Cancer Treatment Guidelines.

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DIAGNOSIS

WORKUP

PRIMARY
TREATMENT

RISK REDUCTION

SURVEILLANCE/FOLLOW-UP

Lobular carcinoma
in situ (LCIS)
Stage 0
Tis, N0, M0^a

- History and physical
- Diagnostic bilateral mammogram
- Pathology review^b

→ Observation^c →

Counseling regarding risk reduction with tamoxifen for premenopausal women,^d or with tamoxifen or raloxifene for postmenopausal women (category 1, see also [NCCN Breast Cancer Risk Reduction Guidelines](#)) or
In special circumstances, bilateral mastectomy (see also [NCCN Breast Cancer Risk Reduction Guidelines](#)) ± reconstruction^e may be considered for risk reduction

- Interval history and physical exam every 6-12 mo
- Mammogram every 12 mo, unless postbilateral mastectomy
- If treated with tamoxifen, monitor per [NCCN Breast Cancer Risk Reduction Guidelines](#)

^aSee [NCCN Breast Cancer Screening and Diagnosis Guidelines](#).

^bThe panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and non-invasive carcinomas of the breast. http://www.cap.org/apps/docs/cancer_protocols/protocols_index.html

^cHistologically aggressive variants of LCIS ("pleomorphic LCIS") may have a similar biological behavior to that of DCIS, but outcome data regarding the efficacy of surgical excision to negative margins and/or radiotherapy are lacking.

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

^eSee [Principles of Breast Reconstruction Following Mastectomy \(BINV-G\)](#).

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DIAGNOSIS

WORKUP

PRIMARY TREATMENT

Ductal carcinoma
in situ (DCIS)
Stage 0
Tis, N0, M0^a



- History and physical exam
- Diagnostic bilateral mammogram
- Pathology review^b
- Determination of tumor estrogen receptor (ER) status



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



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

^a[See NCCN Breast Cancer Screening and Diagnosis Guidelines.](#)

^bThe panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and non-invasive carcinomas of the breast.
http://www.cap.org/apps/docs/cancer_protocols/protocols_index.html

^cRe-resection(s) may be performed in an effort to obtain negative margins in patients desiring breast conserving therapy. Patients not amenable to margin-free lumpectomy should have total mastectomy.

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

^eAxillary lymph node staging is discouraged in women with apparent pure DCIS. However, a small proportion of patients with apparent pure DCIS will be found to have invasive cancer at the time of their definitive surgical procedure. Therefore, the performance of a sentinel lymph node procedure may be considered if the patient with apparent pure DCIS is to be treated with mastectomy or with excision in an anatomic location compromising the performance of a future sentinel lymph node procedure.

^f[See Principles of Radiation Therapy \(BINV-H\).](#)

^gComplete resection should be documented by analysis of margins, specimen mammography and where appropriate post-excision mammography.

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

ⁱ[See Special Considerations Breast-Conserving Therapy \(BINV-F\).](#)

^jWhole breast radiation therapy following lumpectomy reduces recurrence rates in DCIS by about 50%. Approximately half of the recurrences are invasive and half DCIS. A number of factors determine that local recurrence risk, include size, tumor grade, margin status and patient age. Some patients may be treated by excision alone, if the patient and physician view the individual risks as "low". All data evaluating the three local treatments show no differences in patient survival.

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

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DCIS POSTSURGICAL TREATMENT

SURVEILLANCE/FOLLOW-UP

Risk reduction therapy for ipsilateral breast following breast conserving surgery:

Consider tamoxifen^l for 5 years for:

- Patients treated with breast-conserving therapy (lumpectomy) and radiation therapy (category 1),^m especially for those with ER-positive DCIS. The benefit of tamoxifen for ER-negative DCIS is uncertain
- Patients treated with excision alone^m

Risk reduction therapy for contralateral breast:

- Counseling regarding consideration of tamoxifen for risk reduction (category 2B)^l. [See also NCCN Breast Cancer Risk Reduction Guidelines](#)



- Interval history and physical exam every 6-12 mo for 5 y, then annually
- Mammogram every 12 mo
- If treated with tamoxifen, monitor per [NCCN Breast Cancer Risk Reduction Guidelines](#)

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

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

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MARGIN STATUS IN DCIS

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

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CLINICAL STAGE

WORKUP

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



- General workup including:**
- History and physical exam
 - CBC, platelets
 - Liver function tests and alkaline phosphatase
 - Diagnostic bilateral mammogram, ultrasound as necessary
 - Pathology review^a
 - Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status^b
- Optional additional studies for breast imaging:**
- Breast MRI^c
- Optional additional studies or as directed by symptoms for Stage I (only in the presence of symptoms or other abnormal staging studies) or for Stage IIA, Stage IIB, and Stage IIIA (T3, N1, M0)**
- Bone scan indicated if localized symptoms or elevated alkaline phosphatase (category 2A) or if T3, N1, M0 (category 2B)
 - Abdominal ± pelvis CT or US or MRI (Indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, abnormal physical examination of the abdomen or pelvis, or if T3, N1, M0)
 - Chest imaging (if pulmonary symptoms are present)



[See Locoregional Treatment \(BINV-2\)](#)

^aThe panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and non-invasive carcinomas of the breast.

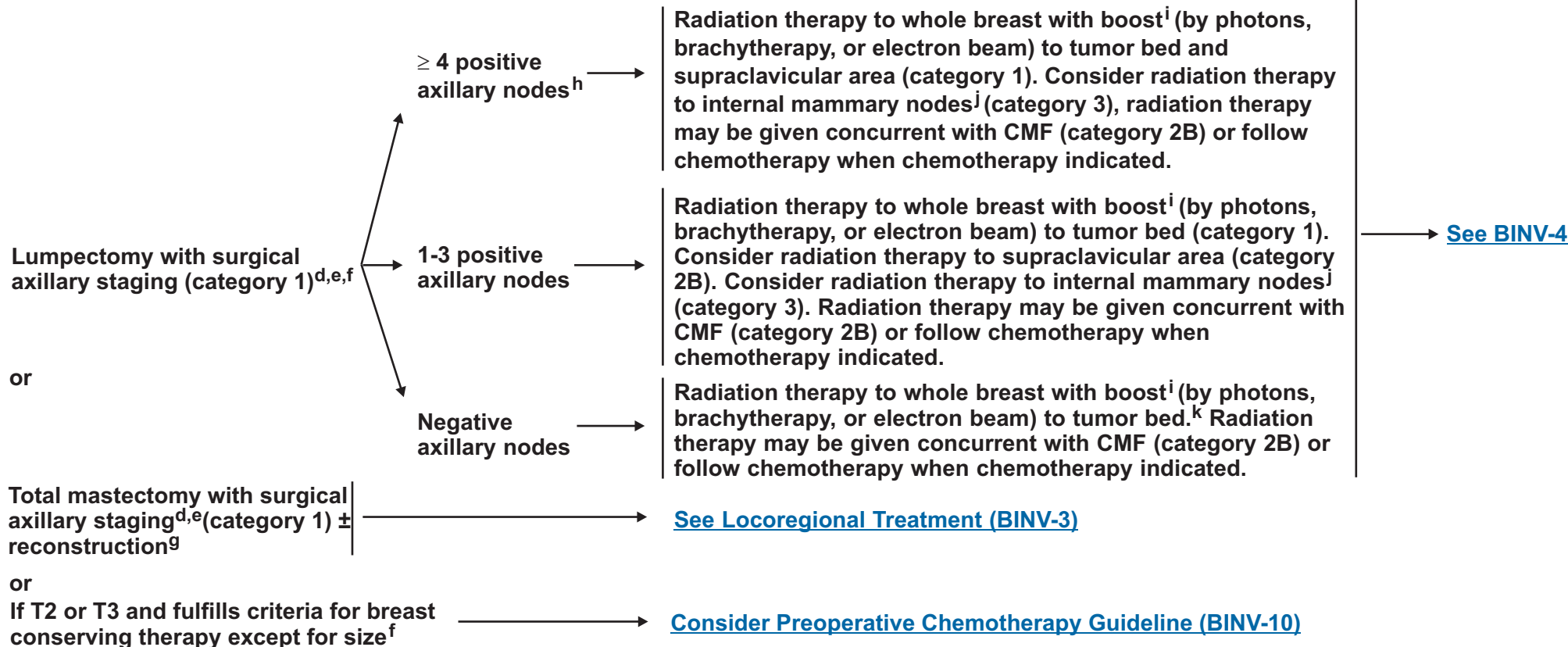
http://www.cap.org/apps/docs/cancer_protocols/protocols_index.html

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

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

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



^dSee [Surgical Axillary Staging \(BINV-C\)](#).

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

^fSee [Special Considerations to Breast-Conserving Therapy \(BINV-F\)](#).

^gSee [Principles of Reconstruction Following Mastectomy \(BINV-G\)](#).

^hConsideration may be given to additional staging including bone scan and abdominal CT/US/MRI; chest CT (category 2B).

ⁱSee [Principles of Radiation Therapy \(BINV-H\)](#).

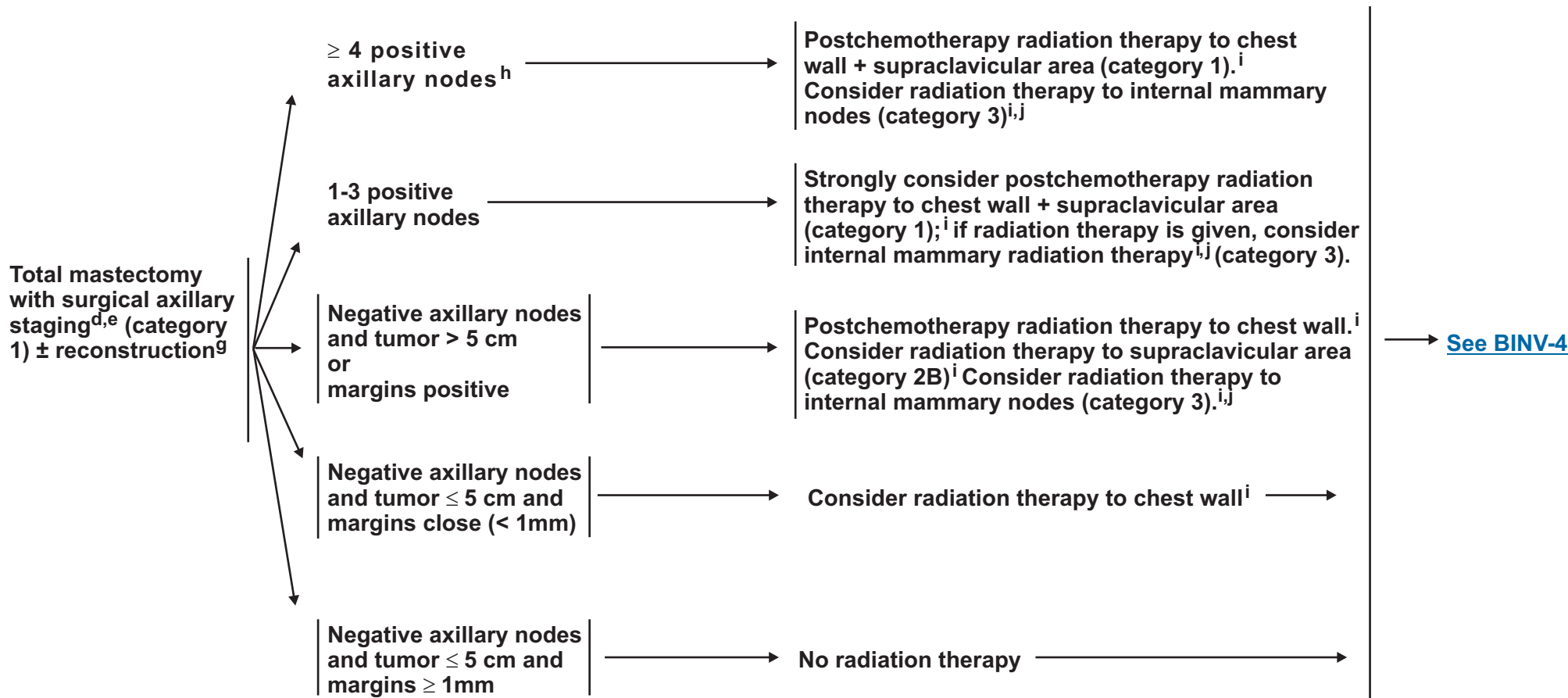
^jRadiation therapy should be given to the internal mammary lymph nodes if they are clinically or pathologically positive, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where radiation therapy is delivered to the internal mammary lymph nodes.

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

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



^d See [Surgical Axillary Staging \(BINV-C\)](#).

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

^g See [Principles of Reconstruction Following Mastectomy \(BINV-G\)](#).

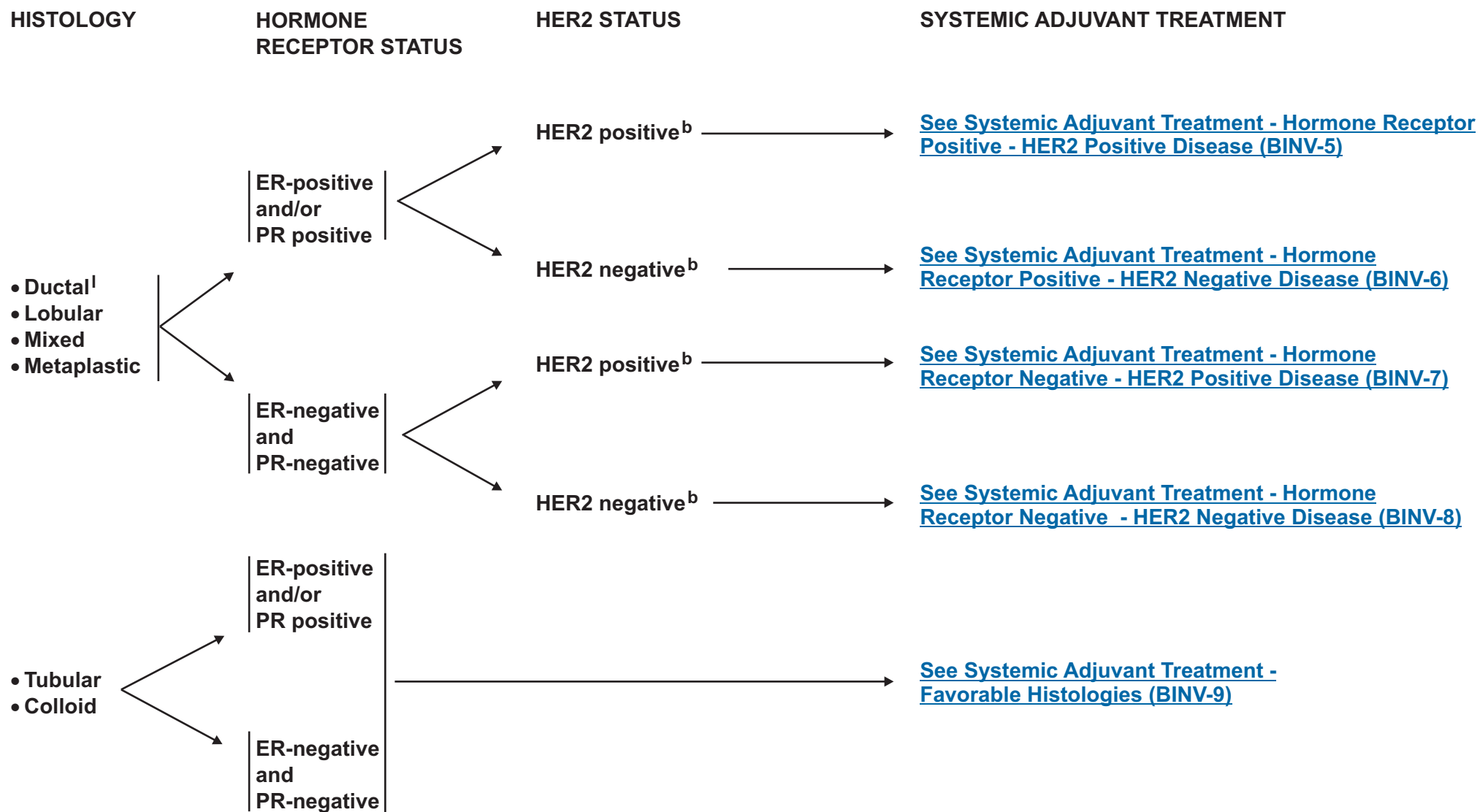
^h Consideration may be given to additional staging including bone scan; abdominal CT/US/MRI; chest CT (category 2B).

ⁱ See [Principles of Radiation Therapy \(BINV-H\)](#).

^j Radiation therapy should be given to the internal mammary lymph nodes that are clinically or pathologically positive, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where radiation therapy is delivered to the internal mammary lymph nodes.

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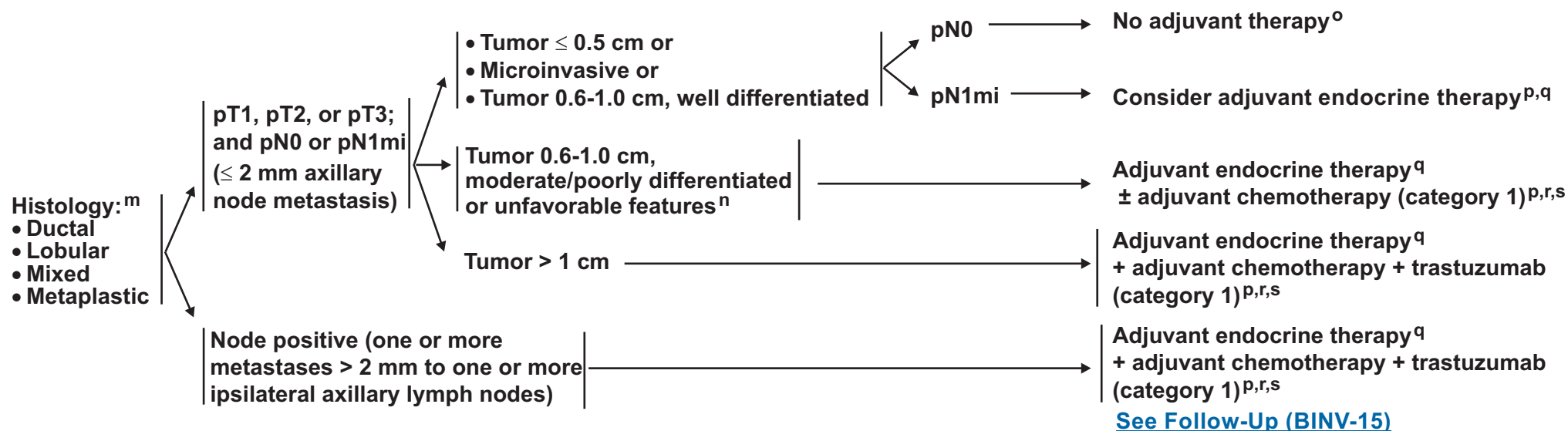


^b See Principles of HER2 Testing (BINV-A).

^l This includes medullary and micropapillary subtypes.

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



[See Adjuvant Endocrine Therapy \(BINV-I\)](#) and [Adjuvant Chemotherapy \(BINV-J\)](#)

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

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

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

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

^pEvidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone-receptor-positive breast cancer is similar to that achieved with CMF alone. Early evidence suggests similar benefits from ovarian suppression (ie, LHRH agonist) as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.

^qSee Adjuvant Endocrine Therapy (BINV-I).

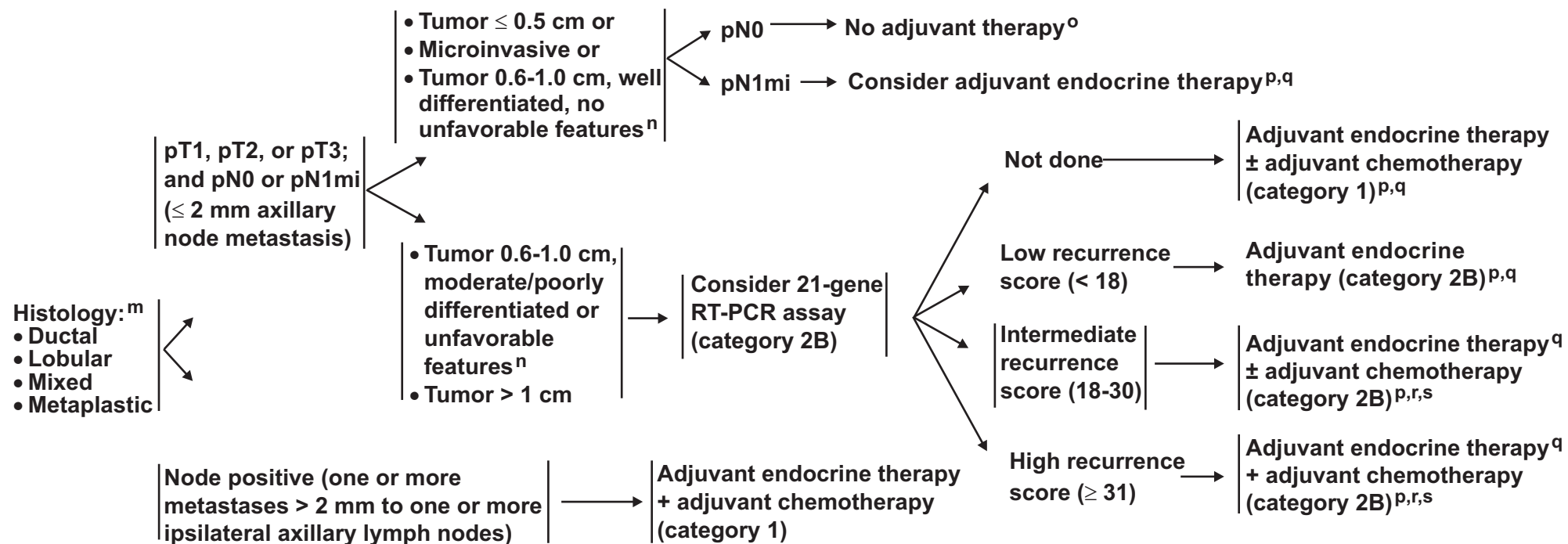
^rChemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. The benefits of chemotherapy and of endocrine therapy are additive. However, the absolute benefit from chemotherapy may be small. The decision to add chemotherapy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

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

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

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

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



See Adjuvant Endocrine Therapy (BINV-I) and Adjuvant Chemotherapy (BINV-J)

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

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

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

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

^pEvidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone-receptor-positive breast cancer is similar to that achieved with CMF alone. Early evidence suggests similar benefits from ovarian suppression (ie, LHRH agonist) as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.

^qSee Adjuvant Endocrine Therapy (BINV-I).

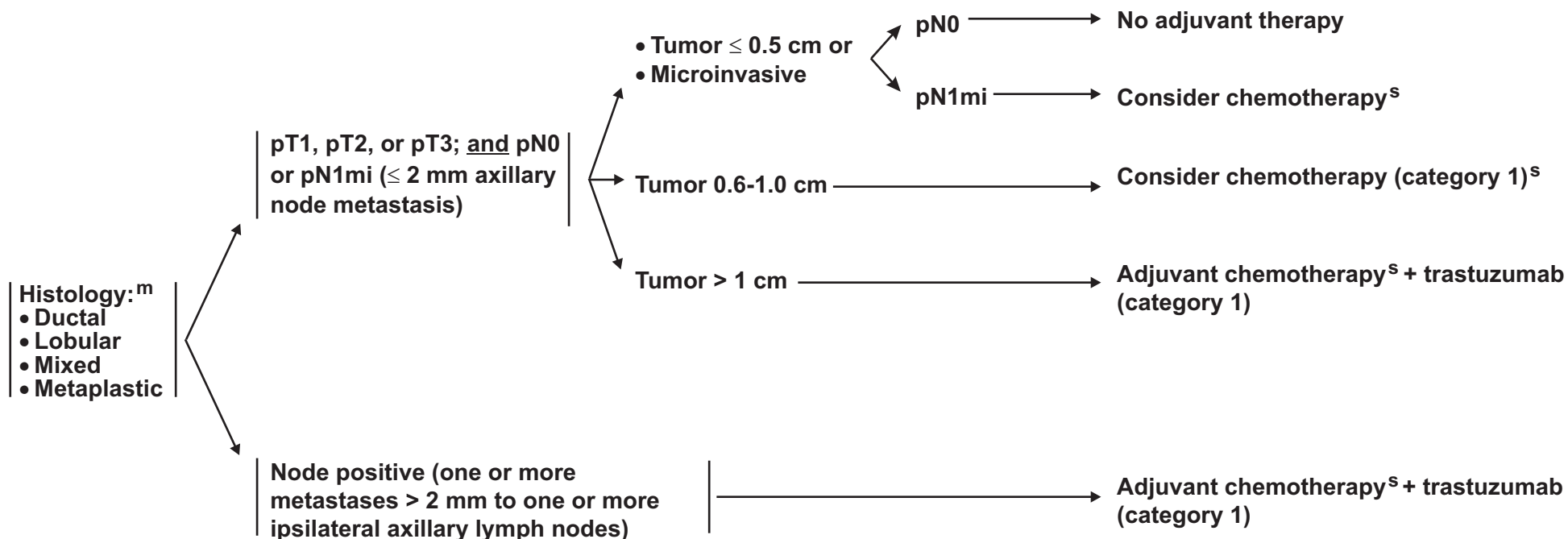
^rChemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. The benefits of chemotherapy and of endocrine therapy are additive. However, the absolute benefit from chemotherapy may be small. The decision to add chemotherapy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

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

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

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



[See Follow-Up \(BINV-15\)](#)

[See Adjuvant Endocrine Therapy \(BINV-I\)](#) and [Adjuvant Chemotherapy \(BINV-J\)](#)

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

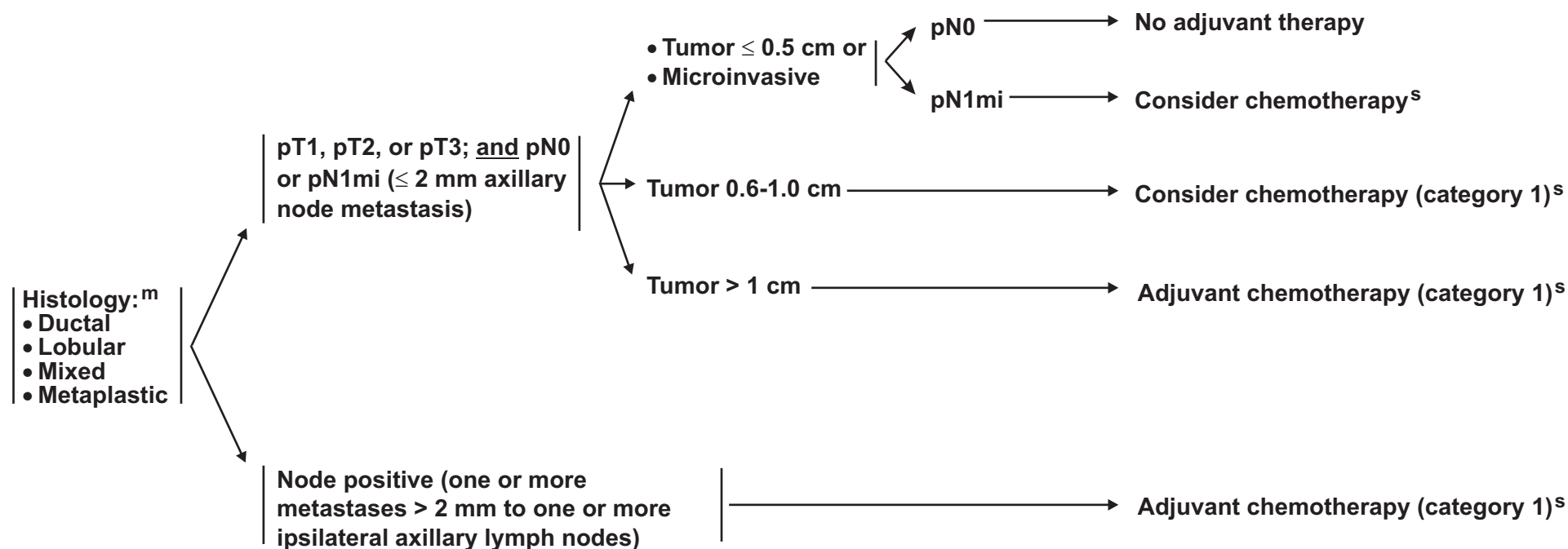
^mMixed lobular and ductal carcinoma as well as metaplastic carcinoma should be graded based on the ductal component and treated based on this grading. The metaplastic or mixed component does not alter prognosis.

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

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



[See Follow-Up \(BINV-15\)](#)

[See Adjuvant Endocrine Therapy \(BINV-I\)](#) and [Adjuvant Chemotherapy \(BINV-J\)](#)

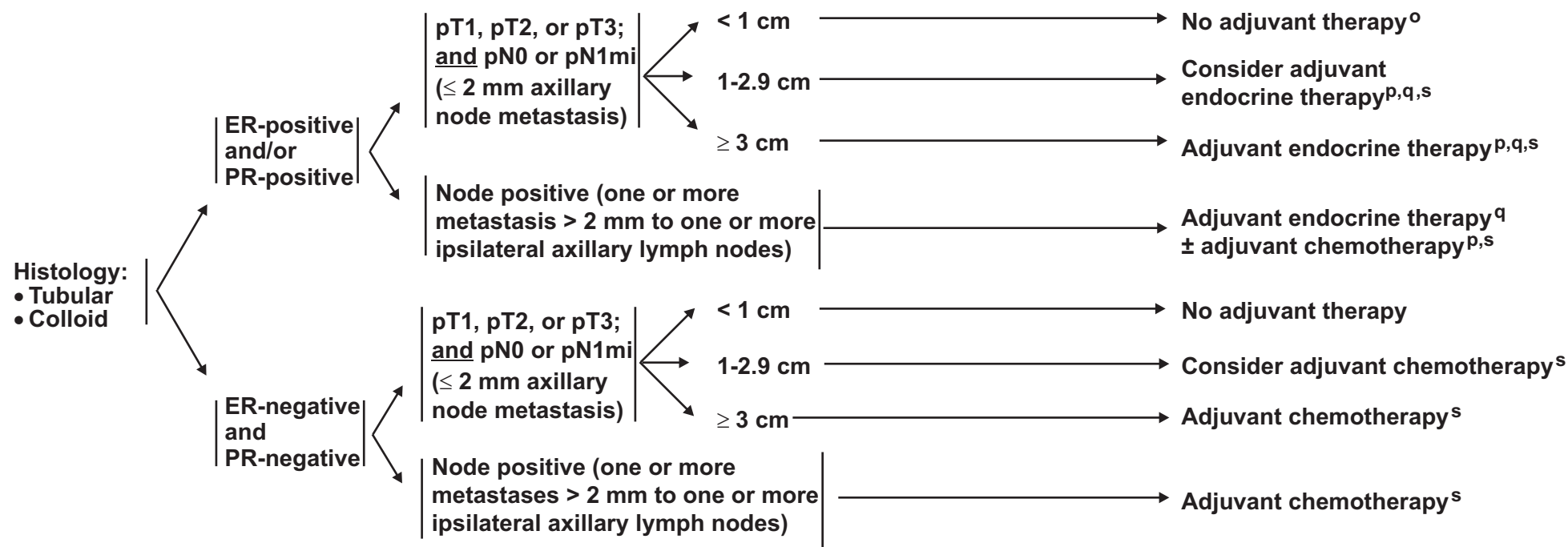
^b[See Principles of HER2 Testing \(BINV-A\)](#).

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

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

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SYSTEMIC ADJUVANT TREATMENT - FAVORABLE HISTOLOGIES



[See Adjuvant Endocrine Therapy \(BINV-I\)](#) and [Adjuvant Chemotherapy \(BINV-J\)](#)

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

^pEvidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone-receptor-positive breast cancer is similar to that achieved with CMF alone. Early evidence suggests similar benefits from ovarian suppression (ie, LHRH agonist or antagonist) as from ovarian ablation. The combination of ovarian ablation/suppression plus endocrine therapy may be superior to suppression alone. The benefit of ovarian ablation/suppression in premenopausal women who have received adjuvant chemotherapy is uncertain.

^q[See Adjuvant Endocrine Therapy \(BINV-I\)](#).

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

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Preoperative Chemotherapy Guideline

CLINICAL STAGE

WORKUP

Stage IIA
T2, N0, M0

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

Stage IIIA
T3, N1, M0

and

Fulfills criteria for breast conserving surgery except for tumor size

General workup including:

- History and physical
- CBC, platelets
- Liver function tests and alkaline phosphatase
- Diagnostic bilateral mammogram, ultrasound as necessary
- Pathology review^a
- Determination of tumor ER/PR status and HER2 status^b

Additional studies or as indicated by symptoms:

- Breast MRI (optional)^c
- Bone scan (optional) (indicated if localized symptoms or elevated alkaline phosphatase or if T3, N1, M0) (category 2B)
- Abdominal ± pelvis CT or US or MRI (optional for stage IIA or IIB, indicated if elevated alkaline phosphatase, abnormal LFTs, abdominal symptoms, abnormal physical examination of the abdomen, or if T3, N1, M0) (category 2B)
- Chest imaging (if pulmonary symptoms are present)

[See Primary Treatment \(BINV-11\)](#)

^aThe panel endorses the College of American Pathology Protocol for pathology reporting for all invasive and non-invasive carcinomas of the breast.
http://www.cap.org/apps/docs/cancer_protocols/protocols_index.html

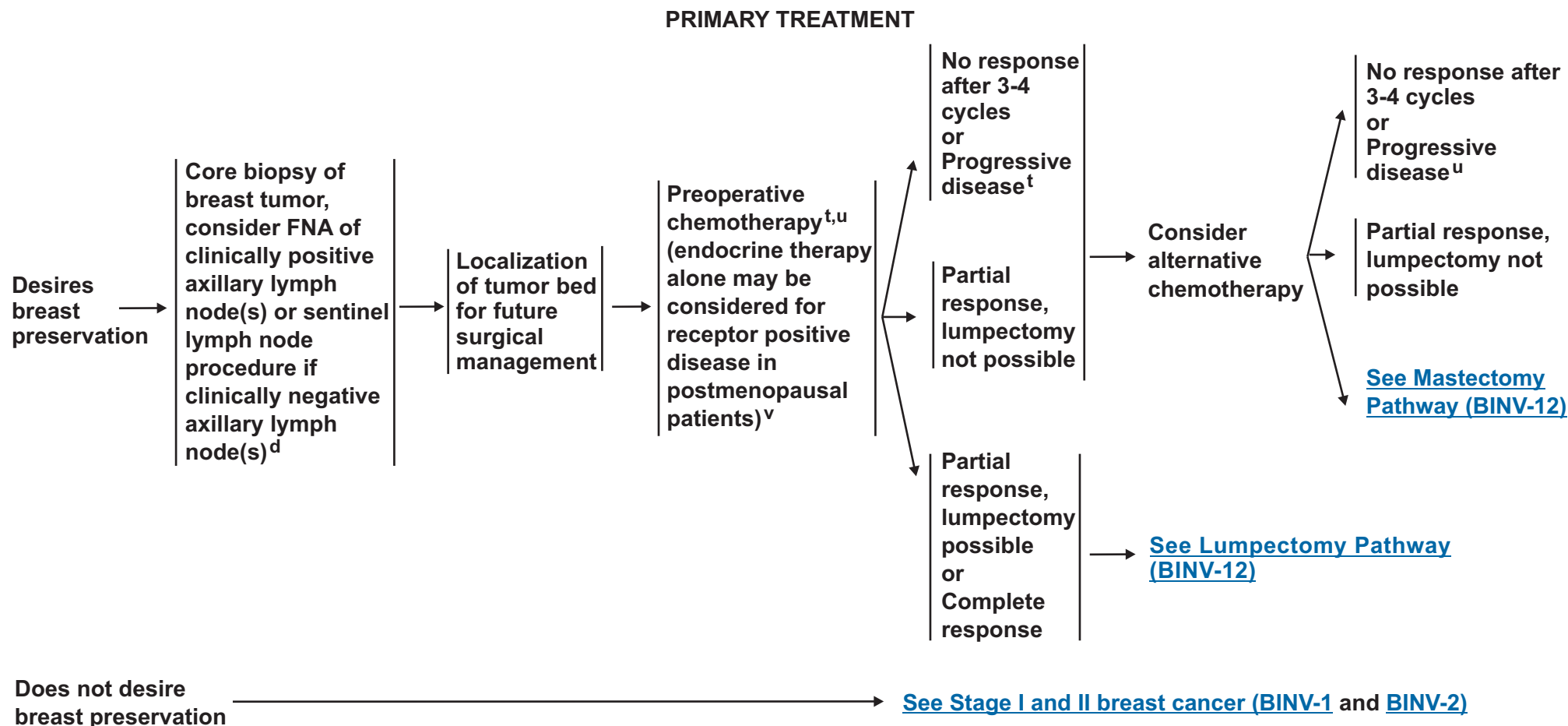
^b[See Principles of HER2 Testing \(BINV-A\).](#)

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

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

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

Preoperative Chemotherapy Guideline



^dSee [Surgical Axillary Staging \(BINV-C\)](#).

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

^uPatients with HER2-positive tumors should be considered for preoperative chemotherapy incorporating trastuzumab ([See BINV-J](#)).

^v[Definition of Menopause \(See BINV-K\)](#).

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

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

Preoperative Chemotherapy Guideline

LOCAL TREATMENT

Mastectomy and surgical axillary staging^w ± reconstruction. If sentinel lymph node biopsy performed prechemotherapy and negative findings, may omit axillary lymph node staging



Consider additional chemotherapy



ADJUVANT TREATMENT

- Adjuvant radiation therapy post-mastectomy is based on prechemotherapy tumor characteristics as per [BINV-3ⁱ](#) and
 - Endocrine therapy if ER-positive (category 1)^{q,r}
- [See Adjuvant Endocrine Therapy \(BINV-I\)](#)

Lumpectomy with surgical axillary staging.^w If sentinel lymph node biopsy performed prechemotherapy and negative findings, may omit axillary lymph node staging



Consider additional chemotherapy



- Adjuvant radiation therapy post-lumpectomy based on prechemotherapy tumor characteristics as per [BINV-2ⁱ](#) and
 - Endocrine therapy if ER-positive (category 1)^{q,r}
- [See Adjuvant Endocrine Therapy \(BINV-I\)](#)



[See Surveillance/
Follow-up \(BINV-15\)](#)

ⁱ[See Principles of Radiation Therapy \(BINV-H\).](#)

^q[See Adjuvant Endocrine Therapy \(BINV-I\).](#)

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

^wAxillary staging may include sentinel node biopsy (category 3) or level I/II dissection.

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

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LOCALLY ADVANCED INVASIVE BREAST CANCER (NON-INFLAMMATORY)

| CLINICAL STAGE | WORKUP |
|--|---|
| Stage IIIA T0, N2, M0 T1, N2, M0 T2, N2, M0 T3, N2, M0 (Stage IIIA patients with T3, N1, M0 disease, see BINV-1) | <ul style="list-style-type: none"> • History and physical exam • CBC, platelets • Liver function tests and alkaline phosphatase • Chest imaging • Diagnostic bilateral mammogram, ultrasound as necessary • Pathology review • Prechemotherapy determination of tumor ER/PR status and HER2 status^b Optional additional studies or as directed by symptoms or other abnormal staging studies: <ul style="list-style-type: none"> • Breast MRI^c • Bone scan (category 2B) • Abdominal ± pelvic CT or US or MRI (category 2B) |
| Stage IIIB T4, N0, M0 T4, N1, M0 T4, N2, M0 | |
| Stage IIIC Any T, N3, M0 | |
| Stage IV Any T, any N, M1 | See Initial Workup for Stage IV Disease (BINV-15) |

[See Preoperative Chemotherapy and Locoregional Treatment \(BINV-14\)](#)

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

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

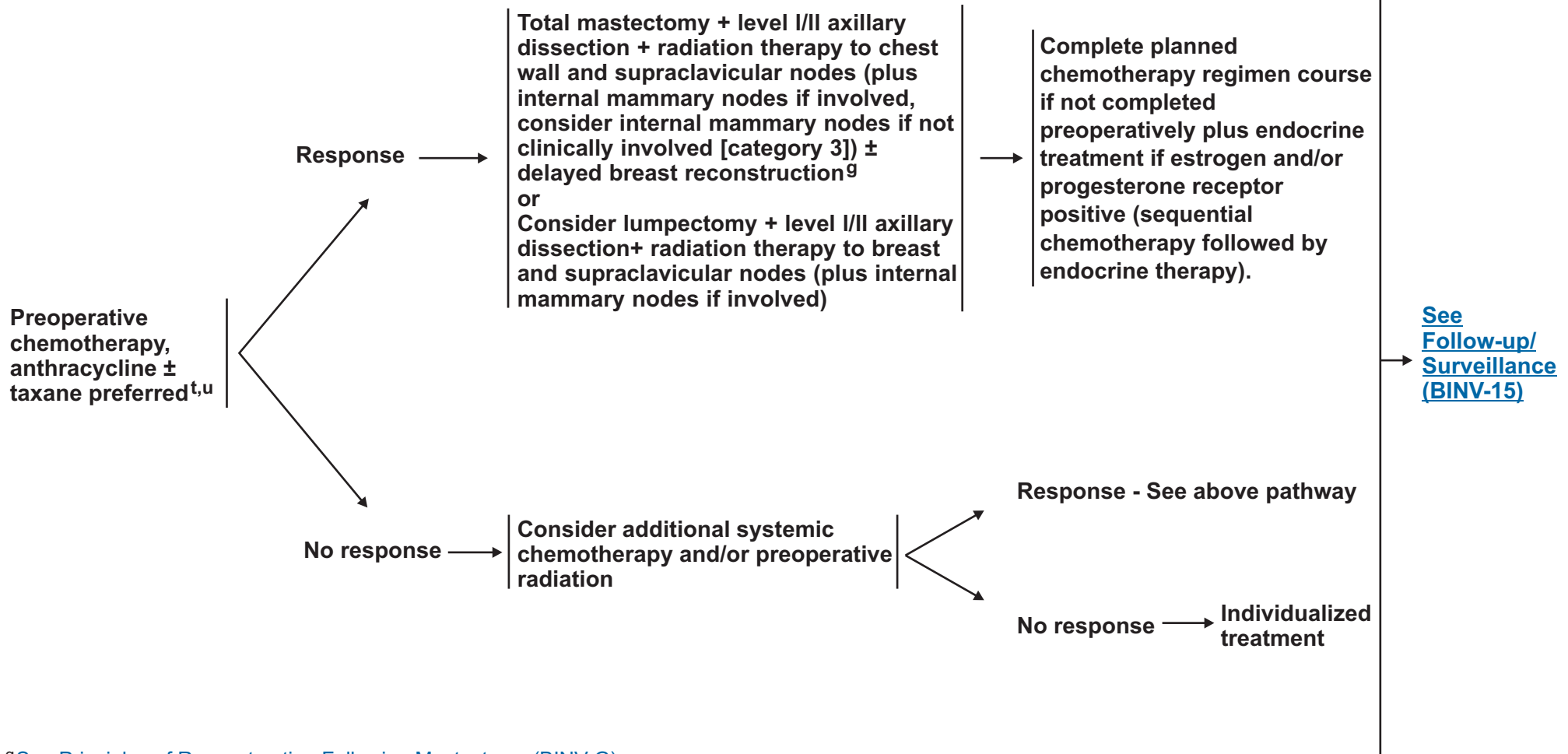
Note: All recommendations are category 2A unless otherwise indicated.

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

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

LOCOREGIONAL TREATMENT

ADJUVANT TREATMENT



^gSee Principles of Reconstruction Following Mastectomy (BINV-G).

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

^uPatients with HER2-positive tumors should be considered for preoperative chemotherapy incorporating trastuzumab (See BINV-J).

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

SURVEILLANCE/FOLLOW-UP

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

RECURRENCE WORKUP or INITIAL WORKUP FOR STAGE IV DISEASE

- History and physical exam
- CBC, platelets
- Liver function tests
- Chest imaging
- Bone scan
- X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan
- Consider abdominal CT or MRI
- Biopsy documentation of first recurrence, if possible
- Consider determination of tumor ER/PR and HER2 status if unknown, originally negative or not over-expressed^b

Local
disease only

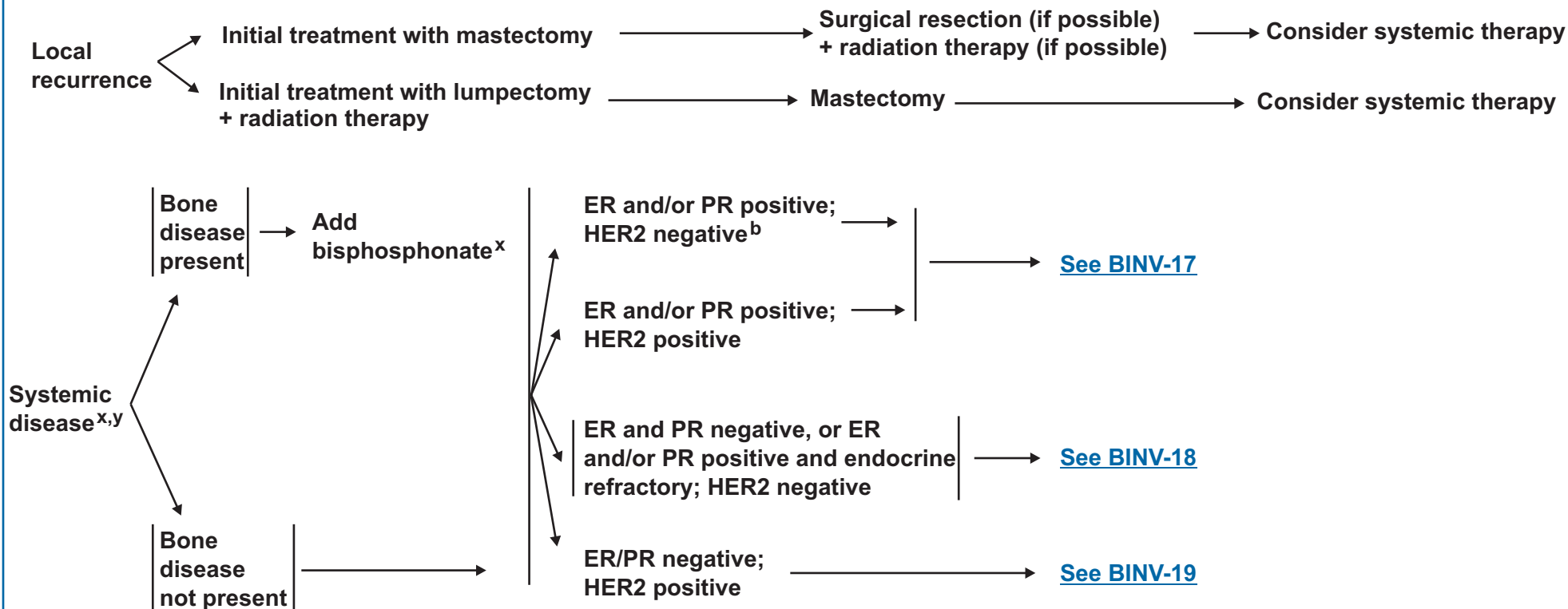
Systemic
disease

[See Treatment of Recurrence / Stage IV Disease \(BINV-16\)](#)

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

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

TREATMENT OF RECURRENCE/STAGE IV DISEASE



TREATMENT OF RECURRENCE
Surgery, radiation ± hyperthermia (category 3 for hyperthermia), or regional chemotherapy (e.g., intrathecal methotrexate) indicated for localized clinical scenarios:

| | |
|---------------------------|---|
| 1. Brain metastases | 8. Impending pathologic fracture |
| 2. Leptomeningeal disease | 9. Pathologic fracture |
| 3. Choroid metastases | 10. Cord compression |
| 4. Pleural effusion | 11. Localized painful bone or soft-tissue disease |
| 5. Pericardial effusion | 12. Chest wall disease |
| 6. Biliary obstruction | |
| 7. Ureteral obstruction | |

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

^x Pamidronate or zoledronic acid (with calcium 1200-1500 mg and vitamin D 400-800 IU daily supplement) should be given (category 1) in addition to chemotherapy or endocrine therapy if bone metastasis present, expected survival ≥ 3 months, and creatinine < 3.0 mg/dL.

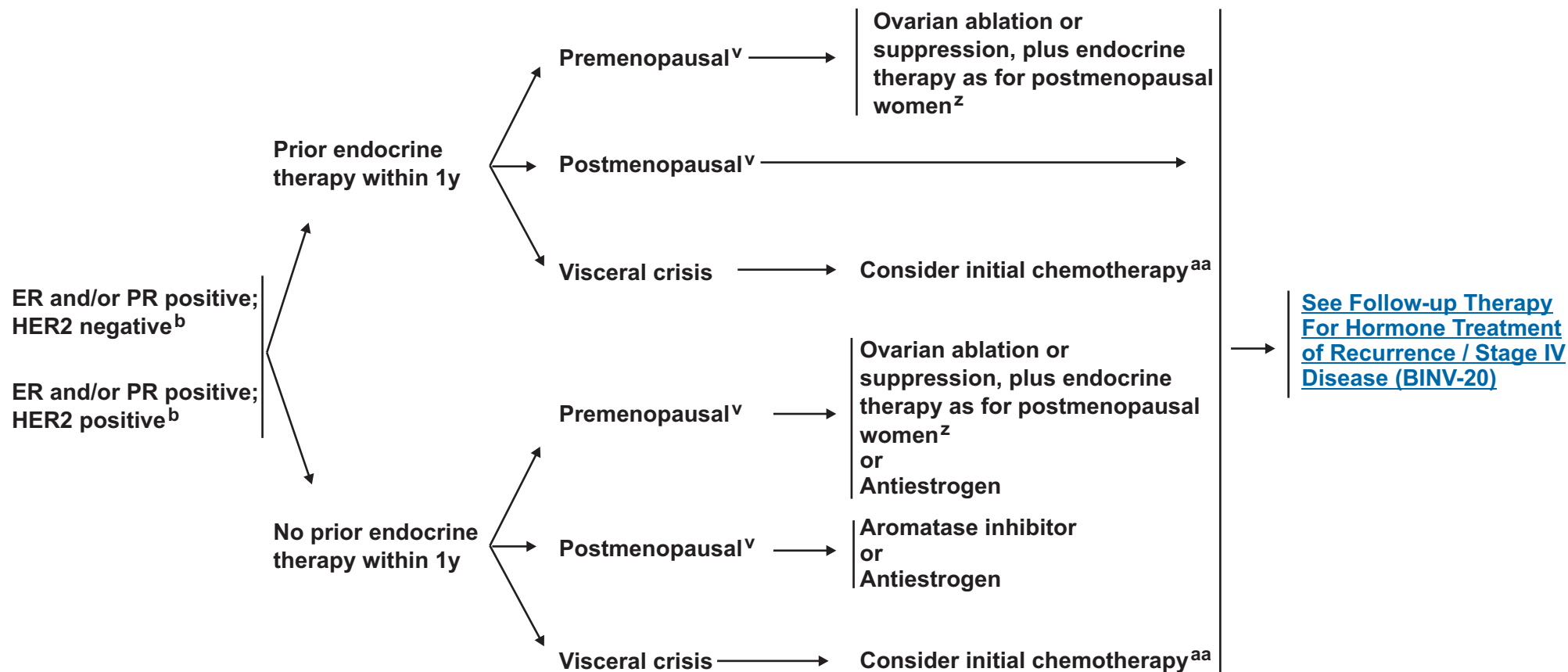
^y See NCCN Palliative Care Guidelines.

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

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

TREATMENT OF RECURRENCE/STAGE IV DISEASE

ER and/or PR POSITIVE; HER2 NEGATIVE OR POSITIVE



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

^v Definition of Menopause (See BINV-K).

^z See Subsequent Endocrine Therapy (BINV-L).

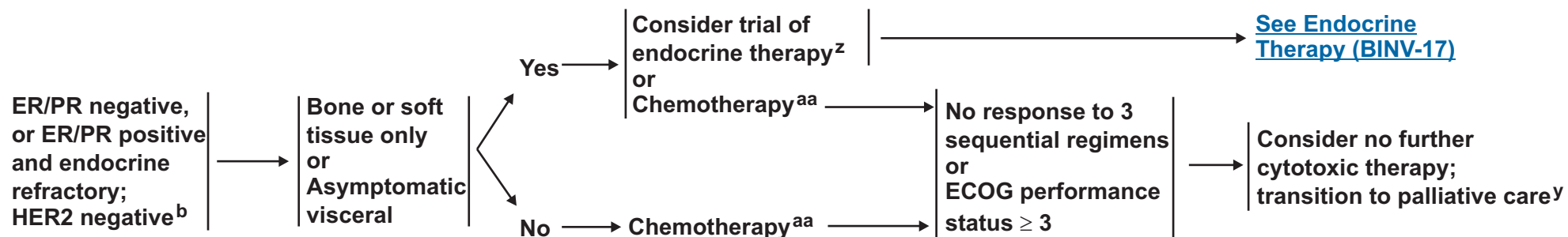
^{aa} See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-M).

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TREATMENT OF RECURRENCE/STAGE IV DISEASE

ER and PR NEGATIVE, OR ER and/or PR POSITIVE AND ENDOCRINE REFRACTORY; HER2 NEGATIVE



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

^y See NCCN Palliative Care Guidelines.

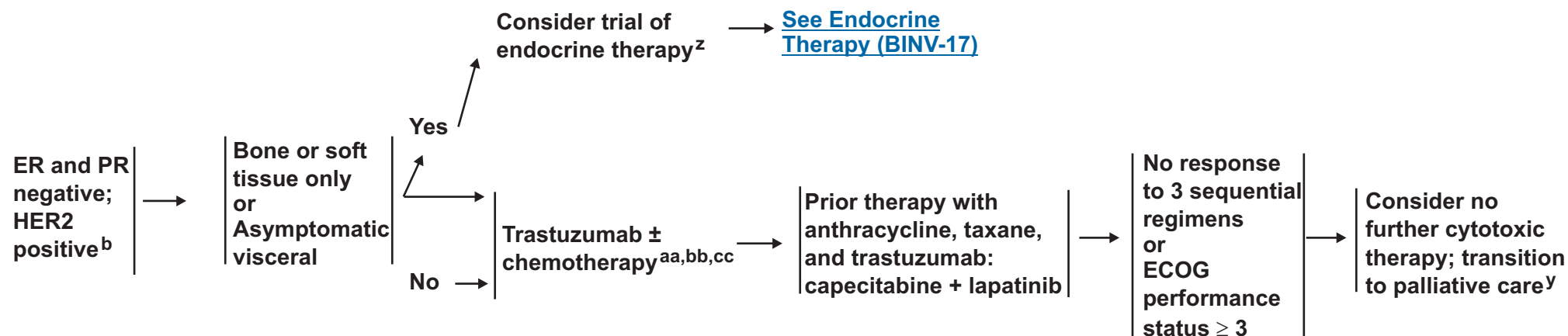
^z See Subsequent Endocrine Therapy (BINV-L).

^{aa} See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-M).

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

TREATMENT OF RECURRENCE/STAGE IV DISEASE

ER and PR NEGATIVE; HER2 POSITIVE



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

^y See NCCN Palliative Care Guidelines.

^z See Subsequent Endocrine Therapy (BINV-L).

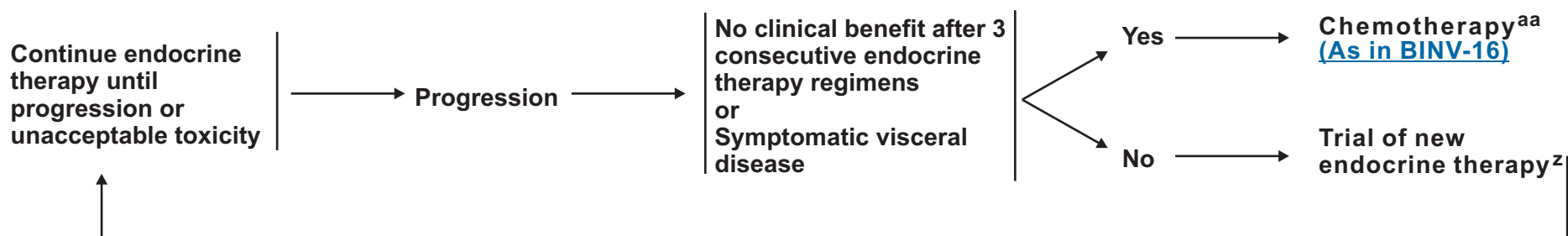
^{aa} See Preferred Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-M).

^{bb} The value of continued trastuzumab following progression on first line-trastuzumab containing chemotherapy for metastatic breast cancer is unknown. The optimal duration of trastuzumab in patients with long-term control of disease is unknown.

^{cc} Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity.

Note: All recommendations are category 2A unless otherwise indicated.
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FOLLOW-UP THERAPY FOR ENDOCRINE TREATMENT OF RECURRENCE/STAGE IV DISEASE

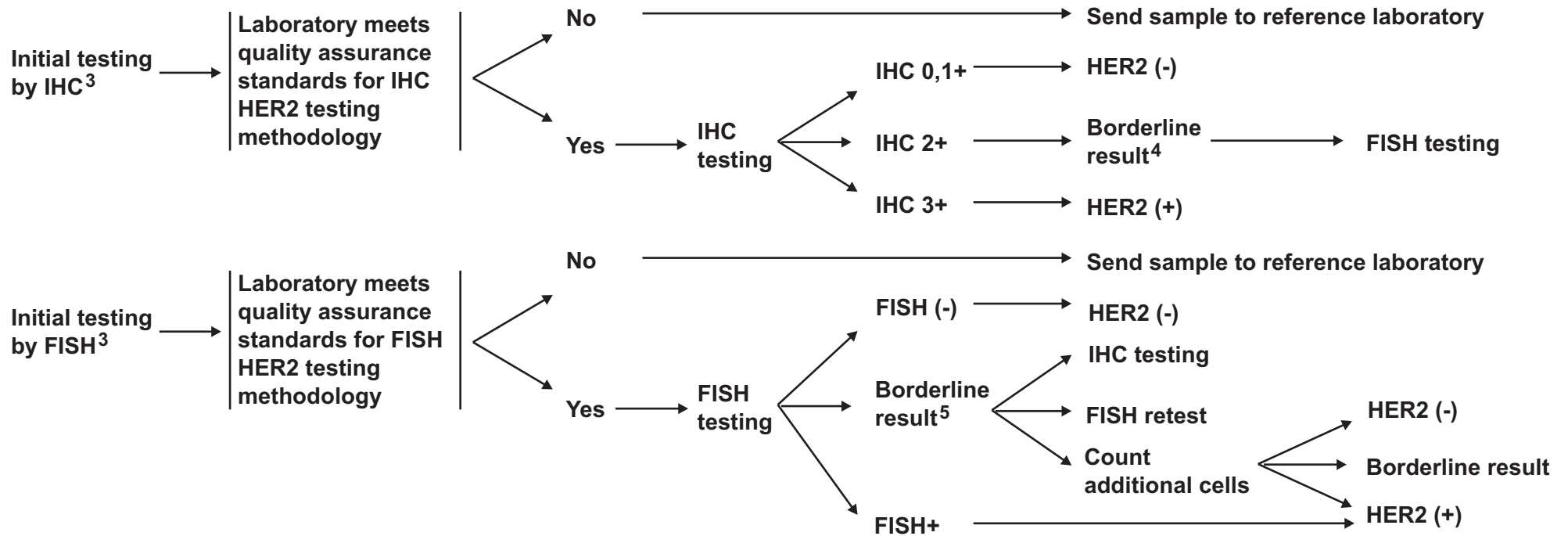


^zSee [Subsequent Endocrine Therapy \(BINV-L\)](#).

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

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF HER2 TESTING^{1,2}



¹ See also, Carlson RW, Moench SJ, Hammond, MEH, et al. HER2 testing in breast cancer: NCCN task force report and recommendations. JNCCN 4:S-1-S-24, 2006.

² HER2 testing should be done only in laboratories accredited to perform such testing. Ongoing proficiency testing and full reporting of HER2 assay methods and results are required. A laboratory may perform only those tests which have been demonstrated to conform to these quality assurance standards. All other HER2 testing should be sent to a qualified reference laboratory.

³ Either an immunohistochemistry (IHC) assay or a fluorescence in situ hybridization (FISH) assay can be used to make an initial assessment of HER2 tumor status. All HER2 assays, whether FDA-approved or not, must be validated. Validation of a HER2 test is defined as at least 95% concordance when the testing method performed in a laboratory is compared with one of the following: a validated HER2 testing method performed in the same laboratory; a validated HER2 testing method performed in another laboratory; or validated reference lab results. Borderline samples should not be included in the validation study. These algorithms are based on the assumption that all validated HER2 tests have been shown to be at least 95% concordant with the complementary form of the HER2 test, either by direct testing or association with the levels of concordance between complementary testing achieved by the validating laboratory.

⁴ Borderline IHC samples (eg, IHC 2+) are subjected to reflex testing by a validated complementary (eg, FISH) method that has shown at least 95% concordance between IHC 0, 1+ results and FISH non-amplified results, and IHC 3+ results and FISH amplified results.

⁵ Borderline FISH samples (eg, an average HER2 gene/chromosome 17 ratio of 1.8-2.2 or an average HER2 gene copy number of > 4 - < 6) should undergo: counting of additional cells; retesting by FISH; or reflex testing by a validated IHC method which is at least 95% concordant with FISH as described above.

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

PRINCIPLES OF DEDICATED BREAST MRI TESTING

Personnel, facility and equipment

- Breast MRI examinations should be performed and interpreted by an expert breast imaging team working in concert with the multidisciplinary treatment team.
- Breast MRI examinations require a dedicated breast coil and breast imaging radiologists familiar with the optimal timing sequences and other technical details for image interpretation. The imaging center should have the ability to perform MRI guided needle sampling and/or wire localization of MRI detected findings.

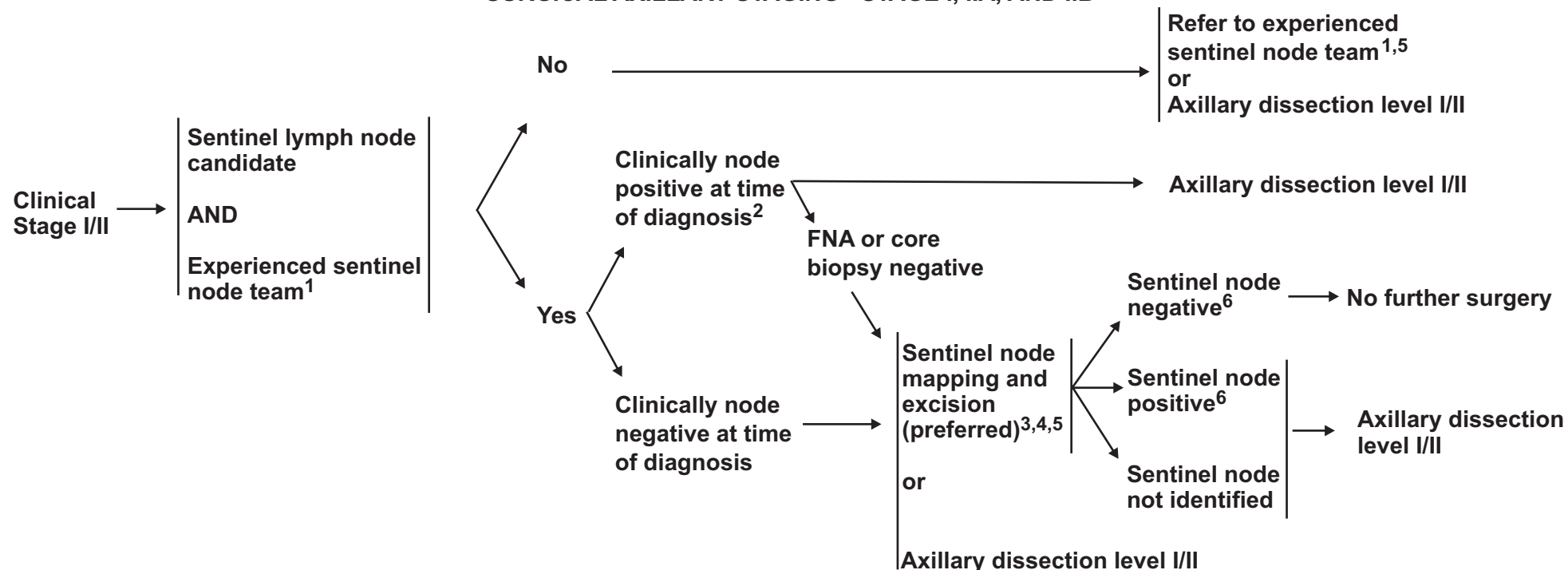
Clinical indications and applications

- Breast MRI examination is an adjunct to other breast imaging and should not be used in lieu of standard breast imaging with mammography and ultrasound.
- For patients with biopsy proven adenocarcinoma presenting in the axilla, a normal clinical breast exam and negative mammogram (TxN1-3), breast MRI examination is indicated to attempt to identify a primary cancer in the breast.
- Breast MRI may be considered for a patient with biopsy-proven breast cancer, when dense breast tissue precludes assessment for extent of disease.
- Breast MRI may be useful in defining the extent of cancer, the presence of multicentric cancer in women with dense breast tissue on mammography, and extent of disease in women with locally advanced breast cancer. Decision making regarding the extent of breast surgery (e.g. breast conservation therapy vs. mastectomy) should not be made solely on the basis of MRI and may require additional tissue sampling of areas of concern identified by breast MRI.

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SURGICAL AXILLARY STAGING - STAGE I, IIA, AND IIB



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

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

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

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

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

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

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

[Return to Locoregional Treatment \(BINV-2\)](#)

AXILLARY LYMPH NODE STAGING

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

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

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MARGIN STATUS IN INFILTRATING CARCINOMA

The use of breast conserving therapy is predicated on achieving a pathologically negative margin of resection. Cases where there is a positive margin should generally undergo further surgery, either a re-excision to achieve a negative margin or a mastectomy. If re-excision is technically feasible to allow for breast conserving therapy, this can be done with resection of the involved margin guided by the orientation of the initial resection specimen or re-excision of the entire original excision cavity. If multiple margins remain positive, mastectomy may be required for optimal local control.

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

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

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

¹An extensive intraductal component is defined as an infiltrating ductal cancer where greater than 25% of the tumor volume is DCIS and DCIS extends beyond the invasive cancer into surrounding normal breast parenchyma.

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SPECIAL CONSIDERATIONS TO BREAST-CONSERVING THERAPY REQUIRING RADIATION THERAPY

Contraindications for breast-conserving therapy requiring radiation therapy include:**Absolute:**

- Prior radiation therapy to the breast or chest wall
- Radiation therapy during pregnancy
- Diffuse suspicious or malignant appearing microcalcifications
- Widespread disease that cannot be incorporated by local excision through a single incision that achieves negative margins with a satisfactory cosmetic result.
- Positive pathologic margin¹

Relative:

- Active connective tissue disease involving the skin (especially scleroderma and lupus)
- Tumors > 5 cm (category 2B)
- Focally positive margin¹
- Women ≤ 35 y or premenopausal women with a known BRCA 1/2 mutation:
 - ▶ May have an increased risk of ipsilateral breast recurrence or contralateral breast cancer with breast conserving therapy
 - ▶ Prophylactic bilateral mastectomy for risk reduction may be considered.
(See [NCCN Breast Cancer Risk Reduction Guidelines](#)).

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

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

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

PRINCIPLES OF BREAST RECONSTRUCTION FOLLOWING MASTECTOMY

- The breast can be reconstructed in conjunction with mastectomy using breast implants, autologous tissue (“flaps”) or a combination of the two (e.g., latissimus / implant composite reconstructions).
- Breast reconstruction for mastectomy can be performed at the same time as mastectomy (“immediate”) or at some time following the completion of cancer treatment (“delayed”).
- As with any mastectomy, there is a risk of local and regional cancer recurrence, and evidence suggests skin sparing mastectomy is probably equivalent to standard mastectomy in this regard. Skin sparing mastectomy should be performed by an experienced breast surgery team that works in a coordinated, multidisciplinary fashion to guide proper patient selection for skin sparing mastectomy, determine optimal sequencing of the reconstructive procedure(s) in relation to adjuvant therapies, and to perform a resection that achieves appropriate surgical margins. Post-mastectomy radiation as outlined in these guidelines should be applied in cases treated by skin sparing mastectomy. The nipple-areolar complex is sacrificed with skin sparing mastectomy for cancer therapy.
- When post-mastectomy radiation is required, delayed reconstruction is generally preferred after completion of radiation therapy in autologous tissue reconstruction, because of reported loss in reconstruction cosmesis (category 2B). When implant reconstruction is used, immediate rather than delayed reconstruction is preferred to avoid tissue expansion of radiated skin flaps. Immediate implant reconstruction in patients requiring post-operative radiation has an increased rate of capsular contracture. Surgery to exchange the tissue expanders with permanent implants can be performed prior to radiation or after completion of radiation therapy. Some experienced breast cancer teams have employed protocols in which immediate reconstructions are followed by radiation therapy (category 2B). Tissue expansion of irradiated skin can result in a significantly increased risk of capsular contracture, malposition, poor cosmesis and implant exposure. In the previously radiated patient the use of tissue expanders/implants is relatively contra-indicated.
- Reconstruction selection is based on an assessment of cancer treatment, patient body habitus, smoking history, co-morbidities and patient concerns. Smoking increases the risk of complications for all types of breast reconstruction whether with implant or flap. Smoking is therefore considered a relative contra-indication to breast reconstruction and patients should be made aware of increased rates of wound healing complications and partial or complete flap failure among smokers.

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PRINCIPLES OF RADIATION THERAPY

Whole Breast Radiation:

Target delineation includes the majority of the breast tissue, and is best done by clinical assessment and CT-based treatment planning. Care should be taken to deliver a relatively uniform dose distribution. This can be achieved, for example, using compensators such as wedges, or forward planning using segments or intensity modulated radiation therapy (IMRT). In some patients, IMRT may provide more optimal dose uniformity resulting in an improved clinical outcome. The breast should receive a dose of 45-50 Gy in 1.8 - 2 Gy per fraction, or 42.5 Gy at 2.66 Gy per fraction. A boost to the tumor bed is recommended in higher risk patients (age < 50, positive axillary nodes, lymphovascular invasion, or close margins). This can be achieved with brachytherapy or electron beam or photon fields. Typical doses are 10-15 Gy at 2 Gy/fx, to a total dose of approximately 60 Gy; or perhaps somewhat lower doses for low risk patients, and higher for high risk patients. All dose schedules given 5 days per week.

Chest Wall Radiation (including breast reconstruction):

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

Regional Nodal Radiation:

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

Dose is 50 Gy, given as 1.8 - 2.0 Gy fraction size (\pm boost at 2 Gy per fraction to a total dose of approximately 60 Gy), all dose schedules given 5 days per week.

If internal mammary lymph nodes are clinically or pathologically positive, radiation therapy should be given to the internal mammary nodes, otherwise the treatment to the internal mammary nodes is at the discretion of the treating radiation oncologist. CT treatment planning should be utilized in all cases where radiation therapy is delivered to the internal mammary lymph node field.

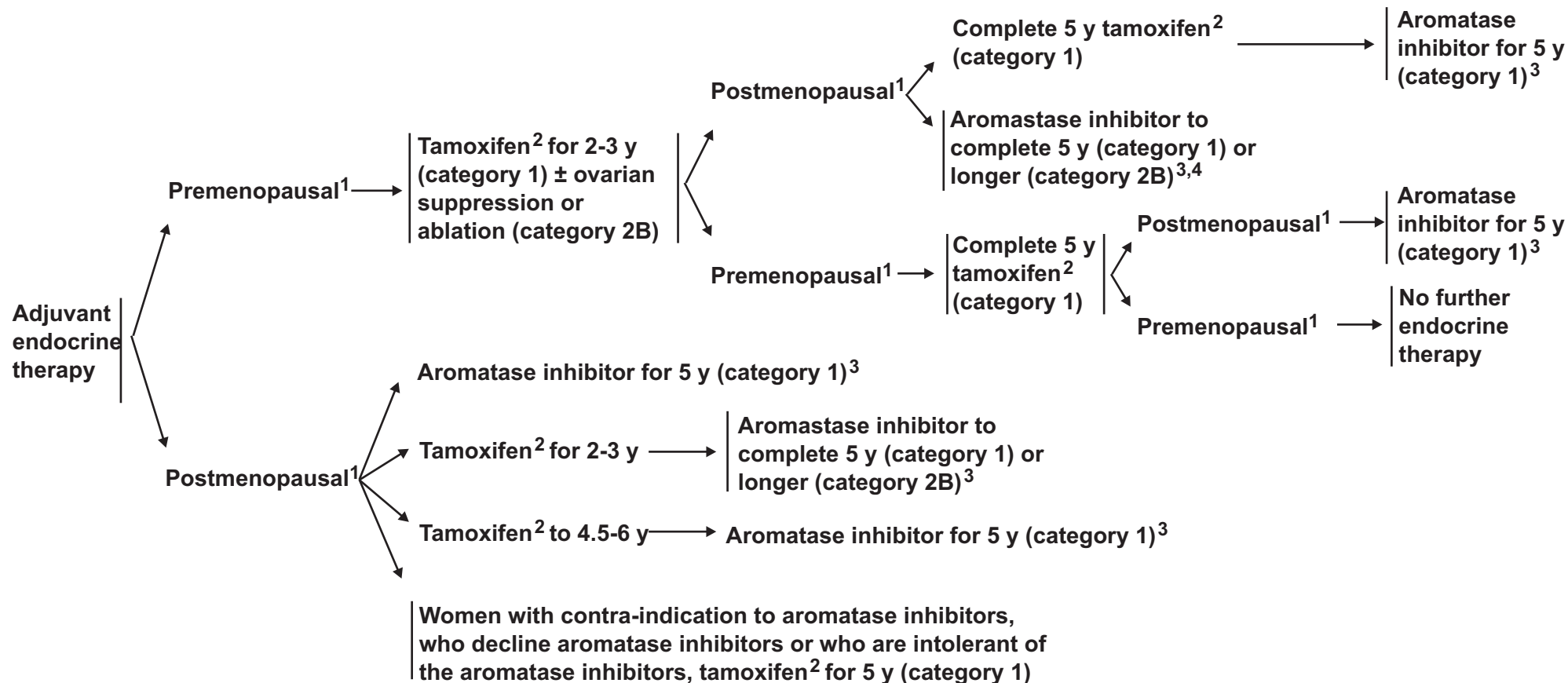
Partial breast radiation (PBI)

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

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

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

ADJUVANT ENDOCRINE THERAPY



¹See Definition of Menopause (BINV-K).

²Some serotonin reuptake inhibitors decrease the formation of endoxifen, an active metabolite of tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. The clinical impact of these observations is not known.

³The panel believes the three selective aromatase inhibitors (anastrozole, letrozole, exemestane) have similar antitumor efficacy and similar toxicity profiles. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.

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

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ADJUVANT CHEMOTHERAPY ^{1,2,3,4,5}**NON-TRASTUZUMAB CONTAINING REGIMENS (all category 1)**

- FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide) or FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)
- AC (doxorubicin/cyclophosphamide) ± sequential paclitaxel⁶
- EC (epirubicin/cyclophosphamide)
- TAC (docetaxel/doxorubicin/cyclophosphamide) with filgrastim support⁶
- A → CMF⁷ (doxorubicin followed by cyclophosphamide/methotrexate/fluorouracil)
- E → CMF (epirubicin followed by cyclophosphamide/methotrexate/fluorouracil)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- AC x 4 (doxorubicin/cyclophosphamide) + sequential paclitaxel x 4, every 2 weekly regimen with filgrastim support
- A → T → C (doxorubicin followed by paclitaxel followed by cyclophosphamide) every 2 weekly regimen with filgrastim support
- FEC → T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel)
- TC (docetaxel and cyclophosphamide)

TRASTUZUMAB CONTAINING REGIMENS (all category 1)**Preferred Adjuvant Regimen:**

- AC → T + concurrent trastuzumab (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab)

Other Adjuvant Regimens:

- Docetaxel + trastuzumab → FEC
- TCH (docetaxel, carboplatin, trastuzumab)
- Chemotherapy followed by trastuzumab sequentially⁸
- AC → docetaxel + trastuzumab

Neoadjuvant:

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

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

²In patients with HER2 positive and axillary lymph node positive breast cancer, trastuzumab should be incorporated into the adjuvant therapy. (category 1) Trastuzumab should also be considered for patients with HER2 positive lymph node negative tumors greater than or equal to 1 cm. (category 1) Trastuzumab may be given beginning either concurrent with paclitaxel as part of the AC followed by paclitaxel regimen, or alternatively after the completion of chemotherapy. Trastuzumab should not be given concurrent with an anthracycline because of cardiac toxicity, except as part of the neoadjuvant trastuzumab with paclitaxel followed by CEF regimen. Trastuzumab should be given for one year, (with the exception of the docetaxel + trastuzumab followed by FEC regimen in which trastuzumab is given for 9 weeks), with cardiac monitoring, and by either the weekly or every three weekly schedule.

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

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

⁵For node-positive patients, anthracycline-containing chemotherapy regimens are preferred.

⁶Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.

⁷The data supporting A followed by CMF are limited to patients with four or more positive nodes.

⁸For specific regimens see Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2 positive breast cancer. N Engl J Med 2005;353:1659-72.

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

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REPRESENTATIVE ADJUVANT CHEMOTHERAPY REGIMENS FOR BREAST CANCER*

NON-TRASTUZUMAB COMBINATIONS**FAC chemotherapy** ^{1,2}

- 5-Fluorouracil 500 mg/m² IV days 1 & 8 or days 1 & 4
- Doxorubicin 50 mg/m² IV day 1 (or by 72 h continuous infusion)
- Cyclophosphamide 500 mg/m² IV day 1
Cycled every 21 days for 6 cycles.

CAF chemotherapy ³

- Cyclophosphamide 100 mg/m² PO days 1-14
- Doxorubicin 30 mg/m² IV days 1 & 8
- 5-Fluorouracil 500 mg/m² IV days 1 & 8
Cycled every 28 days for 6 cycles.

FEC chemotherapy ⁴

- Cyclophosphamide 75 mg/m² PO days 1-14
- Epirubicin 60 mg/m² IV days 1 & 8
- 5-Fluorouracil 500 mg/m² IV days 1 & 8
With cotrimoxazole support.
Cycled every 28 days for 6 cycles.

AC chemotherapy ⁵

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

AC followed by paclitaxel chemotherapy ^{6,7}

- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1
Cycled every 21 days for 4 cycles.
Followed by
- Paclitaxel 175-225 mg/m² by 3 h IV infusion day 1
Cycled every 21 days for 4 cycles.
OR
- Paclitaxel 80 mg/m² by 1 h IV infusion weekly for 12 weeks.

EC chemotherapy ⁸

- Epirubicin 100 mg/m² IV day 1
- Cyclophosphamide 830 mg/m² IV day 1
Cycled every 21 days for 8 cycles.

TAC chemotherapy ⁹

- Docetaxel 75 mg/m² IV day 1
- Doxorubicin 50 mg/m² IV day 1
- Cyclophosphamide 500 mg/m² IV day 1
Cycled every 21 days for 6 cycles.
(All cycles are with filgrastim support).

A followed by CMF chemotherapy ¹⁰

- Doxorubicin 75 mg/m² IV day 1
Cycled every 21 days for 4 cycles.
Followed by
- Cyclophosphamide 600 mg/m² IV day 1
- Methotrexate 40 mg/m² IV day 1
- 5-Fluorouracil 600 mg/m² IV day 1
Cycled every 21 days for 8 cycles.

E followed by CMF chemotherapy ¹¹

- Epirubicin 100 mg/m² IV day 1
Cycled every 21 days for 4 cycles.
Followed by
- Cyclophosphamide 100 mg/m² PO days 1-14
- Methotrexate 40 mg/m² IV days 1 & 8
- 5-Fluorouracil 600 mg/m² IV days 1 & 8
Cycled every 28 days for 4 cycles.
OR
- Cyclophosphamide 750 mg/m² IV day 1
- Methotrexate 50 mg/m² IV day 1
- 5-Fluorouracil 600 mg/m² IV day 1
Cycled every 21 days for 4 cycles.

CMF chemotherapy ¹²

- Cyclophosphamide 100 mg/m² PO days 1-14
- Methotrexate 40 mg/m² IV days 1 & 8
- 5-Fluorouracil 600 mg/m² IV days 1 & 8
Cycled every 28 days for 6 cycles.

Dose-dense AC followed by paclitaxel chemotherapy ¹³

- Doxorubicin 60 mg/m² IV day 1
- Cyclophosphamide 600 mg/m² IV day 1
Cycled every 14 days for 4 cycles.
Followed by
- Paclitaxel 175 mg/m² by 3 h IV infusion day 1
Cycled every 14 days for 4 cycles.
(All cycles are with filgrastim support).

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

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

REPRESENTATIVE ADJUVANT CHEMOTHERAPY REGIMENS FOR BREAST CANCER*

NON-TRASTUZUMAB COMBINATIONSDose-dense A-T-C chemotherapy¹³

- Doxorubicin 60 mg/m² IV day 1

Cycled every 14 days for 4 cycles.

Followed by

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

Cycled every 14 days for 4 cycles.

Followed by

- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 14 days for 4 cycles.

(All cycles are with filgrastim support).

FEC followed by docetaxel chemotherapy¹⁴

- 5-Fluorouracil 500 mg/m² IV day 1

- Epirubicin 100 mg/m² IV day 1

- Cyclophosphamide 500 mg/m² day 1

Cycled every 21 days for 3 cycles.

Followed by

- Docetaxel 100 mg/m² day 1

Cycled every 21 days for 3 cycles.

TC¹⁵

- Docetaxel 75 mg/m² IV day 1

- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 4 cycles

TRASTUZUMAB CONTAINING COMBINATIONSAC followed by T chemotherapy with Trastuzumab¹⁶

- Doxorubicin 60 mg/m² IV day 1

- Cyclophosphamide 600 mg/m² IV day 1

Cycled every 21 days for 4 cycles.

Followed by

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

Cycled every 21 days for 4 cycles

OR

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

Cardiac monitoring at baseline, 3, 6, and 9 mo.

Docetaxel + trastuzumab followed by FEC¹⁷

- Docetaxel 100 mg/m² by 1 h IV day 1

Cycled every 21 days for 3 cycles

With

- Trastuzumab 4 mg/kg IV with first dose of docetaxel day 1

Followed by

- Trastuzumab 2 mg/kg IV weekly to complete 9 weeks of trastuzumab.

Followed by

- 5-Fluorouracil 600 mg/m² IV day 1

- Epirubicin 60 mg/m² day 1

- Cyclophosphamide 600 mg/m² day 1

Cycled every 21 days for 3 cycles

Cardiac monitoring at baseline, after last FEC cycle, at 12 and 36 mo after chemotherapy.

TCH (docetaxel, carboplatin, trastuzumab)¹⁸

- Docetaxel 75 mg/m² IV day 1

Followed by

- Carboplatin AUC 6 IV day 1

Cycled every 21 days for 6 cycles

With

- Trastuzumab 4 mg/kg week 1

Followed by

- Trastuzumab 2 mg/kg for 17 weeks

Followed by

- Trastuzumab 6 mg/kg IV every 3 weeks to complete 1 year of trastuzumab therapy

Cardiac monitoring at baseline, 3, 6, and 9 mo.

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

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REPRESENTATIVE ADJUVANT CHEMOTHERAPY REGIMENS FOR BREAST CANCER*

TRASTUZUMAB CONTAINING COMBINATIONSChemotherapy followed by trastuzumab¹⁹

- Approved adjuvant chemotherapy regimen for at least 4 cycles

Followed by

- Trastuzumab 8 mg/kg IV times 1 dose

Followed by

- Trastuzumab 6 mg/kg IV every 21 days for 1 y

Cardiac monitoring at baseline, 3, 6, and 9 mo.

AC followed by docetaxel with trastuzumab¹⁷

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

Cycled every 21 days for 4 cycles

Followed by

- Docetaxel 100 mg/m²

Cycled every 21 days for 4 cycles

With

- Trastuzumab 4 mg/kg IV week one

Followed by

- Trastuzumab 2 mg/kg IV weekly for 11 weeks

Followed by

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

Cardiac monitoring at baseline, 3, 6, and 9 mo.

Neoadjuvant T followed by FEC chemotherapy with trastuzumab²⁰

- Trastuzumab 4 mg/kg IV for one dose beginning just prior to first dose of paclitaxel

Followed by

- Trastuzumab 2 mg/kg IV weekly for 23 wks
- Paclitaxel 225 mg/m² by 24 h IV infusion every 21 days for 4 cycles

Followed by

- 5-Fluorouracil 500 mg/m² on days 1 and 4
 - Epirubicin 75 mg/m² IV on day 1
 - Cyclophosphamide 500 mg/m² on day 1
- Cycled every 21 days for 4 cycles.

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

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DEFINITION OF MENOPAUSE

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

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

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

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SUBSEQUENT ENDOCRINE THERAPY FOR SYSTEMIC DISEASE
([For first-line endocrine therapy see BINV-16](#))

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

POSTMENOPAUSAL PATIENTS

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

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PREFERRED CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER¹ (page 1 of 6)Preferred Single Agents

- Doxorubicin
- Epirubicin
- Pegylated liposomal doxorubicin
- Paclitaxel
- Docetaxel
- Capecitabine
- Vinorelbine
- Gemcitabine
- Albumin-bound paclitaxel

Preferred Agents with Bevacizumab

- Paclitaxel²

Preferred Combinations

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

Other Active Options

- Cisplatin
- Carboplatin
- Etoposide (po)
- Vinblastine
- Fluorouracil continuous infusion
- Ixabepilone
- Ixabepilone + capecitabine (category 2B)

PREFERRED CHEMOTHERAPY REGIMENS FOR
USE IN COMBINATION WITH TRASTUZUMAB
(HER2 positive metastatic disease)

Paclitaxel ± Carboplatin
Docetaxel
Vinorelbine

PREFERRED CHEMOTHERAPY REGIMENS FOR
USE IN COMBINATION WITH LAPATINIB
(HER2 positive metastatic disease)

Capecitabine

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

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

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REPRESENTATIVE CHEMOTHERAPY REGIMENS FOR METASTATIC BREAST CANCER* (Page 2 of 6)

COMBINATIONS**CAF chemotherapy¹**

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

FAC chemotherapy²

- 5-Fluorouracil 500 mg/m² IV days 1 & 8 or days 1 & 4
 - Doxorubicin 50 mg/m² IV day 1
 - Cyclophosphamide 500 mg/m² IV day 1
- Cycled every 21 days.

AC chemotherapy³

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

CMF chemotherapy⁴

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

Docetaxel and Capecitabine⁵

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

GT Chemotherapy⁶

- Paclitaxel 175 mg/m² IV by 3 h IV infusion day 1
 - Gemcitabine 1250 mg/m² IV days 1 & 8 (following paclitaxel on day 1)
- Cycled every 21 days.

FEC chemotherapy⁷

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

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

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REPRESENTATIVE CHEMOTHERAPY REGIMENS FOR METASTATIC BREAST CANCER* (Page 3 of 6)

SINGLE AGENTS

- Doxorubicin⁸ 60-75 mg/m² IV day 1, cycled every 21 days
OR
- Doxorubicin 20 mg/m² IV, weekly.

- Epirubicin⁹ 60-90 mg/m² IV day 1
Cycled every 21 days.

- Pegylated liposomal encapsulated doxorubicin¹⁰ 50 mg/m² IV day 1
Cycled every 28 days.

- Paclitaxel 175 mg/m² by 3 h IV infusion day 1
Cycled every 21 days.¹¹
OR
- Paclitaxel 80 mg/m² by 1 h IV infusion weekly.¹²

- Docetaxel 60-100 mg/m² by 1 h IV infusion day 1
Cycled every 21 days.^{13,14}
OR
- Docetaxel 40 mg/m² by 1 h IV infusion weekly for 6 wks followed by
a 2 week rest, then repeated.¹⁵

- Vinorelbine 25 mg/m² IV weekly¹⁶

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

- Gemcitabine 800-1200 mg/m² IV days 1, 8 & 15
Cycled every 28 days.¹⁷

- Albumin-bound paclitaxel 260 mg/m² by 30 minute IV infusion
Cycled every 21 days.¹⁸

BEVACIZUMAB CONTAINING REGIMENS

- Paclitaxel plus bevacizumab¹⁹
- Paclitaxel 90 mg/m² by 1 h IV days 1, 8 & 15
 - Bevacizumab 10 mg/kg IV days 1 & 15
Cycled every 28 days.

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

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

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

REPRESENTATIVE CHEMOTHERAPY REGIMENS FOR METASTATIC BREAST CANCER IN COMBINATION WITH TRASTUZUMAB* (Page 4 of 6)

| <u>CHEMOTHERAPY COMPONENT</u> | | <u>TRASTUZUMAB COMPONENT</u> |
|---|--|---|
| <u>COMBINATIONS</u> | <u>SINGLE AGENTS</u> | |
| <p>PCH²⁰</p> <ul style="list-style-type: none"> • Carboplatin AUC of 6 IV day 1 • Paclitaxel 175 mg/m² by 3 h IV infusion day 1 <p>Cycled every 21 days.</p> <p>Weekly TCH²¹</p> <ul style="list-style-type: none"> • Paclitaxel 80 mg/m² by 1 h IV infusion days 1, 8 & 15 • Carboplatin AUC of 2 IV days 1, 8 & 15 <p>Cycled every 28 days.</p> | <ul style="list-style-type: none"> • Paclitaxel 175 mg/m² by 3 h IV infusion day 1 <p>Cycled every 21 days.²²</p> <p>OR</p> <ul style="list-style-type: none"> • Paclitaxel 80-90 mg/m² by 1 h IV infusion weekly²³ <ul style="list-style-type: none"> • Docetaxel 80 to 100 mg/m² by 30 min IV infusion day 1 <p>Cycled every 21 days</p> <p>OR</p> <ul style="list-style-type: none"> • Docetaxel 35 mg/m² by 30 min IV infusion weekly²⁴ <ul style="list-style-type: none"> • Vinorelbine 25 mg/m² IV weekly^{15,25} | <p>Trastuzumab 4 mg/kg IV by 90 min infusion day 1</p> <p>Followed by</p> <p>2 mg/kg IV by 30 min infusion weekly^{22,26}</p> <p>Or</p> <p>Trastuzumab 8 mg/kg IV by 90 min infusion day 1</p> <p>Followed by</p> <p>6 mg/kg IV by 90 min infusion every 3 weeks²⁷</p> |

REPRESENTATIVE CHEMOTHERAPY REGIMENS FOR METASTATIC BREAST CANCER IN COMBINATION WITH LAPATINIB*

Capecitabine plus lapatinib²⁸

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

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

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

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

REFERENCES FOR REPRESENTATIVE CHEMOTHERAPY REGIMENS FOR
METASTATIC BREAST CANCER and in COMBINATION WITH TRASTUZUMAB*

(Page 5 of 6)

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

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

REFERENCES FOR REPRESENTATIVE CHEMOTHERAPY REGIMENS FOR
METASTATIC BREAST CANCER and in COMBINATION WITH TRASTUZUMAB* (Page 6 of 6)

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

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

CLINICAL PRESENTATION

WORKUP

FINDINGS

TREATMENT

Clinical suspicion of phyllodes tumor:
 • Palpable mass
 • Rapid growth
 • Large size (> 2 cm)
 • Imaging with ultrasound suggestive of fibroadenoma except for size and/or history of growth

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

Excisional biopsy^b

Fibroadenoma

Phyllodes tumor includes benign, borderline and malignant

Invasive or in situ cancer

Core needle biopsy^a

Fibroadenoma or indeterminate

Phyllodes tumor

Observe

Wide excision^c without axillary staging

See appropriate guideline

Excisional biopsy^b → Observe

Wide excision^c without axillary staging

^aFNA will not, and core biopsy may not distinguish fibroadenoma from phyllodes tumor in most cases.

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

^cWide excision means excision with the intention of obtaining surgical margins ≥ 1 cm. Narrow surgical margins are associated with heightened local recurrence risk, but are not an absolute indication for mastectomy when partial mastectomy fails to achieve margin width ≥ 1 cm.

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PHYLLODES TUMOR RECURRENCE

CLINICAL PRESENTATION

WORKUP

FINDINGS

TREATMENT

Locally recurrent breast mass following excision of phyllodes tumor

- History and physical exam
- Ultrasound
- Mammogram
- Tissue sampling (histology preferred)
- Consider chest imaging

No metastatic disease

Metastatic disease

Re-excision with wide margins without axillary staging

Metastatic disease management following principles of soft tissue sarcoma
[See NCCN Soft Tissue Sarcoma Guidelines](#)

Consider post-operative radiation (category 3)^d

Consider surgery/radiation therapy for local control (category 3)

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

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CLINICAL
PRESENTATION

WORKUP

Clinical suspicion
of Paget's disease^a

- Clinical breast exam
- Diagnostic bilateral mammogram,
ultrasound as necessary
- Breast MRI (optional)^b

Examination or imaging
positive for breast lesion

Examination and imaging
negative for breast lesion

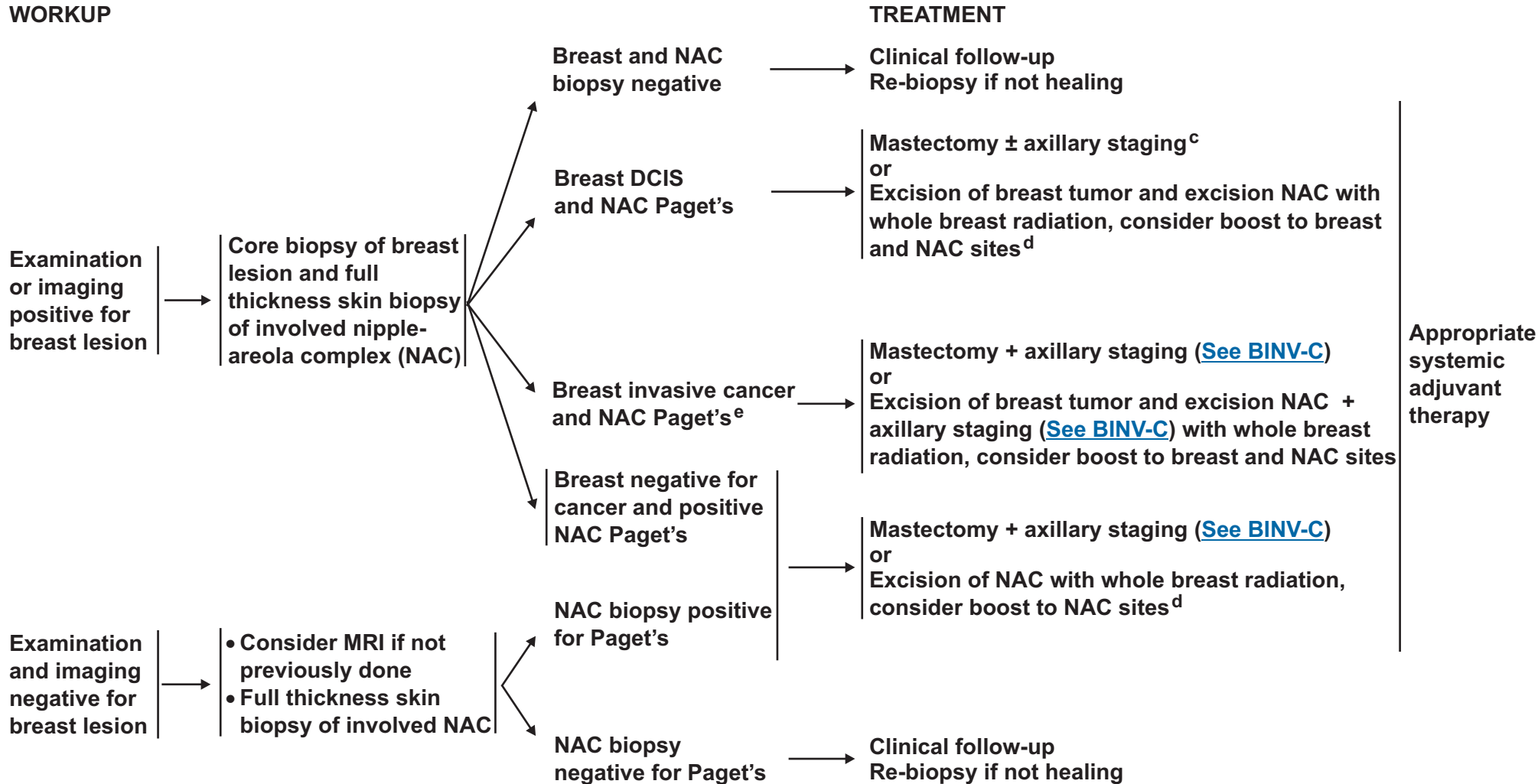
[See PAGET-2](#)

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

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

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

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^cMastectomy is always an option with any manifestation of Paget's disease (see manuscript text).

^dWith Paget's disease and no associated peripheral cancer, or with associated DCIS, consider tamoxifen 20 mg per day for 5 years.

^eWith associated invasive breast cancer, treat with appropriate systemic adjuvant therapy (See BINV-4)

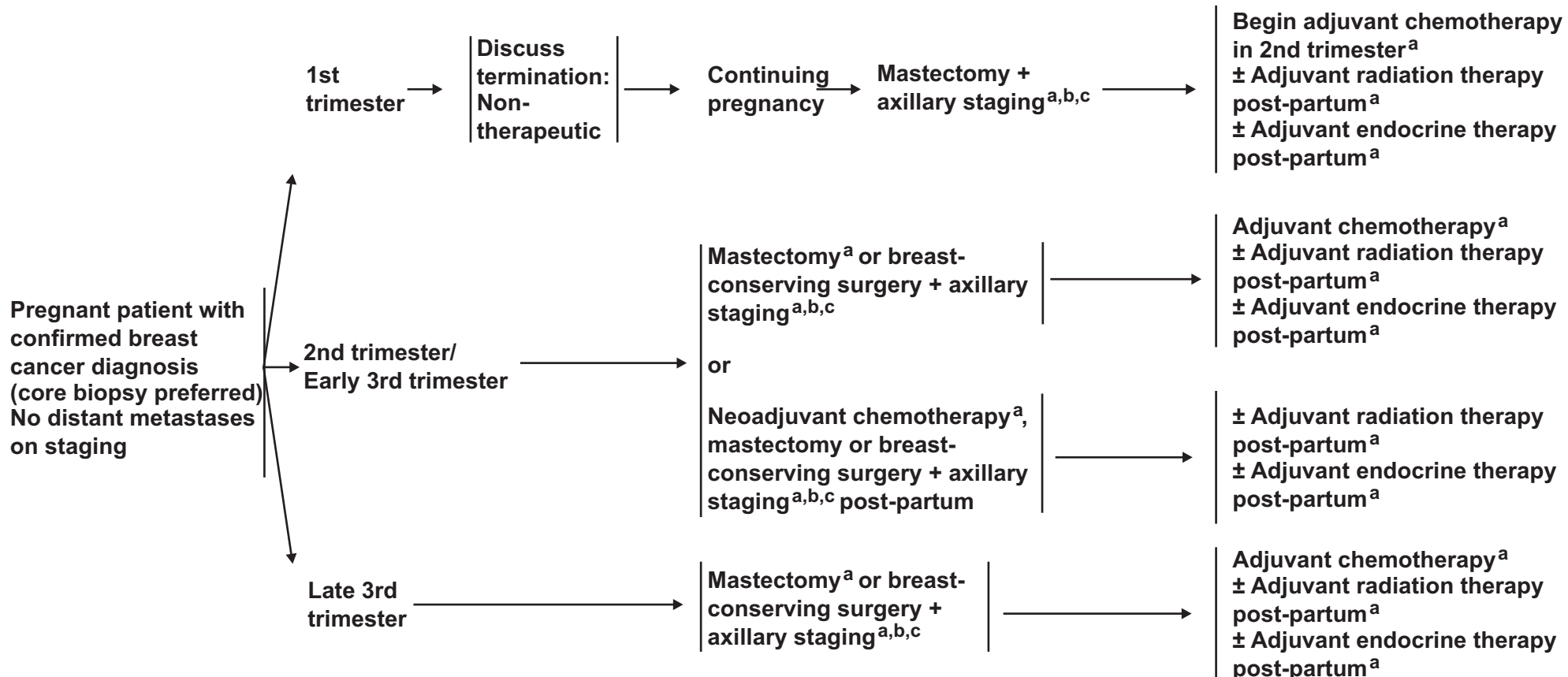
Note: All recommendations are category 2A unless otherwise indicated.

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CLINICAL PRESENTATION

PRIMARY TREATMENT^a

ADJUVANT TREATMENT^a



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

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

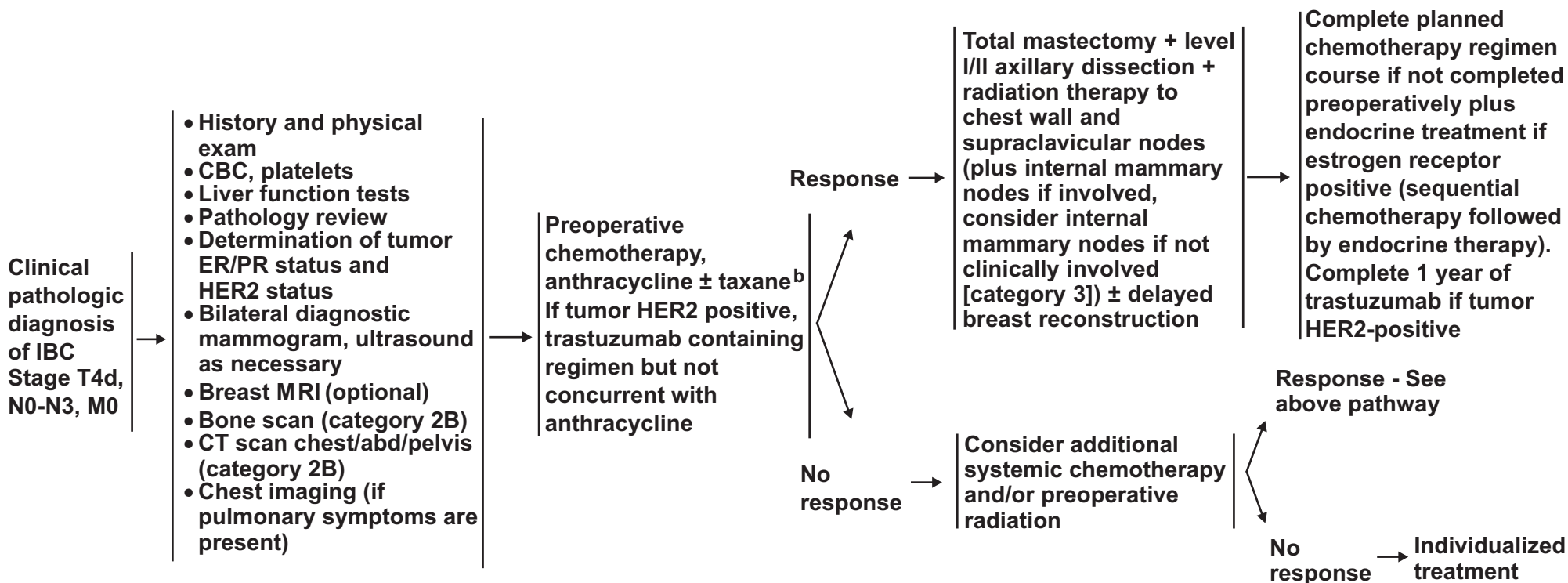
^c Due to limited data the use of isosulfan blue in pregnancy, and to the possibility of teratogenic effects of methylene blue dye, these colloids should not be used in pregnant patients.

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

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

CLINICAL PRESENTATION^a WORKUP

TREATMENT



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

^bPatients with HER2-positive tumors should be considered for chemotherapy incorporating trastuzumab ([See BINV-J](#)).

^c[See Principles of Reconstruction Following Mastectomy \(BINV-G\)](#).

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

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

Staging

Table 1

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

Primary Tumor (T)

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

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ

Tis (DCIS) Ductal carcinoma in situ

Tis (LCIS) Lobular carcinoma in situ

Tis (Paget's) Paget's disease of the nipple with no tumor

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

T1 Tumor 2 cm or less in greatest dimension

T1mic Microinvasion 0.1 cm or less in greatest dimension

T1a Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension

T1b Tumor more than 0.5 cm but not more than 1 cm in greatest dimension

T1c Tumor more than 1 cm but not more than 2 cm in greatest dimension

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

T3 Tumor more than 5 cm in greatest dimension

T4 Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below

T4a Extension to chest wall, not including pectoralis muscle

T4b Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast

T4c Both T4a and T4b

T4d Inflammatory carcinoma

Regional Lymph Nodes (N)

Clinical

NX Regional lymph nodes cannot be assessed (e.g., previously removed)

N0 No regional lymph node metastasis

N1 Metastasis to movable ipsilateral axillary lymph node(s)

N2 Metastases in ipsilateral axillary lymph nodes fixed or matted, or in *clinically apparent** ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis

N2a Metastases in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures

N2b Metastasis only in *clinically apparent** ipsilateral internal mammary nodes and in the *absence* of clinically evident axillary lymph node metastasis

N3 Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in *clinically apparent** ipsilateral internal mammary lymph node(s) and in the *presence* of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

N3a Metastasis in ipsilateral infraclavicular lymph node(s)

N3b Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)

N3c Metastasis in ipsilateral supraclavicular lymph node(s)

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

[Staging continued on next page \(ST-2\)](#)

Table 1 (continued)

Pathologic (pN)^a

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

pN0 No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITC)

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

pN0(i-) No regional lymph node metastasis histologically, negative IHC

pN0(i+) No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm

pN0(mol-) No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)^b

pN0(mol+) No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)^b

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

^bRT-PCR: reverse transcriptase/polymerase chain reaction.

pN1 Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not *clinically apparent***

pN1mi Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)

pN1a Metastasis in 1 to 3 axillary lymph nodes

pN1b Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not *clinically apparent***

pN1c Metastasis in 1 to 3 axillary lymph nodes and in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not *clinically apparent*** (If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden)

pN2 Metastasis in 4 to 9 axillary lymph nodes, or in *clinically apparent** internal mammary lymph nodes in the *absence* of axillary lymph node metastasis

pN2a Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)

pN2b Metastasis in *clinically apparent** internal mammary lymph nodes in the *absence* of axillary lymph node metastasis

pN3 Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in *clinically apparent** ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes

pN3a Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes

pN3b Metastasis in *clinically apparent** ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not *clinically apparent***

pN3c Metastasis in ipsilateral supraclavicular lymph nodes

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

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

Staging continued on next page (ST-3)

Table 1 (continued)

Distant Metastasis (M)

- MX** Distant metastasis cannot be assessed
- M0** No distant metastasis
- M1** Distant metastasis

STAGE GROUPING

| | | | |
|-------------------|-----|----|----|
| Stage 0 | Tis | N0 | M0 |
| Stage I | T1* | N0 | M0 |
| Stage IIA | T0 | N1 | M0 |
| | T1* | N1 | M0 |
| | T2 | N0 | M0 |
| Stage IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| Stage IIIA | T0 | N2 | M0 |
| | T1* | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N1 | M0 |
| | T3 | N2 | M0 |

* T1 includes T1mic

| | | | |
|-------------------|-------|-------|----|
| Stage IIIB | T4 | N0 | M0 |
| | T4 | N1 | M0 |
| | T4 | N2 | M0 |
| Stage IIIC | Any T | N3 | M0 |
| Stage IV | Any T | Any N | M1 |

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

HISTOPATHOLOGIC TYPE

The histopathologic types are the following:

In situ Carcinomas

- NOS (not otherwise specified)
- Intraductal
- Paget's disease and intraductal

Invasive Carcinomas

- NOS
- Ductal
- Inflammatory
- Medullary, NOS

- Medullary with lymphoid stroma
- Mucinous
- Papillary (predominantly micropapillary pattern)
- Tubular
- Lobular
- Paget's disease and infiltrating
- Undifferentiated
- Squamous cell
- Adenoid cystic
- Secretory
- Cribriform

HISTOPATHOLOGIC GRADE (G)

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

¹ Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histologic grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology* 1991;19:403-410.

² Fitzgibbons PL, Page DL, Weaver D et al. Prognostic factors in breast cancer. College of American Pathologists consensus statement 1999. *Arch Pathol Lab Med* 2000;124:966-978.

HISTOLOGIC GRADE (NOTTINGHAM COMBINED HISTOLOGIC GRADE IS RECOMMENDED)

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

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Manuscript

NCCN Categories of Evidence and Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

The American Cancer Society estimates that 180,510 new cases of breast cancer will be diagnosed and 40,910 will die of breast cancer in the United States in 2007.¹ Breast cancer is the most common malignancy in women in the United States and is second only to lung cancer as a cause of cancer death.

The incidence of breast cancer has increased steadily in the United States over the past few decades, but breast cancer mortality appears to be declining,^{1,2} suggesting a benefit from early detection and more effective treatment.

The etiology of the vast majority of breast cancer cases is unknown. However, numerous risk factors for the disease have been established. These risk factors include: female gender; increasing patient age; family history of breast cancer at a young age; early menarche; late menopause; older age at first live childbirth; prolonged hormone

replacement therapy; previous exposure to therapeutic chest wall irradiation; benign proliferative breast disease; and genetic mutations such as of the *BRCA1/2* genes. However, except for female gender and increasing patient age, these risk factors are associated with only a minority of breast cancers. Women with a strong family history of breast cancer should be evaluated according to the [NCCN Genetic/Familial High-Risk Assessment Guidelines](#). Women at increased risk for breast cancer (generally those with a greater than 1.67% 5-year risk of breast cancer using the Gail model of risk assessment³) may consider risk reduction strategies (see [NCCN Breast Cancer Risk Reduction Guidelines](#)).

Proliferative abnormalities of the breast are limited to the lobular and ductal epithelium. In both the lobular and ductal epithelium, a spectrum of proliferative abnormalities may be seen, including hyperplasia, atypical hyperplasia, in situ carcinoma, and invasive carcinoma.⁴ Approximately 85% to 90% of invasive carcinomas are ductal in origin. The invasive ductal carcinomas include unusual variants of breast cancer, such as colloid or mucinous, adenoid cystic, and tubular carcinomas, which have especially favorable natural histories.

Staging

Effective January 2003, the American Joint Committee on Cancer (AJCC) implemented a revision of the Cancer Staging Manual (sixth edition) containing important changes and additions in the TNM staging system for breast cancer ([Table 1](#)).^{5,6} This revision differs from the 1997 edition of the AJCC staging by incorporating the increasing use of novel imaging and pathology techniques employed at diagnosis (eg, sentinel node biopsy and immunohistochemistry [IHC] evaluation of nodes) and the number of lymph nodes involved as a factor in staging allocation.

The most substantial changes are:

1. Micrometastases to ipsilateral axillary lymph nodes are distinguished from isolated tumor cells on the basis of size and histological evidence of malignant activity. All metastatic lesions to ipsilateral axillary lymph nodes no larger than 0.2 mm, whether detected by hematoxylin and eosin (H&E) staining or IHC, will be described as pN0(i+). pN0(i-) is used to indicate no detectable tumor cells by either H&E or IHC. The designation pN1mi with no additional identifiers will be used for micrometastases greater than 0.2 mm but no greater than 2.0 mm in greatest dimension.⁷
2. Identifiers are added to indicate the use of sentinel lymph node resection and IHC or molecular pathology techniques.
3. The number of involved nodes as determined by routine H&E staining (preferred method) or by IHC staining impacts pathologic N staging (pN1 if 1 to 3 lymph nodes, pN2 if 4 to 9 lymph nodes, and pN3 if 10 or more lymph nodes are involved).
4. Metastases to infraclavicular nodes are categorized as N3 disease.
5. Metastases to internal mammary (IM) nodes impact staging according to the method of detection and presence or absence of concomitant axillary lymph node involvement (N1 disease if involved IM lymph nodes are detected exclusively using sentinel lymph node detection procedure; N2 disease if detected using any other imaging study or clinical examination; or N3 disease if concomitant axillary lymph node involvement is present).
6. Metastasis to ipsilateral supraclavicular lymph nodes is no longer considered M1 disease and is classified as N3 disease.

Although determination of the specific TNM status has become more complex (especially with regard to lymph node staging), the allocation of specific TNM combinations to different stage groupings remains the same, with the exception of the creation of stage IIIC to specifically identify patients with TanyN3M0 disease. This revised staging system

recognizes the heterogeneity of breast cancer and the need to create uniform data collection standards to better assess both the long-term outcome of specific patient subgroups and the impact of novel imaging or pathology techniques.⁶

Pathology Assessment

A central component of the treatment of breast cancer is full knowledge of extent of disease and biologic features. These factors contribute to the determination of the stage of disease, assist in the estimation of the risk that the cancer will recur, and provide information that predicts response to therapy (eg, hormone receptors and human epidermal growth factor receptor 2 [HER2]). These factors are determined by examination of excised tissue and provided in a written pathology report. Accurate pathology reporting requires communication between the clinician and the pathologist relating to relevant patient history, prior breast biopsies, prior irradiation to the chest, pregnancy status, characteristics of the abnormality biopsied (eg, palpable, mammographically detected, microcalcifications), clinical state of lymph nodes, presence of inflammatory change or other skin abnormality, and any prior treatment administered (eg, chemotherapy or radiotherapy). The specimens should be oriented for the pathologist, and specific requests for determination of biomarkers should be stated (eg, estrogen receptor, progesterone receptor, and HER2 status). The use of consistent, unambiguous standards for reporting is strongly encouraged. Data from both national and local surveys show that as many as 50% of pathology reports for breast cancer are missing some elements critical to patient management.^{8,9} Significant omissions include failure to orient and report surgical margins, and failure to report tumor grade consistently.

The College of American Pathologists (CAP) has developed pathology reporting protocols to promote complete and standardized reporting of malignant specimens. CAP provides a protocol for each disease site

that includes cancer case summaries (checklists) along with background documentation. These checklists form the basis for a synoptic, standardized reporting of pathologic findings. The checklists are available without charge through the CAP website at www.cap.org.

Consistent, unambiguous, and complete pathology reporting is a cornerstone of quality breast cancer care, and the Panel endorses the use of the CAP protocols for reporting the pathological analysis of all breast specimens.

Treatment Approach

Conceptually, the treatment of breast cancer includes the treatment of local disease with surgery, radiation therapy, or both, and the treatment of systemic disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy or combinations of these. The need for and selection of various local or systemic therapies are based on a number of prognostic and predictive factors. These factors include tumor histology, clinical and pathologic characteristics of the primary tumor, axillary node status, tumor hormone receptor content, tumor HER2 status, presence or absence of detectable metastatic disease, patient comorbid conditions, patient age, and menopausal status. Breast cancer does occur in men, and men with breast cancer should be treated similarly to postmenopausal women, except that the use of aromatase inhibitors is ineffective without concomitant suppression of testicular steroidogenesis.^{10,11} Patient preference is a major component of the decision-making process, especially in situations in which survival rates are equivalent among the available treatment options.

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

invasive carcinoma with or without associated noninvasive carcinoma (clinical stage IIIB, stage IIIC, and some stage IIIA tumors); and 4) metastatic or recurrent carcinoma (stage IV).

The Breast Cancer Clinical Practice Guidelines presented here are the work of the members of the NCCN Breast Cancer Clinical Practice Guidelines Panel. Categories of evidence were assessed and are noted on the algorithms and in the text. Although not explicitly stated at every decision point of the Guidelines, patient participation in prospective clinical trials is the preferred option of treatment for all stages of breast cancer.

Pure Noninvasive Carcinomas (Stage 0)

Both LCIS and DCIS may be difficult to distinguish from atypical hyperplasia or from carcinomas with early invasion.^{12,13} Therefore, pathology review of all cases is recommended. Bilateral diagnostic mammography should be performed to identify the presence of multiple primary tumors and to estimate the extent of the noninvasive lesion.

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

Lobular carcinoma in situ

Observation alone is the preferred option for women diagnosed with LCIS because their risk of developing invasive carcinoma is low (approximately 21% over 15 years).¹⁴ The histologies of the invasive carcinomas tend to be favorable, and deaths from second invasive cancers are unusual in appropriately monitored women.¹⁵ Bilateral

mastectomy, with or without reconstruction, should be considered in special circumstances such as in women with a *BRCA1/2* mutation or a strong family history of breast cancer. The consensus of the Panel is that consideration of a risk-reduction mastectomy is an option for a woman with LCIS without additional risk factors; however, it is not a recommended approach for most of these women. Individualized decision-making relating to the choice of a risk-reduction mastectomy for a woman with LCIS should be made only following careful evaluation and multidisciplinary counseling.

The risk of an invasive breast cancer after a diagnosis of LCIS is equal in both breasts.¹⁶ If mastectomy is considered as a risk reduction strategy, then a bilateral procedure is required to optimally minimize risk. Women treated with bilateral mastectomy are appropriate candidates for breast reconstruction (see [BINV-G](#)).

There is evidence to support the existence of histologically aggressive variants of LCIS (eg, “pleomorphic” LCIS) which may have a greater potential than classic LCIS to develop into invasive lobular carcinoma.¹⁷ However, outcome data regarding treatment of patients with pleomorphic LCIS are lacking, due, in part, to a paucity of histologic categorization of variants of LCIS. Therefore, recommendations on the treatment of pleomorphic LCIS as a distinct entity of LCIS have not been made by the Panel.

Women with LCIS, whether they undergo observation only or are treated with bilateral mastectomy, have an excellent prognosis. Recent data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial show that tamoxifen given for 5 years is associated with an approximately 46% reduction (hazard ratio 0.54; 95% CI 0.27-1.02) in the risk of developing invasive breast cancer among women with LCIS.^{18,19} Results from the NSABP Study of Tamoxifen and Raloxifene (STAR) trial have shown raloxifene to be as effective as tamoxifen in reducing the risk of invasive cancer in

postmenopausal patients with LCIS.²⁰ Therefore, the use of tamoxifen in premenopausal women or tamoxifen or raloxifene in postmenopausal women should be considered as a risk reduction strategy in women with LCIS who are followed with observation (category 1). (For recommendations on risk reduction, see also the [NCCN Breast Cancer Risk Reduction Guidelines](#).)

Follow-up of patients with LCIS includes physical examinations every 6 to 12 months for 5 years and then annually. Annual diagnostic mammography is recommended in patients being followed with clinical observation.

Ductal carcinoma in situ

Patients with DCIS and evidence of widespread disease (ie, disease in 2 or more quadrants) on mammography or other imaging, physical examination, or biopsy require a total mastectomy without lymph node dissection. For the vast majority of patients with more limited disease and in whom negative margins are achieved with the initial excision or with re-excision, breast-conserving therapy or total mastectomy are appropriate treatment options. Although mastectomy provides maximum local control, the long-term, cause-specific survival with mastectomy appears to be equivalent to that with excision and whole breast irradiation.²¹⁻²³ Women treated with mastectomy are appropriate candidates for breast reconstruction (see [BINV-G](#)). Contraindications to breast-conserving therapy with radiation therapy are listed in the algorithm (see [BINV-F](#)).

Prospective randomized trials have shown that the addition of whole breast irradiation to a margin-free excision of pure DCIS decreases the rate of in-breast disease recurrence, but does not affect overall survival.²²⁻²⁴ The use of whole breast radiation after breast-conserving surgery reduces the relative risk of a local failure by approximately one half. The use of a radiation boost (by photons, brachytherapy, or

electron beam) to the tumor bed is recommended to maximize local control, especially in patients 50 years of age or younger.

There is retrospective evidence suggesting that selected patients have a low risk of in-breast recurrence with excision alone without breast irradiation.^{25, 26} A recently reported multi-institutional prospective study of patients with low-risk DCIS treated without radiation has also provided some support for the use of excision without radiation for DCIS.²⁷ In the latter study, the risk of ipsilateral breast recurrence at 5 years was 6.8% in the subset of patients with low/intermediate grade DCIS with a median tumor size of 6mm, and a median surgical margin of 5-10 mm. A higher rate of local ipsilateral recurrence (13.7%) was observed in the group of patients with small, high-grade DCIS. In both groups, the ipsilateral recurrences were approximately equally divided between DCIS and invasive cancer.

Many factors, including patient age, tumor size, tumor grade, and margin width, impact recurrence risk. The definition of a negative margin has not been firmly established in DCIS. There appears to be a consensus that margins greater than 10 mm are adequate and margins less than 1 mm are inadequate, but no uniform consensus exists for margin status between these values. 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 1mm and greater than or equal to 6 mm.²⁸ Further complicating the issue of margin width is the impact of the fibroglandular boundary – the pectoral fascia and the superficial skin where narrower tumor free margins may provide adequate local control. Finally, because the choice of local treatment does not impact disease-related survival, the individual patient's acceptance of the potential for an increased risk of local recurrence must be considered.

Axillary dissection is not recommended for patients with pure DCIS, and axillary nodal involvement in DCIS is rare.²⁹ However, a small proportion of women with apparent pure DCIS on initial biopsy will be found to have invasive breast cancer at the time of the definitive surgical procedure and thus ultimately require axillary lymph node staging. In patients with apparent pure DCIS to be treated with mastectomy or with excision in an anatomic location (eg, tail of the breast), which could compromise the performance of a future sentinel lymph node procedure, a sentinel lymph node procedure may be considered.³⁰⁻³²

The primary treatment options for women with DCIS along with their respective categories of consensus are:

- 1) Lumpectomy plus radiation (category 1);
- 2) Total mastectomy, with or without reconstruction (category 2A);
- 3) Lumpectomy alone followed by clinical observation (category 2B).

There is no evidence that survival differs between the three treatment options. Decreased rates of local recurrence following lumpectomy have been observed in randomized trials with the addition of whole breast radiation (category 1). Although randomized trials evaluating the effectiveness of total mastectomy in DCIS have not been performed, mastectomy is a highly effective strategy to decrease risk of local recurrence (category 2A). The option of lumpectomy alone should be considered only in cases where the patient and the physician view the individual risks as “low” (category 2B).

Patients with mammographically detectable DCIS who elect breast conservation therapy should undergo post-excision mammography of the involved breast and specimen radiography to ensure that all mammographically detectable disease has been excised. Alternatively, some Panel members believe that specimen radiographs are adequate documentation of complete excision if such radiographs show that the

abnormality (the mass and/or microcalcifications) is clearly within the specimen. Clips are used by some NCCN institutions to demarcate the biopsy area because DCIS may be clinically occult and further surgery may be required, pending the margin status review by pathology.

DCIS falls between atypical ductal hyperplasia and invasive ductal carcinoma within the spectrum of breast proliferative abnormalities. The NSABP Breast Cancer Prevention Trial showed a 75% reduction in the occurrence of invasive breast cancer in patients with atypical ductal hyperplasia treated with tamoxifen.^{18,19} These data also showed that tamoxifen led to a substantial reduction in the risk of developing benign breast disease.³³ The Early Breast Cancer Trialists' overview analysis showed that, with 5 years of tamoxifen therapy, women with estrogen receptor- (ER)- positive or receptor-unknown invasive tumors had a 39% reduction in the annual odds of recurrence of invasive breast cancer.²

Similarly, the NSABP B-24 trial found a benefit from tamoxifen for women with DCIS after treatment with breast conservation surgery and radiation therapy. In that study, women with DCIS who were treated with breast-conserving therapy were randomized to receive placebo or tamoxifen. The women treated with tamoxifen had a 5% absolute reduction in recurrence risk and a 37% reduction in relative risk. The women receiving tamoxifen had an 8.2% total incidence of breast cancer (4.1% invasive and 4.2% noninvasive) compared with a 13.4% incidence of breast cancer (7.2% invasive and 6.2% noninvasive) in the placebo-treated women at a median follow-up of 74 months.³⁴ The cumulative incidence of invasive breast cancer at 5 years in the ipsilateral breast was 4.2% and 2.1% in women receiving placebo and tamoxifen, respectively, and in the contralateral breast, 2.3% and 1.8% in the placebo and tamoxifen groups, respectively). A retrospective analysis of estrogen receptor expression in NSABP B-24 suggests that increased levels of ER expression predict for tamoxifen benefit in terms

of reduction of risk for the development of both ipsilateral and contralateral breast cancer following breast-conserving therapy.³⁵

Tamoxifen treatment, therefore, may be considered as a strategy to reduce the risk of ipsilateral breast cancer recurrence in women with DCIS treated with breast-conserving therapy, especially in those with ER-positive DCIS (category 1 for those undergoing breast-conserving surgery plus radiation therapy; category 2A for those undergoing excision alone). Tamoxifen may also be considered as a risk reduction therapy to decrease risk of contralateral breast cancer in women with DCIS who have undergone a lumpectomy (with or without radiation) and in women with DCIS treated with mastectomy (category 2B).

Follow-up of women with DCIS includes a physical examination every 6 to 12 months for 5 years and then annually, as well as yearly diagnostic mammography.

Stage I, IIA, IIB, or T3N1M0 Invasive Breast Cancer

The recommended work-up and staging of invasive breast cancer includes: history and physical exam; a complete blood cell count; platelet count; liver function tests; bilateral diagnostic mammography; breast ultrasonography, if necessary; tumor estrogen and progesterone receptor determinations; HER2 tumor status determination; and pathology review (see [BINV-1](#)).

Use of MRI to evaluate women considering breast-conserving therapy is optional. If MRI imaging of the breast is performed, it should be done with a dedicated breast coil, with consultation with the multidisciplinary treatment team, and by a breast imaging team capable of performing MRI-guided biopsy (see [BINV-B](#)). The limitations of breast MRI include a high percentage of false-positive findings.^{36, 37} MRI imaging of the breast, therefore, should generally be considered in the staging of breast cancer for patients whose breasts cannot be imaged adequately with mammography and ultrasound (eg, women with very dense breast

tissue, women with positive axillary nodal status and occult primary tumor presumed to originate in the breast, or to evaluate the chest wall). Patients should not be denied the option of breast conservation therapy based upon MRI findings alone in the absence of tissue sampling.

Additional staging studies involving bone scan or abdominal imaging using CT, ultrasound, or MRI are optional. These studies are not indicated in patients with stage I disease without signs/symptoms of metastatic disease, nor are they needed in many other patients with early-stage breast cancer.³⁸ Radionuclide bone scanning and abdominal imaging with CT, ultrasound, or MRI are typically indicated only for patients with signs or symptoms related to bone or abdomen (eg, bone scan if alkaline phosphatase is elevated, abdominal scan if liver function tests are abnormal) or in T3N1M0 disease (category 2B for bone scan in T3N1M0 disease). These recommendations are supported by a study evaluating patients with newly diagnosed breast cancer by bone scan, liver ultrasonography, and chest radiography.³⁹ 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. A Positron Emission Tomography (PET) scan is not recommended in the staging of these patients.⁴⁰

The determination of HER2 status for all newly diagnosed invasive breast cancers is recommended. HER2 status can be assessed by measuring the number of HER2 gene copies (fluorescence in situ hybridization [FISH]), or by a complementary method in which the quantity of HER2 cell surface receptors is assessed (immunohistochemistry [IHC]).⁴¹ Only 4 methods currently have United States Food and Drug Administration approval for determining the HER2 status of breast cancer tumors. These methods include: 1) the IHC HercepTest[®] (DAKO, Glostrup, Denmark)⁴²; 2) the IHC Pathway[®]

HER2 test (Ventana Medical Systems, Tucson, AZ)⁴³; 3) the INFORM[®] HER2 FISH test (Ventana Medical Systems)⁴⁴; 4) and the PathVysion[®] HER2 FISH test (Vysis, Downers Grove, IL),⁴⁵ although modifications of these methods are currently in use in many anatomic pathology laboratories. The accuracy of HER2 assays used in clinical practice is a major concern, and results from several studies have shown that false-positive⁴⁶⁻⁵⁰ as well as false-negative^{46,51} HER2 test results are common. An NCCN Task Force has recently reviewed this topic and issued recommendations on HER2 testing in breast cancer⁵² which are summarized in the guideline (see [BINV-A](#)). The Panel considers either an IHC or FISH test as an acceptable method for making an initial determination of HER2 tumor status provided that the test method has been validated and shown to be at least 95% concordant with another validated method. Evidence for 95% concordance between the HER2 assay used and a validated complementary HER2 testing method is also required. Breast cancer tumors are classified as HER2-positive if they demonstrate HER2 gene amplification by a FISH method or are scored as 3+ by an IHC method. Strategies for evaluating tumors with borderline or indeterminate HER2 status (eg, FISH [Pathvysion[®]] scores of 1.8-2.2 HER2 genes/chromosome 17/cell, FISH [INFORM[®]] scores of greater than 4 to less than 6 HER2 genes/cell, or 2+ scores by IHC) are described in the guideline (see [BINV-A](#)). HER2 testing should be performed only in laboratories accredited to carry out such testing. Further, these laboratories should have standardized HER2 testing procedures in place, as well as programs to periodically evaluate the proficiency of personnel performing HER2 testing. HER2 test reports must provide information on site of tumor; specimen type; histologic type; fixation method and time; block examined; HER2 testing method used; results of ongoing validation and concordance studies of the HER2 testing methods used in that laboratory, as well as other laboratory quality assurance information. Clinicians should be familiar with the significance of these criteria when making clinical recommendations for an individual patient.

A joint panel from ASCO and CAP has recently issued HER2 testing guidelines which are fully consistent with those recommended by NCCN, but which also provide detailed recommendations for a substantial ongoing quality assurance program for laboratory accreditation from CAP.⁵³ The Panel endorses CAP accreditation for anatomic pathology laboratories performing HER2 testing.

A determination of the HER2 status of the tumor is recommended for prognostic purposes for patients with node-negative breast cancer.⁵⁴ HER2 tumor status also provides baseline predictive information used in selecting optimal adjuvant/neoadjuvant therapy and in the selection of therapy for recurrent or metastatic disease (category 1). For example, retrospective analyses have demonstrated that anthracycline-based adjuvant therapy is superior to non-anthracycline-based adjuvant chemotherapy in patients with HER2-positive tumors,⁵⁵⁻⁵⁹ and that the dose of doxorubicin may be important in the treatment of tumors that are HER2-positive.⁶⁰ However, prospective evidence of the predictive utility of HER2 status in early-stage⁶¹⁻⁶⁴ and metastatic breast cancer⁶⁵⁻⁶⁷ is currently available only for trastuzumab-containing therapies.

ER- and PR- tumor status is normally determined by IHC testing. Although this method is considered reliable when performed by experienced pathology personnel, there have been a number of reports indicating that the reliability of ER and PR determinations can vary widely from one laboratory to another.⁶⁸⁻⁷⁰ These interlaboratory differences may be attributable to the diverse methodologies and diverse interpretation schema used to evaluate tumor hormonal status.

Local-regional treatment

A number of randomized trials document that mastectomy with axillary lymph node dissection is equivalent to breast-conserving therapy with lumpectomy, axillary dissection, and whole breast irradiation, as primary breast treatment for the majority of women with stage I and

stage II breast cancers (category 1).⁷¹⁻⁷⁴ When breast-conserving therapy with lumpectomy and radiation therapy is performed, the Panel finds the data inadequate to support the use of partial breast irradiation outside the confines of a high-quality, prospective clinical trial.⁷⁵ The Panel recommends whole breast irradiation to include the majority of the breast tissue; breast irradiation should be performed following CT-based treatment planning so as to limit irradiation exposure of the heart and lungs, and to assure adequate coverage of the primary tumor and surgical site. Tissue wedging, forward planning with segments (step and shoot), or intensity-modulated radiation therapy (IMRT) is recommended.⁷⁶ Dose/fraction schedules of either 50 Gy in 25 fractions over 35 days or 42 Gy in 16 fractions over 35 days have been prospectively evaluated and are comparable with respect to DFS and overall survival in a study of women with node-negative early-stage breast cancer with a median follow-up of 69 months.⁷⁷ Randomized trials have demonstrated a decrease in breast recurrences with an additional “boost” dose of radiation (by photons, brachytherapy, or electron beam) to the tumor bed, especially in those under age 50 years.^{78,79} There is a demonstrated benefit in patients with positive axillary nodes, lymphovascular invasion, or close margins. (See [BINV-H](#) [Principles of Radiation Therapy]).

The use of breast-conserving therapy is absolutely contraindicated for patients who have received previous moderate- or high-dose radiation to the breast or chest wall, are pregnant and would require radiation during pregnancy, have diffuse suspicious or malignant-appearing microcalcifications on mammography, have widespread disease that cannot be incorporated by local excision through a single incision with a satisfactory cosmetic result, or have positive pathologic margins (see [BINV-E](#); [BINV-F](#)). Patients with a pathologically positive margin should generally undergo re-excision(s) to achieve a negative pathologic margin. If the margins remain positive after re-excision(s), then mastectomy is required for optimal local disease control. In order to

adequately assess margins following lumpectomy, the Panel recommends that the surgical specimens be oriented, that the pathologist provide descriptions of the gross and microscopic margin status, and the distance, orientation, and type of tumor (invasive or DCIS) in relation to the closest margin.

Relative contraindications to breast-conserving therapy include active connective tissue disease involving the skin (especially scleroderma and lupus), tumors greater than 5 cm (category 2B), and focally positive pathologic margins (see [BINV-F](#)). Those patients with focally positive pathologic margins who do not undergo re-excision should be considered for a higher radiation boost dose to the tumor bed.

Several studies of women with early-stage breast cancer treated with breast-conserving therapy have identified young age as a significant predictor of an increased likelihood of ipsilateral breast tumor recurrence after breast conserving surgery or mastectomy.⁸⁰⁻⁸² Risk factors, such as a family history of breast cancer or a genetic predisposition for breast cancer (eg, *BRCA 1/2* or other mutation), are more likely to exist in the population of young women with breast cancer, thereby confounding the independent contributions of age and treatment to clinical outcome.⁸³ Survival outcomes for young women with breast cancer receiving either breast-conserving therapy or mastectomy are similar.⁸⁴ The Panel recommends that women with breast cancer who are less than 35 years or premenopausal and carriers of a known *BRCA 1/2* mutation consider additional risk reduction strategies (see [BINV-F](#); [NCCN Breast Risk Reduction Guidelines](#) and [NCCN Genetic/Familial High-Risk Assessment Guidelines](#))

In a study of women with clinical stage I, estrogen receptor-positive breast cancer, who were 70 years of age or older at diagnosis, patients were randomized to receive lumpectomy with whole breast radiation or lumpectomy alone, both with tamoxifen for 5 years. Local-regional

recurrence rates were 1% in the lumpectomy, radiation and tamoxifen arm, and 4% in the lumpectomy plus tamoxifen arm. There were no differences in overall survival, disease-free survival or need for mastectomy.⁸⁵ These results were confirmed in an updated analysis of this study with a median follow-up of 8.2 years.⁸⁶ Similar results were obtained in another study of similar design.⁸⁷ The Guidelines allow for the use of breast-conserving surgery (pathologically negative margin required) plus tamoxifen or an aromatase inhibitor without breast irradiation in women age 70 or older with clinically negative lymph nodes and ER positive breast cancer (category 1 with tamoxifen; category 2A with an aromatase inhibitor).

If adjuvant chemotherapy is indicated following breast-conserving surgery, radiation should typically be given after chemotherapy is completed.⁸⁸ Breast-conserving radiation therapy may be given concurrent with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy, but methotrexate should either be withheld during the radiation or limited to no more than 2 doses concurrent with the radiation. Concurrent CMF chemotherapy with radiation has been demonstrated to decrease the cosmetic outcome of breast-conserving therapy in some, but not all studies.⁸⁹⁻⁹¹ The guideline includes a recommendation for regional lymph node irradiation in patients treated with breast-conserving surgery (see [BINV-2](#)) in situations analogous to those recommended for patients treated with post-mastectomy regional lymph node irradiation (see [BINV-3](#); subsequent discussion; Principles of Radiation [[BINV-H](#)]).

The NCCN Breast Cancer Treatment Guidelines include a guideline for surgical staging of the axilla for stages I, IIA, and IIB breast cancer (see [BINV-C](#)). A typical woman with clinical stage I or stage II breast cancer requires pathologic assessment of the axillary lymph node status.

Performance of sentinel lymph node mapping and resection in the surgical staging of the axilla is recommended by the Panel as the

preferred method to assess the pathologic status of the axillary lymph nodes for patients with stage I or stage II breast cancer^{32,92-99} (see [BINV-C](#)). This recommendation is supported by results of recent randomized clinical trials showing decreased arm and shoulder morbidity (eg, pain, lymphedema, and sensory loss) in patients with breast cancer undergoing sentinel lymph node biopsy compared with patients undergoing standard axillary node dissection.^{98,100} No significant differences in the effectiveness of the sentinel lymph node procedure or level I and II dissection in determining the presence or absence of metastases in axillary nodes were seen in these studies. However, not all women are candidates for sentinel lymph node resection. The availability of an experienced sentinel lymph node team is mandatory for the use of sentinel lymph node mapping and excision.^{101, 102} Women who have clinical stage I or II disease and do not have immediate access to an experienced sentinel node team should be considered for referral to an experienced sentinel lymph node team for the definitive surgical treatment of the breast and surgical axillary lymph node staging. In addition, potential candidates for sentinel lymph node mapping and excision should have clinically negative axillary lymph nodes, or a negative core or fine needle aspiration (FNA) biopsy of any clinically suspicious axillary lymph node(s). If the sentinel lymph node cannot be identified or is positive for metastasis, a formal axillary lymph node dissection should be performed (category 2A) or axillary irradiation administered (category 2B). The optimal technique for axillary radiation is not established in studies, but the axillary nodes can be included in the breast tangential fields. If lymph node mapping identifies sentinel lymph nodes in the internal mammary chain, internal mammary node excision is considered optional (category 3). In many institutions, sentinel lymph nodes are assessed for the presence of metastases by both H&E staining and cytokeratin IHC. The clinical significance of a lymph node that is negative by H&E staining but positive by cytokeratin IHC is not clear. Because the historical and clinical trial data on which treatment

decisions are based have relied on H&E staining, the Panel believes that current treatment decisions should be made based solely on H&E staining (category 3). In the uncommon situation in which H&E staining is equivocal, reliance on the results of cytokeratin IHC is reasonable.

Level I or II axillary dissection is an appropriate staging study in women with invasive breast cancer. Although the option of sentinel lymph node mapping and excision is preferred by the Panel over axillary lymph node dissection as the initial axillary lymph node staging for women with clinically node-negative stage I or stage II breast cancer, it is not a mandatory replacement for a level I and II axillary dissection. Axillary lymph node dissection remains indicated in women found to have axillary lymph node involvement on sentinel lymph node excision. Traditional level I and level II axillary dissection required that at least 10 lymph nodes should be provided for pathologic evaluation to accurately stage the axilla.^{103,104} Axillary dissection should be extended to include level III nodes only if gross disease is apparent in the level I or II nodes.

Furthermore, in the absence of definitive data demonstrating superior survival with axillary lymph node dissection or sentinel lymph node resection, these procedures may be considered optional in patients who have particularly favorable tumors, patients for whom the selection of adjuvant systemic therapy is unlikely to be affected by the results of the procedure, elderly patients, and patients with serious co-morbid conditions (see [BINV-D](#)). Women who do not undergo axillary dissection or axillary lymph node irradiation are at increased risk for ipsilateral lymph node recurrence.¹⁰⁵ Women who undergo mastectomy are appropriate candidates for breast reconstruction.

Preoperative chemotherapy for large clinical stage IIA and IIB tumors and T3N1M0 tumors

Preoperative chemotherapy should be considered for women with large clinical stage IIA, stage IIB, and T3N1M0 tumors who meet the criteria for breast-conserving therapy except for tumor size and who wish to

undergo breast-conserving therapy. In the available clinical trials of preoperative chemotherapy, pretreatment biopsies have been limited to core needle biopsy or FNA cytology. Therefore, in patients anticipated to receive preoperative chemotherapy, core or FNA biopsy of the breast tumor should be performed, and core or FNA biopsy of clinically suspicious axillary lymph nodes should be considered. Preoperative chemotherapy is not indicated unless invasive breast cancer is confirmed. Recommended staging studies are outlined on [BINV-10](#) and include history and physical examination, CBC, platelet count, liver function tests, diagnostic bilateral mammogram (with ultrasound as necessary), pathology review, and determination of tumor ER/PR and HER2 status. Breast MRI, bone scan, and abdominal imaging are optional unless the patient is symptomatic or as directed based upon other abnormal or suspicious staging evaluations; chest imaging is recommended if pulmonary symptoms are present.

The current guideline lists pre-chemotherapy sentinel lymph node resection as the preferred option for surgical axillary staging in those women with clinically negative ipsilateral axillary examinations (see [BINV-C](#)). If the sentinel lymph node is histologically negative, omission of the axillary dissection may be considered at the time of local, surgical therapy. If the sentinel lymph node is histologically positive, then level I and II axillary dissection should be performed at the time of definitive surgical therapy. If a pre-chemotherapy sentinel lymph node excision is not performed, then a level I and II axillary dissection (category 2A) or sentinel lymph node excision (category 3) (with level I and II axillary dissection if sentinel lymph node is positive) should be performed at the time of definitive surgical therapy. The Panel generally recommends a pre-chemotherapy sentinel lymph node excision because it provides additional information to guide local and systemic treatment decisions. In the event that sentinel lymph node resection is performed after administration of preoperative chemotherapy, both the pre-chemotherapy clinical and the post-chemotherapy pathologic nodal

stages must be used to determine the risk of local recurrence. Close communication between members of the multidisciplinary team, including the pathologist, is particularly important when any treatment strategy involving preoperative chemotherapy is planned.

In some patients, preoperative chemotherapy results in sufficient tumor response that breast-conserving therapy becomes possible. Because complete or near-complete clinical responses are common, the use of percutaneously placed clips into the breast under mammographic or ultrasound guidance or other method of localizing pre-chemotherapy tumor volume aids in the post-chemotherapy resection of the original area of tumor and is encouraged. The results of the NSABP B-18 trial show that breast conservation rates are higher after preoperative chemotherapy.¹⁰⁶ However, preoperative chemotherapy has no demonstrated disease specific survival advantage over postoperative adjuvant chemotherapy in patients with stage II tumors. NSABP B-27 is a 3-arm, randomized phase III trial of women with invasive breast cancer treated with preoperative doxorubicin and cyclophosphamide (AC) chemotherapy for 4 cycles followed by local therapy alone, preoperative AC followed by preoperative docetaxel for 4 cycles followed by local therapy, or AC followed by local therapy followed by 4 cycles of postoperative docetaxel. Results from this study which involved 2411 women documented a higher rate of complete pathologic response at the time of local therapy in patients treated preoperatively with 4 cycles of AC followed by 4 cycles of docetaxel versus 4 cycles of preoperative AC. Disease-free survival and overall survival have not been shown to be superior following docetaxel treatment in B-27.¹⁰⁷ A disease-free survival advantage was observed (hazard ratio 0.71; 95% CI, 0.55 – 0.91; P=0.007) favoring preoperative versus postoperative docetaxel in the subset of patients experiencing a clinical partial response to AC.

A number of chemotherapy regimens have been studied as preoperative chemotherapy in the neoadjuvant setting. The Panel believes that the regimens recommended in the adjuvant setting (see [BINV-J](#)) are appropriate to consider in the preoperative chemotherapy setting. In women with HER2-positive tumors treated with neoadjuvant chemotherapy, the addition of neoadjuvant trastuzumab to paclitaxel followed by FEC chemotherapy was associated with an increase in the pathologic complete response rate from 26% to 65.2% (P=0.016).¹⁰⁸ Thus, the incorporation of trastuzumab into neoadjuvant chemotherapy regimens appears important in HER2-positive tumors.

Several randomized trials have assessed the value of neoadjuvant endocrine therapy in postmenopausal women with estrogen receptor-positive breast cancer. These studies have generally compared the rates of objective response and rates of breast-conserving surgery among treatment with tamoxifen, anastrozole, anastrozole plus tamoxifen, or letrozole. These studies consistently demonstrate that the use of either anastrozole or letrozole alone provides superior rates of breast-conserving surgery and usually objective response.^{109,110} On the basis of these trials, preoperative endocrine therapy with an aromatase inhibitor is an option in the treatment of postmenopausal women with hormone receptor-positive disease.

If the tumor responds to preoperative chemotherapy, lumpectomy plus (if pre-chemotherapy sentinel lymph node staging was not done or was positive) axillary lymph node dissection (category 2A) or (if pre-chemotherapy axillary lymph node staging not performed) sentinel lymph node procedure (category 3) may be considered if the requirements for breast-conserving therapy are fulfilled (see [BINV-11](#); [BINV-12](#)). If a pre-chemotherapy sentinel lymph node procedure was performed and the sentinel lymph node was pathologically negative, then further axillary lymph node staging is not necessary. If a pre-chemotherapy sentinel lymph node procedure was performed and the

sentinel lymph node was positive, then a level I/II axillary lymph node dissection should be performed. Surgery should be followed by individualized chemotherapy such as taxanes (category 2B) if the full course of planned chemotherapy was not administered preoperatively, as well as breast and regional lymph node irradiation. The consensus of the Panel is that there is no role for postoperative chemotherapy if a full course of standard chemotherapy has been completed preoperatively. Whether the internal mammary lymph nodes should be included in the regional lymph node field generated substantial controversy among Panel members (category 3). If after several cycles of preoperative chemotherapy, the tumor fails to respond, the response is minimal, or if the disease progresses at any point, an alternative chemotherapy should be considered, followed by local therapy, usually a mastectomy plus axillary dissection, with or without breast reconstruction. Postoperative treatment for these patients consists of individualized chemotherapy, endocrine therapy in women with estrogen and/or progesterone receptor-positive tumors, and radiation to the chest wall and supraclavicular lymph nodes (see Principles of Radiation Therapy [\[BINV-H\]](#)). Inclusion of the internal mammary lymph nodes in the radiotherapy field can be considered, but this recommendation generated substantial controversy among Panel members (category 3). Postmastectomy radiation therapy in patients with T2N0M0 tumors may be considered optional.

Radiation therapy after mastectomy

Node positive disease

Three randomized clinical trials have shown that a disease-free and overall survival advantage is conferred by the addition of chest wall and regional lymph node irradiation in women with positive axillary lymph nodes after mastectomy and axillary lymph node dissection.¹¹¹⁻¹¹⁵ In these trials, not only the ipsilateral chest wall but also the ipsilateral local-regional lymph nodes were irradiated. These studies contrast, however, with a number of other studies, including a randomized trial

from an NCCN institution that failed to show a survival advantage with postmastectomy chest wall and regional node irradiation.¹¹⁶ However, on the basis of the studies demonstrating a survival advantage with postmastectomy chest wall and regional lymph node irradiation in node-positive breast cancer, the current Guidelines call for postmastectomy irradiation in women with 4 or more positive axillary lymph nodes and strong consideration of postmastectomy irradiation in women with 1-3 positive axillary lymph nodes.

For women with 1 to 3 involved axillary lymph nodes, the Panel recommends strong consideration of radiation to the chest wall and supraclavicular area after chemotherapy (category 1), with consideration also given to the inclusion of the ipsilateral internal mammary field (category 3). The recommendation for chest wall and supraclavicular irradiation in women with 1-3 involved axillary lymph nodes generated substantial controversy among Panel members. The use of regional nodal irradiation is supported by a subgroup analysis of studies from the Danish Breast Cancer Collaborative Group.¹¹⁷ In this analysis, a substantial survival benefit was associated with postmastectomy radiation therapy for women with 1-3 positive axillary lymph nodes. Some Panel members believe chest wall and supraclavicular irradiation should be used routinely after mastectomy and chemotherapy in this subgroup of patients. However, other Panel members believe radiation should be considered in this setting but should not be mandatory given the studies that do not show an advantage. This is an unusual situation in which high-level evidence (category 1) exists but is contradictory.^{72,112,113,115,117} Women with 1 to 3 involved axillary lymph nodes and with tumors greater than 5 cm or with tumors with positive pathologic margins postmastectomy should receive post-chemotherapy radiation therapy to the chest wall and supraclavicular areas (category 1) with consideration of inclusion of the ipsilateral internal mammary field (category 3).

There is considerable disagreement regarding the inclusion of the ipsilateral internal mammary field. Some Panel members believe that irradiation of the internal mammary nodes is unnecessary and produces possible morbidity. Internal mammary node radiation has not been isolated as an independent factor in decreasing recurrence. Others believe internal mammary nodes should be included in the radiation fields, as used in the studies that demonstrated an advantage for postmastectomy, post-chemotherapy radiation therapy. Therefore, this recommendation is identified as category 3.

Women with 4 or more positive axillary lymph nodes are at substantially increased risk for locoregional recurrence of disease. The use of postmastectomy, post-chemotherapy chest wall and regional lymph node irradiation is recommended (category 1). The use of prophylactic chest wall irradiation in this setting substantially reduces the risk of local recurrence.⁷² Again, there was substantial disagreement among Panel members regarding the inclusion of the ipsilateral internal mammary field (category 3).

Postmastectomy irradiation should be performed using CT-based treatment planning to assure reduced radiation dose to the heart and lungs. The recommended radiation is 50 Gy in fractions of 1.8-2.0 Gy to the ipsilateral chest wall, mastectomy scar, and drain sites. Additional “boost” dose of radiation to the mastectomy scar can be delivered (eg, 2 Gy fractionated in 5 doses, typically with electrons). Radiation dose to regional lymph nodes is 50 Gy given using 1.8-2.0 Gy fraction size.

Node negative disease

Features in node-negative tumors that predict a high rate of local recurrence include primary tumors greater than 5 cm and close (less than 1 mm) or positive pathologic margins. Chest wall irradiation is recommended for these patients.¹¹⁸ Consideration should be given to radiation to the ipsilateral supraclavicular area (category 2B) and to the

ipsilateral internal mammary lymph nodes (category 3), especially in patients with inadequate axillary evaluation or extensive lymphovascular invasion. Postmastectomy radiation therapy is not recommended for patients with negative margins, tumors 5 cm or smaller, and no positive axillary lymph nodes.

Breast reconstruction following mastectomy

A number of factors must be considered in the decision-making about breast reconstruction following mastectomy (see [BINV-G](#)). First, there are a number of different types of breast reconstruction. These include reconstruction using implants, autologous tissue, or both implants and autologous tissue. Implant reconstruction typically involves the placement of a sub-pectoralis major expander implant, a series of expansions, followed by replacement of the expander with a permanent sub-pectoralis major implant. A number of different techniques are available for the performance of autologous reconstruction using various combinations of muscle, fat and skin from a variety of donor sites. 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. For many patients, reconstruction may be performed as an immediate procedure under the same anesthetic as the mastectomy. 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.

When breast reconstruction following mastectomy is planned, close prospective evaluation and collaboration between members of the breast cancer treatment team is essential including both the oncologic and reconstructive surgeons, as well as the other members of the multidisciplinary team.

Systemic adjuvant therapy

After surgical treatment, adjuvant systemic therapy should be considered. The published results of the Early Breast Cancer Trialists' Collaborative Group overview analyses of adjuvant polychemotherapy and tamoxifen show convincing reductions in the odds of recurrence and of death in all age groups under 70 years for polychemotherapy and in all age groups for tamoxifen.² Thus, for those under age 70, the current Guidelines recommend adjuvant therapy without regard to patient age (category 1). The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of the therapy and comorbidity.^{119, 120} The decision-making process requires a collaboration involving the health care team and the patient.

Estimating risk of relapse or death and benefits of systemic treatment

A number of 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 axillary lymph nodes, and possibly HER2 tumor status. Algorithms have been published estimating rates of recurrence,¹¹⁹ and a validated computer-based model (Adjuvant! Online; www.adjuvantonline.com) is available to estimate 10-year disease-free and overall survival that incorporates all of the above prognostic factors except for HER2 tumor status.^{120,121} 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, costs, and benefits of systemic adjuvant therapy.¹²²

Use of DNA microarray technologies to characterize breast cancer has allowed the development of classification systems of breast cancer by

gene expression profile.¹²³ Five major subtypes of breast cancer have been identified by DNA microarray gene expression profiling: ER-positive/HER2-negative (Luminal A and Luminal B subtypes); ER-negative/HER2-negative (Basal subtype); HER2-positive; and tumors that have characteristics similar to normal breast tissue (Normal breast-like).¹²⁴⁻¹²⁶ In retrospective analyses, these gene expression subtypes are associated with differing relapse-free and overall survival. A similar approach has been used to define more limited sets of genes for prognostic and predictive purposes.¹²⁷ For example, the Mammprint assay uses microarray technology to analyze a 70-gene expression profile from frozen breast tumor tissue as a means of selecting patients with early-stage, node-negative breast cancer who are more likely to develop distant metastases.¹²⁸⁻¹³⁰

Another gene-based approach is the 21-gene assay using reverse transcription polymerase chain reaction (RT-PCR) on RNA isolated from paraffin-embedded breast cancer tissue (Oncotype Dx). On retrospective analysis of two trials (NSABP B-14 and B-20) performed in women with hormone receptor-positive, axillary lymph node-negative invasive breast cancer, this assay system was able to quantify risk of recurrence as a continuous variable (eg, Oncotype Dx recurrence score) and to predict responsiveness to both tamoxifen and CMF or methotrexate/5-fluorouracil/leucovorin chemotherapy.^{131,132} A recent comparison of simultaneous analyses of breast cancer tumors using 5 different gene-expression models indicated that 4 of these methods (including Mammprint and Oncotype Dx) provided similar predictions of clinical outcome.¹³³

While many of the DNA microarray technologies are able to stratify patients into prognostic and/or predictive subsets on retrospective analysis, the gene subsets differ from study to study, and prospective clinical trials testing the utility of these techniques have yet to be reported. Currently, 2 prospective randomized clinical trials (TAILORx

and MINDACT) are addressing the use of Oncotype DX and Mammprint, respectively, as predictive and/or prognostic tools in populations of women with early-stage lymph node-negative breast cancer. Pending the results of the prospective trials, the Panel considers the 21-gene RT-PCR assay as an option when evaluating patients with primary tumors characterized as 0.6-1.0 cm with unfavorable features or > 1cm, and node-negative, hormone receptor-positive and HER2-negative (category 2B). In this circumstance, the recurrence score may be determined to assist in estimating likelihood of recurrence and benefit from chemotherapy (category 2B). The Panel emphasizes that the recurrence score should be used for decision making only in the context of other elements of risk stratification for an individual patient. All recommendations involving use of the recurrence score in treatment decision-making are categorized as 2B (see [BINV-6](#)).

Axillary lymph node negative tumors

Small tumors (up to 0.5 cm in greatest diameter) that do not involve the lymph nodes are so favorable that adjuvant systemic therapy is of minimal incremental benefit and is not recommended as treatment of the invasive breast cancer. Tamoxifen may be considered to reduce the risk of a second contralateral breast cancer, especially in those with estrogen receptor-positive disease. The NSABP database demonstrated a correlation between the estrogen receptor status of a new contralateral breast tumor and the original primary tumor, which reinforced the notion that tamoxifen is unlikely to be an effective strategy to reduce the risk of contralateral breast cancer in patients diagnosed with estrogen receptor-negative tumors.¹³⁴ Patients with invasive ductal or lobular tumors 0.6 to 1 cm in diameter and no lymph node involvement may be divided into patients with a low risk of recurrence and those with unfavorable prognostic features that warrant consideration of adjuvant therapy. Unfavorable prognostic features include intramammary angiolymphatic invasion, high nuclear grade,

high histological grade, HER2-positive status, or hormone receptor-negative status (category 2B). The use of endocrine therapy and chemotherapy in these relatively lower risk subsets of women must be based on balancing the expected absolute risk reduction and the individual patient's willingness to experience toxicity to achieve that incremental risk reduction.

Patients with lymph node involvement or with tumors greater than 1 cm in diameter are appropriate candidates for adjuvant systemic therapy (category 1). For women with lymph node-negative, hormone receptor-negative tumors greater than 1 cm in diameter, chemotherapy is recommended (category 1). For those with lymph node-negative, hormone receptor-positive breast cancer tumors greater than 1 cm, endocrine therapy with chemotherapy is recommended (category 1). The incremental benefit of combination chemotherapy in patients with lymph node-negative, hormone receptor-positive breast cancer may be relatively small.¹³⁵ Therefore, the Panel recommends that tumor hormone receptor status be included as one of the factors considered when making chemotherapy-related treatment decisions for patients with node-negative, hormone receptor-positive breast cancer. Patients for whom this evaluation may be especially important are those with tumors characterized as 0.6-1.0 cm and hormone receptor-positive with unfavorable features, or greater than 1 cm and hormone receptor-positive and HER2-negative (see [BINV-5](#); [BINV-6](#)). However, chemotherapy should not be withheld from these patients solely on the basis of estrogen receptor-positive tumor status.^{2,135,136}

The use of both endocrine therapy and chemotherapy must be based on balancing the expected absolute risk reduction and the individual patient's willingness to experience toxicity to achieve that incremental risk reduction. The use of genomic/gene expression array data which also incorporate additional prognostic/predictive biomarkers (eg, Oncotype Dx recurrence score) may provide additional prognostic and

predictive information beyond anatomic staging and determination of ER/PR and HER2 status. Assessment of the role of the genomic/gene expression array technology is difficult because of the retrospective nature of the studies, the evolution of chemotherapy and hormone therapy regimens, and the overall more favorable prognosis of the patients with lymph node-negative disease compared with those enrolled in the historically-controlled clinical trials. Some NCCN institutions consider performing RT-PCR analysis (eg, Oncotype DX assay) to further refine risk stratification for adjuvant chemotherapy for patients with node-negative, estrogen receptor-positive, HER2-negative breast cancers greater than 0.5 cm, whereas others do not (category 2B).

Axillary lymph node positive tumors

Patients with lymph node-positive disease are candidates for chemotherapy and, if the tumor is hormone receptor-positive, for the addition of endocrine therapy (category 1). In postmenopausal women, with hormone receptor-positive disease, an aromatase inhibitor should be utilized either as initial adjuvant therapy, sequential with tamoxifen, or as extended therapy following tamoxifen. In premenopausal women, adjuvant tamoxifen is preferred. If both chemotherapy and tamoxifen are used, data from the Intergroup trial 0100 suggest that delaying initiation of tamoxifen until after completion of chemotherapy improves disease-free survival compared with concomitant administration.¹³⁶ Consequently, chemotherapy followed by endocrine therapy should be the preferred therapy sequence.

The paucity of clinical trial data regarding adjuvant chemotherapy in women over age 70 prohibits definitive recommendations in this age group. Adjuvant treatment in women over age 70 should be individualized, with consideration of comorbid conditions.

Guideline stratification for systemic adjuvant therapy

The current version of the Guidelines first recognizes subsets of patients with early breast cancer of the usual histologies based upon responsiveness to endocrine therapy and trastuzumab (ie, hormone receptor status, HER2 status) (see [BINV-4](#)). Patients are then further stratified based upon risk for recurrence of disease based upon anatomic and pathologic characteristics (ie, tumor grade, tumor size, axillary lymph node status, angiolymphatic invasion) (see [BINV-5](#); [BINV-6](#); [BINV-7](#); [BINV-8](#)).

Adjuvant endocrine therapy

The NCCN Guidelines call for the determination of estrogen and progesterone receptor content in all primary invasive breast cancers. Patients with invasive breast cancers that are estrogen or progesterone receptor-positive should be considered for adjuvant endocrine therapy regardless of patient age, lymph node status, or whether or not adjuvant chemotherapy is to be administered.¹³⁷ 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.^{57,138-145} A retrospective analysis of tumor blocks collected in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trial indicated that HER2 amplification is a marker of relative endocrine resistance independent of type of endocrine therapy.¹⁴⁶ However, given the favorable toxicity profile of the available endocrine therapies, the Panel recommends the use of adjuvant endocrine therapy in the majority of women with hormone receptor-positive breast cancer regardless of menopausal status, age, or HER2 status of the tumor. The exceptions to the recommendation of adjuvant endocrine therapy for patients with hormone receptor-positive disease are those patients with lymph node-negative cancers less than or equal to 0.5 cm or 0.6 to 1.0 cm in diameter with favorable prognostic features where the prognosis is so favorable that the benefits of adjuvant endocrine therapy are very small.

The most firmly established adjuvant endocrine therapy is tamoxifen for both premenopausal and postmenopausal women.² In women with estrogen receptor-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 axillary lymph node status.² Prospective, randomized trials demonstrate that the optimal duration of tamoxifen appears to be five years. In patients receiving both tamoxifen and chemotherapy, chemotherapy should be given first, followed by sequential tamoxifen.¹³⁶

Several studies have evaluated aromatase inhibitors in the treatment of postmenopausal women with early-stage breast cancer. These studies have utilized the aromatase inhibitors as initial adjuvant therapy, as sequential therapy following 2-3 years of tamoxifen, or as extended therapy following 4.5 -6 years of tamoxifen. The aromatase inhibitors are not active in the treatment of women with functioning ovaries and should not be used in women whose ovarian function cannot be reliably assessed owing to treatment-induced amenorrhea (see Definition of Menopause, [BINV-K](#)). The results from two prospective, randomized clinical trials have provided early evidence of an overall survival benefit for patients with early-stage breast cancer receiving initial endocrine therapy with tamoxifen followed sequentially by anastrozole or exemestane when compared with tamoxifen as the only endocrine therapy.^{147,148} In addition, the National Cancer Institute Canada Clinical Trials Group (NCIC CTG) MA-17 trial demonstrated a survival advantage with extended therapy with letrozole compared with placebo in women with axillary lymph node-positive (but not lymph node-negative), estrogen receptor-positive breast cancer.¹⁴⁹ Tamoxifen and aromatase inhibitors have different side effect profiles. Both contribute to hot flashes, 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 of uterine cancer and deep venous thrombosis.

Two studies have examined initial adjuvant endocrine treatment with either tamoxifen or an aromatase inhibitor. The ATAC Trial demonstrated that anastrozole is superior to tamoxifen or the combination of tamoxifen and anastrozole in the adjuvant endocrine therapy of postmenopausal women with hormone receptor-positive breast cancer.^{150,151} With a median of 68 months follow-up, results in 9366 postmenopausal women with early breast cancer enrolled in the ATAC trial demonstrated fewer recurrences (hazard ratio 0.87; 95% CI 0.78 - 0.97; P = 0.01) with anastrozole compared with tamoxifen. In the subset of women with hormone receptor-positive breast cancer the benefit was greater (hazard ratio 0.83; 95% CI 0.73 - 0.94; P = 0.005).¹⁵¹ No difference in survival has been observed (hazard ratio 0.97; 95% CI, 0.85-1.12; P=0.7). 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. ATAC trial sub-protocols show a lesser effect of anastrozole compared with tamoxifen on endometrial tissue,¹⁵² similar effects of anastrozole and tamoxifen on quality of life, with most patients reporting that their overall quality of life was not significantly impaired,¹⁵³ a greater loss of bone mineral density with anastrozole,¹⁵⁴ a small pharmacokinetic interference of anastrozole in the presence of tamoxifen of unclear significance,¹⁵⁵ and no evidence for an interaction between prior chemotherapy and anastrozole.¹⁵⁶

Breast International Group (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 two years of treatment only.¹⁵⁷ With 8,010 women included in the analysis, disease-free survival was superior in the letrozole treated women (hazard rate 0.81; 95% CI 0.70 – 0.93; log rank P=0.003). No interaction between progesterone receptor expression and benefit was observed. No difference in overall survival has been observed.

Four trials have studied the use of tamoxifen for 2-3 years followed sequentially by a third generation aromatase inhibitor versus continued tamoxifen. The Italian Tamoxifen Anastrozole (ITA) trial randomized 426 postmenopausal women with breast cancer who had completed 2-3 years of tamoxifen to either continue tamoxifen or to switch to anastrozole to complete a total of 5 years of endocrine therapy.¹⁵⁸ The hazard rate for relapse strongly favored sequential treatment with anastrozole (hazard ratio 0.35; 95% CI, 0.18 - 0.68; P=0.001) with a trend towards fewer deaths (P=0.10).¹⁵⁸ The Intergroup Exemestane Study (IES) trial randomized 4742 postmenopausal women with breast cancer who had completed a total of 2-3 years of tamoxifen to either continue tamoxifen or to switch to exemestane to complete a total of 5-years of endocrine therapy.¹⁵⁹ The results at a median of 30.6 months of follow-up demonstrated the superiority of sequential exemestane in disease-free survival (hazard ratio 0.68; 95% CI 0.56 - 0.82; log rank P<0.001) with no difference in overall survival (hazard ratio 0.88; 95% CI 0.67 - 1.16; log rank P=0.37). Similar to the ATAC trial, women with estrogen receptor-positive, progesterone receptor-negative breast cancer appeared to benefit to a greater degree in disease-free survival in comparison to other receptor subsets (hazard ratio in ER-positive, PR-negative 0.58; 95% CI 0.38 - 0.90; P not stated). However, results from the IES trial after 58 months of follow-up indicated that switching to exemestane was associated with statistically significant beneficial effects on both disease-free survival (hazard ratio 0.74; 95% CI 0.64-0.85; P<0.0001) and overall survival (hazard ratio 0.83).¹⁴⁷ A prospectively planned, combined analysis of 3,224 patients enrolled in

the Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial 8 and the Arimidex Nolvadex[®] (ARNO 95) trial has also been reported.¹⁶⁰ Patients in this combined analysis had been randomized following 2 years of tamoxifen to complete 5 years of adjuvant tamoxifen or to 3 years of anastrozole. With 28 months median follow-up available, event-free survival was superior with cross-over to anastrozole (hazard ratio 0.60; 95% CI 0.44-0.81; P=0.0009). No statistically significant difference in survival has been observed. An analysis of the ARNO 95 trial alone after 30.1 months of follow-up demonstrated that switching from tamoxifen to anastrozole was associated with significant increases in both disease-free survival (hazard ratio 0.61; 95% CI 0.40-0.93; P=0.023) and overall survival (hazard ratio 0.48; 95% CI 0.25-0.91; P=0.025).¹⁴⁸

Results of the MA-17 trial in 5187 women who had completed 4.5-6 years of adjuvant tamoxifen demonstrated that extended therapy with letrozole provides benefit in postmenopausal women with hormone receptor-positive, early breast cancer.^{149,161} At a median follow-up of 2.5 years, the results showed fewer recurrences or new contralateral breast cancers with extended letrozole (hazard ratio 0.58; 95% CI 0.45 - 0.76; P<0.001). No difference in overall survival was demonstrated (hazard rate 0.82; 95% CI 0.57-1.19; P=0.3), although there was a survival advantage in the subset of patients with axillary lymph node-positive disease (hazard rate 0.61; 95% CI 0.38-0.98; P=0.04). A formal quality of life analysis demonstrated reasonable preservation of quality of life during extended endocrine therapy, although women may experience ongoing menopausal symptoms and loss of bone mineral density.^{162,163}

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. Thus, it is not known whether initial, sequential, or extended use of adjuvant aromatase inhibitors is the optimal strategy. The optimal duration of aromatase inhibitor treatment is also

not known, nor is the optimal use vis-à-vis chemotherapy established. Further, the long-term (greater than 5 year) safety and efficacy of these agents are still under investigation. The various studies are consistent in demonstrating that the use of a third generation aromatase inhibitor in postmenopausal women with hormone receptor-positive breast cancer lowers the risk of recurrence, including ipsilateral breast tumor recurrence, contralateral breast cancer, and distant metastatic disease, compared to tamoxifen alone when the aromatase inhibitor is used as initial adjuvant therapy, sequential therapy, or extended therapy. Thus, the current version of the guideline recommends that postmenopausal women with early breast cancer receive an aromatase inhibitor as initial adjuvant therapy, sequential with tamoxifen, or as extended therapy in those situations where endocrine therapy is to be utilized. The Panel finds no compelling evidence that there are meaningful efficacy or toxicity differences between anastrozole, letrozole, and exemestane. In postmenopausal women, the use of tamoxifen alone for 5 years is limited to those who decline or who have a contraindication to aromatase inhibitors (see [BINV-I](#)).

It should be re-emphasized that the aromatase inhibitors are associated with the development of benign ovarian pathology and do not adequately suppress ovarian estrogen synthesis in women with functioning ovaries, and premenopausal women should not be given therapy with an aromatase inhibitor outside the confines of a clinical trial. Women who are premenopausal at the time of diagnosis and who become amenorrheic with chemotherapy may have continued estrogen production from the ovaries in the absence of menses. Serial assessment of circulating LH, FSH, and estradiol to assure a true postmenopausal status is mandatory if this subset of women are to be considered for therapy with an aromatase inhibitor^{164,165} (see [BINV-K](#)).

Adjuvant cytotoxic chemotherapy

A number of combination chemotherapy regimens are appropriate to consider when adjuvant cytotoxic chemotherapy is utilized. These regimens include fluorouracil, doxorubicin, and cyclophosphamide (FAC/CAF) or cyclophosphamide, epirubicin, and fluorouracil (CEF); doxorubicin or epirubicin and cyclophosphamide (AC/EC); docetaxel, doxorubicin, and cyclophosphamide (TAC); doxorubicin or epirubicin followed by CMF; cyclophosphamide, methotrexate and fluorouracil (CMF); AC with sequential paclitaxel or docetaxel administered by a variety of schedules; doxorubicin, paclitaxel, cyclophosphamide each as a single agent for four cycles given every 2 weeks with filgrastim support (Dose-dense A – T– C); FEC followed by docetaxel; and docetaxel plus cyclophosphamide (TC). The current version of the guideline does not distinguish appropriate chemotherapy regimens by axillary lymph node status. Recent studies document substantial improvement in outcome with the incorporation of trastuzumab in the adjuvant treatment of HER2-positive breast cancer (see [Adjuvant trastuzumab therapy](#)). The guideline includes specific representative doses and schedules for the recommended adjuvant chemotherapy regimens (see [BINV-J](#)).

Studies of CMF chemotherapy versus no chemotherapy have shown disease-free and overall survival advantages with CMF chemotherapy.¹⁶⁶ Studies using CAF/FAC (cyclophosphamide, doxorubicin, 5-fluorouracil) chemotherapy have shown that the use of full-dose chemotherapy regimens is important.¹⁶⁷ In the Early Breast Cancer Trialists' overview of polychemotherapy, comparison of anthracycline-containing regimens with CMF showed a 12% further reduction in the annual odds of recurrence ($P = 0.006$) and an 11% further reduction in the annual odds of death ($P = 0.02$) with anthracycline-containing regimens.¹⁶⁶ 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 Early Breast Cancer Trialists' 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.^{56,58,141,168,169} The retrospective finding across several clinical trials that anthracycline-based chemotherapy may be more efficacious in patients whose tumors are HER2-positive,^{55,56,58,59} 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 (see [BINV-J](#)).

Doxorubicin and cyclophosphamide chemotherapy for 4 cycles has been studied in randomized trials, resulting in relapse-free and overall survival equivalent to CMF chemotherapy.¹⁷⁰⁻¹⁷² No benefit from dose escalation of either doxorubicin or cyclophosphamide was shown.^{173,174} A single study in women with 4 or more involved axillary lymph nodes compared the use of sequential versus alternating doxorubicin and CMF chemotherapy and found the sequential regimen superior.^{175,176}

The results of two randomized trials comparing AC chemotherapy with or without sequential paclitaxel chemotherapy in women with axillary node-positive breast cancer suggest improved disease-free rates and results from one of the trials showed an improvement in overall survival with the addition of paclitaxel.^{174,177} On retrospective analysis, the apparent advantage of the paclitaxel-containing regimen appears greater in women with estrogen receptor-negative breast cancers.

A randomized trial evaluated the use of concurrent versus sequential chemotherapy (doxorubicin followed by paclitaxel followed by cyclophosphamide versus doxorubicin plus cyclophosphamide followed by paclitaxel) given either every two weeks with filgrastim support versus every three weeks. The results show no significant difference

between the two chemotherapy regimens, but demonstrate a 26% reduction in hazard of recurrence (P=0.01) and a 31% reduction in the hazard of death (P=0.013) for the dose-dense regimens.¹⁷⁸

Two randomized prospective trials of CEF chemotherapy in axillary lymph node-positive breast cancer are available. In one trial, premenopausal women with node-positive breast cancer were randomized to receive classic CMF therapy versus CEF chemotherapy using high-dose epirubicin. Both ten-year relapse-free survival (52% vs. 45%; P = 0.007) and overall survival (62% vs. 58%; P =0.085) favored the CEF arm of the trial.¹⁷⁹ The second trial compared CEF given all intravenously every 3 weeks at 2 dose levels of epirubicin (50 mg/m² vs. 100 mg/m²) in premenopausal and postmenopausal women with node-positive breast cancer. Five-year disease-free survival (55% vs. 66%; P =0.03) and overall survival (65% vs. 76%; P =0.007) both favored the epirubicin 100 mg/m² arm.¹⁸⁰ Another trial compared 2 dose levels of EC chemotherapy with CMF chemotherapy in women with node-positive breast cancer.¹⁸¹ This study showed that higher dose EC chemotherapy was equivalent to CMF chemotherapy and superior to moderate dose EC in event-free survival and overall survival. An additional randomized trial in women with axillary lymph node-positive breast cancer compared six cycles of FEC with three cycles of FEC followed by three cycles of docetaxel.¹⁸² Five-year disease-free survival (78.3% versus 73.2%, P=0.014) and overall survival (90.7% versus 86.7%, P=0.017) were superior with sequential FEC followed by docetaxel.

Final results from a randomized trial comparing docetaxel, doxorubicin, and cyclophosphamide (TAC) versus FAC chemotherapy in axillary lymph node-positive breast cancer demonstrated that TAC is superior to FAC.¹⁸³ Estimated 5-year disease-free survival with TAC was 75% and FAC 68% (hazard ratio 0.72; 95% CI 0.59-0.88; P=0.001) and survival 87% with TAC and 81% with FAC (hazard ratio 0.70; 95% CI

0.53-0.91; P=0.008). Disease-free survival favored TAC in both estrogen receptor-positive and estrogen receptor-negative tumors.

The Eastern Cooperative Oncology Group E1199 study was a four arm trial that randomized 4,988 women to receive AC chemotherapy followed by either paclitaxel or docetaxel given by either an every three weekly schedule or a weekly schedule. With a median 46.5 months follow-up, no statistically significant differences in disease-free or overall survival have been observed when comparing the two taxanes or the two schedules of administration.¹⁸⁴

Combination docetaxel and cyclophosphamide (TC) was compared with AC chemotherapy in a trial that randomized 1016 women with stage I – III breast cancer.¹⁸⁵ Five-year disease-free survival was superior with TC compared with AC (86% versus 80%, P=0.015), but with no difference in overall survival (90% versus 87%, P=0.13).

Several retrospective studies have evaluated the potential interaction of chemotherapy benefit and estrogen receptor status.^{2,135} These studies assessed the effect of chemotherapy on the risk of breast cancer recurrence in patients with estrogen receptor-positive tumors receiving adjuvant endocrine therapy when compared with patients with estrogen receptor-negative tumor status not undergoing adjuvant endocrine therapy. These analyses suggest that the benefits of chemotherapy are significantly greater in patients with estrogen receptor-negative disease. For example, the results of Berry et al. demonstrated that 22.8% more patients with estrogen receptor-negative tumors survived without disease for 5 years if they received chemotherapy; this benefit was only 7% for patients with estrogen receptor-positive tumors receiving chemotherapy.¹³⁵ The guideline therefore includes a recommendation for endocrine therapy and consideration of chemotherapy for patients with node-negative disease and tumors characterized as estrogen receptor-positive which are greater than 1 cm and HER2-negative (see [BINV-6](#)).

Adjuvant trastuzumab therapy

Trastuzumab is a humanized, monoclonal antibody with specificity for the extracellular domain of the human epidermal growth factor receptor 2 (HER2/neu; HER2).¹⁸⁶ Results of five randomized trials testing trastuzumab as adjuvant therapy were recently reported.⁶¹⁻⁶⁴ In NSABP B-31 patients with HER2-positive, node-positive breast cancer were randomly assigned to 4 cycles of AC every three weeks followed by paclitaxel 4 cycles every three weeks or the same regimen with 52 weeks of trastuzumab commencing with the paclitaxel. In the North Central Cancer Treatment Group (NCCTG) N9831 trial, patients with HER2-positive breast cancer that was node-positive, or, if 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 were jointly analyzed with the merged control arms for both trials compared with the merged arms using trastuzumab begun concurrently with the paclitaxel.⁶¹ There were 3,351 patients included in the joint analysis performed at 2 years median follow-up. A 52% reduction in the risk of recurrence (hazard ratio 0.48; 95% CI 0.39-0.59; P<0.0001) and a 33% reduction in the risk of death (hazard ratio 0.67; 95% CI 0.48-0.93; log-rank P = 0.015) were documented. Similar significant effects on disease-free survival 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.^{61,187,188}

A third trial (HERA) (N=5081) tested trastuzumab for one or for two 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 ≥ 1 cm.⁶² At a median follow-up of one year, comparing one year versus not of trastuzumab,

trastuzumab resulted in a 46% reduction in the risk of recurrence compared to no trastuzumab (hazard ratio 0.54; 95% CI 0.43-0.67; P < 0.0001), no difference in overall survival, and acceptable cardiac toxicity. The two year data indicate that 1-year of trastuzumab therapy is associated with an overall survival benefit when compared with observation (hazard ratio for risk of death=0.66; 95% CI, 0.47-0.91; P=0.0115).¹⁸⁹

The Breast Cancer International Research Group (BCIRG) 006 study randomized 3,222 women with HER2-positive, node-positive or high-risk node negative breast cancer to AC followed by docetaxel, AC followed by docetaxel plus trastuzumab for one year, or carboplatin, docetaxel plus trastuzumab for one year.⁶³ At 36 months of follow-up, patients receiving AC followed by docetaxel with trastuzumab (AC→TH) had a hazard ratio for disease-free recurrence of 0.61 (95% CI, 0.48-0.76; P<0.0001) when compared with the group of patients in the control arm receiving the same chemotherapy regimen without trastuzumab (AC→T). The hazard ratio for disease-free survival was 0.67 (95% CI, 0.54-0.83; P=0.0003) when patients in the carboplatin/docetaxel/ trastuzumab (TCH) containing arm were compared to patients in the control arm. No statistically significant difference in the hazard ratio for disease-free survival was observed between the two trastuzumab-containing arms. An overall survival advantage was reported for patients in both trastuzumab-containing arms relative to the control arm (hazard ratio for AC-TH vs AC-T=0.59; 95% CI, 0.42-0.85; P=0.004; hazard ratio for TCH vs AC-T=0.66; 95% CI, 0.47-0.93; P=0.017). Cardiac toxicity was significantly lower in the TCH arm (8.6% patients with >10% relative decline in left ventricular ejection fraction) compared with the AC-TH arm (18%; P<0.0001); differences in cardiac toxicity between the TCH arm and the AC-T control arm (10%) were not significant.

A fifth trial (FinHer) randomized 1010 women to either 9 weeks of vinorelbine followed by 3 cycles of FEC chemotherapy versus docetaxel for 3 cycles followed by 3 cycles of FEC chemotherapy.⁶⁴ Patients (N=232) with HER2-positive cancers that were either node-positive or node-negative and ≥ 2 cm and progesterone receptor-negative were further randomized to receive or not 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 (hazard ratio 0.42; 95% CI 0.21-0.83; P=0.01). No statistically significant differences in overall survival (hazard ratio 0.41; 95% CI 0.16 – 1.08; P=0.07) or cardiac toxicity were observed with the addition of trastuzumab.

All of the adjuvant trials of trastuzumab demonstrate clinically significant improvements in disease-free survival, and the combined analysis from the NSABP B31 and NCCTG N9831 trials, and the HERA trial, significant improvement in overall survival 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 (category 1) (see [BINV-J](#)). The benefits of trastuzumab are independent of estrogen receptor status.⁶¹ The Panel recommends AC followed by paclitaxel with trastuzumab for 1 year commencing with the first dose of paclitaxel as the preferred trastuzumab-containing adjuvant regimen since the efficacy of this regimen has been demonstrated in two randomized clinical trials, and it has been associated with significant improvements in overall survival. The TCH regimen is an acceptable alternative, especially in those with risk factors for cardiac toxicity. Since patients with borderline FISH (Pathvysion®) scores of greater than 2.0 to 2.2 HER2 genes/chromosome 17/cell in early-stage breast cancer were eligible for the adjuvant trials, the Panel cannot recommend exclusion of these patients from adjuvant treatment with trastuzumab if HER2 tumor status remains equivocal following retesting

by the same or a complementary method (see [BINV-A](#)). At present, the panel does not recommend adjuvant trastuzumab in women with small (<1 cm), node negative tumors as patients with these characteristics were not included in the available randomized trials, their risk overall for recurrence is relatively low, and the occurrence of cardiac toxicity diminishes the overall benefit. In the adjuvant trastuzumab trials, the rates of grade III/IV congestive heart failure (CHF) or cardiac-related death for patients receiving treatment regimens containing trastuzumab ranged from 0% (FinHer trial) to 4.1% (NSABP B-31 trial) overall.^{61-64,187,188} The frequency of cardiac dysfunction appears to be related to both age and baseline left ventricular ejection fraction. 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.^{190,191}

Adjuvant therapy of favorable histology tumors

The Guidelines provide systemic treatment recommendations for the favorable-histology invasive breast cancers, such as tubular and colloid cancers, based on tumor size and axillary lymph node status (see [BINV-9](#)). If used, the treatment options for endocrine therapy, chemotherapy, and sequencing of treatment with other modalities are similar to those of the usual histology breast cancers. The vast majority of tubular breast cancers are both estrogen receptor-positive and HER2-negative. Thus, the pathology evaluation and accuracy of the estrogen receptor and/or HER2 determination should be questioned if a tubular breast cancer is found to be estrogen receptor-negative and/or HER2-positive. The Panel acknowledges that prospective data regarding systemic adjuvant therapy of favorable histology tumors is lacking. Medullary carcinoma is an uncommon variant of infiltrating ductal carcinoma characterized by high nuclear grade, lymphocytic

infiltration, a pushing tumor border, and the presence of a syncytial growth pattern. It was previously thought that medullary carcinoma has a lower potential for metastases and a better prognosis than typical infiltrating ductal carcinoma. However, the best available evidence suggests that the risk of metastases equals that of other high-grade carcinomas, even for cases that meet all the pathologic criteria for typical medullary carcinoma. Furthermore, typical medullary carcinoma is uncommon, and there is marked interobserver variation in diagnosing this entity. Many cases classified as medullary carcinoma do not have all the pathologic features on subsequent pathologic review. Given these facts, there is concern that patients may be harmed if a high-grade infiltrating ductal carcinoma is misclassified as typical medullary carcinoma and this classification used as the basis for withholding otherwise indicated adjuvant systemic therapy. Therefore, the NCCN Panel believes that including medullary carcinoma with other special histology cancers that carry a very favorable prognosis and often do not require systemic therapy is not appropriate. The Panel recommends that cases classified as medullary carcinoma be treated as other infiltrating ductal carcinomas based on tumor size, grade, and lymph node status.

Stage III Invasive Breast Cancer

The staging evaluation for patients with stage III invasive breast cancer is similar to the one for patients with stage I or stage II disease. The workup includes history and physical exam, a complete blood cell count, platelet count, a bone scan (category 2B), chest imaging, pathology review, pre-chemotherapy determination of tumor ER/PR receptor status and HER2 status, diagnostic bilateral mammogram and breast ultrasound as clinically warranted, and an abdominal CT, ultrasound, or MRI scan, even in the absence of symptoms, liver enzyme abnormalities, or abnormal alkaline phosphatase.

Operable locally advanced breast cancer (clinical stage T3N1M0)

Locally advanced breast cancer describes a subset of invasive breast cancer where the initial clinical and radiographic evaluation documents advanced disease confined to the breast and regional lymph nodes. The AJCC clinical staging system used in these Guidelines and for the determination of operability is recommended and locally advanced disease is represented by the stage III category. Patients with stage III disease may be further divided into those where an initial surgical approach is unlikely to be successful in removal of all disease or to provide long-term local control and those with disease where a reasonable initial surgical approach is likely to achieve pathologically negative margins and provide long-term local control. Thus, stage IIIA patients are divided into those who have clinical T3N1M0 disease versus those who have clinical TanyN2M0 disease, based on evaluation by a multidisciplinary team. For patients with operable locally advanced disease, generally patients with clinical T3N1M0 disease, treatment is as outlined in [BINV-1](#) through [BINV-6](#).

Postsurgical systemic adjuvant therapy for patients with stage IIIA breast cancer who do not receive neoadjuvant chemotherapy is similar to that for patients with stage II disease.

Inoperable locally advanced breast cancer (clinical stage IIIA [except for T3N1M0], clinical stage IIIB, or clinical stage IIIC)

The workup of locally advanced breast cancer is described on [BINV-13](#). For patients with inoperable non-inflammatory locally advanced disease at presentation, the initial use of anthracycline-based preoperative chemotherapy with or without a taxane is standard therapy.¹⁹² Local therapy following a clinical response to preoperative chemotherapy usually consists of (1) total mastectomy with level I/II axillary lymph node dissection, with or without delayed breast reconstruction, or (2) lumpectomy and level I/II axillary dissection. Both local treatment groups are considered to have sufficient risk of local recurrence to

warrant the use of chest wall (or breast) and supraclavicular node irradiation. If internal mammary lymph nodes are involved, they should also be irradiated. In the absence of detected internal mammary node involvement, consideration may be given to including the internal mammary lymph nodes in the radiation field (category 3) (see [BINV-14](#)). Adjuvant therapy may involve completion of planned chemotherapy regimen course if not completely preoperatively, followed by endocrine therapy in patients with hormone receptor-positive disease. (see [BINV-14](#)). It was the consensus of the Panel that there is no role for non-endocrine-, non-trastuzumab-containing regimens following completion of the planned course of chemotherapy.

Patients with an inoperable stage III tumor with disease progression during preoperative chemotherapy should be considered for palliative breast irradiation in an attempt to enhance local control. In all subsets of patients, further systemic adjuvant chemotherapy after local therapy is felt to be standard. Tamoxifen (or an aromatase inhibitor if postmenopausal) should be added for those with hormone receptor-positive tumors. Post-treatment follow-up for women with stage III disease is the same as for women with earlier-stage, invasive breast cancer. Treatment recommendations for inflammatory locally advanced breast cancer are described on [IBC-1](#).

Post-therapy Surveillance and Follow-up

Post-therapy follow-up is optimally performed by members of the treatment team and includes the performance of regular physical examinations and mammography. In patients undergoing breast-conserving therapy, the first follow-up mammogram should be performed approximately 6 months after the completion of breast-conserving radiation therapy. The routine performance of alkaline phosphatase and liver function tests are not included in the Guidelines.¹⁹³⁻¹⁹⁵ 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, Positron Emission Tomography (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.^{40,196}

The use of dedicated breast MRI may be considered as an option for post-therapy surveillance and follow-up in women at high risk of bilateral disease, such as carriers of *BRCA 1/2* mutations. Rates of contralateral breast cancer following either breast-conserving therapy or mastectomy have been reported to be increased in women with *BRCA 1/2* mutations when compared with patients with sporadic breast cancer.¹⁹⁷⁻¹⁹⁹ (see [NCCN Genetic/Familial High-Risk Assessment: Breast](#) and [Ovarian Guidelines](#); [NCCN Breast Cancer Screening and Diagnosis Guidelines](#)).

The Panel recommends that women with intact uteri who are taking 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 women²⁰⁰ (see [BINV-15](#)). The performance of routine endometrial biopsy or ultrasonography in the asymptomatic woman is not recommended. Neither test has demonstrated utility as a screening test in any population of women. The vast majority of women with tamoxifen-associated uterine carcinoma have early vaginal spotting.

Symptom management for women on adjuvant endocrine therapies often requires treatment of hot flashes and the treatment of concurrent depression. Venlafaxine has specifically been studied and is an effective intervention in decreasing hot flashes.²⁰¹ Recent evidence has suggested that concomitant use of tamoxifen with certain selective serotonin reuptake inhibitors (SSRIs) (eg, paroxetine and fluoxetine) may decrease plasma levels of endoxifen, an active metabolite of tamoxifen.^{202,203} These SSRIs may interfere with the enzymatic conversion of tamoxifen to endoxifen by inhibiting a particular isoform of

cytochrome P-450 enzyme (CYP2D6) involved in the metabolism of tamoxifen. However, the SSRIs citalopram and venlafaxine appear to have only minimal effects on tamoxifen metabolism.

Premenopausal women who experience early ovarian failure secondary to adjuvant chemotherapy and postmenopausal women who are treated with an aromatase inhibitor are at increased risk for the development of osteopenia or osteoporosis with an associated increased risk of bone fracture. The guideline thus recommends monitoring of bone health during surveillance in these high risk women²⁰⁴ (see [BINV-15](#)).

A special situation arises in women who are premenopausal at diagnosis, who develop amenorrhea during or following treatment, and for whom the use of an aromatase inhibitor is considered. The continuation or return of ovarian function following chemotherapy with or without amenorrhea has been documented.^{164,165} If an aromatase inhibitor is considered in women with amenorrhea following treatment, baseline levels of estradiol and gonadotropin followed by serial monitoring of these hormones should be performed if endocrine therapy with an aromatase inhibitor is initiated¹⁶⁵ (see [BINV-K](#)). Bilateral oophorectomy assures postmenopausal status in young women with therapy-induced amenorrhea and may be considered prior to initiating therapy with an aromatase inhibitor in a young woman.

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.²⁰⁵ 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 (see [BINV-15](#)).

Stage IV Metastatic or Recurrent Breast Cancer

The staging evaluation of women who present with metastatic or recurrent breast cancer includes history and physical exam, the performance of a CBC, platelet count, liver function tests, chest imaging, bone scan, radiographs of any long or weight-bearing bones that are painful or appear abnormal on bone scan, consideration of CT or MRI scan of the abdomen, biopsy documentation of first recurrence if possible, and determination of hormone receptor status (estrogen receptor and progesterone receptor) and HER2 status if not previously performed.

Local disease only

Patients with local recurrence only are divided into those who had been treated initially by mastectomy and those who had received breast-conserving therapy. Mastectomy-treated patients should undergo surgical resection of the local recurrence (if it can be accomplished without heroic surgery) and involved-field radiation therapy (if the chest wall was not previously treated or if additional radiotherapy may be safely administered). The use of surgical resection in this setting implies the use of limited excision of disease with the goal of obtaining clear margins of resection. Unresectable chest wall recurrent disease should be treated with radiation therapy if no prior radiation has been given. Women whose disease recurs locally after initial breast-conserving therapy should undergo a total mastectomy. After local treatment, women with local recurrences should be considered for systemic chemotherapy or endocrine therapy.

The current Guidelines add, in the localized clinical scenarios of the treatment of recurrence/stage IV disease guideline (see [BINV-16](#)), the consideration of the addition of hyperthermia to irradiation for localized

recurrences/metastasis (category 3). There have been several prospective randomized trials comparing radiation to radiation plus hyperthermia in the treatment of locally advanced/recurrent cancers, primarily breast cancer chest wall recurrences.^{206,207} While there is heterogeneity among the study results, a recent series with strict quality assurance demonstrated a statistically significant increase in local tumor response and greater duration of local control with the addition of hyperthermia to radiation compared to radiation alone.²⁰⁷ No differences in overall survival have been demonstrated. Delivery of local hyperthermia is technically demanding and requires specialized expertise and equipment (eg, the monitoring of temperatures and management of possible tissue burns). The Panel thus recommends that the use of hyperthermia be limited to treatment centers with appropriate training, expertise, and equipment. The addition of hyperthermia generated substantial discussion and controversy among the Panel and is a category 3 recommendation.

Systemic disease

The treatment of systemic recurrence of breast cancer prolongs survival and enhances quality of life but is not curative. Therefore, treatments associated with minimal toxicity are preferred. Thus, the use of the minimally toxic endocrine therapies is preferred to the use of cytotoxic therapy whenever reasonable.

Guideline stratification for therapy in systemic disease

Patients with recurrent or metastatic breast cancer are initially stratified according to whether or not bone metastasis is present (see section on Bisphosphonates, below). These 2 patient subsets are then stratified further by tumor hormone receptor and HER2 status (see [BINV-16](#)).

Bisphosphonates

Bisphosphonate treatment is of value in patients with metastatic breast cancer in bone.^{204,208} Women with bone metastasis, especially if lytic, should be given a bisphosphonate (eg, pamidronate or zoledronic acid)

in combination with calcium citrate and vitamin D if expected survival is 3 months or longer and creatinine levels are below 3.0 mg/dL (category 1).^{204,209-214} Bisphosphonates are given in addition to chemotherapy or endocrine therapy. Zoledronic acid may be superior to pamidronate in lytic breast metastasis.^{215,216}

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 includes the use of zoledronic acid and pamidronate in the United States and ibandronate and clodronate in European countries.^{210,211,216-221} In metastatic bone disease, bisphosphonate treatment is associated with fewer skeletal-related events, 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 overall survival has been observed in patients treated with bisphosphonates. The data indicate that zoledronic acid and pamidronate may be given on a 3-5 weekly schedule in conjunction with antineoplastic therapy (ie, endocrine therapy, chemotherapy or biologic therapy). The use of bisphosphonates should be accompanied by calcium and vitamin D supplementation with daily doses of calcium of 1200 to 1500mg and Vitamin D₃ 400 – 800 IU. Recommended agents for use in the United States are pamidronate 90mg intravenously over 2 hours or zoledronic acid 4mg 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.²²¹⁻²²³ 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.

Osteonecrosis of the jaw, a recently reported complication of bisphosphonate treatment, has been described. In a review of more

than 16,000 cancer patients, an increased risk of jaw or facial bone surgery along with an increased risk of being diagnosed with inflammatory conditions or osteomyelitis of the jaw with the use of intravenous bisphosphonates was documented. An absolute risk of 5.48 events per 100 patients treated was seen, with an increase in risk associated with an increase in cumulative dose of drug.²²⁴

A dental examination with preventive dentistry intervention is recommended prior to treatment with intravenous bisphosphonates and dental procedures during treatment with intravenous bisphosphonates should be avoided if at all possible. Additional risk factors for the development of osteonecrosis of the jaw include administration of chemotherapy or corticosteroids and poor oral hygiene with periodontal disease and dental abscess.²²⁵

Confirmation of metastatic disease by imaging including x-ray, CT or MRI; and initial evaluation of serum calcium, creatinine, phosphorous and magnesium levels should be undertaken prior to the initiation of intravenous bisphosphonate treatment in patients with metastatic disease. Frequent measurement of calcium, phosphorous and magnesium may be prudent since hypophosphotemia and hypocalcemia have been reported.

Endocrine therapy

Women with recurrent or metastatic disease characterized by tumors that are estrogen receptor- and/or progesterone receptor-positive are appropriate candidates for initial endocrine therapy (see [BINV-17](#)). This includes women with hormone receptor-negative disease or hormone receptor-positive disease that was refractory to prior endocrine therapy if disease is characterized as bone or soft tissue only or asymptomatic visceral (see [BINV-18](#); [BINV-19](#))

In postmenopausal women with previous antiestrogen therapy and who are within one year of antiestrogen exposure, recent evidence

supports the use of a selective aromatase inhibitor as the preferred first-line therapy for their recurrent disease.^{226,227} For postmenopausal women who are antiestrogen naive or who are more than 1 year from previous antiestrogen therapy, the aromatase inhibitors appear to have superior outcome compared with tamoxifen, although the differences are modest.²²⁸⁻²³² Therefore, either tamoxifen or an aromatase inhibitor is an appropriate option in this setting.

In premenopausal women with previous antiestrogen therapy who are within 1 year of antiestrogen exposure, the preferred second-line therapy is either surgical or radiotherapeutic oophorectomy or leuteinizing hormone-releasing hormone (LHRH) agonists with endocrine therapy as for postmenopausal women. In premenopausal women without previous exposure to an antiestrogen, initial treatment with an antiestrogen with or without a LHRH agonist or ovarian ablation is preferred²³³ (see [BINV-17](#)).

Many premenopausal and postmenopausal women with hormone-responsive breast cancer benefit from sequential use of endocrine therapies at the time of disease progression. Therefore, women whose breast cancers respond to an endocrine maneuver with either shrinkage of the tumor or long-term disease stabilization (clinical benefit) should receive additional endocrine therapy at the time of disease progression (see [BINV-20](#)). Additional endocrine therapies for second-line and subsequent therapy are listed in the endocrine algorithm (see [BINV-L](#)). The antiestrogen fulvestrant recently became available for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer previously treated with an antiestrogen. Fulvestrant lacks the estrogen agonistic activity of tamoxifen and is well tolerated as a single monthly gluteal intramuscular injection. Fulvestrant appears to be at least as effective as anastrozole in patients whose disease progressed on previous endocrine therapy,^{234,235} and a recent reanalysis of these studies

suggests a longer duration of response favoring fulvestrant.²³⁶

Endocrine therapies in postmenopausal women include selective, nonsteroidal aromatase inhibitors (anastrozole and letrozole); steroidal aromatase inhibitors (exemestane); pure anti-estrogens (fulvestrant); progestin (megestrol acetate); androgens (flouxymesterone); and high-dose estrogen (ethinyl estradiol). In premenopausal women, therapies include LHRH agonists (goserelin and luprolide); surgical or radiotherapeutic oophorectomy; progestin (megestrol acetate); androgens (flouxymesterone); and high-dose estrogen (ethinyl estradiol). After second-line endocrine therapy, little high-level evidence exists to assist in selecting the optimal sequence of endocrine therapy.

Cytotoxic chemotherapy

Women with hormone receptor-negative tumors not localized to the bone or soft tissue only or that are associated with symptomatic visceral metastasis, or that have hormone receptor-positive tumors that are refractory to endocrine therapy, should receive chemotherapy (see [BINV-18](#); [BINV-19](#); [BINV-20](#)). A variety of chemotherapy regimens are felt to be appropriate, as outlined in the treatment algorithm (see [BINV-M](#)). 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.²³⁷⁻²⁴⁰ Thus, the Panel finds little compelling evidence that combination chemotherapy is superior to sequential single agents. Standard clinical practice is to continue first-line chemotherapy until progression. Adverse effects may require dose reduction and cessation of chemotherapy prior to disease progression. Limited information suggests that progression-free survival can be prolonged with the use of continuous chemotherapy versus shorter course chemotherapy.^{241,242} Due to the lack of overall survival differences, the use of prolonged versus shorter chemotherapy needs to be weighted against the detrimental effects of continuous chemotherapy on overall quality of life.

Preferred first-line chemotherapies thus include sequential single agents or combination chemotherapy. Among preferred first-line single agents, the Panel includes doxorubicin, epirubicin, pegylated liposomal doxorubicin, paclitaxel, docetaxel, capecitabine, vinorelbine and gemcitabine. Among preferred first-line combination regimens, the Panel includes cyclophosphamide, doxorubicin, and fluorouracil (FAC/CAF); fluorouracil, epirubicin, cyclophosphamide (FEC); doxorubicin, cyclophosphamide (AC); epirubicin, cyclophosphamide (EC); doxorubicin in combination with either docetaxel or paclitaxel (AT); cyclophosphamide, methotrexate, fluorouracil (CMF); docetaxel, capecitabine; gemcitabine, paclitaxel. Other active agents include cisplatin, carboplatin, etoposide orally, vinblastine, and fluorouracil by continuous infusion. As with endocrine therapy, sequential responses are often observed with chemotherapy, supporting the use of sequential single agents and combination chemotherapy regimens. The current guideline includes doses and schedules of representative chemotherapy single agents and combination regimens for metastatic breast cancer (see [BINV-M](#)).

A recent trial randomized 715 women with recurrent or metastatic breast cancer to first-line chemotherapy with paclitaxel with or without bevacizumab, a humanized monoclonal antibody against the vascular endothelial growth factor (VEGF).²⁴³ This trial documented superior progression-free survival (11.3 months vs. 6.0 months; hazard ratio 0.60; log rank test $P < 0.0001$) favoring bevacizumab plus paclitaxel compared with paclitaxel alone. No significant difference in overall survival was observed when the 2 groups were compared.

Ixabepilone, an epothilone B analogue, is a new agent and has been added to the chemotherapy guideline for treatment of recurrent or metastatic breast cancer as an active single agent (category 2A) or in combination with capecitabine (category 2B), both in the “other active options” grouping (see [BINV-M](#)). Use of ixabepilone as monotherapy

has been evaluated in several phase II trials of women with metastatic breast cancer: in a first-line setting in patients previously treated with anthracycline chemotherapy²⁴⁴; in patients with taxane-resistant metastatic breast cancer²⁴⁵; and in patients with advanced breast cancer resistant to an anthracycline, a taxane, and capecitabine.²⁴⁶ In the phase II trials, objective response rate, median duration of response, and median overall survival duration was 41.5% (95% CI, 29.4% to 54.4%), 8.2 months (95% CI, 5.7 to 10.2 months), and 22.0 months (95% CI, 15.6 to 27.0 months) in the first line setting,²⁴⁴ 12% (95% CI, 4.7% to 26.5%), 10.4 months, and 7.9 months for the taxane-resistant patients,²⁴⁵ and 11.5% (95% CI, 6.3% to 18.9%), 5.7 months, and 8.6 months for the patients previously treated with an anthracycline, a taxane, and capecitabine.²⁴⁶ In the study of Perez et al., grade 3/4 treatment-related toxicities included peripheral sensory neuropathy (14%) and neutropenia (54%).²⁴⁶ In addition, a phase III study compared ixabepilone plus capecitabine to capecitabine alone in women with metastatic breast cancer which progressed after anthracycline and taxane treatment.²⁴⁷ The primary endpoint, progression-free survival (PFS), was 5.8 months vs. 4.2 months (hazard ratio=0.75, 95% CI, 0.64 to 0.88; P=0.0003), and objective response rate was 35% vs. 14% (P<0.0001) in the 2 arms of the trial. No data on overall survival were reported, although the incidence of treatment-related death resulting from neutropenia was substantially higher in the combination arm.

Failure to achieve a tumor response to 3 sequential chemotherapy regimens or an Eastern Cooperative Oncology Group (ECOG) performance status of 3 or greater is an indication for supportive therapy only (category 2B). In this context, failure to respond to a chemotherapy regimen means the absence of even a marginal response to the use of a given chemotherapy regimen. Response to a chemotherapy regimen followed by progression of disease is not considered a failure to experience response.

Patients with metastatic breast cancer frequently develop a number of anatomically localized problems that may benefit from local irradiation, surgery, or regional chemotherapy (eg, intrathecal methotrexate for leptomeningeal carcinomatosis).

HER2-targeted therapy

Patients with tumors that are HER2-positive may derive benefit from treatment with trastuzumab as a single agent or in combination with selected chemotherapeutic agents, or the combination of capecitabine plus lapatinib for those refractory to therapy with an anthracycline, a taxane, and trastuzumab ([BINV-19](#)). The Panel recommends selecting patients for HER2-targeted therapy if their tumors are either positive for HER2 by FISH or 3+ by IHC. HER2 testing recommendations are described in the guideline (see [BINV-A](#)). Patients with tumors IHC 0 or 1+ for HER2 or FISH not amplified have very low rates of HER2-targeted response, and therapy with trastuzumab or lapatinib is not warranted. Adequate standardization and validation of HER2 assays by FISH and IHC used in clinical practice is a concern, and data suggest that false-positive determinations are common.^{47,49,52,53,248}

Recommendations regarding HER2 testing have been published.^{52,53}

In patients with metastatic or recurrent breast cancer with HER2-positive tumors, trastuzumab as a single agent^{65,67} or in combination with selected chemotherapeutics⁶⁶ may be considered. A single randomized trial demonstrates benefit from adding trastuzumab to paclitaxel chemotherapy in patients with IHC 2+ or 3+ for HER2.⁶⁶ Early nonrandomized data are available supporting the addition of agents such as docetaxel, vinorelbine, and platinum compounds in combination with trastuzumab. The Panel believes the 27% frequency of significant cardiac dysfunction in patients treated with the combination of trastuzumab and doxorubicin/cyclophosphamide chemotherapy in the metastatic setting is too high for use of this combination outside the confines of a prospective clinical trial.^{66,249} The

regimen of capecitabine plus lapatinib is an option for patients with HER2-positive disease. A phase III study compared lapatinib plus capecitabine with capecitabine alone in women with advanced or metastatic breast cancer refractory to trastuzumab in the metastatic setting and with prior treatment with an anthracycline and a taxane in either the metastatic or adjuvant setting.²⁵⁰ 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; hazard ratio=0.49, 95% CI, 0.34-0.71; P<0.001). The current guideline includes doses and schedules of representative chemotherapy single agents and regimens for use in combination with either trastuzumab or lapatinib for metastatic breast cancer (see [BINV-M](#)).

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 nipple areolar complex.²⁵¹ 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 80% of cases.^{252,253} The associated cancers are not necessarily located adjacent to the nipple areolar complex (NAC) and may be either DCIS or invasive cancer.

Women with clinical signs that raise suspicion for Paget's disease require a complete history and physical examination and diagnostic breast imaging (see [PAGET-1](#)). If no other breast lesion is identified, breast MRI may be considered before or after biopsy of the nipple areolar complex.²⁵⁴ Any breast lesion identified by imaging or examination should be evaluated according to the [NCCN Breast Screening and Diagnostic Guidelines](#). The skin of the nipple areolar

complex should undergo surgical biopsy including the full thickness of the epidermis including at least a portion of any clinically involved nipple areolar complex.

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.²⁵² Recent 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 nipple areolar complex followed by whole breast radiotherapy.²⁵⁵⁻²⁵⁹ The risk of ipsilateral breast recurrence after breast-conserving NAC resection and radiotherapy with or without an associated cancer is similar to that with breast-conserving surgery and radiotherapy 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 nipple areolar complex 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 nipple areolar complex and the peripheral cancer in continuity in a single surgical specimen or through a single incision. Mastectomy also remains an appropriate treatment option (see [PAGET-2](#)).

Axillary lymph node staging is not necessary when breast-conserving therapy is used to treat Paget's disease with underlying DCIS in the absence of 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 guideline (see [BINV-C](#)). 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 because the final pathology may reveal an invasive cancer in the mastectomy specimen and the mastectomy precludes subsequent sentinel node biopsy. Two recently reported 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.^{260,261} 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 [BINV-2](#). A radiation boost should be considered to the site of the resected nipple areolar complex and any associated resected cancer site, if applicable.

Women with an associated invasive cancer have substantial risk of developing metastases. Adjuvant systemic therapy should be administered according to the stage of the cancer. Women with Paget's disease treated with breast conservation and without an associated cancer or those with associated DCIS should consider tamoxifen for risk reduction. Those with an associated invasive cancer should receive adjuvant systemic therapy based on the stage and hormone receptor status as outlined in [BINV-4](#) to [BINV-9](#).

Phyllodes tumors of the breast (also known as phylloides tumors, cystosarcoma phyllodes)

Phyllodes tumors of the breast are rare tumors comprised of both stromal and epithelial elements. 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.²⁶² 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 in the 40's.²⁶³ Phyllodes tumors often enlarge rapidly and are usually painless. Phyllodes tumors often appear on ultrasound and mammography as fibroadenomas, and fine needle aspiration cytology and even core needle biopsy are inadequate to reliably distinguish phyllodes tumors from fibroadenoma.²⁶³ 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 the Li-Fraumeni Syndrome (germ line p53 mutation, see [NCCN Genetic/Familial High Risk Assessment Guidelines](#)) have an increased risk of phyllodes tumors.²⁶⁴ 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 mastectomy²⁶⁵ (see [PHYLL-1](#)). Since phyllodes tumors rarely metastasize to the axillary lymph nodes, surgical axillary staging or axillary lymph node dissection is not necessary unless the lymph nodes

are pathologic on clinical examination.²⁶⁶ In those patients who experience a local recurrence, resection of the recurrence with wide tumor-free surgical margins should be performed (see [PHYLL-2](#)). Some members of the Panel recommend local radiation therapy of the remaining breast or chest wall following resection of a local recurrence, but this recommendation is controversial (category 3).²⁶⁷

While the epithelial component of most phyllodes tumors contains estrogen receptor (58%) and/or progesterone receptor (75%),²⁶⁸ 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 Soft Tissue Sarcoma Guidelines](#).

Breast cancer during pregnancy

Breast cancer occurring concurrent with pregnancy is an infrequent clinical event. In a California registry study, there were 1.3 breast cancers diagnosed per 10,000 live births.²⁶⁹ Unfortunately, breast cancer during pregnancy is most often axillary lymph node-positive and with larger primary tumor size. Histologically the tumors are poorly differentiated, more frequently estrogen and progesterone receptor-negative and approximately 30% are HER2-positive.^{270,271} 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%.²⁷² 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.²⁷² Biopsies for cytologic evaluation of a suspicious breast mass may be done with a fine needle aspiration (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 providing adequate tissue for hormone receptor and HER2 analyses.

Staging assessment of the pregnant patient with breast cancer may be guided by clinical disease stage. For clinically node-negative T1-T2 tumors, a chest x-ray (with shielding), liver function and renal function assessment and complete blood count 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, Kuerer et al. have shown that breast-conserving surgery is possible if radiation therapy can be delayed to the postpartum period,²⁷³ and breast-conserving therapy during pregnancy does not appear to have a negative impact on survival.^{273,274} When surgery is performed at 25 weeks gestation or

later, obstetrical and prenatal specialists must be on site and immediately available in the event of precipitous delivery of a viable fetus.

Sentinel lymph node biopsy with radioactive tracer (eg, technetium 99m sulfur colloid) should be safe. There are limited data with only case reports and estimations of fetal radiation dose.^{275,276} Isosulfan blue or methylene blue dye for sentinel node biopsy procedures is not recommended during pregnancy. Sensitivity and specificity of sentinel node procedures have not been established in pregnant women. A recent review of the relative and absolute contraindications to sentinel node biopsy concluded that sentinel node biopsy should not be offered to pregnant women under 30 weeks gestation.²⁷⁷

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 greatest experience in pregnancy has been with anthracycline and alkylating agent chemotherapy.^{278,279} Collected data of chemotherapy exposure in utero indicates that the first trimester has the greatest risk of fetal malformation.^{280,281} 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 at the time of delivery. Recent data from a single institution prospective study indicate that FAC chemotherapy (5-FU 500 mg/m² IV day 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.²⁷⁹ Ondansetron, lorazepam and dexamethasone can be used as part of

the pre-chemotherapy antiemetic regimen. As reported by Gwyn et al., the median gestational age at delivery was 38 weeks, more than 50% of the patients had vaginal delivery and there have been no fetal deaths. An update of this experience reported on 57 women treated with FAC in the adjuvant or neoadjuvant setting. There were 57 live births. A survey of parents/guardians reported on the health of 40 children. There was 1 child with Down's syndrome and 2 with congenital abnormalities (club foot; congenital bilateral ureteral reflux). The children are reported to be healthy and progressing well in school.^{279,282}

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 and their use is not recommended during pregnancy.²⁸³⁻²⁸⁵ If a taxane is indicated clinically, it may be used in the post-delivery setting. Preferred chemotherapy choices are those doxorubicin-based regimens that have already been evaluated in pregnant patients.

There are only case reports of trastuzumab use during pregnancy.²⁸⁶⁻²⁹⁰ Three of these case reports indicated oligohydramnios with administration of trastuzumab; fetal renal failure occurred in one case. If trastuzumab is otherwise indicated, it should be administered in the postpartum period.

A single case report of first trimester exposure to lapatinib during treatment for breast cancer reported an uncomplicated delivery of a healthy female neonate.²⁹¹

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

Communication between the oncologist and maternal fetal medicine specialist is essential at every visit and treatment decision point for the patient (see [PREG-1](#))

Inflammatory breast cancer

Inflammatory breast cancer (IBC) is a rare, aggressive form of breast cancer estimated to account for 1%-6% of breast cancer cases in the United States.^{292,293} 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 with a palpable border to the erythema. IBC is classified according to the 6th edition of the *AJCC Cancer Staging Manual* as either 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 is 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 for, nor sufficient by itself, to assign a diagnosis of IBC.^{5,294} 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 those with noninflammatory forms of locally advanced breast cancer, are more likely to have disease that is HER2-positive and hormone receptor-negative^{295,296}, to have a less favorable prognosis^{297,298} (ie, DFS at 5 years were 35% and 50% for inflammatory vs. non-inflammatory status [P=0.020]²⁹⁹), and to be younger at the time of disease presentation.³⁰⁰ The 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 options.^{301,302} Nevertheless, current evidence provides justification for a separate guideline for the work-up and treatment of patients diagnosed with IBC (see [IBC-1](#)).

Women with a clinical/pathologic diagnosis of IBC without distant metastasis (stage T4d, N0-N3, M0) should undergo a thorough staging evaluation. Recommendations include a complete history and physical examination involving a complete blood cell count and platelet count. Evaluations for the presence of distant metastasis include liver function testing, bone scan (category 2B), CT imaging of the chest, abdomen and pelvis (category 2B; category 2A for CT imaging of the chest when pulmonary symptoms are present). Evaluation of the extent of local disease is determined using diagnostic bilateral mammogram, with the addition of ultrasound as necessary. A breast MRI scan is optional. A pathology review and pre-chemotherapy determinations of tumor hormone-receptor and HER2-receptor status should be carried out.

The treatment of patients with IBC should involve a combined modality approach.²⁹³ The benefit of preoperative chemotherapy followed by mastectomy over preoperative chemotherapy 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.³⁰³ Results from a retrospective study of patients with IBC performed over a 20-year period at M.D. Anderson demonstrated that initial treatment with doxorubicin-based chemotherapy followed by local therapy (ie, radiotherapy or mastectomy, or both) and additional postoperative chemotherapy resulted in a 15-year disease-free survival rate of 28%.³⁰⁴ Additional support for the use of anthracycline-based preoperative chemotherapy comes from the only randomized trial of patients with IBC. In this study, 5-year survival rates of 44% were observed when

epirubicin/cyclophosphamide-based regimens were administered as initial therapy.³⁰⁵ A recent retrospective study has demonstrated that addition of a taxane to an anthracycline-based regimen improved PFS and overall survival in patients with estrogen receptor-negative IBC.³⁰⁶

It has been known for many years that primary surgical treatment of patients with IBC is associated with very poor outcomes.³⁰⁷ 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.

The Panel recommends preoperative chemotherapy with an anthracycline-based regimen with or without taxanes for the initial treatment of patients with IBC (see [IBC-1](#); [BINV-14](#)). Inclusion of trastuzumab in the chemotherapy regimen is recommended for patients with HER2-positive disease. Patients with a clinical/pathologic diagnosis of IBC should not be treated with pre-chemotherapy surgery. Patients responding to preoperative chemotherapy should undergo mastectomy with axillary lymph node dissection; breast-conserving therapy is not recommended for patients with IBC. Any remaining planned chemotherapy should be completed postmastectomy followed sequentially by endocrine therapy in patients with hormone receptor-positive disease. If the IBC is HER2 positive, completion of one year of trastuzumab is recommended. Finally, post-mastectomy chest wall and regional node irradiation is recommended following the completion of any planned chemotherapy (see [IBC-1](#)). Mastectomy is not recommended for patients with IBC who do not respond to preoperative chemotherapy. Additional systemic chemotherapy and/or preoperative radiation should be considered for these patients, and patients responding to this secondary therapy should undergo mastectomy and subsequent treatment as described above. Patients with stage IV or recurrent IBC should be treated according to the guideline for recurrence/stage IV disease ([BINV-15](#) to [BINV-20](#)).

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 rare 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 of future patients.

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