Chapter 151: Breast Cancer

Bonnie Lin Boster; Neelam K. Patel; Jaime Kaushik

UPDATE SUMMARY

Update Summary

March 25, 2023

The following updates to this chapter were made:

- Treatment, Curative Breast Cancer (Stages I–III), Systemic Therapy, Cytotoxic Chemotherapy section: included information about adding pembrolizumab to neoadjuvant and adjuvant chemotherapy regimens to improve outcomes
- Treatment, Curative Breast Cancer (Stages I–III), Systemic Therapy, Biologic or Targeted Therapy section: added paragraphs about PARP inhibitor and CDK inhibitor adjuvant therapy
- Treatment, Metastatic Breast Cancer (MBC, Stage IV) Chemotherapy and Immunotherapy sections and Table 151-8: removed atezolizumab + albumin-bound paclitaxel as it is no longer approved
- Treatment, Metastatic Breast Cancer (MBC, Stage IV) Chemotherapy section: added that indication for sacituzumab govitecan-hziy for those with HR-positive, *HER2*-negative MBC
- Treatment, Metastatic Breast Cancer (MBC, Stage IV) Biologic or Targeted Therapy, HER2-Targeted Agents section: added information about fam-trastuzumab deruxtecan in *HER2*-low MBC and revised third-line *HER2*-targeted therapy paragraph to include ado-trastuzumab emtansine or tucatinib + trastuzumab + capecitabine

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 61, Breast Cancer.

KEY CONCEPTS

KEY CONCEPTS

1. Breast cancer is usually diagnosed in the early stages when it is highly curable.
2. Although controversial, regular screening mammography in women younger than 50 years of age is beneficial, and many studies demonstrate that annual or biennial screening mammography in women aged 50 to 74 years reduces the breast cancer mortality rate.
3. Local therapy of early-stage breast cancer consists of modified radical mastectomy or lumpectomy plus external-beam radiation therapy. The surgical approach to the ipsilateral axilla may consist of a lymph node mapping procedure with sentinel lymph node biopsy or a full-level I/II axillary lymph node dissection. Breast conserving therapy (BCT) includes lumpectomy, surgical evaluation of the lymph node basin, and radiation.
4. The goal of adjuvant and neoadjuvant chemotherapy is cure while the goal of chemotherapy in the metastatic setting is palliation.
5. Adjuvant endocrine therapy reduces the rates of relapse and death in patients with hormone receptor–positive early breast cancer. Adjuvant chemotherapy reduces the rates of relapse and death in all patients with early-stage breast cancer.
6. The choice of the most appropriate chemotherapy, endocrine therapy, and human epidermal growth factor receptor-2 (*HER2*) targeted therapy regimen is complex and rapidly changes as results from ongoing randomized clinical trials are reported.
7. Neoadjuvant chemotherapy and biotherapy are appropriate for selected patients with early breast cancer and most patients with locally advanced and inflammatory breast cancer (IBC) followed by local therapy and further adjuvant systemic therapy as indicated.
8. About 55% of women with metastatic breast cancer (MBC) will respond to chemotherapy regimens; anthracycline- and taxane-containing regimens are the most active.
9. Initial therapy of MBC in most women with hormone receptor–positive tumors should include endocrine therapy.
10. *HER2*-targeted therapies and other biologic or targeted agents (eg, everolimus, cyclin-dependent kinase [CDK] inhibitors) in combination with chemotherapy or endocrine therapy are options for patients with MBC.

BEYOND THE BOOK

BEYOND THE BOOK

Activity #1

Learners are encouraged to review “Breast Cancer: An Opportunity Lost Level II” in the *Pharmacotherapy Casebook: A Patient-Focused Approach* to practice applying their knowledge to develop a patient-centered care plan for a patient with breast cancer.

INTRODUCTION

In this chapter, the terms “women” and “men” are used to reflect gender identified in previous research studies and other literature on breast cancer and to recognize the biological sex of individuals at birth. In doing so, we recognize that not all patients with breast cancer identify as females or males at the time of diagnosis and treatment of breast cancer. Breast cancer is the most common cancer and is second only to lung cancer as a cause of cancer death in American women. About 300,600 new cases of breast cancer are expected to be diagnosed and 43,700 people are expected to die of breast cancer in 2023.[1] In addition to invasive breast cancers, about 55,700 cases of noninvasive, ductal carcinoma in situ (DCIS), cancer are expected to

be diagnosed among women in the United States in 2023.[1]

Breast cancer incidence rates increased in the 1980s and decreased starting in 2000. The decreased incidence is thought to be related to decreased use of menopausal hormone therapy, also known as hormone replacement therapy (HRT), in postmenopausal individuals.[2] The incidence of DCIS also increased during the 1980s, due to the increased use of screening mammography.[2] Since 2004, breast cancer has slowly increased by about 0.3% per year, and during 2012 to 2016, DCIS has decreased by about 2.1% per year.[2] The increase in breast cancer incidence has been attributed to increases in body mass index (BMI) and declines in the average number of births per individual.[2]

Breast cancer incidence rates vary considerably across racial and ethnic groups in the United States. For example, the average annual age-adjusted incidence rate from 2012 to 2016 was 130.8 cases per 100,000 among non-Hispanic White women, 126.7 cases among non-Hispanic Black women, 94.7 cases in American Indian/Alaska Native women, 93.7 cases in Hispanic women, and 93.2 cases among Asian/Pacific Islander women.[2] The higher incidence rates in White women than in other racial and ethnic groups may be related to differences in reproductive and lifestyle factors and access to and use of screening.

1 For all racial and ethnic groups, most breast cancers are diagnosed at an early stage when tumors are small and localized. Unfortunately, breast cancer mortality is higher among Black women compared to White women despite the lower incidence. The cause of this disparity between White and Black women is widely debated and multifactorial, and proposed explanations include differences in stage at diagnosis, tumor characteristics, obesity, comorbidities, access to care, early detection, and treatment.[2] Overall breast cancer mortality rates in the United States have declined since 1990; this decline has been attributed to improvements in early detection and treatment.[2]

The median age at diagnosis for breast cancer is 62 years.[2] Although lung cancer is the leading cause of cancer deaths for women regardless of age, breast cancer is the leading cause of cancer deaths for women between the age of 20 and 59 years.[1]

EPIDEMIOLOGY AND ETIOLOGY

The two variables most strongly associated with the occurrence of breast cancer are biological sex and age. Although one commonly thinks of breast cancer as a disease confined to women, about 2,650 cases of breast cancer are estimated to be diagnosed in men in the United States in 2021.[1] Men are more likely to have more advanced disease at the time of diagnosis. Men also have lower unadjusted rates of overall survival than women with breast cancer. This difference is not only due to advanced disease at diagnosis but also older age at diagnosis as well as shorter life expectancy in general.[3] Treatment of breast cancer is similar regardless of sex or gender.

The incidence of breast cancer increases with advancing age. A frequently quoted breast cancer statistic is that one in eight women will develop breast cancer during her lifetime. It should be emphasized that this is a cumulative lifetime risk of developing the disease from birth to death. The one-in-eight women figure is often misinterpreted by women who assume that it translates into one in eight women being diagnosed with breast cancer each year. A more useful method of presenting the risk data is based on age intervals. For example, the 10-year probability of breast cancer diagnosis of a 20-year-old individual is 1 in 1,479, but this risk changes to 1 in 28 for a 60-year-old individual.

A number of calculators are available to estimate a woman's risk of developing breast cancer. The National Cancer Institute (NCI) has an online version of the Breast Cancer Risk Assessment Tool (https://bcrisktool.cancer.gov/calculator.html). This tool is based on a statistical model known as the Gail model, derived from a mammography screening project conducted in the 1970s. It was designed for health professionals to project an individualized risk for invasive breast cancer over a 5-year period and over their lifetime. This model has been shown to provide accurate estimates in several racial and ethnic groups, but it has not been validated for those with genetic risk factors, a previous history of in situ or invasive breast cancer, or for certain subgroups. Other risk assessment models also exist, each taking into account different risk factors.

Endocrine Factors

Many endocrine factors have been associated with the risk of breast cancer. Many of these relate to the total duration of menstrual life. Early menarche, generally defined as menstruation beginning before age of 11 years, increases the cumulative lifetime risk of breast cancer development. Similarly, a late age of natural menopause (age 55 years or later) increases the risk of breast cancer development.[2] Conversely, bilateral oophorectomy

before the age of 45 years reduces the risk of developing breast cancer.[4] Nulliparity and a late age at first birth (greater than or equal to 30 years) are reported to increase the lifetime risk of developing breast cancer.[2] Investigators postulate that international differences in age of menarche, age at menopause, and childbearing may account for a substantial part of the international differences in the incidence of breast cancer.

Many studies have evaluated the relationship between exogenous hormones and the development of breast cancer. The Women's Health Initiative (WHI) is a series of clinical trials designed to investigate the risks and benefits of treatment strategies that could affect women's health issues, such as breast cancer. The estrogen plus progestin trial reported an increased risk of breast cancer in women taking combined estrogen and progestin. In the estrogen alone trial, which included postmenopausal women with prior hysterectomy, the incidence of breast cancer was lower in those who received estrogen alone compared with those who received placebo.[2] Unresolved issues remain as to whether lower doses or short-term use of estrogen or estrogen–progestin for menopausal symptoms can be safe and effective. A longer duration of HRT and concurrent use of progestins contribute to breast cancer risk. In addition, the impact of HRT use on breast cancer risk also varies according to BMI and breast density.[2] The use of postmenopausal HRT in individuals with a history of breast cancer is generally contraindicated. Individuals who are considering HRT should carefully consider the risks versus benefits (see Chapter 102, "Hormone Therapy in Women" for a detailed discussion of HRT).

Epidemiologic studies of oral contraceptives do not show a consistent relationship between the use and breast cancer risk. Results are conflicting, and assessment of the studies should consider the particular oral contraceptive products involved, daily and cumulative doses of the hormones administered, and latency period for development of breast cancer. It is also important to note that oral contraceptives are known to reduce the risk of ovarian and endometrial cancers.[5] Benefits and risk associated with oral contraceptives should be considered and discussed with each patient.

Genetic Factors

Both personal and family histories influence a woman's risk of developing breast cancer. A personal history of breast cancer is associated with an increased risk of developing contralateral breast cancer. Cancers of the uterus and ovary are also associated with an increased risk of developing breast cancer. Several cancer family syndromes include breast cancer in association with other types of cancers.

About 10% of all breast cancers in the US population can be attributed to family history. Empirical estimates of the risks associated with particular patterns of family history of breast cancer indicate the following[2,4]:

1. Having any first-degree relative with breast cancer increases a woman's risk of breast cancer about 50%. Risk increases with increasing numbers of affected first-degree relatives.
2. The risk is affected by both the woman's age and the age of the relative when diagnosed. A higher risk is seen when a woman and her relative at diagnosis are younger than 50 years.
3. The risk associated with having any second-degree relative with breast cancer is complex and depends on other family history patterns. The risk is generally lower than that of first-degree relatives.
4. Affected family members on both the maternal and the paternal sides are important to consider in the evaluation of risk.

Although individuals with a family history of breast cancer are at increased risk for the disease, the diagnosis of breast cancer is still uncommon in young individuals even with a positive family history.

Germline mutations in either *BRCA1* or *BRCA2* are associated with an increased risk for breast and ovarian cancer. These genes function as tumor suppressor genes, maintaining genomic integrity and DNA repair. Compared with an average individual's 10% lifetime risk of developing breast cancer, the probability of developing breast cancer by the age of 80 years in individuals with a *BRCA1* or *BRCA2* mutation is estimated to be 70%.[2]

The probability of being a *BRCA* gene mutation carrier is related to ethnicity and family history. Ashkenazi (Eastern European) Jewish descendants have an unusually high (2.5%) carrier rate of germline mutations in *BRCA1* and *BRCA2* compared with the rest of the US population.[2] Conversely, clinically significant *BRCA* mutations occur at a frequency of about one in 400 persons in the general, non-Jewish US population.[2] Testing for *BRCA1* and *BRCA2* mutations is now widely available, but it is generally recommended only when there is personal or family history suggestive of hereditary cancer, when the test results can be adequately interpreted, and when results will assist with diagnosis and management. The decision to test an

individual for a genetic mutation related to breast cancer risk is complex, and several organizations have published recommendations on genetic susceptibility testing for individuals who meet the criteria for increased risk.[6]

Although most genetic causes of breast cancer are attributed to *BRCA1* and *BRCA2*, other genes that have been associated with hereditary breast cancer include *TP53*, *CHEK2*, *PALB2*, *PTEN*, *ATM*, *STK11*, *CDH1*, and others.[6]

Environmental and Lifestyle Factors

Breast cancer incidence rates vary considerably among countries, which suggests that environmental and lifestyle factors play an important role. See Table 151-1 for details.

TABLE 151-1

Environmental and Lifestyle Factors

Factor	Comments
Elevated Risk	
Alcohol consumption	Some evidence that consumption before first pregnancy may affect risk; women who have 2-3 alcoholic drinks per day have a 20% higher risk compared to non-drinkers
Tobacco	Slight increase, notably in long-term, heavy smokers who started smoking before first pregnancy
Radiation exposure	Exposure particularly if before 10-30 years of age, eg, Hodgkin lymphoma
Reduced Risk	
Diet: Fruit and vegetable intake	Limited but increased evidence
Physical activity	Has protective effect independent of BMI
No Association	
Diet: Fat intake	No association based on recent meta-analysis
Mixed Results	
Diet: Soy	Reduced risk in Asian women but not the case with Western populations
Excess body weight/weight gain	Reduced risk in premenopausal women but elevated risk in postmenopausal women

Data from Reference 2.

Several endocrine, genetic, environmental, and lifestyle factors are associated with the development of breast cancer to varying degrees. Some factors are modifiable, but others are not. The impact of individual risk factors may vary depending on other confounding variables such as age, family history, estrogen use, and menopausal status. Further studies are needed to confirm the importance of factors that are associated with the risk of developing breast cancer.

PREVENTION AND EARLY DETECTION

Current efforts at breast cancer prevention are directed toward the identification and removal of risk factors often referred to as risk-reducing strategies. Prophylactic bilateral mastectomies or bilateral salpingo-oophorectomy are considered for individuals who are at high risk for the development of breast or ovarian cancer, particularly if the breast tissue is difficult to evaluate by both physical examination and mammography and if the individual have persistent disabling fears that they will be diagnosed with cancer. Guidelines for the incorporation of surgical risk-reducing strategies are largely based on genetics and other known risk factors for the development of breast (or ovarian) cancer.

Numerous agents are available for pharmacologic risk reduction, including the selective estrogen receptor modulators (SERMs), tamoxifen and raloxifene, and aromatase inhibitors (AIs), anastrozole and exemestane. Tamoxifen (20 mg/day × 5 years) reduces the risk of invasive and noninvasive estrogen receptor (ER)-positive breast cancers in individuals with a high risk for breast cancer by about 50%.[4] Tamoxifen has been shown to be a relatively safe drug with an acceptable toxicity profile when used to treat pre- or postmenopausal patients with breast cancer. Toxicities associated with tamoxifen are described in the "Endocrine Therapy" section under Curative Breast Cancer. Similarly, raloxifene (60 mg/day × 5 years), reduces the rates of noninvasive and invasive breast cancers in high-risk, postmenopausal individuals, but not to the same degree as tamoxifen does. Both agents increased thromboembolic events while only tamoxifen increases rates of endometrial cancer.[4] Although the benefits of raloxifene have decreased compared to tamoxifen, it may still be the treatment of choice when considering toxicities.[4]

A similar reduction in the risk of contralateral primary breast cancers was demonstrated with the AIs, exemestane and anastrozole. Both exemestane (25 mg/day × 3 years) and anastrozole (1 mg/day × 5 years) reduce rates of invasive breast cancers in high-risk, postmenopausal individuals and have tolerable adverse drug reactions. AIs have not been compared to SERMs and both classes of agents are appropriate options.[4] Although neither exemestane nor anastrozole is Food and Drug Administration (FDA)-approved for breast cancer risk reduction, the American Society of Clinical Oncology, or ASCO, and National Comprehensive Cancer Network (NCCN) guidelines include AIs as acceptable options for risk reduction in postmenopausal women.[4,7] Any decision to use tamoxifen, raloxifene, or the AIs for risk reduction should be made after a thorough discussion of the woman's risk of breast cancer, the potential benefits, and the potential serious adverse drug reactions.

The rationale for early detection of breast cancer is based on the relationship between the stage of breast cancer at diagnosis and the probability of cure. If all breast cancer cases could be detected at an early stage of the disease (ie, small primary tumor and negative lymph nodes), then more patients theoretically could be cured of their disease. Screening guidelines for early detection of breast cancer in women at average risk have been developed by several organizations, including but not limited to the American Cancer Society (ACS), the United States Preventive Services Task Force (USPSTF), and the NCCN (see Table 151-2).[8–10] The ACS guidelines are most commonly cited. However, it is important to note that the expert panels developing these guidelines often differ in their approach and analysis of the available data, as is evident in the different recommendations in the guidelines.

TABLE 151-2

Breast Cancer Screening Guidelines

Risk Category	ACS	USPSTF	NCCN
Average Risk			
BSE	Not recommended but encourages breast awareness	Not recommended	Age ≥25 years: breast awareness
CBE	Evidence does not support	Insufficient evidence	Age ≥25-39 years: every 1-3 years
			Age ≥40 years: annually
Mammography	Age 40-44 years: opportunity annually	Age 40-50 years: individualized decision	Age ≥40 years: annually; consider tomosynthesis
	Age 45-54 years: annually	Age 50-74 years: biennial	
	Age ≥55 years: biennially or opportunity annually (as long as in good health and at least 10-year life expectancy)	Age >75 years: insufficient evidence	
High Risk[a,b]			
BSE	NA	NA	All ages: breast awareness
CBE	NA	NA	All ages: every 6-12 months
Mammography	Age ≥30 years: annually with MRI	NA	Prior RT or strong family history or genetic predisposition, age ≥25 years: annually (+ CBE); consider tomosynthesis
			All other categories: annually (+ CBE); consider tomosynthesis
Breast MRI	Age ≥30 years: annually with mammogram	NA	Annually with mammogram + CBE for (a) prior RT, age ≥25 years; (b) lifetime risk >20%; (c) consider MRI if history of LCIS or ADH/ALH and lifetime risk >20%

ACS, American Cancer Society; ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; BSE, breast self-examination; CBE, clinical breast examination by a healthcare professional; LCIS, lobular carcinoma in situ; MRI, magnetic resonance imaging; NA, not addressed; NCCN, National Comprehensive Cancer Network; RT, thoracic radiation therapy; USPSTF, United States Preventive Services Task Force.

[a]High risk is defined by the ACS as women with (1) a known *BRCA1/2* gene mutation; (2) untested woman with first-degree relative with a known *BRCA1/2* gene mutation; (3) lifetime risk of breast cancer of 20%-25% or greater using a risk-assessment tool based largely on family history; (4) radiation therapy to the chest between the ages of 10 and 30 years; (5) LiFraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome or have first-degree relatives with one of these syndromes.

[b]High risk is defined by the NCCN as women with (1) prior thoracic radiation therapy before age 30 years, (2) 5-year risk of ≥1.7% of invasive breast cancer in women

≥35 years old, (3) lifetime risk of >20% as defined by models that are largely based on family history, (4) strong family history or genetic predisposition, (5) LCIS or ADH/ALH and lifetime risk of >20%, (6) prior history of breast cancer.

Data from References 2, and 8–10.

2 The most controversial screening recommendation for breast cancer is annual mammography. Although screening mammography clearly decreases mortality from breast cancer, the controversies surround the balance of benefits and harms associated with a less than perfect screening test in individuals of different ages at average risk of developing breast cancer. The largest benefit for the number needed to invite for screening to prevent one breast cancer death was seen for women aged 60 to 69 years old.[11] Incorporation of this information into national guidelines differs with each organization (Table 151-2).

Other radiologic methods of breast imaging are also being investigated (eg, digital mammography [two-dimensional, 2D], digital breast tomosynthesis [also known as tomosynthesis or three-dimensional mammography], ultrasonography, and magnetic resonance imaging [MRI]). Recommendations regarding these other radiologic methods vary among the national guidelines and definitions of "high risk" also vary among the guidelines (Table 151-2). It should also be noted that any screening procedure has risks and they should be discussed with patients so they are able to make an informed decision regarding these procedures. The risks involved with screening mammograms include false-negative results, false-positive results, overdiagnosis (true positives that will not become clinically significant), and radiation risk. The rate of false-negative results with the current technology is about 20%.[12] Although the specificity of mammography is quite high (90%), most abnormal examinations are false-positive results, leading to additional biopsies and psychological distress.[11] The term "overdiagnosis" refers primarily to the increased detection of DCIS from screening mammography (see "Noninvasive Carcinoma" section for a detailed discussion of DCIS).

CLINICAL PRESENTATION

CLINICAL PRESENTATION

General

- The patient may not have any symptoms because breast cancer may be detected in asymptomatic patients through routine screening mammography.

Local Signs and Symptoms

- A painless, palpable lump is most common.
- Less common: pain; nipple discharge, retraction, or dimpling; skin edema, redness, or warmth.
- Palpable local–regional lymph nodes may also be present.

Signs and Symptoms of Systemic Metastases

- Varies depending on the site of metastases, but may include bone pain, difficulty breathing, abdominal pain or enlargement, jaundice, or mental status changes.

Laboratory Tests

- Tumor markers such as cancer antigen 15-3, or CA 15-3, or carcinoembryonic antigen, or CEA, may be elevated in patients with metastatic disease.
- Alkaline phosphatase or liver function test results may be elevated in patients with metastatic disease.

Other Diagnostic Tests

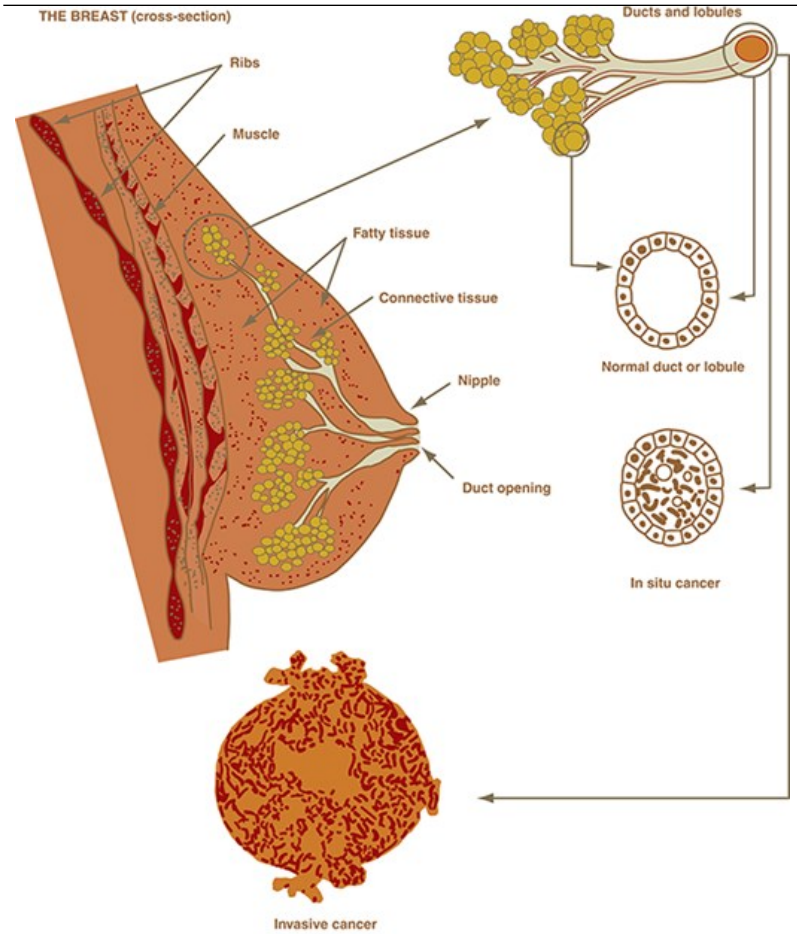
- Mammography (with or without ultrasonography, breast MRI, or both).
- Biopsy for pathology review and determination of tumor ER, progesterone receptor (PR), and *HER2* status.
- Systemic staging tests may include chest radiography, chest computed tomography (CT), bone scan, abdominal CT or ultrasonography, or MRI.

A painless lump is the initial sign of breast cancer in most women. The typical malignant mass is solitary, unilateral, solid, hard, irregular, and nonmobile. In small numbers of cases, stabbing or aching pain is the first symptom. Less commonly, nipple discharge, retraction, or dimpling may herald the onset of the disease. In more advanced cases, prominent skin edema, redness, warmth, and induration of the underlying tissue may be observed.

The breast is a complex organ composed of skin, subcutaneous tissue, fatty tissue, and branching ductal and glandular structures (Fig. 151-1). Various diseases that affect these structures can produce a palpable mass. In addition, the physiologic changes associated with the menstrual cycle can cause normal breast changes. Common causes of breast masses in young individuals are fibroadenoma, fibrocystic disease, carcinoma, and fat necrosis.

FIGURE 151-1

Breast anatomy. An illustration shows the cross-section of the breast. The breast lies posterior to the ribs and muscles and consists of fatty tissues and connective tissues. The ducts in the breast lead to the opening in the nipple. A normal duct or lobule is hollow, while the one with cancer is blocked.

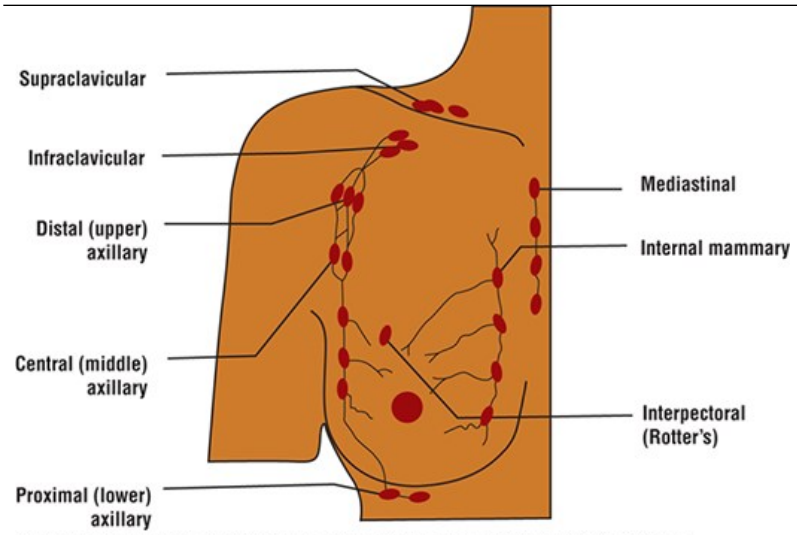


Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Breast cancer that is confined to a localized breast lesion is often referred to as *early*, *primary*, *localized*, or *curable*. Breast cancer that has spread to local–regional lymph nodes is still considered early stage (see Fig. 151-2). Unfortunately, breast cancer cells often spread by contiguity, through lymph channels, and through the blood to distant sites. When breast cancer cells can be detected clinically or radiologically in sites distant from the breast, the disease is referred to as *advanced* or *metastatic* breast cancer (MBC). Tissues most commonly involved with distant metastases are lymph nodes (other than local–regional lymph nodes), skin, bone, liver, lungs, and brain. Symptoms of bone pain, difficulty breathing, abdominal enlargement, jaundice, and mental status changes may herald the clinical presentation of MBC. A small percentage of women have signs and symptoms of distant metastases when they first seek treatment. In virtually all of them, a neglected breast mass has been present for several months to years. In addition, 20% to 30% of all patients who initially present with early breast cancer will eventually develop signs and symptoms of MBC.[13]

FIGURE 151-2

Lymph node anatomy. An illustration shows that the position of nodes as follows: supraclavicular, mediastinal, internal mammary, interpectoral or Rotter's, proximal or lower axillary, central or middle axillary, distal or upper axillary, and supraclavicular.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

DIAGNOSIS

The initial workup for a woman presenting with a breast mass or symptoms suggestive of breast cancer should include a careful history, physical examination of the breast, three-dimensional diagnostic mammography, and possibly other breast imaging techniques such as ultrasonography or MRI. Most breast cancers can be visualized on a mammogram as a mass, a cluster of calcifications, or a combination of these findings. One major factor that affects the ability of mammography to detect cancer includes breast density, which may be affected by age, menopausal status, and HRT use. Ultrasonography, MRI, digital mammography, and tomosynthesis are alternate breast imaging methods that are being investigated for women with dense breasts or other specific subsets of patients with breast cancer (eg, MRI in patients with IBC).[14] The technical quality of the examination and the expertise of the radiologist are also important factors affecting reliability.

Breast biopsy is indicated for a mammographic abnormality that suggests malignancy or for a palpable mass on physical examination. Three techniques are available: fine-needle aspiration, core-needle biopsy, and excisional biopsy.[14] Excisional biopsy completely removes the abnormal tissue. Needle biopsies are performed percutaneously and include both core-needle biopsy (which removes a core of tissue) and fine-needle aspiration (which removes cells from the suspicious site). Core-needle biopsy is the preferred biopsy method for mammographically detected, nonpalpable abnormalities.[14] Core-needle biopsy offers a more definitive histologic diagnosis, avoids inadequate samples, and can distinguish invasive from in situ breast cancer (which fine-needle biopsy cannot). After confirmation of malignancy via core-needle biopsy, subsequent surgical procedures are performed (either before or after systemic therapy) to assure complete removal of the abnormal tissue.

PATHOPHYSIOLOGY

The pathologic evaluation of breast tissue serves to establish the histologic diagnosis and to confirm the presence or absence of other factors believed to influence prognosis.

Invasive Carcinoma

Invasive breast cancers are a histologically heterogeneous group of lesions. Most breast cancers are adenocarcinomas and are classified on the basis of their microscopic appearance as ductal or lobular, corresponding to the ducts and lobules of the normal breast (see Fig. 151-1). The various histologic types of breast cancer have different prognoses, but it is unknown whether their response to therapy differs because patients in therapeutic trials are not typically stratified according to histologic type. The five most common types of invasive breast cancer are briefly described below.

Invasive or *infiltrating ductal carcinoma* is the most common histology, accounting for about 75% of all invasive breast cancers. These tumors commonly spread to the axillary lymph nodes, and their prognosis is poorer than for some other histologic types. *Invasive or infiltrating lobular*

carcinoma accounts for 15% of breast tumors.[2] Both clinical and radiologic findings for these tumors may be quite subtle. The typical presentation is an area of ill-defined thickening in the breast in contrast to a prominent lump characteristic of infiltrating ductal carcinoma (IDC). *Infiltrating lobular carcinoma* (ILC) can also be more difficult to detect by mammography. Overall, ILC and IDC have similar likelihoods of axillary node involvement and disease recurrence and death, but the sites of metastases may differ. While IDC more frequently metastasizes to the bone or to the liver, lung, or brain, ILC tends to metastasize to the leptomeninges, peritoneal surfaces, retroperitoneum, gastrointestinal tract, reproductive organs, and other unusual sites.

The most common special types of invasive cancer are *cribriform*, *mucinous*, *tubular,* and *papillary*. The prognosis may be more favorable with these rare and unusual histologies.[2] Special situations seen clinically and histologically include Paget's disease of the breast, phyllodes tumors, and IBC. Paget's disease of the breast is characterized by neoplastic cells in the nipple areolar complex. The patient presents clinically with eczematous changes in the nipple with itching, burning, oozing, bleeding, or some combination of these. Phyllodes tumors of the breast are rare tumors with subtypes that range from benign to malignant. These tumors often enlarge rapidly, are painless, and can appear as fibroadenomas.[14] IBC is rare, aggressive, and characterized clinically by prominent skin edema, redness and warmth, and induration of the underlying tissue. Biopsies of the involved skin reveal cancer cells in the dermal lymphatics. IBC typically has a rapid onset and is often mistaken for infectious cellulitis or mastitis. The prognosis of patients with IBC is poor even if the disease is apparently localized.[14]

Noninvasive Carcinoma

As with invasive carcinoma, the noninvasive lesions may be divided broadly into ductal and lobular categories. The development of malignancy is a multistep process and invasive breast cancer has a pre-invasive (ie, in situ) phase. During the carcinoma in situ phase, normal epithelial cells undergo genetic alterations that result in malignant transformation. Transformed epithelial cells proliferate and pile up within lobules or ducts but lack the required genetic alterations that enable the cells to penetrate the basement membrane. Carcinoma in situ is diagnosed when malignant transformation of cells has occurred, but the basement membrane is intact.

The widespread use of screening mammography with subsequent biopsy and greater recognition of noninvasive breast carcinoma by pathologists has resulted in a significant increase in the diagnosis of in situ breast cancer. An estimated 49,290 new cases of female noninvasive DCIS were diagnosed in 2021.[1] The natural history of these disorders is not well described, and thus the debate continues whether carcinoma in situ is a pre-invasive cancer or simply a marker of unstable epithelium that represents an increased risk for the development of subsequent aggressive cancer. DCIS is more frequently diagnosed than lobular carcinoma in situ (LCIS). Most cases of DCIS today are found by biopsies performed for clustered microcalcifications seen on screening mammography, a hallmark of this disorder.

Treatment

The ultimate goal of treatment for noninvasive carcinomas is to prevent the development of invasive disease. If left untreated, 15% to 50% of DCIS lesions will progress to invasive breast cancer.[15] Therefore, more than 50% of these tumors do not progress to invasive disease, but identifying this group of patients is not yet possible and all diagnoses should be treated.

Locoregional treatment of DCIS depends on its location, size, and pathology.[14] Treatment options include surgery (mastectomy or lumpectomy), radiation therapy, and adjuvant endocrine therapy if hormone receptor-positive. Axillary lymph node dissection (ALND) is generally not indicated, although sentinel lymph node biopsy (SLNB) (see the "Curative Breast Cancer" section) may be considered in selected patients.[14]

Cytotoxic chemotherapy has no role in the treatment of patients with pure DCIS. It is important to determine hormone receptor status on the cancer cells. Tamoxifen treatment for 5 years may be considered in premenopausal and postmenopausal women with hormone receptor–positive DCIS. Anastrozole for 5 years may also be considered in postmenopausal women with hormone receptor–positive DCIS, particularly if they are less than 60 years.[14]

Unlike DCIS, LCIS is a microscopic diagnosis; generally no palpable mass and no specific clinical abnormality exists. LCIS does not generally demonstrate calcifications on mammography and the diagnosis is usually an incidental finding in biopsy specimens obtained because of symptoms or mammography findings consistent with benign lesions. It is unclear whether LCIS is a precursor lesion or serves as a marker of risk for developing invasive carcinoma in the breast. The 10-year incidence of developing invasive carcinoma is 13.9%.[16] The risk for the development of breast cancer is

equally high in either breast, which makes the management of LCIS controversial. Some experts favor a program of observation, with physical examination every 6 to 12 months, annual mammography, and consideration of annual breast MRI or ultrasound.[10] In selected women with high-risk genetic mutations or strong family history and in women who are anxious about the development of cancer, bilateral mastectomies may be considered.[4] Radiation and systemic chemotherapy have no role in the management of LCIS. The use of chemoprevention with tamoxifen in premenopausal women or tamoxifen, raloxifene, anastrozole, or exemestane in postmenopausal women may also be considered for risk reduction (see the "Prevention and Early Detection" section for details).[4] These decisions are often difficult to discuss with patients because these treatments have toxicities. Nonetheless, a discussion regarding the risks and benefits is warranted.

STAGING AND PROGNOSIS

The natural history of breast cancer varies among patients, with some having extremely aggressive disease that progresses rapidly and others following a more indolent course. The ability to predict prognosis is extremely important in designing personalized treatment recommendations. Several pathologic prognostic and predictive factors have been identified. Prognostic factors are characteristics or measurements available at diagnosis or at the time of surgery that in the absence of neoadjuvant or adjuvant systemic therapy are associated with recurrence rate, death rate, or other clinical outcomes. Predictive factors are measurements available at diagnosis that are associated with response to a specific therapy. Prognostic and predictive factors fall into these general categories: (a) patient characteristics that are independent of the disease, such as age; (b) cancer characteristics, such as tumor size or histologic type; (c) other biomarkers that are measurable parameters in tissues, cells, or fluids, such as hormone-receptor status; and (d) genetic variables. The use of prognostic and predictive factors can personalize treatment to patients, increase the likelihood of clinical benefit, and reduce the risk of unnecessary toxicities.

Age at diagnosis and ethnicity can affect prognosis. Some younger patients, particularly those younger than 35 years, have more aggressive forms of breast cancer and a worse prognosis. Younger patients are more likely to present with poor prognostic features, such as affected lymph nodes, large tumor size, and tumors negative for hormone receptors. Black individuals have decreased survival compared with White individuals. The cause of this racial disparity is widely debated, with possible explanations including access to care, socioeconomic status, cultural differences, higher stage at diagnosis, and more aggressive biologic features.

Potentially modifiable prognostic factors include alcohol use, dietary factors, weight, and exercise. Agencies such as the ACS have recognized that physical activity, weight control, and diet are potentially modifiable risk factors for reducing the risk of recurrent breast cancer and other comorbidities (eg, heart disease, diabetes).[17]

Tumor size and the number of involved lymph nodes are established independent factors that influence the risk for breast cancer recurrence and subsequent metastatic disease. The number of affected lymph nodes is directly related to the risk of disease recurrence. The staging system for breast cancer recognizes the absolute number of positive nodes as a prognostic factor (see Table 151-3 for further details).[18] The relationship between tumor size and lymph node status is complex and is not a simple grouping.

TABLE 151-3

Definitions for Tumor, Node, Metastasis

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)	Ductal carcinoma in situ
Tis (Paget)	Paget's disease of the nipple NOT associated with invasive carcinoma or carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension

	T1mi	<0.1 cm; microinvasion
	T1a	>0.1 cm ≤0.5 cm
	T1b	>0.5 cm ≤1 cm
	T1c	>1 cm ≤2 cm
T2	Tumor >2 cm ≤5 cm	
T3	Tumor >5 cm	
T4	Tumor of any size with direct extension to the chest wall and/or to the skin	
	T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in the absence of invasion of chest wall structures
	T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria of inflammatory carcinoma
	T4c	Both T4a and T4b present
	T4d	Inflammatory carcinoma
Regional Lymph Nodes: Clinical (cN)		
cNX	Regional lymph nodes cannot be assessed	
cN0	No regional lymph node metastases	
cN1	Metastases to movable ipsilateral level 1, II axillary lymph node(s)	
	cN1mi	Micrometastases (approximately 200 cells, >0.02 cm <0.2 cm)
cN2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases	
	cN2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
	cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in ipsilateral internal mammary lymph node(s) with level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement	
	cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
	cN3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
	cN3c	Metastases in ipsilateral supraclavicular lymph node(s)
Regional Lymph Nodes: Pathologic (pN)		

pNX	Regional lymph nodes cannot be assessed	
pN0	No regional lymph node metastasis identified or ITCs only	
	pN0(i+)	ITCs only, no larger than 0.02 cm in regional lymph nodes
	pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction; no ITCs detected
pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy	
	pN1mi	Micrometastases, (approximately 200 cells, >0.02 cm <0.2 cm)
	pN1a	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
	pN1c	pN1a and pN1b combined
pN2	Metastases in 4-9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases	
	pN2a	Metastases in 4-9 lymph nodes (at least one deposit >0.2 cm)
	pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases ≥10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the presence ≥1 positive level I, II axillary lymph nodes; or in >3 axillary lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes; or in ipsilateral mammary lymph nodes	
	pN3a	Metastases in ≥10 axillary lymph nodes (at least one tumor deposit >0.2 cm) or metastases to infraclavicular (level III axillary lymph) nodes
	pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging) or pN2a in presence of pN1b
	pN3c	Metastases in ipsilateral supraclavicular lymph nodes
Distant Metastasis (M)		
M0	No clinical or radiographic evidence of distant metastases	
	cM0(i+)	No clinical or radiographic evidence of distant metastases in the presence of tumor cells or deposits <0.02 cm detected microscopically or by molecular techniques in circulating blood, bone marrow, or other nonregional nodal tissue in a patient without symptoms or signs of metastases
cM1	Distant metastases detected by clinical and radiographic means	
pM1	Any histologically proven metastases in distant organs; or if in nonregional nodes, metastases >0.02 cm	

ITCs, isolated tumor cells.

Reproduced, with permission, from Hortobagyi GN, Connolly JL, D'Orsi CJ, et al. Breast. In: Amin EB, Edge SB, Gress DM, et al., AJCC Cancer Staging Manual. 8th Ed. Chicago, IL: Springer. 2017:589–638.

Certain histologic subtypes and clinical presentation of breast cancer have prognostic importance. As mentioned earlier, treatment recommendations may differ because women with pure *tubular* or *mucinous* tumors have more favorable outcomes than those with *invasive ductal carcinomas.*[14] IBC, a clinical designation and not a distinct histologic subtype, is associated with a poor prognosis.[14]

Nuclear grade and tumor (histologic) differentiation are also independent prognostic indicators. Several histologic grading systems have been developed, most of which grade tumors with a score from 1 to 3: grade 1, well differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated. Grading is incorporated as part of the staging system (see Table 151-4 for details regarding grading).[18] Higher grade tumors are associated with higher rates of distant metastasis and poorer survival. This factor aids in making treatment decisions, particularly for patients with small tumors and negative lymph nodes. Additional factors may include lymphovascular invasion and proliferation indices.

TABLE 151-4

Clinical Staging System

TNM	Grade	HER2	ER	PR	Stage	TNM	Grade	HER2	ER	PR	Stage
Tis N0 M0	Any	Any	Any	Any	0						
T1[a] N0 M0	G1[b]	Positive	Positive	Positive	IA	T0 N1[c] M0	G1	Positive	Positive	Positive	IB
T0 N1mi M0				Negative		T1[a] N1[c] M0				Negative	IIA
T1[a] N1mi M0			Negative	Positive		T2 N0 M0			Negative	Positive	
				Negative						Negative	
		Negative	Positive	Positive				Negative	Positive	Positive	IB
				Negative						Negative	IIA
			Negative	Positive					Negative	Positive	
				Negative	IB					Negative	
	G2[d]	Positive	Positive	Positive	IA		G2	Positive	Positive	Positive	IB
				Negative						Negative	IIA
			Negative	Positive					Negative	Positive	
				Negative						Negative	
		Negative	Positive	Positive				Negative	Positive	Positive	IB
				Negative						Negative	IIA
			Negative	Positive					Negative	Positive	
				Negative	IB					Negative	IIB

	G3[e]	Positive	Positive	Positive	IA		G3	Positive	Positive	Positive	IB
				Negative						Negative	IIA
			Negative	Positive					Negative	Positive	
				Negative						Negative	
		Negative	Positive	Positive				Negative	Positive	Positive	
				Negative	IB					Negative	IIB
			Negative	Positive					Negative	Positive	
				Negative						Negative	
T2 N1[f] M0	G1	Positive	Positive	Positive	IB	T0 N2 M0	G1	Positive	Positive	Positive	IIA
T3 N0 M0				Negative	IA	T1[a] N2 M0				Negative	IIIA
			Negative	Positive		T2 N2 M0			Negative	Positive	
				Negative	IIB	T3 N1[f] M0				Negative	
		Negative	Positive	Positive	IIA	T3 N2 M0		Negative	Positive	Positive	IIA
				Negative	IIB					Negative	IIIA
			Negative	Positive					Negative	Positive	
				Negative						Negative	IIIB
	G2	Positive	Positive	Positive	IB		G2	Positive	Positive	Positive	IIA
				Negative	IIA					Negative	IIIA
			Negative	Positive					Negative	Positive	
				Negative	IIB					Negative	
		Negative	Positive	Positive	IIA			Negative	Positive	Positive	IIA
				Negative	IIB					Negative	IIIA
			Negative	Positive					Negative	Positive	
				Negative	IIIB					Negative	IIIB
	G3	Positive	Positive	Positive	IB		G3	Positive	Positive	Positive	IIB
				Negative	IIB					Negative	IIIA

			Negative	Positive					Negative	Positive	
				Negative						Negative	
		Negative	Positive	Positive				Negative	Positive	Positive	
				Negative	IIIA					Negative	IIIB
			Negative	Positive					Negative	Positive	
				Negative	IIIB					Negative	IIIC
T4 N0 M0	G1	Positive	Positive	Positive	IIIA	Any T Any N M1	Any	Any	Any	Any	IV
T4 N1[f] M0				Negative	IIIB						
T4 N2 M0			Negative	Positive							
Any T N3 M0				Negative							
		Negative	Positive	Positive							
				Negative							
			Negative	Positive							
				Negative	IIIC						
	G2	Positive	Positive	Positive	IIIA						
				Negative	IIIB						
			Negative	Positive							
				Negative							
		Negative	Positive	Positive							
				Negative							
			Negative	Positive							
				Negative	IIIC						
	G3	Positive	Positive	Positive	IIIB						
				Negative							
			Negative	Positive							
				Negative							

	Negative	Positive	Positive							
			Negative	IIIC						
		Negative	Positive							
			Negative							

[a]T1 includes T1mi.

[b]N1 does not include N1mi. T1N1miM0 and T0N1miM0 are included for prognostic staging with T1N0M0 cancers of the same prognostic factor status.

[c]N1 includes N1mi, T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2N1, T3N1, and T4N1, respectively.

[d]G1 Low combined histologic grade (favorable), SBR (Scarf-Bloom Richardson grading system, Nottingham Modification) score of 3-5 points.

[e]G2 Intermediate combined histologic grade (moderately favorable), SBR score of 6-7 points.

[f]G3 High combined histologic grade (unfavorable), SBR score of 8-9 points.

Reproduced, with permission, from Hortobagyi GN, Connolly JL, D'Orsi CJ, et al. Breast. In: Amin EB, Edge SB, Gress DM, et al., AJCC Cancer Staging Manual. 8th Ed. Chicago, IL: Springer. 2017:589–638.

Hormone receptors are not strong prognostic markers but are used clinically to predict responses to endocrine therapy. Determination of both ER and PR status is an established procedure that is important in the management of breast cancer. Most patients with primary or MBC have hormone receptor–positive tumors. Hormone receptor positivity, more common in postmenopausal individuals, is associated with a higher response to endocrine therapy and longer disease-free survival.

The *HER2* protein is normally expressed at low levels in the epithelial cells of normal breast tissue. *HER2* overexpression occurs in about 15% to 20% of breast cancers and is associated with increased tumor aggressiveness, increased rates of recurrence, and increased mortality rates.[2,19] *HER2* overexpression is associated with poor prognosis and is measured by fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC). Tumors that are either IHC 3+ or FISH positive are considered to be positive for *HER2*.[14] *HER2*-positive status clearly predicts response to *HER2*-targeted therapy. Patients with *HER2*-positive MBC treated with trastuzumab, a monoclonal antibody (mAb) directed against the extracellular domain of the *HER2* receptor, have improved survival rates compared to patients with *HER2*-negative MBC or patients with *HER2*-positive MBC who do not receive trastuzumab.

Genetic profiling is also being used to provide prognostic and predictive information on clinical outcomes of breast cancer.[14] Further details on these assays are available in the "Genomic Testing" section under Curative Breast Cancer.

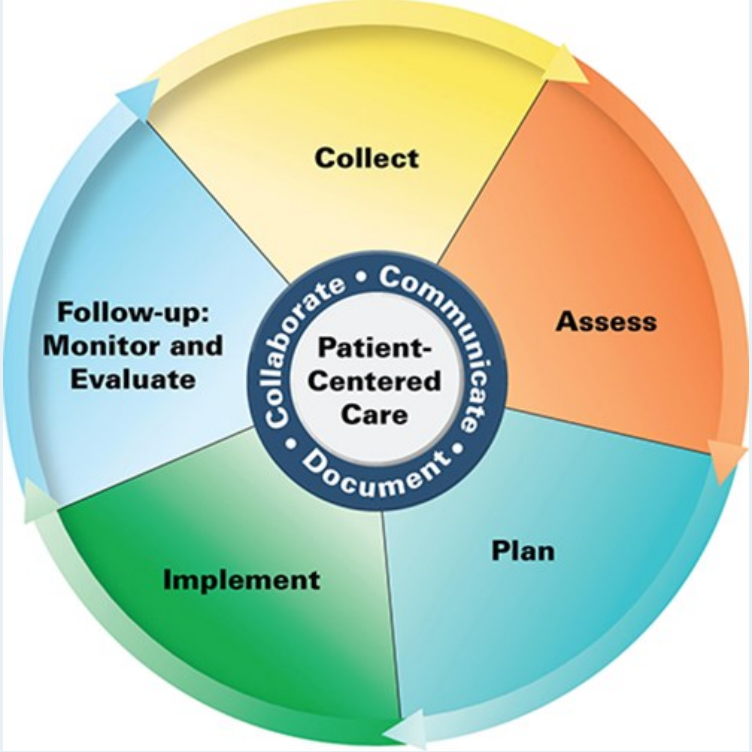
Breast cancer stage is based on the primary tumor extent and size, presence and extent of lymph node involvement, and presence or absence of distant metastases (Fig. 151-2, Tables 151-3 and 151-4). Although many possible combinations of T and N are possible within a given stage, simplistically, stage 0 represents carcinoma in situ (Tis) or disease that has not invaded the basement membrane of the breast tissue. Stage I represents a small primary invasive tumor without lymph node involvement or with micrometastatic nodal involvement, and stage II disease usually involves regional lymph nodes. Stages I and II are often referred to as *early breast cancer*. It is in these early stages that the disease is highly curable (99% 5-year survival in patients with disease confined to the breast, node negative).[2] Stage III, also referred to as *locally advanced disease*, usually represents a large tumor with extensive nodal involvement in which either node or tumor is fixed to the chest wall. A wide variety of clinical scenarios can be seen within this group of patients, including neglected tumors that have spread locally to IBCs that are a unique clinical entity. IBC is associated with similar clinical findings compared with neglected, locally advanced breast tumors (eg, erythema representing skin involvement). The distinction between the two diagnoses lies in the rapidity of onset of symptoms. Many locally advanced breast cancers are diagnosed in patients who have had symptoms for months to years and have neglected to seek medical attention. Although these women have a poor prognosis because of the delay in diagnosis, they are not classified as IBC. Stage IV disease is characterized by the presence of metastases to organs distant from the primary tumor and

is often referred to as *advanced or metastatic disease* as described earlier (27% 5-year survival rate in patients with distant metastases).[2] Most individuals with breast cancer in the United States present in early stages where the prognosis is favorable (91% of newly diagnosed patients have disease confined to the breast or local lymph nodes).[2]

Staging for breast cancer is separated into clinical and pathologic staging. Clinical stage is assigned before surgery and is based on physical examination (assessment of tumor size and presence of axillary lymph nodes), imaging (eg, mammography, ultrasonography), and pathologic examination of tissues (eg, biopsy results). Pathologic staging occurs after surgery and adds data from surgical exploration and resection. The American Joint Committee for Cancer (AJCC) publishes staging criteria for cancers.

PATIENT CARE PROCESS

Patient Care Process for Breast Cancer



Collect

- Patient characteristics (eg, age, biological sex)
- Physical examination, including clinical breast examination (if appropriate) and general examination to evaluate for MBC
- Patient medical history (personal and family history for breast and ovarian cancers, start of menstruation, time of menopause, surgical history [eg, hysterectomy, oophorectomy])
- Social history (eg, tobacco/ethanol use) and dietary habits
- Current medications including OTC use, herbal products, birth control, and dietary supplements
- Objective data
    - Height, weight

- Laboratory findings including complete blood count with differential, SCr, total bilirubin, AST, ALT, alkaline phosphatase
- Staging
- Tumor genomics if appropriate (eg, Oncotype DX, MammaPrint, Prosigna). For other details, see "Genomic Testing" under Systemic Therapy section
- For other details, see section "Clinical Presentation"

Assess

- Comorbidities
- Current medications and medication adherence
- Ability/willingness to pay for treatment options, insurance coverage
- Emotional status (eg, presence of anxiety, depression)
- Type of and response to prior treatment(s) and need for dose reductions and/or supportive care
- For other details, see section "Clinical Presentation"

Plan*

- Drug therapy regimen including specific chemotherapy, endocrine therapy, or targeted therapy and include dose, route, frequency, duration, and supportive care (see Fig. 151-3, Tables 151-5–151-8 and 151-10 in "Curative Breast Cancer" and "Metastatic Breast Cancer" sections)
- Monitoring parameters including efficacy (eg, staging studies such as CT chest, abdomen/pelvis, bone scan, CT/MRI brain in the cases of metastatic disease; ultrasound in the cases of neoadjuvant therapy), adverse drug reaction management (eg, nausea/vomiting, mucositis, neutropenia, hot flashes, myalgias), and safety (eg, CBC with differential, SCr, total bilirubin, AST/ALT, DEXA scan for bone health); frequency and timing of follow-up
- Patient education (eg, goal of treatment, dietary and lifestyle modification, drug-specific information; see "Curative Breast Cancer" and "Metastatic Breast Cancer" sections and Table 151-9)
- Self-monitoring for resolution of nausea/vomiting, mucositis, fever, when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, dietician, supportive care services, psychiatry, bone health, cardiology, genetics)

Implement*

- Provide patient education regarding all elements of the treatment plan. If patient has completed curative therapy, review survivorship care plan (ie, frequency of clinic visits)
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, labs, staging scans, monitoring tests [eg, ECHO/MUGA, DEXA scan, ultrasound])

Follow-up: Monitor and Evaluate

- Resolution of adverse drug reactions (eg, nausea/vomiting, mucositis, myalgia)
- Presence of adverse drug reactions (eg, constipation, diarrhea)
- Patient adherence to treatment plan using multiple sources of information

- Re-evaluate duration of therapy, depending on specific regimen

Collaborate with patient, caregivers, and other healthcare professionals.

TREATMENT

Curative Breast Cancer (Stage I-III)

Desired Outcomes

In the curative setting, through the use of different modalities of treatment—surgery, radiation, and systemic therapy, the desired outcome is cure of disease. This differs significantly from the desired outcomes when treating metastatic disease. Locoregional and systemic therapy and their roles in curing breast cancer are discussed below. While the desired outcome is the same for patients with stage I-III breast cancer, the terminology and sequence of therapies may differ. For example, *locally advanced breast cancer (stage III)* generally refers to breast carcinomas with significant primary tumor and nodal disease but in which distant metastases cannot be documented. In this setting, neoadjuvant systemic therapy may be administered to decrease tumor size prior to surgery and/or to allow for breast conserving surgery if desired by the patient. This approach to systemic therapy also allows for assessment of response to therapy. In contrast, the intent of adjuvant systemic therapy is to eradicate micrometastatic disease. A predetermined number of cycles or duration of systemic therapy is given in the neoadjuvant and adjuvant settings. Clinicians and patients must weigh the short- and long-term effects of systemic therapy against the benefits of lowering the risk of breast cancer recurrence.

Locoregional Therapy

3 Most patients presenting with breast cancer have an *in situ* tumor (stage 0), a small invasive tumor with negative lymph nodes (stage I), or a small invasive tumor with axillary lymph node involvement (stage II). Surgery alone can cure most, if not all, patients with in situ cancers: 70% to 80% of patients with stage I and about half of patients with stage II cancers. The choice of surgical procedures has changed drastically over the past 50 years, which is related to an increased understanding of the biology of breast cancer and the results of a series of well-conducted clinical trials performed over this time period.

Most patients diagnosed with breast cancer can be treated with BCT, a less extensive surgery than mastectomy (complete removal of the breast) that maintains acceptable cosmetic results and rates of local and distant recurrence and mortality.[14] BCT includes removal of part of the breast, surgical evaluation of the axillary lymph node basin, and radiation therapy to the breast. The amount of breast tissue removed as a part of BCT varies from removing the cancerous “lump” (ie, lumpectomy) with a small margin of adjacent normal-appearing tissue to removing the “lump” with a wider excision of adjacent normal-appearing tissue (ie, wide local excision) to removing the entire quadrant of the breast that includes the cancerous “lump” (ie, quadrantectomy). All these techniques are referred to as segmental or partial mastectomy. Overall survival rates are similar to BCT compared with mastectomy; however, a small increase in the risk of locoregional recurrence occurs with BCT.[14]

Several factors should be considered in selecting patients for BCT, such as younger age, family history, and genetic predisposition. The NCCN guidelines recommend that women who carry a known *BRCA1* or *BRCA2* mutation undergo mastectomy and consider additional risk reduction strategies (eg, bilateral mastectomies).[6] Bilateral total mastectomy and oophorectomy reduce the risk of breast cancer recurrence in patients with *BRCA1* or *BRCA2* mutations. Multiple sites of cancer within the breast and the inability to attain negative pathologic margins on the excised breast specimen are indications for mastectomy. Other relative contraindications may need to be considered when making the decision for the type of surgery. Local recurrence after BCT has not been consistently associated with an increased mortality rate, but it can be distressing to the patient and requires surgical removal of the remaining breast tissue. Other considerations include previous radiation to the breast, expected cosmetic result, and extent of local disease. The availability of an external-beam radiation facility and the patient’s willingness to comply with the prescribed course of radiotherapy must also be considered. Radiotherapy after BCT reduces the 10-year risk of first recurrence by 16% and the 15-year risk of breast cancer death by 4% as compared with no radiotherapy.[14] External-beam radiation therapy after BCT usually involves 3 to 5 weeks of radiation therapy directed to the entire breast tissue to eradicate residual disease. Local tumor control is similar with shorter courses versus longer courses of radiation, and toxicities, such as breast shrinkage, telangiectasias, and breast edema are less common with shorter regimens. The NCCN guidelines recommended radiation course is 40 to 42.5 Gy in 15 to 16 fractions or 46 to 50 Gy in 23 to 25 fractions.[14] Complications associated with radiation therapy to the breast

are generally minor and include reddening and erythema of the breast tissue and subsequent shrinkage of the total breast mass beyond that predicted on the basis of breast tissue removal.

Postmastectomy radiation therapy to the chest wall and regional lymph nodes (if indicated) may also be required in certain situations when tumors are large or the number of positive axillary lymph nodes is high. Post-mastectomy radiation is recommended for patients with ≥4 positive axillary lymph nodes and should be considered in situations where the tumor is ≤5 cm with negative axillary lymph nodes and margins <1 mm, the tumor is >5 cm with negative lymph nodes, 1 to 3 lymph nodes are positive, and if there are positive margins.[14]

The optimal sequence of radiation therapy and chemotherapy is somewhat controversial, but it is common to begin radiation after completion of chemotherapy when chemotherapy is recommended. If chemotherapy is not indicated, radiation is administered after surgery (see the "Biologic or Targeted Therapy" section under Curative Breast Cancer for a discussion of sequencing trastuzumab).

Accurate assessment of the spread of breast cancer cells to the axillary lymph nodes is critical for prognosis and personalizing local and systemic treatments. The number of positive axillary lymph nodes remains the most powerful predictor of breast cancer recurrence and survival, but other benefits may include a therapeutic effect of removing the lymph nodes and obtaining information to guide treatment selection. However, axillary dissection is associated with significant morbidity, including lymphedema, arm pain or numbness, and reduced quality of life.[14] About 60% of patients with early-stage breast cancer (ESBC) present with lymph node–negative disease, which indicates that many women would derive no therapeutic benefit but would be exposed to the complications from the full ALND.

For these reasons, a procedure involving lymphatic mapping and SLNB is recommended for patients with clinically negative lymph nodes.[20] The sentinel lymph node(s) is the first lymph node(s) that receives lymph drainage from the primary tumor. Injection of a vital blue dye, a radiocolloid, or both, around the primary breast tumor identifies the sentinel lymph node(s) in most patients, and the status of this lymph node(s) predicts the status of the remaining nodes in the nodal basin. Patients with lymph nodes that are suspicious for cancer involvement either by physical examination or imaging should have a biopsy performed to exclude lymph node involvement.[14] Historically, patients with positive sentinel nodes have proceeded to a level I and II ALND. However, ALND after SLNB in women with clinically node-negative tumors smaller than 5 cm, fewer than three involved sentinel lymph nodes, and undergoing BCT with subsequent breast irradiation results in higher morbidity, no improvement in local recurrence, and no difference in disease-free or overall survival as compared with SLNB alone.[21] Therefore, the ASCO and NCCN guidelines do not recommend ALND for women with ESBC with one or two positive sentinel lymph nodes who will receive BCT followed by radiation.[14,20] Women undergoing mastectomy with positive sentinel lymph nodes should be offered ALND.

Systemic Therapy

As stated previously, the desired therapeutic outcome of curative systemic therapy for breast cancer differs significantly from that of metastatic disease. Systemic therapy—chemotherapy, biologic or targeted therapy, and endocrine therapy— in this setting is administered with curative intent. For patients with inflammatory or locally advanced/unresectable breast cancer, neoadjuvant chemotherapy is considered the treatment of choice.[22]

Genomic Testing

Intensive research efforts have been directed toward identifying characteristics of the primary tumor (eg, pathologic or molecular prognostic factors) that may predict for a higher or lower likelihood of distant metastases and death in node-negative patients. Although many prognostic factors continue to be investigated, no single factor or combination of factors sufficiently identifies those at risk of metastases or is sufficiently standardized to be reproducibly applicable to all patients. Several multigene expression assays are commercially available as decision-support tools for adjuvant chemotherapy.[23] Oncotype DX® is one test that screens for expression of 21 genes with reverse transcription polymerase chain reaction (RT-PCR), and reports a recurrence score that correlates with the risk of distant recurrence or death from breast cancer in women with ER-positive, node-negative, invasive breast cancer. This test was initially validated in node-negative invasive breast cancer. A low recurrence score (≤15) indicates a low risk of recurrence with endocrine therapy alone indicating that perhaps adjuvant chemotherapy could be avoided. A high recurrence score (≥26) indicates a high risk of recurrence despite endocrine therapy, suggesting a need for adjuvant chemotherapy followed by endocrine therapy. For premenopausal patients with a score of 16 to 25, chemotherapy followed by endocrine therapy may be considered.[14,24] Postmenopausal patients with ER-positive, node-positive (1-3 positive lymph nodes) with a recurrence score of <26 may receive only endocrine therapy in the adjuvant setting. Premenopausal patients with a risk score less than 26 may derive benefit from chemotherapy followed by endocrine therapy and should be considered based on other

factors. Patients with 1 to 3 positive lymph nodes and a recurrence score of ≥26 should be offered chemotherapy regardless of menopausal status.[14] Other commercially available multigene assays include MammaPrint® and Prosigna®. MammaPrint® screens the tumor for 70 genes with microarray technology in breast cancer patients with ESBC, regardless of hormone-receptor status. The assay reports the predicted rates of recurrence as high or low. PAM50 (Prosigna®) is a multigene test that screens the tumor for 50 genes (plus 5 control genes) to predict distant relapse-free survival and likelihood of recurrence at 10 years in postmenopausal women with ER-positive breast cancer treated with endocrine therapy regardless of nodal status.[23]

Cytotoxic Chemotherapy

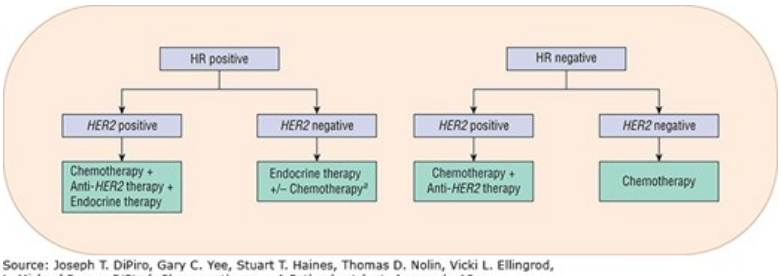
Systemic adjuvant therapy is defined as the administration of systemic therapy after definitive local therapy (surgery, radiation, or both) when there is no evidence of metastatic disease but a high likelihood of disease recurrence. By the time breast cancers become clinically detectable, they have likely been present for a number of years and have had an opportunity to establish distant micrometastases. Micrometastatic disease can travel from the primary breast tumor and spread to distant organs through several different routes (eg, hematogenous spread through blood vessels, lymphangitic spread through lymph channels, local extension to surrounding structures). Local therapies, such as breast surgery and irradiation, do not eradicate distant micrometastases; therefore, systemic therapy is required to target these tumor cells that may have escaped the local area of the breast. The risk of micrometastatic disease is one factor used to identify patients with a high risk of recurrence who would require systemic adjuvant therapy. Chemotherapy, endocrine therapy, targeted therapy, or some combination of these agents improves disease-free and/or overall survival for high-risk patients in specific prognostic subgroups (eg, nodal involvement, menopausal status, hormone-receptor status, or *HER2* status) based on the results of several hundred randomized clinical trials.

The benefit of adjuvant chemotherapy has been studied and established through several clinical trials over the years. With the evolution of chemotherapy regimens to the current standard, disease-free survival is increased with the addition of chemotherapy regardless of ER/PR status. A 12.4% increase in 5-year disease-free survival is seen when taxanes are added to anthracycline chemotherapy.[25] Five-year overall survival is increased with the addition of chemotherapy, but longer follow-up may be needed to solidify this benefit. Adjuvant chemotherapy is recommended in most women with lymph node metastases or with primary breast cancers larger than 1 cm in diameter (both node-negative and node-positive).[26]

6 Several international and national groups have developed guidelines for the treatment of ESBC based on specific patient and disease characteristics and as newer data are available. The four most commonly referenced guidelines are the St. Gallen International Expert Consensus Conference, European Society of Medical Oncology, or ESMO, the American Society of Clinical Oncology (ASCO), and the NCCN guidelines.[14,27–29] These guidelines are updated annually to every 2 years or more frequently based on available evidence. Recommendations from the NCCN guidelines for patients with tumors 1 cm or larger or positive lymph nodes are summarized in Fig. 151-3. For patients with tumors smaller than 1 cm, micrometastatic lymph node involvement, or negative lymph nodes, treatment is highly individualized and based on multiple patient- and tumor-related factors, including hormone-receptor status, *HER2* status, comorbidities, and patient preferences. Specific treatment recommendations are complex and readers are referred to the guidelines for further details.

FIGURE 151-3

Treatment of patients with breast cancers larger than 1 cm or with positive lymph nodes. Refer to the text for definitions of HR and *HER2* positivity. Refer to the text for the management of patients with tumors smaller than 1 cm, micrometastatic lymph node involvement, or negative lymph nodes.



[a]Oncotype DX® may identify patients who derive little benefit from chemotherapy (see the "Genomic Testing" section under Curative Breast Cancer for details). (HR, hormone receptor; *HER2*, human epidermal growth factor receptor-2.)

The use of neoadjuvant systemic therapy is the standard of care for patients with locally advanced breast cancer and IBC and represents an important treatment option for patients with ESBC. This approach to therapy usually consists of chemotherapy, either alone or combined with biologic or targeted therapy, but in special circumstances may also include endocrine therapy (eg, in inoperable patients with significant comorbidities or in tumors with high sensitivity to endocrine therapy). Advantages of preoperative systemic therapy include a decrease in tumor size to minimize surgery, determination of response to chemotherapy or hormone therapy (an important prognostic indicator), and other theoretical advantages (eg, delivery of chemotherapy through an intact vascular system). Preoperative chemotherapy has similar disease-free or overall survival rates compared with adjuvant chemotherapy (the same chemotherapy and the same number of cycles), but is associated with higher rates of BCT.[14] Patients who receive neoadjuvant chemotherapy may experience a pathological complete response (defined as no tumor left at surgery [pCR]) after chemotherapy. Patients who achieve a pCR have a significantly longer disease-free and overall survival compared to patients who do not achieve a pCR.[14] The use of preoperative systemic therapy in patients with ESBC is generally recommended because of the ability to assess the response to therapy as well as the potential to decrease the size of the tumor, allowing for less radical surgery and better cosmetic results.

The most common cytotoxic drugs that have been used alone and in combination as adjuvant therapy for breast cancer include doxorubicin, epirubicin, cyclophosphamide, methotrexate, fluorouracil, carboplatin, paclitaxel, and docetaxel. Combination chemotherapy regimens (polychemotherapy) are more effective than single-agent chemotherapy. Table 151-5 lists the most common combination chemotherapy regimens used.

TABLE 151-5

Selected Neo/Adjuvant Chemotherapy Regimens for Breast Cancer

Dose-Dense AC → Paclitaxel[a]	**AC → Paclitaxel**
Doxorubicin 60 mg/m^2 IV bolus, day 1	Doxorubicin 60 mg/m^2 IV, day 1
Cyclophosphamide 600 mg/m^2 IV, day 1	Cyclophosphamide 600 mg/m^2 IV, day 1
Repeat cycles every 14 days for 4 cycles (must be given with growth factor support)	Repeat cycles every 21 days for 4 cycles
Followed by:	*Followed by:*
Paclitaxel 80 mg/m^2 IV weekly	Paclitaxel 80 mg/m^2 IV weekly
Repeat cycles every 7 days for 12 cycles	Repeat cycles every 7 days for 12 cycles
TC[a]	
Docetaxel 75 mg/m^2 IV, day 1	
Cyclophosphamide 600 mg/m^2 IV, day 1	
Repeat cycles every 21 days for 4 cycles	
Dose-Dense AC → Dose Dense Paclitaxel[a]	
Doxorubicin 60 mg/m^2 IV bolus, day 1	
Cyclophosphamide 600 mg/m^2 IV, day 1	
Repeat cycles every 14 days for 4 cycles (must be given with growth factor support)	
Followed by:	
Paclitaxel 175 mg/m^2 IV over 3 hours	
Repeat cycles every 14 days for 4 cycles (must be given with growth factor support)	

AC, Adriamycin (doxorubicin), Cytoxan (cyclophosphamide); TC, Taxotere (docetaxel), cyclophosphamide.

[a]Designated as a preferred regimen in the NCCN Breast Cancer Guidelines.

Data from Reference 14.

Anthracyclines (doxorubicin or epirubicin) and taxanes (paclitaxel or docetaxel) have become the cornerstones of modern chemotherapy for the adjuvant treatment of breast cancer. Anthracycline-containing chemotherapy regimens decrease the 10-year risk of recurrence from 47% to 39% and 10-year overall mortality from 40% to 35%. As mentioned previously, the addition of taxanes to anthracycline-based chemotherapy has a modest

added benefit in disease-free survival.[25,26] Proportional reductions in recurrence and breast cancer mortality were largely independent of age, nodal status, tumor size, tumor differentiation, or ER status. Most of these trials enrolled node-positive patients only, but some high-risk node-negative patients were also included.[26,30]

Cytotoxic chemotherapy is a particularly important treatment modality for patients with tumors that do not express ER or PR and do not overexpress *HER2* (often referred to as triple-negative breast cancer [TNBC]).[31] TNBC represents an uncommon subtype (10%-15%) and has a relatively poor prognosis.[32] Patients with TNBC treated with anthracycline- and taxane-based chemotherapy have significantly decreased survival compared to patients with other breast cancer subtypes. Ironically, this patient subgroup is more likely to respond to neoadjuvant chemotherapy. Furthermore, patients with TNBC who achieve a pCR have excellent long-term survival, but those who have residual disease at the time of surgery have a worse prognosis than non-TNBC patients. The optimal type and duration of chemotherapy for patients with TNBC is unknown. More recently, the addition of carboplatin to a neoadjuvant anthracycline- and taxane-based chemotherapy regimen resulted in a higher pCR rate as compared to chemotherapy without carboplatin, but with increased toxicity.[31] Adding pembrolizumab, an immune checkpoint inhibitor, to neoadjuvant chemotherapy and as adjuvant therapy following surgery, improves pCR rates even more and prolongs time to disease recurrence compared with chemotherapy alone.[33] Identification of actionable molecular targets for this aggressive breast cancer subtype is needed and ongoing (eg, [EGFR] and poly-ADP ribose polymerase [PARP]). Adjuvant capecitabine for 6 to 8 cycles may be offered because it improves disease-free and overall survival as compared to those who did not receive additional chemotherapy.[34]

Although the optimal duration of chemotherapy administration is unknown, it takes between 12 and 24 weeks and depends on the regimen being used. Optimally, chemotherapy should be initiated within 12 weeks of surgical removal of the primary tumor.[35] “Dose intensity” and “dose density” are critical factors in achieving optimal outcomes in adjuvant breast cancer therapy. *Dose intensity* is defined as the amount of drug administered per unit of time and is typically reported in milligrams per square meter of body surface area per week (mg/m^2/week). Increasing dose, decreasing time between doses, or both can increase dose intensity. *Dose density* is one way of achieving dose intensity but not by increasing the amount of drug given, as occurs with dose escalation, but instead by decreasing the time between treatment cycles. Dose reductions for standard treatment regimens should be avoided unless necessitated by severe toxicity. Increasing doses beyond those contained in standard treatment regimens does not appear to be beneficial and may be harmful.

The short-term toxicities of chemotherapy used in the adjuvant setting are generally well tolerated. Supportive therapy of patients receiving systemic adjuvant chemotherapy has improved over the past decades. More effective antiemetics have become available to manage chemotherapy-induced nausea and vomiting, and myeloid growth factors can prevent febrile neutropenia, particularly in elderly patients and patients receiving dose-dense chemotherapy regimens. The use of myeloid growth factors to support some adjuvant chemotherapy regimens may be required (eg, with dose-dense regimens), but these are not routinely used with adjuvant chemotherapy regimens. Many other adverse drug reactions are common with the chemotherapy regimens used for the treatment of ESBC, and patients should be appropriately counseled regarding the likelihood of alopecia, weight gain, fatigue, peripheral neuropathy, and myelosuppression. Patients who are menstruating often experience a cessation of menses that may not return; cessation of menses may be accompanied by signs and symptoms of menopause. Leukemia and other hematologic disorders have long been associated with the alkylating agents (eg, cyclophosphamide) and the topoisomerase II inhibitors (eg, doxorubicin and epirubicin; see Chapter 150, “Supportive Care in Cancer” for more information).

Cardiomyopathy induced by doxorubicin occurs in fewer than 1% to 2% of individuals whose total dose of anthracycline is less than 300 mg/m^2 of doxorubicin equivalents.[36] This risk may be further decreased by the use of continuous infusion or weekly doxorubicin. It should be noted that epirubicin in the adjuvant setting is usually given at a dose of 100 mg/m^2.[14] At this dose, epirubicin has an equal risk of cardiomyopathy as standard doxorubicin doses when both agents are given as bolus or short infusions. Taxanes are often associated with hypersensitivity reactions, peripheral neuropathy, or myalgias and arthralgias for a few days after the infusion.

It is currently not possible to accurately predict who will attain this survival benefit. Genetic prognostic tools, such as Oncotype DX®, can help to identify patients who may derive little or no benefit from chemotherapy. However, these tests are only appropriate in specific subsets of patients. Many adjuvant chemotherapy regimens are available, but most of these regimens have not been directly compared in randomized clinical trials. NCCN guideline recommendations are purposefully vague, and they do not differentiate between patients with node-positive or -negative breast cancer. The NCCN guidelines have designated preferred chemotherapy regimens, as listed in Table 151-5, although detailed information is not provided regarding the rationale behind these designations.

Biologic or Targeted Therapy

Therapies directed at molecular targets through novel mechanisms are often referred to as targeted therapy. Many of the targeted therapies are also biologic therapies because they are mAbs. Trastuzumab is a mAb targeted against the *HER2*-receptor protein.

HER2-Targeted Agents

Trastuzumab in combination with or sequentially after adjuvant chemotherapy is recommended for patients with early-stage, *HER2*-positive breast cancer, resulting in a 48% reduction in the risk of recurrence as well as superior disease-free and overall survival, compared with chemotherapy alone (Table 151-6).[14] Although the benefit of adding trastuzumab to these regimens is clear, the optimal trastuzumab-based regimen is less clear because the type of chemotherapy, sequence of administration, and duration of trastuzumab differed among the trials.

TABLE 151-6

Selected Regimens for HER2-Positive Early-Stage Breast Cancer

Neo/Adjuvant Regimen	Drugs	Doses	Frequency	Cycles
PH → H[a]	Paclitaxel	80 mg/m^2 IV over 1 hour	Every 7 days	12 weeks
	Trastuzumab	4 mg/kg IV → 2 mg/kg IV	Every 7 day	12 weeks
	Followed by			
	Trastuzumab	6 mg/kg IV	Every 21 days	Complete 1 year
TCH[a]	Docetaxel	75 mg/m^2 IV	Every 21 days	6
	Carboplatin	AUC 6 IV	Every 21 days	6
	Trastuzumab	4 mg/kg IV → 2 mg/kg IV	Every 7 days	18 weeks
	Followed by			
	Trastuzumab	6 mg/kg IV	Every 21 days	Complete 1 year
TCHP[a]	Docetaxel	75 mg/m^2 IV	Every 21 days	6
	Carboplatin	AUC 6 IV	Every 21 days	6
	Trastuzumab	8 mg/kg IV → 6 mg/kg IV	Every 21 days	6
	Pertuzumab	840 mg IV → 420 mg IV	Every 21 days	6
	Followed by			
	Trastuzumab	6 mg/kg IV	Every 21 days	Complete 1 year
	Pertuzumab	420 mg IV	Every 21 days	Complete 1 year

PH (paclitaxel, trastuzumab); TCH (docetaxel, carboplatin, trastuzumab); TCHP (docetaxel, carboplatin, trastuzumab, pertuzumab).

[a]Designated as a preferred regimen in the NCCN Breast Cancer Guidelines.

Data from Reference 14.

Most of the regimens investigated in these adjuvant trials included an anthracycline and a taxane given concurrently with trastuzumab or sequentially before trastuzumab. Administration of a taxane with trastuzumab may be more effective than trastuzumab administered after chemotherapy. Sequential and concomitant use of trastuzumab with chemotherapy prolongs disease-free survival as compared with chemotherapy alone. Concomitant trastuzumab also improves overall survival, but sequential trastuzumab does not.[14] The adjuvant use of trastuzumab without an anthracycline provides similar benefit with diminished cardiac adverse drug reactions as compared with traditional anthracycline-containing adjuvant trastuzumab regimens.[14] The optimal duration of trastuzumab therapy is unknown, although the majority of data support the use of trastuzumab for a total of 52 weeks (range, 9-104 weeks). The most commonly used trastuzumab-based neo/adjuvant chemotherapy regimens are listed in Table 151-6.

The addition of mAb pertuzumab is another important treatment option for patients with *HER2*-positive breast cancer in the neoadjuvant setting.[37] The addition of pertuzumab to trastuzumab and chemotherapy produces high rates of pCR at the time of surgery in patients with tumors larger than 2 cm or positive lymph nodes (see Table 151-6 for details regarding the most commonly used regimens). Additionally, an approximately 1% absolute benefit in invasive disease-free survival at 3 years that continues for at least 6 years as well as an improvement in overall survival can occur with the addition of pertuzumab. The FDA added an indication for pertuzumab in combination with trastuzumab in the adjuvant setting for high-risk *HER2*-positive breast cancer based on this trial.[38] A newer formulation containing pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use is approved for the treatment of *HER2*-positive breast cancer in all settings.[39]

The incidence of adverse cardiac drug reactions associated with the addition of trastuzumab increases when an anthracycline is included in the regimen before administration of trastuzumab. The risk of symptomatic heart failure with adjuvant trastuzumab ranges from 0.5% to 4%.[40] The higher risk of cardiac complications may be acceptable in many patients, given the significant reductions in breast cancer recurrence and death. Sequential administration of trastuzumab after chemotherapy produces a lower incidence of cardiac toxicity. Also, the use of a non-anthracycline–based regimen (see Table 151-6) is associated with a low incidence of symptomatic heart failure as compared with other regimens.[14] Concurrent administration of trastuzumab with an anthracycline is controversial because of potentially higher rates of cardiac dysfunction (see the "*HER2-Targeted Agents*" section under MBC [Stage IV] for more toxicity details) and not generally recommended outside of a clinical trial.

Patients who received concurrent radiation therapy with adjuvant trastuzumab do not experience a significant increase in cardiac events or acute radiation-related adverse drug reactions.[41] Therefore, if radiation therapy is clinically indicated, trastuzumab is typically administered concomitantly with radiation.

Many questions remain regarding the optimal use of trastuzumab in the adjuvant or neoadjuvant therapy of ESBC. The use of trastuzumab with chemotherapy in the adjuvant or neoadjuvant setting is now considered to be the standard of care for patients with node-positive and high-risk node-negative *HER2*-positive breast cancer.[14] The use of *HER2*-targeted therapy in patients with small, *HER2*-positive, node-negative tumors is controversial. A single arm, nonrandomized clinical trial demonstrated an excellent 3-year disease-free survival (98.7%) in patients who received weekly paclitaxel and trastuzumab for 12 weeks, followed by trastuzumab every 3 weeks for a total of 1 year in patients with lymph-node negative, *HER2*-positive, breast cancers smaller than 3 cm.[42] Seven-year follow-up data reported disease-free survival of 93% and an overall survival of 97% which confirms the benefit of this regimen in small, *HER2*-positive, node-negative tumors.[43] The NCCN guidelines recommend consideration of this regimen for patients who have pathologic T1N0M0 *HER2*-positive breast cancer.[14] Neratinib (240 mg by mouth daily for 1 year), an oral tyrosine kinase inhibitor of EGFR, *HER2*, and *HER4*, is indicated for extended adjuvant therapy after completion of trastuzumab (within previous 2 years) based on small improved disease-free survival. The most common adverse drug reactions of neratinib include diarrhea, which requires aggressive management, as well as nausea, fatigue, and vomiting. Neratinib may be an option for extended adjuvant therapy in some patients at higher risk of recurrence.[44]

The use of ado-trastuzumab emtansine (also known as T-DM1) in the adjuvant setting following neoadjuvant therapy when residual disease is found at the time of surgery is the standard of care because it improves invasive disease-free survival at 3 years compared with trastuzumab (88% vs 77%).[14,45] Patients should be counseled on adverse drugs reactions of ado-trastuzumab emtansine that are different than trastuzumab. Ado-trastuzumab emtansine is associated with peripheral neuropathy, thrombocytopenia, and liver dysfunction.

PARP Inhibitors

PARP is a family of enzymes partially responsible for repairing single-strand DNA breaks. Patients who harbor a germline mutation in *BRCA1* or *BRCA2* have impaired ability to repair double-strand DNA breaks. TNBC is strongly associated with germline mutations in the *BRCA1* gene.[46] Patients with a *BRCA1* or *BRCA2* mutation are candidates for adjuvant therapy with the PARP inhibitor olaparib for 1 year. Olaparib is associated with anemia, fatigue, and nausea.

CDK Inhibitors

CDK, in coordination with their regulatory cyclin partners, form CDK-cyclin heterodimer complexes that control cell cycling. CDK-4 and -6 are critical components of this process. In some breast cancer cell lines, these complexes are responsible for phosphorylating the retinoblastoma tumor

suppressor gene product, or RB, thus inactivating the suppression of cell division and allowing unregulated progression through the cell cycle. Patients with HR-positive, *HER2*-negative and high risk disease are candidates for 2 years of adjuvant abemaciclib with endocrine therapy. Neutropenia and dose-limiting diarrhea are common adverse drug reactions. Abemaciclib is also associated with a "false" elevation in serum creatinine.

Endocrine Therapy

5 Endocrine therapies that have been studied in the treatment of primary or early-stage breast cancer include tamoxifen, toremifene, oophorectomy, ovarian irradiation, luteinizing hormone–releasing hormone (LHRH) agonists, and AIs. The choice of agent(s) depends on menopausal status of the individual.

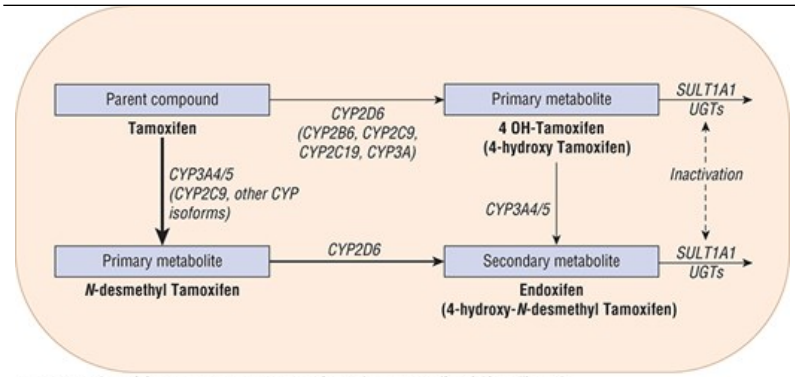
If chemotherapy and radiation therapy are not indicated, adjuvant endocrine therapy is generally initiated shortly after surgery or as soon as pathology results are known. When adjuvant chemotherapy is also indicated, endocrine therapy should be administered after chemotherapy is completed.[14] Some clinicians also recommend the initiation of endocrine therapy after completion of radiation therapy, but this recommendation is controversial because few trials have addressed the issue of concurrent versus sequential endocrine therapy and radiation therapy.

Tamoxifen is historically considered as the gold standard adjuvant endocrine therapy and has been used in this setting for several decades. Tamoxifen is antiestrogenic in breast cancer cells, but it has estrogenic properties in other tissues and organs.[47] More recent studies show that tamoxifen, and other similar drugs, have many estrogenic and antiestrogenic effects that depend on the tissue and the gene in question, and they are more appropriately considered SERMs. Women receiving adjuvant tamoxifen therapy have reduced risk of recurrence and mortality compared with women not receiving adjuvant tamoxifen therapy.[47] In the United States, tamoxifen is generally considered the adjuvant endocrine therapy of choice for premenopausal women, although newer data also support the use of LHRH agonists or oophorectomy in combination with AIs.

The pharmacologic disposition of tamoxifen in humans is complex (see Fig. 151-4). Tamoxifen is considered a prodrug. Although the parent compound has significant clinical activity, tamoxifen is metabolized through multiple enzymes, including cytochrome P450 (CYP)3A4, CYP2C19, CYP2D6, and others, to metabolites that are more active than the parent compound.[47] The active metabolites 4-hydroxytamoxifen (4OH-tamoxifen) and 4-hydroxy-*N*-desmethyltamoxifen (endoxifen) have nearly a 100-fold higher affinity for the ER as compared with tamoxifen. Endoxifen is present in the serum at a 6- to 12-fold higher concentration as compared with 4OH-tamoxifen, and is considered to be the most important metabolite for the clinical activity of tamoxifen. Polymorphisms in CYP2D6 can increase or decrease the formation of endoxifen and may improve or diminish clinical outcomes, respectively. Although some studies have reported an association between certain CYP2D6 polymorphisms and poorer disease-free or relapse-free survival in patients receiving tamoxifen, other studies report either no relationship or the opposite effect between clinical outcomes and CYP2D6 polymorphisms. Multiple commercially available CYP2D6 assays are available, but widespread testing for patients receiving tamoxifen is not currently recommended based on available evidence.[14] Potent inhibitors of CYP2D6, such as paroxetine and fluoxetine, may decrease endoxifen levels in patients receiving tamoxifen.[14] The clinical outcomes related to such drug-drug interactions in an individual patient are largely unknown and may depend on their underlying CYP2D6 genetic status (eg, poor metabolizer, extensive metabolizer). Although high-quality evidence on strong CYP2D6 inhibitors and breast cancer outcomes in patients receiving tamoxifen is limited, many experts recommend avoidance of known strong inhibitors of CYP2D6, if possible, in patients receiving tamoxifen.

FIGURE 151-4

Tamoxifen metabolism. Widths of the arrows approximate the allocation of parent compound to various metabolites. An equation shows the metabolism of tamoxifen. The parent compound tamoxifen forms primary metabolite 4 OH-tamoxifen or 4-hydroxy tamoxifen in the presence of CYP2D6, CYP2B6, CYP2C9, CYP2C19, and CYP3A, and forms primary metabolite *N*-desmethyl tamoxifen in the presence of CYP3A45 or CYP2C9 and other CYP isoforms. Secondary metabolite endoxifen or 4-hydroxy-*N*-desmethyl tamoxifen is formed from 4 OH-tamoxifen in the presence of CYP3A4 5 and from *N*-desmethyl tamoxifen in the presence of CYP2D6. SULT1A1 and UGTs inactivate 4 OH-tamoxifen and endoxifen.



The duration of tamoxifen therapy in the adjuvant setting is 5 to 10 years. Results of several studies suggest that a longer duration (eg, 10 years vs 5 years) of tamoxifen may be more effective in some patients. Some studies showed improved disease-free survival (ATLAS trial, aTTom trial) and improved overall survival (ATLAS trial), whereas other trials showed detrimental effects.[14,48] Increased adverse drug reactions occur with 10 years of tamoxifen therapy, including an increased risk of developing endometrial cancer (ATLAS and aTTom trials) and pulmonary embolism (ATLAS trial only) compared with those receiving tamoxifen for 5 years.[14] Based on these data, the administration of tamoxifen for 10 years can be considered in women with a higher risk of breast cancer recurrence.

The most reliable information regarding the adverse drug reactions of tamoxifen comes from the NSABP Breast Cancer Prevention Trial (P-1).[4] This trial randomized women 35 years of age or older who were at increased risk for breast cancer to placebo or to 20 mg/day of tamoxifen for 5 years. Although the primary finding of this study is that tamoxifen reduces the risk of invasive breast cancer by 49%, this study also provides comprehensive data on the risk of adverse drug reactions associated with tamoxifen. The only symptomatic differences noted between the placebo and tamoxifen group were related to hot flashes and vaginal discharge, both of which occurred more often in the tamoxifen group. No important differences between the two groups were observed in the various self-reported instruments (eg, depression scale, a global quality-of-life, and a sexual function scale). Tamoxifen did not increase the risk of ischemic heart disease but did reduce the risk of hip radius and spine fractures. The risks of stroke, pulmonary embolism, and deep vein thrombosis were higher in the tamoxifen group, particularly in women aged 50 years or older. The rate of endometrial cancer was also increased in the tamoxifen group, and this increased risk occurred primarily in women aged 50 years or older. The increased risk of endometrial carcinoma is similar in magnitude to that associated with postmenopausal estrogen replacement therapy and is likely related to an estrogenic effect of tamoxifen on the endometrium. Some experts argue that this risk is acceptable because endometrial cancer induced by tamoxifen is low stage, low grade, easily treated with surgery and does not pose a life-threatening risk to women. Tamoxifen was also associated with an increased risk of uterine sarcomas (a more aggressive form of endometrial cancer), but this risk is lower than the more common endometrial cancers identified in the study. Routine endometrial biopsy is not currently recommended for women receiving tamoxifen therapy. However, women receiving tamoxifen therapy should be counseled to have regular gynecologic examinations and immediately report unusual vaginal bleeding to their primary clinicians for further evaluation.[4]

In premenopausal women, the use of LHRH agonists (ovarian suppression) or ovarian ablation provides benefit in the adjuvant setting. Agents used to suppress ovarian function in this setting include goserelin, triptorelin, and leuprolide. A benefit was observed with goserelin as compared with CMF (cyclophosphamide, methotrexate, fluorouracil) chemotherapy in patients with hormone-sensitive premenopausal breast cancer but not in patients with hormone-receptor–negative tumors.[14] It is not clear whether the benefit of chemotherapy in this population is a result of the antitumor activity of chemotherapy or the endocrine effects of chemotherapy-induced amenorrhea. Consequently, some studies have investigated the benefits of adding ovarian ablation or suppression to chemotherapy either with or without tamoxifen. Results from these studies clearly indicate a benefit from ceasing menses regardless of whether this is caused by chemotherapy or ovarian ablation or suppression.[14] The optimal duration of adjuvant LHRH agonist use is unknown, with trials ranging from 18 months to 5 years of treatment. Two published clinical trials evaluated an LHRH agonist combined with tamoxifen or an AI in premenopausal women. In the Tamoxifen and Exemestane Trial (TEXT), premenopausal patients with hormone receptor–positive ESBC were randomized to receive 5 years of tamoxifen or exemestane, both concomitantly with triptorelin for ovarian suppression. In the Suppression of Ovarian Function Trial (SOFT), premenopausal patients with hormone receptor–positive ESBC were randomized to receive 5 years of tamoxifen alone, tamoxifen with triptorelin, or exemestane with triptorelin. Combined results of the tamoxifen/triptorelin arms and exemestane/triptorelin arms from SOFT and TEXT showed significantly prolonged 5-year disease-free survival with exemestane as compared to tamoxifen.[49] In a subsequent

analysis of SOFT, the estimated 5-year disease-free survival rate was similar with tamoxifen alone versus tamoxifen with ovarian suppression.[50] As expected, patients who received tamoxifen with ovarian suppression experienced more menopausal symptoms such as hot flushes, sweating, and vaginal dryness as compared to patients who received tamoxifen alone. Based on these data, the combination of ovarian suppression and an AI is recommended in premenopausal women with hormone receptor–positive ESBC. Tamoxifen is still considered an option for adjuvant endocrine therapy in certain patients (eg, low-risk of recurrence and/or intolerance to ovarian suppression plus AI).[14]

In postmenopausal women, AIs are the standard of care in the adjuvant setting. Four different approaches to therapy have been undertaken with these agents as outlined in Table 151-7.

TABLE 151-7

Adjuvant Endocrine Therapy Options for Postmenopausal Women

Aromatase inhibitor for 5 years
Tamoxifen for 2-3 years followed by aromatase inhibitor to complete 5 years of endocrine therapy
Tamoxifen for 2-3 years followed by up to 5 years of aromatase inhibitor
Aromatase inhibitor for 2-3 years followed by tamoxifen to complete 5 years of endocrine therapy
Tamoxifen for 4.5-6 years followed by aromatase inhibitor for 5 years *or* consider tamoxifen for an additional 5 years to complete 10 years
If contraindication to aromatase inhibitors, patients who decline or are intolerant of aromatase inhibitors, tamoxifen for 5 years ≤10 years

Data from Reference 14.

Most national and international guidelines currently recommend incorporation of an AI into the adjuvant endocrine therapy regimen for all postmenopausal, hormone-sensitive breast cancers.[14] The NCCN guidelines consider the three available AIs (anastrozole, letrozole, and exemestane) to have similar antitumor efficacy and toxicity profiles. AIs are generally well tolerated. Adverse drug reactions include bone loss or osteoporosis, hot flashes, myalgias or arthralgias, vaginal dryness or atrophy, mild headaches, and diarrhea. Bone modifying agents, which are often coadministered with AIs in the metastatic setting, may also be beneficial in patients treated with AIs in the adjuvant setting (see Chapter 112, "Osteoporosis" for more detail). Other worrisome adverse drug reactions include questionable effects on the cardiovascular system (eg, hypercholesterolemia), cognitive functioning, and joint health.

All patients with ER/PR-positive breast cancer should be offered adjuvant endocrine therapy determined by their menopausal status and risk of recurrence.

Metastatic Breast Cancer (MBC, Stage IV)

Treatment of MBC with cytotoxic, endocrine, or targeted therapy often results in regression of disease and improvements in quality of life. More recent advances have also improved overall survival with the addition of biologic or targeted therapies. The choice of therapy for metastatic disease is based on the presence or absence of certain tumor characteristics. The most important predictive factors are *HER2*, estrogen, and progesterone receptors in the primary or metastatic tumor tissue. Tumors overexpressing *HER2* receptor protein are more likely to benefit from *HER2*-targeted therapy. Regimens that combine *HER2*-targeted therapy with chemotherapy are preferred first-line therapy for these patients.[51] Tumors expressing high levels of ER, PR, or both are more likely to respond to endocrine therapy. The addition of targeted therapies that overcome endocrine resistance are first-line regimens in this patient population. For TNBC, tumors expressing programmed death-ligand (PD-L1) benefit from the addition of immunotherapy to cytotoxic chemotherapy. For cases where hormone receptors and *HER2* receptors are over-expressed, an endocrine agent combined with a *HER2*-targeted agent may be considered in patients who cannot tolerate cytotoxic chemotherapy.[51] Patients with symptomatic visceral or central nervous system involvement generally have more rapidly growing cancers that require initial chemotherapy regardless of tumor marker status (eg, ER/PR).

Patients who respond to first-line therapy often respond to a second- (or even third-) line of therapy. The response rate, however, is lower and the duration of response is shorter with second- (and third-) line therapy. Patients with hormone receptor-positive MBC typically receive several sequential endocrine therapy regimens (alone or with a targeted agent) until their tumors cease to respond or the patient ceases to benefit from endocrine therapy, at which time cytotoxic chemotherapy can be administered. Subsequent chemotherapy after endocrine/targeted therapy combinations is recommended for patients who can tolerate chemotherapy. Concurrent administration of more than one endocrine therapy or combining chemotherapy plus endocrine therapy is generally avoided in the setting of MBC because of increased toxicity and no substantial improvement in overall survival. Women with hormone receptor–negative tumors; or those with rapidly progressive or symptomatic lung, liver, or bone marrow involvement (a visceral crisis); or progressive disease while on initial endocrine therapy (with or without a targeted agent) are treated with cytotoxic chemotherapy.[14] If a patient's disease progresses while on the first-line chemotherapy regimen or if the patient is unable to tolerate the regimen due to toxicities, a subsequent regimen is selected.

All breast cancer patients with bone metastases should be considered for treatment with a bone-modifying agent (eg, pamidronate, zoledronic acid, or denosumab) because these agents decrease the risk of skeletal-related events, such as fractures, spinal cord compression, and pain, and the need for radiation to the bones or surgery.[52] These agents do not act as anticancer agents and should be co-administered with other therapies targeting the cancer cells. The frequency of administration is dependent on the agent selected and could be every month versus every 3 months. See Chapter 150, "Supportive Care in Cancer" for more information.

Desired Outcomes

4 MBC is currently incurable and palliation is the goal of treatment. However, some patients live for many years with metastatic disease, making this a chronic disease requiring long-term management strategies that improve or maintain quality of life. Therefore, sequential single-agent chemotherapy is often chosen over combination chemotherapy regimens, but specific clinical situations may require more rapid responses in which combination chemotherapy may be indicated. Endocrine therapy is generally better tolerated than chemotherapy and may be a more appropriate option for patients with hormone receptor–positive breast cancer. Tumor response to a particular treatment regimen may be measured by changes in laboratory tests, diagnostic imaging, and physical signs and symptoms. The patient usually continues treatment with the regimen, unless the patient cannot tolerate the regimen or the cancer is progressing at a rate that will cause symptoms (or is causing symptoms already). Optimizing quality of life is an important therapeutic end point in the treatment of patients with MBC and eventually requires discontinuation of active cancer therapy and a shift to supportive care with hospice services. Oncology clinicians, in close collaboration with their patients, consider these tradeoffs between quantity and quality of life when making treatment decisions.

Chemotherapy

8 Cytotoxic chemotherapy is eventually required in most patients with MBC. Most patients with MBC have tumors that lack *HER2*-overexpression. Hormone receptor–positive tumors that fail to respond to initial endocrine/targeted therapy regimens or become refractory to endocrine therapy require chemotherapy. Patients with TNBC require chemotherapy as initial therapy of metastases.

Combination chemotherapy results in an objective response in about 47% to 55% of unselected, chemotherapy-naïve patients.[14] The clinical use of biomarkers and genetic panels to assist treatment decisions is relatively new. In the absence of predictive biomarkers, chemotherapy is chosen based on overall efficacy, the risk of toxicity, performance status and presence of comorbidities in the patient, aggressiveness of disease (eg, indolent vs visceral crisis), and patient preferences related to schedules, dosing route (eg, oral vs intravenous), and frequency (eg, weekly vs every 3 weeks) of the chemotherapy.

While response rates are high with combination chemotherapy, sequential use of single-agent therapies is also an effective strategy that may be preferred due to decreased rates of adverse drug reactions. In the palliative setting, when efficacy is similar, the least toxic approach is preferred. In clinical practice, patients who require a rapid response (eg, those with symptomatic bulky metastases or a visceral crisis) should receive combination chemotherapy despite the added toxicity. This decision is complex and should be made on an individual patient basis.

Most patients experience partial responses to chemotherapy. The median duration of response is highly variable, ranging from 3 to 15 months. Some patients with small volume metastatic disease will have an excellent response to an initial course of chemotherapy and may live 5 to 10 years or longer without evidence of disease. The median overall survival for patients after commonly used chemotherapy combinations ranges between 10 and 33

months. After a chemotherapy regimen has been initiated, it is usually continued until progressive disease or intolerable adverse drug reactions occur.[53] Table 151-8 lists some selected chemotherapy agents used in the metastatic setting.

TABLE 151-8

Selected Regimens for *HER2*-Negative Metastatic Breast Cancer

Single Agent Chemotherapy	
Paclitaxel[a]	**Vinorelbine**[a]
Paclitaxel 175 mg/m^2 IV Repeat cycle every 21 days *or* Paclitaxel 80 mg/m^2/week IV Repeat dose every 7 days	Vinorelbine 25 mg/m^2/week IV Repeat dose every 7 days
Capecitabine[a]	**Gemcitabine**[a]
Capecitabine 1,000-1,250 mg/m^2 orally twice daily for 14 days Repeat cycle every 21 days	Gemcitabine 800-1,200 mg/m^2/week IV, days 1, 8, and 15 Repeat cycle every 28 days
Eribulin[a]	**Liposomal Doxorubicin**[a]
Eribulin 1.4 mg/m^2 IV, days 1 and 8 Repeat cycle every 21 days	Liposomal doxorubicin 50 mg/m^2 IV Repeat cycle every 28 days
Combination Chemotherapy Regimens	
Gemcitabine + Carboplatin	**Docetaxel + Capecitabine**
Gemcitabine 1,000 mg/m^2 IV, days 1 and 8 Carboplatin AUC 2 IV, days 1 and 8 Repeat cycle every 21 days	Docetaxel 75 mg/m^2 IV, day 1 Capecitabine 950 mg/m^2 orally twice daily for 14 days Repeat cycle every 21 days
Additional Targeted Therapies	
Olaparib[a]	**Talazoparib**[a]
Olaparib tablet 300 mg orally twice daily Repeat cycle every 28 days	Talazoparib tablet 1 mg orally daily Repeat cycles every 28 days
Atezolizumab + albumin bound paclitaxel[a]	**Pembrolizumab + chemotherapy (albumin-bound paclitaxel, paclitaxel, or gemcitabine + carboplatin)**[a]
Atezolizumab 840 mg IV, days 1 and 15 Albumin-bound paclitaxel 100 mg/m^2 IV, days 1, 8, and 15 Repeat cycle every 28 days	Pembrolizumab 200 mg IV, day 1 (given every 21 days) Albumin-bound paclitaxel 100 mg/m^2 IV, days 1, 8, and 15 (given every 28 days) *OR*

	Paclitaxel 90 mg/m^2 IV, days 1, 8, and 15 (given every 28 days) *OR* Pembrolizumab 200 mg IV, day 1 Gemcitabine 1,000 mg/m^2 IV, days 1 and 8 Carboplatin AUC 2 IV, days 1 and 8 Repeat cycle every 21 days

[a]Designated as a preferred regimen in the NCCN Breast Cancer Guidelines.

Data from Reference 14

Factors associated with an increased likelihood of response to chemotherapy include good performance status, a limited number (one to two) of disease sites (or involved organ systems), and prolonged previous response to chemotherapy or hormonal therapy (ie, long disease-free interval). Patients who develop progressive disease during chemotherapy have a lower likelihood of response to subsequent chemotherapy. However, this is not necessarily true for patients who are given chemotherapy after a treatment-free interval of substantial duration (eg, more than 1 year). Contrast to this, TNBC is an aggressive phenotype and is associated with poor prognosis because duration of response to chemotherapy is often short.

Many chemotherapeutic agents have demonstrated activity in the treatment of breast cancer, including doxorubicin (conventional and liposomal), epirubicin, paclitaxel (conventional and albumin-bound), docetaxel, capecitabine, fluorouracil, cyclophosphamide, methotrexate, vinblastine, vinorelbine, gemcitabine, ixabepilone, eribulin, carboplatin, cisplatin, mitomycin, thiotepa, and melphalan. The most active classes of chemotherapy in MBC are the anthracyclines and the taxanes, producing response rates as high as 50% in patients who have not received prior chemotherapy for metastatic disease.[14] Doxorubicin (conventional and liposomal) and epirubicin are generally considered therapeutically equivalent when dosed appropriately. Administration of these agents is limited by their cumulative cardiotoxicity. Paclitaxel, docetaxel, and albumin-bound paclitaxel are also FDA-approved for the treatment of MBC and are generally considered therapeutically equivalent but lack complete cross-resistance. Taxane administration is limited by cumulative peripheral neuropathy. Most patients will likely receive each of these agents at some point in the course of their MBC.

Many patients with MBC have been exposed to adjuvant chemotherapy consisting of an anthracycline and a taxane. If metastases are found within 6 to 12 months of completing treatment with these agents, many clinicians will choose a treatment from a different chemotherapy class. If it has been a long time since their adjuvant therapy, then retreating with the same agents may be considered. However, given the cardiotoxicity associated with the anthracyclines, the use of these agents in the metastatic setting has been generally avoided until the availability of liposomal anthracyclines. Pegylated liposomal doxorubicin is associated with less cardiotoxicity and similar efficacy compared with conventional doxorubicin and is a viable option for women who recur more than 1 year after their adjuvant anthracycline-containing chemotherapy regimen.[53]

Weekly administration of paclitaxel and albumin-bound paclitaxel results in higher response rates, time-to-progression, and survival and a more favorable adverse drug reaction profile compared with administration every 3 weeks.[14] With weekly administration, the toxicity profile of paclitaxel changes with less myelosuppression and delayed onset of peripheral neuropathy but slightly more fluid retention and skin and nail changes. Although the risk of hypersensitivity reactions is also slightly less at these lower doses (requiring fewer premedications), it remains at about 3% despite the incorporation of all available preventive measures. The most appropriate weekly dose of albumin-bound paclitaxel in the metastatic setting is not clear. Doses of 100 to 150 mg/m^2/week administered on days 1, 8, and 15 of a 28-day cycle have been investigated, demonstrating some evidence of a dose-response relationship. In the metastatic palliative setting, a lower dose is generally given to minimize toxicity while not significantly compromising efficacy. Docetaxel is most appropriately dosed on an every 3-week schedule for MBC. Weekly dosing did not produce improvements in disease response and was associated with significantly more toxicities than the every 3-week dosing strategy.

After patients have been treated with an anthracycline and a taxane, single-agent capecitabine, vinorelbine, or gemcitabine have resulted in response rates of 20% to 30%.[14] Of these agents, only capecitabine is FDA-approved as a single agent for MBC. Gemcitabine is only FDA-approved in combination with paclitaxel for MBC. However, all of these are included in most national and international guidelines as appropriate therapy for MBC. Decisions regarding which agent to choose are based on patient characteristics, expected toxicities, and previous exposure to chemotherapy.

Other antimicrotubule agents have also been approved for the management of MBC, demonstrating significant benefits in patients who have had prior exposure to other chemotherapy agents. Ixabepilone is an epothilone with a similar but distinct mechanism of action from the taxanes, binding to β-microtubulin in a unique manner but ultimately leading to microtubule stabilization and cell death, similar to the taxanes. It is approved for use in combination with capecitabine and as a single agent. Eribulin is another antimicrotubule agent with a unique mechanism of action. The first synthetic analogue of halichondrin B, eribulin inhibits polymerization of tubulin into microtubules and suppresses the microtubule growth phase, similar to the vinca alkaloids. The mechanism of action for eribulin differs from the vinca alkaloids, in that eribulin does not appear to have any effect on the microtubule shortening phase. These subtle differences may be important for eribulin's efficacy in patients who have been exposed to multiple therapies, including other antimicrotubule agents. It is approved for use as a single agent who have received at least two prior chemotherapies for their MBC.[14] Both of these agents are associated with similar toxicities compared with the taxanes and vinca alkaloids, respectively (eg, myelosuppression, neuropathy, myalgias or arthralgias, alopecia, and skin and nail changes with ixabepilone and myelosuppression and neuropathy with eribulin). Hypersensitivity is occasionally seen with ixabepilone because it is also solubilized in Cremophor-EL, the likely causative agent in paclitaxel-associated hypersensitivity. However, eribulin has not been associated with hypersensitivity reactions and is not formulated in a complex solvent system that may predispose patients to allergic-type reactions. Neuropathy may become problematic in patients who have received numerous sequential neurotoxic chemotherapy agents.

Sacituzumab govitecan-hziy, an antibody-drug conjugate (ADC), is approved for adult patients with metastatic TNBC and HR-positive, *HER2*-negative MBC who have received multiple other therapies. This ADC is combined with a topoisomerase I inhibitor (SN-38) that allows the antibody to target trophoblast cell surface antigen, or Trop-2, expressing cancer cells and then release the topoisomerase I inhibitor. The most common adverse drug reactions are nausea, diarrhea, and myelosuppression.[54]

Endocrine Therapy

9 Endocrine therapy should be considered in combination with a targeted agent as first-line therapy for patients with hormone-positive MBC, when feasible. The choice of endocrine therapy is based on the menopausal status of the patient, prior therapies and previous response, duration of response, or disease-free interval. Combinations of targeted therapies with endocrine agents may not be appropriate for all patients, and individual decisions should consider other comorbidities, the complexity of the regimen, expected adverse drug reactions, and drug or disease interactions.

The pharmacologic goal of endocrine therapy for breast cancer is to either (a) decrease circulating levels of estrogen or (b) prevent the effects of estrogen on breast cancer cells by blocking the hormone receptors or downregulating the presence of these receptors. The first goal depends on the menopausal status of the patient while the second goal is independent of menopausal status. Combinations of endocrine therapy with different mechanism of action have not demonstrated benefits over single-agent endocrine therapy and are generally not recommended outside the context of a clinical trial.

Several different classes of targeted agents are now approved in combination with endocrine therapy. These combinations address de novo or acquired resistance with endocrine therapy alone and have demonstrated efficacy over single agents in specific patient populations. However, combination therapy is generally associated with increased toxicity compared with single agent endocrine therapy. Optimal subsequent therapy after progression on initial targeted-endocrine treatment is largely unknown and the subject of ongoing clinical trials. However, most patients with hormone-positive MBC will receive several lines of targeted-endocrine combination regimens or endocrine therapy alone sequentially before chemotherapy is considered.

Outside of regimens that include novel targeted agents, little evidence exists that the survival benefit from one endocrine therapy is clearly superior to that achieved with other therapies in women with MBC. Prior to the availability of targeted agents, randomized controlled trials comparing different endocrine therapies (eg, antiestrogens, AIs, progestins, estrogens, androgens) and surgical procedures (eg, oophorectomy, adrenalectomy, and hypophysectomy) showed similar overall survival in patients with MBC. Therefore, the choice of a particular endocrine therapy was based primarily on the mechanism of action, toxicity, and patient preference (see Tables 151-9 and 151-10). Based on these criteria, AIs, tamoxifen or toremifene, and fulvestrant are the preferred initial agents in MBC except when the patient's cancer recurs during or within 1 year of adjuvant therapy with the same class of agent. In these cases, therapies from a different pharmacologic class were indicated.

TABLE 151-9

Drug Monitoring for Endocrine Therapies

Drug	Adverse Drug Reaction	Monitoring Parameters	Comments
Aromatase inhibitors	• Hot flashes • Arthralgias or myalgias • Osteoporosis • Hypercholesterolemia	• Patient assessment • BMD • Lipid panel	• Interval of monitoring controversial
Antiestrogens: SERMs[a]	• Hot flashes • Endometrial hyperplasia or cancer • Venous thromboembolism • Osteopenia (premenopausal women only)	• Patient assessment • Annual gynecologic assessment • Consider BMD for premenopausal women	• Routine transvaginal ultrasonography and endometrial biopsies are not recommended in the absence of symptoms
Antiestrogens: SERDs[a]	• Hot flashes • Injection-site reactions	• Patient assessment	
LHRH agonists	• Hot flashes • Injection-site reactions • Osteoporosis	• Patient assessment • BMD	

BMD, bone mineral density.

[a]Liver function tests obtained periodically to screen for changes in hepatic elimination, hepatotoxicity and the presence of hepatic metastases.

TABLE 151-10

Therapies Used for Hormone Receptor–Positive Metastatic Breast Cancer

Drug	Initial Dose	Special Population Dose	Comments
Aromatase Inhibitors: Nonsteroidal			
Anastrozole	1 mg orally daily		
Letrozole	2.5 mg orally daily	Caution in severe liver impairment[a]	
Aromatase Inhibitor: Steroidal			
Exemestane	25 mg orally daily		Take after meals
Antiestrogens: SERMs			

Tamoxifen	20 mg orally daily	See text regarding *CYP2D6*	
Toremifene	60 mg orally daily		
Antiestrogen: SERD			
Fulvestrant	500 mg IM every 28 days (after loading days 1, 15, 29)	Moderate liver impairment[a] administer 250 mg IM every 28 days (after loading days 1, 15, 29)	
LHRH Agonists			
Goserelin	3.6 mg SC every 28 days	Premenopausal women only	
Leuprolide	3.75 mg IM every 28 days	Premenopausal women only	Not FDA-approved for breast cancer; other formulations are administered differently
Triptorelin	3.75 mg IM every 28 days	Premenopausal women only	Not FDA-approved for breast cancer
Biologic/Targeted Therapies			
Abemaciclib (+/− Letrozole or Fulvestrant)	Single agent 200 mg orally twice a day continuously **OR** Combination 150 mg orally twice a day continuously	Adjust dose for diarrhea, myelosuppression, and/or severe hepatic impairment. Monitor for hepatotoxicity and thromboembolism. Avoid concomitant strong inhibitors of *CYP3A4* and moderate/strong inducers of *CYP3A4*	Do not split tablets
Palbociclib (+ Letrozole or Fulvestrant)	125 mg orally daily × 21 days, followed by 7 days off, repeated every 28 days	Adjust dose for myelosuppression and severe hepatic impairment. Monitor for nausea, diarrhea, and hepatotoxicity. Avoid concomitant strong inhibitors of *CYP3A4* and moderate/strong inducers of *CYP3A4*	Do not split tablets Take with meals (capsules only)
Ribociclib (+ Letrozole or Fulvestrant)	600 mg orally daily × 21 days, followed by 7 days off, repeated every 28 days	Adjust dose for myelosuppression and/or severe hepatic or renal impairment. Monitor for hepatotoxicity and QT prolongation. Avoid concomitant strong inhibitors of *CYP3A4* and moderate/strong inducers of *CYP3A4*	Do not split tablets
Alpelisib (+ Fulvestrant)	300 mg orally daily	Adjust dose for dermatologic toxicity, hyperglycemia and diarrhea. Monitor for hyperglycemia and dermatologic toxicity. Avoid concomitant strong inducers of *CYP3A4*	Take after meals. Do not split tablets
Everolimus (+ Exemestane or Fulvestrant or Tamoxifen)	10 mg orally daily	Adjust dose in mild, moderate and severe liver impairment; also monitor for myelosuppression, hyperglycemia, dyslipidemia, renal dysfunction. May need to adjust dose with concomitant CYP3A4 inhibitors/inducers	Do not split tablets

IM, intramuscular; SC, subcutaneous.

[a]Severe liver impairment: Child-Pugh class C; moderate liver impairment: Child-Pugh class B; minor liver impairment: Child-Pugh class A.

In postmenopausal women, the main source of estrogen is derived from the peripheral conversion of androstenedione produced by the adrenal gland into estrone and estradiol. This conversion requires the enzyme aromatase. Aromatase also catalyzes the conversion of androgens to estrogens in the ovary in premenopausal women and in extraglandular tissues (eg, the breast and breast cancer cells) in postmenopausal women. Therefore, AIs effectively reduce the levels of estrogens in circulation and in the target organ. Third-generation AIs include anastrozole, letrozole, and exemestane. A major advantage of these specific compounds is their toxicity profile, which consists mainly of bone loss and osteoporosis, mild nausea, hot flashes, arthralgias/myalgias, and mild fatigue. Anastrozole and letrozole are nonsteroidal triazole compounds that reversibly and competitively inhibit aromatase; they have no intrinsic hormonal activity. Exemestane is a steroidal compound that binds irreversibly to aromatase, forming a covalent bond. Although this mechanism may have theoretical advantages to the reversible binding of the nonsteroidal agents, no clinical evidence that this drug is superior to other agents in this class exists. AIs should only be used in postmenopausal women. Pre- or perimenopausal women, whose ovaries are functioning, are not appropriate candidates for these therapies, but the use of AIs in addition to ovarian ablation or suppression (eg, oophorectomy or LHRH agonists) is appropriate and acceptable.

Antiestrogens bind to ERs, which inhibit receptor-mediated gene transcription and therefore block the effect of estrogen on the end target. This class of agents is subdivided into two pharmacologic categories, SERMs and selective estrogen receptor downregulators (SERDs). SERMs include tamoxifen and toremifene (and raloxifene for breast cancer–risk reduction in high-risk women) and demonstrate tissue-specific activity, both estrogenic and antiestrogenic, as described previously. The agonist activity is thought to be responsible for many of the adverse reactions seen with these agents, including the increased risk of endometrial cancer, and has led to the development of pure ER antagonists that lack estrogen agonist activity. SERDs are also referred to as pure antiestrogens. These molecules bind to ER, inhibit estrogen binding, and degrade the drug–ER complex, thus decreasing the amount of ER expressed. Fulvestrant is currently the only pure antiestrogen currently commercially available in the United States.

The most commonly utilized SERM in the treatment of breast cancer is tamoxifen. The toxicities of tamoxifen are described in the "Endocrine Therapy" section under Curative Breast Cancer. The only additional toxicity that may be observed in the setting of MBC (specifically bone metastases) is a tumor flare or hypercalcemia, which occurs in about 5% of patients after the initiation of any SERM therapy and is not an indication to discontinue the drug. It is generally accepted that this reaction is associated with response to endocrine therapy, but patients who do not experience such a reaction may still respond. This reaction is seen less frequently with the concurrent use of bisphosphonates as a result of their inhibition of osteoclasts, subsequently preventing the release of calcium from the bone.

Toremifene is another commercially available SERM for the treatment of breast cancer. It exhibits similar efficacy and tolerability compared with tamoxifen in the metastatic setting. Cross-resistance to toremifene has been demonstrated in patients with tamoxifen-refractory disease. Details regarding its metabolism are available and indicate it may be an alternative to tamoxifen in settings where there are concerns regarding drug interactions. However, toremifene use in the United States is minimal.[55] Raloxifene, another SERM, was originally approved for the prevention of osteoporosis in postmenopausal women. Available data with raloxifene as a treatment for breast cancer show low response rates and no significant clinical benefit. Consequently, the use of this agent for breast cancer treatment should be discouraged. The clinical benefits of raloxifene for breast cancer risk reduction in high-risk postmenopausal women have been discussed (see the "Prevention and Early Detection" section).

Fulvestrant, an SERD, is approved for the second-line therapy of postmenopausal patients with hormone receptor–positive tumors either alone or in combination with targeted therapy. When combined with ovarian suppression or ablation, fulvestrant is an appropriate therapy in premenopausal women. It is unique, in that it is given as an intramuscular injection. Adverse drug reactions related to fulvestrant include injection-site reactions, hot flashes, asthenia, and headaches.

In premenopausal women, one of the goals of endocrine therapy is to reduce estrogen production which can be accomplished with surgery, radiation, or medication. While radiotherapeutic ablation of the ovaries is effective, this approach is typically not used in the United States because of its morbidity. Medical ovarian suppression with LHRH analogs is increasingly used instead of oophorectomy in premenopausal women. Because the effects of the LHRH analogs are reversible, the administration of these agents may also determine how a patient will tolerate estrogen deprivation. If the patient tolerates this therapy, then an oophorectomy may be recommended as a permanent therapeutic intervention.

The activity of LHRH analogs is related to its ability to downregulate LHRH receptors in the pituitary and decrease luteinizing hormone levels, which

subsequently decreases circulating estrogen to suppressed/ablated levels. Therefore, the effect of LHRH analogs on circulating estrogen levels in premenopausal breast cancer is similar to an oophorectomy. The three agents available in the United States are leuprolide, goserelin, and triptorelin, but only goserelin is FDA-approved for the treatment of MBC. These agents are administered as an injection every 4 weeks (all products have extended formulations, lasting 3 months to 1 year, but they are not recommended for the initial treatment of breast cancer) and are associated with minimal adverse drug reactions, including amenorrhea, bone loss or osteoporosis, hot flashes, and occasional nausea (see Table 151-9). LHRH analogs may also produce a flare response because of an initial surge in luteinizing hormone and estrogen production lasting 2 to 4 weeks. This flare response is similar to that seen with tamoxifen, and patients with high-volume, bulky disease should be monitored for increasing pain and hypercalcemia during the initiation period.

Biologic or Targeted Therapy

10 Therapies directed at molecular targets through novel mechanisms are often referred to as targeted therapy. Many of the targeted therapies are also biologic therapies because they are mAbs. For breast cancer, several agents are directed at targets that are differentially expressed in breast cancer cells and play a critical role in their proliferation and survival.

CDK Inhibitors

Three CDK-inhibitors have an FDA-approved indication for MBC (abemaciclib, palbociclib, and ribociclib). These agents selectively inhibit CDK-4 and -6, effectively preventing retinoblastoma tumor suppressor gene product phosphorylation and leaving it in an active state that is able to appropriately regulate cell division. CDK inhibitors have improved progression-free survival in combination with AIs (as first-line therapy) and fulvestrant (as first- and second-line therapy) (see Table 151-10). A CDK inhibitor-containing regimen should be considered as first-line therapy in newly diagnosed patients with *HER2*-negative, hormone receptor–positive MBC. The addition of the CDK inhibitor to endocrine therapy increases the toxicity of the regimen. Neutropenia (all grades) is the dose-limiting toxicity of palbociclib and ribociclib and is also fairly common with abemaciclib. However, low rates of neutropenic fever and other infections have been reported. The dose-limiting adverse drug reaction with abemaciclib is diarrhea and occurs in nearly all patients. Diarrhea is typically managed with dose reductions and medical interventions, allowing most patients to continue therapy. Abemaciclib is also associated with a “false” elevation in serum creatinine. Ribociclib also has a warning in its labeling for QT prolongation and requires electrocardiogram monitoring for the first two cycles.[56]

Mammalian Target of Rapamycin (mTOR) Inhibitors

The phosphatidylinositol 3-kinase (PI3K)/protein kinase-B (also called Akt) pathway includes many different proteins, of which one of the most important is the mTOR tyrosine kinase. mTOR is an important mediator for cell proliferation and regulation of apoptosis, angiogenesis, and cellular metabolism. Everolimus, an oral mTOR inhibitor, improved progression-free survival when given in combination with either exemestane, fulvestrant, or tamoxifen and should be considered in patients with hormone receptor–positive MBC whose disease has progressed within a year of or while receiving endocrine therapy (see Table 151-10). The choice of endocrine therapy depends on what endocrine therapy the patient received previously.

The most common serious (grade 3 or 4) adverse drug reactions reported in the combination everolimus/exemestane trial were stomatitis, anemia, dyspnea, and pneumonitis. Adverse metabolic effects can be seen and monitoring should include fasting glucose, hemoglobin A1C, and lipid panel.

PI3K Inhibitors

PI3Ks play a critical role in regulating many biological functions including cell growth, proliferation, and survival.[57] Alpelisib, a PI3K inhibitor, is approved in combination with fulvestrant for postmenopausal women and men, with hormone receptor–positive, *HER2*-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

Several important toxicities associated with alpelisib require close monitoring and may lead to dose reductions due to intolerability. Hyperglycemia, including ketoacidosis, may occur with alpelisib and patients’ fasting glucose should be monitored closely especially upon initiation of this agent. Many patients will require medical intervention with antidiabetic medications. Other adverse drug reactions that may be significant include rash and diarrhea. Antihistamine administration prior to rash onset may decrease rash incidence/severity and should be considering upon initiation of alpelisib.

PARP Inhibitors

Olaparib and talazoparib, given as single agents, improve progression-free survival compared with single-agent chemotherapy in patients with *HER2*-negative MBC who had a germline mutation in *BRCA1* or *BRCA2*. Rates of severe adverse drug reactions (grade 3 or higher) are less common with the PARP inhibitors compared with chemotherapy. Commonly reported adverse drug reactions of PARP inhibitors include anemia, nausea, vomiting, diarrhea, and fatigue.[58]

HER2-Targeted Agents

HER2 is an important protein for maintenance of breast cancer cell proliferation and survival. The *HER2*-targeted agents currently available in the United States are trastuzumab, pertuzumab, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan, margetuximab, lapatinib, neratinib, and tucatinib. To date, no benefit has been observed with the administration of trastuzumab to patients with *HER2*-negative tumors (IHC score of 0-1+, or FISH negative) and a questionable benefit has been observed with administration of trastuzumab to women with tumors that are 2+ for *HER2* by IHC staining alone. As mentioned previously, trastuzumab is a mAb targeted against the *HER2*-receptor protein. Pertuzumab is also a mAb but binds to a different epitope on *HER2* and prevents protein dimerization and subsequent cell signaling. Ado-trastuzumab emtansine and fam-trastuzumab deruxtecan are ADC with a trastuzumab backbone linked to cytotoxic chemotherapy. In the case of ado-trastuzumab, the chemotherapy portion is a potent tubulin inhibitor and in fam-trastuzumab deruxtecan, a topoisomerase inhibitor. Lapatinib, neratinib, and tucatinib are small-molecule tyrosine kinase inhibitors targeted against the *HER2* protein, leading to cell signaling blockade and decreased cell proliferation.

First-line therapy with a pertuzumab-trastuzumab-taxane combination is the preferred option for *HER2*-overexpressing MBC in patients who have not received pertuzumab in the neoadjuvant or adjuvant setting. Docetaxel administered every 3 weeks in combination with trastuzumab and pertuzumab (both administered every 3 weeks) has the most evidence to support its use in this setting. Substitution of docetaxel with weekly paclitaxel may be used if patients cannot tolerate docetaxel.[59]

Fam-trastuzumab deruxtecan is recommended as second-line therapy in patients with *HER2*-low MBC defined as IHC1+ or 2+/ISH negative.[60] This is the first time a *HER2*-targeted therapy has shown benefit in those with *HER2*-low MBC. It was shown to prolong progression-free and overall survival, regardless of HR-status.

Third-line *HER2*-targeted therapy options include ado-trastuzumab emtansine or tucatinib + trastuzumab + capecitabine (preferred if brain metastases). Subsequent therapy (fourth-line) for *HER2*-positive MBC is controversial. Choice of regimen may depend on the presence of brain metastases, organ function, and residual toxicities from previous regimens. Possible options include a lapatinib combination regimen, a chemotherapy + trastuzumab combination, margetuximab-cmkb + chemotherapy, or neratinib + capecitabine. For patients with tumors that are hormone receptor-positive, endocrine therapy, either alone or with trastuzumab or lapatinib, is an option.

Brain metastases are common in patients with *HER2*-positive MBC, with over 50% of patients experiencing brain metastases over their lifetime. This statistic is somewhat misleading because the brain is an uncommon site of first recurrence in patients with ESBC (1%-3%); this observation is related to the overall success of *HER2*-targeted therapy at extracranial sites and the ability of the blood-brain barrier to prevent *HER2*-targeted mAb from accessing these tissues, creating a sanctuary site for breast cancer cells. Nonetheless, responses in the brain have been reported with the large, *HER2*-targeted antibodies and are likely due to disruptions in the blood-brain barrier from disease or prior local therapy (surgery or radiation). The small molecule tyrosine kinase inhibitors, particularly tucatinib, have shown efficacy in patients with brain metastases, but local therapies tend to offer the best approach in combination with systemic therapy. Local therapy including surgery, whole-brain radiation, stereotactic radiosurgery, or some combination of these approaches is considered as initial therapy. Systemic therapy is continued if the other metastatic sites are stable. If extracranial metastases are progressing, a change in the *HER2*-targeted therapy according to guidelines is appropriate. If local therapy fails to control disease in the brain, best supportive or palliative care may be indicated, depending on the status of their extracranial sites of disease and their overall performance status.[61]

Adverse drug reactions of *HER2*-targeted therapies are primarily related to the heart. All therapies in this class, regardless of their exact mechanism of receptor blockade, have some degree of cardiotoxicity. Heart failure associated with trastuzumab is somewhat reversible with pharmacologic management, and some patients have continued therapy with trastuzumab after their left ventricular ejection fraction has returned to normal with medical management and/or a pause in therapy. Close monitoring for clinical signs and symptoms of heart failure and routine echocardiography are recommended in order to intervene with appropriate cardiac treatments for all patients on *HER2*-targeted agents. Rare QT prolongation has also been

reported with lapatinib, but the clinical significance of this effect is unclear. Concurrent administration of drugs that increase systemic exposure to lapatinib or have similar effects on QT interval may predispose patients to this rare complication and warrant closer monitoring.

Infusion-related reactions (primarily fever and chills) are associated with mAbs and are seen with trastuzumab, pertuzumab, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan, and margetuximab. These reactions can range depending on the agent but may occur in up to 40% of patients receiving trastuzumab.[40] Postmarketing surveillance data have identified pulmonary toxicity and anaphylaxis as rare but potentially life-threatening reactions associated with trastuzumab. Other infusion-related reactions may include mild nausea, pain at tumor sites, rigors, headaches, dizziness, hypotension, rash, and asthenia, which are much less common. If patients experience mild hypersensitivity reactions, they may require the addition of premedications to mitigate this response. If the reaction is more severe, they may be unable to safely receive subsequent doses.

Several *HER2*-targeted therapies, particularly fam-trastuzumab deruxtecan, have been associated with interstitial lung disease. Drug-induced interstitial lung disease includes conditions like pulmonary fibrosis and inflammation that may be life-threatening.[62] Treatment for this toxicity may include corticosteroids and depending on severity may require patient to discontinue therapy with the agent.

Other adverse drug reactions associated with *HER2*-targeted therapies may include rash and diarrhea. Diarrhea is more significant for patients treated with pertuzumab and when *HER2* TKIs are used in combination with chemotherapy (eg, neratinib plus capecitabine). This adverse drug reaction is generally manageable with aggressive antidiarrheal therapy or dose reductions. Other rare effects have been reported (QT prolongation, hepatotoxicity) and patients should be counseled regarding these effects. Drug-drug and drug-food interactions are particularly important with the *HER2* TKIs because of their metabolism through CYP enzymes and other pharmacokinetic and pharmacodynamic issues. Many of the adverse drug reactions listed previously may be exacerbated by drug or food interactions, and careful review of patients' medication lists and education regarding these issues is extremely important.

Immunotherapy

While mAbs against programmed cell death protein 1 (PD-1) and programmed death-ligand (PD-L1) have failed to demonstrate antitumor activity as single agents in MBC, combining these agents with traditional chemotherapy have proven effective in certain patient populations. Most recently, several chemotherapy-immunotherapy combinations have been FDA-approved for treatment of patients with metastatic TNBC whose tumors express PD-L1. Pembrolizumab (mAb against PD-1) is approved in combination with albumin-bound paclitaxel, paclitaxel, or the combination of carboplatin + gemcitabine (see Table 151-8). Adverse drug reactions reported with the addition of immune therapies to traditional chemotherapy can be substantial and require close monitoring. Immune-related toxicities may include rash, colitis, hepatitis, hyper/hypothyroidism, and pneumonitis.

Radiation Therapy

Radiation is an important modality in the treatment of symptomatic MBC. The most common indication for treatment with radiation therapy is painful bone metastases or other localized sites of disease refractory to systemic therapy. Radiation therapy provides significant pain relief to about 90% of patients who are treated for painful bone metastases. Radiation is also an important modality in the palliative treatment of metastatic brain lesions and spinal cord lesions, which respond poorly to systemic therapy, as well as eye or orbit lesions and other sites where significant accumulation of tumor cells occurs. Skin and lymph node metastases confined to the chest wall area may also be treated with radiation therapy for palliation (eg, open wounds or painful lesions). Chemotherapy may also be added to radiation for sensitization purposes in certain circumstances.

EVALUATION OF THERAPEUTIC OUTCOMES

The desired therapeutic outcome for ESBC differs significantly from that of MBC. Surgery, radiation, neoadjuvant/adjuvant therapy—chemotherapy, biologic or targeted therapy, and endocrine therapy—is conducted and administered, respectively, with curative intent. Adjuvant therapy is intended to eradicate micrometastases and thus cure the patient of breast cancer. Neoadjuvant therapy is administered to reduce the tumor size prior to surgery and/or to allow breast conserving surgery if the patient desires. In addition, neoadjuvant therapy allows assessment of response or sensitivity to chemotherapy and/or biologic/targeted therapy. In the neoadjuvant setting, local imaging, such as mammogram or ultrasound, is done to assess tumor response to chemotherapy, biologic or targeted therapy, or endocrine therapy. The overall goal of neoadjuvant and adjuvant therapy is to cure the disease, which cannot be fully evaluated for years after initial diagnosis and treatment. Patients are recommended to have a history and physical every 3 to 6 months for the first 3 years after completion of primary therapy, every 6 months for the following 2 years, and then yearly thereafter.

Routine laboratory tests or imaging are not recommended unless there is suspicion of recurrence or metastatic disease.[63]

Palliation is the therapeutic outcome in the treatment of MBC. Optimizing benefits and minimizing toxicity are general therapeutic goals of any therapy administered in this setting. Careful consideration of quality of life is important in this setting. Tumor response to a particular treatment regimen may be measured by changes in laboratory tests, diagnostic imaging, or physical signs or symptoms. The patient usually continues treatment with the regimen, unless the patient cannot tolerate the regimen or the cancer is progressing at a rate that will cause symptoms (or is causing symptoms already). Optimizing quality of life is an important therapeutic end point in the treatment of patients with MBC and eventually requires discontinuation of active cancer therapy and a shift to supportive care with hospice services.

ABBREVIATIONS

ACS	American Cancer Society
ADC	antibody-drug conjugate
AI	aromatase inhibitor
ALND	axillary lymph node dissection
ASCO	American Society of Clinical Oncology
BCT	breast-conserving therapy
BMI	body mass index
CDK	cyclin-dependent kinases
CT	computed tomography
CYP	cytochrome P450 enzyme
DCIS	ductal carcinoma in situ
EGFR	epidermal growth factor receptor; also known as HER1
ER	estrogen receptor
ESBC	early-stage breast cancer
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
HER2	human epidermal growth factor receptor-2
HRT	hormone replacement therapy
IBC	inflammatory breast cancer
IDC	infiltrating ductal carcinoma

IHC	immunohistochemistry
ILC	infiltrating lobular carcinoma
LCIS	lobular carcinoma in situ
LHRH	luteinizing hormone–releasing hormone
MBC	metastatic breast cancer
mAb	monoclonal antibody
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
PARP	poly-ADP ribose polymerase
pCR	pathological complete response
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PI3K	phosphatidylinositol 3-kinase
PR	progesterone receptor
SERD	selective estrogen receptor downregulator
SERM	selective estrogen receptor modulators
SLNB	sentinel lymph node biopsy
TNBC	triple negative breast cancer
USPSTF	United States Preventive Services Task Force
WHI	Women's Health Initiative

REFERENCES

1. Siegel RL, Miller KD, Wagel NS, et al. Cancer statistics, 2023. *CA Cancer J Clin.* 2023;73:17–48. https://doi-org.online.uchc.edu/10.3322/caac.21763.

2. American Cancer Society. *Breast Cancer Facts and Figures 2019–2020*. Atlanta: American Cancer Society, Inc; 2019.

3. Giordano SH. Breast cancer in men. *N Engl J Med.* 2018;378:2311–2320. 10.1056/NEJMra1707939.

4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer Risk Reduction V1.2021. National Comprehensive Cancer Network, Inc 2021. All rights reserved. Last accessed, June 12, 2021.

5. Del Pup L, Codacci-Pisanelli G, Peccatori F. Breast cancer risk of hormonal contraception: Counselling considering new evidence. *Crit Rev Oncol Hematol.* 2019;137:123–130. doi: 10.1016/j.critrevonc.2019.03.001.

6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Cancer V2.2021. National Comprehensive Cancer Network, Inc 2021. All rights reserved. Last accessed, June 12, 2021.

7. Visvanathan K, Fabian CJ, Bantug E, et al. Use of endocrine therapy for breast cancer risk reduction: ASCO clinical practice guideline update. *J Clin Oncol.* 2019;37:3152–3165. 10.1200/jco.19.01472.

8. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2019: A review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin.* 2019;69:184–210. doi: 10.3322/caac.21557.

9. Siu AL. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med.* 2016;164:279–296. doi: 10.7326/m15-2886.

10. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer Screening and Diagnosis V1.2021. National Comprehensive Cancer Network, Inc 2021. All rights reserved. Last accessed, June 12, 2021.

11. Breast Cancer Screening (PDQ) Health Professional Version was originally published by the National Cancer Institute. https://www.cancer.gov/types/breast/hp/breast-screening-pdq#cit/section_1.9. Last accessed June 12, 2021.

12. Mammograms was originally published by the National Cancer Institute. https://www.cancer.gov/types/breast/mammograms-fact-sheet. Last accessed June 12, 2021.

13. Claessens AKM, Ibragimova KIE, Geurts SME, et al. The role of chemotherapy in treatment of advanced breast cancer: An overview for clinical practice. *Crit Rev Oncol Hematol.* 2020;153:102988. doi: 10.1016/j.critrevonc.2020.102988.

14. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer V2.2023. National Comprehensive Cancer Network, Inc 2023. All rights reserved. Last accessed, February 20, 2023.

15. Hwang ES, Solin L. De-escalation of locoregional therapy in low-risk disease for DCIS and early-stage invasive cancer. *J Clin Oncol.* 2020;38:2230–2239. 10.1200/jco.19.02888.

16. Wong SM, King T, Boileau J, et al. Population-based analysis of breast cancer incidence and survival outcomes in women diagnosed with lobular carcinoma in situ. *Ann Surg Oncol.* 2017;24:2509–2517. doi: 10.1245/s10434-017-5867-6.

17. Demark-Wahnefried W, Rogers LQ, Alfano CM, et al. Practical clinical interventions for diet, physical activity, and weight control in cancer survivors. *CA Cancer J Clin.* 2015;65:167–189. doi: 10.3322/caac.21265.

18. Hortobagyi GN, Connolly JL, D'Orsi CJ, et al. Breast. In: Amin EB, Edge SB, Gress DM, et al., *AJCC Cancer Staging Manual*. 8th Ed. Chicago, IL: Springer. 2017:589–638.

19. Loibl S, Gianni L. HER2-positive breast cancer. *Lancet*. 2017;389:2415–2429. doi: 10.1016/S0140-6736(16)32417-5.

20. Lyman GH, Temin S, Edge SB, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2014;32:1365–1383. doi: 10.1200/jco.2013.54.1177.

21. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive

breast cancer and sentinel node metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. *JAMA.* 2017;318:918–926. doi: 10.1001/jama.2017.11470.

22. Korde LA, Somerfield MR, Carey LA, et al. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO Guideline. *J Clin Oncol.* 2021;39:1485–1505. doi: 10.1200/jco.20.03399.

23. Adaniel C, Jhaveri K, Heguy A, et al. Genome-based risk prediction for early stage breast cancer. *Oncologist*. 2014;19:1019–1027. doi: 10.1634/theoncologist.2014-0124.

24. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med.* 2018;379:111–121. doi: 10.1056/NEJMoa1804710.

25. Goldvaser H, Ribnikar D, Majeed H, et al. Absolute benefit from adjuvant chemotherapy in contemporary clinical trials: A systemic review and meta-analysis. *Cancer Treat Rev.* 2018;71:68–75. doi: 10.1016/j.ctrv.2018.10.010.

26. Shah AN, Gradishar WJ. Adjuvant anthracyclines in breast cancer: What Is Their Role?. *Oncologist*. 2018;23(10):1153–1161. doi: 10.1634/theoncologist.2017-0672.

27. Burstein HJ, Curigliano G, Thürlimann B, et al. Customizing local and systemic therapies for women with early breast cancer: The St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. *Ann Oncol.* 2021: doi: 10.1016/j.annonc.2021.06.023.

28. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2019;30:1194–1220. doi: 10.1093/annonc/mdz173.

29. Denduluri N, Somerfield MR, Chavez-MacGregor M, et al. Selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer: ASCO Guideline Update. *J Clin Oncol.* 2021;39:685–693. doi: 10.1200/jco.20.02510.

30. Blum JL, Flynn PJ, Yothers G, et al. Anthracyclines in early breast cancer: The ABC Trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). *J Clin Oncol.* 2017;35:2647–2655. doi: 10.1200/jco.2016.71.4147.

31. Kumar P, Aggarwal R. An overview of triple-negative breast cancer. *Arch Gynecol Obstet.* 2015: doi: 10.1007/s00404-015-3859-y.

32. SEER Cancer Stat Facts: Female breast cancer subtypes. https://seer.cancer.gov/statfacts/html/breast-subtypes.html. Last accessed, June 13, 2021.

33. Schmid P, Cortes J, Dent R, et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. *N Engl J Med.* 2022;386:556–567. 10.1056/nejmoa2112651.

34. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med.* 2017;376:2147–2159. doi: 10.1056/NEJMoa1612645.

35. Chavez-MacGregor M, Clarke CA, Lichtensztajn DY, et al. Delayed initiation of adjuvant chemotherapy among patients with breast cancer. *JAMA Oncol.* 2016;2(3):322–329. doi: 10.1001/jamaoncol.2015.3856.

36. Doxorubicin Hydrochloride. Prescribing information. Pfizer Labs; 2020. Accessed September 4, 2021. http://labeling.pfizer.com/showlabeling.aspx?id=530.

37. Jhaveri K, Esteva FJ. Pertuzumab in the treatment of HER2+ breast cancer. *J Natl Compr Canc Netw.* 2014;12:591–598. doi: 10.6004/jnccn.2014.0059.

38. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med.* 2017;377:122–131. doi: 10.1056/NEJMoa1703643.

39. Gao JJ, Osgood CL, Gong Y, et al. FDA approval summary: Pertuzumab, trastuzumab, and hyaluronidase–zzxf injection for subcutaneous use in patients with HER2-positive breast cancer. *Clin Cancer Res.* 2021;27:2126–2129. doi: 10.1158/1078-0432.ccr-20-3474.

40. Herceptin (trastuzumab). Prescribing information. Genentech; 2021. Accessed July 1, 2021. https://www.gene.com/download/pdf/herceptin_prescribing.pdf.

41. Mignot F, Ajgal Z, Xu H, et al. Concurrent administration of anti-HER2 therapy and radiotherapy: Systematic review. *Radiother Oncol.* 2017;124(2):190–199. doi: 10.1016/j.radonc.2017.07.006.

42. Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med.* 2015;372:134–141. doi: 10.1056/NEJMoa1406281.

43. Tolaney SM, Guo H, Pernas S, et al. Seven-year follow-up analysis of adjuvant paclitaxel and trastuzumab trial for node-negative, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol.* 2019;37:1868–1875. doi: 10.1200/jco.19.00066.

44. Chan A, Delaloge S, Holmes FA, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2016;17:367–377. doi: 10.1016/S1470-2045(15)00551-3.

45. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med.* 2019;380:617–628. doi: 10.1056/NEJMoa1814017.

46. Tong CWS, Wu M, Cho WCS, et al. Recent advances in the treatment of breast cancer. *Front Oncol.* 2018;8:227. doi: 10.3389/fonc.2018.00227.

47. Soltamox (tamoxifen). Prescribing information. Midatech Pharma US; 2018. Accessed September 4, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021807s005lbl.pdf.

48. Tremont A, Lu J, Cole JT. Endocrine therapy for early breast cancer: Updated review. *Ochsner J.* 2017;17(4):405–411. [PubMed: 29230126]

49. Pagani O, Regan MM, Walley BA, et al. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med.* 2014;371:107–118 doi: 10.1056/NEJMoa1404037.

50. Francis PA, Regan MM, Fleming GF, et al. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med.* 2015;372:436–446. doi: 10.1056/NEJMoa1412379.

51. Giordano SH, Temin S, Chandarlapaty S, et al. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol.* 2018;36:2736–2740. doi: 10.1200/JCO.2018.79.2697.

52. Van Poznak C, Somerfield MR, Moy B. Role of bone-modifying agents in metastatic breast cancer: An American Society of Clinical Oncology-Cancer Care Ontario Focused Guideline Update Summary. *J Oncol Pract.* 2017;13:822–824. doi: 10.1200/JOP.2017.027672.

53. Partridge AH, Rumble RB, Carey LA, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2014;32:3307–3329. doi: 10.1200/JCO.2014.56.7479.

54. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. *N Engl J Med.* 2021;384:1529–1541. doi: 10.1056/NEJMoa2028485.

55. Vogel CL, Johnston MA, Capers C, et al. Toremifene for breast cancer: A review of 20 years of data. *Clin Breast Cancer*. 2014;14:1–9. doi: 10.1016/j.clbc.2013.10.014.

56. Hecht KA, Selby C. Review of cyclin-dependent kinase 4/6 inhibitors for the treatment of hormone receptor-positive advanced breast cancer. *Ann*

Pharmacother. 2018:1060028018793656. doi: 10.1177/1060028018793656.

57. Ellis H, Ma CX. PI3K inhibitors in breast cancer therapy. *Curr Oncol Rep.* 2019;21:110. doi: 10.1007/s11912-019-0846-7.

58. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med.* 2018;379:753–763. doi: 10.1056/NEJMoa1802905.

59. Giordano SH, Temin S, Davidson NE. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: ASCO Clinical Practice Guideline Update Summary. *J Oncol Pract.* 2018;14:501–504. doi: 10.1200/JOP.18.00290.

60. Modi S, Jacot W, Yamashita T, et al. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. *N Eng J Med.* 2022;387:9–20. 10.1056/nejmoa2203690.

61. Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2014;32:2100–2108. doi: 10.1200/JCO.2018.79.2713.

62. Hackshaw MD, Danysh HE, Singh J, et al. Incidence of pneumonitis/interstitial lung disease induced by HER2-targeting therapy for HER2-positive metastatic breast cancer. *Breast Cancer Res Treat.* 2020;183:23–39. doi: 10.1007/s10549-020-05754-8.

63. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. *CA Cancer J Clin.* 2016;66:43–73. doi: 10.3322/caac.21319.

SELF-ASSESSMENT QUESTIONS

1. Which of the following accurately describes breast cancer?

   A. Breast cancer mortality has increased since the 1990s.

   B. Incidence of breast cancer is lower in White women compared to Black women.

   C. Most breast cancers are diagnosed at an early stage.

   D. Median age at diagnosis of breast cancer is 54 years of age.

2. CB is a 35-year-old woman with a known *BRCA1* mutation. According to the American Cancer Society, which of the following screening modalities would be recommended for CB annually?

   A. Mammogram and clinical breast examination

   B. Mammogram alone

   C. Breast MRI and mammogram

   D. Breast MRI and clinical breast examination

3. JR is a patient with newly diagnosed hormone receptor-positive, *HER2*-negative MBC. The metastatic disease is in the spine and liver and causes pain. JR has not been previously treated for MBC and needs chemotherapy. Which would be the most appropriate treatment for JR?

   A. Capecitabine

   B. Vinorelbine

C. Gemcitabine

D. Paclitaxel

4. Which of the following agents is appropriate regarding the treatment of patients with hormone receptor–positive DCIS?

A. Raloxifene may be used in premenopausal patients.

B. Raloxifene, exemestane, and anastrozole may be used in postmenopausal patients.

C. Anastrozole may be used in premenopausal patients.

D. Tamoxifen may be used in premenopausal and postmenopausal patients.

5. The treatment of early-stage breast cancer is complex because rapid changes in clinical trials for chemotherapy are reported. Although this is the case, what information is now well-established?

A. Patients with lymph node metastases should not receive chemotherapy.

B. NCCN guidelines and ASCO guidelines are not reliable to go to for treatment updates.

C. Patients with ER/PR positive tumors do not benefit from chemotherapy.

D. Taxanes added to anthracycline chemotherapy provide beneficial treatment.

6. When comparing BCT to a modified radical mastectomy, which of the following statements is true?

A. BCT is associated with similar survival outcomes

B. BCT is associated with decreased local recurrence rates

C. A modified radical mastectomy is associated with improved survival

D. BCT is associated with increased local recurrence rates and decreased survival

7. Which of the following adjuvant chemotherapy combinations is most appropriate for the treatment of early-stage breast cancer?

A. Doxorubicin, cyclophosphamide (AC) followed by weekly paclitaxel

B. Fluorouracil, leucovorin, oxaliplatin (FOLFOX)

C. Cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)

D. Doxorubicin, paclitaxel (AT)

8. Which of the following adjuvant endocrine therapy regimens is most appropriate for a postmenopausal woman with early-stage breast cancer?

A. Anastrozole × 5 years

B. Letrozole × 2 years

C. Fulvestrant × 2 years

D. Tamoxifen × 5 years

9. MR is a 42-year-old individual with newly diagnosed inflammatory right breast cancer. What is the best option for primary therapy?

A. Surgery

B. Radiation

C. Neoadjuvant chemotherapy

D. Neoadjuvant endocrine therapy

10. Which of the following is correct regarding goal of treatment?

A. Adjuvant anastrozole in early breast cancer is for palliation

B. Margetuximab in MBC is for cure

C. Sacituzumab govitecan in breast cancer is for cure

D. Capecitabine in MBC is for palliation

11. Which of the following hormonal therapies is most appropriate for adjuvant treatment in a premenopausal individual?

A. Anastrozole

B. Fulvestrant

C. Exemestane

D. Tamoxifen

12. SW is a 66-year-old postmenopausal individual with newly diagnosed MBC to the lung (ER/PR positive; *HER2*-negative). This was found on a chest x-ray and was confirmed by CT scan and biopsy. SW is otherwise asymptomatic from the cancer and feels well. Which of the following regimens would be best to treat the cancer?

A. Letrozole plus palbociclib

B. Lapatinib plus capecitabine

C. Trastuzumab

D. Paclitaxel

13. DB is a 35-year-old premenopausal individual with a germline mutation in *BRCA1* and newly diagnosed metastatic TNBC. Adjuvant chemotherapy (anthracycline- and taxane-containing regimen) was completed for a locally advanced breast cancer approximately 7 months ago. DB now has liver metastases with normal blood work and minimal symptoms. Which of the following regimens would benefit the patient the most?

A. Letrozole

B. Docetaxel with trastuzumab

C. Capecitabine

D. Olaparib

14. Which of the following agents prevent *HER2*-protein dimerization and subsequent cell signaling?

A. Lapatinib

B. Pertuzumab

C. Everolimus

D. Trastuzumab

15. MM is a 56-year-old postmenopausal individual with newly diagnosed *HER*2-positive, hormone receptor-negative, metastatic breast cancer to the liver and lungs. This cancer was originally diagnosed 3 years prior and received neoadjuvant TCHP (docetaxel, carboplatin, trastuzumab, pertuzumab) with excellent results. The plan for therapy is ado-trastuzumab emtansine. Which of the following adverse drug reactions should be discussed with the patient during the informed consent process?

    A. Renal dysfunction

    B. Seizures

    C. Cardiotoxicity

    D. Hypertension

SELF-ASSESSMENT QUESTION-ANSWERS

1. **C.** Most breast cancers are diagnosed in early stages. A is incorrect because mortality has decreased since the 1990s. B is incorrect because the incidence is higher in White individual. D is incorrect because the median age at diagnosis of breast cancer is 62 years. Refer to the "Introduction" section for further details.

2. **C.** Breast MRI and mammogram are recommended annually for this specific group of individuals by ACS. A is incorrect because ACS does not recommend clinical breast examination, B is incorrect because annual breast MRI is recommended with annual mammography, and D is incorrect because ACS does not recommend clinical breast examination and recommends both annual breast MRI is recommended with annual mammography, instead of breast MRI alone. Refer to Table 151-2 for further details.

3. **D.** This cancer has not been previously been treated, and paclitaxel is a taxane which is one of the most active classes of chemotherapy in breast cancer. A, B, and C are incorrect because these are options for patients once they have been treated with anthracyclines and taxanes. Refer to the "Chemotherapy" section under MBC (Stage IV) section for further details.

4. **D.** Tamoxifen may be used in premenopausal and postmenopausal patients. A is incorrect because raloxifene is not to be used in treatment of DCIS but rather in the prevention setting and is to be given only to postmenopausal patients. B is incorrect because raloxifene and exemestane are not to be used in treatment of DCIS but rather in the prevention setting. C is incorrect because although anastrozole may be given in the treatment of DCIS, it is only for postmenopausal patients. Refer to the "Noninvasive Carcinoma" and "Treatment" sections under Pathophysiology section and for specifics about prevention, and see the Prevention and Early Detection section for further details.

5. **D.** There is benefit when taxanes are added to anthracycline chemotherapy. A is incorrect because in patients with lymph node metastases chemotherapy is recommended in most patients. B is incorrect because NCCN guidelines and ASCO guidelines are reliable to go for treatment updates. C is incorrect because patient benefits from chemotherapy are seen regardless of ER/PR status. Refer to "Systemic Therapy" and "Cytotoxic Chemotherapy" sections under Curative Breast Cancer (Stages I-III) for further details.

6. **A.** BCT is associated with similar survival outcomes. B is incorrect because BCT is associated with a small increase in the risk of local recurrence. C is incorrect because mastectomy is associated with similar survival rates compared to BCT. D is incorrect because BCT is associated with a small increase in the risk of local recurrence and similar survival rates compared to mastectomy. Refer to the "Locoregional Therapy" section under Curative Breast Cancer (Stages I-III) for further details.

7. **A.** Doxorubicin, cyclophosphamide (AC) followed by weekly paclitaxel is the only one of the four regimens now used in breast cancer. B and C are incorrect because these are not chemotherapy regimens used in breast cancer. D is incorrect because "doxorubicin, paclitaxel (AT)" is not a chemotherapy regimen used in breast cancer. Refer to Table 151-5 for further details.

8. **A.** This is a postmenopausal individual being treated with adjuvant endocrine therapy and of the choices, anastrozole × 5 years is the most appropriate. B is incorrect because letrozole should be either for 5 years or the 2 years of treatment should be followed by tamoxifen. C is incorrect because fulvestrant is not appropriate in the adjuvant setting for breast cancer. D is incorrect because in a postmenopausal patient, tamoxifen is

followed by an AI for 5 years or 5 additional years of tamoxifen. Refer to Table 151-7 for further details.

9. **C.** Since MR has inflammatory breast cancer, neoadjuvant chemotherapy is the best option for primary therapy rather than surgery (answer A) or radiation therapy (answer B). D is incorrect because this is neoadjuvant endocrine therapy and in the case, hormone receptor status is unknown. Refer to "Systemic Therapy" and "Cytotoxic Chemotherapy" sections under Curative Breast Cancer (Stages I-III) for further details.

10. **D.** The goal of treatment in MBC is palliation. A is incorrect because adjuvant anastrozole in early breast cancer is for cure. B is incorrect because margetuximab in MBC is for palliation. C is incorrect because sacituzumab govitecan in breast cancer is only for use in the MBC setting and in that setting, the goal is palliation. Refer to "Desired Outcomes" and "Systemic Therapy; Endocrine Therapy" sections under Curative Breast Cancer (Stage I-III), "Biologic or Targeted Therapy", "HER2-Targeted Agents", "Chemotherapy", and "Desired Outcomes" under MBC (Stage IV).

11. **D.** Of the listed option, tamoxifen would be the most correct due to the patient's premenopausal status. A, B, and C are incorrect because these are all to be given to only postmenopausal and not to premenopausal patients. Refer to "Endocrine Therapy" section under Curative Breast Cancer (Stage I-III).

12. **A.** For an asymptomatic patient with HR-positive, *HER2*-negative metastatic breast cancer, the first-line of therapy should be an endocrine-based regimen. Data with the CDK-inhibitors indicate improvements in progression-free survival with the addition of palbociclib to letrozole (and fulvestrant). B, C, and D are incorrect because these are not endocrine-based regimens. See "Biologic or Targeted Therapy" and "CDK Inhibitors" section under MBC (Stage IV) section.

13. **D.** A patient such as this with *BRCA*-mutation and TNBC would benefit from a PARP inhibitor such as olaparib in favor of single agent chemotherapy due to improved progression-free survival. A is incorrect because letrozole is endocrine therapy and this patient has TNBC. B is incorrect because trastuzumab is for patients with *HER2*-positive breast cancer and this patient is not *HER2*-positive. C is incorrect because capecitabine is single agent chemotherapy for which olaparib showed better progression-free survival. See "Biologic or Targeted Therapy" and "Poly-ADP ribose polymerase (PARP) inhibitors" section under MBC (Stage IV) section.

14. **B.** Pertuzumab is the only agent that prevents *HER2* dimerization and subsequently inhibits cell cycle signaling. A, C, and D are incorrect because this is not the mechanism of action for any of these agents. See "Biologic or Targeted Therapy" and "HER2-Targeted Agents" sections under MBC (Stage IV) section.

15. **C.** Ado-trastuzumab emtansine is a mAb against *HER2* linked to a cytotoxic drug, and thus it imparts some increased risk of cardiotoxicity associated with its use. A, B, and D are not associated with ado-trastuzumab emtansine. See "Biologic or Targeted Therapy" and "HER2-Targeted Agents" sections under MBC (Stage IV) and "Biologic or Targeted Therapy" section under Curative Breast Cancer (Stage I-III).